Neuropharmacology 116 (2017) 160–173

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Serotonergic mechanisms of trigeminal meningeal nociception: Implications for migraine pain

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ARTICLE INFO

Article history:
Received 15 April 2016
Received in revised form
2 December 2016
Accepted 22 December 2016
Available online 23 December 2016

Keywords:
Migraine
Trigeminal nerve
Spike
Serotonin
5-HT3 receptor

ABSTRACT

Serotonergic mechanisms play a central role in migraine pathology. However, the region-specific effects of serotonin (5-HT) mediated via multiple types of receptors in the nociceptive system are poorly understood. Using extracellular and patch-clamp recordings, we studied the action of 5-HT on the excitability of peripheral and central terminals of trigeminal afferents. 5-HT evoked long-lasting TTX-sensitive firing in the peripheral terminals of meningeal afferents, the origin site of migraine pain. Cluster analysis revealed that in majority of nociceptive fibers 5-HT induced either transient or persistent spiking activity with prevailing delta and theta rhythms. The 5-HT3-receptor antagonist MDL-72222 or 5-HT1B/D-receptor antagonist GR127935 largely reduced, but their combination completely prevented the excitatory pro-nociceptive action of 5-HT. The 5-HT3 agonist mCPBG activated spikes in MDL-72222-dependent manner but the 5HT-1 receptor agonist sumatriptan did not affect the nociceptive firing. 5-HT also triggered peripheral CGRP release in meninges, which was blocked by MDL-72222.5-HT evoked fast membrane currents and Ca^{2+} transients in a fraction of trigeminal neurons. Immunohistochemistry showed expression of 5-HT3A receptors in fibers innervating meninges. Endogenous release of 5-HT from degranulated mast cells increased nociceptive firing. Low pH but not histamine strongly activated firing. 5-HT reduced monosynaptic inputs from trigeminal Aδ- and C-afferents to the upper cervical lamina I neurons and this effect was blocked by MDL-72222. Consistent with central inhibitory effect, 5-HT reduced CGRP release in the brainstem slices. In conclusion, 5-HT evokes powerful pro-nociceptive peripheral and anti-nociceptive central effects in trigeminal system transmitting migraine pain.

1. Introduction

Migraine is a common neurological disorder which pathophysiology is still poorly understood. For decades, serotonergic mechanisms were supposed to play a key role in migraine pathology (Lance et al., 1967; Dussor, 2014; Hamel, 2007). During migraine attacks, the plasma level of serotonin (5-HT) raises dramatically, whereas between attacks it goes down (Ferrari et al., 1989). Early studies reported the ability of 5-HT to inhibit migraine

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http://dx.doi.org/10.1016/j.neuropharm.2016.12.024
0028-3908/