Blockade of P2Y$_1$ Receptors Prevents Microgliosis, Neurodegeneration and the Loss of Synaptic Markers in a Kainate Model of Epilepsy

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Introduction: ATP has been proposed to act as a danger signal upon brain damage and some studies have shown an ability of ATP P2 receptors (P2Rs) to control seizure-induced astrogliosis and microgliosis suggesting their involvement in the etiopathology of seizures. In this study we evaluated if P2Rs, mainly P2Y1R, control convulsions-induced brain damage. Material and Methods: Wistar rats received an intracerebroventricular administration of the P2R antagonist PPADS (1 nmol) or the P2Y$_1$R antagonist MRS2500 (1 nmol) 15 min before intraperitoneal kainate injection (10 mg/kg). Hippocampal microgliosis and neurodegeneration were evaluated through CD11b and FluoroJade C staining, respectively. Analysis of several terminal markers was performed in hippocampal membranes through Western blot. Results: Kainate administration triggered a period of convulsions, followed by the appearance after 24 hours of a strong microgliosis and neurodegeneration in all hippocampal subregions, which were prevented by both PPADS and MRS2500. Western blot analysis showed that administration of kainate induced a decrease of the density of SNAP-25 (6% of the control group; p<0.001); that was only rescued by MRS2500 (66% of the control). PSD-95 was also decreased by seizures (45% of the control; p<0.05), albeit not significantly prevented by PPADS or MRS2500. No differences were found in synaptophysin, whereas, there was significant loss of syntaxin (41% of the control; p<0.01), which was completely prevented by MRS2500 (101% of control). The administration of kainate resulted in a decrease of vGLUT1 (34% of control; p<0.01) which was rescued only by MRS2500 (78% of control). Moreover, the blockade of P2Y1 receptors also prevented the loss of vGAT (32% of control; p<0.001) and of gephyrin (41% of control; p<0.01). Conclusion: Our results provide direct evidence that P2Y1Rs control convulsions-induced neurodegeneration and suggest that this neuroprotection afforded by P2Y1R blockade might involve a combined control of synaptotoxicity and of neuroinflammation.

Key words: Epilepsy, Neuroprotection, P2 receptors

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