Bv8/PK2 and prokineticin receptors: implication in ischemia and preconditioning

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Stroke causes brain dysfunction and neuron death, and the lack of effective therapies heightens the need for new therapeutic targets. Here we study as a possible mediator for cerebral ischemic injury the amphibian prokineticin Bv8, a small protein originally isolated from 'Bombina variegata' skin secretions. Multiple biological roles for mammmalian Bv8 (also called prokineticin 2, PK2) have been discovered, including circadian rhythms, angiogenesis, and neurogenesis. Using primary cortical cultures, we found that Bv8 is neuroprotective in oxygen-glucose deprivation (OGD) and this effect is mediated by prokineticin receptors as well as PC7 a PKR antagonist revert this effect. Ischemic tolerance is a phenomenon in which exposure to a mild preconditioning stress results in resistance to a subsequent lethal ischemic insult. Here we investigated the role of PK and prokineticin receptors in the development of ischemic tolerance by using organotypic rat hippocampal slices exposed to 30 min OGD, which leads to selective injury of the CA1 subregion 24 h later. We used model of pharmacological preconditioning by exposing slices to 3 μM of N-methyl-d-aspartate (NMDA) for 1 h and then, 24 h later, to 30 min OGD. Under these conditions, we observed a significant reduction in OGD-induced CA1 damage. Exposure of slices to PC7 a PKR antagonist during preconditioning prevented the development of OGD tolerance. We found that PK2 mRNA is increased by NMDA preconditioning stimuli, as detected by PCR real time. NMDA preconditioning increased the protein level of PK2, PKR1 and PKR2 as detected by immune blots. These findings indicate that the PK system can be activated by subtoxic stimuli such as pharmacological preconditioning with NMDA and identify PK2 as a mediator involved in cerebral ischemia.