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Research Report

Antinociceptive effects of histamine H_3 receptor antagonist in the preclinical models of pain in rats and the involvement of central noradrenergic systems

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ABSTRACT

The histamine H_3 receptor is predominantly expressed in the central nervous system and plays a role in diverse physiological mechanisms. In the present study, the effects of GSK189254, a potent and selective H_3 antagonist, were characterized in preclinical pain models in rats. Systemic GSK189254 produced dose-dependent efficacy (ED_{50}=0.77 mg/kg i.p.) in a rat model of monoiodoacetate (MIA) induced osteoarthritic (OA) pain as evaluated by hindlimb grip force. The role of H_3 receptors in regulating pain perception was further demonstrated using other structurally distinct H_3 antagonists. GSK189254 also displayed efficacy in a rat surrogate model indicative of central sensitization, namely phase 2 response of formalin-induced flinching, and attenuated tactile allodynia in the spinal nerve ligation model of neuropathic pain (ED_{50}=1.5 mg/kg i.p.). In addition, GSK189254 reversed persistent (CFA) (ED_{50}=2.1 mg/kg i.p,), whereas was ineffective in acute (carrageenan) inflammatory pain. When administered intrathecally (i.t.) to the lumbar spinal cord, GSK189254 produced robust effects in relieving the OA pain (ED_{50}=0.0027 mg/kg i.t.). The systemic GSK189254 effect was completely reversed by the α-adrenergic receptor antagonist phentolamine (i.p. and i.t.) but not by the opioid receptor antagonist naloxone (i.p.). Furthermore, the i.t. GSK189254 effect was abolished when co-administered with phentolamine (i.t.). These results suggest that the spinal cord is an important site of action for H_3 antagonism and the effect can be associated with activation of the noradrenergic system. Our data also provide support that selective H_3 antagonists may represent a class of agents for the treatment of pain disorders.

1. Introduction

Histamine is a biogenic amine that is released by neuronal and non-neuronal sources and is involved in a number of physiological responses (Haas et al., 2008). The effects of histamine occur through activation of four distinct G protein coupled receptor subtypes, H_1, H_2, H_3, and H_4 that differ in their pharmacology, signal transduction characteristics, and

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molecular biology (Parsons and Ganellin, 2006). The H_3 receptor has been identified as a mainly presynaptic autoreceptor in the histaminergic neurones in the central nervous systems (CNS), regulating the release of histamine (Arrang et al., 1983), as well as a heteroreceptor on non-histaminergic neurons that is capable of regulating the release of many other important neurotransmitters, such as acetylcholine, norepinephrine, dopamine, and serotonin (Gemkow et al., 2009; Giannoni et al., 2010). The wide expression of H_3 receptors in CNS areas, combined with the ability of regulating the release of various neurotransmitters, make this receptor an attractive drug target (Gemkow et al., 2009; Esbenshade et al., 2008; Leurs et al., 2005).

The H_3 receptors are expressed in the tissues known to be involved in nociception (specific thalamic areas, dorsal root ganglia, spinal cord, and skin tissues) and therefore, might offer treatment opportunities for different modalities of pain (Gemkow et al., 2009; Medhurst et al., 2008; Cannon et al., 2007a). In fact, the potential involvement of H_3 receptors in pain processing has been suggested by previous studies. The H_3 agonist immepip was shown to attenuate mechanical (tail pinch) responses in rats, but neither tail flick nor hot plate reflexes were affected (Cannon et al., 2003). Subsequently, the same laboratory also provided a line of evidence showing that activation of H_3 receptors by immepip attenuated formalin-induced flinching (both early and late phase) and the effect was reversed by systemic and intrathecal administration of the H_3 antagonist thioperamide (Cannon et al., 2007b). Interestingly, Huang et al. (2007) showed that central application of thioperamide helped to increase the pain threshold in a partial nerve-ligation model, while systemic application reduced it. However, Farzin and Nosrati (2007) demonstrated that thioperamide was able to reverse the H_3 agonist imetit-induced hyperalgesia but only in the late phase of the formalin model. These data would seem to indicate that H_3 agonists may be useful for the treatment of certain types of pain stimuli and H_3 antagonists for other pain stimuli (Cannon and Hough, 2005). Using a much more selective H_3 antagonist/inverse agonist, Medhurst et al. (2007a) showed that GSK334429 and GSK207040 significantly inhibited capsaicin-induced secondary allodynia. In a recent publication, the same group further demonstrated that the H_3 selective antagonist GSK189254 is efficacious in the rat models of neuropathic pain induced by sciatic nerve chronic constriction injury and varicella-zoster virus (Medhurst et al., 2008). This suggests that H_3 antagonists may be more beneficial than a H_3 agonist, although more research is certainly needed to clarify the involvement of peripheral, spinal and brain H_3 receptors in various pain states.

In the present study, we have demonstrated that selective H_3 receptor antagonists relieve osteoarthritic pain in a preclinically relevant model. A series of experiments were therefore conducted to explore the involvement of central mechanisms related to antinociceptive activity mediated through H_3 receptor antagonism. We also investigated the potential effects of H_3 antagonist GSK189254 in animal models of inflammatory pain and spinal nerve ligation (SNL) of neuropathic pain to further provide support that H_3 receptor antagonism exhibits antinociceptive properties in a broad range of the preclinical pain models.

2. Results

The antinociceptive effects of the selective H_3 receptor antagonist GSK189254 (H_3 Ki=0.13 nM/human and 0.68 nM/rat, Medhurst et al., 2007b) were evaluated in three rat chronic models of preclinical pain. In a rat model of monoiodoacetate (MIA)-induced osteoarthritis joint pain (Fig. 1), observed 20 days following the i.a. injection of MIA, animals exhibited a significant decrement in hind limb grip forces from 1119±28 g (naïve rats) to 446±30 g (MIA injected rats), demonstrating movement-induced pain behavior. Systemic administration of GSK189254 potently reversed MIA-decreased hind limb grip force in a dose-dependent manner, resulting in a 74±4% reversal effect ($p<0.01$, vs. vehicle-treated rats, $n=12$) at 3 mg/kg i.p. (ED_{50}=0.77 mg/kg, 95% CI=0.43–1.1). In the same study, a 79% reversal effect ($p<0.01$, vs. vehicle-treated group) was elicited by 30 mg/kg, i.p. celecoxib (Fig. 1), a clinically used non-steroid anti-inflammatory drug (NSAID) for OA pain. In order to ensure that the doses of GSK189254 used were not impairing grip force assessment on their own, a group of naïve rats were administered GSK189254 to evaluate if the compound reduced grip force. None of the GSK189254-treated naïve rats demonstrated any deficits on grip force readouts.

To further validate the histamine H_3 receptor as a potential antinociceptive target, three structurally distinct, selective H_3 antagonists including GSK 334429 (rat H_3 Ki=0.6 nM; Medhurst et al., 2007b), ABT-239 (rat H_3 Ki=1.2 nM; Esbenshade et al., 2005), and compound 1 ((S)-3-Hydroxy-1-[2-(3-piperidin-1-yl-cyclobutyl)-benzothiazol-6-yl]-pyrrolidin-2-one) (rat H3 Ki=0.2 nM; Cowart et al., 2007; Zhao et al., 2007) were also

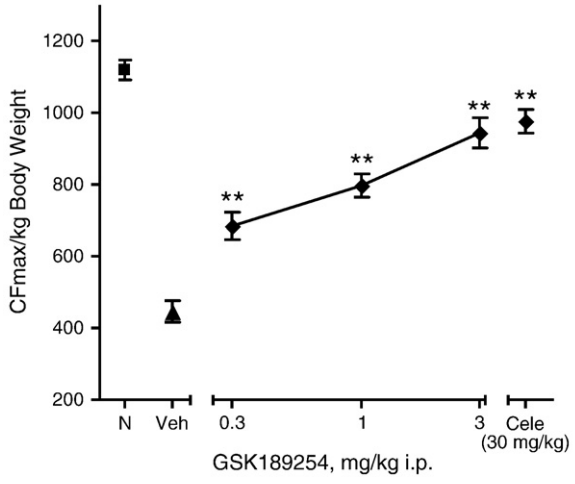

Fig. 1 – The antinociceptive effects of GSK189254 (i.p.) on hindlimb grip force in OA rats 20 days following intra-articular injection of monoiodoacetate (MIA). GSK189254 (♦) produced a dose-related reversal of movement-induced pain behavior in osteoarthritic rats (vs. vehicle treated group ▲, veh), with effects comparable to celecoxib (Cele, 30 mg/kg, i.p.,), a clinically relevant analgesic for OA pain ($n=12$). The age matched naïve group was assigned as being normal (■, N). The compound was administered 30 min before grip force measurement. Data represent mean±S.E.M ($n=12$). $^{**}p<0.01$ as compared to vehicle-treated animals.