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Inhibition of the firing activity of locus coeruleus neurons by EP_3 receptors in rat brain slices

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***Introduction*:** Prostaglandin E_2 (PGE_2) is involved in inflammation and other physiological functions. PGE_2 receptors (EP) are members of the G protein-coupled receptor family and comprise four subtypes: EP_2 and EP_4 (coupled to G_s proteins), EP_1 (coupled to G_q proteins) and EP_3 (coupled to $G_{i/o}$ proteins). The synthetic enzyme for PGE_2 COX-2 has been described to be constitutively present in the brain[1]. However, the function of prostanoid system in the brain is not yet well understood. The locus coeruleus (LC), the main noradrenergic nucleus of the brain, has high expression of the EP_3 receptor[2]. Thus, our aim was to characterise pharmacologically the EP_3 receptors in LC neurons by electrophysiological recordings in rat brain slices.

***Method*:** Adult male Sprague-Dawley rats were anaesthetised with chloral hydrate (400 mg/kg i.p.) and decapitated. Brain pontine slices (600 µm) were obtained as previously described[3]. Single-unit extracellular recordings of LC neurons were carried out *in vitro*. We performed concentration-effect curves for different agonists of the EP_3 receptor until a maximal effect was reached, including sulprostone (EP_1/EP_3 agonist, 0.3-80 nM), the endogenous PGE_2 (0.3 nM-1.28 µM) and the PGE_1analogue misoprostol (0.3-320 nM). The involvement of EP_3 receptor was tested by perfusing the selective EP_3 receptor antagonist L-798,106 (3-10 µM), and compared to selective antagonists of EP_2 receptors (PF-04418948, 10 µM) and EP_4 receptors (L-161982, 10 µM). Data was analysed by one-way ANOVA followed by Dunnett's post hoc test.

***Results*:** Increasing concentrations of sulprostone completely inhibited the firing rate of LC cells, with the EC_{50} being 15 nM (n = 9). The EP_3 receptor antagonist L-798,106 induced a rightward shift (>8 fold) in the concentration-effect curve for sulprostone (n = 6, $p < 0.001$), but neither PF-04418948 nor L-161982 caused similar changes in the sulprostone effect (n = 4). Likewise, perfusion with PGE_2 or misoprostol induced a concentration-dependent inhibition of the neuronal activity of LC cells (EC_{50} = 51 and 112 nM; n = 5 and n = 5; respectively). In both cases, only the EP_3 antagonist L-798,106 caused a rightward shift (>8 fold) in the concentration-effect curves for the prostanoid agonists (n = 5, $p < 0.001$).

***Conclusion*:** LC neurons are regulated in an inhibitory manner by the prostanoid system, likely through the EP_3 receptor.

***References*:** 1. Hétu PO and Riendeau D (2005). *Biochem J* **391**: 561-566. 2. Ek M *et al.* (2000). *J Comp Neurol* **428**: 5-20. 3. Pablos P *et al.* (2015). *Neuropharmacology* **99**: 422-431.