The selective antagonism of $P2Y_1$ purinergic receptors prevents synaptic failure and affects cell proliferation induced by in vitro ischemia in rat dentate gyrus

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$P2Y_1$ receptors (P2Y1R) are widely expressed in the brain, including the dentate gyrus (DG), on both neurons and glial cells. Multipotent neural stem cells are present in the subgranular zone (SGZ) of the DG. They are able to proliferate and differentiate into neurons, astrocytes and oligodendrocytes in response to hypoxic-ischemic injury (Liu et al.,1998). The purpose of our research was to study the contribution of P2Y1R to the recovery of neurotransmission and to the modulation of proliferation and differentiation in the DG, in acutely isolated hippocampal slices (Maraula et al., 2013, 2014).
A severe period of oxygen and glucose deprivation (OGD, 9 min duration) in acute rat hippocampal slices induced the appearance of anoxic depolarization (AD), a clear sign of tissue damage, and the irreversible block of synaptic activity in all the slices examined, as assessed by extracellular recordings of field excitatory post-synaptic potentials (fEPSPs) in the dentate molecular layer of the hippocampal slices. Synaptic failure persisted up to 24 hours from the end of the OGD. The selective P2Y1R antagonist 2'-Deoxy-N^6-methyladenosine 3',5'-bisphosphate (MRS2179, 10 μM, n=23) prevented the appearance of AD, allowing an almost complete fEPSP recovery (96.0±12.5%, calculated 50 min from the end of OGD) in comparison to that obtained in the absence of the drug (4.0±4.5%, n=26). Data indicate that P2Y1R exacerbates the early damage induced by OGD in the DG likely contributing to glutamate-induced excitotoxic effects that causes AD and irreversible synaptic failure after severe OGD.
In hippocampal slices prepared from bromodeoxyrudine (BrdU)-treated rats and incubated with the immature neuronal marker doublecortin (DCX), the number of $BrdU^+$ cells of the SGZ was significantly decreased 6 hours after OGD, but returned to control values 24 hours thereafter, when a significant increase of DCX immunofluorescence was also observed. MRS2179 significantly decreased the number of $BrdU^+$ cells 24 hours after OGD. Since it has been demonstrated that P2Y1R stimulation promotes cell proliferation in the SGZ niche (Suyama et al., 2012), it is likely that the antagonism of P2Y1R in the DG, at times later from OGD, reduces cell proliferation.

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