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RESPONSE TO LETTER TO THE EDITOR

Antiepileptic activity of zonisamide on hippocampal CA3 neurons does not depend on carbonic anhydrase inhibition

Dear Colleague,

First of all I would like to thank you for responding to our paper and the editor for the opportunity to comment on your criticism. Our decision to choose ZNS for our study was originally based on the notion that it inhibits carbonic anhydrase activity in brain tissue and, therefore, might influence intracellular steady state pH and/or pHi regulation, which was in the focus of our interest. At that time subtype specificity of ZNS was of minor importance such that experiments were carried out with a comparatively high concentration of ZNS (50 μM), which presumably allowed better tissue penetration. Nevertheless, we found neither inhibition of pHi regulation nor any effect on pH-sensitive caffeine-induced epileptic discharges. These and other results led us to conclude that a CA inhibitory activity of ZNS plays no active role in the hippocampal slice model.

It may have been misleading to highlight CAII as one isoform being expressed in the hippocampus and whose ''...inhibition may be a potent antiepileptic mechanism'', which in fact was an idea retrieved from the work of Ilies et al. (2004). The authors speculate in several passages about the antiepileptic potency of CAII inhibition (''Due to ... the abundance of CA II in the brain, the selectivity toward CA II isozyme should be favorable to the anticonvulsant activity.''). They also provided the K_i value of ZNS for CAII (35 nM), albeit they did not explicitly claim a causality between CAII inhibition and antiepileptic effect. In a latter work (De Simone et al., 2005), the inhibitory binding of ZNS to CAII was impressively demonstrated by X-ray crystallography. This paper further strengthened the impression that ZNS is a potent inhibitor of CAII. We admit that ZNS should not have been designated ''a highly selective CAII inhibitor'', as has been erroneously done by us in the introduction and which certainly prompted your confusion.

The conclusion we drew from published knowledge about ZNS and its interaction with CAII, and from the fact that CAII is expressed in the hippocampus was that ZNS has no antiepileptic effect *at least* via CAII inhibition. Due to the data provided in your recent review (Supuran, 2008) we now might extent this conclusion to nearly all currently known CA isoforms, since most K_i values are in the nanomolar to lower micromolar range. We nevertheless feel that the failure of ZNS does not generally deny the concept of using CA isoforms as potential antiepileptic target structures. Lipophilicity, resulting tissue distribution, as well as targeting complementary isoforms may be a successful strategy for future drug development.

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