

Substance P and vasoactive intestinal peptide in serotonin-induced nasal secretions in normal subjects

P. TØNNESEN¹ and O. B. SCHAFFALITZKY DE MUCKADELL²

¹Pulmonary Dept., Gentofte Hospital and ²Dept. of Clinical Chemistry, Bispebjerg Hospital, Copenhagen, Denmark

The aim of this study was to examine if nasal secretions contained substance P and/or vasoactive intestinal peptide. Serotonin nasal challenge was performed in 14 normal subjects 15 min after intranasal pretreatment (double-blind) with atropine, methysergide, chlorpheniramine or isotonic saline. Serotonin induced a dose dependent increase in secretion ($P < 0.05$), and only pretreatment with atropine reduced the secretion ($P < 0.02$). Substance P, measured by radioimmunoassay, was found in all of the examined secretions ($n = 100$) with a median concentration of 13.7 pmol/l (range 1.7-125.0). Serotonin challenge increased the concentration or content of substance P in a dose-related fashion ($P < 0.01$). The different pretreatments did not affect the concentration of substance P. Vasoactive intestinal peptide was found in low concentration in 37% of the secretions with a median concentration of 0 pmol/l (range 0-50.0).

Key words: nasal challenge; rhinitis; serotonin; substance P; vasoactive intestinal peptide.

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CLINICAL ASPECTS

Nasal challenge with serotonin induced a dose-dependent secretion in 14 normal subjects. Pretreatment with atropine reduced the secretions, while an anti-serotonin and an anti-histamine drug had no effect on secretion volume. Substance P was found in all of the secretions. If serotonin and substance P play a role in diseases with nasal hypersecretion, a substance P antagonist for clinical use might be useful.

In normal persons serotonin nasal challenge produces sneezing, itching and rhinorrhoea in a dose dependent way, and this secretory response is partly antagonized by atropine (15, 17). We have also found that nasal discharge induced by histamine, methacholine and allergen contain serotonin in concentrations many times higher than in plasma (16). The origin of serotonin in nasal secretions remains obscure, but glands, nerves and/or endocrine cells are possible sources. Endocrine cells containing serotonin have been demonstrated in the lower respiratory tract, but not in the nasal epithelium (3). Coexistence of serotonin and substance P (SP) is found in the gastro-intestinal tract (8), and for that reason it would be of interest to investigate if regulatory peptides are present in nasal secretions.

SP is present in both central and peripheral sensory neurons (6). SP-nerves have been demonstrated in the human bronchi and the nasal mucosa within or under the epithelium and around blood vessels in afferent sensory branches of trigeminal origin (12). SP is a powerful secretagogue (2), and is also a possible mediator of vasodilation and smooth muscle contraction in the "axonreflex" (5, 9).

Vasoactive intestinal peptide (VIP) is present around glands and blood vessels of the nasal mucosa (18), and has been located in postganglionic, parasympathetic, cholinergic neurons in coexistence with acetylcholine (11). Activation of these nerves results in secretion (21).

The purpose of the present study was there-

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the concentration was low (median 0 pmol/l, range 0–50.0) (Fig. 3). When the lower concentration of SP was compared to those higher than 11 pmol/l, a larger number of the secretions contained detectable VIP (14% versus 52%), and more samples showed concentrations of VIP above 10 pmol/l (3% versus 14%), but no overall correlation was found between concentrations of SP and VIP. The different pretreatments did not affect the concentration of VIP (Fig. 3).

DISCUSSION

The dose-dependent secretion induced by serotonin has been discussed in detail elsewhere (15, 17). The most important finding in the present study is that all of the nasal secretions contained SP and often in concentrations several times higher than in plasma. The highest median concentration or content of SP was found after the highest provocation dose of serotonin. That SP might be involved in nasal secretion is supported by these findings.

This is the first report of SP in nasal secretions in man. We have tried to minimize the possible degradation of SP by enzymes in the nasal secretions by immediate freezing and extraction with ethanol. Since the concentration of SP is up to several times higher than in plasma, transudation from vessels can only contribute to a minor part of the total content of SP in secretions. Furthermore, it has previously been demonstrated that about 10% of total secretion might be transudate (7). Another more plausible source of SP could be from the afferent, sensory neurons located in the nose within and under the epithelium and around blood vessels (12). Serotonin might stimulate these neurons and the released SP might then reach the mucosal surface. This hypothesis is supported by *in vitro* experiments in cats, in which vagal stimulation increased the concentration of SP in the antral lumen (20). The possible effect of released SP is supported by its powerful effect on secretion in canine airways *in vitro* (1), and its effect on vascular permeability and bronchoconstriction (10). In the present study, atropine pretreatment only partly re-

duced the secretions in response to serotonin. The atropine-sensitive part could be the reflex-mediated secretion by serotonin, while the remaining part of the secretions not affected by atropine could be a result of SP released by an axon reflex. In dogs intranasally applied SP evoked an atropine resistant secretion (13), which is a characteristic feature of regulatory peptides such as SP. For further research an SP antagonist might be useful.

The concentrations of VIP were low, and VIP was only detected in a third of the specimens examined. No increase in the concentration or content of VIP was found in response to higher doses of serotonin, and no overall correlation between the concentrations of SP and VIP was observed. VIP has a role in glandular secretion (11, 19), and for that reason further studies on the role of VIP in nasal secretions in diseases with hypersecretion should be undertaken.

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Address:

Philip Tønnesen, M.D.
Rudolph Berghs Gade 20
DK-2100 Copenhagen
Denmark

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