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Serotonin in Pain and Analgesia

Actions in the Periphery

Claudia Sommer

Department of Neurology, University of Würzburg, Germany;
E-mail: sommer@mail.uni-wuerzburg.de

Abstract

The purpose of this article is to summarize recent findings on the role of serotonin in pain processing in the peripheral nervous system. Serotonin (5-hydroxtryptamine [5-HT]) is present in central and peripheral serotonergic neurons, it is released from platelets and mast cells after tissue injury, and it exerts algesic and analgesic effects depending on the site of action and the receptor subtype. After nerve injury, the 5-HT content in the lesioned nerve increases. 5-HT receptors of the 5-HT_3 and 5-HT_{2A} subtype are present on C-fibers. 5-HT, acting in combination with other inflammatory mediators, may ectopically excite and sensitize afferent nerve fibers, thus contributing to peripheral sensitization and hyperalgesia in inflammation and nerve injury.

Index Entries: Serotonin; pain; hyperalgesia; peripheral nerve; inflammation; neuropathy.

Introduction

Serotonin (5-hydroxtryptamine [5-HT]) in the central nervous system (CNS) has long been associated with pain processing and modulation *(1).* Pivotal studies have shown a spinal analgesic action of 5-HT released from brainstem structures *(2,3).* Since 1969, researchers have investigated stimulation-induced analgesia, which reveals that 5-HT (released in the dorsal horn by stimulation in the PAG) excites inhibitory interneurons, resulting in inhibition of dorsal horn neurons *(4).* 5-HT_1, 5-HT_2, or 5-HT_3 receptors have been implicated in this process *(5–7).* Others have questioned a major role of 5-HT in descending analgesia *(8)* or found it limited to the C-fibers in raphe-spinal pathways *(9).* A 5-HT-mediated central analgesic effect was expected to occur with the use of selective serotonin reuptake inhibitors (SSRIs), but these proved less successful as

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analgesics than tricyclic antidepressants, which exhibit mixed 5-HT and noradrenalin (NA) reuptake inhibition *(10,11).* In fact, only a few SSRIs proved effective for neuropathic pain in clinical trials *(12,13).*

Another field of longstanding interest has been the role of 5-HT in the pathophysiology of headaches and this has been characterized most extensively in migraines *(14,15).* In particular, with the advent of the 5-$HT_{1B/D}$ agonists (triptans) in migraine treatment, the pathophysiology of serotonin metabolism in migraine and related fields experienced revived interest *(16).* A genetically determined alteration of 5-HT metabolism may be one of the factors that determines migraine susceptibility *(17).*

The peripheral action of serotonin is different from the central actions and those involved in migraine. 5-HT is considered an inflammatory mediator in the periphery, is released from platelets and mast cells after tissue injury *(18),* and exerts direct actions on C-fibers. This article summarizes the evidence for 5-HT as an excitatory or sensitizing mediator in the peripheral nervous system as well as the present knowledge regarding the 5-HT receptors involved.

5-HT Levels in Tissue Injury and Inflammation

Prerequisites for an excitatory action of 5-HT in the periphery are its presence, or increased presence, and the presence of its receptors in the situations associated with pain (i.e., tissue or nerve injury or inflammation). Like in other peripheral tissues, the cellular sources of 5-HT in peripheral nerves are mostly platelets and mast cells *(19,20).* In skin wounds of guinea pigs, 5-HT was shown to increase for up to 24 h after the injury *(21).* After peripheral nerve transection and chronic constriction injury (CCI) of the sciatic nerve, the 5-HT content in the lesioned nerve increased *(22,23).* Furthermore, CCI led to a decrease of 5-HT in the spinal cord *(23).* In the same model of nerve injury, others found an increase in the spinal 5-HT concentration within the first 2 wk after nerve lesion and no change in postoperative weeks 3 and 4 *(24).* In a previous study using the spinal nerve ligation model, spinal 5-HT was not affected *(25).* Capsaicin injection into the hindleg of cats led to a bilateral increase in 5-HT levels in the spinal cord *(26).* Experimental spinal cord or brain injury led to a rapid and marked increase of extracellular 5-HT levels *(27,28).* Therefore, there is consensus that injury of nerves or the spinal cord leads to an increase in 5-HT in the injured tissue directly, but data on remote effects in the nervous system remain controversial.

Some early studies deduced an increase of 5-HT in inflammation based on the ability of 5-HT antagonists to reduce inflammation *(29,30).* In carrageenin inflammation, extracellular 5-HT increased in the spinal cord between 3 and 5 h after injection *(31).*

In humans, elevated 5-HT levels in the masseter muscle as retrieved by microdialysis were associated with increased pain and allodynia *(32).* In a group of patients with temporomandibular joint pain, 5-HT was detected in a subgroup with pain perceived on mandibular movement *(33).*

Presence of 5-HT Receptors on Peripheral Nerves

Messenger RNA for the 5-HT1B, 5-HT1D, 5-HT2A, 5-HT2C, 5-HT3, and 5-HT7 receptor subtypes was detected in dorsal root ganglia *(34),* suggesting the presence of the receptors on peripheral sensory nerves. The presence of 5-HT3 receptors on C-fibers was postulated according to functional studies *(35).* Later, 5-HT2A receptors were directly demonstrated on unmyelinated axons at the dermal-epidermal junction *(36),* proposing that 5-HT can act directly on these fibers. 5-HT receptors were detected on Schwann cells in rat sciatic nerve, where they appear to be downregulated after injury *(37).* The functional role of these receptors has not been elucidated yet.

Peripheral Actions of Exogenous 5-HT

Early studies found an excitatory effect of 5-HT on single peripheral nerve fibers, which was not specific for nociceptors *(38,39).* Later, more specific effects on nociceptors were described. In cats, 5-HT was able to excite muscle afferents in group IV although with less potency than bradykinin *(40).* When 5-HT was applied in a mixture of inflammatory mediators ('inflammatory soup'), more than 80% of the mechano-heat sensitive afferents with slow conduction velocities were excited in rats *(41);* similar data were obtained from monkeys *(42).* In rats, intradermally injected serotonin produced a dose-dependent hyperalgesia with a very short latency, indicating a direct effect on primary afferent neurons. Using specific 5-HT1, 5-HT2, or 5-HT3 receptor agonists, this hyperalgesia could only be mimicked by agonists for the 5-HT_{1A} receptor subset *(43).* In another study, intraplantar 5-HT (0.05, 0.25, 0.5, or 1.0 μmols) produced paw edema and concentration-dependent increases in the nociceptive response, as indicated by paw lifting and licking *(44).* Pain behavior in the second phase of the formalin model was shown to be dependent on 5-HT release from mast cells *(45).*

In healthy volunteers, 5-HT infused into muscle at a dose of 20 nmol did not induce pain or hyperalgesia by itself but enhanced the effect of bradykinin in producing muscle hyperalgesia *(46).* Administered through intradermal microdialysis membranes, 5-HT (100 μmol) produced pain *(47)* and, in some volunteers, itching *(48).* Injections of 5-HT (30 mmol) into the masseter muscle in healthy human females, but not in patients with fibromyalgia, induced pain and hyperalgesia that could be antagonized by a 5-HT_3-antagonist *(49,50).*

There is some indirect evidence that 5-HT may have a stronger effect on lesioned or inflamed tissues and peripheral nerve fibers than on those that are intact. Articular bolus injections of 5-HT excited about 43% of group III and 73% of group IV nerve fibers from normal joints, with a pronounced tachyphylaxis. Inflammation induced an enhanced sensitivity of group III articular afferent units to close intra-arterial application of 5-HT. The total duration of each response was prolonged, and the tachyphylaxis seen under normal conditions was greatly reduced. Furthermore, after inflammation (but not in normal joints), 5-HT sensitized fibers in groups III and IV for movement-induced responses. However, after inflammation, a distinct sensitization to such movements by 5-HT application could be observed in fiber ranges in both groups III and IV *(51).* In an earlier study, 5-HT excited C-fibers from rat knee joints, with a slightly longer duration if these were arthritic *(52).*

After application of an inflammatory soup consisting of bradykinin, 5-HT, prostaglandin E_2 (PGE_2), and histamine, the rate of ongoing spontaneous activity recorded from dorsal root fibers was increased in rats with CCI. Inflammatory soup evoked activity in a subpopulation of previously silent fibers in rats with CCI but not those of unoperated controls. Dorsal root ganglion (DRG) neurons from rats with CCI had lower thresholds to depolarizing currents and a greater depolarization in response to inflammatory soup *(53).* In rats with previous carrageenin injections into the hindpaw, a subsequent injection of 5-HT or other inflammatory mediators induced a prolonged phase of hyperalgesia *(54).*

In fact, 5-HT seems to be more potent in enhancing algesic effects of other mediators than in inducing pain by itself. 5-HT_{2A}agonists enhanced the algesic action of PGE_2 and NA in rats *(55).* In a rat skin-saphenous nerve in vitro preparation, 5-HT increased the responses to bradykinin *(56).* In combination with other inflammatory mediators, 5-HT was shown to ectopically excite and sensitize acutely axotomized afferent nerve fibers in the rat *(57,58).* Also, in DRG neurons in culture, 5-HT alone had no major effect, but a proton-induced current was increased by the combination of 5-HT with other inflammatory mediators *(59).*

Data From Studies Using Selective Inhibitors or Antidepressants

Several 5-HT receptors have been implicated in the peripheral algesic or analgesic actions of 5-HT (Table 1). As stated earlier, hyperalgesia in rats could be evoked by intradermal injection of a 5-HT_{1A} receptor agonist *(43).* Similarly, in a rat model of visceral hypersensitivity, 5-HT-induced allodynia was mediated via 5-HT_{1A}, as shown in a study using antagonists and agonists to this receptor *(60).* Although sumatriptan, a 5-$HT_{1B/D}$ agonist, reduces thermal hyperalgesia in mice with peripheral inflammation (carrageenin), it had no effect on nerve injury-induced hyperalgesia *(61).* Sumatriptan also prevented capsaicin-induced hyperemia, a sign of neurogenic inflammation *(62).* Thus, conditions in the microenvironment may be important determinants for the specific action of 5-HT.

Injection of 5-HT (30 μg) and of a 5-HT_{2A} receptor agonist (α-methyl 5-HT) reduced the paw-withdrawal latency to noxious heat in rats, indicating a role of the 5-HT_{2A} receptor in peripheral thermal hyperalgesia *(63).* Furthermore, 5-HT_2 agonists injected intraperitoneally in rats induced lifting and licking, which was greatly enhanced in combination with PGE_2 and NA. This could be inhibited by the 5-$HT_{2A/2C}$ antagonist ketanserin *(55).* Pretreatment, but not posttreatment, with this 5-HT_{2A} antagonist reduced the pain response in rats injected with formalin, indicating a peripheral sensitization induced by 5-HT *(64).* However, others found local and systmic pre- and posttreatment with the 5-HT_{2A} antagonist sarpogrelate equally effective *(65).* Interestingly, 5-HT_{2A} has been identified on peripheral sensory axons *(36),* and it is upregulated in inflammation *(66).*

Other investigators identified 5-HT_1, 5-HT_3, and 5-HT_4 as the receptors involved in nociceptive behavior in formalin-induced paw inflammation in the rat *(67).* 5-HT_3 receptor antagonists applied subcutaneously did not change acute responses to painful stimuli in naïve mice but reduced formalin and Freund's complete adjuvant (FCA)-induced pain *(68,69).* Pain, but not edema, induced by carrageenin-induced inflammation was blocked by preventive treatment with a 5-HT_3 antagonist *(70).* Some hypoalgesia was also observed when applying a 5-HT_4 antagonist locally in naïve rats *(71).*

Topical application of the 5-HT_3 receptor antagonist ondasetran reduced capsaicin-induced pain and hyperalgesia in human volunteers *(72).* Various studies using 5-HT_3 receptor antagonists locally in humans with fibromyalgia or similar pain states produced equivocal results *(73–76).*

Animal studies using tricyclic antidepressants (TCA) or selective serotonergic drugs show variable effects in different pain models. Several recent studies demonstrated a peripheral site of action of the antidepressants *(77–79).* However, whether peripheral 5-HT is involved in the peripheral action of TCA is unknown. Given the strong local anesthetic action of the TCA and the action via adenosine, the serotonergic action might be a minor component *(79,80).*

Data From Knockout Animals

In mice deficient in 5-HT_3 receptors, assays for acute pain, phase 1 of the formalin test, and tests for hyperalgesia and allodynia after partial nerve lesion produced normal results; however, pain-related behavior in phase 2 of the formalin test was reduced in these mice, indicating a role of the 5-HT_3 receptor in tissue injury-induced persistent nociception *(81).* Furthermore, the visceral response to intraperitoneal 5-HT was reduced in the mutant mice, indicating a role of the 5-HT_3 receptor in 5-HT-induced visceral pain.

We performed studies with mice with a deficiency of the 5-HT-transporter (5-HTT–/– mice), which is necessary for 5-HT reuptake into cells from the extracellular space *(82).* In the CNS, these mice had increased extracellular 5-HT levels, but the overall tissue content of 5-HT was reduced *(83).* The 5-HT receptors 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A} are downregulated in these mice *(83,84).* We recently used 5-HTT–/– mice and a model of an experimental

mononeuropathy (CCI) to further investigate the role of 5-HT in neuropathic pain. The most prominent behavioral finding was that 5-HTT–/– mice, in contrast to wild-type littermates, did not develop thermal hyperalgesia after CCI.

They did develop allodynia to von Frey hairs (tactile allodynia), which was unchanged in magnitude compared to wild-type mice; however, in contrast to wild-type mice, they appeared bilaterally. CCI led to increased 5-HT levels in the injured nerve and to a decrease in 5-HT in the spinal cord. Both these changes were attenuated in the 5-HTT–/– mice, where tissue 5-HT levels were markedly reduced *(23).* These findings led us to conclude that 5-HT in the peripheral nerve is necessary for the development of thermal hyperalgesia, thus confirming the role of 5-HT as a factor in the sensitization of nerve fibers. Another explanation for reduced thermal hyperalgesia in 5-HTT–/– mice might be the downregulation of 5-HT_{1A}, 5-HT_{1B}, and 5-HT_{2A} *(83,84).* An influence of this receptor plasticity on the behavioral results in the knock-outs cannot be ruled out. However, whether 5-HT_{2A} receptors are also downregulated in the periphery is not known.

To further test the role of 5-HT in peripheral sensitization, we used an inflammatory model, intraplantar injection of FCA. The inflammatory reaction as measured by paw swelling was not different between genotypes. This is in accordance with previous data showing a lack of effect of 5-HT receptor antagonists on edema formation *(67,70).* Thermal hyperalgesia, which was present for 5 d in wild-type mice after FCA injection, was apparent for only 1 d in 5-HTT –/– mice. Ipsilateral tactile allodynia was equally present in both genotypes for 7 d, with a tendency for 5-HTT –/– mice to develop a contralateral reduction of withdrawal thresholds. 5-HT levels were increased in the sciatic nerves of wild-type mice but not of 5-HTT –/– mice ipsilaterally to intraplantar FCA injection *(85).* Therefore, in both models (CCI of the sciatic nerve and FCA-induced inflammation), the development of thermal hyperalgesia was dependent on an increase of 5-HT in the sciatic nerve. The peripheral nerve 5-HT content did not appear to play a role in the induction of tactile allodynia. However, these conclusions have to be drawn with caution, because data are lacking on possible changes of peripheral 5-HT receptors.

Table 1
5-HT as a Peripheral Mediator of Pain: Receptors Involved

5-HT_{1A}	Agonist induces hyperalgesia *(43).*
	Agonist induces allodynia; antagonist inhibits allodynia *(60).*
5-$HT_{1B/D}$	Agonist reduces thermal hyperalgesia in carrageenin inflammation *(61).*
	Agonist prevents capsaicin-induced hyperemia *(62).*
5-HT_{2A}	Agonist induces thermal hyperalgesia *(63).*
	Agonists enhance the algesic action of PGE_2 and noradrenalin *(55).*
	Antagonist reduces formalin induced pain *(64,65).*
5-HT_3	Antagonist reduces formalin and Freund's complete adjuvant (FCA)-induced pain *(67–69).*
	Antagonist blocks pain in carrageenin-induced inflammation *(70).*
	Topical antagonist reduces capsaicin-induced pain and hyperalgesia in human volunteers *(72).*
	5-HT3 receptor knockout mice have reduced pain-related behavior in phase 2 of the formalin test *(81).*
5-HT_4	Antagonist induces hypoalgesia in mice *(71).*
	Antagonist reduces formalin induced pain *(67).*

Mechanisms of Peripheral Actions of 5-HT

Direct and indirect mechanisms of action have been postulated. The most compelling evidence of a direct action on nociceptors was the discovery that 5-HT, like other inflammatory mediators, modulates tetrodotoxin resistant sodium

currents. 5-HT increased the magnitude of the current, shifted its conductance-voltage relationship in a hyperpolarized direction, and increased its rate of activation and inactivation *(86)*. The 5-HT_3 receptor, which has been identified as one important receptor for 5-HT actions in the periphery, differs from the others because it is a ligand-gated ion channel. Therefore, activation of this receptor might directly enhance neuronal activity. Most studies investigating physiological actions of 5-HT in the periphery found an effect on pain or on neuronal activity only in combination with other inflammatory mediators (i.e., inflammatory soup, *see* earlier). Given that 5-HT can sensitize nerve fibers to the actions of bradykinin, an effect on bradykinin receptors that either increases their sensitivity or their number might be expected. Alternatively, downstream signaling of the mediators might converge and mutually enhance the effects. Protein kinase A was identified as a factor in the signaling cascade of 5-HT after its intraplantar injection *(87)* and nitric oxide was suggested to facilitate this process in analogy to findings with PGE_2 *(88)*.

In conclusion, the release of 5-HT into inflamed or injured tissues contributes to peripheral sensitization of nerve fibers. Several 5-HT receptors are involved in this process. Further knowledge on this process may aid in the development of peripherally acting analgesic drugs.

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