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PROPERTIES OF THE TRPV4 ACTIVATOR GSK1016790A AND THE TRPV4 ANTAGONIST GSK2193874

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TO THE EDITOR: We write in response to the recent article by White, Cibelli, Urban, Nilius, McGeown, and Nagy (4). We commend the authors for compiling such a wide literary review on this interesting ion channel, TRPV4. However, we have read with concern the description of the properties of the agonist GSK1016790A and antagonist GSK2193874, and would like to bring the following specific items to your attention.

1) Structures of GSK1016790A and GSK2193874 are incorrect in Figure 7 (p. 933). In Figure 7 GSK2193874, GSK1016790A, and GSK205 are quoted with Refs. 417, 432, and 417, respectively; these molecules cannot be found in the quoted references.
2) The authors provide extensive detail in *Section V. ACTIVATORS OF TRPV4*. Quite surprisingly, GSK1016790A is not reviewed, only being displayed in Figure 7 (with an incorrect structure) where the authors have designated it as a "non-selective" TRPV4 agonist. There are no references to support this non-selective connotation. We, and others, have provided evidence of the selectivity of GSK1016790A as an agonist of TRPV4, both in in vitro selectivity assays as well as in vivo (2, 5). GSK1016790A has been reported in 80 of a total of 985 publications on TRPV4 (PubMed search, November 10, 2016) as a highly utilized, selective tool to elucidate TRPV4 biology.
3) On p. 931, *subsection G*, the authors indicate that "The phorbol ester, 4a-PDD, is the most specific known agonist of TRPV4 and one of its most effective activators." We disagree with this statement, since GSK1016790A compared with 4a-PDD has demonstrated both a 300-fold enhanced potency for TRPV4 activation and a heightened magnitude of activation. Furthermore, 4a-PDD has been deemed less selective (2).
4) In *Section VII. ANTAGONISTS OF TRPV4*, the authors state, "A selective antagonist of TRPV4 has yet to be definitively identified . . ." and ". . . none has been shown to be selective for TRPV4." Furthermore, the authors have also deemed GSK2193874 as "non-selective" in Figure 7, citing Ref. 401, in which we provided evidence supporting the selectivity of GSK2193874 for TRPV4 vs. 200 other targets, including other TRP channel isoforms. Hence, we would argue that GSK2193874 is quite a selective TRPV4 antagonist, perhaps the most selective reported in the literature to date.
5) To provide a comprehensive list of selective TRPV4 antagonists in Figure 7, the authors should include GSK2263095 (3), and GSK2220691 and GSK2337429A (1), which represent novel and selective TRPV4 antagonists for use in in vitro and/or in vivo studies. GSK2220691 and GSK2337429 were mentioned on p. 943 but were not included in Figure 7.
6) In *Section VII. ANTAGONISTS OF TRPV4*, the authors state the following without supporting reference: "Given the problems of collateral injury presented even by a selective TRPV4 antagonist when administered for a therapeutic purpose . . ." We feel that this is not a fair statement due to the lack of reference to support it and that administration of a selective TRPV4 antagonist to humans has yet to be reported.
7) On p. 912 and 943, the authors summarize the conflicting studies in the literature that have used TRPV4 KO mice to evaluate an in vivo role for TRPV4 in osmoregulation. On p. 935 they state that "In the case of animals that have been genetically engineered, there is always a question as to whether loss of the 'knocked-out gene' has led to compensatory changes . . . that the knockout phenotype ceases to be a reliable indicator of the function of the knocked out gene." We agree with the authors that interpretation of KO phenotypes must be done with caution. Hence, we performed rigorous osmoregulatory studies with the selective antagonist GSK2198374 in rats, in which no significant osmoregulatory impact was observed with acute or chronic pharmacological TRPV4 inhibition under various osmolar perturbations (1). It is surprising the authors did not reference our osmoregulatory study with GSK2193874, given their acute awareness of issues surrounding KO phenotypes and the conflicting osmoregulatory data reported with TRPV4 KOs.
8) On p. 935, *TRPV4 KNOCKOUT MICE*, the first sentence states that two independent TRPV4 KOs have been developed. However, the TRPV4 KOs developed by GSK (reported in Ref. 2) have not been considered as a third TRPV4 KO strain currently utilized by researchers.

Therefore, we would like to request the publication of an erratum. In particular to correct the references to, and er-

A reply to this has been published concurrently (White JPM, Cibelli M, Urban L, Nilius B, McGeown G, Nagy I. Reply to Thorneloe et al. *Physiol Rev* 97: 1233–1234, 2017).

rors in, chemical structures, as well as to address the selectivity characterization of GSK compounds.

DISCLOSURES

All authors are employees and stockholders of GlaxoSmithKline.

REFERENCES

1. Balakrishna S, Song W, Achanta S, Doran SF, Liu B, Kaelberer MM, Yu Z, Sui A, Cheung M, Leishman E, Eidam HS, Ye G, Willette RN, Thorneloe KS, Bradshaw HB, Matalon S, Jordt SE. TRPV4 inhibition counteracts edema and inflammation and improves pulmonary function and oxygen saturation in chemically induced acute lung injury. *Am J Physiol Lung Cell Mol Physiol* 307: L158–L172, 2014. doi:10.1152/ajplung.00065.2014.

2. Thorneloe KS, Sulpizio AC, Lin Z, Figueroa DJ, Clouse AK, McCafferty GP, Chendrimada TP, Lashinger ES, Gordon E, Evans L, Misajet BA, Demarini DJ, Nation JH, Casillas LN, Marquis RW, Votta BJ, Sheardown SA, Xu X, Brooks DP, Laping NJ, Westfall TDN. N-((1S)-1-[4-((2S)-2-[(2,4-dichlorophenyl)sulfonyl]amino-3-hydroxypropanoyl)-1-piperazinyl]carbonyl-3-methylbutyl)-1-benzothiophene-2-carboxamide (GSK1016790A), a novel and potent transient receptor potential vanilloid 4 channel agonist induces urinary bladder contraction and hyperactivity: Part I. *J Pharmacol Exp Ther* 326: 432–442, 2008. doi:10.1124/jpet.108.139295.

3. Thorneloe KS, Cheung M, Bao W, Alsaid H, Lenhard S, Jian MY, Costell M, Maniscalco-Hauk K, Krawiec JA, Olzinski A, Gordon E, Lozinskaya I, Elefante L, Qin P, Matasic DS, James C, Tunstead J, Donovan B, Kallal L, Waszkiewicz A, Vaidya K, Davenport EA, Larkin J, Burgert M, Casillas LN, Marquis RW, Ye G, Eidam HS, Goodman KB, Toomey JR, Roethke TJ, Jucker BM, Schnackenberg CG, Townsley MI, Lepore JJ, Willette RN. An orally active TRPV4 channel blocker prevents and resolves pulmonary edema induced by heart failure. *Sci Transl Med* 4: 159ra148, 2012. doi:10.1126/scitranslmed.3004276.

4. White JP, Cibelli M, Urban L, Nilius B, McGeown JG, Nagy I. TRPV4: molecular conductor of a diverse orchestra. *Physiol Rev* 96: 911–973, 2016. doi:10.1152/physrev.00016.2015.

5. Willette RN, Bao W, Nerurkar S, Yue TL, Doe CP, Stankus G, Turner GH, Ju H, Thomas H, Fishman CE, Sulpizio A, Behm DJ, Hoffman S, Lin Z, Lozinskaya I, Casillas LN, Lin M, Trout RE, Votta BJ, Thorneloe K, Lashinger ES, Figueroa DJ, Marquis R, Xu X. Systemic activation of the transient receptor potential vanilloid subtype 4 channel causes endothelial failure and circulatory collapse: Part 2. *J Pharmacol Exp Ther* 326: 443–452, 2008. doi:10.1124/jpet.107.134551.