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Different role of spinal 5-HT(hydroxytryptamine)7 receptors and descending serotonergic modulation in inflammatory pain induced in formalin and carrageenan rat models

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Editor's key points

- The spinal serotonergic system may be involved in inflammatory pain conditions.
- This study examined whether the role of serotonin differed between inflammatory models
- 5-HT7 had antinociceptive effects in the formalin model, with limited effects in the carrageenan model.
- 5-HT3 effects were predominantly pronociceptive.

Background. Spinal serotonin (5-HT) receptors 3 (5-HT3R) and 7 (5-HT7R) are differentially involved in facilitatory or inhibitory descending modulation, respectively. Electrophysiological studies of the spinal cord have demonstrated that 5-HT3R is involved in nociception induced by intraplantar injection of formalin, but not carrageenan. In addition, depletion of spinal serotonin has been shown to attenuate pain behaviour in the formalin test, but there have been no such reports regarding the carrageenan model. This study compared the role of 5-HT7R and the influence of descending serotonergic modulation between formalin- and carrageenan-induced inflammatory pain.

Methods. Effects of intrathecal (i.t.) AS-19 (5-HT7R agonist) and SB-269970 (5-HT3R antagonist) on flinching response in the formalin test and mechanical allodynia in the carrageenan model were evaluated in male Sprague–Dawley rats. The effect of serotonin depletion by i.t. 5,7-dihydroxytryptamine was also examined in the two models.

Results. Intrathecal AS-19 significantly reduced the flinching responses in the formalin test ($P<0.01$), which was reversed by i.t. SB269970. However, neither AS-19 nor SB269970 produced a significant change in mechanical allodynia in the carrageenan model. Depletion of spinal serotonin attenuated the flinching response in phase 2 of the formalin test ($P<0.01$), but increased mechanical allodynia in the carrageenan model compared with controls ($P<0.01$).

Conclusions. Spinal 5-HT7R plays a significant inhibitory role in descending serotonergic modulation in pain induced by formalin but not carrageenan. Descending serotonergic modulation is differentially involved in inflammatory pain induced by formalin and carrageenan, with facilitatory and inhibitory effects, respectively.

Keywords: carrageenan; formalin; serotonin receptor 7; spinal cord

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It has been noted that the role of spinal serotonin (5-hydroxytryptamine, 5-HT) in nociceptive processing is different depending on the modality of pain stimuli and activated receptor subtypes. Accordingly, spinal 5-HT can modulate nociceptive processing in either a facilitatory or inhibitory manner.[1–4]

The 5-HT7 receptor (5-HT7R), the most recently identified 5-HT receptor subtype, has been shown to be involved in nociceptive processing. Activation of 5-HT7R has a significant antinociceptive effect on capsaicin- and nerve injury-induced pain, and blockade of 5-HT7R reduces the analgesic effects of several drugs,[5–11] although a pronociceptive role of 5-HT7R has also been reported in a few studies involving the formalin test or spinal nerve ligation.[12–14] Unlike 5-HT7R, there is a great deal of evidence supporting a facilitatory role of the 5-HT3 receptor (5-HT3R) in descending pain modulation in various pain states; however, some controversy remains.[15–17]

Recently, a clear distinction between 5-HT3 and 5-HT7Rs was demonstrated in a study in which allodynia and hyperalgesia elicited by spinal nerve ligation or cholecystokinin injection into the rostroventral medulla was reduced by spinal administration of a 5-HT3R antagonist, but not by a 5-HT7R antagonist.[18] In addition, an antagonist of 5-HT7R blocked the antinociceptive effect of morphine administered systemically

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or into the rostroventral medulla, but 5-HT3R antagonist did not influence the effect of morphine. However, 5-HT7R was also shown to be pronociceptive in the formalin test, although confirmatory data on 5-HT7R are still lacking.[12 14] Interestingly, electrophysiological studies have shown that 5-HT3R is involved in nociception induced by intraplantar injection of formalin, but not carrageenan, where no significant difference is observed between naïve and carrageenan-injected rats in the neuronal response to mechanical and thermal stimuli in the spinal cord pre-treated with the 5-HT3R antagonist ondansetron.[19–21] The findings outlined above suggest that the role of spinal 5-HT7R could be different from that of 5-HT3R in formalin- and carrageenan-induced pain, and it is more likely that the activation of 5-HT7R could be inhibitory rather than facilitatory.

In addition, molecular depletion of 5-HT in the spinal cord may attenuate the pain behaviour elicited by intraplantar injection of formalin,[22] suggesting that the facilitatory role is predominant over the inhibitory role in descending serotonergic modulation of formalin-induced pain, probably mediated by 5-HT3R. However, the relative contributions of inhibitory and facilitatory serotonergic modulation have not been examined in carrageenan-induced pain.

The present study compared the role of spinal 5-HT7R in inflammatory pain induced by formalin and carrageenan. We also evaluated the differences in the nature of descending serotonergic modulation between the two pain models.

Methods

Animals and intrathecal catheter implantation

Male Sprague–Dawley rats weighing 225–250 g were used, and all the animals were housed in a room maintained at a constant temperature of 22–23°C with an alternating 12 h light/dark cycle. Free access was given to both water and food. All experiments were performed in accordance with the International Association for the Study of Pain guidelines for the Use of Animals in Research. The protocol (CNU IACUC-H-2011-10) was approved by the Institutional Animal Care and Use Committee, Chonnam National University Medical School, Republic of Korea.

A polyethylene-5 (PE-5) catheter was implanted into the intrathecal (i.t.) space for experimental drug administration as described previously.[23 24] Under general anaesthesia using sevoflurane (adequate anaesthesia assessed using response to skin pinch), a PE-5 catheter was introduced through the atlantooccipital membrane and advanced caudally 8.5 cm to the level of the lumbar enlargement. The other end of the PE-5 catheter, which was connected to a short PE-10 catheter, was tunnelled subcutaneously, externalized through the skin of the top of the head, and plugged with a stainless steel wire for drug administration. Any rat with a neurological deficit after catheter implantation was killed immediately with an overdose of inhalation anaesthetic. Four rats, ~2% of the animals implanted with the i.t. catheter, were excluded due to motor impairment after i.t. catheter implantation. Animals were housed in individual cages after surgery. Ketorolac 0.3 mg kg^{-1}, dissolved in 5 ml of lactated Ringer's solution was given subcutaneously immediately after the surgery. Upon completion of the following experiments and euthanasia (using high concentrations of sevoflurane, and confirming death by lack of breathing or heart beat, and cyanotic change of the skin), the lumbar spine of each animal was cut and dissected to ensure correct placement of the i.t. catheter.

Drugs

The following drugs were used in this study: AS-19 (5-HT7R agonist; Tocris, UK); SB269970 (5-HT7R antagonist; Tocris, UK). The doses tested were selected based on previous studies using AS-19 and SB269970 and adjusted according to the body weight of the animals and the route of administration used.[5 6 13 18] The selectivity of the drugs for 5-HT7R was demonstrated in a binding affinity study, in which the affinity for 5-HT7R was 149.5-fold higher than for the 5-HT1A receptor.[6] The drugs were dissolved in dimethyl sulphoxide and diluted with saline. They were delivered in a volume of 10 μl, followed by an additional 10 μl saline to flush the catheter.

5,7-Dihydroxytryptamine creatinine sulphate salt (5,7-DHT; a serotonergic neurotoxin; Sigma-Aldrich, USA) and desipramine hydrochloride (Sigma-Aldrich, USA) were also used. 5,7-DHT was dissolved in saline containing 0.1% ascorbic acid and injected intrathecally in a volume of 20 μl followed by flushing with a 10 μl vehicle. Desipramine was dissolved in saline and injected intraperitoneally.

Nociceptive test and behavioural study

Intraplantar injection of formalin or carrageenan, which are well characterized and highly reproducible rodent inflammatory pain models, was used in this study.[25 26] Animals were randomly allocated, using a random integer generator, to subcutaneous injection of either 50 μl 5% formalin or 100 μl 2% carrageenan (degraded λ-carrageenan; Sigma Aldrich, USA) into the centre of the plantar surface of the hind paw using a 30 G needle. The formalin test was conducted with the rats restrained in a cylinder, while carrageenan was injected under sevoflurane anaesthesia. Carrageenan was dissolved in saline to form a 2% solution and stored at room temperature for 24 h before use.

Nociceptive behaviour in response to intraplantar injection of formalin was quantified by counting the number of flinching responses at 1 and 5 min (phase 1, 0–9 min), and thereafter every 5 min up to 60 min after formalin injection (phase 2, 10–60 min). Counting was performed for 1 min each time. Phase 1 behaviour originates essentially from the direct stimulation of nociceptors and results in acute and rapid flinching responses, but dissipates within a few minutes.[27] Following phase 1, phase 2 response begins to increase gradually and involves a period of sensitization during which inflammatory phenomena occur. Although the origin of phase 2 response remains debatable, it has been shown to be closely related to the peripheral inflammatory mechanisms including peripheral sensitization, ongoing input from primary afferent fibres, and the sensitization within the dorsal horn.[27–30]

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