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Histamine H_3 receptor activation inhibits neurogenic sympathetic vasoconstriction in porcine nasal mucosa

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Abstract

Histamine release from mast cells is a primary mediator of rhinorrhea, nasal mucosal swelling, increased secretion, sneezing, pruritis and congestion that occur in allergic rhinitis. It is well known that histamine H_1 receptor antagonists inhibit the itch and rhinorhea, but do not block the allergic nasal congestion. A growing body of evidence shows that in addition to histamine H_1 receptors, activation of H_3 receptors may contribute to the procongestant nasal actions of histamine. Activation of the prejunctional histamine H_3 receptor modulates sympathetic control of nasal vascular tone and resistance. The present study was conducted to further characterize the role of histamine H_3 receptors on neurogenic sympathetic vascular contractile responses in isolated porcine nasal turbinate mucosa. We presently found that the histamine H_3 receptor agonist, (*R*)-α-methylhistamine (10–1000 nM), inhibited electrical field stimulation-induced sympathetic vasomotor contractions in a concentration-dependent fashion. Pretreatment with either of the selective histamine H_3 receptor antagonists, thioperamide and clobenpropit, blocked the sympathoinhibitory effect of (*R*)-α-methylhistamine in porcine turbinate mucosa. The effect of compound 48/80, an agent that elicits the release of endogenous histamine from mast cells on nasal sympathetic contractile responses, was also tested. The action of compound 48/80 to release mast cell-derived histamine in the nose mimics many of the nasal responses associated with allergic rhinitis, extravascular leakage and decreased nasal patency. We presently found that compound 48/80 also inhibited the electrical field stimulation-induced sympathetic response. Pretreatment with the H_3 receptor antagonist clobenpropit blocked the sympathoinhibitory action of compound 48/80 on sympathetic contractile responses in nasal mucosa. Taken together, these studies indicate that histamine H_3 receptors modulate vascular contractile responses by inhibition of noradrenaline release from sympathetic nerve terminals in nasal mucosa. It is further suggested that histamine H_3 receptors may play a role in the regulation of vascular tone and nasal patency in allergic nasal congestive disease.

Keywords: Histamine H_3 receptor; Nasal mucosa; Porcine; Sympathetic; Thioperamide

1. Introduction

Allergic rhinitis is the most common chronic immunologic disease in humans (Howarth, 1995). Allergic rhinitis can be triggered by perennial or seasonal allergens such as house dust, animal dander, mold spores and pollen. Encounter with the allergen in sensitized individuals induces sneezing, nasal itch, rhinorrhea, nasal blockage, glandular hypersecretion, increased vascular permeability and the infiltration of inflammatory cells (Kaliner, 1994). In this proinflammatory cascade, mast cells play an essential role in promoting the response to allergen. Upon antigen cross-linkage of immunoglobulin E (IgE), mast cells are activated; they degranulate and release their stored mediators (Christodoulopoulos et al., 2000). Furthermore, during prolonged, recurrent and chronic nasal allergic inflammation, histamine may be chronically released, leading to persistent activation of histamine receptors that further promote the proinflammatory pathophysiology of allergic congestive nasal disease (Baraniuk, 1998).

Histamine is an ubiquitous autocoid, primarily associated with mast cells, that is widely distributed in peripheral mammalian tissues. In the nose, mast cell-derived histamine acts on histamine H_1 receptors on endothelial cells to increase vascular permeability leading to the rhinorrhea

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that occurs in acute allergic rhinitis. Activation of postjunctional histamine H_1 receptors also elicits glandular mucus production, itch and activation of parasympathetic reflexes.

Nasal mucosal blood vessels receive rich sympathetic innervation, and noradrenaline is the neurotransmitter mediating the vasoconstrictor events and regulation of vasculature in postganglionic perivascular sympathetic nerves (Eccles and Eccles, 1981; Stjärne et al., 1991). Airflow through the nasal passages is regulated by the state of engorgement of the venous erectile tissue in the nasal turbinates (Widdicombe, 1986; Bende and Laurin, 1986; Corey et al., 2000). Vascular swelling and engorgement of nasal mucosal erectile tissue leads to the resultant decrease in nasal patency and increased nasal resistance causing nasal congestion (Eccles, 1982).

Prophylactic treatment with sympathomimetics to reduce the vascular swelling that occurs in allergic rhinitis reduces the congestion, but does not ameliorate the increased nasal secretions, itching and sneezing, indicating that vascular congestion is regulated independently of the effector system regulating nasal secretions (International Rhinitis Management Working Group, 1994).

Nasal blood vessels of various species have been shown to receive dense innervation of sympathetic nerves. Activation of the sympathetic nerve section results in increased nasal blood flow in rats (Kawarai and Koss, 2001), cats and dogs (Lacroix et al., 1994a,b). Histamine H_3 receptors are widely distributed on peripheral autonomic nerves and found presynaptically on postganglionic sympathetic nerve terminals. Activation of prejunctional histamine H_3 receptors on the sympathetic nerve terminals inhibits noradrenaline release leading to vasodilatation (Hey et al., 1992; McLeod et al., 2001). This mechanism has been proposed to contribute to the nasal procongestant effect of histamine in vivo (McLeod et al., 1999a,b; 2001). The present study was conducted to determine the role of prejunctional histamine H_3 receptors on sympathetic contractile effector responses in isolated porcine turbinate nasal mucosa.

2. Materials and methods

2.1. Tissue preparation of pig nasal turbinate

Turbinate strips were prepared from isolated turbinate from domestic pig snouts. Abattoir porcine turbinate was provided by Animal Parts (Scotch Plains, NJ, USA). The snouts used were obtained from male and female pigs (250–500 lb). Fresh tissue was shipped on wet ice in Leibovitz's L-15 solution (Gibco, Grand Island, NY, USA) and was received ≤ 2 h after removal. Turbinate strips were cut to a length of 2 cm by 0.5 cm wide. Turbinate mucosa strips were tied with 6–0 silk at each end and attached to tissue supports. Tissue supports were used to anchor each tissue in a 25 ml bath (Radnoti Glass Technology, Monrovia, CA, USA). Tissues were then attached to Grass FT-03 model force displacement transducers (AstroMed, West Warwick, RI, USA) for continuous recording of isometric tension. Tissue responses were recorded using an AstroMed recorder (model K2G, AstroMed).

2.2. Functional bioassay

Baths were filled with 37 °C Krebs' buffer (118 mM NaCl, 4.7 mM KCl, 1.2 mM $MgSO_4$, 1.2 mM KH_2PO_4, 24.9 mM $NaHCO_3$, 11.1 mM glucose, 2.55 mM $CaCl_2$), continuously aerated with 95% O_2/5% CO_2 gas. Chlorpheniramine (1 μM) and cimetidine (1 μM) were added to the buffer to block histamine H_1 and H_2 receptor-mediated effects, respectively. Tissues were equilibrated and washed twice at 2.0 g initial tension for 1 h. Tissue responsiveness was then tested with noradrenaline (100 μM) after 1 h followed by three additional washings. Only tissue strips that responded to noradrenaline were used in these experiments. Studies to evaluate the effects of antagonists on (*R*)-α-methylhistamine-induced inhibition of sympathetic responses in pig turbinate strips were performed as follows: (*R*)-α-methylhistamine, histamine H_3 receptor agonist, was tested against electrically induced prazosin-sensitive, sympathetic contractions. Voltage was adjusted accordingly to produce contractile responses that were approximately 50% of the maximum electrically field stimulation-induced contraction response. Antagonist equilibration time was one h before the start of (*R*)-α-methylhistamine challenges. Electrical field stimulation of porcine nasal mucosa was run for 30 min in the absence or presence of (*R*)-α-methylhistamine, followed by 30 min in the presence of prazosin (1 μM). In separate experiments, porcine nasal mucosa was electrically field stimulated for 30 min in the absence or presence of compound 48/80, followed by a 30 min incubation with prazosin (1 μM).

2.3. Data analysis and statistics

Data was taken as percent inhibition of the noradrenergic (prazosin-sensitive) portion of electrical field stimulation (blocked with prazosin). Activity in the functional bioassay was expressed as a percent of antagonist blockade of the (*R*)-α-methylhistamine-induced inhibition of the electrical field stimulation contractile responses. Values displayed in the table and the figures represent the mean ± S.E.M. Statistical significance is achieved with $P < 0.05$ using a one-way analysis of variance (ANOVA) in conjunction with a Dunnett's *t*-test.

2.4. Materials

Noradrenaline, (*R*)-α-methylhistamine, clobenpropit, thioperamide, tetrodotoxin and compound 48/80 were obtained

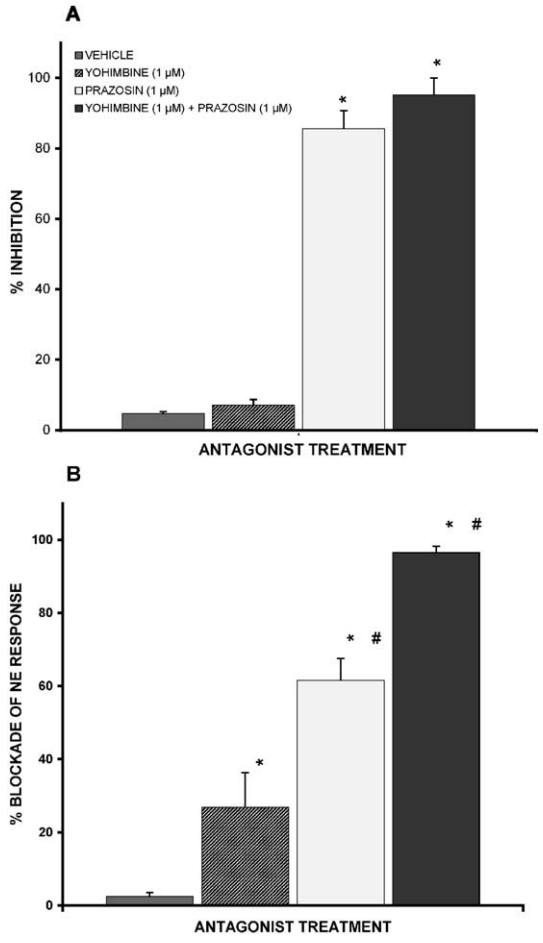

Fig. 1. (A) Percent inhibition of electrical field stimulation-induced contractions by yohimbine (1 μM, $n=4$); prazosin (1 μM, $n=4$); combined yohimbine + prazosin (1 μM, $n=4$); or vehicle ($n=4$). (B) Percent blockade of exogenous noradrenaline contractions (10 μM) with yohimbine 1 μM ($n=4$), prazosin 1 μM ($n=5$), or a combination of yohimbine 1 μM + prazosin 1 μM ($n=4$). Values are mean ± S.E.M. of individual tissue responses. (*) Significantly different from vehicle; (#) significantly different from yohimbine (1 μM); $p<0.05$.

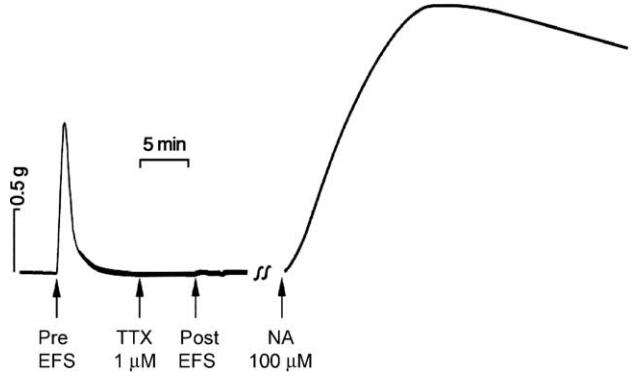

Fig. 2. Representative polygraph of electrical field stimulation-induced contractile response in isolated porcine nasal mucosa. Pre- and posttreatment effect tetrodotoxin on electrical field stimulation are shown. Following the tetrodotoxin (1 μM) treatment, addition of exogenous noradrenaline elicited a contractile response.

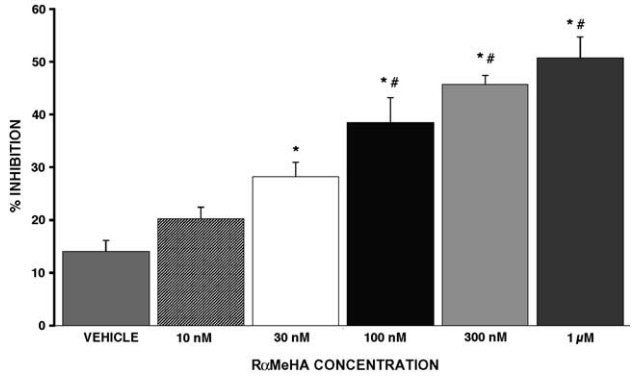

Fig. 3. Inhibition of electrical field stimulation-induced contraction due to (*R*)-α-methylhistamine. Bars represent the mean ± S.E.M. of individual tissue responses ($n=8–21$). (*) Significantly different from vehicle; (#) significantly different from 10 and 30 nM (*R*)-α-methylhistamine; $p<0.05$.

from RBI/Sigma (St. Louis, MO, USA). RPMI and L-15 were purchased from Gibco.

3. Results

The inhibition of electrical field stimulation-induced contraction was evaluated with α_1-adrenoceptor antagonist prazosin and α_2-adrenoceptor antagonist yohimbine in porcine nasal mucosa. Prazosin (1 μM), as well as the combination of yohimbine (1 μM) and prazosin (1 μM), inhibited the electrical field stimulation-induced contraction by 86% and 95%, respectively (Fig. 1A). Electrical field stimulation contraction of the porcine nasal mucosa was not significantly inhibited with yohimbine (1 μM) given alone (Fig. 1A). In contrast, the contractile effect of exogenous noradrenaline on porcine nasal mucosa was partially blocked by yohimbine (27%) and prazosin (62%), given alone, respectively. Furthermore, the combination of yohimbine and prazosin completely blocked the noradrenaline response (97% blockade, Fig. 1B). In addition, electrical field stimulation-induced contractions were completely inhibited with tetrodotoxin (1 μM), a selective neuronal Na^+ channel blocker (Fig. 2). Tetrodotoxin (1 μM) did not inhibit the contractile response to exogenous noradrenaline (Fig. 2).

Table 1
Effect of (*R*)-α-methylhistamine (300 nM) on contractions due to exogenous noradrenaline in nasal mucosa

	Tension (gm)	Percent of noradrenaline contraction
Pre-noradrenaline contraction	0.95 ± 0.08	–
Post-noradrenaline contraction (vehicle)	0.93 ± 0.19	98.1%
Post-noradrenaline contraction ((*R*)-α-methylhistamine)	0.93 ± 0.08	97.9%

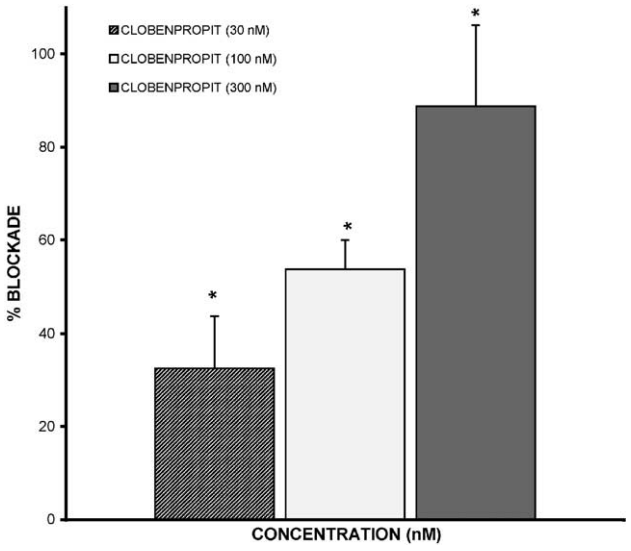

Fig. 4. Effect of the histamine H_3 receptor antagonist clobenpropit on (*R*)-α-methylhistamine (300 nM) inhibition of electrical field stimulation-induced contraction in porcine mucosa. Bars represent the mean ± S.E.M. of individual tissue responses ($n = 5–6$). (*) Significantly different from vehicle; $p < 0.05$.

In separate studies, treatment with the selective histamine H_3 receptor agonist, (*R*)-α-methylhistamine, inhibited electrical field stimulation-induced sympathetic porcine nasal mucosa contractile responses in a concentration-dependent manner (10–1000 nM; Fig. 3). The maximum inhibitory effect that was observed with (*R*)-α-methylhistamine was 51% at 1 μM (Fig. 3). A near maximal concentration of (*R*)-α-methylhistamine (300 nM) did not inhibit contractions due to exogenous noradrenaline (10 μM) (Table 1). Pretreatment with the selective histamine H_3 receptor antagonist clobenpropit at 30, 100 and 300 nM blocked the inhibitory

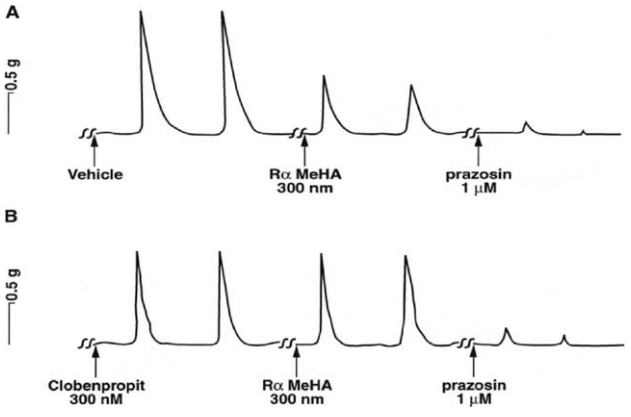

Fig. 5. (A) Representative tracing of electrical field stimulation-induced contraction in porcine nasal mucosa. Electrical field stimulation-induced contractions were inhibited with (*R*)-α-methylhistamine (300 nM). (B) Selective histamine H_3 receptor antagonist, clobenpropit (300 nM), blocked the inhibition due to the histamine H_3 receptor agonist (*R*)-α-methylhistamine (300 nM). The noradrenergic portion of the electrical field stimulation-induced contraction was blocked by the α_1-adrenoceptor antagonist prazosin (1 μM).

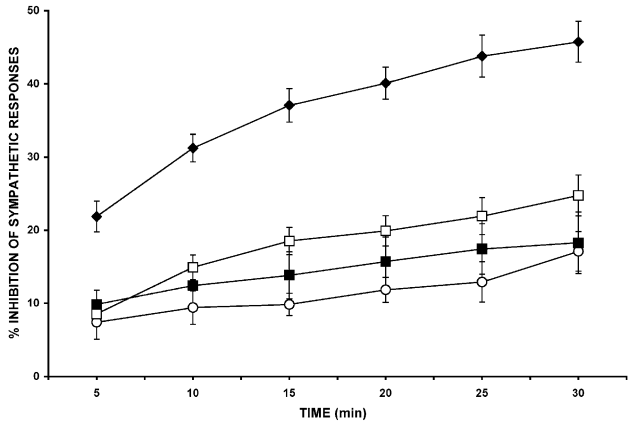

Fig. 6. Activity of H_3 receptor antagonists, clobenpropit (300 nM; ■, $n = 6$), thioperamide (300 nM; □, $n = 5$) and vehicle (○, $n = 8$) on the inhibitory effect of (*R*)-α-methylhistamine (300 nM; ◆, $n = 10$) against neurogenic sympathetic contractile responses in porcine nasal mucosa. Values are the mean ± S.E.M. of individual tissue responses. (*) Clobenpropit and thioperamide groups are significantly different from (*R*)-α-methylhistamine alone group; $p < 0.05$.

effect of 300 nM of (*R*)-α-methylhistamine by 33%, 54% and 89%, respectively (Figs. 4 and 5). The histamine H_3 receptor antagonists, clobenpropit (300 nM) and thioperamide (300 nM), both blocked the inhibitory action of (*R*)-α-methylhistamine (300 nM) on electrical field stimulation-induced contractions (Fig. 6). Thioperamide (300 nM) or clobenpropit (300 nM), given alone, did not significantly affect the electrical field stimulation-induced responses ($n = 6$, data not shown).

Compound 48/80, a mast cell histamine-releasing agent, was used to evaluate the effect of the release of endogenous histamine on electrical field stimulation-induced responses in isolated porcine nasal mucosa. Compound 48/80 (1%)

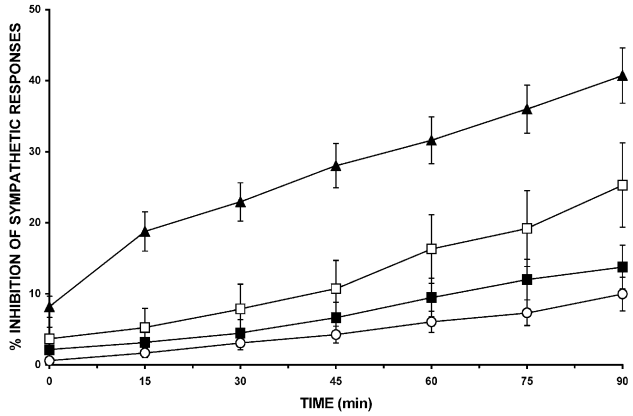

Fig. 7. Activity of clobenpropit (0.3 μM □ and 3 μM ■; $n = 10–12$) and vehicle (○, $n = 10$) on the inhibitory effect of compound 48/80 (1% ◆; $n = 15$) on neurogenic sympathetic contractile responses in porcine nasal mucosa. Values are the mean ± S.E.M. of individual tissue responses. Clobenpropit (0.3 μM, 0–75 min) and clobenpropit (3 μM, 0–90 min) are significantly different from the respective time points in the compound 48/80 group; $p < 0.05$.

inhibited the electrically induced sympathetic responses porcine nasal turbinate by approximately 40%. Pretreatment with histamine H_3 receptor antagonist clobenpropit (300 nM and 3 μM) blocked the effect of compound 48/80 in a concentration-dependent manner, over the 90-min time course (Fig. 7). Also, compound 48/80 (1%), given alone, did not inhibit contractions due to exogenous noradrenaline (10 μM). Both the post-noradrenaline contractions in the vehicle group and the compound 48/80 (1%) group were 97% of the pre-noradrenaline contraction ($n = 5$; data not shown).

4. Discussion

The present findings demonstrate the presence of functional presynaptic histamine H_3 receptors on sympathetic nerve terminals that regulate neurogenic vasomotor contractility in porcine nasal mucosa. Specifically, activation of prejunctional histamine H_3 receptors most likely inhibited the electrical field stimulation-evoked sympathetic vascular contractile responses by inhibiting the release of noradrenaline from sympathetic nerve terminals. These findings are consistent with earlier studies in human saphenous vein showing histamine H_3 receptor inhibition of sympathetic nerve-derived noradrenaline release from sympathetic nerve terminals (Göthert et al., 1984; Molderings et al., 1992) and sympathetic evoked contractions in human saphenous vein (Valentine et al., 1999). These findings also represent the first study to show the functionally active histamine H_3 receptors in isolated turbinate nasal mucosa.

These results are consistent with the evidence indicating that activation of prejunctional histamine H_3 receptors inhibits endogenous sympathetic tone to the nasal blood vessels, thereby causing a decrease in neurotransmitter release (i.e. noradrenaline), an action that contributes to vasodilatation. Thus, prejunctional histamine H_3 receptors may play an important physiologic role in the regulation of vascular tone and nasal resistance. For example, activation of the H_3 receptor with (*R*)-α-methylhistamine modulates sympathetic control of nasal blood flow and nasal resistance in the cat (Hey et al., 1998; McLeod et al., 2001). The present in vitro findings in porcine nasal mucosa are consistent with a sympathoinhibitory mechanism mediated by activation of prejunctional histamine H_3 receptors that contribute to vasodilation, as has been suggested to occur in vivo (Hey et al., 1992; Hutchison and Hey, 1994; McLeod et al., 1999a,b; 2001). In further support, activation of peripheral histamine H_3 receptor has also been shown to be an important presynaptic modulator of other sympathetic effector systems such as renal noradrenergic neurotransmission in dogs (Yamasaki et al., 2001), the cat nictitating membrane (Koss and Hey, 1992), human saphenous vein (Molderings et al., 1992), human heart (Imamura et al., 1995) and guinea pig ileum (Valentine et al., 1999), and guinea pig vas deferens (Luo et al., 1994).

It is known that in vascular smooth muscle tissue, α_1-adrenoceptors occur postsynaptically, where they are activated by neurally released noradrenaline from sympathetic nerve endings. In contrast, postsynaptic α_2-adrenoreceptors are predominately located extrajunctionally and are preferentially activated by circulating catecholamines, particularly adrenaline (Langer et al., 1980; Yamaguchi and Kopin, 1980; Guimaraes and Moura, 2001). Consistent with this, the α_2-adrenoceptor antagonist yohimbine produced a partial blockade of the exogenous noradrenaline-induced response, while it did not affect sympathetic responses due to electrical field stimulation. In turn, the α_1-adrenoceptor antagonist prazosin significantly inhibited both the noradrenaline-induced contraction and the electrical field stimulation. The combination of the α_1- and α_2-adrenoceptor antagonists, prazosin and yohimbine, completely blocked the contraction due to exogenous noradrenaline. These results are also consistent with studies showing that the sympathetic regulation of vascular responses in dog and human nasal mucosa is also mediated by postjunctional α_1- and α_2-adrenergic vasoconstrictor tone (Andersson and Bende, 1984; Berridge and Roach, 1986; Johannssen et al., 1997). Taken together, this shows that the electrical field stimulation-induced contraction, an event mediated by release of endogenous noradrenaline from sympathetic nerve terminals, is predominately mediated by α_1-adrenoceptors, while the contractile responses elicited by exogenous noradrenaline were mediated by both α_1- and α_2-adrenoceptor activation. This finding is in agreement with a study by Yamaguchi and Kopin (1980) who showed in the pithed rat that the pressor response to sympathetic nerve stimulation is the result of activation of α_1-adrenoreceptors, whereas α_2-adrenoreceptors mediate the pressor effect due to exogenous catecholamines. Evidence of postjunctional α_2-adrenoceptor-mediated contractile responses have also been demonstrated in the isolated rabbit ear vein (Daly et al., 1988). In further agreement, Langer et al. (1980) showed in the autoperfused hind limb of the dog that prazosin blocked the responses to sympathetic stimulation, whereas responses to injected noradrenaline were largely unaffected. Hind limb pressor responses to exogenous noradrenaline were inhibited with the selective α_2-adrenoceptor antagonist rauwolscine and further reduced by prazosin. Moreover, sympathetic control of nasal vascular tone in the rat has been shown to be mediated exclusively by activation of α_1-adrenoceptors (Kawarai and Koss, 2001). The present findings indicate that sympathetic regulation of vascular tone in the nose shows a similar pattern of adrenergic control, namely, that neuronally release noradrenaline acts mainly upon α_1-adrenoreceptors, whereas exogenous noradrenaline (and adrenaline) acts postsynaptically on α_1- and α_2-extrajunctional adrenoreceptors.

Presently, we found that electrical field stimulation-induced contractions were inhibited with the selective histamine H_3 receptor agonist (*R*)-α-methylhistamine in the porcine nasal mucosa, whereas exogenous noradrena-

line-induced contractions (10 μM) were not attenuated. These results demonstrate that in nasal mucosa the histamine H_3-receptor is located presynaptically because the endogenous neuronal mediated event (electrical field stimulation-induced contractions) was inhibited with (*R*)-α-methylhistamine, whereas the exogenously induced contractions with noradrenaline were not attenuated by (*R*)-α-methylhistamine.

Treatment with tetrodotoxin (1 μM, a selective sodium channel blocker that inhibits neuronal action potential propagation and neurotransmission) completely abolished the electrical field stimulation-induced contractile responses, but did not affect the contractions mediated by exogenous noradrenaline. These findings provide further support for a presynaptic site of action which is in agreement with the known location of peripheral histamine H_3 receptors on sympathetic nerve terminals (Göthert et al., 1984; Molderings et al., 1992; Valentine et al. 1999).

Compound 48/80 was presently used for its action as a potent releaser of endogenous, mast cell-derived histamine (Johnson and Moran, 1969; Lagunoff et al. 1983). For example, studies involving exposure of compound 48/80 to the dog and cat have shown that the vasodilatory action of compound 48/80 is caused by the endogenous release of histamine (Paton, 1951). In the present porcine nasal mucosa study, the selective histamine H_3 receptor antagonists clobenpropit and thioperamide blocked the inhibitory effect of compound 48/80 on electrical field stimulation-induced sympathetic contractile responses. Similar to the effects observed with exogenous (*R*)-α-methylhistamine, treatment with the H_3 receptor antagonist clobenpropit (0.3-3 μM) blocked the inhibitory effect of compound 48/80 in a concentration-dependent manner. This finding further indicates that endogenously released histamine can assess functional H_3 receptors to inhibit sympathetic vasomotor responses in nasal vasculature.

The similarities between pigs and humans affords numerous and important research applications for the use of pigs (Almond, 1996; Ghoshal and Khamas, 1986; Rinder and Lundberg, 1996). These similarities in physiological regulation include sympathetic and adrenergic control of the nasal vascular bed, transitional mucosa, inflammatory cells, arterial and venous blood supply to the nose, and mucosal swelling in response to allergens. Thus, porcine turbinate mucosa is a useful tool to elucidate the neurogenic and humoral mechanisms controlling vascular tone in nasal mucosa and may aid in developing new therapies for nasal congestive disorders (Eccles and Eccles, 1981). Furthermore, this model may also be useful in characterizing the functional role of histamine H_3 receptors in the regulation on nasal vasculature tone in allergic congestive nasal disease.

In summary, the present results show that histamine H_3 receptor activation modulates sympathetic control of vascular tone in porcine nasal mucosa most likely by a prejunctional inhibitory mechanism. These findings also suggest that H_3 receptors may play a role in the modulation of sympathetic nasal vasomotor tone, but further investigations are needed to substantiate this.

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