5-HT₃ receptors mediate inflammation-induced unmasking of functional tachykinin responses in vitro

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Moore, Kimberly A., Eun Joo Oh, and Daniel Weinreich. 5-HT₃ receptors mediate inflammation-induced unmasking of functional tachykinin responses in vitro. J Appl Physiol 92: 2529–2534, 2002. First published March 8, 2002; 10.1152/japplphysiol.00974.2001.—Exogenously applied tachykinins produce no measurable electrophysiological responses in the somata of vagal afferent neurons (nodose ganglion neurons [NGNs]) isolated from naive guinea pigs. By contrast, after in vitro antigen challenge of nodose ganglia from guinea pigs immunized with chick ovalbumin, ~60% (53 of 89) of NGNs were depolarized an average of 13 ± 1.2 mV by substance P (SP; 100 nM; n = 53). Receptor antagonists and enzyme inhibitors were utilized to screen a number of mast cell-derived mediators for their role in the uncovering or “unmasking” of functional tachykinin receptors after antigen challenge. Two chemically distinct 5-hydroxytryptamine-3-receptor antagonists significantly reduced the percentage of NGNs displaying depolarizing SP responses. Treatment with Y-25130 (1 or 10 μM) or tropisetron (1 μM) 15 min before and during antigen challenge reduced the percentage of SP-responsive neurons to ~20 and ~15%, respectively. These results suggest that activation of 5-hydroxytryptamine-3 receptors plays an integral role in the unmasking of functional tachykinin receptors after specific antigen challenge. The mediator(s) underlying tachykinin-receptor unmasking in the remainder of the NGNs has yet to be characterized. However, it does not appear to be histamine, prostanoids, or peptidoleukotrienes.

VAGAL PRIMARY AFFERENT NEURONS [nodose ganglion neurons (NGNs)] isolated from normal adult guinea pigs fail to respond electrophysiologically to exogenously applied tachykinins [e.g., substance P (SP) or neurokinin A]. This suggests that NGNs lack electrically competent neurokinin receptors: either tachykinin receptors are not present, or they are functionally uncoupled from effector ion channels. Under pathological conditions (e.g., allergic airway inflammation in vivo), however, the majority of NGNs express functional tachykinin receptors (14). Functional tachykinin receptors can also be expressed in vitro after antigenic activation of nodose ganglion mast cells: ~80% of NGNs are depolarized by SP (25). Pharmacological characterization of these newly expressed SP responses indicated that they are mediated by neurokinin-2 (NK₂) tachykinin receptors (25). This upregulation or “unmasking” of functional NK₂ tachykinin receptors that follows allergic inflammation in vitro is independent of new protein synthesis, suggesting that NK₂ tachykinin receptors are present but nonfunctional in control NGNs.

On antigenic activation, mast cells release a host of preformed (e.g., histamine, serotonin, and heparin) and de novo synthesized mediators [e.g., prostanoids and leukotrienes (5)]. Any of these inflammatory mediators acting alone, or in combination, may underlie the unmasking of functional NK₂ receptors. Previously, our laboratory has screened a number of mast cell-derived mediators for their ability to unmask functional NK₂-receptor responses by using acutely isolated NGNs (13). These studies demonstrated that exogenous serotonin [5-hydroxytryptamine (5-HT)] application could mimic the effects produced by allergic inflammation. After incubation of isolated NGNs with 5-HT (10 μM) for as little as 5 min, ~65% of the NGNs were depolarized by subsequently applied SP, acting via NK₂ receptors. Pharmacological analysis revealed that the unmasking effect of 5-HT in isolated NGNs was potent (EC₅₀ = 14 nM), was mediated by 5-HT₃ receptors, and required an intracellular calcium-nitric oxide signaling cascade.

In the present work, we ask whether 5-HT is also critical for NK₂-receptor unmasking in response to in vitro mast cell activation in the intact nodose ganglion. Our results illustrate that the percentage of SP-responsive NGNs was significantly reduced (to ~20%) when ganglia were challenged in the presence of a 5-HT₃-receptor antagonist. Incubation with a cocktail of 5-HT-receptor antagonists did not further diminish antigen-induced NK₂-receptor unmasking. These results suggest that endogenous 5-HT release and 5-HT₃-receptor activation are critical for the unmasking of SP responses provoked by in vitro allergic activation of mast cells within nodose ganglia.

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**METHODS**

*Immunization of animals.* Adult male Hartley guinea pigs (200–250 g; Charles River, Wilmington, MA) were actively immunized with ovalbumin [chicken egg albumin (OVA); Sigma Chemical, St. Louis, MO], as described previously (26). The animals were killed by asphyxiation with CO₂ as approved by the Institutional Animal Care and Use Committee of the University of Maryland, Baltimore. Nodose ganglia were dissected bilaterally and placed in ice-cold (4°C) Locke solution (composition in mM: 136 NaCl, 5.6 KCl, 1.2 MgCl₂, 2.2 CaCl₂, 14.3 NaHCO₃, 1.2 NaH₂PO₄, and 10 dextrose) equilibrated with 95% O₂-5% CO₂, pH 7.2.

In vitro antigenic challenge. Ganglia were prewarmed to 37°C in Locke solution for 10 min and then transferred to a Locke solution (37°C) containing 10 µg/ml antigen (OVA) for 15 min (23). To test the involvement of various inflammatory mediators, one of each pair of nodose ganglia (chosen randomly) was incubated with either an enzyme inhibitor or receptor antagonists 15 min before and during the OVA challenge. Ganglia were treated with either tropisetron [ICS 205–930, 1 µM (18) or Y-25130, 1 or 10 µM (14)] to block 5-HT₃ receptors; a combination of methiothepin [1 µM (9)], RS-39604 [1 µM (9)], and Y-25130 (1 µM) to nonselectively block metabotropic 5-HT receptors (19); pyrilamine (1 µM) and burimamide (50 µM) to inhibit H₁, H₂, and H₃ histamine receptors (8); indomethacin (3 µM), a cyclooxygenase inhibitor, to prevent prostaglandin synthesis; or ZD-2138 (3 µM), a 5'-lipoxigenase inhibitor, to suppress peptidoleukotriene synthesis (4). The other ganglion of the pair was treated in the same fashion, except vehicle was substituted for drug. After challenge with OVA, ganglia were returned to Locke solution (37°C) for at least 45 min before enzymatic dissociation.

*Tissue preparation.* Acutely dissociated neurons were prepared enzymatically as described (14) and maintained at 37°C for at least 8 h before recording. Nerve growth factor was prepared enzymatically as described (14) and maintained at 37°C for at least 45 min before enzymatic dissociation.

*Electrophysiological recording.* Intracellular recording, micropipette fabrication, data acquisition, and data analysis were accomplished after the procedures previously described (14). Neurons were accepted for study only if they showed a stable resting membrane potential (Eₘ; less than or equal to −50 mV) and had action potentials overshooting 0 mV. The temperature of the Locke solution flowing through the recording chamber was maintained at 33–35°C.

*Preparation of drug solutions and sources.* Drug solutions were prepared daily from concentrated (10 mM) stock solutions stored at −20°C. ZD-2138 was a gift from Zeneca (Wilmington, DE), and burimamide was a gift from Smith Kline Beecham (Philadelphia, PA). 3-Tropanyl-indole-3-carboxylic acid hydrochloride (IC5 205–930; tropisetron) was obtained from Research Biochemicals (Natick, MA). N-(1-azabicyclo[2.2.2]oct-3-yl)-6-chloro-4-methyl-3-oxo-3,4-dihydro-2H-1,4-benzoxazine-8-carboxamide (Y-25130 hydrochloride), methiothepin, and RS-39604 were procured from Tocris Cookson (Ballwin, MO). All other reagents were acquired from Sigma Chemical.

*Data analysis.* Data are expressed as means ± SE. Student’s two-tailed t-test was utilized to assess significant differences between calculated means; P ≤ 0.05 was considered significant. The z-test was utilized to compare differences in the percentage of neurons responding to SP after various treatments. Statistical analysis was performed by using Sigmastat software (Jandel Scientific, San Rafael, CA).

**RESULTS**

Antigenic activation in nodose ganglia induces functional tachykinin receptors. NGNs obtained from nodose ganglia removed from control or from actively immunized unchallenged guinea pigs rarely (<5%) show measurable membrane potential or membrane current changes to bath-applied SP (13, 14, 25). However, after antigen challenge of nodose ganglia isolated from actively immunized guinea pigs, 53 of 89 (60%) of the NGNs were depolarized an average of 13 ± 2 mV by bath-applied SP (100 nM; Fig. 1). The SP-induced membrane depolarization was accompanied by a 34 ± 4.0% decrease in membrane input resistance (Rₘ) in 72% of the NGNs in which it was monitored (n = 26 of

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**Fig. 1.** Responses produced by substance P (SP) in nodose neurons isolated from nodose ganglia challenged with ovalbumin (OVA) in the presence or absence of 5-hydroxytryptamine (5-HT₃)-receptor antagonists. A₁: in a nodose neuron from a chick OVA-challenged ganglion, a 50-s bath application of SP (100 nM; horizontal bar) evoked a membrane depolarization. Downward deflections are electronic voltage transients elicited by hyperpolarizing current pulses (100 pA, 300 ms, 0.6 Hz); the magnitude of these transients reflects membrane input resistance (Rₘ). The SP-induced depolarization was accompanied by a decrease in Eₘ. The resting membrane potential (Eₘ) and Rₘ were −62 mV and 40 MΩ, respectively. A₂: a nodose neuron from the contralateral nodose ganglion OVA challenged in the presence of tropisetron (1 µM) does not respond to SP. Resting Eₘ and Rₘ were −76 mV and 50 MΩ, respectively. Sixteen percent of neurons from tropisetron-treated ganglia responded to SP (see Table 1). B₁: electrophysiological responses to SP in nodose neurons from another animal. SP (100 nM, 40 s) depolarizes a nodose neuron isolated from the OVA-challenged ganglion to action potential threshold. Resting Eₘ was −60 mV; resting Rₘ was 20 MΩ. Electronic voltage transients were elicited by hyperpolarizing current pulses (200 pA, 300 ms, 0.6 Hz). B₂: the contralateral ganglion was incubated with Y-25130 (1 µM); a 5-HT₃-receptor antagonist chemically distinct from tropisetron) 15 min before and during OVA challenge. SP produces no measurable changes in electrophysiological properties of neurons isolated from this ganglion. Resting Eₘ and Rₘ were −72 mV and 30 MΩ, respectively. Nineteen percent of neurons from Y-25130-treated ganglia responded to SP (see Table 1).
36 neurons). In the remaining 28%, there was either no change (n = 5) or an 11 ± 2.8% increase in R_{in} (n = 5). When NGNs were voltage clamped to their E_{m} (approximately −60 mV), SP evoked an inward current averaging 955 ± 241.7 pA (n = 9) accompanied by a 55 ± 27.2% increase in membrane conductance. Resting membrane properties (E_{m}, −64 ± 0.9 mV and R_{in}, 39 ± 4.2 MΩ; n = 62) in NGNs from allergically activated ganglia were not significantly different from those recorded previously in control NGNs [E_{m}, −63 ± 0.7 mV and R_{in}, 39 ± 2.3 MΩ; n = 156 (14)].

5-HT_{3} receptors in intact ganglia are required for the unmasking of SP responses after allergenic activation. The role of 5-HT, acting via 5-HT_{3} receptors, in antigen-induced unmasking of SP responses was investigated by incubating ganglia with receptor antagonists 15 min before and during antigen (OVA) challenge. The percentage of nodose neurons depolarized by SP was significantly reduced when ganglia were challenged in the presence of the 5-HT_{3}-receptor antagonist tropisetron (1 μM; P < 0.001). Bath-applied SP evoked a membrane depolarization in 16% of nodose neurons from ganglia treated with tropisetron, compared with 64% in neurons from contralateral antigen-challenged ganglia (Table 1). The average amplitude of the SP-induced depolarization in the small percentage of neurons that responded after tropisetron treatment (11 ± 2.4 mV, n = 6) did not differ significantly (P = 0.566) from contralateral OVA-challenged ganglia (13 ± 1.8 mV, n = 18; Table 1).

Analogous results were observed when ganglia were treated with another, chemically distinct 5-HT_{3}-receptor antagonist, Y-25130 (1 μM). In this series of experiments, 54% of the neurons from OVA-challenged ganglia were depolarized an average of 13 ± 3.1 mV (n = 13) by SP (Table 1). The percentage of SP-responsive NGNs was reduced to 19% in contralateral ganglia challenged with OVA in the presence of Y-25130 (P = 0.022). However, the peak SP-induced depolarization (10 ± 1.8 mV, n = 5; Table 1) was comparable to that observed in ganglia challenged with OVA in the absence of Y-25130. The number of NGNs showing SP response was not reduced further by incubation with a mixture of 5-HT_{3}-receptor antagonists (methiothepin 1 μM, RS-39602 1 μM, and Y-25130 1 μM) to block most known 5-HT receptors (5-HT_{1}, 5-HT_{2}, 5-HT_{5}).

Sixteen percent of NGNs from ganglia challenged in the presence of the 5-HT-receptor antagonist “cocktail” displayed SP responses (15 ± 5.0 mV, n = 4), compared with 49% of NGNs from contralateral ganglia challenged in the absence of antagonists (Table 1). Increasing the concentration of Y-25130 by an order of magnitude to 10 μM and adding indomethacin (3 μM, a cyclooxygenase inhibitor) also failed to further reduce the percentage of NGNs with SP responses after antigen challenge (P = 0.687; Table 1). Twenty-six percent of NGNs from a ganglion challenged in the presence of both Y-25130 and indomethacin responded to bath-applied SP (Table 1).

The above data suggest that antigen-induced unmasking of NK_{2} responses in many NGNs is abolished when 5-HT_{3} receptors are inactivated in the nodose ganglion. However, in ~20% of the NGNs, SP still evoked depolarizing responses, despite the presence of various 5-HT-receptor antagonists (Table 1). These results imply that mediators other than 5-HT contribute to the unmasking of NK_{2} responses in intact ganglia. The experiments described below test whether several of the known mast cell-derived mediators can mediate antigen-induced SP responses.

<table>
<thead>
<tr>
<th>Drug</th>
<th>OVA (Drug Treated)</th>
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<tr>
<td></td>
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<tr>
<td>Pyrillamine (1 μM)</td>
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<tr>
<td>Burimamide (50 μM)</td>
<td>3</td>
<td>16*(6/38)</td>
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<tr>
<td>Tropisetron (1 μM)</td>
<td>2</td>
<td>19±(5/26)</td>
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<tr>
<td>Y-25130 (1 μM)</td>
<td>3</td>
<td>26(8/31)</td>
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<td>Y-25130 (10 μM)</td>
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<td>63(10/16)</td>
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<tr>
<td>Indomethacin (3 μM)</td>
<td>4</td>
<td>16*(6/37)</td>
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<td>ZD-2138 (3 μM)</td>
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Depolarization values are means ± SE. Values in parentheses represent the number of substance P (SP)-responsive neurons vs. the total number of neurons tested n. No. of animals for each condition. To examine the contribution of histamine, 5-hydroxytryptamine (5-HT), prostaglandins, and peptidoelukotrienes to allergen-induced unmasking of SP responses, one of each pair of nodose ganglia removed from an actively immunized guinea pig was challenged with ovalbumin (OVA) in the presence of selective receptor antagonists or enzyme inhibitors. The other ganglion of the pair was OVA challenged in the absence of drugs and served as a positive control. Subsequently, membrane potential changes in response to bath-applied SP (100 nM, 30–60 s) were recorded in isolated neurons by using standard intracellular recording techniques. 5-HT_{3}-receptor antagonists significantly reduced the percentage of nodose neurons with unmasked SP responses. Pyrillamine, H_{1}-receptor antagonist; burimamide, and H_{1}-receptor antagonist; tetrodotoxin (IC50 = 930), 5-HT_{2A}-receptor antagonist; Y-25130, 5-HT_{2C}-receptor antagonist; methiothepin, nonselective 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1C}, 5-HT_{1D}, and 5-HT_{1E}-receptor antagonist; RS-39604, 5-HT_{3}-receptor antagonist; indomethacin, cyclooxygenase inhibitor that prevents prostaglandin formation; ZD-2138, 5'-lipoxygenase inhibitor that prevents peptidoelukotriene synthesis. *Significantly reduced compared with contralateral OVA-challenged ganglia, P ≤ 0.05.
Histamine does not contribute to the unmasking of SP responses after in vitro allergic inflammation. Histamine is one of many mast cell-derived mediators released on specific antigen challenge of nodose ganglia (23). Histamine-receptor antagonists (H1, H2, and H3) were utilized to examine whether histamine-receptor activation contributes to the unmasking of SP responses evoked by antigenic activation. Incubation with a combination of pyrilamine (1 μM, H1-receptor antagonist) and burimamide (50 μM, at this concentration both H2 and H3 receptors are blocked) did not significantly reduce the percentage of SP-responsive NGNs or the average amplitude of the SP-induced depolarization (P = 0.492 and 0.668, respectively; Table 1). Fifty percent of NGNs from ganglia that were antigen challenged in the presence of histamine-receptor antagonists were depolarized 14 ± 3.0 mV (n = 9) by SP. Sixty-two percent of NGNs from contralateral ganglia challenged in the absence of antagonists were depolarized an average of 17 ± 2.5 mV (n = 13) by SP.

De novo synthesized prostanoids and peptidoleukotrienes do not contribute to allergen-induced unmasking of SP responses. A number of inflammatory mediators are synthesized de novo on antigenic activation of mast cells. The contribution of some of these lipid mediators to antigen-induced unmasking of SP responses was examined by using enzyme antagonists. As described above, indomethacin (3 μM, a cyclooxygenase inhibitor) was ineffective in reducing the percentage of SP-responsive NGNs observed after OVA challenge of nodose ganglia. These results suggest that prostanoids do not play a role in the unmasking of functional tachykinin receptors in NGNs.

Peptidoleukotrienes also do not appear essential for antigen-induced unmasking of SP responses. Inhibition of 5'-lipoxygenase by ZD-2138 (3 μM) during OVA challenge of nodose ganglia did not significantly reduce (P = 0.594) the percentage of cells with unmasked SP responses (63% after antigen challenge with ZD-2138 present vs. 67% in contralateral antigen-challenged ganglia; Table 1). Furthermore, the amplitude of unmasked SP responses recorded in NGNs isolated from ganglia antigenically activated in the presence of ZD-2138 was not significantly different from that recorded in NGNs from contralateral OVA-challenged ganglia (P = 0.529; Table 1).

DISCUSSION

Our principal finding is that the unmasking of NK2 tachykinin receptors in nodose neurons (NGNs) by allergic inflammation in the nodose ganglia in vitro requires activation of 5-HT3 receptors. Both tropisetron and Y-25130, two chemically distinct 5-HT3-receptor antagonists, substantially reduced the percentage of NGNs expressing NK2 receptors after specific antigen challenge. SP application does not evoke measurable membrane potential changes in NGNs from naive animals or from immunized, but nonantigen challenged, animals. Subsequent to OVA challenge of the ganglia, SP depolarizes 59% of nodose neurons. In the presence of 5-HT3-receptor antagonists, NK2 receptors are unmasked in only ~20% of NGNs. Thus it appears that 5-HT3-receptor activation mediates two-thirds of the NK2-receptor unmasking observed after antigenic challenge. The mediator(s) responsible for upregulation of NK2 receptors in the remaining 20% of NGNs is unknown. However, it appears from the present work that histamine, prostanoids, and peptidoleukotrienes are not essential for the functional expression of tachykinin receptors after acute allergic inflammation.

Endogenous source of 5-HT. Given that 5-HT3-receptor activation is essential for NK2-receptor unmasking in the majority of NGNs, release of 5-HT on antigenic activation is requisite. There are several potential sources of 5-HT in the nodose ganglion, including mast cells, platelets, and NGNs themselves. Most reports suggest that guinea pig mast cells do not contain appreciable levels of 5-HT (17). However, the EC50 for 5-HT-induced unmasking of tachykinin receptors is ~15 nM (13). Therefore, mast cell 5-HT content could be relatively low but still achieve a concentration in the ganglionic extracellular space [0.4 ml/g (6)] sufficient to unmask NK2 receptors. One group (12) has reported that the concentration of 5-HT in trigeminal ganglion mast cells of the guinea pig was 66 nmol/kg wet wt. If nodose ganglion mast cells contain similar levels of 5-HT and antigen challenge releases ~15% of granular-stored 5-HT (23), then the 5-HT concentration in the ganglion could reach 25 nM. This estimate is approximately two times the EC50 for 5-HT-induced unmasking of NK2-receptor unmasking in isolated NGNs (13). Another possibility is that antigen-mediated activation of ganglionic mast cells evokes 5-HT release indirectly, through a multicellular cascade involving platelets. Antigenic activation of mast cells elicits the release of a number of lipid-derived mediators, including platelet-activating factor (PAF) (24). PAF can mobilize 5-HT from platelets and thus may evoke NK2-receptor unmasking. It is noteworthy that incubation of nodose ganglia isolated from nonimmunized guinea pigs with PAF (0.1–1 μM, 30 min) resulted in the unmasking of SP responses in ~40% of neurons (n = 15 of 39 neurons; unpublished observations). However, the actions of exogenously applied PAF were not blocked by tropisetron (1 μM), suggesting that PAF-induced unmasking of SP responses may not be mediated through 5-HT. Furthermore, PAF (1 μM) also induced SP responses in 50% (n = 3 of 6) of acutely isolated NGNs (i.e., under conditions in which platelets are absent), suggesting that this unmasking effect may be either through PAF receptors on NGNs or a nonselective lipid effect.

NGNs represent yet another source of 5-HT in the nodose ganglion. 5-HT immunoreactivity was found in neurons scattered throughout feline nodose ganglia (7). By contrast, in the rat nodose ganglia, 5-HT immunoreactivity is only observed after pretreatment with the 5-HT precursor, 5-hydroxytryptophan methyl ester hydrochloride (16). Furthermore, rat NGNs lack tryptophan hydroxylase immunoreactivity, suggesting that they do not synthesize 5-HT endogenously (27). Be-
cause 5-HT immunoreactivity has not been examined in guinea pig nodose ganglia, it is unknown whether there are neuronal 5-HT stores that could contribute to NK2-receptor unmasking.

Other inflammatory mediators involved in antigen-induced NK2-receptor unmasking. In the absence of 5-HT3-receptor activation, allergic inflammation in the nodose ganglion still elicits unmasking in ~20% of neurons. Incubation with a prostaglandin mixture (PGE2, PGF2α, PGD2; 1 μM each) unmasked depolarizing SP responses in ~20% of acutely isolated nodose neurons (13), suggesting that prostanoids may mediate the remainder of NK2-receptor unmasking. However, it does not appear that endogenously released prostaglandins contribute to antigen-induced unmasking of SP responses in intact ganglia. When cyclooxygenase was used to inhibit the synthesis of prostanoids during antigenic activation of the ganglia, there was no measurable reduction in the percentage of neurons with SP responses. It will be interesting to learn whether selective prostaglandin-receptor antagonists prevent prostaglandin-induced unmasking in isolated NGNs.

Mast cells release a number of other granule-stored and de novo synthesized mediators that we have not yet surveyed. Any one, or perhaps a combination of these, may account for the unmasking of SP responses in the remaining 20% of neurons. Previously, using acutely isolated NGNs, we screened a number of inflammatory mediators for the ability to evoke unmasked SP responses (13). We do not expect that heparin and nerve growth factor, two other granular-stored mast cell mediators, will contribute to allergen-induced tachykinin-receptor unmasking in nodose ganglia (unpublished observations). However, there are an abundance of other mast cell mediators that are potential candidate unmasking factors, including inflammatory cytokines [e.g., tumor necrosis factor-α and the interleukins (20)]. Interestingly, tumor necrosis factor-α and interleukin-1 have been linked to increases in neuronal tachykinin (SP) content (21) and may perhaps also regulate tachykinin receptors in NGNs (2).

Functional importance of unmasking tachykinin receptors in vagal afferents. After allergic airway inflammation in vivo, profound changes occur in airway-projecting guinea pig NGNs. A phenotypic switch in neurotransmitter type occurs wherein NGNs projecting to the airway begin expressing tachykinin mRNA and protein (3, 11), and NGNs develop newly functional NK2 receptors that evoke depolarizing responses (14). To date, these inflammation-induced changes have been characterized only in the somata of the NGNs; whether a similar upregulation of the tachykininergic systems occurs at peripheral and central nerve terminals of these afferents remains undetermined. It is well documented that tachykinins are released from primary sensory nerve cell bodies (10, 15, 22). In guinea pig trigeminal ganglia, KCl, capsaicin, or nerve impulses release SP, and unilateral orofacial inflammation greatly increased both basal and evoked SP release from the inflamed side (15). Thus inflammation-induced unmasking of functional NK2 receptors may allow excitatory autoreceptor signaling and/or permit extrasynaptic communication between primary sensory somata. The existence of chemical communication between dorsal root somata is well documented (1), and similar chemical “cross talk” may also exist between NGNs (unpublished observations). Whether the tachykininergic system contributes to cross talk remains to be tested.

In conclusion, 5-HT, a proinflammatory neurotransmitter, can activate 5-HT3 receptors to depolarize vagal afferent neurons. Activation of 5-HT3 receptors can, in addition, sensitize vagal afferents to SP, a pain-producing neurotransmitter, via the unmasking of tachykinin receptors. The rapid and long-lasting unmasking of functional tachykinin receptors in a large number of vagal primary afferent neurons represents a potential mechanism for the persistent sensitization of visceral sensory neurons by inflammation.

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