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ORIGINAL PAPER

Attenuation of serotonin-induced itch by sumatriptan: possible involvement of endogenous opioids

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Abstract

Serotonin (5-hydroxytryptamine or 5-HT) is a neurotransmitter in itch and impaired serotonin signaling has been linked to a variety of itch conditions. Intradermal injection of 5-HT induces scratching behavior in mice through stimulation of 5-HT receptors. Previous studies have demonstrated that selective 5-HT1B/1D receptors agonists, including sumatriptan, inhibits neurotransmission. We have also reported that sumatriptan suppresses chloroquine-induced itch. Therefore, we investigated if sumatriptan has inhibitory effects on serotonin-induced itch in mice. Here, we show that intradermal and intraperitoneal administration of sumatriptan significantly reduce 5-HT-induced scratching behavior in mice. While intradermal injection of GR-127935, a selective 5-HT1B/1D receptors antagonist, reverses the anti-pruritic effects of sumatriptan. In addition, we show that intradermal and intraperitoneal naltrexone (NTX), a non-specific opioid receptor antagonist, and methylnaltrexone (MNTX), a peripherally acting opioid receptor antagonist, significantly decrease the 5-HT-induced scratching behavior. Additionally, combined treatment with sub-effective doses of sumatriptan and an opioid receptor antagonist, naltrexone, decreases 5-HT-evoked scratching responses. We conclude that sumatriptan inhibits 5-HT-induced itch by activating the peripheral 5-HT1B/1D receptors. Moreover, peripheral opioid receptors have a role in serotonin-induced itch, and anti-pruritic effects of sumatriptan seem to involve the opioid system. These data suggest that 5-HT1B/1D receptors agonists maybe useful to treat a variety of pathologic itch conditions with impaired serotonergic system.

Keywords Itch · Sumatriptan · 5-HT1B/1D serotonin receptors · Opioid · Mice

Introduction

Pruritus (itch) is an irritating sensation triggering a desire to scratch [3]. Serotonin, an inflammatory mediator, is secreted from skin mast cells, platelets and melanocytes [28, 45, 49], participates in acute and chronic itch [50] mediated by the histamine-independent pathway [23]. The impaired serotonergic system is also associated with a variety of pruritic skin diseases and systemic disorders including atopic dermatitis, psoriasis, allergy, uremia, and cholestasis [39]. Serotonin directly activates 5-HT receptors on sensory neurons to evoke itch [20]. Consistent with non-histaminergic nature of serotonin-induced itch, antihistamines are not effective to reduce it. A variety of 5-HT receptors subtypes expressing in sensory nerves participate in itch pathway including 5-HT2, 5-HT3, and 5-HT7 receptors. It has been reported that ondansetron and tropisetron, the 5-HT3 antagonists, reduce 5-HT-induced scratching responses in mice [40]. However, some previous studies have shown that 5-HT3

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antagonists have no anti-pruritic effects on 5-HT-induced scratching behavior in rodents and itch in humans [36, 52, 54]. A 5-HT2 antagonist, ketanserin, also reduces 5-HT-evoked scratching in mice [54]. Additionally, 5-HT7 receptor has been associated with 5-HT-induced itch in mice [33]. While, there is no data on effectiveness of 5-HT7 or 5-HT2 antagonists on itch in humans [1]. Altogether, the therapies targeting 5-HT receptors involved in pruritus must be more effective to reduce 5-HT-induced itch.

Another subtypes of serotonin receptors are 5-HT1B and 5-HT1D expressed on trigeminal ganglia and peripheral afferents in humans and rodents [8]. Activation of 5-HT1B/1D receptors, inhibits the release of pro-inflammatory neuropeptides, e.g., calcitonin gene-related peptide (CGRP) and substance P (SP), and causes neurotransmission to decrease [32]. Accordingly, triptans, the selective 5-HT1B/1D agonists, are widely used to treat migraine [10] and cluster headache attacks [30]. It seems that migraine is linked to allergic conditions associated with itch [9] and there is the possibility of common basic mechanisms underlying itch and migraine. Hence, antimigraine drugs might be effective to treat some types of itch. Given that triptans are almost safe and well-tolerated by patients [26], if effective, their use for treating pruritus would be valuable. The first reports of the possible anti-pruritic effect of triptans in guinea pig and human were published as a patent in 1996 [53] and 1998 [7]. Also, we recently showed that sumatriptan has tremendous anti-pruritic effect on chloroquine (CQ)-induced scratching behavior in mice [19]. However, its effect on 5-HT elicited itch has not yet been assessed.

Separately, it has been shown that naloxone, an opioid receptor antagonist, decreases 5-HT-induced itch in mice, presumably via a central mechanism [54]. Now it is evident that the peripheral opioid system is also associated with itch [4]. Opioid receptors are found in keratinocytes and cutaneous peripheral nerve endings which influence inflammation, proliferation, differentiation, and apoptosis of skin cells. Furthermore, opioids act on the peripheral nerve system to modulate the release of pro-inflammatory cytokines and neuropeptides [4]. Thus, we aimed to investigate whether peripheral opioid system is involved in 5-HT-induced itch. Additionally, we tested if sumatriptan is effective to inhibit 5-HT-induced scratching behavior in mice and we evaluated that whether the anti-pruritic action of sumatriptan is partially mediated through inhibition of the opioid system.

Materials and methods

Animals

5–6 weeks of age NMRI, Naval Medical Research Institute, male mice with a weight range of 23–30 g were used. Animals were obtained from Pasteur Institute, Tehran, Iran. Animals housed in a normal room temperature (23–25 °C) and regular light/dark cycle (lights on from 08:00 AM to 08:00 PM) with free access to food and water. Experiments were performed according the European Communities Council Directive of 24 November 1986 (86/609/EEC) and Guide to the Care and Use of Experimental Animals [37] with approval of committee for animal ethics and experiments at Tehran University of Medical Sciences, Tehran, Iran.

Chemicals

Sumatriptan succinate (PubChem CID 59772), serotonin hydrochloride (PubChem CID 160436), naltrexone (PubChem CID 5360515), methylnaltrexone (PubChem CID 5361918 and GR-127935) (PubChem CID 11497466) were purchased from Sigma, (St. Louis, MO, USA). All substances were dissolved in physiological saline and used freshly.

Behavioral experiments

The rostral back model is a valid model in study of itch [22] which has been used as a study method in previous literature [15, 18]. Briefly, the nape of the neck region is removed by a depilatory cream 2 days prior to the start of treatment. On treatment day, all animals are held in an acrylic box ($10 \times 10 \times 13$ cm) at 23 °C ± 1 for 1 h before behavioral test to acclimatize to the box. In all the chambers a small amount of bedding is placed. Hence, a vacuum line, smoothly pulls the air through the boxes. Intradermal (ID) treatments are administered into the shaved area in a volume of 50 µl per site using the syringes 24–25G insulin injection needles. After the injections, the mice are quickly returned into the observation chamber to record their scratching behavior for 30 min in an unmanned condition. Later, the video is played back to assess the scratching behavior by an expert observer who is blind to the details of the experiment. The scratching behavior is quantified by counting the number of lifting of the ipsilateral hind paw on the injected site. It should be noted that each mouse is used only for one test [15, 18, 38].

Drug administration

In a rostral back model, serotonin was injected intradermally at a dose of 141 nmol/site for induction of scratching behavior [40].

Sumatriptan, a selective 5-HT1B/1D receptors agonist, was administered ID at doses of 0.02 pMoles/liter (pM), 0.02, 20 and 200 nM simultaneously with 5-HT (141 nmol/site). We also injected intraperitoneal (IP) sumatriptan at a dose of 0.5 mg/kg 15 min before ID 5-HT [6, 35].

GR-127935 (20 nM, ID), a selective and competitive 5-HT1B/1D receptors antagonist [55], was concurrently injected with effective dose of sumatriptan (20 nM) and 5-HT (141 nmol/site). Additionally, GR-127935 was administered ID at dose of 20 nM simultaneously with 5-HT (141 nmol/site, ID) in mice pre-treated with systemic sumatriptan (0.5 mg/kg, IP).

Naltrexone (NTX), a non-specific opioid receptor antagonist, was injected IP at doses of 0.1 and 0.3 mg/kg 15 min before 5-HT (141 nmol/site, ID) [29, 43]. Naltrexone was also administered ID at a dose of 100 nmol/site simultaneously with 5-HT 141 nmol/site.

Methylnaltrexone (MNTX), a peripherally restricted opioid receptors antagonist, was injected IP at dose of 1 and 0.3 mg/kg, 30 min prior to 5-HT (141 nmol/site, ID). Furthermore, MNTX was injected ID at dose of 10 nmol/site simultaneously with 5-HT 141 nmol/site.

One-tenth milligram per kilogram of NTX was considered as sub-effective dose and was injected 15 min before concomitant injection of sub-effective doses of sumatriptan (0.02 nM) and 5-HT (141 nmol/site).

Data analysis

We used GraphPad Prism 6.07, the graphing and statistics software, for data analysis and drawing the figures. The obtained data were evaluated by independent *t* test and one-way ANOVA analysis of variances followed by Dunnett's test or Dunn's test for multiple comparisons. A value of $P < 0.05$ was considered to be significant and values are presented as mean ± SEM.

Results

Local and systemic sumatriptan attenuated 5-HT scratchiscratchingr

Previous studies have revealed that activation of 5-HT1B/1D receptors inhibits the neurotransmission and pain [32]. To investigate the role of 5-HT1B/1D receptors agonist, sumatriptan, in 5-HT-induced itch, a pharmacological approach was used. Intradermal co-administration of sumatriptan and 5-HT (141 nmol/site), significantly reduced the scratching behavior elicited by 5-HT, in a dose-dependent manner [$F_{(5, 42)} = 13.84$, $P < 0.0001$]. Sumatriptan was significantly effective at doses of 20 and 200 nM (Fig. 1a). Interestingly, intraperitoneal injection of sumatriptan at a dose of 0.5 mg/kg, 15 min before 5-HT (141 nmol/site, ID), significantly attenuated the scratching behavior [$F_{(2, 21)} = 63.07$, $P < 0.0001$] (Fig. 1b).

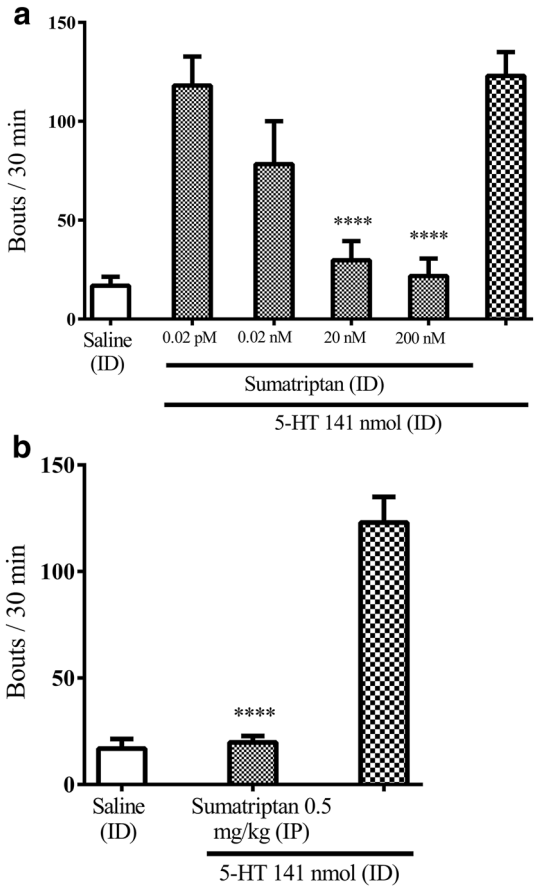

Fig. 1 Intradermal and systemic administration of sumatriptan significantly attenuate 5-HT-induced scratching behavior. **a** Bar graph shows the mean number of scratch bouts/30 min after ID injection of saline alone, 5-HT alone or 5-HT combined with sumatriptan. Intradermal administration of sumatriptan at doses of 20 and 200 nM, significantly suppressed scratching behavior induced by 5-HT 141 nmol/site (ID). Error bars are SEM ($n = 8$/group). ****$P < 0.0001$, significantly different from 5-HT-treated group (one-way ANOVA followed by Dunnett's test). **b** Systemic injection of sumatriptan significantly reduced 5-HT-induced scratching behavior. Sumatriptan (0.5 mg/kg, IP) was injected 15 min before 5-HT 141 nmol/site (ID). Error bars are SEM ($n = 8$/group). ****$P < 0.0001$, significantly different from 5-HT-treated group (one-way ANOVA followed by Dunnett's test)

GR-127935 reversed inhibitory effects of sumatriptan on scratching behavior induced by 5-HT

Administration of GR-127935 (20 nM, ID), significantly reversed the anti-pruritic effects of sumatriptan (20 nM, ID) on 5-HT-induced scratching behavior [$F_{(3, 26)} = 28.40$, $P < 0.0001$] (Fig. 2a). To exclude any possible drug reactions in combined treatment with intradermal GR-127935, sumatriptan, and 5-HT, GR-127935 was injected ID simultaneously with 5-HT (141 nmol/site, ID) in mice pre-treated with systemic sumatriptan. Intradermal GR-127935 significantly reversed the inhibitory effects of

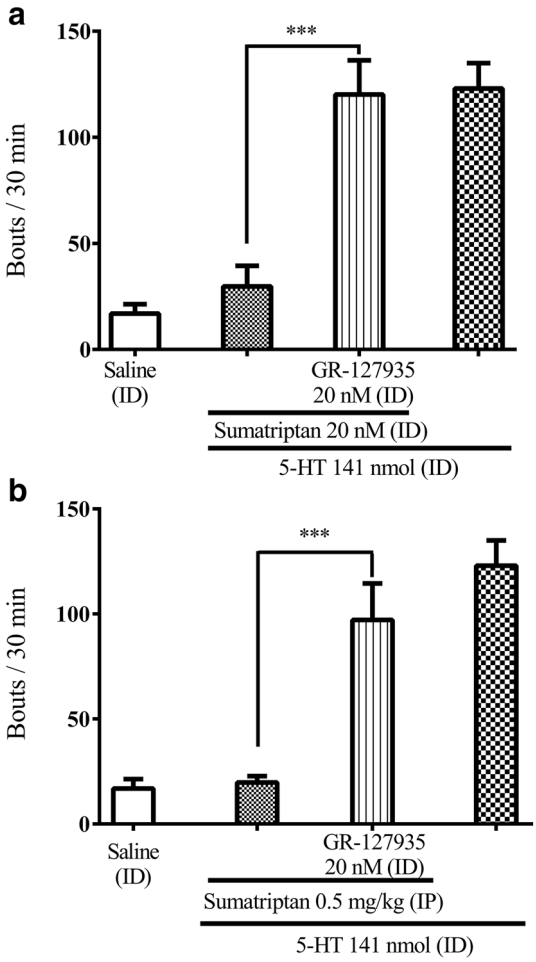

Fig. 2 Intradermal injection of GR-127935 reverses anti-pruritic effects of sumatriptan on 5-HT-induced scratching behavior. **a** Combined treatment with GR-127935 and sumatriptan significantly reversed inhibitory effects of sumatriptan on 5-HT-induced scratching behavior. GR127935 (20 nM, ID), sumatriptan (20 nM, ID) and 5-HT (141 nmol, ID) were injected concurrently in volume of 50 µl. Error bars are SEM ($n=8$/group). ***$P<0.001$, significantly different from the group treated with co-injection of 5-HT with sumatriptan (one-way ANOVA followed by Dunnett's test). **b** Intradermal injection of GR-127935 significantly reversed anti-scratching effects of systemic sumatriptan on 5-HT-induced scratching behavior. Sumatriptan (0.5 mg/kg, IP) was injected 15 min before concurrent injection of 5-HT (141 nmol/site, ID) and GR127935 (20 nM, ID). Error bars are SEM ($n=8$/group). ***$P<0.001$, significantly different from the 5-HT-treated group pre-treated with IP sumatriptan (one-way ANOVA followed by Dunnett's test)

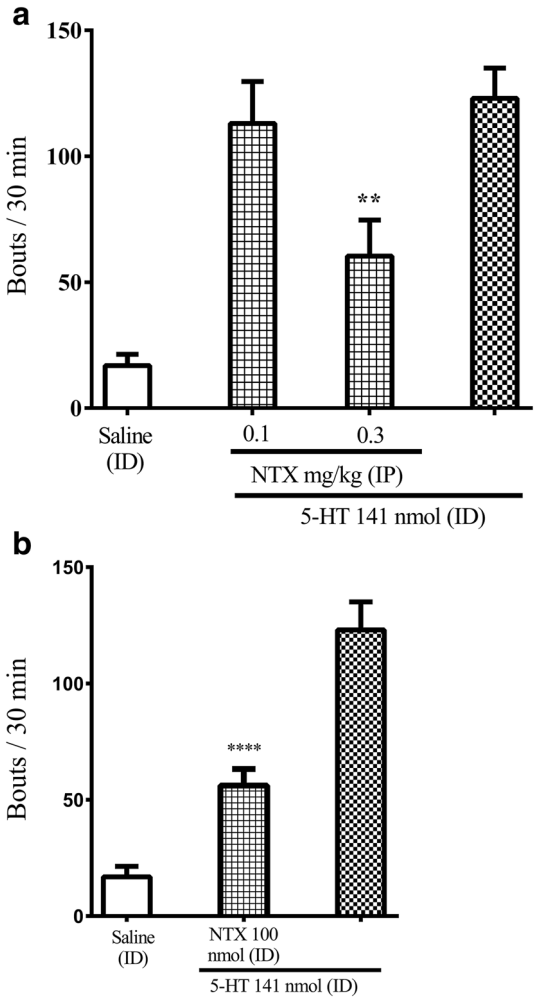

Fig. 3 Naltrexone decreases serotonin-induced scratching behavior. **a** Naltrexone significantly reduced the 5-HT-induced scratching responses. Naltrexone (0.1 and 0.3 mg/kg, IP) was injected 30 min before 5-HT 141 nmol/site (ID). Error bars are SEM ($n=8$/group). **$P<0.01$ compared to 5-HT-treated group (one-way ANOVA followed by Dunnett's test). **b** Intradermal injection of naltrexone (100 nmol/site) significantly decreased 5-HT-induced scratching behavior. Error bars are SEM ($n=8$/group). ****$P<0.0001$ compared to 5-HT-treated group (one-way ANOVA followed by Dunnett's test)

IP sumatriptan (0.5 mg/kg) on 5-HT-induced scratching responses [$F_{(3,28)}=24.50$, $P<0.0001$] (Fig. 2b). Additionally, 5-HT-induced scratching behavior was not influenced by GR-127935 (20 nM, ID) ($P>0.05$, data not shown). Furthermore, GR-127935 (20 nM, ID) per se did not ($P=0.48$) induce any significant scratching responses in mice ($P>0.05$, data not shown).

Naltrexone and methylnaltrexone decreased 5-HT scratchiscratchingr

Intraperitoneal NTX at a dose of 0.3 mg/kg, significantly decreased the scratching behavior induced by 5-HT [$F_{(3,28)}=15.01$, $P<0.0001$]. There was no significant reduction of itch responses by NTX at dose of 0.1 mg/kg IP and considered as a sub-effective dose (Fig. 3a). This is consistent with previous reports which show that opioid antagonist, naloxone, inhibits 5-HT-induced scratching behavior in mice [54]. Moreover, peripheral opioid system is associated with itch signaling and opioid receptors are found in

the skin [4]. We thus asked if peripherally restricted opioid receptors antagonists would decrease scratching behavior from serotonin. Intradermal injection of NTX (100 nmol/site) reduced the scratching behavior by 5-HT 141 nmol/site [$F_{(2,21)} = 40.22$, $P < 0.0001$] (Fig. 3b). Interestingly, our data show that intraperitoneal MNTX at dose of 1 mg/kg but not 0.3 mg/kg, significantly attenuated the serotonin-induced scratching behavior [$F_{(3, 28)} = 22.23$, $P < 0.0001$] (Fig. 4a). Furthermore, ID administration of methylnaltrexone at dose of 10 nmol/site significantly decreased 5-HT-induced scratching responses [$F_{(2, 19)} = 39.72$, $P < 0.001$] (Fig. 4b).

Involvement of peripheral opioid system in inhibitory effects of sumatriptan on scratching behavior induced by 5-HT

As sumatriptan and opioid receptors antagonists can suppress 5-HT-induced itch, we next asked if low, thus individually sub-effective doses of such compounds, would have additive effects and decrease 5-HT-induced scratching behavior. Concurrent injection of sub-effective doses of sumatriptan (0.02 nM, ID) and NTX (0.1 mg/kg, IP) significantly reduced the scratching responses elicited by 5-HT (141 nmol/site) [$F_{(3, 28)} = 11.91$, $P < 0.0001$] (Fig. 5).

Discussion

Recently, we have reported that intradermal injection of serotonin induces dose-dependent scratching behavior in mice [40]. Our present results here show that intradermal and intraperitoneal injections of sumatriptan, a 5-HT1B/1D receptors agonist, inhibit serotonin-induced scratching behavior. While, intradermal GR-127935, a potent and selective 5-HT1B/1D receptors antagonist, reverses the anti-pruritic effects of sumatriptan indicating the role for peripheral 5-HT1B/1D receptors. On the other hand, previous studies have revealed that an opioid receptor antagonist, naloxone, inhibits 5-HT-induced scratching behavior [54]. Here we extend these findings with the demonstration that peripheral opioid system is involved in serotonin-induced itch. Our data shows that intradermal and intraperitoneal injections of naltrexone, a non-specific opioid receptor antagonist, and methylnaltrexone, a peripherally restricted opioid receptor antagonist, significantly reduce the 5-HT-induced scratching behavior. In addition, combined treatment with sub-effective doses of naltrexone and sumatriptan attenuates 5-HT-evoked scratching responses. The data thus supports the role for the opioid system in anti-pruritic properties of sumatriptan on serotonin-induced itch. Given that 5-HT is associated with pruritic dermatologic and systemic diseases, targeting 5-HT1B/1D receptors may be of benefit in treating itch associated with these conditions.

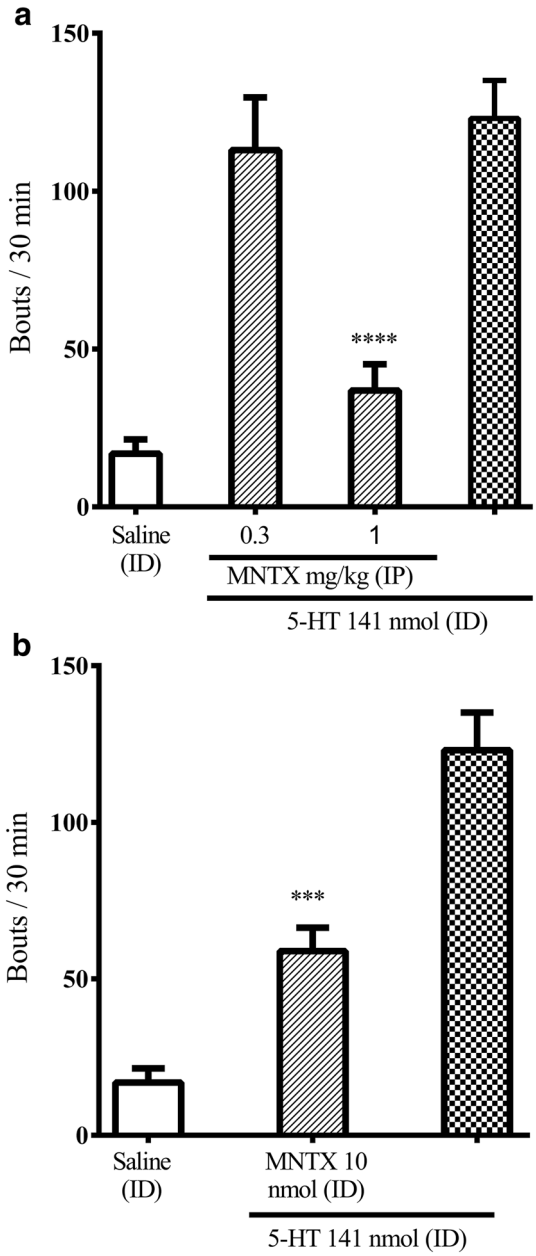

Fig. 4 Methylnaltrexone decreases serotonin-induced scratching behavior. **a** Systemic administration of methylnaltrexone significantly suppressed scratching behavior evoked by 5-HT. Methylnaltrexone (0.3 and 1 mg/kg, IP) was injected 30 min before 5-HT 141 nmol/site (ID). Error bars are SEM ($n = 8$/group). ****$P < 0.0001$ compared to 5-HT group (one-way ANOVA followed by Dunnett's test). **b** Intradermal injection of methylnaltrexone (10 nmol/site), significantly reduced 5-HT-induced scratching behavior. Error bars are SEM ($n = 8$/group). ***$P < 0.001$ compared to 5-HT-treated group (one-way ANOVA followed by Dunnett's test)

Serotonin is a known neurotransmitter of acute and chronic itch mediated by the histamine-independent pathway [20]. In the periphery, 5-HT is mainly released from skin mast cells, as a component of inflammatory soap. It

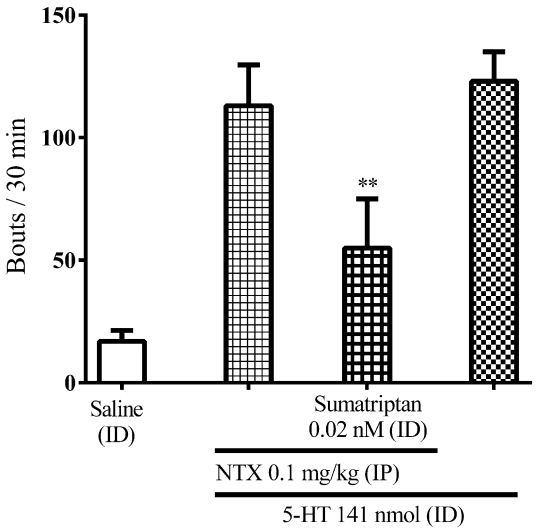

Fig. 5 The effect of sumatriptan and naltrexone on serotonin-induced scratching behavior. Combined treatment with sub-effective doses of naltrexone (0.1 mg/kg, IP) and sumatriptan (0.02 nM, ID) significantly reduced scratching behavior evoked by 5-HT 141 nmol/site (ID). Intraperitoneal naltrexone was injected 30 min before co-injection of 5-HT with sumatriptan. Error bars are SEM ($n=8$/group). $^{**}P<0.01$ compared to 5-HT-treated group (one-way ANOVA followed by Dunnett's test)

directly activates sensory afferents to induce itch, via 5-HT2, 5-HT3, and 5-HT7 receptors [48]. While, 5-HT1B/1D receptors are not well-known in itch, their crucial role in pathophysiology of migraine is evident. Recent studies report a higher prevalence of migraine in patients with pruritic allergic conditions; i.e., atopic dermatitis [34, 41], allergic rhinitis [27], and hives [9]. This suggest that some common mechanisms are shared among itch, allergy and migraine. Thus, the antimigraine drugs might be effective to treat some types of itch and allergy. Hence, studies in migraine show that sumatriptan resolves nasal mucosal swelling occur during a migraine attack [12]. A patent published in 1996, for the first time claimed that 5-HT1 agonists, partial agonists, and antagonists have anti-pruritic effects in guinea pigs with allergic conjunctivitis [53]. Later, in 1998, it was suggested that agonist of human 5HT1D receptors in a cosmetic composition is effective in preventing and treating itch, inflammation, skin irritation and erythema [7]. Morita et al. [33], then in 2015 found that 5-HT1D receptor co-regulates with chloroquine-induced itch and thus suggested this receptor to be a candidate mediator of atopic dermatitis and itch. We recently showed that sumatriptan significantly attenuates CQ-induced itch in mice through activating 5-HT1B/1D receptors and inhibition of nitric oxide pathway [19].

Except for 5-HT1B/1D receptors, stimulation of other 5-HT receptors associated with itch, excites primary sensory neurons as their antagonists suppress itch [33, 40, 54]. While 5-HT1B/1D receptors are inhibitory G-protein-coupled receptors (GPCRs) that suppress adenylate cyclase and cAMP production via Gi/Go. Decreased cAMP reducing the release of pro-inflammatory neuropeptides, including SP and CGRP, and subsequently suppressing the neurotransmission [17, 32]. Activation of G_i-protein-coupled receptors also leads to stimulation of G-coupled K^+ channels by impacting negatively on adenylyl cyclase [21, 24]. Our findings that sumatriptan suppresses the 5-HT-induced scratching behavior is also explained by inhibitory function of 5-HT1B/1D receptors agonists on neurotransmission. Although, sumatriptan is known to activate a number of 5-HT1-like receptors [42] its anti-itch effect seems to involve 5-HT1B/1D receptors since it was reversed by GR-127935. GR-127935 has a 100-fold selectivity for 5-HT1B/1D receptors with negligible affinity for 5-HT1F and 5-HT1A. It shows a non-negligible affinity for 5-HT2A receptors [51]. Although, this subtype does not seem relevant in the present study, since our results show that GR127935 at the current dose does not have any significant effects on 5-HT-induced itch. In addition, sumatriptan does not bind to 5-HT2A receptors to a significant extent [24]. The 5-HT1B/1D receptors are found on the trigeminal ganglia and peripheral afferents in humans and rodents [8]. Likewise, it has been shown that actions of triptans are not limited to trigeminal nerve and they are also effective to suppress peripheral pain [2, 6, 11, 57]. Here we showed that intradermal sumatriptan has anti-pruritic effects even at very low doses, suggesting that the skin would be the primary site of its action.

Our results also show that anti-pruritic effect of sumatriptan is partly mediated through opioid system. It is evident that peripheral opioid system participates in itch [4]. Human studies have revealed that topically applied naltrexone is effective to treat itch in patients with atopic dermatitis [5]. Interestingly, orally administered methylnaltrexone suppresses morphine-induced itch [56]. Opioid receptors are G-protein coupled receptors [31] present on cutaneous sensory fibers and non-neuronal cells of the skin including hair follicle epithelium, fibroblasts, keratinocytes, and melanocytes [4]. It has been suggested that opioid receptors have a direct role in transmission of itch signals [46]. Opioid receptors also modulate the release of pro-inflammatory cytokines and neuropeptides [4] and there are reports of pro-inflammatory effects of mu-opioid receptors activation [14]. Likewise, significantly elevated serum levels of the endogenous mu-opioid receptor–ligand and endorphin, are found in inflammatory skin diseases including psoriasis vulgaris and atopic dermatitis [16, 44]. Additionally, a number of pro-inflammatory neuropeptides which are modulated by 5-HT1B/1D receptors agonists, function through opioid system. It has been shown that the anti-nociceptive effects of CGRP is attenuated by an opioid receptor antagonist, naloxone, in rats [25]. Thus, the pro-inflammatory neuropeptides

could be considered as the link between opioid system and 5-HT1B/1D receptors.

In addition, previous studies show that triptans interact with transient receptor potential (TRP) channels, specifically TRPV1 [13]. TRPV1 is strongly associated with itch [47], thus modulating these channels might be another mechanism for action of sumatriptan in reducing itch sensation.

A limitation of this study is that rostral back model of itch used in the current study does not allow for differentiation between itch and pain behavior [22]. Considering the involvement of both serotonin and triptans in pain, it is possible that some of the inhibitory effects observed in the experiments may be a result of pain inhibition. However, sumatriptan decreases serotonin-induced itch to baseline, thus it reduces the probability of confounding effect of pain inhibition.

In conclusion, our findings show that low-dose sumatriptan is effective to diminish 5-HT-provoked itch via 5-HT1B/1D receptors. Additionally, peripheral opioid receptors are involved in serotonin-induced itch and anti-pruritic action of sumatriptan seems to involve the opioid system. Given that triptans are safe and well tolerated by patients, they might be acceptable drugs to treat itch. However, further studies are demanded to explore the exact mechanism of triptans to inhibit itch and clarify their role in pruritic diseases in humans.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Experiments were performed according the European Communities Council Directive of 24 November 1986 (86/609/EEC) and Guide to the Care and Use of Experimental Animals [37] with approval of committee for animal ethics and experiments at Tehran University of Medical Sciences, Tehran, Iran. In addition, this article does not contain any studies with human participants performed by any of the authors.

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