LETTER TO THE EDITOR

To Close Voltage Dependent Anion-Selective Channel on Cell Surface Equals Blocking Azaspirazid-1-Induced Cytotoxicity

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Sir,

The paper presented by Vale et al. (2010) in Toxicological Sciences 113, 158–168, can be read as supporting that plasmalemma-integrated mammalian type-1 porin/VDAC is involved in effects induced by azaspirazid-1 on cultured neurons.

The expression of type-1 porin/voltage-dependent anion-selective channel (VDAC) in cytoplasmic membrane was demonstrated 20 years ago. Concerning its function in this compartment, it was shown that the channel forms part of the cell volume-regulating system and also gives way to ATP. Cell outside applied anti-type-1 porin antibodies or the anion channel blocker 4,4'-diisothiocyanato-2,2'-stilbenedisulfonate (DIDS), respectively, blocked regulatory volume decrease of HeLa cells, as demonstrated by video camera monitoring (Thinnes et al., 2000; http://www.fthin.de) and meanwhile confirmed by a study on VDAC1 knockout mice (Okada et al., 2004).

With regard to early apoptosis, Elinder et al., (2005) demonstrated that opening of plasmalemmal type-1 porin precedes caspase activation in neuronal cells under toxic stimuli. The group furthermore showed that VDAC here plays a role in differentiated neurons but not in neuronal stem cells (Akanda et al., 2008). The results rest on the application of anti-type-1 porin antibodies in several experimental settings and show that the channel is included in apoptotic volume decrease (AVD).

Now, Vale et al. (2010) reveal differences of cerebellar granule cells concerning effects of azaspirazid-1 in correlation to time of cell culture, pointing to differences in the expression level of the agonist’s receptor. They furthermore show that the application of the anion blockers DIDS, 5-acetamido-2-[(E)-2-(4-isothiocyanato-2-sulfophenyl)ethenyl]benzenesulfonic acid, and 5-nitro-2-(3-phenylpropylamino)benzoic acid, established as inhibitors of apoptosis, decreases its neurotoxic effects while phosphorylated c-Jun-N-terminal kinase is raised.

Correspondingly, there are early data on the interaction of native human type-1 porin, the N-terminally acetylated gene product of VDAC1, with DIDS in artificial lipid bilayer experiments. In addition, type-1 porins purified from human B-lymphocyte membranes or bovine muscle, respectively, were shown to reversibly bind to the stilbene disulfonate group of immobilized DIDS (Thinnes and Reymann, 1997).

Finally, the data presented by Vale et al. (2010) on normotonic shrinkage and secondary upraise of c-Jun-N-terminal kinase of the cells under AZA-1 together with a recent study of Kellmann et al. (2009), which showed that neuroblastoma cells under AZA-1 temporarily deplete ATP levels while VDAC1 is upregulated, support the agonist as working as an inductor of apoptosis.

In conclusion, plasmalemma-standing type-1 porin/VDAC is a candidate to form the channel part of the AVD channel phenotype (Thinnes, 2010). It might thus pay to remember the channel in this compartment in studies trying to elucidate mechanisms involved in effects of AZA-1 on several cell types.

REFERENCES


