GPR17: A NEW DUAL RECEPTOR FOR BOTH EXTRACELLULAR NUCLEOTIDES AND CYSTEINYL-LEUCOTRIENES INVOLVED IN BRAIN ISCHEMIA

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GPR17 is a newly identified dualistic receptor for two endogenous unrelated ligand families, uracil nucleotides and cysteinyl-leukotrienes. The evidence that this receptor is highly expressed in brain, and that levels of both uracil nucleotides and cysteinyl-leukotrienes are increased in stroke prompted us to investigate the role of GPR17 in an animal model of cerebral ischemia obtained by permanent occlusion of middle cerebral artery (MCAo) in the rat. In our previous study we have demonstrated that, in rat cortex, GPR17 is present in neurons and its expression markedly increases within and at the borders of the ischemic infarct (1). The direct involvement of this receptor in ischemia was demonstrated by pharmacological studies showing that the post-MCAo administration of either montelukast or cangrelor, antagonists at CysLT or nucleotide-P2Y receptors, respectively, prevented the progression of ischemic damage as assessed by magnetic resonance imaging (MRI) analyses. Similar results on ischemic injury were obtained when an antisense oligonucleotide for GPR17 was used to specifically inhibit its expression in vivo. We recently investigated if the increased neuronal expression of GPR17 is strictly related to neural damage. HSP70 is commonly considered a sensitive and early marker of sublethal neuronal stress and, in the ischemic penumbra, its expression is upregulated primarily in neurons. This cytoplasmatic protein is implicated in the cytoprotection against various types of invasive stresses, such as ischemia and inflammation. In our preliminary studies we found that the expression of HSP70 was clearly higher in the ipsilateral cortex than in the contralateral and several HSP70-positive cells were also positively colocalized with GPR17. This result adds another evidence that GPR17 sensitizes neurons to ischemic damage. Since both uracil nucleotide and cysteinyl-leukotrienes are mediators of the inflammatory process in the ischemic lesion, we focused our attention on the two major inflammatory cells involved in the development of brain damage in our model. Data showed a positive colocalization of several GPR17-expressing cells with activated microglia and macrophages after MCAo. The present results suggest the possibility of counteracting both neuroinflammatory and neurodegenerating processes during ischemia through the inhibition of a unique pharmacological target. More in general, the better knowledge of GPR17 function might lead to the development of new chemical compounds more effective in halting brain ischemia.

1. The orphan receptor GPR17 identified as a new dual uracil neuclotides/cystenyl-leukotriene receptor. Ciana P., Fumagalli M. et al.(2006) The EMBO Journal 25:4615-4627