Comparison of Antinociceptive Effect of Octreotide With Morphine in a Rat Model of Acute Inflammatory Pain

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Abstract

Background: Opioids such as morphine are used for treating moderate to severe pain. However, they also produce adverse effects such as nausea, constipation, addiction, and respiratory depression. Thus, other suitable analgesics need to be identified. Somatostatin is an inhibitory neuropeptide that modulates the transmission of pain. However, the half-life of somatostatin is short. In the present study, the antinociceptive effect of octreotide (a stable long-acting analog of somatostatin) was evaluated in rats with acute inflammatory pain.

Methods: Sprague Dawley rats (n = 42) were divided into control (n = 6) and carrageenan injected groups (n = 36). The Carra group was divided into three equal subgroups and treated with saline, morphine (10 mg/kg), and octreotide (3 µg). Rats belonging to each subgroup (n = 12) were again randomly divided into two equal sets. They were subjected to (a) behavioral evaluation of pain (allodynia) and estimation of paw edema, followed by immunohistochemical analysis of the expression of somatostatin type 2 receptor (sst2r) in the spinal cord and (b) estimation of open-field activity. Allodynia and paw edema were measured by von Frey filaments and plethysmometer, respectively, at 3 and 4 h after carrageenan injection. Expression of sst2r was examined after 24 hours, whereas open-field activity was evaluated after 3 hours.

Results: In comparison to the saline-treated group, allodynia was partially attenuated by octreotide, though this was almost completely reversed by morphine. Paw edema was unaffected by octreotide, though it was marginally increased by morphine. This was not related to increased activity of rats, following relief from pain. Immunohistochemistry revealed a significant increase in the expression of sst2r in saline-treated rats, but a decrease in other groups.

Conclusion: Octreotide has an antinociceptive effect, which was less than morphine. Increased edema following morphine could result from venodilation. Variations in the sst2r expression suggest its involvement in pain modulation at the spinal level. This information may have clinical relevance.

Keywords

Local, Mechanical hypersensitivity, Peripheral, Somatostatin, Somatostatin receptor, Rodent

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Introduction

Somatostatin (SST), also known as the somatotropin-release inhibitory factor, was first extracted from the hypothalamus in 1973.[1] SST acts as a paracrine factor, inhibiting the release of several hormones such as the growth hormone, insulin, glucagon, and gastrin. It exists as a 14- and 28-amino-acid peptide. Apart from hypothalamus, it is present in the cerebral cortex, amygdala, limbic lobe, periaqueductal gray, and the spinal cord.[2] Within the superficial part of the dorsal horn of the spinal cord, SST is present within a group of excitatory interneurons.[3] Their axon terminals end on inhibitory interneurons, suggesting that SST could have a pronociceptive effect resulting from disinhibition. In fact, intrathecal administration of antibody to SST reduces nociception and edema resulting from carrageenan injection in rats.[4] However, contradictory findings have also been reported.[5]

SST receptors belong to the G protein-coupled receptor family and are divided into five subtypes (sst1–5).[6] Among

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these, the sst2A subtype is the most common receptor in the rat brain.[7] This receptor is expressed in the superficial laminae of the dorsal horn, a key area in the transmission of pain signals.[8] The signal transduction pathway includes the inhibition of adenylyl cyclase activity and the closure of voltage-gated calcium channels. However, calcium ion mobilization through phospholipase C activity can occur at higher concentrations.

Tissue damage is followed by pain, an outcome of direct activation of nociceptors. Nociceptors are sensitized by the varied mix of inflammatory mediators such as prostaglandins and bradykinin.[9] In the periphery, SST appears to have a tonic inhibitory effect on nociceptors mediated by the sst2A receptor.[10] Despite this, the clinical use of SST is limited by its extremely short half-life (1–3 min). Instead, its synthetic analog, octreotide, has a longer half-life (~120 min), and is used for treating endocrine tumors arising from the pituitary and the gut.[11] Both SST and octreotide cross the blood–brain barrier poorly and act peripherally after systemic administration.[12] Similar to SST, octreotide has an antinociceptive effect in rats.[13,14] Besides, it also diminished hyperalgesia arising from antigen-induced arthritis.[15] Also, TT-232, another synthetic analog of SST, inhibited acute somatic and visceral nociception in rodents.[16] Despite this, the role of octreotide in acute inflammatory pain has not been completely delineated.

In the current study, the anti-inflammatory and antinociceptive effect of octreotide was investigated in rats subjected to intraplantar injection of Lambda carrageenan, a common method for inducing acute inflammation.[17] Carrageenans (Iota, Kappa, and Lambda varieties) are polysaccharides derived from red seaweeds. Within two to three hours of injection, the affected hind paw becomes swollen and edematous, and the rats demonstrate guarding behavior characterized by the inability to use the paw for weight bearing. The experimental parameters measured were paw swelling (an important feature of inflammation) and mechanical allodynia by plethysmometer (using the water displacement method) and von Frey filaments (up-down method), respectively. This is because SST reportedly has both anti-inflammatory and antinociceptive effects.[18] The results were compared to morphine, which is a gold standard drug for treating pain.[19] Animals were euthanized after 24 hours, and immunohistochemical localization of the sst2A receptor was performed in the spinal cords. Finally, open-field activity was also evaluated after drug administration.

Methods

Experimental Animals

The study was conducted in male Sprague Dawley rats (n = 42; weight ~250 g). They were issued from the Central Animal Facility, AIIMS, New Delhi. Rats were housed at temperatures between 20°C and 25°C. A 12 h light/dark cycle was maintained, and food and water were provided *ad libitum*. Prior permission was obtained from the Institutional Animal Ethics Committee (28/IAEC-1/2017, dated: 10-17-2017). Rats were divided into the control (Group I; n = 6) and carrageenan-injected groups (Group II; n = 36). The carrageenan group was further randomly divided into three equal subgroups (n = 12 per subgroup), which received one of the following drugs: saline, morphine, or octreotide.

Carrageenan Injection in the Paw

A 2% solution of λ-Carrageenan (Sigma-Aldrich, USA) was prepared in physiological saline with the use of an ultrasonicator. It was freshly prepared on the day of experiment. A sterile tuberculin syringe was filled with 0.1 mL of the solution. Intraplantar injection was given in the right hind paw with a 30G needle under isoflurane inhalation anesthesia. A subcutaneous bleb formed at the site of drug administration. By the end of two hours, the paw was swollen and edematous. The control group received an equal volume of saline.

Drug Administration

Two hours after carrageenan injection, the following drugs were administered subcutaneously in the gluteal region by a tuberculin syringe under light physical restraint—Group IIA: saline for injection I.P., Group IIB: morphine sulphate I.P. (10 mg/kg; Vermor-15, Verve Health Care, New Delhi), and Group IIC: octreotide I.P. (3 µg per animal; Wockhardt Limited, Mumbai). The dose of 3 µg was selected after a preliminary evaluation of different doses of octreotide (3, 10, and 30 µg; Figure 1).

Evaluation of Mechanical Allodynia

Testing was done three and four hours after carrageenan injection. Rats were placed over a wire mesh platform and covered with plexiglass cages (16 cm × 16 cm × 16 cm). Following acclimatization for 30 min, mechanical allodynia was evaluated by calibrated nylon von Frey filaments of different sizes (3.61, 3.84, 4.08, 4.31, 4.56, 4.74, 4.93, and 5.18; North Coast Medical Inc., San Jose, USA) using the up-down method.[20] The maximum pressure exerted by these filaments varies between 0.4 and 15 g. Testing was performed at the center of the inflamed region. The behavioral end point was reflex withdrawal of the right paw, and the pressure (g) designated as the "withdrawal threshold." If there was no withdrawal till the filament size of 5.18, the value was presumed to be 15 g. An algorithm was used to calculate the 50% withdrawal threshold (g). Higher values of threshold indicate less pain as rats were able to withstand more pressure before withdrawal.

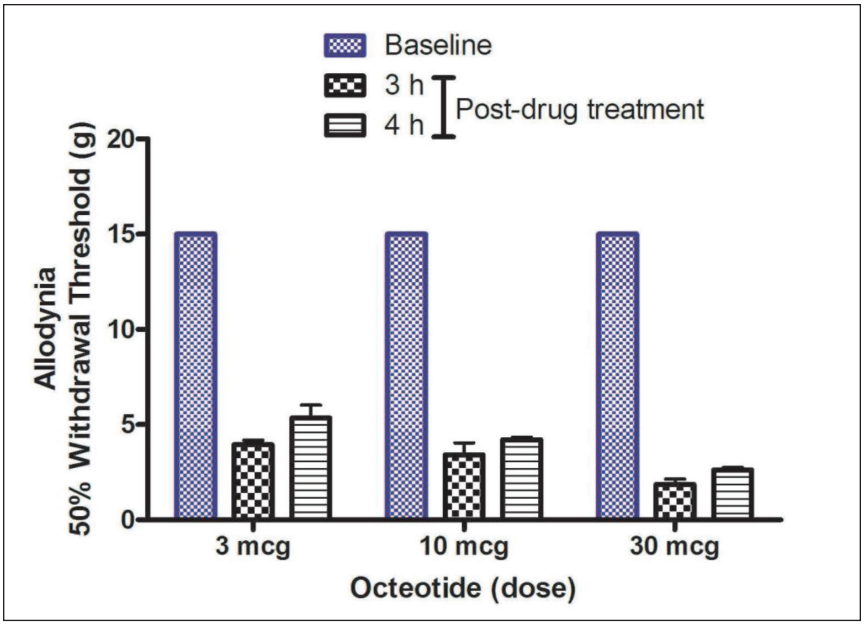

Figure 1. Preliminary study with three different doses of octreotide showed greater antinociceptive effect with the lower dose (3 µg) in comparison to higher doses (10 and 30 µg). Values are expressed as mean ± sem. *N* = 3 rats/group.

Estimation of Paw Volume

Paw volume was determined after the estimation of allodynia at 3 h 15 min and 4 h 15 min after carrageenan injection. Digital plethysmometer (Laboratory Enterprises, Nashik, Maharashtra) was used for determining the swelling in the paw (edema). Rats were restrained while the right hind paw was immersed in water to a specified extent (marked with ink). The value represented the paw volume using the water displacement method.

Immunohistochemistry

Rats (n = 24 including the control group) were sacrificed 24 hours after carrageenan injection. These were anesthetized with pentobarbital injection (100 mg/kg intraperitoneal) and then perfused with cold 0.1 M phosphate buffered saline (PBS), followed by cold 4% paraformaldehyde solution by the transcardiac route. The lumbar part of the spinal cord containing L4 and L5 segments was dissected out and the left side scratched with a capillary tube. The tissue was immersed in the fixative for three more days. Then, the tissue was washed and transferred to the 15% sucrose solution, followed by the 30% sucrose solution for 24 hours each at 4°C. Finally, transverse sections (of 20 µm thickness) of the spinal cord were cut in a cryostat (Leica, Germany) and floated in PBS in multivial trays. These were stored at −20°C. Tissue sections were incubated with anti-sst2A receptor polyclonal antibody (ab134152, Abcam, 1:250) for 48 hours at 4°C and then processed for staining by the avidin–biotin complex method (Vector Labs, Burlingame, USA). The chromogen used was 0.025% diaminobenzidine in PBS. Finally, sections were mounted onto gelatin-coated slides, dehydrated, cleared, and mounted with DPX. Some of the sections were stained with 0.5% Cresyl violet stain for visualization of the Rexed's laminae. Images were captured using a Nikon Eclipse 80i microscope attached to a CCD camera. Quantification of receptor expression (Rexed's lamina I and outer part of lamina II) was done using the Image J software (National Institutes of Health, Maryland, USA) over the superficial laminae. Three to four sections per rat were used for analysis. Nonspecific binding was deducted from the raw values to obtain specific binding.

Activity Monitoring

Open-field activity in the rats (n = 18) was evaluated using the Smart Video Tracking software V3.0 (Panlab Harvard apparatus, Spain). Testing was done three hours after carrageenan injection. A chamber of size 45 cm × 45 cm was used to measure the activity of rats. This chamber was cleaned with 70% alcohol before and after each experiment. A monitoring video camera was fixed on the roof just above the plexiglass chamber. The camera was connected to a computer where activity was automatically recorded in the software. Activity (in inches) was measured in individual rats for 5 min.

Statistical Analysis

Statistical analysis was done using the GraphPad Prism software (version 8, GraphPad, San Diego, USA). Values are expressed as mean ± sem. The values for mechanical allodynia and paw volume were analyzed using one-way analysis of

variance, followed by Tukey's multiple comparison test. The quantitative data of immunohistochemical analysis was analyzed using the same method. Data related to activity was evaluated using paired *t*-test. $P < .05$ was considered statistically significant. Individual *P*-values are indicated in the figures.

Results

Evaluation of Mechanical Allodynia

Before carrageenan injection, all the rats showed a baseline value of 15 g (Figure 2). Four hours after injection, the withdrawal threshold in the saline-treated group decreased to 0.7 ± 0.1 g, whereas it was 3.9 ± 0.6 g in the octreotide group. After three hours, this was lower for the octreotide group (2.86 ± 0.4 g). The morphine-treated group showed pain (14 ± 0.7 g) after three hours and minimal baseline values after four hours. The values for morphine- and octreotide-treated groups were significantly higher than the saline-treated group. Also, values for the morphine-treated group were significantly higher than the octreotide-treated group.

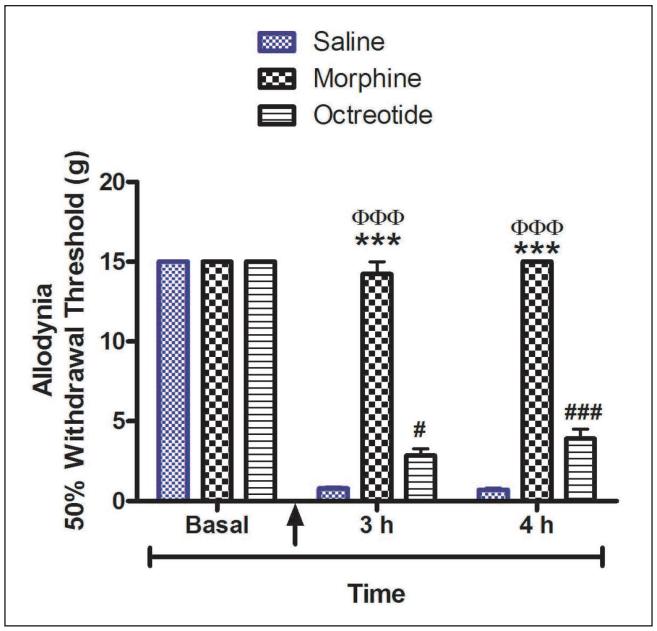

Figure 2. Comparison of antinociceptive effect of octreotide with morphine in the carrageenan-induced acute inflammatory pain model in rats. Basal values for all the three groups (before carrageenan injection) were 15 g. Following inflammation, saline-treated rats showed acute nociception as evident from the decreased values of withdrawal threshold. This was reversed by morphine at both 3 h and 4 h compared to saline (Φ). Octreotide partially reversed the nociception as observed from the higher values of withdrawal threshold (#). Also, values for the morphine group were higher than the octreotide group (*). $P < .05$, #; $P < .001$, Φ Φ Φ/***/###. Values are expressed as mean ± sem. $N = 6$ per group.

Evaluation of Paw Volume

Edema occurred in all the groups after carrageenan injection (Figure 3). At 3 h 15 min, swelling in the morphine-treated group (2 ± 0.16) was significantly higher than the saline (1.48 ± 0.15) and octreotide (1.5 ± 0.14) treated groups. However, at 4 h 15 min, the values for saline (1.9 ± 0.11), morphine (2.4 ± 0.22), and octreotide (2.03 ± 0.15) treated groups were not significantly different.

Expression of sst2A Receptor in Spinal Cord

With reference to Nissl-stained sections, the sst2A expression was observed over the superficial laminae (Rexed's lamina I and outer part of lamina II) of the dorsal horn in the control group (Figure 4). Expression over the remaining part of the dorsal horn was comparatively less. Across the mediolateral extent, a higher expression was observed toward the lateral part. Expression of sst2A increased after carrageenan injection in the saline group. Also, this was higher toward the central and lateral parts of the dorsal horn. In the morphine-treated group, expression was almost absent. However, the octreotide-treated group showed a diffuse pattern of expression over the superficial laminae, which was higher than that of the morphine-treated group. Image analysis of receptor expression showed an increased expression following carrageenan injection (Figure 5). However, the expression decreased significantly following treatment with morphine. Compared to morphine, the octreotide-treated group showed a higher expression, though this was less than the saline-treated group.

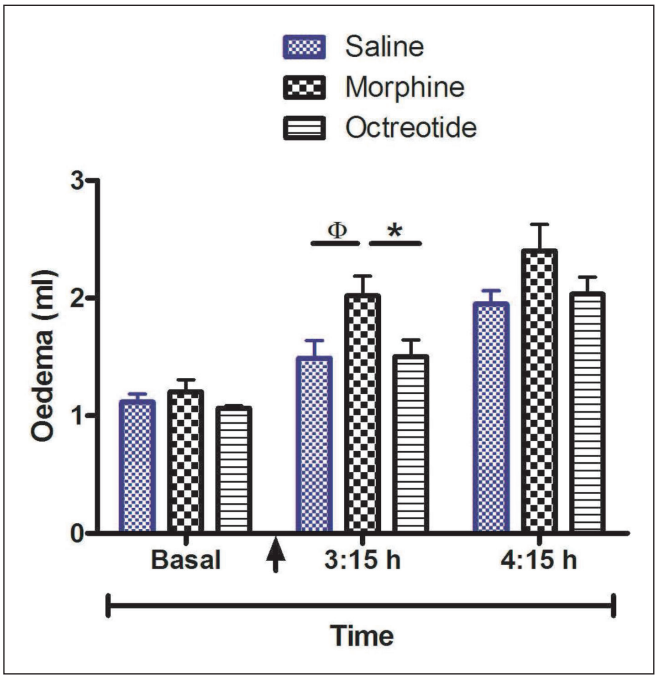

Figure 3. Paw edema following carrageenan injection. It was higher in the morphine-treated group compared to others at 3 h. $P < .05$, Φ/*. Values are expressed as mean ± sem. $N = 6$ per group.

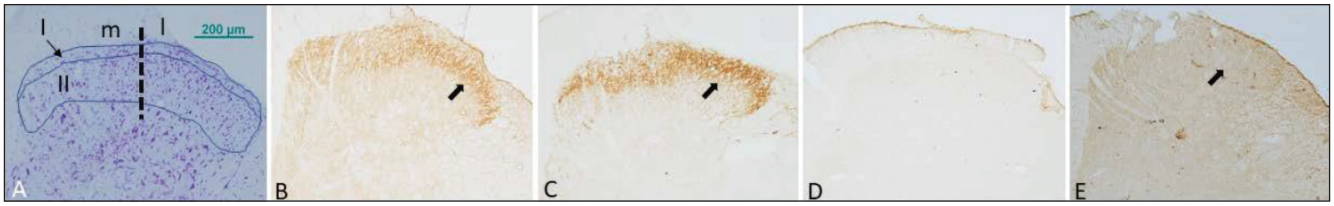

Figure 4. (A) Nissl-stained section of the spinal cord dorsal horn showing the arrangement of cell bodies of neurons and glia over the superficial laminae (Rexed's laminae I and II; the dashed line separates medial [m] and lateral [l] half). (B) The control group (without carrageenaninjection) showed the expression of sst2A receptor over lamina I and outer part of lamina II, particularly in the lateral half (arrow). (C) 24 hours after carrageenan injection, receptor expression increased over lamina I and lamina II (outer). Again, a higher expression was observed in the lateral half (arrow). (D) After morphine, a washed-out appearance was noted corresponding to a decrease in expression, likely because of the internalization of the receptors. (E) However, after octreotide, an increased expression, compared to the morphine-treated group, was noted over the superficial laminae as well as the remaining part of dorsal horn. Scale bar—200 µm. *N* = 6 per group.

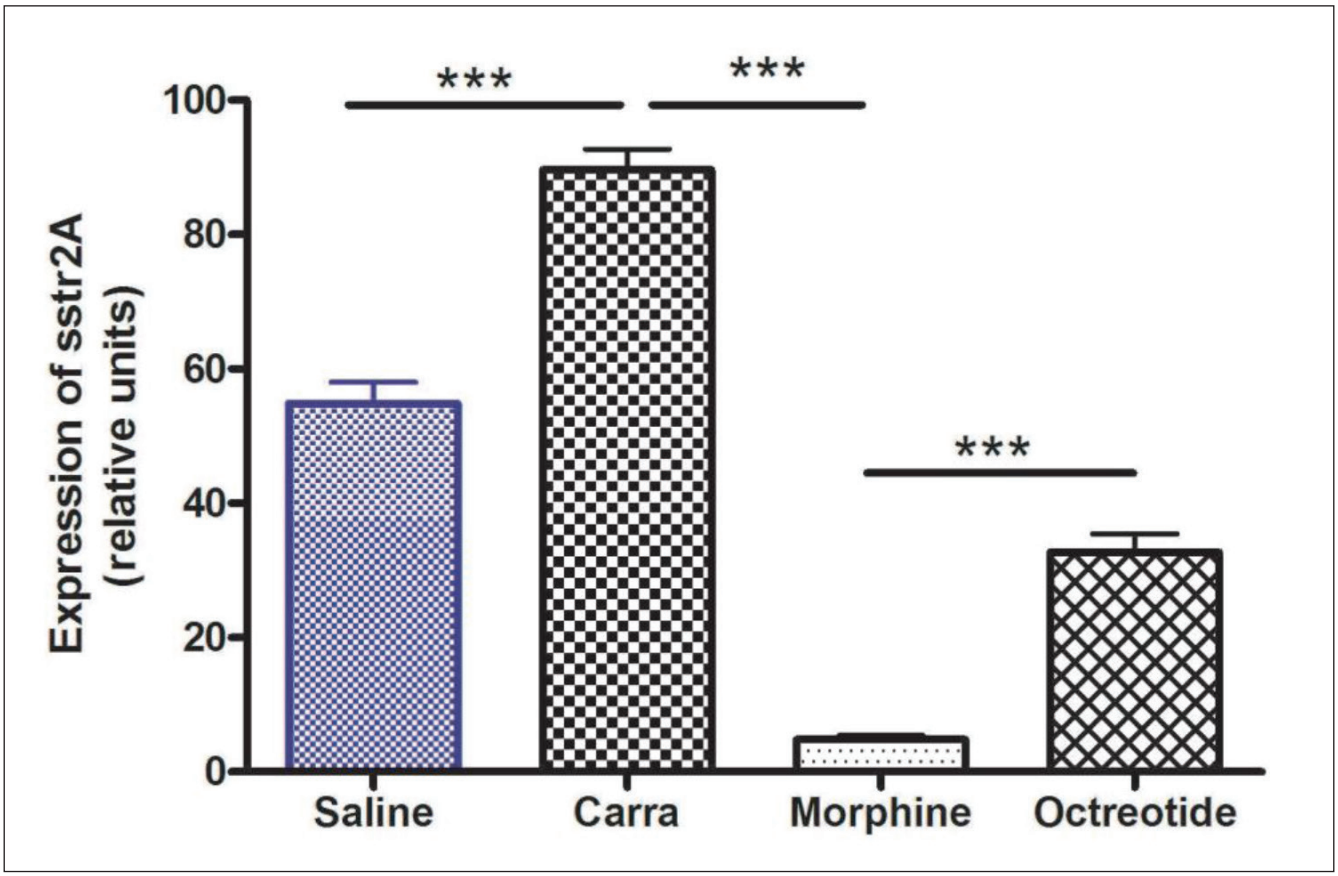

Figure 5. Estimation of sst2A receptor expression over superficial laminae (laminae I and II outer) by the Image J software. There was an increased expression after carrageenan injection in comparison to the control group. Morphine treatment attenuated receptor expression, whereas there was an increased expression after octreotide treatment, compared to morphine. The groups showed a significant difference between each other. $P < .001$, *** $N = 3$–4 sections per rat.up.

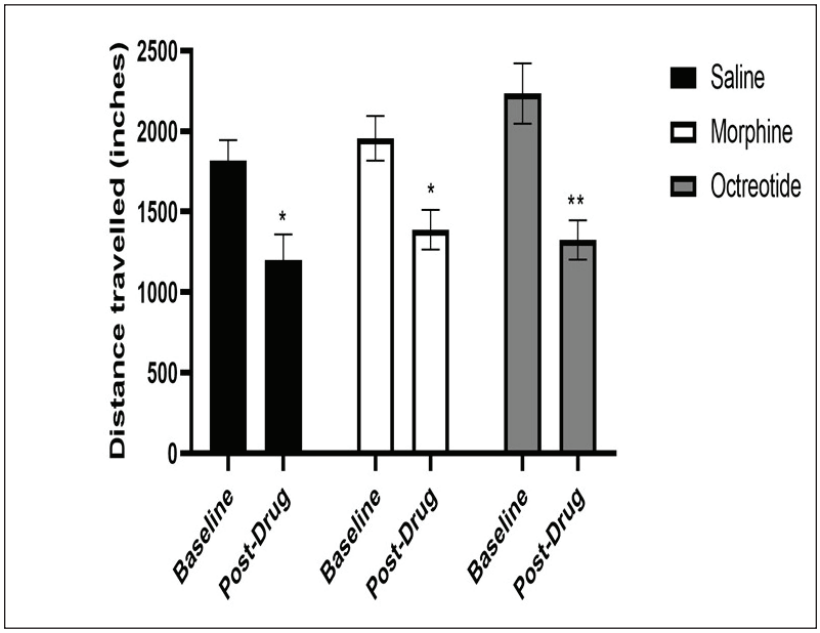

Figure 6. Evaluation of activity in carrageenan-injected rats following saline, morphine, or octreotide treatment. All the groups showed a decrease compared to baseline values. $P < .05$, *; $P < .01$, **. Values are expressed as mean ± sem. $N = 6$ per group.

Open-Field Activity

Postcarrageenan injection, rats belonging to all the groups (saline, morphine, and octreotide treatment) showed a significant decrease in activity (Figure 6). This was not affected by the antinociceptive effect of morphine or octreotide.

Discussion

The results of the current study show that acute inflammatory pain induced by carrageenan was almost completely reversed by morphine, though octreotide could only partially reverse it (19% to 26% of the morphine effect). Notably, paw edema was more after morphine treatment (approximately 26% to 36% more than saline), though this was not significantly different from the octreotide-treated group. Expression of the sst2A receptor decreased following morphine and octreotide administration (morphine > octreotide). Activity was uniformly decreased in all groups after carrageenan administration.

Carrageenan injection in the paw is followed by a sterile inflammation, associated with redness, swelling, and pain.[17] Since negligible amount of octreotide crosses the blood–brain barrier,[12] it is likely that the observed antinociceptive effect was mediated peripherally at the site of inflammation. Morphine produces antinociception by both central and peripheral mechanisms as it crosses the blood–brain barrier. This could account for its higher antinociceptive effect. Specific SST (e.g., sst2A) receptors are expressed by a proportion of the primary sensory afferents, which were likely activated by octreotide, leading to the observed antinociceptive effect.[14] These receptors exert an endogenous tonic inhibition over the nociceptors.[10] Downstream of sst2A, transient receptor potential vanilloid 1 channels, key receptors for pain, were probably inactivated by octreotide.[21] Notably, octreotide binds with full affinity to the sst2A receptor (subnanomolar) in comparison to other receptor subtypes such as sst5 (low nanomolar).[22] An alternate mechanism could diminish the release of tumor necrosis factor-α from inflammatory cells.[23] Another possibility could be an inhibitory effect on purinergic signaling.[24] Despite the antinociceptive effect, an anti-inflammatory action was lacking with relation to paw swelling. Previously, systemic octreotide treatment (10 μg/kg) in rats did not affect edema following mustard oil injection in the paw.[16] However, repetitive administration of octreotide can diminish edema.[15] Unexpectedly, in preliminary experiments, higher doses of octreotide (10 and 30 μg per rat) did not produce a corresponding increase in the antinociceptive effect compared to the 3 μg dose. Swelling in the paw increased after morphine treatment. Monitoring the activity of these rats did not demonstrate an increase in open-field activity, consequent to the reversal of allodynia. Presumably, morphine-induced venodilation at the site of inflammation could be responsible,[25] though this needs confirmation. This is so because a different study showed a decrease in edema after morphine treatment.[26]

The sst2A receptors are expressed over the superficial laminae of the dorsal horn. More specifically, these receptors are present in GABAergic interneurons in the dorsal horn of the spinal cord. Under higher power, immunostaining was found to be mainly confined to the postsynaptic junctions within these laminae, as reported previously.[8] The presynaptic arbors containing SST could be from local interneurons as

dorsal rhizotomy did not have any effect on its expression.[27] Receptor expression increased following paw inflammation, when evaluated 24 hours after carrageenan injection. A time interval of 24 h was considered sufficient for changes to occur at the level of the spinal cord following inflammation, though maximum pain and inflammation are observed within three hours after carrageenan injection. Earlier, an increased expression of the receptor was noted following peripheral inflammation.[28] Moreover, this was higher toward the central and lateral parts of the superficial laminae as was noted in the current study. Nerve fibers originating from the plantar aspect of the paw terminate in an organized manner along the mediolateral aspect of the spinal cord. The tibial component ends in the medial and central regions, whereas the sural component terminates toward the central and lateral aspect.[29] Morphine treatment significantly reduced receptor expression, although the octreotide-treated group demonstrated a higher expression. A decreased expression correlates with the internalization of the receptor following agonist binding. Rapid recycling is likely less or even absent after morphine treatment. An earlier study in our laboratory revealed that there is a turnover of the sst2A receptors at the spinal cord level following tissue injury.[13]

Conclusion

In conclusion, octreotide, a synthetic SST analog, was partially effective in relieving acute pain following carrageenan injection. This was associated with a decrease of sst2A receptors in the spinal cord. Overall, the results demonstrate that a systemic administration of octreotide, an SST analog, can be effective in relieving acute pain in rodents, albeit to a much lesser degree than morphine. Its inability to penetrate the blood–brain barrier can protect from central nervous system-related side effects.

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Author Contribution

PS performed the experimental work.
SBR did the planning and supervision of the work, statistical evaluation of data, and writing the manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Statement

Permission from IAEC was obtained prior to the work.

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