

Neuroprotection and acidosis induced by cortical spreading depression

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Dear editor

We read with interest the article “Cortical spreading depression produces a neuroprotective effect activating mitochondrial uncoupling protein-5” published in *Neuropsychiatr Dis Treat* by Viggiano et al.¹ The authors showed that cerebral spreading depression (CSD) triggered uncoupling protein-5 (UCP-5),¹ which had been reported to exert a long-term effect upon neuron protection.² The result is another piece in CSD literature on modifying gene expressions to provide neuroprotection to subsequent ischemic episodes.^{3,4}

An unmentioned but additional factor for neuroprotection in CSD could be acidosis.

Acidosis is a known consequence of CSD.⁵ In the literature, brief acidosis in ischemic conditions when oxygen supply is low has been shown to be cytoprotective and neuroprotective,^{6–10} a result related sometimes to the concept of the “pH paradox.”^{9,11,12} Acidosis had been reported to reduce stroke infarct size with CO₂ applied for a short time after reperfusion⁶ as well as during ischemic stroke.¹⁰ Brief acidosis applied after birth asphyxia⁷ was reported to successfully suppress brain alkalosis, which led to seizures. Hence, brief and relatively mild acidosis induced under the condition of CSD may be one of the neuroprotective factors for CSD. The role of acidosis in neuroprotection by CSD warrants further investigation.

Interestingly, CSD-induced acidosis could be one explanation of impaired cerebral vascular reactivity^{13–16} after CSD. It has been reported that once tissue reaches a certain low pH threshold, blood flow increase would be insignificant in response to even stronger CO₂ challenge.¹⁰

Disclosure

The authors report no conflicts of interest in this communication.

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Authors' reply

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Dear editor

Thank you for the attention paid to our article entitled: "Cortical spreading depression produces a neuroprotective effect activating mitochondrial uncoupling protein-5".¹ We do agree that cerebral spreading depression (CSD)-induced acidosis is an intriguing aspect of the neuroprotection puzzle. It is well known that CSD is involved in the pathophysiology of migraine, cerebral ischemia, subarachnoid hemorrhage, and traumatic brain injury.²⁻⁷ Moreover, it is also involved in traumatic and spontaneous intracerebral hemorrhage, as well as in migraine aura and epilepsy.⁸⁻¹⁰ The induction of CSD during ischemia causes an increase in tissue damage, while preconditioning with CSD decreases the damage induced by a subsequent episode of ischemia.¹¹ Anyway, the mechanisms underlying these effects, as well as the neuroprotection induced by CSD, remain unclear.

Our results are consistent with the hypothesis that CSD might induce its neuroprotective effect by means of uncoupling electron transport from ATP synthesis, mediated by the activation of the mitochondrial uncoupling proteins (UCPs). Such an idea is supported by the experimental evidence of the neuroprotective effect due to upregulation of UCPs in response to oxidative stress; in fact, reactive oxygen species seem to play a major role in the phenomenon of ischemia-reperfusion.¹² But, reperfusion itself induces

also an important inflammatory response, characterized by a massive production of free radicals and by the activation of the complement and leukocytes. Therefore, the intracellular acidosis, the oxidative stress, the production of cytokines, and the secondary mitochondrial lesions may represent competing factors involved in the CSD-induced neuroprotection.¹¹⁻¹⁵

Therefore, according to authors' letter, further studies are needed to prove this multifaceted reality.

Disclosure

The authors report no conflicts of interest in this communication.

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