Physiological Reviews

Published and Copyright by
The American Physiological Society
Vol. 68, No. 3, July 1988

The Functional States of the Thalamus and the Associated Neuronal Interplay

MIRCEA STERIADE AND RODOLFO R. LLINÁS

Laboratory of Neurophysiology, Department of Physiology, Faculty of Medicine, University Laval, Quebec, Canada; and Department of Physiology and Biophysics, New York University School of Medicine, New York, New York

Preface .................................................................................................................. 649
I. Introduction ....................................................................................................... 650
  A. Synchronization and desynchronization .................................................. 651
  B. Pioneering steps ....................................................................................... 652
II. Morphological Substrates ............................................................................... 657
  A. Thalamic cell types .................................................................................. 657
  B. Thalamocortical reciprocal projections .................................................. 662
  C. Ascending projections from brain stem core ......................................... 665
III. Experimental Designs in Electrophysiological Study of Thalamocortical
  Relations ........................................................................................................ 671
  A. Electrographic variables of behavioral states ....................................... 672
  B. Activities of physiologically identified neurons ................................... 674
  C. Mimicking arousal by brain stem reticular stimulation ......................... 675
IV. Oscillatory Mode ........................................................................................... 676
  A. Intrinsic neuronal properties .................................................................. 676
  B. Synaptic networks .................................................................................... 693
V. Tonically Activated (Relay) Mode .................................................................. 706
  A. Background activity ................................................................................ 706
  B. Excitatory-inhibitory response sequence ............................................. 714
VI. Conclusions ................................................................................................... 723
  A. Synchronized oscillations ....................................................................... 723
  B. Tonic or relay mode of thalamic function ............................................ 724

PREFACE

The main impetus for our writing this review was the plethora of recent findings relating to the intrinsic electrophysiological properties of central neurons and to the characteristics of various synaptic networks. Indeed, the study of the thalamus has seen a true renaissance based on the combination of modern in vitro electrophysiological techniques with the more classical in vivo approaches to the study of thalamocortical physiology. Although we represent different levels of neurobiological research (M.S. is mainly inter-
ested in an approach to thalamic function to include behavioral, neuronal ensemble, and single-cell properties, whereas R.L. is more interested in the physiology and biophysics of the intrinsic properties of single neurons and their relation to global function), we share enough interests to attempt a joint reductionistic approach to thalamocortical function. Our basic tenets have been that 1) the functional properties of given neuronal networks are engraved to a large extent in the intrinsic electrophysiological character of the neurons involved, and 2) in the intact animal the properties of networks depend, in addition, on specific connectivity of various types of pacemakers and modulatory systems, such that they may generate dissimilar functional states despite the fact that the elements involved have similar intrinsic properties.

The manner in which the field is reviewed here owes more to chance than to a preordained design reflecting the "relevance" of our two fields of study. We hope that this review will help those who work on single cells, since we attempt to present single-cell electrophysiology in a general context, and those who work on general nervous system function, since we point out the relevance of physiological and biophysical studies of single-cell electrophysiology to their work.

I. INTRODUCTION

The world of the thalamus is not to be regarded merely as a set of nuclei that relay afferent impulses en route to the cerebral cortex. Rather, it should be viewed as a unifying entity that operates as the ultimate gatemaster and can, in fact, conjure from the intrinsic properties of neurons the resting and active states of the brain. Such states represent emerging properties of thalamic networks that, as gates, mark the entrance to the forebrain. We envisage a true reductionism from some aspects of behavioral states to intrinsic cell properties. That such reductionism works is clear from studying the firing properties of single neurons and their role in ensemble function. Indeed, rhythmic oscillations of thalamic neurons correspond to the depressed responsiveness that characterizes quiet sleep. Conversely, a stabilized membrane potential associated with tonic firing and enhanced synaptic transmission characterize the waking state. To a large extent, what goes on in the neocortex depends on state-related alterations in thalamic activity. This article discusses the major factors that underlie the oscillatory and tonic modes of activity in thalamocortical systems. Three main elements are responsible for switching from the tonic to the oscillatory modes: 1) the intrinsic membrane properties of the thalamic neurons, 2) the synaptic networks that galvanize these neuronal elements into active groups, and 3) the ascending systems from the brain stem that modulate, in a gentle or startling manner, the intrinsic state of these gatemasters. These ascending systems...
can gently lull one to sleep or brutally discharge one from sleep in the presence of danger.

During the decade between 1968 and 1978, several monographs and reviews were published that dealt with the physiological bases of thalamocortical oscillations and the processes involved in their blockade (15, 431), the state-dependent activities of thalamic and cortical neurons (513, 516, 535), the controlling systems arising in the brain stem core (57, 240, 374, 496, 535), and the synaptic transmitters governing thalamic and cortical function (263). Major breakthroughs have been achieved in this field since 1980 because of the advances in the study of central nervous system development, electrophysiology, anatomy, and immunohistochemistry. Beyond the refinement of electrophysiological methods, the spectacular advances in thalamic and cortical morphology are the elegant product of the retrograde and anterograde transport techniques, intracellular staining of identified elements, and ultrastructural unraveling of synaptic microorganization. Immunohistochemistry has opened avenues that will ultimately define the poliphony of the transmitter substances that populate the thalamic world. Furthermore, microinjection of transmitter substances or potent ligand-dependent agonists can modify, in predictable ways, the electrical activity of the thalamic neurons or even trigger their selective death, far more precisely than can be obtained by electrical means.

The increasing knowledge acquired over the last few years has triggered as much excitement as it has created interpretation frenzy and revisionism. Despite all the above, we nonetheless attempt a synthesis of this wide and nonuniform field of research.

In the first section, we define the commonly used electroencephalographic (EEG) terms of synchronization and desynchronization and review the pioneering steps in the exploration of these phenomena.

A. Synchronization and Desynchronization

In physics, synchronization is a state in which two or more oscillators display the same frequency because of some form of cointeraction (24). From an EEG point of view, synchronization denotes an electrophysiological phenomenon characterized by rhythmic and high-amplitude field-potential waves. As such, the notion of synchronization supposes the coactivation of a large number of neurons, the summed synaptic events of which become sufficiently large to be recorded with rather gross recording techniques.

The epitome of EEG synchronization is seen at the transitional period of drowsiness between waking and sleeping (see Fig. 3). During this time a short set of synchronized field-potential waves, a spindle (so-called because of the spindle shape of the oscillation envelope), can be recorded over most of the cortical surface. This set of synchronous waves has a frequency of 7–14 Hz.
and is present during quiet sleep (EEG-synchronized or quiet sleep). Other oscillatory rhythms visible in EEG recordings are the so-called α-, θ-, and δ-waves, in addition to circumscribed oscillations normally appearing in neocortical foci under specific behavioral conditions. However, the θ-rhythm originates outside the thalamocortical systems, and its occurrence departs from the well-established correlation between diffuse EEG synchronization and quiet sleep. Some of the characteristics of EEG rhythms are discussed in section IIIA.

In contrast to synchronization, desynchronization is the disruption of high-amplitude synchronized EEG oscillations and their replacement by low-amplitude fast rhythms (375). Blockade of high-amplitude spindles and slow waves occurs with transition from EEG-synchronized sleep to either wakefulness or rapid eye movement sleep (REM or EEG-desynchronized sleep). Both waking and REM sleep are brain-activated states because there is an increased responsiveness of thalamocortical and corticofugal neurons to given stimuli (520). Here, cerebral neurons are “activated” and ready to respond to either external stimuli (as in waking) or internal drives (as in REM sleep), whether or not a motor response is generated. The electrophysiological similarity between these two states (very different in their mental content) indicates, along with other findings (221), that EEG desynchronization is a reliable correlate of the increased cellular excitability in thalamocortical systems.

B. Pioneering Steps

1. Thalamic genesis of spindle oscillations

In the late 1930s, Bremer (49) first proposed that the thalamus could be the generator for the 7- to 14-Hz spindles. He demonstrated a clear impairment of cortical oscillations when the diencephalic connections were surgically interrupted. Three years later, Adrian (3) reported that rhythmic thalamic activities, resembling spontaneous spindles, may be observed independently from the presence of cortical connectivity. The definitive demonstration that spindle rhythmicity originates in the thalamus, however, belongs to Morison and Bassett (364). Their 1945 paper convincingly showed that spindles could be recorded in the intralaminar thalamic region of a cat, 3 days after the bilateral removal of the neocortex and optic nerves and the transection of the brain stem at the intercollicular level. Later it was found that thalamic spindles survive the removal of the striatum and most of the rhinencephalon (574) in addition to total decortication. On the other hand, whereas spontaneous spindle sequences are completely absent in the isolated cortex (58, 59) or the cortex of athalamic animals (574), slow waves at 2-4 Hz persist in cortical EEG after thalamectomy (574) or transections of thalamic connections (250, 533).
The demonstration by Morison and colleagues (364, 367) that spindle rhythmicity originates in the thalamus\(^1\) led to the belief that these authors were proposing the existence of a thalamic pacemaker. Although Morison et al. (367) postulated that the spontaneous activity of thalamic nuclei could be "under the additional control of a master area associated especially with the internal medullary area," elsewhere they stated that "the 8 to 12 per second activity could result from constant bombardment by subliminal impulses which sum periodically in the cortex" (96). Some years later, Jasper (218) expressed the same uncertainty about "the essentially rhythmic character of this (thalamic) system, or perhaps of the cortex upon which it acts."

Jasper (220) introduced the idea of an intrathalamic spread of rhythmic activity involving a system of short, multisynaptic connections from the posterior intralaminar nuclei to the ventromedial (VM), ventroanterior (VA), and the rostral pole of reticular thalamic (RE) nucleus (187). This proposal recalls the "complex interneuronal system" of Morison and Dempsey (366) that was thought to control the rhythmic activity and precedes Purpura’s (104, 431) electrophysiological studies of reciprocal connections between medial and lateral thalamic nuclei. Other early studies (571, 572) also suggested that spontaneous synchronization depends on sequential neuronal discharges in adjacent thalamic neuronal pools, in line with Jasper’s conceptual framework. Although connections from intralaminar central lateral (CL)-paracentral (PC) nuclei to VA-ventrolateral (VL) nuclei were sometimes mentioned in Golgi studies (481), have been traced with retrograde transport techniques (545), and are supported by electrophysiological data (224), internuclear fiber systems are the exception, rather than the rule, in the thalamus.

2. Intracellular studies of thalamic networks

In the 1960s, Purpura and colleagues (323, 433-436) investigated the synaptic events underlying synchronizing and desynchronizing processes in

---

\(^1\) Any discussion of the genesis of spindles, that is, their thalamic as opposed to cortical origin, should emphasize several points regarding the characterization of spindle waves by a frequency of 7-14 Hz and by being grouped in sequences that recur periodically with a slow rhythm of 0.1-0.3 Hz (see sect. IVB). A case of variance with the view that these rhythms are thalamic in origin was reported (362). Indeed one train of spontaneous waves at 7-8 Hz is seen in a figure depicting the activity of the isolated cortex. However, typical spindle waves and their grouping in rhythmic sequences recurring every 3-10 s have never been detected in the cerebral cortex after thalamic disconnection (528, 533). Second, the occurrence of spindle rhythmicity in the cortically disconnected thalamus does not imply that corticothalamic pathways have no role in reinforcing the thalamic spindling circuitry. Indeed, as demonstrated by Morison and Dempsey (366), the amplitudes of thalamic spindle waves increase after local application of prostigmine and acetylcholine (ACh) to the appropriate cortical area. Third, although the role of corticofugal projections in triggering the thalamic pacemaker of spindle oscillations was denied in the 1960s (cf. Ref. 15), more recent evidence (520, 551) indicates that orthodromic volleys in corticothalamic pathways are the most efficient way to evoke spindling. This may be due to the setting into motion of the reticular thalamic nucleus (see sect. IVB).
MIRCEA STERIADE AND RODOLFO R. LLINÁS Volume 68

the thalamus using intracellular recording techniques in encéphale isolé preparations. The major finding of these studies was that thalamic neurons, regardless of their location or connectivity, basically displayed similar sequences of excitatory and inhibitory postsynaptic potentials (EPSPs, IPSPs) during synchronization processes. These events were the same whether occurring spontaneously (324) or elicited by medial thalamic stimulation within the frequency range of spindle waves (433, 434). These studies also demonstrated a long-lasting hyperpolarization that was associated with a marked increase in membrane conductance (142) that rendered the neurons unresponsive to incoming synaptic input during synchronization (431). In another series of experiments (435, 436), the prolonged hyperpolarizing potentials were found to be attenuated or suppressed during high-frequency stimulation of the rostral brain stem reticular formation. This is known to generate the arousal response (375), thus suggesting that the inhibition of thalamic inhibitory elements promotes arousal from sleep (435).

Purpura (432) noted a similarity in the amplitude and duration of the hyperpolarizing potentials among randomly recorded neurons in different thalamic nuclei. He envisaged the possibility that medial thalamic stimulation could activate a common pool of inhibitory cells but prudently relegated the postsynaptic potential (PSP) sequences "to the activity of subsets of excitatory-inhibitory interneurons organized in some reciprocally related fashion." The synchronizing process was repeatedly ascribed by Purpura (431) to "complex organizations of excitatory and inhibitory interneurons," as he probably felt that the precise diagrams (cf. Ref. 15) were, at that time, at best simplistic. As to the suppressing effect of brain stem reticular stimulation on the long-lasting hyperpolarizations of thalamic neurons (435, 436), the finding was confirmed in the 1970s (495) and again in recent experiments (7). These results led some investigators to conclude that the enhancement of thalamic excitability is exclusively due to disinhibition and that inhibitory circuits are globally blocked during EEG desynchronization and arousal (see sects. II3 and v).

The extra- and intracellular recordings of ventrobasal (VB) thalamic cells by Andersen, Eccles, and Sears (17, 19, 21) led to a theory of barbiturate spindle activity. According to the model elaborated in the 1968 monograph by Andersen and Andersson (15), a thalamic spindle sequence starts by a discharge of the thalamocortical cell that propagates along the intranuclear axonal recurrent collaterals and excites local-circuit cells. The latter generate recurrent inhibition on projection neurons, producing a long-lasting IPSP followed by a postinhibitory rebound burst that is transferred along the thalamocortical axons and their collaterals. This enhancement of activity leads to further activation of inhibitory interneurons and a wide distribution of the rebound events within the thalamus at the spindle wave frequency. The theory assumed that multiple facultative pacemakers located in all thalamic nuclei are endowed with the ability of generating spindle rhythmicity: "no particular area serves as a general pacemaker" (15). Compared with
Purpura’s views, Andersen’s line of thinking was characterized by two points: the simplification of the hypothetical circuit, which was reduced to three precise elements (the relay cell, its intranuclear axonal collaterals, and the local inhibitory interneuron), and the notion of postanodal exaltation (cf. Ref. 129), regarded as an intrinsic property of thalamic relay cells.

Based on Ramón y Cajal’s (444) data and subsequent Golgi studies (482), Eccles (119) had already remarked in the mid-1960s that there were too few intranuclear axonal collaterals to support the recurrent inhibitory model. In fact, intracellular staining with horseradish peroxidase (HRP) has since revealed that there are no recurrent collaterals in relay cells of the VB (189, 600), VL (527), mediodorsal (MD) (254), and centrum medium (CM)-parafascicular (PF) (386, 597) nuclei of cats and rats. The only thalamic nucleus showing any HRP-filled intranuclear axonal collaterals is the lateral geniculate (LG) (154, 440, 507, 508). Most thalamocortical axons leave the nucleus of origin without branching and, instead, give collaterals on to a special peripheral nucleus known as the nucleus reticularis thalami (RE). The pacemaking role of the RE nucleus in spindle genesis is discussed in section 4vB.

3. Brain stem control of thalamocortical activation

Moruzzi and Magoun (375) were the first to investigate the brain stem substrate of EEG desynchronization. The replacement of slow high-amplitude EEG rhythms by fast low-amplitude waves was best elicited by stimulating the rostral reticular core, with the conclusion that the effect was mediated by diffusely projecting thalamocortical systems.²

Although Moruzzi and Magoun’s experiments were conducted on acute preparations with bulbo-spinal cuts (some under chloralose anesthesia), they (375) decided to go far beyond the observed facts and proposed that the activity of brain stem reticular system is “an important factor contributing to the maintenance of the waking state, and (the) absence of such activity . . . may predispose to sleep.” This is the passive deafferentation concept of sleep, as it has been proposed since antique times (cf. Ref. 373). In the 1950s, Moruzzi and his pupils in Pisa (cf. Ref. 374) moved from the notion of passive sleep focused on the mechanisms of wakefulness to the idea of active hypnogenic (EEG-synchronizing) structures located in the bulbar reticular formation in the vicinity of the nucleus of the solitary tract. Later on the preoptic hypothalamic area was added to the list of possible sleep-promoting struc-

²The EEG desynchronization with low-voltage activity is the most usual electrographic correlate of arousal reaction. Another aspect of reticular-elicited arousal was revealed by Bremer et al. (53) and consists of rhythms with high frequencies and increased amplitudes. These rhythms at 45 Hz (see their Fig. 5) can be related to high-amplitude and fast (35–45 Hz) rhythms that appear in circumscribed thalamic and cortical foci when the animal is hypervigilant and immobile in an attitude of focused attention, while the rest of the cortex is desynchronized (460; see also sect. IIIA).
tures (cf. Ref. 50). When, more recently, the deoxyglucose autoradiography was used to investigate more than a dozen brain structures that have been suggested as hypnogenic, no region was found to increase the metabolic rate during sleep, and the deafferentation theory once again came in favor (252, 384). Recent papers were concerned with the possible sleep-promoting role of basal forebrain neurons. One study (109) failed to find any convincing evidence of neuronal discharges related to EEG-synchronized sleep. In another study (560), ~25% of sampled elements could be termed sleep active (the other 75% were either state indifferent or more active in waking), and they were located in heterogenous basal forebrain structures. We are forced to admit that the theory of an active induction of sleep still awaits cellular data on homogenous samples with known input-output organization.

The concept of a brain stem reticular-activating system has been supported by much subsequent work. Unilateral lesions of the midbrain reticular formation induce EEG-synchronized rhythms in the ipsilateral hemisphere associated with a contralateral, trimodal sensory neglect (584). That the brain stem reticular effect is mediated by thalamic nuclear groups with diffuse projections to the neocortex is now fully supported by the demonstration of direct excitation of intralaminar thalamocortical neurons from the midbrain reticular core (534). Stimulation of the midbrain reticular formation also leads to a significant increase in the metabolic activity in intralaminar thalamic nuclei (172). On the other hand, lesions of the intralaminar complex may produce behavioral disturbances indicating an impairment of attentional systems (498). In humans, a bilateral vascular lesion mainly involving medial and intralaminar thalamic nuclei and partially affecting the midbrain tegmentum induces a very prolonged lethargic syndrome (139).

The hypothesis of reticular activation (375) was proposed only on the basis of changes in the patterns of spontaneous EEG rhythms. In the late 1950s, evoked-potential studies carried out in Bremer’s (52) and Dell’s (117) laboratories demonstrated that the cortical response to prethalamic volleys was enhanced by high-frequency stimulation of the midbrain reticular core. The concomitant reticular-elicited facilitation of responses recorded from thalamic relay nuclei (523) raised the issue of whether cortical activation is entirely dependent on enhanced synaptic transmission through the thalamus. In this respect, it was shown (513) that facilitation of cortical responsiveness may occur independently of thalamic facilitation, as seen by stimulating the cortical radiations directly. Moreover, midbrain reticular stimulation was found to enhance cortical responses to radiation stimuli after destruction of the specific relay thalamic nuclei (540). This effect is probably due to excitatory projections from the midbrain reticular core to the intralaminar thalamic nuclei (534) that bypass thalamic relay nuclei and project over widespread cortical areas (236) or it may be ascribed to activation of cortically projecting cholinergic neurons of the basal forebrain (see sects. III C and III D).
In 1958, a decade after the proposal that the reticular system be viewed as a globally activating network, Jasper (219) considered that inhibitory events play a key role in integrative functions during arousal and concluded that "the activating effect of the ascending reticular system . . . cannot be adequately described in terms of either gross excitation or inhibition, since both processes seem to be present." It was expected that with an increased level of activation during arousal, both the excitatory and inhibitory components of thalamic and cortical cellular responses would increase. However, some studies reached the conclusion that brain stem reticular activation and arousal were associated with a global disinhibition in thalamic circuits (see sect. I&B2). These results were viewed as embarrassing (530) or perplexing (289). In fact, inhibitory processes of thalamic and cortical neurons are at least as effective, but much shorter in duration, during waking than during synchronized sleep (520; see sect. V&B2).

The severe methodological problems with the original reticular-activating concept, based on experiments with electrical stimulation and electrolytic lesions, consist of the unavoidable activation or destruction of fibers of passage. Jouvet (240) believed that the EEG effects elicited by stimulating the rostral reticular formation were not due to activation of cell bodies in that region. Rather, he thought that the enduring cortical activation was produced by costimulation of fibers of passage issuing from the locus ceruleus. Later it was found that bilateral lesions of the locus ceruleus, with a consequent 85–90% depletion of norepinephrine (NE) in the neo- and paleocortex, resulted in normal EEG desynchronization and behavioral signs of wakefulness immediately after recovery from surgery (227). The postulated role of midbrain reticular neurons in ascending activation processes has been confirmed in recent years following chemical excitation and lesion (256, 519). We review these findings in detail in section V&B3.

II. MORPHOLOGICAL SUBSTRATES

Before a description of the electrophysiological basis of oscillations and activation in thalamocortical systems, it is useful to summarize their morphological substrates, namely: 1) the three major types of thalamic neurons and their synaptic contacts, 2) the reciprocal thalamocortical pathways, and 3) the brain stem modulatory systems that control thalamic and cortical excitability.

A. Thalamic Cell Types

The innumerable varieties of thalamic neurons described in morphological studies can be reduced to three major types: the thalamocortical relay neurons, the local-circuit neurons, and the reticular thalamic neurons (Fig.
1). For a systematization of thalamic nuclei, the reader is referred to Jones' monograph (233).

1. Thalamocortical neurons

The largest population (85–90%) of long-axonated neurons are of medium to large size (soma area: 300–400 \(\mu m^2\)), have radially arranged (tuftlike or

![Diagram of synaptic organization in the thalamus.](image)

**FIG. 1.** Synaptic organization in the thalamus. There are 3 main cellular types in the thalamus: thalamocortical (Th-cx), local-circuit (L-circ), and reticular thalamic (RE) neurons. Synaptic contacts between Th-cx, cortical (Cx), RE, and L-circ neurons. Inset, contacts between ascending specific afferent fiber (Spec aff; aff) and dendrites of Th-cx (Th-cx d) and 2 L-circ (L-c d1, L-c d2) cells within a thalamic glomerulus (Glom). Events that result after arrival of an afferent volley in the thalamus are described in text. [Modified from Steriade (520a).]**
bushy) dendrites, and project with high-conduction velocities to medium (IV-III) and deep (VI) cortical layers; the remaining 10–15% of projecting cells are half the size of the former, have slender dendrites, and project with lower conduction velocities toward superficial layers I-II of the appropriate cortical area (183, 280, 413, 445, 504, 507, 565, 599). There is a good match between the highly organized distribution of afferent fibers in sensory [LG, medial geniculate (MG), VB] and motor (VA-VL) relay nuclei and their relatively circumscribed cortical projections compared with the more heterogeneous afferent source and the more widespread cortical projections of intralaminar CL-PC nuclei (cf. Refs. 233, 527). Fast- and slow-conducting afferent axons contact thalamic relay neurons with matching conduction velocities (154).

Without exception, the initial effect of afferent stimulation is the excitation of thalamic neurons. The probable transmitters of prethalamic as well as thalamocortical axons are glutamate and/or aspartate (402, 474). Neuropeptides are present in various thalamic nuclei (325, 348, 578). Double-labeling immunohistochemistry combined with the retrograde transport of HRP reveals the coexistence of cholecystokinin (CCK)-like and vasoactive intestinal polypeptide (VIP)-like immunoreactivity in some medial and intralaminar CL-PC-central medial (CeM) neurons projecting to the cerebral cortex or striatum (245, 557). Potent excitatory effects on cortical neurons are induced by both glutamate (265) and VIP (417).

2. Local-circuit neurons

Neurons with locally ramifying axons have spheroid or ovoid somata, with sizes similar to those of the smallest thalamocortical neurons (200 μm²), and dendrites with appendages and vesicle-containing synaptic profiles (141, 362, 443, 559, 563). Since the late 1970s a number of studies combining Golgi, HRP, and immunohistochemical methods have shown that 20–30% of the neurons in various thalamic nuclei of primates, carnivores, and rodents are short axoned and immunoreactive to glutamic acid decarboxylase (GAD), the enzyme for the synthesis of inhibitory neurotransmitter γ-aminobutyric acid (GABA) (190, 271, 278, 397, 412, 504). Direct evidence for GABA-immunopositive LG interneurons was shown recently (161). All these data provide the substrate of local (intranuclear) inhibitory processes involved in discrimination processes. The number of GAD-immunoreactive cells diminishes from monkey and cat to lower mammals (411).

3. Reticular thalamic neurons

Golgi studies and intracellular HRP injections show that RE neurons are characterized by a medium to large soma (300–400 μm²). They have several thick primary dendrites that give rise to secondary, tiny branches cov-
erated by long and filamentous appendages (381, 444, 479, 527, 598). Following Ramón y Cajal's (444) observation, subsequent studies have confirmed that, instead of projecting to the cerebral cortex, RE axons run caudally and medially to terminate in various thalamic territories (232, 479, 545). Double-labeling of RE neurons after injections of fluorescent tracers in thalamic nuclei reveal that >90% of axons originating in a given RE district terminate essentially in one nuclear group (545). The RE-thalamic projections are reciprocal. For example, RE-intralaminar pathways (545) originate in the districts that represent the targets of the intralaminar-RE pathways (232).

Virtually all RE neurons of rat, cat, and monkey are GABAergic (161, 190, 202, 598). In cat, the GAD immunoreactivity coexists with the somato-statinlike immunoreactivity (179, 395). Although the GABAergic nature of RE neurons would unequivocally point to inhibitory influences on thalamocortical neurons, these influences may change with shifts in the behavioral state of vigilance (532). Such variations may depend, at least partially, on the fact that RE neurons establish connections not only with thalamocortical cells but also with GABAergic local-circuit neurons (359), with the consequence of converting the negative feedback on relay thalamic neurons during EEG-synchronized sleep into a positive one on arousal (532; see sect. v.A.1).

4. Synaptic organization of thalamic neurons

Thalamocortical, local-circuit, and RE cells make synaptic contacts on one another (Fig. 1). Most of the present knowledge of synaptic organization in nuclei of the dorsolateral thalamus arose from ultrastructural work in the late 1960s and the 1970s (141, 184, 188, 237, 238, 281, 282, 362, 443, 559). The ultrastructure of the RE nucleus was investigated more recently in cats (101, 209, 358, 598) and rats (396).

1) GLomerulus. A common pattern of synaptic organization characterizes cortically projecting relay and intralaminar thalamic nuclei (188). Contacts between thalamocortical and local-circuit cells occur in synaptic islands encapsulated by glial sheets, referred to as glomeruli; the extraglomerular neuropil contains terminals of corticothalamic and RE-thalamic axons (Fig. 1).

The glomeruli contain two presynaptic and two postsynaptic elements. The first type of presynaptic element consists of axon terminals of ascending afferent fibers that have round and large vesicles and make asymmetrical synaptic contacts with dendrites of both thalamocortical and local-circuit cells (see Fig. 1, inset). The second type of presynaptic element is dendrites of GABAergic local-circuit cells. They are postsynaptic to afferent terminals, contain pleomorphic vesicles, and make symmetrical synaptic contacts on the proximal dendrites of thalamocortical cells and on dendrites of local-circuit cells. In the latter case, synaptic contacts may be reciprocal. Presynaptic dendrites may outnumber the terminals of ascending afferent axons. The
synaptic contacts of the prethalamic afferent axon may form triads. These occur when a single afferent contacts the dendrites of both relay cells and local circuit neurons; the latter is also presynaptic. It is commonly agreed that terminals with round vesicles at asymmetrical synapses are most often associated with excitatory processes, whereas terminals with pleomorphic and flattened vesicles at symmetrical synapses give rise to inhibition. The synaptic contacts within the glomerulus and the extraglomerular neuropil depicted in Figure 1 may account in large part for the events following the arrival of an afferent volley in the thalamus.

The following description of the events elicited by a synchronized unique stimulus to thalamic afferents may not hold for the continuously asynchronous afferent activation that characterizes thalamic function in the free-moving unanesthetized animal. Action potentials in a specific afferent fiber depolarize the dendrites of both thalamocortical and local-circuit cells. Since the dendrites of the local-circuit cells have presynaptic pleomorphic vesicles, their depolarization should cause release of GABA and, hence, hyperpolarization of the relay cells. However, local-circuit cells are inhibiting each other as well. This inhibition is also short lasting. Indeed, the monosynaptic EPSP elicited in the relay cell by the specific afferent fiber could be cut short by the feed-forward inhibition (through contacts between the afferent fibers and local-circuit dendrite neuron 1; see Fig. 1), and this inhibition could in turn be promptly terminated by disinhibition by local-circuit dendrite neuron 2 to neuron 1 contacts. Thus the short duration of the EPSP induced by stimulation of prethalamic fibers (323, 461, 567) may be due to the glomerular microorganization that would allow the relay cell to transfer high-rate (>200/s) messages with high fidelity. However, the intraglomerular EPSP-IPSP sequence is complicated by the addition of synaptic contacts made by corticothalamic and RE-thalamic axons in the extraglomerular neuropil.

II) NONGLOMERULAR SYNAPSES. The extraglomerular neuropil contains terminals of corticothalamic axons having round and small vesicles that make asymmetrical synaptic contact with the distal part of relay-cell dendrites and the dendrites of local-circuit cells. The other presynaptic elements often seen with cylindrical flattened vesicles are the terminals of RE axons; they make symmetrical contacts on the dendrites or somata of thalamocortical neurons (357, 398) and, as shown recently (359), on GAD-positive local-circuit neurons.

III) SYNAPTIC ORGANIZATION OF RETICULAR NUCLEUS. The RE nucleus has a single neuronal type (Ila3) and three types of terminals belonging to axons that originate in the cerebral cortex, thalamic nuclei, and the RE nucleus.

---

3 Two other factors account for the ability of thalamocortical neurons to follow very fast stimuli. One is the production of fast prepotentials (102, 323) that represent voltage-dependent Ca2+ spikes (217, 461). The other is a persistent Na+ current (216, 382). These neuronal properties are discussed in section IVA.
itself. The cortico-RE and thalamo-RE axonal terminals have spherical vesicles and make asymmetrical synaptic contacts on dendritic spines, dendritic shafts, and more rarely on somata of RE-cells, whereas terminals with flattened synaptic vesicles of RE axonal collaterals make symmetrical synaptic contacts with dendrites, somata, and axon hillocks of RE neurons (358, 396, 598). An important species difference should be mentioned: in cat the RE nuclear complex contains neurons with presynaptic dendrites (101, 358, 598) that are not present in the RE nucleus of the rat (396). This may be related to the presence of large bundles of extremely long, tight dendrites with hairlike appendages in cat’s RE nucleus (479) that are not seen in Golgi preparations or HRP-filled neurons of rat’s RE nucleus (396).4

B. Thalamocortical Reciprocal Projections

Lorente de Nó (310) was the first to postulate a dual system of thalamocortical projections. This concept has been supported by morphological and electrophysiological investigations with anterograde tracing techniques, combined field-potential and single-unit data, and current source density analyses.

1. Prevalent thalamic projection to cortical midlayers

The sensory (MG, LG, VB), motor (VL), and association [pulvinar (PUL)-lateral posterior (LP)] thalamic nuclei have a trilaminar pattern of projections. They terminate heavily in midlayer IV and the supervening part of layer III and have additional minor projections to the upper part of layer VI and layer I of the appropriate cortical areas (116, 143, 193, 234, 274, 279). These data, resulting from autoradiography and HRP staining of single thalamocortical axons, corroborate the results obtained by means of depth profiles of centrally evoked field potentials, current source density, and intracellular analyses (144, 255, 353, 363).

The field potential evoked by stimulation of thalamic relay nuclei is positive-negative at the cortical surface. The initial surface positivity is viewed as resulting from excitatory synaptic actions flowing along the vertical core conductors represented by the dendrites of the different cortical neurons. These excitatory inputs create sinks in layers IV to VI (cf. Ref. 352)

4 In a recent study, Ohara and Lieberman (396) point to other significant differences between the RE nucleus of rat and cat. In rat RE thalamic projections are entirely ipsilateral, whereas bilateral RE projections to the ventral nuclear group are present in cat (449). It also seems that, in rat, direct projections from RE nucleus to the brain stem reticular formation and reciprocal brain stem-RE pathways are absent or at best extremely sparse (42), whereas such projections are present in cat (406, 545). Finally, the somatostatin-like immunoactivity characterizes the RE neurons of cat and monkey (179, 395) but is not present in rat RE neurons.
where thalamocortical fibers make asymmetrical synaptic contacts mostly with dendritic spines and shafts of pyramidal cells but also with a variety of excitatory and inhibitory interneurons (cf. Ref. 76). The surface negativity of the primary thalamocortical response is thought to be produced by the additional projection to layer I and to result from synaptic depolarization of dendrites in this superficial layer. There is evidence that thin axons arising from small-size thalamocortical neurons project to layer I (143, 413, 445). Whereas midlayer projections arborize in a quite restricted region, the superficial projections ramify quite widely in layer I (143). These data explain why the surface-positive response is immersed in, and surrounded by, a larger region of surface negativity (365).

Repetitive activation of thalamocortical fibers at frequencies of 7–15 Hz result in cortical responses that increase in size during the train (365, 502). The above is the typical feature of the cortical augmenting responses underlined by a marked increase in amplitude of the secondary excitation and an attenuation of hyperpolarizing potentials (87, 257, 438). These events occur in conjunction with the decrement of the primary response (363, 520).

Although earlier studies emphasized the dependence of augmenting phenomenon on thalamic function (366), the intrinsic cortical circuits are sufficient, however, to generate augmenting responses. This is indicated by the fact that such incremental waves can actually be generated by direct white matter stimulation in preparations with thalamic lesions (363). Moreover, cortical circuits may also generate augmenting responses by antidromic activation of corticothalamic axons (145).

2. Thalamic projections to superficial cortical layers

The thalamocortical systems that project to the more superficial cortical strata (predominantly layer I) on stimulation generate surface-negative responses that develop into incremental waves of the recruiting type (95, 502, 503). There are three such projection systems. They arise from the VM nucleus, the rostral intralaminar nuclei, and the VA nucleus.

Anterograde transport studies show that the VM-cortical axons project predominantly to the outer one-third of layer I over a widespread region of the cerebral cortex (166, 192, 260). The VM-evoked cortical response is characterized by a surface-negative wave that reverses at a depth of 0.15–0.3 mm (166, 392). The origin of this surface negativity has been postulated to be due to direct synaptic depolarization of the superficial dendritic arbor of cortical neurons (166).

The superficial cortical projection of the intralaminar CL-PC and rostral part of CM-PF nuclear complexes has been studied morphologically (92, 231, 463, 545) and by depth field-potential analysis (150). The axons of intralaminar thalamic neurons form asymmetrical synaptic contacts with dendritic shafts and spines of cortical neurons (92, 116) that may corroborate depolar-
izing effects and increment EPSPs in deep lying cortical cells (127). In addition to their projection to layer I, intralaminar CL-PC nuclei project quite diffusely on different cortical areas. In contrast, individual intralaminar neurons have remarkably restricted zones of axonal distribution. Indeed, <5% of intralaminar thalamic neurons of cat are double labeled after injections of fluorescent tracers into the two major projection sites in the cerebral cortex: the pericruciate and anterior suprasylvian gyri (40). In agreement with these results, only a negligible proportion of intralaminar cells are antidromically activated from both these regions (534). The idea of a restricted distribution of single intralaminar axons is also valid when considering the long-standing issue of branched intralaminar axons to both the neocortex and striatum. Although such axonal collaterals may arise from some neurons in the caudal parts of the intralaminar complex, very few neurons are double labeled more rostrally (where the CL-PC complex fully develops) after injections of fluorescent tracers in the striatum and cerebral cortex (462). Less than 10% of CL neurons are double labeled with injections into the caudate nucleus and the pericruciate cortex of cat (316). Furthermore, in agreement with electrophysiological studies (534), no double-labeled cells were found by Macchi et al. (316) in the intralaminar nuclei after injections of fluorescent tracers into the caudate and neocortical areas other than the pericruciate ones. The segregation of intralaminar neurons into two classes, with caudate or cortical projections, is also indicated by the fact that thalamostriatal neurons seem to be cholinergic (467, 494), like the thalamo-Wulst neurons in the pigeon (33, 577), whereas cortically projecting thalamic neurons are glutaminergic and/or aspartatergic (402).

The projection of the VA nucleus to the superficial layer of suprasylvian areas 5 and 7 of cat was first demonstrated electrophysiologically (476) and was recently confirmed morphologically (399).

3. Corticothalamic projections

Thalamic nuclei receive reciprocal pathways from the same cortical areas to which they project (78, 166, 191, 215, 242, 246, 451, 561, 590). This general rule has been considered valid since Walker’s 1938 monograph (579). However, during the past year a paper dealing with intralaminar CL projections to primary visual cortex in cat mentions that no retrograde labeling is seen in area 17 after wheat germ agglutinin-HRP injections in the CL nucleus (92). Corticothalamic neurons originate from layer VI as well as the lower part of layer V (cf. Ref. 233) and are known to be glutaminergic and aspartatergic (37, 54, 148, 312, 604). They are quite different from corticofugal

5 These two major sites of cortical projections, revealed with modern tracing techniques (28, 191, 236), confirm Morison and Dempsey’s (365) data on the distribution of cortical recruiting responses to intralaminar thalamic stimulation.
neurons projecting to the brain stem or spinal cord, as indicated by double-labeling (65) and antidromic invasion (553) techniques. At variance with earlier studies that regarded corticothalamic projections as exclusively ipsilateral, present findings indicate a contralateral component as well. Indeed, contralateral cortical projections have been traced to the dorsal thalamus, at least from the frontal association (171) and the visual (409) cortices. In addition to these direct projections, extra- and intracellular recordings show that the contralateral cortex disynaptically influences VL (530, 551) and ventroposterolateral (VPL) (275) thalamic neurons of monkey and cat through callosal and corticothalamic pathways.

From an electrophysiological viewpoint, the direct orthodromic action of cortical stimulation on thalamocortical cells is a short-latency (2-4 ms), slowly rising EPSP. Typically this synaptic potential may last for 40-50 ms when it is not curtailed by the IPSP (102). The rather slower rise time of this EPSP (compared with that elicited by stimulation of ascending afferent pathways) is ascribable to the distal dendritic termination of corticothalamic axonal terminals on thalamic neurons (see sect. 11A4). This corticothalamic input seems to play a definite role in thalamic function. Thus the excitatory influences of the visual cortex on LG thalamic neurons (6, 566) account for the decreased responsiveness of relay LG cells after cryogenic blockade of the visual cortex (243, 248, 338, 355, 484). Inhibitory effects exerted by cortical stimulation on thalamocortical neurons have often been reported in the literature. This synaptic inhibition follows from the fact that corticothalamic cells activate inhibitory RE and local-circuit neurons (77, 188, 396, 408).

C. Ascending Projections From Brain Stem Core

The systems involved in the control of the excitability of thalamic and cortical neurons originate, for the most part, from the upper brain stem core. There are two groups of control systems. The first group consists of the rostral midbrain reticular formation (unknown neurotransmitter substance) and the cholinergic reticular nuclei at the midbrain-pontine junction (the latter are related with the cholinergic diagonal band nuclei and substantia innominata of the basal forebrain). The second group consists of the aminegic locus ceruleus and raphe nuclei. The old tendency to include the monoaminergic systems within the reticular formation pertained to the ancestral notion of nonspecificity. This notion originated from the lack of morphological sophistication during the 1950s.

In the early 1950s the question of brain stem regulatory systems was left ill-defined from morphological and functional points of view. In particular, the role of the rostral reticular formation in the ascending activation processes was neglected during the 1960s and 1970s. This lapse was because of the lack of proper morphological techniques. In experiments based on anterograd degradation after electrolytic lesions of the brain stem core (388) and
in Golgi studies (478), axons of given reticular neurons appeared to project widely to the thalamus, as well as to the cerebral cortex and spinal cord. It turned out later that most of these brain stem projections to the neocortex did not arise in classic reticular fields but rather from the more recently discovered monoaminergic systems. In addition, double-labeling (330) and electrophysiological (123, 457) studies agree that <4% of rhombencephalic and midbrain reticular neurons have axons that both ascend and descend in the neuraxis. Modern tracing techniques combined with electrophysiological studies have largely eliminated the problems of passing fibers and allowed a better understanding of the input-output organization of brain stem reticular formation. Recent results emphasize specificity as the key feature of both connectivity and transmitter actions for the different brain stem control systems.

At least three basic differences point to a clear distinction between the brain stem reticular nuclei and the monoaminergic neuronal aggregates. 1) Whereas the ascending axons of reticular neurons are overwhelmingly relayed in different thalamic and subthalamic-hypothalamic areas, monoaminergic neurons project directly to widespread allo- and neocortical areas. 2) The depolarizing effect of brain stem reticular stimulation on thalamocortical and corticofugal neurons stands in contrast to the hyperpolarizing actions exerted by aminergic (especially raphe) neurons on their target elements (419, 450, 603; see also sect. v). Stimulation of brain stem reticular neurons directly excites thalamocortical neurons (100, 531, 534), effectively blocks their rhythmic hyperpolarizing oscillations (495, 520), desynchronizes the EEG (375), and leads to an increase in the metabolic activity of the thalamic nuclei (172). Monoaminergic neurons do not seem to be involved in the tonic activation processes of the thalamocortical systems, since their destruction fails to induce changes in EEG activity (227, 454). Instead, locus ceruleus neurons are involved in enhancement of the signal-to-noise ratio (26, 149). 3) Rostrally projecting reticular neurons have state-related firing properties that are quite dissimilar to those of locus ceruleus and raphe neurons. The former exhibit precursor signs of increased discharge rates in both EEG-desynchronized states of wakefulness (543) and REM sleep (549), whereas monoaminergic neurons typically cease firing during REM sleep (25, 199, 343; cf. Ref. 198). The above differences strongly indicate that the brain stem reticular nuclear groups (cholinergic and noncholinergic) must be considered quite separate from the monoaminergic system.

1. Brain stem reticular nuclei

The upper brain stem reticular formation includes the following nuclei. At the rostral midbrain level, the central tegmental field occupies the territory dorsal and lateral to the red nucleus, between the substantia nigra and the superior colliculus. This large reticular area is characterized by small-
sized and less numerous medium-sized cells and virtually no cholinergic neurons (cf. Refs. 253, 587). At the midbrain-pontine junction, there are two groups of medium-sized cholinergic reticular neurons. One is located around the brachium conjunctivum and is termed here the peribrachial (PB) nucleus. The PB nucleus extends from the decussation of the two brachii conjunctivi in the caudal mesencephalon to the upper pons where its neurons merge into the other cholinergic group, the laterodorsal tegmental (LDT) nucleus. The PB nucleus is within the boundaries of a region that, in rodents and some primates, is termed by some authors the pedunculopontine nucleus (cf. Ref. 350). At least in cat, however, the pedunculopontine nucleus is not a cytoarchitecturally distinct cell group (360). The second group is the dorsomedial extension of the PB at the caudal part of the periaqueductal gray merging into the periventricular gray and is the LDT nucleus. In the nomenclature proposed by Mesulam et al. (350) the PB and LDT nuclei correspond to the Ch5 and Ch6 groups.

It has been often reported that choline acetyltransferase (ChAT)-positive neurons are intermingled in both Ch5 and Ch6 groups with noncholinergic cells, usually of smaller size (cf. Refs. 146, 350). Moreover, at least in rat, many cholinergic PB and LDT cells also show immunoreactivity for substance P, corticotropin-releasing factor, and bombesin/gastrin-releasing peptide (575, 576). This issue is of interest in the characterization of the physiological results obtained by rostral midbrain reticular formation stimulation. Since this is the classic site that induces EEG desynchronization and arousal, such stimulation has been assumed to activate cholinergic neurons. However, the cholinergic effects induced by stimulating the rostral midbrain reticular formation are due to activation of axons that originate in the more caudally located cholinergic neurons. Furthermore, peptidergic and other noncholinergic populations may also be involved in the arousal response (see sect. III C).

The brain stem reticular neurons are the site of convergence of a wide and heterogenous set of afferent systems. They arise from the dorsal horn of the spinal cord, the sensory cranial nerves, deep cerebellar nuclei, as well as parts of the brain stem reticular formation and amimergic nuclei. In addition, supramesencephalic structures, such as parts of the intralaminar thalamic nuclei, zona incerta, hypothalamic areas, pallidal complex, and cerebral cortex, also project to this reticular area (for details, cf. Refs. 66, 177, 200, 322, 336, 387, 425, 470, 481, 547). With the exception of the projections from monoaminergic nuclei, which are believed (without direct physiological evidence) to exert inhibitory effects on reticular neurons (198, 334), the initial effect exerted by all other inputs on single reticular neurons is commonly reported to be excitatory. Thus intra- and extracellular studies in chronically implanted unanesthetized preparations indicate that most inputs are excitatory, and only a very small proportion of hyperpolarizing potentials were recorded (214, 386, 457, 548).
The actual extent of the ascending projections of reticular neurons has been investigated in two types of studies. The first employs anterograde or retrograde transport techniques and antidromic invasion of single cells. The second, conducted in recent years, combines ChAT immunohistochemistry with the retrograde transport of HRP.

Autoradiographic experiments (125, 178, 230, 360, 452, 570), HRP retrograde labeling (192, 230), and antidromic identification studies (5, 159, 457, 548) all agree that rostrally projecting axons of reticular neurons originate predominantly in upper brain stem areas. In most of those studies, the reticular projections to major thalamic relay and associational nuclei remained unidentified.

The identification of thalamic projections from cholinergic reticular neurons was achieved in recent works. Studies conducted in rats indicate that cholinergic PB and LDT neurons were retrogradely labeled after massive HRP thalamic injections (350, 501) or more localized injections of HRP or fluorescent tracers into some thalamic nuclei and extrapyramidal structures (185a, 466a, 594). More recent studies used HRP injections confined within the limits of all types of thalamic nuclei of cat and in associational nuclei of macaque monkey (404, 500a, 544). The general conclusion of these latter investigations is summarized diagrammatically in Figure 2, showing that noncholinergic neurons in rostral parts of the midbrain central tegmental field as well as PB and LDT neurons project to major sensory, motor, associational, intralaminar, and RE nuclear complex of cat. Of all HRP-positive elements in PB and LDT nuclei, ~80% were cholinergic, as shown by concurrent visualization of the retrogradely transported HRP and ChAT immunohistochemistry. Recent work in guinea pig (277a) has confirmed these observations by visualizing double-labeled neurons in the PB and LDT with a fluorescent marker retrogradely transported from the dorsolateral thalamus and NADPH-diaphorase histochemistry, which stains cholinergic neurons in this region (cf. Ref. 576). A set of extrinsic cholinergic fibers has been shown to contact the dendrites of LG relay cells in extraglomerular territories, presynaptic dendrites of local-circuit LG cells within synaptic glomeruli, and dendritic spines and shafts of perigeniculate (PG) neurons (93).

In addition to the excitation of thalamocortical neurons from the upper brain stem reticular neurons (534), a direct cholinergic system to the cerebral cortex originates in the basal forebrain neurons (Ch4 group). These cells, collectively known as the nucleus basalis (or substantia innominata), receive afferent fibers from cholinergic and monoaminergic brain stem nuclei, medial thalamic nuclei, preoptic hypothalamic areas, some amygdaloid nuclei, and cortical areas (235, 428, 465, 475). The synaptic profiles of input fibers onto Ch4 neurons are asymmetrical (210). The efferent pathways of nucleus basalis are directed to the cerebral cortex (349, 350, 466) where individual basal forebrain neurons have quite circumscribed (<2 mm) territories of projections (27, 429). In addition, afferents are given to RE and MD thalamic
FIG. 2. Thalamic projections of brain stem reticular cholinergic peribrachial (PB) and laterodorsal tegmental (LDT) nuclei in cat. Bottom: parasagittal section shows some thalamic nuclei where horseradish peroxidase conjugated with wheat germ agglutinin (WGA-HRP) was injected and major brain stem territories where retrogradely labeled neurons were found: central tegmental field (FTC) in rostral midbrain and PB and LDT nuclei at the midbrain-pontine junction. Frontal stereotaxic planes from anterior 4 (A4) to posterior 4 (P4) are indicated. Top: 2 computer-generated graphs show percentage (ordinates) of HRP-positive cells at various rostrocaudal levels (abscissas) from total number of retrogradely labeled elements in brain stem reticular formation. For all depicted thalamic nuclei [ventrobasal (VB), ventroanterior–ventrolateral (VA–VL), lateral posterior (LP), central lateral (CL), reticular (RE)], peak of retrogradely labeled neurons is found between A1 and P3, i.e., levels where cholinergic PB and LDT nuclei fully develop. At these levels, 75–88% of HRP-positive cells were also cholinergic, as shown by concurrent visualization of retrogradely transported WGA-HRP and choline acetyltransferase (ChAT) immunohistochemistry. AC, anterior commissure; IC, inferior colliculus; MM, medial mammillary nucleus; OC, optic chiasma; PAG, periaqueductal gray; RFB, retroflex bundle; RN, red nucleus; SC, superior colliculus; V4, fourth ventricle; ZI, zona incerta. [Modified from Steriade et al. (544) and Paré et al. (404).]
nuclei (546) and to the PB brain stem reticular neurons (558). Ultrastructural studies show that cholinergic afferent fibers (probably from nucleus basalis) to cortical neurons have pleomorphic synaptic vesicles at symmetrical junctions (201).

Basal forebrain Ch4 neurons are apparently involved in EEG activation because their chemical lesion produces slow waves in the ipsilateral EEG (60a, 554), similar to the alterations in wave frequencies seen in Alzheimer's patients (74), and increased incidence of spindle waves (60a). Extracellular studies report that excitatory and inhibitory responses are seen equally in PB reticular neurons after basal forebrain stimulation (558) and that short-latency excitations are elicited in neocortical neurons (124).

2. Monoaminergic nuclei

The NE-containing locus ceruleus is homogeneous and well defined in rats; in cats it comprises many non-NE cells (228, 322; cf. Ref. 149). The ascending projections of locus ceruleus innervate hypothalamic areas and some thalamic nuclei, particularly the RE nucleus of rat (286) and monkey (369) and the allo- and neocortex in rat (229, 280, 285, 421). In early studies only sparse numbers of NE fibers were found in the molecular layer of limbic cortical areas (13,160), and a very low proportion of NE axons were seen to be engaged in genuine synaptic relations (99). However, more recent studies report a denser distribution of NE fibers in the cortex, with a distinct laminar pattern in various areas (370-372) and synaptic profiles in at least 50% of NE terminals (354, 400; cf. Ref. 38 for some methodological issues of studies reporting junctional versus nonjunctional relations of NE terminals). The effects of locus ceruleus stimulation and NE application are discussed in section v together with the actions of other monoaminergic systems. The afferent projections to locus ceruleus arise in the spinal cord, fastigial cerebellar nuclei, nucleus raphe dorsalis, central gray, various hypothalamic areas, and some fields of the cerebral cortex (67, 472). Other results point, however, to a much more restricted afferent control that essentially arises in two bulbar nuclei (26a).

The serotonin (5-HT)-containing raphe nuclei are heterogeneous, consisting of both 5-HT and non-5-HT neurons (4, 511); some of these neurons are dopaminergic (98) or GABAergic (39). The nucleus raphe dorsalis gives rise to most of the ascending projections of the 5-HT system. These projections distribute to the thalamus, hypothalamus, septum, olfactory bulb, hippocampus, and neocortex (405) where the axons have a distinct lamination pattern, as compared with that of NE fibers (371).

There are no known dopaminergic projections to the thalamus. The dopaminergic projections to the cerebral cortex originate in ventral tegmental neurons (97, 140, 326, 564).
III. EXPERIMENTAL DESIGNS IN ELECTROPHYSIOLOGICAL STUDY OF THALAMOCORTICAL RELATIONS

There are multiple approaches to the study of the physiological basis for oscillations and tonic activation in thalamocortical systems. Of necessity, the best experimental condition is the one that allows natural transitions between these two functional modes. This requirement is met, so far, only in the behaving unanesthetized animal, and the only methodology capable of providing precise answers concerning the electrophysiological properties of these neurons is intracellular recording. During the past decade, intracellular studies have been carried out in spinal motoneurons and in some brain stem reticular neurons, with emphasis on particular events of REM sleep (69, 70, 164, 165, 213, 335, 361, 385). For thalamic neurons, however, technical difficulties account for the present lack of a detailed electrophysiological picture during natural sleep-wake behavioral states. The single intracellular studies in chronic preparations report that LG thalamic relay neurons are hyperpolarized during EEG-synchronized sleep as compared with both the waking state and REM sleep (197) and suggest also that slow depolarizations are uncovered by membrane hyperpolarization (151, 197). These studies indicate that the mechanism of postinhibitory rebound excitation, demonstrated in thalamic neurons studied in vitro (300) and in vivo (103), may be operant during natural sleep with EEG synchronization. However, lack of recording stability during the long periods of the sleep-waking cycle in chronic preparations makes such studies very difficult. In addition, ambiguities in the definition of the resting membrane potential in behavioral states with intense synaptic activity further exacerbate the problem. At this time, therefore, investigators are obliged to settle for extracellular recording studies in physiologically identified single neurons during natural behavioral states.

Within limits the barbituratized animal may be a suitable experimental paradigm to study spindle oscillations intracellularly. However, as shown in sections III C and V, barbiturate anesthesia masks major components of thalamic responses evoked by brain stem reticular formation stimulation. Probably the best condition for intracellular studies related to tonic activation processes is the preparation transected at either the midpontine pretrigeminal level or at the bulboospinal junction, the latter combined with lesions of the sensory trigeminal nuclei. The midpontine pretrigeminal preparation is mostly stabilized, demonstrating an EEG state resembling that of wakefulness (35, 36). When signs of EEG synchronization occur, they can be blocked by midbrain reticular stimulation. The encephale isolé preparation, with a cut at C1 (48) and deafferentation of the trigeminothalamic pain pathways, is particularly adequate for the study of shifts between epochs with EEG synchronization and desynchronization. Spontaneously occurring "sleepy" EEG and the excellent EEG reactivity to naturally arousing sensory stimuli (521) indicate that the encephale isolé preparation is neither stressed nor coma-
tose. Intracellular investigations on brain stem-transected preparations have been performed in thalamic (100, 203) and cortical neurons (211, 212, 401; see sect. v).

A. Electrographic Variables of Behavioral States

Active and resting behavioral states are characterized by a set of three cardinal physiological correlates: brain wave activity (EEG), muscle tone, and eye movements. The EEG desynchronization in wakefulness is indistinguishable from that in REM sleep, but the EEG-synchronized rhythms during quiet sleep (consisting of high-amplitude spindle oscillations and slow waves) are easily distinguishable from the other two states (Fig. 3). Because the intrinsic neuronal properties and synaptic networks that underlie the spindle rhythms are largely known, section IV is devoted to this major type of oscillation. To distinguish them from spindle oscillations, the characteristics of other synchronized rhythms are briefly discussed.

Although many authors consider α-waves, at 8-12 Hz, as embryos of

![Electrographic criteria of behavioral states and characteristics of spindle oscillations. A: behaving cat with chronically implanted electrodes. Electroencephalogram (EEG) from neocortical surface, electroculeogram (EOG), and electromyogram (EMG). Spindle waves appear during transitional period between wake and sleep (WS). B: cebreau isolé cat, with an intercollicular transection. Top trace, field electrical activity recorded by means of a microelectrode in intralaminar central lateral thalamic nucleus; bottom trace, spindle waves (filtered from 7 to 14 Hz) from same period. Note sequences of spindle waves recur periodically with a slow rhythm. [Modified from Steriade et al. (532) and Paré et al. (403).]]
spindles, there are major reasons to differentiate these two phenomena. Their topography is different: the α-rhythm is recorded from striate, peri-striate, and posterior temporal areas, whereas spindles are predominantly distributed over anterior areas (46, 277). Their structure is also dissimilar: α-waves form very long trains, whereas spindles are grouped in short (<2 s) sequences that recur periodically (Fig. 3). Most important, their origin and behavioral connotations are different. Although spindles are generated in the thalamus (364), the origin of α-waves is not definitely known. Some experiments point to the role of deeply lying pyramidal cells of the visual cortex in α-genesis and to the role played by intrinsic cortical connections in α-distribution (307–309, 415). Spindling characteristically occurs during unconsciousness and is associated with depressed synaptic transmission through the thalamus (see Fig. 13 and sects. IV and V). The occurrence of α-waves may increase and their amplitude be enhanced during attentional demands (85, 380, 446). The view of an α-to-spindling continuum is, therefore, questionable on those grounds, although ultimately they may be subserved by similar neuronal mechanisms. Although the description of the α-rhythm dates back to Berger (41), little is known about its cellular mechanisms.

Oscillations at 14–16 Hz may develop in the sensorimotor cortex during behavioral immobility of awake animals (458, 460). Faster oscillations, at 35–45 Hz, appear in circumscribed foci of cortical areas 5 and 6 during combined attentive behavior and immobility, while the rest of the neocortex is fully desynchronized (45, 459, 460). These fast rhythms are probably controlled by a dopaminergic system, since they are suppressed after bilateral lesions of the midbrain ventral tegmental area (356). Because of their critical localization in small territories of the neocortex, the disclosure of such rhythms requires a high density of EEG electrodes. Clearly, these oscillations must be dissociated from spindles because of their higher frequencies, their confinement to distinct cortical foci, and their behavioral context. The pacemaker(s) and the intimate cellular substrates of these rhythms have not yet been elucidated.

Slow or δ-waves at 0.5–4 Hz prevail during the late stages of EEG-synchronized sleep. Their amplitudes show rhythmic slow oscillations with periods of 6–12 s (393, 394). A cortical origin for slow waves was suggested during the 1960s (239), and stratigraphic studies showed that the generators of slow waves are mostly located between cortical layers III and V (64, 414). It is doubtful, however, that the cortex is the only site of their genesis because high-amplitude slow waves are seen in focal thalamic recordings after cortical disconnection (533). There is no systematic intracellular analysis of slow waves.

Since the 1960s θ-waves at 5–7 Hz have been studied intracellularly (156). They are presently regarded as generated by rhythmic inputs from both septohippocampal cholinergic fibers and perforant paths, which drive dendrites of CA1 pyramidal neurons and inhibitory interneurons as well as dentate granule cells (44, 61, 351). We consider the θ-rhythm that character-
izes REM sleep and arousal (180, 568) to be beyond the scope of this review because of its site of generation.

B. Activities of Physiologically Identified Neurons

Several cell types have been identified with electrophysiological criteria. 1) The long-axoned thalamocortical and corticofugal neurons are formally identified by the use of conventional criteria of antidromic invasion (cf. Ref. 287). 2) The RE thalamic neurons can be recognized by their cortically evoked spike bursts and spontaneously occurring, long-lasting, and complex spike barrages during EEG-synchronized sleep (532, 550). This is in contrast with the short, stereotyped bursts of thalamocortical cells (see sect. vA2). During the waking state, however, the tonic discharge pattern of RE cells is very similar to that of thalamic relay neurons (see sect. vB1). 3) Electrophysiological criteria of bursting thalamic and cortical short-axoned interneurons (516) are similar to those proposed for inhibitory local-circuit cells in the cerebellum, brainstem, and some forebrain structures (20, 121, 297, 488). The criterion of burst patterns may be too selective, thus omitting some non-bursting interneurons such as found in the spinal cord (120). Without intracellular staining to confirm their location and morphology or immunocytochemistry to determine the transmitter of these cells, purely electrophysiological identifications must be regarded as tentative. There is at this time no direct evidence that thalamic or cortical short-axoned cells have been recorded in vivo.

Both action potentials and slow waves can be examined simultaneously with extracellular recordings. Indeed, such studies provide information on the relations between single neuron discharge and focal waves, the latter which may reflect summated PSPs in a restricted population of adjacent neurons. In thalamic neuronal pools characterized electrophysiologically as closed fields (cf. Ref. 204), the negative focal waves are usually associated with spike discharges, and the long-lasting positive focal waves are associated with silenced firing (542).

Once a neuron is physiologically identified, its spontaneous firing and excitability should be investigated across different behavioral states. In addition to the so-called steady states, spontaneous discharges should be examined sequentially to detect fluctuations in neuronal activity during shifts in states of vigilance. The possibility that a given neuronal type is the precursor of key mechanisms related to the oscillatory or tonic operations may be roughly measured by setting probability bounds on discharge rate fluctuations during base-line periods in both single cells and neuronal ensembles (cf. Refs. 200, 535; see sect. vB3). Electrographic criteria of transitional epochs between steady states are described elsewhere (543, 549).

Direct tests of neuronal excitability are required because one cannot determine if a cell is inhibited unless it demonstrates depressed responsive-
ness to antidromic or orthodromic activation. There are many examples of thalamic and cortical neurons that cease their spontaneous firing but simultaneously increase their responses to various types of stimuli, thus leading to an increased signal-to-noise ratio (289, 529).

The main advantage of antidromic testing is that it can be used in chronic experiments with extracellular recordings. The antidromic discharges provide useful information about the soma responsiveness and inhibitory processes. Indeed, increased delay between the initial segment and soma-dendritic spikes or the appearance of initial segment spikes in isolation during EEG-synchronized sleep in both thalamic (167, 521, 542) and cortical (529, 530) neurons can often be observed during postsynaptic inhibition. It is known that the initial segment-soma-dendritic break or initial segment abortive spikes can be induced by hyperpolarization either from injected currents or from IPSPs (81, 102, 302), even when the inhibition is restricted to the dendrites (290).

Synaptic responses of thalamic and cortical neurons can be studied by applying electrical stimuli to prethalamic and precortical pathways. Although such stimulations are abnormally synchronous, their advantage is to avoid unknown alterations at multiple intercalated synapses as they may occur with the use of peripheral stimuli. One of the best and simplest methods to investigate changes in excitability during primary synaptic excitation in thalamic or cortical neurons is to study the field potential evoked by prethalamic or precortical stimulation. Under normal circumstances the presynaptic component may be monitored, thus allowing a direct determination of the postsynaptic field-potential amplitude, independent of the size of the afferent volley (see Fig. 13).

Inhibitory processes can be determined by measuring, during different states of vigilance, the duration of suppressed spontaneous discharges and the diminished probability of evoked discharges after a conditioning stimulus in afferent or recurrent inhibitory circuits (see Fig. 22).

C. Mimicking Arousal by Brain Stem Reticular Stimulation

High-frequency stimulation of the rostral brain stem reticular core mimics the natural activation processes (375). Since the 1960s it has been assumed by some that the effects of the brain stem reticular “arousing” stimulation are exerted through the ascending cholinergic fibers that originate in nuclear groups at the midbrain-pontine junction (see sect. IIC7).

In brain stem-transected preparations, high-frequency (200–300 Hz) stimulation of the rostral brain stem reticular core with trains of 20–30 pulses elicits an EEG-desynchronizing reaction that lasts for only 0.5–1 s (540). Much shorter stimulations, consisting of one or a few shocks, are needed to obtain evidence for mono- or oligosynaptic response latencies. Under such conditions, however, the stimuli do not elicit the slightest EEG
modification and no modification of the “state” of the animal. Changes in EEG can barely be elicited during deep barbiturate anesthesia where EEG activity usually remains uniformly synchronous.

It is clear that electrical stimuli of the brain stem tegmentum may activate fibers of passage from locus ceruleus and raphe nuclei. Even if stimuli are confined within the limits of the cholinergic PB cell group (Ch5), costimulation of noradrenergic fibers from locus ceruleus, coursing through this very spot, is unavoidable. Presently there are two techniques that avoid such problems: chemical stimulation of PB neurons by means of excitatory agents or previous bilateral lesions of locus ceruleus and extensive lesions of the pontine tegmentum just behind the stimulating electrodes, allowing several days for anterograde degeneration of passing fibers (532, 534). The lack of sensitivity to muscarinic blockers of some components of thalamic responses evoked by brain stem reticular stimulation (see sect. V) is probably due to coactivation of other systems, to coactivation of peptidergic release from cholinergic brain stem reticular neurons (575, 576), and to the probable coexistence of nicotinic and muscarinic receptors in the thalamus.

IV. OSCILLATORY MODE

The oscillatory mode dominates the resting states of drowsiness and quiet sleep with synchronized brain electrical activity. Although the appearance of oscillations is now known to be subserved by the intrinsic electrophysiological properties of single cells, the spontaneous rhythms resembling those occurring during natural behavioral states, where many neurons are synchronously activated, require synaptic interactions between significant numbers of neurons. Such investigations should then address the intrinsic electrophysiological properties of neurons as well as the mechanisms for rhythmicity generated by synchronizing synaptic networks.

A. Intrinsic Neuronal Properties

The intrinsic properties of thalamic and cortical cells have been studied by in vitro as well as in vivo preparations. Most data on the ionic requirements for cellular electroresponsiveness result from experiments on slices. Studies on the electrical activity of the LG thalamic neurons in thin sections have been attempted since 1974 (596), and during the late 1970s the PSPs evoked in LG neurons by optic tract stimulation were investigated in slices of rat and cat LG nuclei (169, 251). Since 1982 a series of in vitro studies (216, 217, 300) have defined the electrophysiological properties and the complex set of ionic conductances in thalamic cells. More recently a new series of in vitro results has confirmed the initial findings (89–91, 196, 341, 586). Parallel investigations have explored the properties of neocortical neurons in vitro (29, 80, 176, 185, 339) and in culture (110). In vivo experiments have investi-
gated intracellularly the electrophysiological properties of thalamic neurons and have put them in the context of behavioral responses (102, 103, 254, 381-383, 461, 528).

In addition to the conventional Na⁺ and K⁺ conductances that underlie the electrogenesis of fast action potentials, the electroresponsive properties of thalamic neurons are implemented by conductance changes to three main ions: Na⁺, Ca²⁺, and K⁺. The properties of these conductances are discussed next, with emphasis on their relevance to distinct behavioral states.

1. Noninactivating (persistent) Na⁺ conductance

The voltage-dependent noninactivating, or very slowly inactivating, Na⁺ conductance will be referred to as $g_{\text{Na}(P)}$, where P signifies persistent (i.e., noninactivating). The $g_{\text{Na}(P)}$ was first described in Purkinje cells (301) where it was shown to generate a slow depolarizing response that was tetrodotoxin (TTX) sensitive and which required the presence of Na⁺ in the extracellular bath. This persistent inward current is located at the soma and has a lower activation threshold and slower kinetics than those generating the fast action potentials. Inward currents via $g_{\text{Na}(P)}$ produce ramp-like voltage trajectories preceding spike activation (Fig. 4). As illustrated in Figure 4, $g_{\text{Na}(P)}$ can generate plateau potentials that outlast the duration of the initial stimulus. This potential does not reach the equilibrium potential for Na⁺ ($E_{\text{Na}}$) because as the depolarization increases it is countered by the voltage-dependent $g_K$. These two currents generate the steady-state voltage that characterizes the plateau potential. The blockage of $g_Ca$ enhances the plateau potential by preventing the activation of the very powerful $g_{\text{Ca}}$.

In the thalamus the $g_{\text{Na}(P)}$ was demonstrated in vitro where it has a definite role in the generation of rhythmic firing in these cells (216, 217). Its presence was found to be crucial in the generation of the 10-Hz oscillation, as it counterbalances $g_K$ to generate a slow rebound depolarization (216; see Figs. 4 and 10). Similar electrophysiology was encountered in vivo, where the ionic mechanisms were inferred from the in vitro findings. In agreement with the above data, $g_{\text{Na}(P)}$ was proposed as assisting thalamocortical neurons in maintaining high rates of discharges by counteracting K⁺ current during the late phase of afterpotentials (AHP) potentials (527). The role of the persistent Na⁺ current in the patterning of thalamic cell membrane oscillations during spindling becomes evident after Na⁺ channels are inactivated by addition of quaternary derivatives of local anesthetics (cf. Ref. 62). For example, after intracellular injection of QX-314, the spontaneous and evoked hyperpolarizations of thalamic relay cells become exceedingly long lasting (due to the dominance of K⁺ currents, $g_K$, $g_{\text{K(Ca)}}$, and $g_{\text{K(A)}}$, unopposed by the slow Na⁺ conductance; cf. Ref. 216) and rhythmic postinhibitory rebounds disappear (382). Besides its role in the patterning of oscillations, the persistent Na⁺ current may be decisive in determining the slowly adapting (or tonic) proper-
FIG. 4. Plateau depolarization generated by noninactivating (sustained) Na⁺ conductance [\(g_{Na(noninact)}\)]. A: direct activation of an intracellularly recorded cerebellar Purkinje cell in vitro. Voltage-dependent Ca²⁺ conductance was blocked by addition of cadmium chloride to the bathing solution. Transmembrane current steps (lower trace) depolarized cell to threshold for spike initiation. Activation consisted of action potentials firing repetitively on a slowly rising depolarizing response that terminates on a plateau potential and spike inactivation. Higher 2 stimuli generate plateaux that outlast stimulus duration. A fast burst of spikes is seen as plateau depolarization returns to resting membrane potential. This plateau is generated by an equilibrium state between \(g_k\) and \(g_{Na(noninact)}\) (1). (From R. Llinás and M. Sugimori, unpublished data). B: similar set of responses as in A but for a thalamic neuron. A very small depolarizing current step is given, which triggers a rapid depolarization of the thalamic cell and a plateau that lasts for several seconds. This plateau is partly produced by \(g_{Na(noninact)}\), and part of voltage is produced by outward current pulse. However, latter component is small, and \(g_{Na(noninact)}\) is responsible for much of plateau amplitude. Superimposed on this plateau are short-lasting depolarizing pulses that generate single spikes and, as plateau reaches a steady level, generate repetitive firing. On termination of current pulse, \(g_{Na(noninact)}/g_k\) equilibrium is tilted toward \(g_k\) and plateau potential terminates. For thalamic neurons, noninactivating Na⁺ conductance is powerful enough to generate a plateau response without blockage of voltage-dependent Ca²⁺ conductances. [Modified from Jahnsen and Llinás (216).]

ties in some subpopulations of thalamic relay neurons. As yet it is not known whether the slowly versus rapidly adapting discharges evoked by stimulation of the receptive field are set at the level of first-order afferents or largely depend on membrane properties of different thalamocortical cell types (cf. Ref. 527). More recently \(g_{Na(p)}\) has been encountered in spinal motoneurons (486) and in neocortical neurons (80, 506).

2. Low-threshold Ca²⁺ spike: basis for sleep bursts

One of the key properties of thalamic neurons that, in conjunction with their long-lasting hyperpolarizations, allows them to oscillate in the frequency range of spindles is the presence of a low-threshold somatic Ca²⁺ conductance, which is inactive at rest and is deinactivated with membrane hyperpolarization. The low-threshold Ca²⁺-dependent spike (LTS) was discovered in the neurons of the inferior olive (303, 304) where it plays a central role in the generation of the inferior olive rhythm probably related to physio-
logical tremor and to the temporal organization of motion (294). Thereafter, this conductance was observed in thalamocortical neurons studied in vitro (300, Fig. 5). Very similar results were obtained in vivo (103) and, by analogy to the in vitro results, were assumed to have the same ionic basis. Since then such findings have been confirmed in a variety of studies of thalamic neurons (89, 90, 102, 196, 197, 216, 217, 254, 383, 403). The only thalamic nucleus that

![Graphs and diagrams](https://example.com/graphs)

**FIG. 5.** Inferior olive and thalamic neurons have 2 different firing levels. 

- **A-B:** activation of guinea pig inferior olivary cell in vitro. 
  - A: subthreshold depolarizing pulse from resting potential. 
  - B: similar pulse riding on a direct current depolarization generates activation of inferior olive neuron, which is characterized by a fast response followed by a sizeable afterdepolarization (ADP) and a prolonged afterhyperpolarization (AHP). ADP is due to activation of high-threshold Ca$^{2+}$ spike present in dendrites, and AHP is due to activation by a dendritic $g_{K(Ca)}$. 
  - If cell is hyperpolarized from rest by 10 mV, same pulse subthreshold in B generates neuron activation. In this case ADP is shorter and is also Ca$^{2+}$ dependent. Ca$^{2+}$ conductance is inactivated at resting potential and is deinactivated by hyperpolarizations beyond resting potential. From this level a small depolarization can generate the so-called “low threshold spike” (R. Llinás and Y. Yarom, unpublished data).
- **C-F:** a comparable set of results for a thalamic neuron. 
  - D: cell was directly stimulated while being hyperpolarized by a constant current injection. Outward current pulse triggers an all-or-none burst of spikes. 
  - E: same current pulse produces a subthreshold depolarization if superimposed on a slightly depolarized membrane potential level. 
  - F: after further depolarization by a direct current, pulse produces a train of action potentials.

[Modified from Llinás and Jahnsen (300).]
apparently lacks a Ca\textsuperscript{2+}-dependent LTS is the ventral LG (89), which has a different developmental history than the other thalamic nuclei.

The LTS is prevented by Ca\textsuperscript{2+} blockers such as cobalt or cadmium, and it underlies Na\textsuperscript{+} action potentials that can be blocked by TTX (300; Fig. 6). The process of deinactivation has a sigmoidal shape beginning at -55 mV and reaching a maximum level at -75 mV (300). In the presence of TTX the switching property of tonic to phasic firing, as demonstrated in Figure 5B by changing the membrane potential, is altered in that fast action potentials cannot be obtained either from a resting level or from a hyperpolarized membrane potential. As shown in Figure 6, after TTX only the slow and broad LTS devoid of spikes is observed. The Ca\textsuperscript{2+} origin of this potential was demonstrated by the addition of CoCl\textsubscript{2} to the bath (Fig. 6), which produces a complete blockage of this potential. Similarly, the reversal of extracellular Ca\textsuperscript{2+} has a similar effect on this response.

On the average, deinactivation to allow the necessary level of regenerative response is attained at -65 mV. At the normal resting potential the response to an excitatory synaptic input may be a simple EPSP that occasionally triggers single spikes. The response to a depolarizing current pulse via the recording electrode is tonic repetitive firing. Either stimulus applied to a hyperpolarized cell by a few millivolts from rest leads, on the other hand, to an LTS crowned by a short burst of high-frequency (>250/s) action potentials (102, 216). Deinactivation of the LTS, as originally described in the inferior olive (303), is also time dependent (Fig. 7). Hyperpolarizing pulses of increasing duration produce graded deinactivation (102, 216), and short-lasting hyperpolarizing current pulses subthreshold for rebound excitation can sum and trigger overt LTSs (528). Full recovery of the LTS occurs after a refractory period up to 170-200 ms, which is voltage dependent. At -74 mV a complete recovery occurs at ~170 ms (216). This is in contrast to the findings in the inferior olive neuron where refractoriness is over by 100 ms (303). These properties appear to be crucial for the genesis of spindle-related rhythmic burst discharges in thalamocortical neurons in vivo (102) and spike

![Figure 6](https://via.placeholder.com/150)

**FIG. 6.** Ionic basis for low-threshold spike (LTS). A: LTS generated by direct stimulation from a slightly hyperpolarized guinea pig thalamic neuron in vitro. B: blockage of LTS by tetrodotoxin (TTX) removes fast spike but leaves LTS unmodified. C: addition of CoCl\textsubscript{2} to the bath abolishes LTS even when current pulse is increased in amplitude by 2.5 times, demonstrating that LTS is generated by low-threshold \( \varphi_{\text{Ca}} \). [Modified from Llinás and Jahnsen (300).]
FIG. 7. Voltage and time dependency of low-threshold spike (LTS) deinactivation. A: depolarizing current pulses from different holding potentials produced a LTS of different amplitude (bottom traces) after tetrodotoxin addition to the bath. Differentiation of these responses (after subtraction of passive component of depolarization) gives an estimate of rate of rise of LTS from different membrane potentials (upper traces). B: an estimate of deinactivation of LTS conductance is obtained by plotting rate of rise against holding potential ($V_m$). Conductance is fully inactivated at potentials positive to $-55$ mV and is completely deinactivated at values negative to $-70$ mV. C and D: time course of deinactivation of burst response. C: a neuron was depolarized with a direct current. A hyperpolarization of 30 mV was then produced with a long-lasting inward current pulse. At different times during hyperpolarization, membrane response was tested by injection of a depolarizing pulse. Nine such tests at different intervals are superimposed. LTS increased in amplitude and duration as interval increased. D: plot of voltage and time dependence for deinactivation. Cell was hyperpolarized from $-44$ mV to $-54$, $-64$, $-74$, and $-84$ mV. Full deinactivation was only obtained for hyperpolarizations to $-74$ and $-84$ mV. No deinactivation was seen at $-54$ mV. [Modified from Jahnsen and Llinás (216).]

bursts with a particular rhythmicity in thalamocortical neurons disconnected from the RE nucleus (528).  

The low-threshold Ca$^{2+}$ spike of inferior olivary cells studied in vitro is effectively blocked by very low concentrations of high-molecular-weight alcohols (such as octanol) that do not have an effect on the high-threshold Ca$^{2+}$ spike (306). The effect of octanol on the low-threshold Ca$^{2+}$ spike of thalamic neurons is less powerful. However, at a concentration of 15–18 mg/kg, octanol effectively and reversibly blocks spindle waves and rhythmic bursting of thalamic neurons (300a).
Similar to the inferior olivary cells where simultaneous intra- and extracellular recordings demonstrated a somatic location for the LTS (304), a somatic or perisomatic origin of this spike was also indicated for thalamocortical neurons (102). Hyperpolarizing currents that left intact the antidromically elicited initial segment spike were shown to be sufficient to trigger the LTS, but when the antidromic invasion failed, the LTS was not induced.

In contrast to thalamocortical neurons, where the LTS has probably a somatic origin, the LTS of cat RE neurons may be located more distally (381), as is the case for the substantia nigra cells (298) or the developing mammalian motoneurons (293). This was concluded because it required somatic hyperpolarizations to 85–90 mV for its deinactivation (381), much larger than necessary in relay cells of the dorsal thalamus. Similar to the LTS of thalamic relay cells, the LTS of cat RE neurons is probably Ca\(^{2+}\) mediated because it is resistant to QX-314. In addition to the above, electrophysiological studies of the RE neurons in vitro have demonstrated that these cells have three different firing levels (see Fig. 9F). Of these, two are low threshold and correspond to two low-threshold Ca\(^{2+}\) conductances, one probably somatic and the second probably dendritic. In addition, these cells demonstrate Na\(^{+}\)-dependent dendritic spikes. These conductances, in addition to those present in thalamic relay nuclear cells, facilitate the intrinsic oscillatory property demonstrated to be present in these cells in vivo experiments. The hypothesized dendritic origin of cat RE bursts fits in with the ultrastructural features of the feline RE nucleus, which shows dendrodendritic synapses that were identified as inhibitory on morphological grounds (101, 598). Such vesicle-containing presynaptic dendritic profiles are not present in the rodent RE nucleus (396) where these neurons may be quite similar to the thalamocortical relay neurons, at least in the guinea pig (216). The interplay of dendrodendritic inhibitory interactions probably underlies the spindle rhythmicity in the intact and deafferented RE nucleus of cat (533, sect. IVB).

Although the LTS has been detected in virtually all thalamocortical and RE neurons, this response has been seen in only a small fraction of cortical cells. Only ~10% of neocortical neurons studied in vitro (80, 505) or in mature cultures (110) exhibit Ca\(^{2+}\)-dependent spikes after K\(^{+}\) currents had been depressed by tetraethylammonium (TEA). In the guinea pig prefrontal cortex, all pyramidal-shaped neurons demonstrate the ability to generate rebound Ca\(^{2+}\)-dependent bursts (176), whereas in the guinea pig sensorimotor cortex, the burst-producing cells are only found within a narrow range comprising layer IV and the superficial part of layer V (80). In the rat cortex only layer V pyramidal cells, as identified by HRP staining, have the ability to generate intrinsic bursts (276). The possibility that both pyramidal cells and spiny stellate cells are bursting neurons is still open (339). The mechanism of neocortical bursts may be similar to that generating the voltage-dependent Ca\(^{2+}\) response in the CA3 area of the hippocampus (226, 592), and the switch
between the tonic and bursting modes at different levels of membrane polarization may resemble that of thalamic neurons. The results obtained in behaving animals are in agreement with those from cortical slices, which show a lesser propensity to rebound bursting in long-axoned cortical neurons compared with that of thalamocortical cells.

In chronic experiments, the bursts of thalamocortical neurons typically appear during EEG-synchronized sleep. This is quite different from the sustained discharges during the EEG-desynchronized behavioral states of wakefulness and REM sleep (cf. Refs. 200, 520). That bursting occurs in thalamic neurons during quiet sleep, totally independent from the activity of pretalamic fibers, was first observed by Hubel (206) in the LG nucleus. The independence of bursting firing patterns of thalamic VL neurons from afferent fiber activation was also shown by the unchanged distribution of interspike intervals after destruction of their input sources, the deep cerebellar nuclei (521).7

These data do not imply that changes in afferent activity cannot influence the thalamic activity toward bursting, but they emphasize that the bursts of thalamic cells are essentially attributable to their intrinsic properties rather than to brisk inputs from incoming pathways. In fact, the structure and mechanism of bursts occurring in thalamocortical neurons during natural EEG-synchronized sleep (115, 167, 197, 333) are identical to those of thalamic neurons studied in vitro or in acutely prepared animals. Quantitative analyses (115, 333) show that the sleep burst of thalamic relay cells is a stereotyped event, generally consisting of 3–5 spikes at 250–400 Hz, and its defining feature is a progressive increase in the duration of successive interspike intervals, much the same as the aspect of the LTS elicited at the break of a hyperpolarizing pulse (102, 217) or after spontaneous, long-lasting hyperpolarizing potentials (461). Long periods of neuronal silence before bursts, as seen by studying burst parameters and periburst histograms in thalamic

---

7 The independence of VL cells' bursting on neuronal activities in their major input sources (deep cerebellar nuclei) requires special consideration. Interpositus and dentate neurons with identified projections to the VL thalamus change their tonic discharges during EEG desynchronization into burst discharges during epochs of EEG synchronization (521). However, the structure of nuclear cerebellar bursts and their relation to EEG rhythms are quite distinct from those of bursts displayed by thalamocortical neurons. Indeed, intraburst frequencies in interpositus and dentate cells are lower (80–200/s) and total burst durations are much longer (150–250 ms) than those in VL thalamocortical neurons. The burst structure consists of an initial acceleration followed by deceleration of spike frequency, and spike bursts may be related in time to focal slow waves (2–4 Hz) recorded in the target VL thalamic nucleus but not to spindle waves (521). The possibility is open that nuclear cerebellar bursts with a 2–4-Hz frequency reflect oscillations of ~4 Hz of inferior olive neurons (305). As to the prolonged acceleration-deceleration pattern of bursts recorded from interpositus and dentate neurons (521), such features resemble those of RE thalamic cells (115, 532) and neurons of substantia nigra pars compacta (298). Recent in vitro studies of cerebellar nuclear cells report an acceleration-deceleration pattern of spike trains elicited by depolarizing pulses from hyperpolarized levels at about −85 mV and conclude that the LTS of these neurons is of dendritic origin (379).
cells of chronically implanted preparations (115, 333), also indicate that sleep bursts are generated through deinactivation by membrane hyperpolarization, as revealed in intracellular studies. The fact that burst discharges are state specific (115, 167, 206, 333) and depend on cell hyperpolarization fits in with measurements of the resting membrane potential in chronic experiments, which show that hyperpolarization of LG relay cells is specific for the EEG-synchronized sleep (197). The duration of the hyperpolarization that generates this rebound phenomenon must be clearly aided by the presence of early K+ current ($I_A$) described in thalamic cells in vitro (217; Fig. 8). This conductance, initially described in gastropods (79), is quite prominent in thalamic neurons and can prevent the abrupt recovery of neurons from a hyperpolarized condition.

Similar to thalamocortical neurons, the RE neurons exhibit two distinct discharge modes: tonic firing during waking and burst firing during EEG-synchronized sleep (34, 115, 532). Throughout the entire RE nuclear complex, the sleep burst is essentially different from that of thalamocortical neurons. The differences especially concern the intrinsic burst structure and its duration. Whereas the burst of thalamocortical neurons is a unique event, consisting of a few intervals with progressively lengthening durations, the burst of RE cells consists of two distinct components: an initial part (the core of the burst) with frequency acceleration up to 250 Hz, followed by frequency deceleration and a long-lasting tonic barrage of spikes at $\sim 100$ Hz (115, 532). The duration of RE bursts may reach 1.5 s, with only 6% of the bursts being $<50$ ms, whereas virtually all bursts of thalamocortical neurons are $<30$ ms (115). These exceedingly long bursts of RE neurons extend over a whole spindle

![FIG. 8. Demonstration of $g_{K(A)}$. Delayed return of membrane potential after injection of hyperpolarizing pulse; cell was initially depolarized to $-45$ mV. A: duration of hyperpolarizing pulse is varied to demonstrate time dependence for both afterhyperpolarization (AHP) and low-threshold spike (LTS). B: hyperpolarizing pulse is kept constant to demonstrate features of $g_{K(A)}$. At break of current pulse membrane potential returns to base line with a concave trajectory. Hyperpolarization eventually results in a rebound burst (amplitude of fast spikes is truncated). [Modified from Jahnsen and Llinás (216).]
sequence; the unit and field events have been recorded simultaneously with a single microelectrode (532; see Fig. 14). This temporal relation indicates that GABAergic RE neurons are depolarized throughout a sequence of spindle waves while, simultaneously, thalamocortical neurons display long-lasting hyperpolarizations and brief rebounds.

These aspects of spontaneously occurring RE bursts, described in experiments on naturally sleeping animals (115, 532), are quite different from those obtained under barbiturate anesthesia when smooth acceleration and deceleration are lacking and the tonic tail of the burst is absent, thus reducing the RE cells' activity to phasic bursts with total durations not exceeding 25–35 ms (381, 581). The very long bursts that appear in RE neurons during natural sleep can be mimicked under barbiturate anesthesia by injecting a depolarizing trapezoidal current pulse on a background of hyperpolarization, a manipulation that presumably activates a slowly inactivating Na⁺ current (381). Probably the barbiturate anesthesia cuts off the prolonged tonic spike barrage that ends the spontaneous RE bursts in unanesthetized preparations, either by a depressing effect on the persistent Na⁺ current and/or by enhancing the K⁺ current responsible for postburst repolarization. The ionic basis of the complex RE bursts (consisting of an initial core plus a tonic tail), as they occur in unanesthetized sleeping animals, should now be elucidated in vitro since the ionic conductances that generate the bursts of RE neurons are likely more complex than those of thalamic relay cells. Because the rat RE nucleus lacks dendrodendritic inhibitory synapses (396) that are involved in the burst generation, in vitro studies should be performed in cat.

The bursting patterns of neocortical cells observed during sleep have been recorded from identified corticospinal (132, 529, 530), corticothalamic, and corticopontine neurons (516) and from presumed local interneurons (516, 529) in chronic monkeys and cats. Long-axonated cortical neurons change their tonic firing during waking into burst firing during EEG-synchronized sleep, but they have lower intraburst frequencies and lack the stereotyped burst features of thalamocortical cells. The latter display burst interval modes at 3–4 ms, reflecting their very high intraburst frequency, whereas the modal intervals of bursts recorded from fast- and slow-conducting pyramidal cells and other corticofugal cells are usually between 10 and 20 ms (516, 529). Putative cortical short-axonated cells, as inferred from electrophysiological criteria, have much shorter interval modes (2.5–4 ms) in both cats (516) and monkeys (529).

The emphasis on the intrinsic nature of bursts analyzed in acute or chronic conditions, namely that they are uncovered by membrane hyperpolarization, should not obscure the fact that synaptic inputs can activate the conductance mechanism responsible for burst generation (147, 196, 317, 521). The LTS amplitude is even linked to that of the underlying EPSP (196). Also the diminution or the sudden drop in discharges of afferent pathways at sleep onset create thalamic hyperpolarization by disfacilitation and may thus produce electrophysiological conditions that favor bursting. This has
been observed during wake-sleep transitions in RE neurons (532). Moreover, the LG cell activity can be modulated by afferent retinal activity independently of changes in behavioral state. For example, transient drops in the frequency of excitatory retinal inputs, during the pauses of the retinal dark discharge, reduce synaptic background activity in LG neurons and create the conditions necessary for the appearance of burst discharges resembling those that occur during EEG-synchronized sleep (151, 152).

3. High-threshold Ca\(^{2+}\) conductance: dendritic spikes

Presumed intradendritic recordings in thalamic cells in vitro (217) and in vivo (461) have also revealed a voltage-dependent, high-threshold Ca\(^{2+}\) conductance. This conductance triggers all-or-none depolarizing responses that are followed by the activation of a Ca\(^{2+}\)-dependent K\(^+\) conductance that is in many ways similar to those recorded in Purkinje cells (299, 301) and inferior olivary neurons (303) as well as other central neurons (292, 293). The importance of this \(g_{K(Ca)}\) was demonstrated in vitro by blocking \(g_{Ca}\) with cobalt or cadmium or by removing Ca\(^{2+}\) from the bathing solution. Under these circumstances, thalamic neurons respond with very high tonic firing frequencies (217). Moreover, the duration of the afterhyperpolarization is drastically reduced, allowing firing frequencies as high as 120 Hz.

When thalamic relay cells are challenged with corticothalamic volleys and the presumed dendritic membrane potential is more negative than \(\sim -55\) mV, a long-lasting hyperpolarization usually follows the antidromic and/or synaptic activation of the neuron. However, if the resting potential level is between \(-45\) mV and \(-52\) mV, a prominent depolarization crowned by spike discharges is observed; the depolarization presumably due to dendritic Ca\(^{2+}\) conductances is sometimes preceded by a small hyperpolarization (461). After intradendritic injections of ethylene glycol-bis(β-aminoethyl ether)-N,N,N',N'-tetraacetic acid (EGTA), a Ca\(^{2+}\) chelator that indirectly diminishes Ca\(^{2+}\)-dependent K\(^+\) conductances (cf. Refs. 10, 268, 303, 347, 391), all-or-none depolarizing plateaus interrupted by burst discharges are observed. In thalamic neurons, these bursts outlast the testing cortical volley or current pulse (461) and occur in \(<30\) s (contrasting with 8–10 min needed for the same effect after somatic impalement). By hyperpolarizing the cell, the occurrence of plateau responses is prevented and, instead, typical rhythmic hyperpolarizations are observed. These dendritic events are attenuated in somatic recordings by, among other factors, the shunting effects of perisomatic IPSPs that may be observed as small convexities in the hollow of the long-lasting hyperpolarization.

At least some of the fast prepotentials (FPPs) seen in thalamic neurons (102, 323) probably represent dendritic spiking because they can be blocked in an all-or-none manner by hyperpolarizing currents (102). Large intracellular injections of QX-314 in thalamic neurons lead to the appearance of numerous
FPPs, presumably because dendritic Ca\(^{2+}\) conductances dominate the cell's behavior when somatic Na\(^{+}\) channels are blocked (382). As in other neurons, it is quite possible that dendritic spiking assists the neuron in the transfer of glomerular EPSPs toward the spike trigger zone (cf. Ref. 527).

4. Voltage- and Ca\(^{2+}\)-dependent K\(^{+}\) conductance

At least four voltage-dependent K\(^{+}\) conductances have been described in thalamic and cortical neurons, in addition to the usual delayed (outward) rectifier that generates the dropping phase of the fast Na\(^{+}\) action potential. Among these voltage-dependent K\(^{+}\) conductances there are a low-threshold current activated by depolarization (termed M current), which was originally described in sympathetic neurons and later found in hippocampal pyramidal cells (1); two anomalous (inward) rectifiers similar to those seen in olfactory cortex (485) and hippocampal pyramidal cells (2); and a fast transient conductance (termed \(I_A\)) first described in invertebrate neurons, which is responsible for the slow return to baseline after hyperpolarization (217, 254).

The AHP potential, which follows the fast spike, is produced by a Ca\(^{2+}\)-dependent K\(^{+}\) conductance, as demonstrated in thalamic slices by its marked reduction in amplitude and duration after application of Ca\(^{2+}\) blockers (217; Fig. 9). Similar in vivo studies support this finding by the abolition of the AHP after intracellular injections of EGTA (102). The AHP has an amplitude of \(\sim 12\) mV and is reversed by passage of hyperpolarizing direct currents (102, 217). That the AHP is a rate-limiting factor is clearly revealed by comparing the AHP duration and the rates of spontaneous discharges in two types of thalamic neurons, thalamocortical and RE cells in the cat. Although the AHP in thalamocortical neurons lasts for \(\sim 70\) ms, in RE cells it terminates after 8-10 ms (381). Correlatively, in behaving animals the median rate of firing of RE neurons is \(\sim 20\) Hz during EEG-synchronized sleep, i.e., two or three times higher than in thalamocortical VL or CL neurons. On arousal RE neurons may reach firing rates between 50 and 100 Hz, rates that are not seen in thalamocortical neurons (532).

The long-lasting (100-150 ms) hyperpolarizations of thalamic neurons, that occur spontaneously during spindling or that are evoked by stimulation of afferent fibers, were regarded in earlier studies as a protracted IPSP resulting from the operation of feedforward (155, 431, 432) or feedback (14, 15) inhibitory circuits. Recently, two different hyperpolarizing components have been identified within the cortically evoked long-lasting hyperpolarization: an early Cl\(^{-}\)-dependent IPSP and a late Ca\(^{2+}\)-dependent K\(^{+}\) current (461). That different mechanisms contribute to the production of long periods of inhibition in thalamic neurons was indicated by the presence of distinct temporal components in the evoked corticothalamic response and by the persistence of the initial inhibitory phase with blockade of the late inhibition-rebound sequence during midbrain reticular stimulation (542).
FIG. 9. Oscillatory properties of thalamic neurons. A: oscillatory responses to injection of double-ramp currents at different frequencies. For each frequency, membrane potential during double-ramp current injection is shown on the left with a corresponding Lissajous figure taken from another cell to the right. At 1 and 3 Hz, low- and high-threshold spike activations can be easily separated, but at higher frequencies (10 Hz) these 2 modes of firing are difficult to separate. B and C: effect of blocking Ca²⁺ conductance on afterhyperpolarization (AHP). B: control firing. C: after equimolar substitution of Ca²⁺ with Co²⁺ and Mg²⁺, AHPs are reduced and firing frequency increases. D and E: 2 most prominent frequencies of oscillation are illustrated. D: recording of 9- to 10-Hz oscillations. Fast Na⁺ spike is followed by AHP generated by a
The early component could be dissociated from the late one since the former was reversed by hyperpolarizing currents and Cl\(^{-}\) injection, whereas the latter was unchanged by these procedures. This result, along with a faster recovery of the late component after the increase of extracellular K\(^{+}\) concentration ([K\(^{+}\)]\(_{o}\) that follows tetanic cortical stimulation (461), indicates that the two components of the long-lasting hyperpolarization are generated by two different mechanisms. The late component is abolished by intracellular injections of EGTA and is, therefore, interpreted as due to a Ca\(^{2+}\)-dependent K\(^{+}\) current. In rats under urethan and ketamine anesthesia, the evoked late hyperpolarizing component includes a disfacilitation mechanism, as suggested by its decrease after acute decortication and by increase in input resistance during the last part of the response (254). The late phase of the hyperpolarization is closely related to the preceding component, a high-threshold active Ca\(^{2+}\) response generated in the dendrites, and eventually leads to rebound excitation (a low-threshold somatic Ca\(^{2+}\) conductance) and cyclic oscillations within the frequency range of spindle waves (see Fig. 12). The mechanisms of cyclic oscillations in molluscan neurons are also viewed as controlled by a voltage-dependent Ca\(^{2+}\) current and a Ca\(^{2+}\)-dependent K\(^{+}\) current (173).

The biphasic nature of the evoked long-lasting hyperpolarization is also reported in studies on cortical neurons. In hippocampal neurons the initial IPSP is more sensitive to reversal by current than is the late part of the hyperpolarization (122). The suggestion was made that the late component resulted from a Ca\(^{2+}\)-activated increase in K\(^{+}\) conductance (10, 391). More recent studies of hippocampal CA1 pyramidal cells have shown that the late hyperpolarization was resistant to EGTA and may not be dependent on intracellular Ca\(^{2+}\) (273). However, EGTA injections are often difficult to interpret because of the low intracellular mobility of this compound. It was concluded that, in contrast to the GABA-mediated initial IPSP, the late hyperpolarizing potential was a bicuculline-resistant IPSP generated in pyramidal cell dendrites by feedforward interneurons. This component may act by increasing the K\(^{+}\) permeability of the membrane (390). Similar indications of a short-latency GABA-mediated IPSP and a late bicuculline-resistant hyperpolarization, presumably representing a K\(^{+}\) outward current, were provided by investigations of the general cortex of reptiles (261) and mammalian neocortex (29).

\[voltage-sensitive K^+ conductance (g_K) and a Ca^{2+}-dependent K^+ conductance (g_K(Ca)). Membrane potential is brought back to threshold by slow Na^+ conductance as g_K decreases after AHP. E: 6-Hz oscillation generated by ramp hyperpolarizing potentials. Cells follow a range frequency of 6 Hz, with smallest current injection, from a hyperpolarized level. F: oscillatory firing of a reticular thalamic neuron that demonstrates double low-threshold spiking properties followed by tonic firing during a ramp current injection. [Modified from Jahnson and Llinás (217) and from Llinás and Geijo-Barrientos (299a).]\]
In summary then, the neurons from the inferior olive and the thalamus belong to a class (among other neurons) having ionic conductances organized such as to exhibit intrinsic voltage oscillatory properties. In the inferior olive (Fig. 10) the cells tend to fire at a frequency centered around 10/s. This frequency is generated by the distribution and kinetics of the ionic channels encountered in their plasmalemmal membrane. As summarized in Fig. 10A,

\[ g_{\text{Na}} \text{ (inactivating)} \]
\[ g_{\text{K}} \text{ (inactivating)} \]
\[ g_{\text{Ca}} \text{ (noninactivating)} \]

\[ g_{\text{K(Ca)}} \]

\[ g_{\text{K(Ca)}} \text{ (inactivating)} \]

\[ g_{\text{Na}} \text{ dendritic spikes} \]

\[ g_{\text{K}} \text{ dendritic after-hyperpolarization} \]

\[ g_{\text{Ca}} \text{ rebound spikes} \]

**FIG. 10.** Summary of conductances \((g)\) and their role in generation of oscillations in inferior olive \((A)\) and thalamus \((B)\). HT, high-threshold spike; \(I\), current; IPSP, inhibitory postsynaptic potential; LT, low-threshold spike. For further explanation, see text. [Modified after Jahnsen and Llinás (217) and Llinás (259).]
the conductances are proposed to be distributed over the neuronal surface, as listed below. It must be remembered, however, that electrophysiological criteria are not sufficient per se to demonstrate location, and thus the statements below must be considered tentative. It is also important to emphasize that in those cases where the distribution of ionic conductances has been ascertained by other means, the results confirmed the electrophysiological analysis. Thus, in the Purkinje cell, dendritic Ca²⁺ entry has been directly visualized by optical techniques (457a). Also, the somatic location of the Na⁺ conductances has been confirmed by TTX labeling (556a).

The distribution of conductances in thalamic neurons on electrophysio-

FIG. 10.—Continued
logical criteria indicate that in the dendrites a noninactivating \( \text{Ca}^{2+} \) conductance \( (g_{\text{Ca}(D)}) \) generates dendritic spikes. The AHP that follows dendritic spikes is generated by a voltage-dependent and a \( \text{Ca}^{2+} \)-dependent conductance, \( g_{K} \) and \( g_{K(Ca)} \), respectively. At the somatic level the action potentials are produced by an inactivating \( \text{Na}^{+} \) conductance \( (g_{\text{Na}}) \) and by a voltage-dependent \( \text{K}^{+} \) conductance \( (g_{K}) \), both of which underlie fast spike generation in every way to action potentials generated by other neurons. In addition, there is a somatic \( \text{Ca}^{2+} \) conductance \( (g_{\text{Ca}(S)}) \) that is inactive at rest but is deinactivated when the membrane potential becomes negative to \(-60\) mV and that can generate a \( \text{Ca}^{2+} \)-dependent spike at somatic level on return of membrane potential to resting level, the so-called somatic rebound spike followed by an AHP due to \( g_{K(Ca)} \).

The set of conductances can impart to the inferior olivary neurons the ability to generate a cyclic firing by generating the set of events seen in Figure 10A, bottom. The somatic firing produced by \( g_{\text{Na}} \) and \( g_{K} \) is electrotonically conducted to the dendrites and activates at the dendritic level a \( \text{Ca}^{2+} \) spike. This \( \text{Ca}^{2+} \) spike, which may last for 10–15 ms, is followed by a rapid AHP generated most prominently by the \( \text{Ca}^{2+} \)-dependent \( \text{K}^{+} \) conductance of the dendrite. This powerful \( \text{Ca}^{2+} \)-dependent \( \text{K}^{+} \) conductance hyperpolarizes the cell to close to the equilibrium potential for \( \text{K}^{+} \) for a period lasting from 80 to 120 ms. After this AHP, as the membrane potential returns to resting level, the low-threshold \( \text{Ca}^{2+} \) conductance is activated, which in turn generates activation of the somatic spike and initiates the sequence once again. Basically the organization of ionic conductances allows and promotes a set of electrophysiological steps that tend to repeat in a stereotyped manner generating an oscillatory response.

In the thalamus, on the other hand, other ionic conductances are present that endow these neurons with a more complicated set of oscillatory properties. First, after depolarization of increasing amplitudes, thalamic cells are capable of firing repetitively in a manner quite similar to that seen in other central neurons. Pertinent to the question of oscillation, however, is the two preferred frequencies of firing: 6 and 10 Hz as shown in Figure 10B, bottom. As in the inferior olive, the ionic conductances in thalamic neurons seem to be segregated over the soma-dendritic plasmalemmal membrane. In the dendritic membrane the voltage-dependent \( \text{Ca}^{2+} \) conductance of the noninactivating variety seems to predominate. As opposed to the inferior olive neuron, however, this \( \text{Ca}^{2+} \) conductance is much smaller in thalamic cells. Because of this difference the dendritic \( \text{Ca}^{2+} \) spike does not dominate as effectively the firing of the thalamic neuron, allowing it a wider range of firing properties in contrast to the inferior olive neuron. The amplitude of the dendritic \( \text{Ca}^{2+} \) spike suggests that the number of \( \text{Ca}^{2+} \) channels in thalamic dendrites is smaller per area than that found in the inferior olive. Also, as in the inferior olive, they appear to be dendritic \( g_{K} \) and \( g_{K(Ca)} \). At the somatic level there are six different ionic conductances: the voltage-dependent inactivating \( g_{\text{Na}} \) and the noninactivating \( g_{\text{Na}} \), the voltage-dependent \( g_{K} \), \( g_{K(Ca)} \), and two conduc-
tances that are activated from a membrane potential negative to rest, the low-threshold Ca\(^{2+}\) conductances: \(g_{Ca(i)}\) and \(g_{K(A)}\). This set of conductances imparts to thalamic neurons the two different oscillatory modes, depending on the resting potential at which the cell is maintained. At a membrane potential positive to rest a repetitive firing having a frequency of 10 Hz can be easily activated by small depolarizations as in Figure 10B. This oscillation is basically produced by a slow depolarization of the cell produced by the \(g_{Na(P)}\), which can serve as a continuous depolarizing drive once it is activated. This slow depolarization generates the usual type of fast action potential followed by \(g_{K}\) and by a dendritic \(g_{K(Ca)}\), which generates an AHP lasting for \(\sim 70\) ms, after which the \(g_{Na(P)}\) takes over and begins to depolarize the cell once again until another spike is generated and the process repeats itself, thus generating a 10-Hz rhythm. If the cell is hyperpolarized beyond rest and particularly if sizeable IPSPs are generated, the return from this hyperpolarized level is delayed beyond the duration of the IPSP by the presence of the \(g_{K(A)}\), since the activation of this conductance occurs after a hyperpolarization at membrane potentials negative to the resting potential. As the membrane approaches resting level, the low-threshold Ca\(^{2+}\) spike is produced \(g_{Ca(i)}\). The 6-Hz frequency is produced by the summation of \(g_{K(A)}\) and \(g_{K(Ca)}\) that follows the low-threshold (or rebound) Ca\(^{2+}\) spike to the duration of an IPSP.

These two rhythms (10 and 6 Hz) can be generated by applying pulses of different frequencies at different resting potentials and suggest that indeed there are two main oscillatory modes to the thalamic neurons. It must be understood, on the other hand, that in the context of thalamic function, synaptic bombardment will clearly alter the rather simple sequence of conductances illustrated here. In principle, and as demonstrable in vivo, other frequencies of oscillation may be observed, depending on the sequence and nature of synaptic bombardment at any given instant. More important, however, is to emphasize once again that this rhythm can be generated by the thalamic projection neurons only in response to a stimulus. The single oscillatory behavior that may be observed in vitro in the absence of external drive is that relating to the activation of the \(g_{Na(P)}\), which triggers a 10/s oscillation (216).

B. Synaptic Networks

Whereas the intrinsic neuronal properties constitute the basic mechanism for the oscillations of single cells, the synchronous activation of a neuronal ensemble, as it occurs in intact animals, requires a mechanism for coordination of the individual oscillations. The role of synaptic networks in bringing together such oscillations to produce concerted rhythms is emphasized by the variety observed among the rhythmicity generated by different networks, despite great similarities in the intrinsic properties of their constituent neurons (see sect. IVB1). The determining role of thalamic networks
in the genesis of spindle oscillations is indicated by the absence of such rhythms in thalamocortical neurons disconnected from the RE nucleus. This section deals with one of the major types of synchronized activity in the brain, the spindle rhythmicity.

1. Intrathalamic circuits

Spindle oscillations are defined as close to sinusoidal waves with a frequency of 7–14 Hz and an amplitude that waxes and wanes. These oscillations are grouped characteristically in sequences that last from 1 to 2.5 s and that recur every 3 to 10 s (see Fig. 3). With the benefit of hindsight, this slow periodicity (0.1–0.3 Hz) of spindle sequences can be recognized even in earlier recordings in different types of preparations. Surprisingly, the slow periodicity of spindle sequences (Fig. 11) was not described until quite recently.

In thalamocortical neurons, the spindle waves at 7–14 Hz are subtended by long-lasting (70–150 ms) rhythmic hyperpolarizations (Fig. 12). Slower or faster spindle waves, within the frequency of 7–14 Hz, depend on the duration of the underlying hyperpolarization, which itself depends on the overall state.
FIG. 12. Cellular basis of electroencephalogram spindles from cat under barbiturate anesthesia. One spindle sequence is depicted as it appears in intracellular recordings of reticular thalamic (RE), thalamocortical (Th-Cx), and pyramidal tract (PT) neurons. Spindle oscillations of RE cells are superimposed on a slowly growing and decaying depolarization; spindles of Th-Cx neurons are characterized by rhythmic hyperpolarizations that, occasionally, deinactivate a low-threshold rebound spike; and burst hyperpolarizations of Th-Cx neurons trigger postsynaptic events in corticofugal neurons within the frequency of spindle waves. [Modified from Steriade and Deschênes (527a).]

of the brain. For example, in unanesthetized drowsy animals the spindle frequency is generally higher than in deeply anesthetized preparations. Spontaneous or cortically evoked spindle hyperpolarizations are attenuated or reversed in polarity by current and chloride injections (102, 461). These data indicate that the hyperpolarizations are generated by rhythmic sequences of IPSPs and suggest that they are imposed onto thalamocortical cells by inhibitory neuronal pools with pacemaking oscillatory properties (see RE cell in Fig. 12).

The spindle-related, long-lasting hyperpolarizations of thalamocortical neurons recorded during drowsiness and quiet sleep would predict a decreased probability of thalamic responses during these EEG-synchronized
states. This is indeed the case, as tested by the use of antidromic and synaptic volleys (167, 521, 542). The monosynaptic wave evoked in thalamic nuclei by prethalamic stimulation in behaving animals progressively decreases in amplitude from the onset of drowsiness (associated with the appearance of spindle sequences), without any change in the magnitude of the presynaptic deflection that monitors the incoming volley (Fig. 13). The thalamus is the first relay station where a significant reduction of sensory information occurs at sleep onset. Thus inhibition of synaptic transmission in the thalamus would deprive the cortex of input required to elaborate a response (537). This deafferentation is probably a prerequisite to falling asleep.

The spindle-related hyperpolarizations of thalamocortical neurons are interrupted occasionally by burst discharges (cf. Refs. 15, 527). The burst rebounds are LTSs deinactivated by the preceding membrane hyperpolarizations and crowned by fast repetitive spikes (see sect. IV.A2). The close relation between focal spindles and bursts must be stressed. In extracellular recordings, the negative components of focal thalamic spindles are consistently related to spike bursts of one, another, or all simultaneously recorded neurons (542, 551). A good correlation has also been found between thalamic and cortical spindles, provided that care is taken to record from the cortical focus where thalamic neurons project (15, 31, 168, 167).

FIG. 13. Blockade of synaptic transmission in thalamus at sleep onset in behaving cat with chronically implanted electrodes. Field potentials evoked in ventrolateral thalamic nucleus by stimulation of brachium conjunctivum. Evoked response consists of a presynaptic (tract, t) component and a monosynaptically relayed (r) wave. Note progressively diminished amplitude of r wave during drowsiness, up to its complete obliteration during electroencephalogram-synchronized sleep, despite lack of changes in afferent volley monitored by t component. (M. Steriade, unpublished data.)
The sequences of spindle waves recorded focally in cortically projecting thalamic nuclei are related to long-lasting neuronal hyperpolarizations in relay neurons. In contrast, the spindles recorded focally in the RE thalamic nuclear complex are related to long-lasting spike barrages that may extend over a whole spindle sequence representing oscillations in a pool of neighboring RE cells (532; Fig. 14). This relation indicates that, unlike the cyclic hyperpolarizing potentials of thalamocortical neurons, RE neurons are depolarized throughout spindle sequences (see also Figs. 11-12). The long-lasting spike bursts in RE cells and the related spindle sequences are specific for the behavioral state of EEG-synchronized sleep (Fig. 14). Such a dramatic rhythmicity is not observed in other thalamic nuclei. The hypothesis was then proposed that GABAergic RE neurons induce, by virtue of their widespread thalamic projections, the spindle rhythm (527).*

This hypothesis was tested, and supportive evidence has been obtained in thalamocortical neurons deprived of RE connections (528) and in deafferented RE neurons (533).

The disconnection of cortically projecting thalamic nuclei from the RE nuclear complex can be attained by surgical means or by chemical lesioning of RE perikarya (528). In the latter case, the neurons recorded in RE-deprived nuclei can be identified by antidromic invasion as thalamocortical elements. The effects of the RE lesion on the oscillatory corticothalamic response can also be investigated because the kainate-induced lesion does not damage the thalamocortical and corticothalamic passing fibers. The spindle rhythmicity is abolished in RE-disconnected thalamic nuclei and in the ipsilateral cortical EEG. This establishes a direct contrast between normal spindling in the contralateral intact hemisphere and its total absence in the lesioned side (528). The disappearance of spontaneous spindle sequences in RE-deprived thalamic nuclei is corroborated by the absence of the prolonged

---

* Is it possible to transfer the concept of a local intranuclear inhibitory circuits into the RE nucleus and still think in the conceptual terms of the multiple pacemakers model (15)? The answer is no, for two reasons. First, in the absence of a general pacemaker, spindle sequences would not beat synchronously. In fact, during a fully synchronized EEG, there is a perfect coincidence of spindle sequences recorded from widely separated cortical areas that points to an underlying simultaneity of spindles throughout the thalamus. The concept of multiple pacemakers (15) postulated that focal spindling in various thalamic territories leads to general thalamic synchronization through “the fast spread of rhythmic activity . . . by distributor neurons,” a cell type described in Golgi studies (480) and hypothesized to transmit informations from one nuclear group to other nuclei. Such “distributor” cells remain something of a mystery since there are very few internuclear thalamic connections (see sect. 1B9). It is known (239, 479, 545), on the other hand, that the RE nucleus has the required connections to distribute its rhythmic activity to virtually all thalamic nuclear groups. Those thalamic nuclei that do not receive RE inputs (545) do not display spindle oscillations (383, 408). Second, although both local-circuit cells and RE cells are GABAergic and inhibitory in nature, they do not seem to have similar oscillatory properties since spindle rhythms are absent in thalamic nuclei disconnected from the RE nucleus (528), whereas they are preserved in deafferented RE neurons (533). Local-circuit neurons play a role in discrimination processes (see sect. vB9).
FIG. 14. Relations between focal spindles and burst discharges of reticular thalamic (RE) neurons and their selective occurrence during electroencephalogram-synchronized sleep in behaving cats with chronically implanted electrodes. A: long spike burst of RE cell extends over whole duration of a focal spindle sequence recorded simultaneously with same microelectrode. Oscilloscopic record of unit activity (left) and ink-written records of neuronal discharges and focal waves (right). Oblique arrows indicate burst onset. B: computer-generated graph indicates state (sleep) specificity of rhythmic spike bursts and focal spindle oscillations simultaneously recorded with same microelectrode in RE nucleus. Sequential mean frequency (SMF) of RE cell discharges (bar graph) and averaged amplitudes of focal spindles (MSP) filtered from 7 to 14 Hz (line graph). C: RE cell firing and focal spindles during transition from waking to sleep. D: sequential RE cell firing showing oscillations of spike bursts during sleep (with the same frequency as the slow rhythm of spindle sequences) and tonically increased firing on arousal. B-D, abscissa indicates real time. [A–C, modified from Steriade et al. (532); D, M. Steriade, unpublished data.]

spindlelike oscillations triggered by cortical stimulation; instead, the response consists of a prominent depolarization, lasting for 40 ms, followed by a single hyperpolarization-rebound sequence (Fig. 15).
FIG. 15. Absence of evoked spindle oscillations in thalamocortical neurons after kainic acid lesion of reticular thalamic (RE) nucleus. Intracellular recordings of ventrolateral (VL) thalamic cells. t, Motor cortex stimulation. Aspects of kainic lesions discussed in Steriade et al. (528). A: typical oscillatory response of a VL neuron in an intact preparation. B: after RE lesion, cortically elicited response consists of an initial prolonged excitation followed by a single period of hyperpolarization leading to a low-threshold slow spike (arrow), but cyclic oscillations within frequency range of spindles are absent. [Modified from Steriade and Deschênes (527a).]

The abolition of spindle oscillations is associated with a peculiar feature of neuronal discharges in RE-deprived nuclei, an all-burst activity comprising high-frequency bicuculline-sensitive bursts (528) and having a structure identical to that of postinhibitory rebounds in intact thalamic neurons (see sect. IV.A.2). In contrast to the spindle-related rhythmic bursting in intact thalamocortical cells, the bursts of RE-deprived cells occur as single events with a low frequency (1–2 Hz) of striking regularity. These low-frequency rhythmic bursts probably result from a temporal integration of the short-lasting (12–20 ms) IPSPs in RE-deprived thalamic neurons, which through a summation of effects succeed in deinactivating the LTS (528).

The appearance of continuous low-frequency bursting in thalamocortical neurons deprived of their inputs from the RE nucleus is emphasized here because, during the 1970s, the idea of a recurrent inhibitory loop involving the RE nucleus led to an almost complete neglect, and even a denial, of intranuclear inhibitory processes. The facts are, however, that inhibitory actions do arise from GABAergic local-circuit thalamic neurons that are effective in generating burst discharges. These rebound bursts are more marked after RE disconnection than under normal conditions and can be blocked by bicuculline (528). This suggests that the activity of local interneurons is released by RE damage as though the RE cells exerted an inhibi-
tory action on thalamic local-circuit cells. In this respect, it has been established anatomically that RE axons have access, not only to projection neurons, but also to intrinsic GABAergic cells (see sect. II.4; cf. also Ref. 88).

The lack of 7- to 14-Hz spindle rhythmicity in thalamic nuclei disconnected from the RE nucleus is not ascribable to unspecific effects. Thus, in the absence of any experimental manipulations, the anterior thalamic neurons normally deprived of afferents from the RE nucleus (545) do not display spontaneous or cortically evoked 7- to 14-Hz spindle oscillations, nor do they exhibit spindle-related rhythmic bursts (383, 403). All this, despite the fact that they appear to be endowed with the same intrinsic membrane properties as other thalamoergic neurons (Fig. 16). A similar case is provided by lateral habenular neurons that possess ionic conductances (586) similar to those described in a variety of thalamic cells (see sect. IV.A). However, instead of spindle oscillations (7-14 Hz) during EEG-synchronized sleep, habenular neurons display rhythms within the frequency range of 5–7 Hz (in synchrony with hippocampal waves) that define the θ-rhythm during activated behavioral states (M. J. Gutnick, personal communication). All these data indicate that the place in different synaptic circuits and the dependence of various rhythm generators determine the frequency and behavioral connotation of oscillations.

In general terms we may consider that the absence of spindle sequences in RE-disconnected thalamic relay nuclei is because of the interruption of reciprocal connections between RE and cortically projecting nuclei. Alternatively, it may be because of the pacemaker properties of RE neurons as generators of spindle rhythmicity, with the implication that spindle rhythmicity would survive in the RE nucleus disconnected from its major input sources. The latter possibility is the most likely because oscillations could be still observed in experiments on cat RE neurons deafferented from their thalamic and cortical inputs (533). In contrast with the lack of spindles in thalamic nuclei disconnected from the RE nucleus and with the absence of spindles in the ipsilateral cortical EEG, both the spindles themselves (7–14 Hz) and their periodic (0.1–0.3 Hz) fluctuations are found to be present in the rostral pole of the deafferented RE nucleus (Fig. 17). The only difference is that spindles appear at the upper frequency range and sometimes even higher (15–16 Hz). Quantitative analyses in a group of deafferented RE neurons show that their burst parameters (533) are in all respects identical to those of RE neurons with intact connections (115; see sect. IV.A2). The long-lasting bursts demonstrate a close temporal relation with spindle sequences recorded simultaneously in the deafferented RE nucleus (Fig. 17C).

The presence of spindle oscillations in the deafferented RE nucleus by no means excludes that, in the normal condition of an intact brain, other events may trigger the RE oscillator. At sleep onset, midbrain reticular neurons with identified thalamic projections decrease their firing rates, leading to neuronal silence ~1 s before spindle sequences (517, 520). Rhythmic hyperpo-
FIG. 16. Absence of spindle oscillations in cat anterior thalamic nuclei, a group that is naturally devoid of inputs from reticular thalamic nucleus. Top: cerveau isolé preparation. Simultaneous recordings of focal waves in intralaminar central lateral (CL) and anteroventral (AV) thalamic nuclei. Abscissas indicate real time. Computer-generated graphs represent amplitudes of spindle (SP) waves, filtered at 7–14 Hz. *, First spindle sequence corresponding to asterisk-marked sequence in inset depicting an ink-written recording at higher speed. Bottom: effect of membrane potential on firing mode of an anteromedial thalamic cell. Tonic firing induced by a depolarizing pulse at rest (–60 mV) developed into a low-threshold spike and spike bursts under steady hyperpolarization when membrane potential reached –72 mV; recovery of tonic mode at right. Oblique arrow, low-threshold spike in isolation. [Modified from Faré et al. (408)].

larizations (through disfacilitation) followed by burst discharges in thalamic targets of midbrain reticular neurons may be decisive factors in setting into motion RE neurons by means of collaterals of thalamocortical axons. Focal spindle oscillations in various thalamic zones would develop, however, into generalized and synchronous spindling in thalamocortical systems only by spread of oscillations throughout the RE nuclear complex that, by virtue of its generalized thalamic projections, will induce rhythmic hyperpolarization-rebound sequences in almost all relay nuclei.
FIG. 17. Spindle oscillations in deafferented reticular thalamic (RE) nucleus in acutely prepared cats with rostral brain stem transections. Rostral pole of RE nucleus was isolated from its thalamic and cortical inputs by bilateral transections in rostral thalamus and corona radiata. Histological aspects of such preparations discussed in Steriade et al. (533). A: spindle sequences in deafferented RE nucleus contrast with absence of spindles in right and left electroencephalogram (EEG-r, EEG-l) from surface of postcruciate gyri. B: evoked spindle oscillations in deafferented RE nucleus by stimulating white matter overlying caudate nucleus (50 averaged traces). C: slow rhythm of spindle sequences and related burst oscillations of deafferented RE neurons. Left: a spike burst of RE cell. Right: computer-generated graph showing sequential mean frequency (SMF) of this neuron and normalized amplitudes of focal waves filtered for spindle waves (MSP) recorded simultaneously through same microelectrode. Abscissa indicates real time. [Modified from Steriade et al. (533).]

The disappearance of spindles in RE-deprived thalamic nuclei (528) and the preservation of spindle rhythmicity in the deafferented RE nucleus (533) demonstrate that the RE nucleus is the pacemaker of spindle rhythmicity. It has been assumed (101, 533) that dendritic hyperpolarization through den-
drodendritic synapses of RE neurons would deinactivate a low-threshold Ca\(^{2+}\) conductance with the consequence of triggering a Ca\(^{2+}\) spike, followed by GABA release and the hyperpolarization of postsynaptic dendrites, hyperpolarization in the latter dendrites would then deinactivate the Ca\(^{2+}\) conductance and thus hyperpolarize synaptically coupled dendrites. In this manner, oscillations could start at any point in the network and spread to adjacent elements. It is expected that in vitro studies of cat RE neurons will find such spontaneous oscillations and will shed light on the ionic conductances underlyng the complex bursts of RE neurons. Because the rodent RE nucleus lacks dendrodendritic synapses (396) involved in the generation of spindle-related bursts of feline RE cells, In vitro studies should be performed in cats.

2. Reciprocal thalamocortical activities

It is now agreed that the spindle sequences seen in the cortical EEG represent postsynaptic events in cortical elements, triggered by thalamocortical presynaptic volleys.

Kittens exhibit spindle waves in thalamic recordings made as early as 6–7 h after birth, a time when there is no trace of spindling at the cortical level (114) and well before the behavioral manifestations of quiet sleep. These are observed only in the second or third week (41, 327, 489). The thalamic spindles are transferred into cortical activity beginning on the third or fourth postnatal day. At the eighth or ninth day, clear-cut spindle sequences having the same characteristics as in adult animals appear simultaneously in both the thalamus and neocortex (114). The presence of thalamic spindle oscillations at birth is not surprising since all thalamic nuclei, including the RE, develop over a brief time span before birth in rodents (11, 12, 22, 332), cats (194), and primates (441). The relatively late appearance of cortical spindles (8th–9th postnatal day) is not attributable to a late maturation of thalamocortical fibers because the axons from LG and VB thalamic nuclei reach the target visual and somatosensory cortices at birth in rats (311, 591), 10 days before birth in cats (589), and 40 days before birth in monkeys (442). Because cortically projecting axons from intralaminar thalamic nuclei are established in cortical layer I quite late, during the first postnatal week (407), and considering that the intralaminar nuclei have a clear propensity to spindling (365), the rather late development of cortical spindles may depend on the delay in maturation of the intralaminar thalamocortical connectivity. Also, cortical spindles may lag thalamic spindles because of the delayed postnatal growth of apical dendrites and dendritic spines of cortical neurons (437, 477) and the fact that, whereas synaptic contacts are established as the thalamocortical axons enter the cortex, synaptogenesis continues for weeks (83, 588).

Pyramidal tract (PT) neurons recorded intracellularly in animals with rostral brain stem transections or under barbiturate anesthesia are quies-
cent during interspindle lulls. During spindles there is a long wave of depolarization with superimposed rhythmic depolarizing potentials and spike discharges, the rhythmic activity occurring at 7-10 Hz in relation with the surface-negative components of the spindles (87, 88, 222; see Fig. 12). The late surface-positive components of cortical spindles are associated with intracellularly recorded hyperpolarizing potentials of PT cells (416, 509, 510). The cortical spindle sequence actually begins with an early positive wave in layer 1 followed by a series of surface-negative waves. Both of these components are related to a single set of depolarizing events in deeply lying PT cells, suggesting that an initial excitation at the level of proximal dendrites is followed by depolarization of distal parts of apical dendrites (222).

Spontaneous cortical spindle sequences may be mimicked by incremental responses evoked by low-frequency stimulation of thalamic nuclei (365). The cellular basis for the augmentation phenomenon seems to be a secondary depolarizing process of increasing amplitude associated with an attenuation or complete blockade of hyperpolarizing potentials (see sect. II B I). Both of these factors (i.e., a prolongation of excitation and a weakening of inhibition) are also involved in the genesis of electrically or penicillin-induced epileptic discharges (32, 111; cf. Refs. 126, 430). Indeed, thalamocortical augmenting responses may lead to spike-and-wave paroxysmal discharges (514). Also, spontaneous spindles may develop into spike-and-wave discharges after systemic or topical application of penicillin (168, 345, 439). The close relation between the state of drowsiness or sleep, the EEG spindle oscillations, and spike-and-wave epilepsy has been observed in behaving monkeys (514) and in humans (249). This view is also supported by the blockade of this epileptic pattern with arousing stimulation of the brain stem reticular formation (423).

In a similar manner, corticothalamic activities can develop from augmenting incremental responses into self-sustained activity. When single-shock cortical stimulation is changed to rhythmic 6- to 12-Hz stimuli, the thalamic response develops an augmenting pattern characterized by an increased secondary depolarizing component and obliteration of the long-lasting hyperpolarization (527). In some bursting thalamic cells, these phenomena lead to a self-sustained activity that resembles spike-and-wave epilepsy (541). Evidence for cortical neurons having a central role in triggering thalamic neurons into self-sustained activity has also been provided by simultaneous recordings of cortical and thalamic neurons during spike-and-wave discharges induced by systemic administration of penicillin (80, 346, 410).

The significance of the reciprocal thalamocortical projections is that, as a consequence of burst discharges in thalamocortical neurons at sleep onset, corticothalamic neurons are effectively driven and reinforce thalamic rhythmicity. The notion of mutually reinforcing thalamocorticothalamic loops, involving just one interposed synapse in the cortex, has been proposed since the late 1930s (68, 118, 366) and has been strongly supported by recent morphological (585) and electrophysiological (144) data. Such structural arrange-
ments favor the reverberation of rhythmic, spindle-related bursting activity. The direct excitation of RE thalamic neurons by cortical stimulation (550) is a key factor in the genesis of cortically triggered thalamic oscillations.

The rhythmic activation of impulses in reciprocal thalamocortical pathways may elucidate the role of the oscillatory activity. Thus, at the onset of cortical stimulation, thalamic neuronal spike bursts are time locked with each corticothalamic volley within the frequency range of spindles. At later stages of stimulation, spontaneous bursts begin to appear and progressively develop during periods free of stimuli, with the same pattern and rhythmicity as responses elicited by rhythmic cortical stimuli (Fig. 18). As mentioned elsewhere (527), these are “resonance” phenomena, and they are reminiscent of the “rhythm assimilation” described in conditioning experiments (225, 288, 368). Indeed, the parallel evolution in ontogeny of thalamocortical and corticofugal networks (84,487) could provide increased synaptic efficacy and dendritic growth, all the more so as the oscillations are associated with

\[ \text{FIG. 18. Cortically evoked activities in a ventrolateral thalamic cell in the cat. Motor cortex stimulation with 5 shocks at 10/s, delivered every 1.3 s. A: pattern of evoked activity (faster speed than subsequent traces). B: responses to 2 shock trains. C-E: responses at later stages of stimulation. Note progressive appearance of spontaneous bursts resembling evoked ones. (M. Steriade, unpublished data.)} \]
high-frequency spike bursts in presynaptic axons. This possibility has been discussed for the role of tremor in the organization of central networks during ontogeny (294).

It is then possible that the state of sleep with spindle oscillations is not merely a period of rest and recuperation. Rather, the perseverative, obsessive mentation during EEG-synchronized sleep (a state that is most often characterized by thoughtlike reminiscence of the recent past) may suggest that the brain is occupied with sifting recently acquired information (200). If spindle oscillations help to organize thalamocortical circuits during early development, they may continue to facilitate the information storage in the adult life by consolidating the synaptic circuitry.

V. TONICALLY ACTIVATED (RELAY) MODE

The sustained discharges of thalamic and neocortical neurons typical of the EEG-desynchronized behavioral states replace the long periods of silence and high-frequency bursts that characterize the oscillatory mode. This section deals with the mechanisms underlying the transformation of oscillatory activity into tonic discharge patterns. The change from oscillations to tonic activity is characterized by an increased excitability and sharpened inhibition in thalamic and cortical neurons. Since brain stem neurons projecting to the diencephalon, basal forebrain, and cerebral cortex are involved in switching from the oscillatory to the tonic mode (see sect. vC), changes occurring during spontaneous shifts in natural states of vigilance are compared with the effects of brain stem core stimulation and the application of putative transmitters of the ascending brain stem systems.

A. Background Activity

The spontaneous discharges of long-axoned thalamic and neocortical neurons are characterized by a repetitive (tonic) single-spike activity during the EEG-desynchronized states of waking and REM sleep. This was shown for antidromically identified thalamocortical (167), corticothalamic, corticopontine (516), and corticospinal neurons (132, 529). The similarity between waking and REM sleep (two behavioral states that are commonly regarded as poles of the wake-sleep cycle) led to the conclusion that discharge patterns in REM sleep are not an extreme type of those in EEG-synchronized sleep but are much closer to those seen in wakefulness (516). This view is supported by the finding of tonic depolarization of thalamocortical LG neurons during REM sleep, as opposed to quiet sleep, and similar to the tonic depolarization seen during waking (197). The change from the oscillatory to the tonic mode is generally accompanied by an increase in discharge rates (cf. Refs. 200 and 535 for reviews).
1. Thalamic neurons

While thalamocortical and RE thalamic neurons exhibit reciprocal images during EEG-synchronized sleep (see sect. ivB1), the RE neurons exhibit tonic firing patterns and increased discharge rates on arousal from sleep, as do thalamocortical cells. The parallel behavior of RE neurons and their thalamic targets was recently found during natural waking in chronic experiments (532) and is corroborated by initially excitatory responses of both thalamocortical and RE neurons to rostral brain stem reticular stimulation. The RE neurons double their discharge rates from EEG-synchronized sleep (15–20/s) to arousal (median: 35/s, with some elements reaching frequencies of up to 100/s) and progressively slow down from arousal to drowsiness, preceding the appearance of cell bursting and oscillations during sleep (532).

The mechanism of tonic activation in thalamocortical systems on arousal is under the control of ascending brain stem reticular systems and consists of the direct excitation of thalamocortical neurons, combined with the blockade of rhythmic oscillations in the thalamic pacemaker, the RE nucleus.

Intracellular recordings from LG thalamic relay cells under deep barbiturate anesthesia failed to reveal consistent powerful direct postsynaptic excitation from brain stem reticular stimulation. In that experimental condition, however, there is reticular-induced facilitation of synaptic transmission through the LG, which has been ascribed to disinhibition (495, 496). Nonetheless, in the unanesthetized encéphale isolé preparation with trigeminal deafferentation, brief train pulses to the rostral brain stem reticular formation in the PB area elicit a short-latency (8-10 ms), slowly-rising, and long-lasting (300-400 ms) depolarization of thalamocortical LG neurons that may trigger spike trains. This early depolarization is followed by a second excitation with a very long latency (1–1.5 s) and duration (2–4 s). Both these components (100, 527a; Fig. 19) are generated by a direct nonvisual input to LG relay cells as they were obtained in animals with bilateral enucleation and ablation of the visual cortex, and therefore suggest direct excitatory effects of reticular formation stimulation on LG cells. Very small (2 mg/kg) doses of barbiturates are sufficient, however, to completely abolish the initial excitation. Under steady hyperpolarizing currents, the initial depolarization gives rise to low-threshold spike bursts.

Direct excitation of thalamocortical neurons (other than the LG) by brain stem reticular stimulation was also elicited in the LP nucleus (531) and the CL-PC intralaminar nuclei (534) in locally anesthetized encéphale isolé preparations and in chronically implanted animals. The reticular-induced monosynaptic excitation of these neurons was established by their ability to follow high-frequency (100–300 Hz) volleys. Indeed, direct projections to all major sensory (MG, LG, VB), associational (PUL-LP), motor (VA-VL, VM),
and intralaminar (CL-PC, CM-PF) cortically projecting thalamic nuclei arise from cholinergic PB and LDT reticular nuclei at the midbrain-pontine junction and from noncholinergic cells in more rostral midbrain reticular fields (see Fig. 2). The latencies of the initial excitation in thalamic neurons are consistent with the relatively slow conduction velocities of the axons of upper brain stem reticular neurons with rostral projections (5, 159, 457).

The probable transmitters involved in the reticular-induced excitation of thalamocortical neurons are acetylcholine (ACh) and some peptides, which are colocalized with ACh in rostral brain stem reticular neurons. The excitatory effect of ACh on VB (18) and LG (381, 420) relay-type neurons is of slow onset and prolonged duration. Similar to the depressant effect of barbiturates on the reticular-induced depolarization of thalamocortical LG neurons, subnarcotic doses of barbiturates abolish the excitatory action of ACh on LG relay cells (135). Recent in vitro studies indicate that the ACh effects on cat’s LG neurons consist of a rapid nicotinic excitation associated with an increase in membrane conductance and a sequence of muscarinic-mediated slow depolarization and hyperpolarization associated, respectively, with a decrease in intracellular recordings in unanesthetized cat with bulbspinal transection and deafferentation of trigeminothalamic pain pathways; retina and visual cortex were also removed. A: 2 shocks to PB nucleus (A) elicit a short-latency excitation followed by a prolonged (1.5–2.5 s) excitation starting at a long (1.5–2 s) latency. B: expanded record showing in more detail 2 components of PB-evoked excitation in LG cell. (B. Hu, M. Deschénes, and M. Steriade, unpublished data.)
and an increase in apparent input conductance (342a). Whereas the short-latency brief excitation of LG relay cells induced by brain stem PB stimulation (see Fig. 19) is probably due to nicotinic actions (381, 342a), the late and prolonged depolarizing response to PB reticular stimulation depicted in Fig. 19 may result from muscarinic effects, noradrenergic actions, or a release of substance P and/or other peptides that are found in the ascending reticular systems originating in PB and LDT cholinergic nuclei (575, 576). These possibilities should be further investigated.

In addition to the direct excitation of thalamocortical neurons, brain stem reticular stimulation is known to reduce their cyclic hyperpolarizing-rebound responses (203, 495, 542; Fig. 20B). The latter effect is due to the reticular-induced blockade of spindle generators and the RE neurons (Fig. 20A).

During the 197Os, a set of extracellular studies in acute experiments indicated that the response of RE thalamic neurons to midbrain reticular stimulation is a prolonged period of suppressed spontaneous discharges (112, 483, 601, 602). This finding led to the common conclusion that facilitation of thalamocortical neurons on arousal results from inhibition of inhibitory RE cells. Recent experiments on chronically implanted unanesthetized preparations with chronic lesions of locus ceruleus indicate that the response of RE neurons to stimulation of the PB reticular nucleus, or more rostra1 fields in the midbrain reticular formation, starts with a short-latency excitation, followed by a period of suppressed spontaneous discharges (532). Both components are state dependent (Fig. 21A). During waking, the peak latency of the initial excitation is ~6 ms, whereas during EEG-synchronized sleep it may reach 15-20 ms, suggesting that the underlying EPSPs are slower rising and longer lasting during sleep. The following period of inhibition is quite short (~30 ms) during waking, whereas it occurs late and lasts longer (100–200 ms) during sleep.

This biphasic, excitatory-inhibitory response of RE neurons to PB or rostral mesencephalic reticular stimulation was analyzed intracellularly (203; Fig. 21B,C). The initial depolarization occurs at latencies <10 ms. This depolarization cannot be ascribed to the activation of collaterals of thalamocortical neurons because it persists in deeply barbiturated animals (in which the short-latency depolarization of thalamocortical cells is abolished) and survives large lesions of dorsolateral thalamic nuclei. The second component of the response is a prolonged (200-500 ms) hyperpolarization, accompanied by a marked conductance increase. The long-lasting hyperpolarization does not appear in scopolamine-treated animals, in which the initial excitation may extend for 50–200 ms (203).

The initial excitation and the following hyperpolarization seem to represent two direct responses of RE neurons. Although the mechanism and transmitter involved in the early excitation have not yet been elucidated, the later hyperpolarization seems ACh dependent. The absence of the long-lasting hyperpolarization after systemic administration of scopolamine (203) is in
agreement with earlier findings of Dingledine and Kelly (112) that the ACh-evoked inhibition of RE neurons is mediated through muscarinic receptors, and they also agree with the recent in vitro studies by McCormick and Prince (341) showing that ACh causes an increase in K⁺ membrane conductance that is blocked by scopolamine. The blocking of RE-generated spindle waves by cholinergic basal forebrain neurons projecting to the RE nucleus (60a, 546) is probably due to the same muscarinic inhibitory effect.
The origin of activity fluctuations in RE and thalamocortical neurons during sleep and wakefulness (reciprocal and parallel profiles, respectively), as described in chronic experiments (532), remains an intriguing issue. Two possibilities are open. First, since RE neurons probably use both GABA and
somatostatin (179, 395), these transmitters might be released differently in different states of vigilance. If the increased depolarizing actions and the reduction of the IPSP due to somatostatin seen in cortical neurons (94) were also true for the thalamus, one could hypothesize that GABA is predominantly released during EEG-synchronized sleep and somatostatin during waking. In support of this view, evidence for a positive relation between the levels of somatostatin and arousal has been reported (82, 468). Second, and more probable, since RE neurons have access to both thalamocortical and GABAergic local-circuit neurons (359), the inhibition exerted by RE neurons on intrinsic interneurons during arousal may be more powerful than that on thalamocortical cells, resulting in enhanced activity in the latter. It is known from studies on other central structures that GABAergic elements may be more sensitive to GABA than other neurons (174, 175).

There is experimental support for the notion that RE neurons exert effective inhibition on the other class of thalamic GABAergic cells. For example, thalamocortical neurons disconnected from the RE nucleus show only high-frequency bursts (528). This pattern was blocked by bicuculline and seems to reflect continuous inhibitory actions from local-circuit cells released from RE inhibitory influences (528). During sleep, on the other hand, the amounts of GABA released by RE axons increase because RE neurons reach high intraburst frequencies. Under these conditions the efficacy of inhibition on thalamocortical neurons would increase, whereas the GABA receptors of the more sensitive local-circuit cells would be saturated (cf. Ref. 128), with the possible consequence of prevalent inhibition on thalamocortical neurons, leading to rhythmic hyperpolarizations and spindling.

2. Cortical neurons

Long-axoned neurons increase their discharge rates in a tonic manner during waking and REM sleep. This is due largely to the enhanced activity in specific thalamocortical systems, as a result of activating brain stem reticular influences, and is accompanied by EEG desynchronization. Enhanced activity of somatosensory cortical neurons after midbrain reticular stimulation can be elicited, however, even after destruction of the VB thalamic complex (540). Such influences, that bypass the specific thalamic nuclei, can also be seen in the visual cortex (500) and are probably mediated by thalamocortical intralaminar neurons (92, 534). Another pathway that should be explored in the future is that arising from the upper brain stem reticular neurons to the cholinergic basal forebrain neurons that have widespread cortical projections (see sect. II C1).

The depolarizing influence of midbrain reticular stimulation on PT neurons was first reported during the 1960s (9) and has been intensively investigated since the late 1970s by Oshima and colleagues (136–138, 211, 212, 401), using intracellular recordings in brain stem-transected preparations.
Two cell types were distinguished after rostral brain stem reticular formation: the D type, which is depolarized and distributed widely through layers II–V of motor precruciate cortex, and the H type, which responds with an initial hyperpolarization and occurs in layers III–VI. All slow-conducting PT neurons (axonal conduction velocities <21 m/s) belong to the D type, whereas fast-conducting PT neurons are mostly of the H type (211). The hyperpolarization of fast-conducting PT cells during the initial phase of reticular-induced EEG desynchronization is associated with a transient increase in the effective membrane resistance. This initial response is followed by depolarization in a later phase, accompanied by a decrease in the membrane resistance (212, 401).

These data are in keeping with earlier results obtained in behaving primates (529, 530) in which a dual activity pattern was seen in fast-conducting PT cells during natural arousal. Initially there was a reduction in spontaneous firing (due to their hyperpolarization) but an increased antidromic and synaptic responsiveness (by the increased input resistance). This eventually led to frank excitation of the same neurons in later stages of wakefulness. In view of the dichotomy between the phasic and tonic control exerted by fast- and slow-conducting PT neurons (cf. Refs. 55, 133), the arrest of firing in fast-conducting PT cells and simultaneous increase in firing of slow-conducting PT cells were regarded (529) as related to the initial phase of the orienting reaction, which consists of an arrest of phasic movements and an increased muscular tone.

The transmitters involved in cortical activation are glutamate and/or aspartate released by thalamocortical axons (402) and ACh, which is released by the few cortically projecting brain stem reticular neurons (575) but mostly by basal forebrain neurons (349). The latter receive direct inputs from the cholinergic brain stem reticular neurons (594). Glutamate elicits a rapid depolarization in cortical neurons that is associated with a marked drop in membrane resistance (270). In contrast, the muscarinic excitation is slow in onset and outlasts the ACh application by tens of seconds (264, 266, 267, 272). The mechanism of ACh excitation was elucidated by Krnjević et al. (269). Acetylcholine induces a depolarization of deep cortical neurons that is associated with a rise in membrane resistance. The reversal potential is close to the expected value for the $K^+$ equilibrium potential, indicating that the mechanism of depolarization is a reduction in $K^+$ conductance. These effects are particularly susceptible to depression by barbiturates (cf. Ref. 263). Acetylcholine effects, similar to those observed in neocortical neurons, were found in CA1 and CA3 hippocampal neurons (75, 113). In vitro experiments showed that the slowly rising and prolonged excitation produced in pyramidal cells by the muscarinic action of ACh was preceded by a short-latency hyperpolarization and a decreased input resistance, due apparently to the rapid muscarinic excitation of GABAergic local-circuit cells (340, 342). It has been proposed that cyclic GMP (cGMP) mediates some ACh effects on cortical neurons (555, 556).
The neocortical effects of monoamines have not been investigated in detail. Extracellular recordings usually report depressant effects of NE on spontaneous activity in neocortical neurons (418, 447), with occasional excitations of deeply lying elements (23). With intracellular recordings of hippocampal pyramidal cells in vitro, Madison and Nicoll (320, 321) have shown that the most common response to NE is a hyperpolarization that is accompanied by a decrease in membrane input resistance. On occasion, NE produces a depolarization mediated by a α-receptor (320), an action that is mediated through cyclic AMP (cAMP). These data are discussed further in section vB in relation to the increased signal-to-noise ratio with arousal.

B. Excitatory-Inhibitory Response Sequence

The relay mode creates conditions of increased response readiness and fine inhibitory sculpturing in thalamic and cortical neurons. Quick responses, input selection, and output tuning are natural requirements for an adaptive state. All these properties have been confirmed during wakefulness (as opposed to synchronized sleep) by testing thalamocortical and corticofugal neurons with antidromic and synaptic volleys. An enhanced excitability of forebrain neurons has also been seen during REM (or EEG-desynchronized) sleep, which exceeded even the level found in the waking state. Few data are available that indicate changes in inhibitory processes during REM sleep. Future studies may be designed to distinguish the degree of inhibition during these two activated states.

This section deals with changes in the excitatory-inhibitory response sequence of thalamic and cortical neurons during shifts from one state of vigilance to another and during "arousal" mimicked by brain stem reticular stimulation. These changes are described for an archetypal response (520) whose components are representative for a large proportion of thalamocortical and corticofugal cells, although the nature of some components may differ somewhat from one to another class of neurons. Briefly, a stimulus to central (prethalamic, precortical, or corticothalamic) pathways elicits a primary excitation and an early inhibition of short duration. This is followed by a late and long-lasting period of inhibition that declines slowly and leads to a rebound excitation. The early inhibition is a Cl⁻-dependent IPSP generated by GABAergic local-circuit cells, whereas the late inhibitory period is a K⁺-mediated IPSP or a Ca²⁺-mediated K⁺ current (88a, 195a, 461). The distinction between these two inhibitory components is supported by their differential alterations during arousal (527a, 542; Fig. 2C).

1. Enhanced excitability

Antidromically activated extracellular responses reflect intracellular events quite faithfully (562). The probability of full antidromic invasion of
thalamocortical (167, 518, 542), corticothalamic, corticopontine, and corticospinal neurons (529, 538) increases by 50–100% during arousal and REM sleep compared with EEG-synchronized sleep.

Enhancement of the primary synaptic excitation during EEG-desynchronized behavioral states occurs in thalamic nuclei despite no change in prethalamic input, as shown by monitoring the presynaptic component of field responses (see Fig. 13). Similar enhancement of primary excitation is seen in neocortical areas during reticular-induced EEG desynchronization (52, 117). Cortical facilitation can be obtained by the use of testing responses to stimulation of the underlying white matter (513). This indicates that the increased cortical excitability on arousal is not merely because of an enhanced synaptic transmission through the thalamus. The thalamic and cortical facilitation probably involve cholinergic mechanisms. Indeed, systemic administration of atropine or scopolamine depresses the primary postsynaptic response (329) and abolishes the potentiating effect of brain stem reticular stimulation (497). Fast (50–150 Hz) waves evoked in the visual cortex as afterdischarges to photic stimuli (cf. Refs. 86, 512, 536) are particularly sensitive to changes in the state of vigilance. They disappear under barbiturate anesthesia (207) but are enhanced by brain stem reticular stimulation (522) or by administration of cholinergic agents (51).

The probability of short-latency unit discharges being evoked in thalamocortical neurons by afferent stimulation is also enhanced during wakefulness and REM sleep, as opposed to EEG-synchronized sleep (167, 473). Burst responses (5–12 ms latency) are occasionally triggered by VL or VM thalamic neurons in response to brachium conjunctivum stimulation during EEG-synchronized epochs. Such bursts develop into constant single-spike responses (1–2 ms latency) during spontaneous EEG desynchronization, during stimulation of midbrain reticular formation, or during administration of cholinergic agents (147, 317, 318, 328, 521). These findings again indicate that thalamocortical neurons are relatively depolarized during EEG-desynchronized states (see sect. iv.A2).

The increased responsiveness of cortical neurons on arousal may appear in the absence of activity change in the thalamocortical axons just beneath the cortex (182). This and other results in acute preparations (500, 540) indicate that arousing brain stem influences may bypass specific thalamic nuclei (see sect. v.A2). As opposed to the unequivocal enhancement of both synaptically evoked and spontaneous discharges in thalamocortical neurons on arousal, cortical neurons may respond in several ways. These may be related to the differences in afferent input (552). Quite often, cortical cells respond strongly to optimally oriented stimuli, while their spontaneous discharges are simultaneously reduced (289). As first shown by Evarts in the early 1960s (130, 131), even when both background and driven discharges of visual cortex neurons are reduced during waking, the ratio of evoked to spontaneous activity becomes greater. The higher signal-to-noise ratio is probably realized by ascending brain stem systems, the modulators of which
FIG. 22. Effects of midbrain reticular stimulation and natural arousal on inhibitory processes of thalamocortical and corticospinal neurons in cat and monkey. A: encephale isolé cat. 2: dotgram showing periods of suppressed firing (a, b, and c) and postinhibitory rebound excitations elicited during electroencephalogram (EEG)-synchronized epoch by single-shock stimulation of cortical area 5 (+) in a thalamocortical neuron of lateral posterior nucleus. & reduction of
induce hyperpolarizations associated with increased input resistance at the level of their cortical targets (cf. Refs. 149, 212, 573, 582, 583). Both ACh (75, 186) and NE (319, 320) decrease the Ca\textsuperscript{2+}-activated K\textsuperscript{+} afterhyperpolarization that follows the action potentials, and hence both can enhance depolarization in response to various inputs. The association between membrane hyperpolarization and the blockade of the afterhyperpolarizing potential may be a decisive factor in preventing neuronal activation to weak stimuli while enhancing responses to stimuli that can overcome the inhibition (320).

The above results derive from either acute experiments or chronically implanted animals that display a limited behavioral repertoire. During the past 15 years, cortical neuronal activity has been extracellularly recorded during set-dependent tasks in primates, in which sophisticated paradigms were used to study switching mechanisms involved in the flexible control of input-output information processing (cf. Ref. 134). Emphasis on the motor (377) or the sensory (453) properties of cortical neurons related, for instance, to visual fixation is different from the alternative between purely motor or sensory cells since the neurons in high cortical stages are beyond the direct effect of unimodal sensory inputs, and their firing is related to movement in a probabilistic manner (cf. Ref. 314).

The effects of diffuse arousal can be dissociated from those of selective attention and the initiation of movements (60, 170, 315; cf. Ref. 378, 595). In the experiments conducted by Mountcastle and collaborators (376), the enhanced responsiveness of parietal cells was specifically related to attentiveness to the target light, rather than to changes in general arousal (376, 378). In the somatosensory cortex, the enhancing influence of attentive behavior on neuronal responses was more commonly observed in superficial layers and layer VI than in midlayers (208). Such effects may be mediated, in part, by

cortically elicited cyclic periods of suppressed firing and replacement of burst firing mode by tonic firing mode after midbrain reticular stimulation (a 110-ms shock-train at 300 Hz preceded cortical stimulation, not depicted). [Modified from Steriade et al. (542).] B: intracellular recording of a thalamocortical cell in ventrolateral (VL) nucleus of cat. 1: cyclic hyperpolarizations within frequency range of spindle waves elicited by a shock to motor cortical area (\textsuperscript{A}). 2: a preceding shock train to midbrain reticular formation facilitates antidromic invasion and transforms cyclic hyperpolarizations into a single hyperpolarization. C: intracellular recording of shortening of evoked inhibitory postsynaptic potentials in lateral geniculate relay neurons by preceding brain stem peribrachial (PB) stimulation in urethan-anesthetized, reserpine-treated cat. Components (a and b) of hyperpolarizing response evoked by optic chiasma (OC) stimulation; OC stimulus was adjusted for enhancing separation between 2 components. When preceded by a conditioning PB pulse train, only a persisted. [Modified from Steriade and Deschênes (526a).] D: inhibition of synaptic discharges evoked in pyramidal tract neuron by stimulation of VL thalamic nucleus in behaving monkey. Left: field-positive (inhibitory) wave evoked by first VL stimulus and facilitation (during waking) of evoked discharges by second stimulus at 75-ms interval. Right: percentage responsiveness of discharges evoked by first stimulus (time 0) and by second stimulus at 3 time intervals during waking (W) and EEG-synchronized sleep (S). [Modified from Steriade and Deschênes (526).]
intralaminar and VM thalamic nuclei. They receive excitatory projections from the rostral brain stem reticular core and project to layers I and VI over widespread cortical areas where they exert depolarizing actions (see sect. II). In addition, this enhanced responsiveness may be mediated, in part, by the direct NEergic projections of the locus ceruleus that potentiate the neuronal activity in some thalamic nuclei (247, 455, 456) and also act directly on cortical neurons (see sect. VA2).

In humans, event-related potentials (ERPs) recorded from the scalp have been used to explore cortical processes related to selective attention (cf. Refs. 105, 162, 422). Desmedt and colleagues (106–108) have explored the parietal cortex by using somatosensory stimulations. Although the early components of ERPs, up to and including N20 (surface-negative wave with a peak latency of 20 ms), remained unaffected by attentional manipulations, later components were enhanced in selective attention tasks. Components P40 (surface-positive wave with peak latency of 40 ms) and N60 are regarded as the electrical signs of "priming" the infrequent target signal that the subject is trying to identify among nontarget stimuli. Component P100 might index the identification of input signals and component P300 may reflect a nonspecific postdecision closure (105, 107).

2. Inhibitory sculpturing

Two main types of inhibitory control are present in thalamic and cortical neurons and seem related to two distinct behavioral states. The first is mediated by RE neurons and underlies the long-lasting cyclic hyperpolarizations within the frequency range of spindles that appear in thalamocortical systems during drowsiness and sleep. This type of widespread inhibition was discussed in section IV. The second inhibitory mechanism is mediated by thalamic and cortical short-axoned neurons and is probably implicated in the center-surround antagonism and other "feature detection" properties of thalamic and cortical neurons during wakefulness. The latter inhibitory processes are the matter of this section.

Although RE neurons should also be incorporated in any tentative scheme of inhibitory thalamic actions during waking because they discharge tonically at high rates on arousal (582), there is no direct evidence for a differential role played by RE and local-circuit thalamic neurons in the processes related to inhibitory sculpturing in thalamocortical cells. It is known that RE neurons are interposed in the recurrent inhibitory circuit of relay cells, whereas local-circuit cells are driven by feedforward collateral pathways (see sect. II). The pattern of GAD immunoreactivity during early development suggests that the PG sector of the RE nuclear complex during fetal life supplies the first source of GABA-mediated inhibition, whereas intrinsic LG interneurons provide the major portion of inhibition during the postnatal life (490). The interactions between the two GABAergic thalamic
cell classes (the local-circuit and RE neurons), their role in the specificity of stimulus response, and their changes as an effect of brain stem reticular stimulation have been especially investigated in the LG nucleus (cf. Refs. 7, 8, 157, 158, 283, 284). It was proposed that local-circuit cells veto the excitatory input within the synaptic glomeruli without hyperpolarizing the remainder of the cell (258, 259).

In what follows, we infer the state-dependent properties of inhibitory neurons from different forms of inhibition investigated in identified long-axoned (thalamocortical and corticofugal) neurons.

In thalamocortical and corticofugal neurons, the transition from the EEG-synchronized oscillatory mode to the EEG-desynchronized relay mode leads to the blockade of cyclic inhibition but does not eliminate the first inhibitory phase evoked by testing stimuli (527a, 530, 542; Fig. 22A C). The recovery time of tested antidromic or synaptic responses is twice as long during sleep than during waking (Fig. 22D). However, the inhibition is very effective and, in most instances, even more pronounced at short delays (10–30 ms) after the conditioning inhibitory volley during arousal, as compared with EEG-synchronized epochs (464, 524, 526). The reinforcement of the early inhibition on arousal is also demonstrated by enhanced amplitude of the early IPSP in visual cortex neurons after midbrain reticular stimulation (500) and by clear improvement of directional selectivity of cortical striate neurons on arousal from sleep (289). All these studies support the conclusion that, during waking, deep but short inhibition provides a mechanism sub-serving an accurate discrimination of incoming messages, the precise control of performances, and the proper following of rapidly recurring activity (515, 526).

With respect to states of consciousness and their relations to inhibition, two opposing hypotheses have been formulated. The first is that of global disinhibition as the correlate of awakening. This was suggested by some studies reporting that brain stem reticular stimulation induces the broadening of orientation tuning and abolition of direction selectivity in visual cortex neurons (cf. Ref. 497). The other view considers that the state of waking is associated with a rather differential effect: the blockade of the late, protracted phase of hyperpolarization due to a K⁺ current and involved in the oscillatory mode of sleep and the preservation or even enhancement of the Cl⁻-dependent IPSP that assists in discriminatory functions at increased levels of vigilance (520; see Fig. 22C). This conclusion that arousal cannot be equated with a global disinhibitory influence is supported by results based on the effects of ACh, the probable transmitter of ascending reticular systems. Indeed, whereas ACh actions on perigeniculate neurons are indeed inhibitory (and are, therefore, involved in the blockade of oscillations triggered by RE thalamic neurons; see Fig. 20), ACh not only facilitates the excitatory responses to an optimal stimulus but also enhances stimulus-specific inhibitory influences on LG relay cells (135, 492, 493). More to the point, the temporally and spatially antagonistic inhibitory effects within the receptive field...
are potentiated by ACh (493), much the same as arousal does (289). The improvement of receptive field function suggests a facilitatory action of ACh on GABAergic local-circuit cells. The role of GABA in shaping various types of inhibition is documented in major thalamic nuclei (cf. Refs. 195, 491). In the cerebral cortex too, the ACh-induced enhanced responsiveness is not associated with a reduction in receptive field specificity but, on the contrary, with an increased receptive field specificity as well as orientation and direction selectivity in \(~30\%\) of visual cortex neurons (492).

The studies on the excitability of short-axoned cortical cells during shifts in natural states of vigilance of behaving primates reported changes in the evoked activity of precentral cortical interneurons during arousal (529). Specifically, during a short-lasting period of arousal, a diminished number of spikes and increased latency of the burst evoked by recurrent collaterals of pyramidal neurons or by thalamic stimulation was observed. In contrast, when quiet wakefulness replaced the orienting response, full recovery of interneuronal responsiveness was observed (529). These data suggest that a diminution of discriminatory functions may occur for a short period of time on arousal. However, the recovery of synaptic excitability of interneurons during the subsequent state of steady wakefulness is congruent with subsequent data showing an increase in cortical discriminatory functions during waking (289) or iontophoretic application of ACh (492). In vitro, ACh induces a rapid muscarinic excitation of cortical inhibitory interneurons (342).

The effects of NE iontophoresis or stimulation of locus ceruleus on thalamic and neocortical neurons consist of an increased signal-to-noise ratio. This response is attained by either depressing the spontaneous firing to a much greater extent than the evoked discharges or by enhancing both excitatory and inhibitory inputs against a depressed background firing (149, 582, 583). These actions are compatible with the idea that NE acts as an enabling device, suppressing weak inputs and enhancing strong inputs, thus increasing the efficiency of feature extraction from sensory information (cf. Ref. 149).

3. Control by brain stem reticular neurons

The evidence that a tonic influence on brain electrical activity arises somewhere between the lower medulla and the midbrain (47, 48), and the candidate structures for tonic ascending activation (240, 374) are discussed in section 1B3. The postulated role of neurons in classic fields of brain stem reticular formation was supported by experiments with the biphasic actions of glutamate analogues, such as kainic or ibotenic acids, that excite and then rapidly destroy cell perikarya, leaving intact passing fibers. Microinjections of kainic acid into the midbrain reticular core induce EEG desynchronization and strong behavioral arousal during a period of 10–24 h, corresponding to the early kainate excitation (256). During a period of 2–4 days after the injection in the midbrain reticular core, a 40–60\% decrease in the duration of the waking state is observed, and the EEG is no longer tonically de-
July 1988

THALAMIC FUNCTION

721

synchronized by arousing stimuli, corresponding to the phase of kainate-induced neuronal destruction (519).

We analyze in this section the firing properties of various brain stem neuronal aggregates that are apparently involved in tonic and phasic events of waking and REM sleep. The investigations have addressed the cellular substrates of three major phenomena: EEG desynchronization, muscular atonia, and ponto-geniculo-occipital (PGO) waves associated with rapid eye movements. The tonic event common to both waking and REM sleep is EEG desynchronization. Another tonic event that characterizes REM sleep is muscular atonia. The phasic events typical for REM sleep are PGO waves and related ocular saccades. We shall finish by describing present models that attempt to account for oscillations of the sleep-wake cycle.

Brain stem reticular neurons with antidromically identified thalamic projections have been implicated in the genesis of EEG desynchronization during wakefulness (543) and REM sleep (549). The firing rates of rostral midbrain reticular neurons double in EEG-desynchronized states compared with quiet sleep, and first- and second-order statistical analyses place them toward the tonic extreme of discharge patterns (543). Similar data on tonically increased firing rates during EEG-desynchronized states have been reported for neurons recorded from the LDT (471) and PB (469) nuclei. Moreover, the firing dynamics during transitional periods from EEG-synchronized to desynchronized epochs show precursor signs of increased firing frequencies in rostral brain stem reticular neurons. This occurs 10–20 s before any EEG change and well in advance of motoric behavioral signs of wakefulness (543, 548). On the other hand, a population of bulbar reticular neurons with projections to intralaminar CL-PC and to VM thalamic nuclei was found to increase their firing rates ~30–60 s before the EEG desynchronization during transition from non-REM to REM sleep (549). Statistical analyses indicated that this increase in discharge frequency is not attributable to the PGO waves that appear during this transitional period but is rather related to the desynchronization of EEG rhythms.

The other tonic event, muscular atonia, is the distinctive sign of REM sleep and results from powerful postsynaptic inhibition of spinal cord motor neurons that prevents all movements but phasic twitches of distal extremities. After the disclosure of the basic mechanism by Pompeiano and colleagues during the 1960s (cf. Refs. 424, 535), a series of intracellular studies have shown that a tonic hyperpolarization, up to 10 mV in amplitude, associated with a striking decrease in input resistance occurs when the animal enters into REM sleep (164, 361; cf. Ref. 71). This hyperpolarization is similar to that observed after electrical activation of the bulbar reticular formation (302). Thus the origin of this phenomenon is probably a pool of medullary reticulospinal neurons that are silent during wakefulness but selectively active during postural atonia of REM sleep (244). Tonic depolarization of bulbar reticulospinal neurons is coincident with the onset of REM sleep (70).

Phasic events in thalamocortical systems are superimposed on the enduring activation processes during EEG-desynchronized behavioral states.
Phasic phenomena in the geniculostriate system follow by 40–50 ms the eye movements during waking, even when the animal is in dark (cf. Ref. 57). Stimuli applied to the rostral brain stem reticular formation produce changes of neuronal activity in the LG thalamic nucleus and visual cortex that are similar to those occurring during spontaneous eye movements in waking. The phasically increased activity of LG neurons has been explored with ion-selective electrodes and intracellular recordings by Singer and Lux (499; cf. also Ref. 496). The PGO waves appear just before and during REM sleep. They are predominantly monophasic negative field potentials, last for \( \sim 0.3 \) s, and occur in groups of up to six waves. They are associated with discharges of LG and visual cortex cells even in darkness or after enucleation (43, 56). The main generators of this phasic activity are located in the peribrachial nucleus at the pontine-midbrain junction, where PGO-burst cells discharge spike bursts, preceding by 10–25 ms the LG wave (337, 470, 471). In addition to these short-lead PGO-burst cells, longer-lead (50–300 ms) PGO-burst neurons have been intracellularly recorded in the medial pontine reticular formation (335). The long-lead pontine neurons are driven from the bulbar reticular formation (335) where 20% of phasic neurons with ascending projections were found to discharge in close time relation to isolated or grouped PGO waves (549). These data point to a distributed brain stem system involved in the genesis of PGO waves. Although the mechanisms by which PGO bursts are generated are not fully elucidated, it has become evident that the Ca\(^{2+}\)-dependent LTS may play an important role. Recent observations indicate that some neurons located in the PB and LDT nuclei have distinctive electrophysiological properties characterized by the presence of a transient K\(^+\) conductance and a low-threshold Ca\(^{2+}\) conductance (277a). Furthermore, a subclass of these neurons has been shown to project to the dorsolateral thalamus and to be cholinergic by combining intracellular dye injections with retrograde transport of fluorescent label and enzyme histochemistry. Thus PGO waves in the thalamus may be generated by Ca\(^{2+}\)-dependent LTS bursting of thalamically projecting cholinergic neurons of the PB and LDT nuclei. There is a three-way correlation between eye movement direction and PGO-burst firing associated with LG waves. For example, rightward eye movements in REM sleep drive right PB neurons that lead to predominantly right LG waves (389). In LG relay neurons, PGO waves are associated with a depolarization (accompanied by an increase in membrane conductance) that can be interrupted by a unitary IPSP, likely resulting from the activation of intra-LG inhibitory interneurons (203a).

The information related to the direction of eye movements during REM sleep is transferred to the thalamus and cerebral cortex. This “efferent copy” signal to central neurons is regarded as the source of intracerebral activation during REM sleep (cf. Ref. 200), “the stuff that dreams are made of.” The widespread distribution of these phasic events outside the geniculostriate system (63, 223) is attributable to the diffuse thalamic projections of cholinergic and noncholinergic neurons of the PB nucleus (404, 544, 594; see Fig. 2).
The models for the periodic oscillations of sleep-wake states (334, 427) are based on reciprocal profiles of discharges displayed by two brain stem cell populations. These models start from data showing that, in contrast with most brain stem reticular neurons that dramatically increase their firing rates during REM sleep, monoaminergic locus ceruleus and dorsal raphe neurons become virtually silent during REM sleep (25, 73, 199, 313, 343; cf. Refs. 149, 198, 200, 569 for reviews). The models, based on extracellularly recorded discharges in chronic experiments (199, 334) or in precollicular decerebrate preparations (426, 427), postulate that REM sleep occurs as a consequence of reciprocal interactions between presumed cholinergic-excitatory pontine reticular neurons and presumed monoaminergic-inhibitory locus ceruleus and raphe neurons. The pontine reticular neurons are regarded as the executive elements of REM sleep events, and their spectacular discharges during REM sleep are ascribed to disinhibition following cessation of firing in locus ceruleus and dorsal raphe cells.

Intracellular recordings in chronic preparations indicate that, indeed, the membrane potential of pontine reticular neurons depolarizes 7-10 mV on passage from waking and EEG-synchronized sleep to REM sleep (213). The fact that pontine reticular neurons discharge vigorously during body movements in waking (cf. Refs. 344, 569) may be due to their recently discovered Ca^{2+}-dependent LTS (181; see sect. IV.A.2) that underlies brisk firing in response to proprioceptive drives induced by movements during the relative membrane potential hyperpolarization seen in wakefulness.

The reciprocal interaction model was discussed recently in detail (see commentaries in Ref. 198). The main problem with this model is that the antinomy between excitatory actions of ACh and inhibitory actions of NE and 5-HT can no longer be maintained. In some central neurons ACh induces hyperpolarization accompanied by a marked conductance increase (see sect. V.A.1). On the other hand, ACh and NE have similar actions on given central neurons by decreasing the Ca^{2+}-activated AHP, and thus the association between the NE-induced hyperpolarization and the AHP blockade is probably instrumental in favoring responses to stimuli that can overcome inhibition (see sect. V.B.1). The study of cellular mechanisms and pharmacological modulation of the brain stem oscillator that generates the periodic recurrence of sleep states should consider that periodic REM sleep episodes occur in a prepontine animal (239) and should, therefore, investigate the unanswered questions in this simplified preparation.

VI. CONCLUSIONS

A. Synchronized Oscillations

Three major factors account for the appearance of spindle oscillations in thalamocortical systems during EEG-synchronized resting behavioral
states. These are the intrinsic properties of thalamic neurons, the synaptic networks that include reticular thalamic neurons, and the dampening activity in rostral brain stem reticular neurons with thalamic projections. 1) Among the intrinsic cell properties the following are involved in the patterning of thalamic cell membrane oscillations: the noninactivating Na\(^+\) conductance, the low-threshold somatic Ca\(^{2+}\) spike, the high-threshold dendritic Ca\(^{2+}\) conductance, and a series of voltage- and Ca\(^{2+}\)-dependent K\(^+\) currents. 2) The cellular bases of synchronized spindle rhythmicity are the depolarizing oscillations in GABAergic reticular thalamic neurons that generate cyclic hyperpolarization-rebound sequences in thalamocortical neurons. The disappearance of spindling in thalamic nuclei deprived of connections from the reticular nucleus and the preservation of spindle oscillations in the reticular nucleus deafferented from its input sources indicate that this thalamic nucleus is the pacemaker of spindle activity. 3) The blockade of synchronized oscillations on arousal can be mimicked by stimulating cholinergic pathways originating in rostral brain stem reticular neurons. In addition to direct excitation of both relay and reticular thalamic neurons, midbrain reticular stimulation leads to suppression of depolarizing oscillations of reticular thalamic cells by inducing a long-lasting hyperpolarization associated with conductance increase to K\(^+\).

Further investigations in this area should address 1) the ionic conductances underlying the pacemaking oscillatory properties of reticular thalamic neurons; 2) the cellular bases and synchronizing mechanisms of fast rhythms that appear in discrete cortical foci during behavioral immobility and at high levels of vigilance; and 3) the synaptic networks involved in the genesis of other undeciphered rhythms, such as the slow waves and \(\alpha\)-waves.

B. Tonic or Relay Mode of Thalamic Function

The main characteristics of the tonic (relay) mode during EEG-desynchronized behavioral states are the sustained discharges of long-axoned thalamic and cortical neurons, their enhanced excitability, and their effective periods of inhibition. The latter demonstrate much shorter duration in waking than during the oscillatory mode. These features assist thalamocortical and corticofugal neurons in sharpening the speed and specificity of sensorimotor integration during the waking state. The stage of REM sleep is marked by patterns of spontaneous discharges that are similar to those in wakefulness, and forebrain neurons have very high levels of excitability.

Further investigations should address: 1) the complete identification of thalamic and cortical inhibitory local-circuit neurons and their role in the discriminatory functions of long-axoned cells; 2) the differential role played by reticular thalamic and local-circuit thalamic neurons in inhibitory sculpturing of thalamocortical neurons and the functional consequences of connections between these two classes of thalamic GABAergic cells; 3) the dis-
tinction in cellular terms between the two EEG-desynchronized states, waking and REM sleep, with emphasis on the efficiency of inhibitory processes of thalamic and cortical neurons during REM sleep; and 4) the neuronal bases of brain stem, thalamic, and cortical phasic (POG) events that represent internal activation of the brain during dreaming sleep.

Research was supported by Medical Research Council Grant MT-3689 to M. Steriade and National Institute of Neurological and Communicative Disorders and Strokes Program Grant NS-13704 to R. Llinás.

REFERENCES


3. ADRIAN, E. D. Afferent discharges to the cerebral cortex from peripheral sense organs. J. Physiol. Lond. 100: 159-191, 1941.


204. Hu, B., M. Steriade, AND M. Deschenes. The effect
of mesencephalic reticular stimulation on thalamic reti-
200A.HU, B., M. STERIADE, AND M. DESCHENES. The cel-
209. IDE, L. S. The fine structure of the perigeniculate nu-
295. HUBEL, D. H. Single unit activity in striate cortex of
204. HUBBARD, J. E., R. LLINÁS, AND D. M. J. QUASTEL.
215. JACOBSON, S. J., AND J. Q. TROJANOWSKI. Cortico-
206. HUBEL, D. H. Single unit activity in lateral geniculate
298. HYVARINEN, J., A. PORANEN, AND Y. JOKINEN. In-
L4ond 150: 91-104, 1940.
227. JONES, B. E., AND R. Y. MOORE. Ascending projections
226. JOHNSTON, D., J. J. HARUTT, AND W. A. WILSON.
Voltage clamp discloses slow inward current in hippo-
225. JOHNSTON, D., J. J. HARUTT, AND W. A. WILSON.
Effects of locus coeruleus lesions upon cerebral mono-
amine content, sleep-wakefulness states and the re-
224. JIBIKI, I., M. AVOLI, P. GLOOR, D. GIARETTA, AND
230. JONES, B. E., AND T. Z. YANG. The efferent projections
235. JONES, E. G., H. BURTON, C. B. SAPER, AND L. W.
233. JONES, E. G. Area1 differences in the
talamic relay nuclei of
239. JOUVET, M. Recherches sur les structures nerveuses et
les mécanismes responsables des différentes phases du
238. JONES, E. G., AND T. P. S. POWELL. Electron micros-
copy of synaptic glomeruli in the thalamic relay nuclei of
237. JONES, E. G., AND T. P. S. POWELL. An anatomical
study of converging sensory pathways within the cere-
236. JONES, E. G., AND R. Y. LEAVITT. Retrograde axonal
transport and the demonstration of non-specific projec-
235. JONES, E. G., H. BURTON, C. B. SAPER, AND L. W.
SWANSON. Midbrain, diencephalic and cortical rela-
tionships of the basal nucleus of Meynert and associated
234. JONES, E. G., AND H. BURTON. Areal differences in the
laminar distribution of thalamic afferents in cortical
fields of the insular, parietal and temporal regions of
233. JONES, E. G., H. BURTON, C. B. SAPER, AND L. W.
SWANSON. Midbrain, diencephalic and cortical rela-
tionships of the basal nucleus of Meynert and associated
231. JONES, E. G. Possible determinants of the degree of
retrograde neuronal labeling with horseradish peroxi-
230. JONES, E. G. Some aspects of the organization of the
228. JONES, E. G. AND H. BURTON. Areal differences in the
laminar distribution of thalamic afferents in cortical
fields of the insular, parietal and temporal regions of
227. JONES, E. G., H. BURTON, C. B. SAPER, AND L. W.
SWANSON. Midbrain, diencephalic and cortical rela-
tionships of the basal nucleus of Meynert and associated
226. JOHNSTON, D., J. J. HARUTT, AND W. A. WILSON.
Ascending projections of the locus coeruleus in the rat. II. Autoradiographic
225. JOHNSTON, D. E., AND T. Z. YANG. The efferent projections
from the reticular formation and the locus coeruleus
studied by anterograde and retrograde axonal transport
224. JIBIKI, I., M. AVOLI, P. GLOOR, D. GIARETTA, AND
230. JONES, B. E., AND T. Z. YANG. The efferent projections
229. JONES, B. E., AND R. Y. MOORE. Ascending projections
228. JONES, E. G., AND H. BURTON. Areal differences in the
laminar distribution of thalamic afferents in cortical
fields of the insular, parietal and temporal regions of
227. JONES, E. G., H. BURTON, C. B. SAPER, AND L. W.
SWANSON. Midbrain, diencephalic and cortical rela-
tionships of the basal nucleus of Meynert and associated
226. JOHNSTON, D. E., AND T. Z. YANG. The efferent projections
from the reticular formation and the locus coeruleus
studied by anterograde and retrograde axonal transport
225. JOHNSTON, D. E., AND T. Z. YANG. The efferent projections
from the reticular formation and the locus coeruleus
studied by anterograde and retrograde axonal transport


373. MULLER, C., A. MADARIAGA, AND M. DESCHEMES. Morphology and electrophysiological properties of reti-


416. PHILLIPS, C. G. Actions of antidromic pyramidal vol-
loos on single Beta cells in the cat. Q. J. Exp. Physiol.
417. PHILLIPS, J. W., AND J. R. KERRPATRICK. The actions of 
metion, lutatinisitng releasing hormones, choleyste-
kinin, somatostatin, vasoactive intestinal peptide, and 
other peptides on rat cerebral cortical neurons. Can. J.
418. PHILLIS, J. W., AND G. K. KOSTOPOULOS. Activation of 
a noradrenergic pathway from the brain stem to rat 
419. PHILLIS, J. W., AND D. H. YORK. The inhibitory action of monoamines on lateral geniculate 
420. POLLEN, D. A. AND K. H. REID. Experimental 
study of cholinceptive cell in the lateral geniculate nu-
421. PICKEL, V. M., M. SEGAL, AND F. P. BLOOM. A radio-
autographic study of the efferent pathways of the nu-
422. PICKTON, T. W., AND D. N. YORK. A study of 
neocortical projections in the lateral geniculate nu-
423. PICKEEL, V. M., M. SEGAL, AND F. P. BLOOM. A radio-
autographic study of the efferent pathways of the nu-
424. ICION, T. W., AND A. K. TEBECIS. 
425. PRINCE, D. A. Mechanisms of epileptogenesis in brain-
426. PRINCE, D. A. AND T. J. CUNNINGHAM. Organi-
tation of cerebello-cortical projection activity. In: The 
Thalamus, edited by D. P. Purpura and M. D. Yahr. New 
427. PURPURA, D. P., AND J. R. SHOFER. Intracellular re-
cording from thalamic neurons during reticulocortical 
428. PURPURA, D. P., AND R. J. SHOFER. F. M. HOUSEPIAN, 
AND C R. NOARK. Comparative ontogenesis of struc-
ture-function relations in cerebral and cerebellar cortex. 
In: Progress in Resarch Research. Growth and Maturation of the 
Brain, edited by D. P. Purpura and J. P. Schach.
429. PURPURA, D. P., R. J. SHOFER, AND F. S. MUS-
GRAVE. Cortical intracellular potentials during aug-
menting and recruiting responses. II. Patterns of synap-
tic activities in pyramidal and nonpyramidal tract 
430. PURPURA, D. P., AND K. MAE-
431. RACEKOWSKIP. Prenatal development of the visual system in 
432. RALSTON, H. J. Evidence for presynaptic dendrites and 
a proposal for their mechanisms of action. Nature Lond. 
433. R AMON Y CAJAL, S. Histologic du Systime Nerveux de 
L'Homme et des Vertébrés (traduit par L. Asoulo). Paris: 
Maloine, 1909, 1011.
434. RAUSSELL, E., AND J. S. VENETOU. Thalamocortical 
nuclear projections to superficial and deep layers in parit-
ial, frontal and prefrontal regions of the 
435. RAY, W. J., AND H. W. COLE. EEG alpha activity re-
flects attentional demands and beta activity reflects 
electromental and cognitive processes. Science Wash, DC 228: 
436. READER, T. A., A. PERRON, L. DESCARRIES, 
AND H. H. JASPER. Modulatory role for biogenic amines in 
the cerebral cortex. Microcortophoretic studies. Brain 
437. RIBAK, C. E. Aspinous and sparsely-spinous stelate 
nucleus in the visual cortex of rats contain glumatic acid 
438. RINVIK, K. Thalamic commissural connection in the rat. 
439. RIVNER, M., AND J. SUTIN. Locus coerulesmodulation of the 
thermum inhibitino in nuclei ventralis lat-
eralis and ventralis anterior. Exp. Neurol. 78: 651-673, 
1981.
440. ROBERTSON, R. T., AND T. J. CUNNINGHAM. Organi-


464. STERIADE, M. Mechanisms underlying cortical activation: neuronal organization and properties of the midbrain reticular core and intralaminar thalamic nuclei.
740  MIRCEA STERIADE AND RODOLFO R. LLINÁS  


585. WHITE, E. L., and S. M. HERSCH. A quantitative study of thalamocortical and other synapses involving the api


587. WILSON, P. M. A photographic perspective on the or
gins, form, course and relations of the acetylcholinester-
ase-containing fibres of the dorsal tegmental pathway in

588. WISE, S. P., J. W. FLESHMAN, JR., and E. G. JONES. Maturation of pyramidal cell form in relation to developing afferent and efferent connections of rat somatic sen-

589. WISE, S. P., F. H. C. HENDRY, and E. G. JONES. Pre-
natal development of sensorimotor cortical projections

590. WISE, S. P., and E. G. JONES. Cells of origin and termi-
nal distribution of descending projections of the rat so-


592. WONG, R. K. S., and D. A. PRINCE. Participation of calcium spikes during intrinsic burst firing in hippoco-


594. WOOLF, N. J., and L. L. BUTCHER. Cholinergic systems in the rat brain. Ill. Projections from the pontomesence-

595. WURTZ, R. H., B. J. RICHMOND, and W. T. NEW-
some. Modulation of cortical visual processing by at-
tention, perception and movement. In: Dynamic Aspects
of Neocortical Function, edited by C. M. Edelman, W. E.
Gall, and W. M. Cowan. New York: Wiley-Interscience,


598. YEN, C. T., M. CONLEY, S. H. C. HENDRY, and E. G.
JONES. The morphology of physiologically identified GABAergic neurons in the somatic sensory part of the
thalamic reticular nucleus in the cat. J. Neurosci. 3:

599. YEN, C. T., M. CONLEY, and E. G. JONES. Morphologi-
cal and functional types of neurons in cat ventral poste-

600. YEN, C. T., and E. G. JONES. Intracellular staining of
physiologically identified neurons and axons in the so-
matosensory thalamus of the cat. Brain Res. 280:

601. YINGLING, C. D., and J. E. SKINNER. Regulation of unit activity in nucleus reticularis thalami by the mesen-
cephalic reticular formation and the frontal granular
625-642, 1975.

602. YINGLING, C. D., and J. E. SKINNER. Gating of tha-
lamic input to cerebral cortex by nucleus reticularis thal-
ami. In: Progress in Clinical Neurophysiology. Attention,
Voluntary Contraction and Event-Related Cerebral Poten-
p. 70-96.

603. YOSHIDA, M., SASA, M., and S. TAKORI. Serotonin-
mediated inhibition from dorsal raphe nucleus of
neurons in dorsal lateral geniculate and thalamic reticu-

604. YOUNG, A. B., M. B. BROMBERG, and J. B. PENNEY,
Jr. Decreased glutamate uptake in subcortical areas
deafferented by sensorimotor cortical ablation in the cat.