REPLY TO OREŠKOVIC ET AL.

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TO THE EDITOR: The criticism by Orešković, Radoš, and Klarica mainly concerns our description of cerebrospinal fluid (CSF) dynamics (15). The focus of our review was in particular the specific ion and water transport mechanisms forming the basis of secretion by the choroid plexus (CP) cells (4). Therefore, we only briefly described the current paradigms relating to CSF dynamics, intracranial pressure, and hydrocephalus. Furthermore, we admittedly have no direct experimental experience of our own on these significant matters. In the review, we also point out where major discrepancies still exist. We chose not to include references to or a description of the work by Orešković, Radoš, and Klarica in our review for the following reasons: 1) the bulk of the research lies mainly in the area of CSF mechanics/dynamics and is therefore slightly out of scope for our review (e.g., Refs. 9–12) and 2) the conclusions of the work are not yet broadly appreciated by other researchers in the discipline (17). Furthermore, authors of Physiological Reviews are asked for opinionated reviews rather than complete overviews of the existing literature. We note that half the citations in the letter by Orešković, Radoš, and Klarica were published after our manuscript was submitted. This literature could therefore not have been taken into account when writing our manuscript. Nevertheless, we would like to comment on the points raised in the criticism.

In our opinion, most of the controversy relates to the reported values of intracranial pressures (ICPs) and the specific spaces pressures were recorded by various researchers. We agree that a pressure gradient is needed to drive a flow of CSF from the site of origin in the ventricle lumen to the site of absorption, whether it is in arachnoid granulations or elsewhere. However, we believe that the pressure gradient needed to drive a relative slow CSF flow would be of modest size in a low-resistance system and probably technically difficult to assess. Orešković, Radoš, and Klarica have provided evidence for a negative pressure in the upright position in cats compared with a zero-pressure gradient in the natural horizontal position (9). This has recently also been reported for humans in the upright position (1, 2).

Since it is not our field of active research, we chose not to go into speculations on the existence of a proper pressure gradient were applied to the drainage of CSF in hydrocephalus caused by obstruction of the CSF flow through the cerebro-ventricular system or is the obstruction a consequence of the developing hydrocephalus by compression of the brain? We acknowledge the fact that there can be many reasons for the development of stenosis in non-communicating hydrocephalus and that treatment today is no longer aimed at removing the CP but rather to alleviate the CSF pressure by drainage. The lack of response to removal of CP could indicate the presence of a compensatory system existing in the ventricular lining ependyma that might take over CSF secretion. However, this does not rule out that CP is the main CSF-producing tissue when present. There is no doubt that hydrocephalus is difficult to study in animal models, both because the causes of hydrocephalus are variable and because small animals may have a different CSF outflow pattern. Rodents, for example, have no arachnoid granulations but only less developed villi (13). We note that, if the same arguments against a pressure gradient were applied to the drainage of CSF in hydrocephalus, flow in the shunt would go from the positive pressure in the abdomen to the negative pressure in the ventricles.

ICP due to build-up of CSF, which highlights the important role of this site in reabsorption of CSF (14). A major point by Orešković, Radoš, and Klarica is an opposition to the idea that CP could be the source of CSF, which is based on a theoretical lack of CSF circulation in the direction from the ventricles to the arachnoidal or lymphatic systems. This goes against many elegant experimental in vivo and in vitro observations of active CSF secretion by CP and, to our minds, against the bulk of research in the area over 100 years (3, 17). For example, the choroid plexus secretes fluid beneath oil installed above the epithelium in vivo (5). Also, cultured CP cells can secrete fluid even with an opposing pressure gradient (6). The CP cells have a secretory rate, which is not surpassed by any mammalian transporting epithelium (4), and genetic ablation of AQP1, Ncbe, or NBCe2 reduces ventricle size and/or CSF secretion rate (7, 8, 16). In these mice, there should be no change in the production of CSF by the brain vasculature proposed by Orešković, Radoš, and Klarica, since these transport proteins are only expressed in the CP. Pharmacological manipulation of ion transport with ouabain, azetazolamide, amiloride, etc. have similar effects on CSF secretion and on CP transport rates. Thus the theoretical objections by Orešković, Radoš, and Klarica are contradicted by a vast literature of direct evidence.

The controversy in the role of the CP and active CSF secretion in the development of hydrocephalus seems to be the question of the chicken and the egg. Is an obstructive hydrocephalus caused by obstruction of the CSF flow through the cerebro-ventricular system or is the obstruction a consequence of the developing hydrocephalus by compression of the brain? We acknowledge the fact that there can be many reasons for the development of stenosis in non-communicating hydrocephalus and that treatment today is no longer aimed at removing the CP but rather to alleviate the CSF pressure by drainage. The lack of response to removal of CP could indicate the presence of a compensatory system existing in the ventricular lining ependyma that might take over CSF secretion. However, this does not rule out that CP is the main CSF-producing tissue when present. There is no doubt that hydrocephalus is difficult to study in animal models, both because the causes of hydrocephalus are variable and because small animals may have a different CSF outflow pattern. Rodents, for example, have no arachnoid granulations but only less developed villi (13). We note that, if the same arguments against a pressure gradient were applied to the drainage of CSF in hydrocephalus, flow in the shunt would go from the positive pressure in the abdomen to the negative pressure in the ventricles.

We of course fully agree that scientists should always be ready to discuss different views and opinions. However, it is
not our task here to comment on the new concept of water filtration that Orešković, Radoš, and Klarica wish to promote. Discussion of this concept, which appeared after the submission of our review, would also require more compelling evidence against a ventricle to arachnoidal pressure gradient and for the filtration across microvessels in the brain, such as direct comparison of the nascent ISF composition and the calculated composition of an ultrafiltrate. This would also be an interesting analysis to perform on CSF after removal of CP. In conclusion, we find the continued studies of CSF dynamics very interesting and important. This includes the work of Orešković, Radoš, and Klarica. Nevertheless, the bulk of direct and compelling evidence for CP secreting the majority of CSF must be acknowledged and therefore forms the basis of our understanding of CSF production.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES