Kynurenic acid modulates cAMP production and intracellular \( \text{Ca}^{2+} \) concentration in HeLA cells and astrocytes in vitro through activation of GPR35.

GPR35 is a newly discovered G protein coupled receptors (GPCRs) and a potential new target for drug discovery. GPR35 is expressed in a variety of tissues. It is highly expressed in the gastro-intestinal tract, immune tissues, uterus and dorsal root ganglion (DRG), and moderately expressed in the spinal cord and in the brain (Wang et al., J. Biol. Chem., 2006, 281; 22021-8; Taniguchi et al., FEBS Lett., 2006, 580; 5003-8). Recently, two agonists for GPR35 have been identified: a natural ligand, kynurenic acid (a byproduct of tryptophan degradation by the kynurenine pathway; Wang et al., 2006), and a synthetic ligand, zaprinast, a well-known cGMP phosphodiesterase inhibitor that possesses other pharmacological activities (Taniguchi et al., FEBS Lett., 2006, 580; 5003-8). We performed biochemical and \( \text{Ca}^{2+} \) imaging experiments in order to explore in more detail the effects of GPR35 activation by kynurenic acid in cultured HeLA cells transfected with GPR35 and in cultured astrocytes. We find that 100 \( \mu \text{M} \) kynurenic acid decreased forskolin induced cAMP production both in HeLA cells transfected with GPR35 (80 % of inhibition of 30 \( \mu \text{M} \) forskolin stimulated adenylate cyclase activity; p<0.05) and in astrocytes in culture (12 % of inhibition of 30 \( \mu \text{M} \) forskolin stimulated adenylate cyclase activity; p<0.05). Moreover, since cAMP has been previously shown to modulate intracellular \( \text{Ca}^{2+} \) concentration ([\( \text{Ca}^{2+} \)]) via different mechanisms, we tested whether kynurenic acid application was able to change [\( \text{Ca}^{2+} \)] in transfected HeLA cells and in astrocytes in culture via GPR35 activation. Indeed, kynurenic acid, zaprinast and MRS 18-45, a selective store operated channel blocker, did not modify [\( \text{Ca}^{2+} \)] peak while significantly decreased [\( \text{Ca}^{2+} \)] area and length following an IP3 producing stimulus (ATP 30 \( \mu \text{M} \)). In conclusion, kynurenic acid modulates cAMP production and [\( \text{Ca}^{2+} \)] in non excitable cells via a possible GPR35 interaction.
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