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Parasympathetic and sympathetic influences on mucociliary activity in vivo

U. Mercke, J.-C. Hybbinette and S. Lindberg, Lund, Sweden

SUMMARY

An in vivo test model has been developed to measure the influence of pharmacological substances on mucociliary activity in the rabbit maxillary sinus. Test solutions are administered via the feeding vessel to the investigated mucous membrane. The model permits administration of test substances and simultaneous recording of the obtained effects under conditions that closely mimic the normal situation. The parasympathomimetic agonist methacholine accelerates the mucociliary wave frequency dose-dependently. Atropine has no influence on the resting mucociliary activity but reduces or abolishes the effect of methacholine. The sympathomimetic β_2-adrenoceptor agonist salbutamol accelerates the mucociliary activity dose-dependently whereas β_1-adrenoceptor stimulation with prenalterol is without effect. Agonists acting on α_1- and α_2-adrenoceptors, phenylephrine and oxymetazoline, retard the mucociliary activity dose-dependently.

β- and α-adrenoceptor antagonists (propranolol and phentolamine, respectively) have no influence on the resting mucociliary activity but reduce the effect of β- and α-adrenoceptor agonists, respectively. It is concluded that the resting mucociliary activity during anesthesia functions independently of parasympathetic and sympathetic nervous activity, and that the role of the parasympathetic and sympathetic innervation is to increase the mucociliary activity.

The influence of parasympathometic and sympathomimetic agonists on mucociliary activity has been studied in a number of in vitro and in vivo investigations in man and animals (Wanner, 1977). However, the measuring methods have been burdened with limitations and the test models that have been used have not been specifically adapted to the study of pharmacological effects on mucociliary activity. Hence both cholinoceptor and adrenoceptor agonists have been ascribed contradictory effects on mucociliary activity in different publications (Asmundsson and Kilburn, 1973; Proctor and Adams, 1976). Moreover, the question whether

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the resting mucociliary activity is under a parasympathetic or a sympathetic tone has remained unsolved.

To make investigations in this field it is first of all necessary to have at one's disposal a test model with which the effect of different pharmacological substances on mucociliary activity may be recorded under as physiologically realistic conditions as possible. We have therefore developed an in vivo test model using the rabbit as experimental animal.

METHODS

The animal is anesthetized with urethane and a 2 × 8 mm hole is drilled into the maxillary sinus. It is immediately sealed with a small window, thereby restoring the sinus ventilation to normal and protecting the mucous membrane from the noxious effects of dry and cold environmental air. The ciliated mucous membrane can be observed through the window and the mucociliary wave frequency recorded with the aid of the non-invasive, photoelectric technique described by Mercke et al. (1974).

On the same side as the opened sinus a catheter is inserted in the maxillary artery, that is to say the feeding vessel of the mucous membrane of the maxillary sinus. The test substance is administered as an intra-arterial bolus dose of 0.2 ml during 3 sec through the catheter. From there it passes directly to the maxillary sinus. Continuous recordings of the mucociliary activity are made before, during and after the injection. Induced frequency changes may be expressed either as absolute figures or as percentages of the basal, resting frequency immediately preceding administration of the test substance (Hybbinette and Mercke, 1982a).

RESULTS

Methacholine has been used as a representative of the whole parasympathomimetic substance group as it acts mainly on postganglionic receptors and also because it is less susceptible than acetylcholine to cholinesterase.

Methacholine accelerated the mucociliary wave frequency in a dose-response relationship in the dose interval 0.01 µg to 2 µg per kg bodyweight.

The antagonist atropine did not influence the basal mucociliary wave frequency, but in a dose of 0.2 mg per kg it reduced or abolished the response induced by methacholine. From this it may be concluded that the responses to methacholine indicate the presence of muscarinic receptors on effector cells that may either directly or indirectly be involved in the control of the mucociliary activity.

Together with the findings of other investigators of parasympathetic nerve fibres in close proximity to the respiratory epithelium, our results suggest the possibility of parasympathetic control of mucociliary activity. Apparently, the resting mucociliary activity functions independently of parasympathetic nervous activity

since atropine did not influence the basal mucociliary wave frequency (Hybbinette and Mercke, 1982b).
In the sympathomimetic group the selective β_1-adrenoceptor agonist prenalterol had no influence on the basal mucociliary activity. In contrast, the β_2-agonist salbutamol and isoprenaline (which acts on both β_1- and β_2-receptors) gave a dose-dependent acceleration of the mucociliary wave frequency. This acceleration can be blocked with propranolol, a non-selective β-adrenoceptor blocking substance. Propranolol per se had no effect at all on the basal mucociliary activity.
Phenylephrine (which acts mainly on α_1-adrenoceptors) and oxymetazoline (which acts mainly on α_2-adrenoceptors) both had a retarding effect on mucociliary activity. This retardation is dose-dependent. Phentolamine, a non-selective α-adrenoceptor blocking substance, had no effect per se on the resting basal mucociliary activity but it inhibited the retarding effect of oxymetazoline. This retarding effect of α-agonists might be caused by a reduced energy supply to the ciliated cells which in turn is an effect of decreased blood flow in the mucous membrane.
From these results it might be concluded that sympathomimetic agonists with selectivity to different groups of adrenoceptors have opposite effects on mucociliary activity, that is to say acceleration by β_2- and retardation by α_1- and α_2-adrenoceptor agonists and no effect at all by β_1-agonists. The resting mucociliary activity functions independently of svmpathetic activity since β- and α-adrenoceptor antagonists on their own do not influence the resting mucociliary activity (Hybbinette and Mercke, 1982c).

DISCUSSION

Thus it seems that the role of parasympathetic and sympathetic innervation is mainly to increase the mucociliary activity. The resting mucociliary activity functions independently of both parasympathetic and sympathetic innervation.
Is there then any endogenous substance or group of substances that is involved in the maintenance of the resting mucociliary activity? At the moment we do not know but quite naturally our interest has turned specifically to the rapidly growing group of neuropeptides. Many of these substances have been found in the upper airways. Our group has performed some introductory experiments with VIP (vasoactive intestinal polypeptide), leu-enkephaline and substance P. Preliminary results show that neither VIP nor leu-enkephaline have any effect on the mucociliary activity in rabbits. On the other hand, substance P has a dose-related accelerating effect which can not be reduced by atropine or hexamethonium but only by a specific substance P blocker. This could indicate that mucociliary activity is influenced via routes not belonging to the cholinergic or adrenergic system. However, further studies concerning function and morphology are necessary before more definite conclusions may be made from these interesting and promising experiments.

ZUSAMMENFASSUNG

Ein Versuchsmodell wurde entwickelt, welches die Registrierung der Wirkungen verschiedener Pharmaka auf die mukoziliäre Aktivität der Schleimhaut in der Kieferhöhle des Kaninchens *in vivo* ermöglicht. Die Testlösungen wurden der Arterie zugeführt, die die Schleimhautareale versorgte an denen die Wirkung gemessen werden sollte. Die Versuchsanordnung lässt die Messung der mukoziliären Aktivität bei gleichzeitiger Applikation der Testsubstanz unter annährend physiologischen Bedingungen zu. Metacholin, ein parasympathomimetischer Agonist, bewirkt eine dosisabhängige Beschleunigung der mukoziliären Wellenfrequenz. Atropin zeigt keinen Einfluss auf die mukoziliäre Grundfrequenz, aber es reduziert oder neutralisiert den Metacholineffekt. Der sympathomimetische β_2- adrenorezeptoragonist Salbutamol hat eine dosisabhängige Steigerung der mukoziliären Aktivität zur Folge, wohingegen Prenalterol, ein β_1-adrenorezeptoragonist, überhaupt keinen Effekt zeigt. Die Agonisten Phenylephrin und Oxymetalozin mit Angriffspunkt an den α_1 und α_2-adrenorezeptoren bewirken eine dosisabhängige Verlangsamung der mukoziliären Aktivität. Die β und α-adrenorezeptorantagonisten (Propranolol bzw. Phentolamin) haben *per se* keinen Einfluss auf die mukoziliäre Basalaktivität, reduzieren jedoch die Wirkungen der entsprechenden β und α-adrenorezeptoragonisten. Aus den Testresultaten lässt sich entnehmen, dass die mukoziliäre Basalaktivität unter Narkose unabhängig vom parasympathischen bzw. sympathischen Tonus ist. Weiterhin wurde gezeigt, dass die Steigerung der mukoziliären Aktivität eine Funktion der parasympathischen-sympathischen Innervation ist.

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U. Mercke, M.D.
Department of Oto-Rhino-Laryngology
University Hospital of Lund
S-221 85 Lund, Sweden