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The influence of neuropharmaca on the nasal glands

Preliminary report

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SUMMARY

Contributions from various sources to the nasal fluid are a serious complicating factor for investigating the isolated role of the nasal glands in the production of this fluid. This study is an attempt to obtain a better insight in the secretory behaviour of the nasal glands and its neural regulation. Radioligand binding strongly suggests that rat nasal glands contain muscarinic receptors. Parasympathomimetic drugs mainly promote the discharge of the secretory proteins from the glandular cells. However, histological sections do not show any change in the number of secretory granules after parasympatholytic drug application. These observations refer to a complex nature of the parasympathetic regulation of the glandular secretory activity.

It is already known for a long period that the nasal fluid is of great importance in the physiology of the airway system (Widdicombe and Wells, 1982). Important constituents of the nasal fluid include glycoproteins, which are secreted by goblet cells and submucosal glands. Glycoproteins are responsible for the viscosity and gel forming properties of the mucus blanket, covering the epithelium. They play an essential role in the defense mechanism of the nose (Sadé et al., 1970).
Contributions from lacrimal glands, transudation from submucosal vessels and condensed water from the expired air are a serious complicating factor for investigating the isolated role of nasal glands in the production of nasal fluid. Generally, basic research on the mechanism of nasal glandular secretion is extremely scarce and no data are available on the effect of drugs, used as therapeutics in rhinopathy, on these glands. In the present study an attempt was made to obtain deeper insight in the secretory activity of the nasal glands and its neural regulation.
The present study was performed on the glands in the lateral nasal wall of the rat (Kuijpers et al., 1983). The character of the neuroreceptors was studied with the use of radioligand receptor binding techniques and with autoradiography. The

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effects of various systematically applied neuropharmaca (pilocarpine, carbachol, methacholine, atropine and reserpine) on the secretion were studied morphologically with the use of light and electron microscopical techniques and biochemically with radio-active precursors of the secretory proteins.

For light microscopy sections of both paraffin and glycolmethacrylate embedded nasal glands were stained with Periodic acid Schiff (PAS). For electron microscopy routine procedures were used.

In the past periacinar acetylcholinesterase containing fibres have been identified in the nasal glands with the use of histochemical and fluorescence techniques (Ishii and Toriyama, 1972; Grote et al., 1975). With these methods no adrenergic innervation of the glands has been demonstrated. More detailed information on the nature and localization of the various neuroreceptors can be obtained by recently developed radioligand receptor binding techniques (Laduron, 1984). It appeared that with respect to the cholinergic innervation radioligand receptor binding shows a concentration dependent binding of ^{3}H-1-Quinuclidinylbenzilate (^{3}H-1-QNB), a specific cholinergic antagonist, to a crude membrane fraction of rat nasal mucosa. This binding is saturable with a receptor density of 8 ± 2 pmol/g tissue and a dissociation constant of 0.06 ± 0.02 nM. The specific binding is further characterized by differential inhibition with the enantiomers of benzetimide. In accordance with the pharmacological profile of both compounds dexetimide ($K_i = 1.2 \times 10^{-9}$M) was 5,000 times as effective in displacing ^{3}H-1-QNB from its receptors than the levorotatory isomer ($K_i = 6 \times 10^{-6}$M). After in vivo administration of ^{3}H-1-QNB autoradiographs of cryostate sections showed a specific uptake of ^{3}H-1-QNB in the acini of rat nasal glands (Klaassen et al., 1984). Although a further pharmacological characterization of the receptors must be performed, these observations strongly suggest that rat nasal glands contain muscarinic receptors.

Concerning the effect of various drugs on the secretory activity of the glands, biochemical studies revealed that the protein content of the whole lateral nasal gland was reduced after both pilocarpine (10 mg/kg body weight) and carbachol (1.25 mg/kg body weight) administration. Pilocarpine appeared to stimulate mainly the exocytosis of granules from the glandular cells. In addition it was found that in the gland of the lateral nasal wall various parts can be distinguished differing in their ductal system and in the nature of the glycoproteins they produce (Klaassen et al., 1981). These glandular parts appeared to react in a different way to the application of either methacholine (1.0 mg/kg body weight) or carbachol. Light and electron microscopy hardly showed any reaction after parasympathomimetic drug application in one part, while the other part revealed a distinct loss of secretory granules. Although a difference of the neural regulation might be an underlying explanation for this phenomenon, there are no morphological indications that these two glandular parts are innervated in a different way. Possibly, receptor

binding studies can contribute to a further elucidation of this difference in response.

The parasympatholytic drug atropine did not show any change in the number of secretory granules, as could be established with morphological methods. This was confirmed by preliminary biochemical studies which failed to reveal any effect of atropine (0.5 mg/kg body weight) either on discharge or on synthesis of secretory products.

These observations refer to a complex nature of the parasympathetic regulation of the acinar cells of rat nasal glands.

The lack of any effect of the sympatholytic drug reserpine, established with both morphological and biochemical methods, fits in with the morphological observation that the nasal glands are exclusively innervated by parasympathetic fibres.

This study demonstrates the importance for the use of more advanced techniques for a better understanding of the role of the autonomic nervous system in nasal (patho)physiology.

ZUSAMMENFASSUNG

Die unterschiedlichen Komponenten, die an der Bildung des nasalen Sekrets beteiligt sind, erschweren die alleinige Untersuchung der Rolle der nasalen Drüsen bei der Produktion dieser Flüssigkeit erheblich. In dieser Studie versuchen wir, einen Einblick in das sekretorische Verhalten und die neurale Regulation der nasalen Drüsen zu gewinnen. Die Existenz von Muskarinrezeptoren in den nasalen Drüsen von Ratten erscheint durch die Bindung von Radioliganden weitgehend gesichert. Durch Parasympathomimetika wird hauptsächlich die Ausschüttung sekretorischer Proteine aus glandulären Zellen gesteigert. Trotzdem zeigt sich in histologischen Schnitten keine Veränderung der Anzahl Sekretorischer Granula nach Applikation von Parasympatholytika. Diese Befunde sprechen für eine komplexe parasympathische Regulation der glandulären sekretorischen Aktivität.

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