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INHIBITORY FUNCTION OF PROSTAGLANDIN E2 EP3 RECEPTORS IN LOCUS COERULEUS NEURONS

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Prostanoids regulate several physiological functions and play a pivotal role in pathophysiological situations including inflammation. The most abundant prostanoid in the body is the prostaglandin E2 (PGE2). PGE2 receptors (EP) are members of the G protein-coupled receptor superfamily, which comprise four subtypes: EP2 and EP4 (coupled to Gs proteins), EP1 (coupled to Gq proteins), and EP3 (coupled to Gi/o proteins). To date, the function of the prostanoid system in the brain has not been well characterized. The locus coeruleus (LC) -the main noradrenergic nucleus in the brain- has been shown to express the EP3 receptor. The aim of this study was to pharmacologically characterize EP3 receptor in the LC by single-unit extracellular recordings in rat brain slices. We performed concentration-effect curves for the endogenous PGE2, the analogue of PGE1 misoprostol or the selective EP3 receptor agonist sulprostone. Thus, increasing concentrations of sulprostone (0.3-80 nM) fully inhibited the neuronal activity of LC cells, with an EC50 value of 15 nM (n = 9). Perfusion with the EP3 receptor antagonist L-798,106 (10 µM) led to a rightward shift (› 8 fold) in the concentration-effect curve for sulprostone. However, administration of the EP2 receptor antagonist PF04418948 (10 µM) or the EP4 receptor antagonist L-161,982 (10 µM) did not cause any rightward shift in the concentration-effect curve for sulprostone. Similarly, administration of the endogenous PGE2 (0.3 nM-1.28 µM) or misoprostol (0.3-320 nM) induced a concentration-dependent inhibition of the firing rate of LC cells, with EC50 values being 51 nM and 112 nM, respectively. These inhibitory effects were shifted (› 8 fold) to the right in the presence of the EP3 antagonist L-798,106 (10 µM, n = 5). Our results suggest that EP3 receptors regulate the firing activity of LC neurons in an inhibitory manner.