Postjunctional $\alpha_2$-adrenoceptors in blood vessels of human nasal mucosa

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Summary. Human nasal mucosa has various types of blood vessels and is a good tissue for demonstrating receptors for many vasoactive substances, including $\alpha$-adrenoceptors. In contrast to the large contractile response induced by $\alpha_1$-agonists, our studies have shown that $\alpha_2$-agonists produce a small maximal contraction. This $\alpha_2$-induced response was easily blocked by $\alpha_1$-antagonists, indicating that it is evoked, at least partially, by the stimulation of $\alpha_1$-adrenoceptors. Noradrenaline (NA)-induced contractions could not be abolished by either $\alpha_1$- or $\alpha_2$-antagonists alone, but were almost completely blocked by the combination of both antagonists. This suggests the presence of postjunctional $\alpha_2$-adrenoceptors. The low-maximal responsiveness to $\alpha_2$-agonists and calcium independency of NA-induced contractions were distinct from our former results obtained on canine nasal specimens.

Key words: $\alpha$-adrenoceptor – Nasal blood vessels – Vasoconstriction – Calcium entry blocker – Nasal allergy

Introduction

Since 1972, a number of studies have shown that multiple $\alpha$-adrenoceptor subtypes are present in various smooth muscle preparations [16]. In 1974, based on their anatomical locations, $\alpha$-receptors were subdivided into two classes by Langer [9]: the receptor located at the target organs or postjunctionally is referred to as $\alpha_1$, while the other located on the nerve terminals or prejunctionally is termed $\alpha_2$.

More recently, an increasing number of tissues have been identified in which both $\alpha_1$- and $\alpha_2$-receptors have been found to reside postjunctionally [4]. The pharmacological differentiation of $\alpha$-adrenoceptors into $\alpha_1$- and $\alpha_2$-subtypes has been accomplished by the use of selective agonists and antagonists, regardless of their anatomical location or function. Namely, $\alpha_1$-adrenoceptors are defined as those in which prazosin (PRA) is a more potent antagonist than yohimbine (YOH). In contrast, at $\alpha_2$-sites, YOH is more potent than PRA. As far as the vascular smooth muscle is concerned, postjunctional $\alpha_2$-receptors have been demonstrated only in certain blood vessels of a limited number of species. These include the pithed rat [2], the dog [5], the cat, the rabbit and man [12].

We have already reported evidence for the presence of postjunctional $\alpha_2$-adrenoceptors in canine nasal mucosa using an in vitro tension-detecting technique [8]. The aim of our present study was to show evidence for the presence of postjunctional $\alpha_2$-adrenoceptors in human nasal mucosa. We also wished to elucidate the difference between postjunctional $\alpha_1$- and $\alpha_2$-adrenoceptors by observing the in vitro vaso-reactivity to agonists and/or antagonists of the receptors involved.

Materials and methods

Specimens were obtained during turbinectomies performed on patients with severe nasal allergy or hypertrophic rhinitis. Nasal mucosa was stored in Krebs solution and was then cut into pieces that were approximately 10 x 25 mm in size. A piece was next suspended in a muscle bath containing 10 ml Krebs solution. The mucosal strip was fixed at the lower end of the bath and the upper end was attached to an isometric transducer with 3-0 silk sutures. The bath solution was constantly irrigated with 95% $O_2$ and 5% $CO_2$. Tension (1.0 g) was applied to the tissue, which was allowed to equilibrate for about 40 min.
The mucosal strips normally contract when treated with vasoconstricting agents. Alpha-agonists were introduced to obtain dose-response curves. First, the tissue was stimulated repeatedly with $10^{-3} M$ noradrenaline (NA) until the size of the contraction became the same. Then, the response to increasing concentrations of other agonists was recorded. The inhibitory potency of $\alpha$-antagonists to agonist-induced contraction was also evaluated. Experiments were conducted in a calcium ion ($Ca^{2+}$)-free medium in order to evaluate the contribution of the influx of extracellular $Ca^{2+}$ to the $\alpha$-agonist-induced contractions.

Drugs used in this study were as follows: noradrenaline bitartrate (Sigma, St. Louis, USA), methoxamine hydrochloride (Nihon-Shinyaku, Kyoto, Japan), clonidine hydrochloride (Sigma), B-HT 920 (Boehringer Ingelheim, FRG), tramazoline hydrochloride (Boehringer), oxymetazoline hydrochloride (Merck, Darmstadt, FRG), prazosin hydrochloride (Taito-Pfizer, Tokyo, Japan), phenoxylbenzamine hydrochloride (Tokyo-Kasei, Tokyo, Japan), yohimbine hydrochloride (Sigma), EDTA (Sigma), verapamil (Eisai, Tokyo, Japan), and angiotensin II (Sigma).

**Results**

Although both $\alpha_1$- and $\alpha_2$-agonists caused a contractile response in the human nasal mucosa, the speed of the contraction induced by all the agonists tested was considerably slower than that obtained with dog nasal mucosa. For example, it took 16 min to reach maximal contraction with $10^{-3} M$ NA. In contrast, it took only 3.5 min when the same dose of NA was applied to the dog specimens.

The size of the response of postjunctional $\alpha$-adrenoceptors of human nasal mucosa to the $\alpha_2$-agonists [clonidine (CLO) and B-HT 920 (6-allyl-2-amino-5,6,7,8-tetrahydro-4H-thiazolo-[4,5-d]-azepin)] was far less in magnitude than that to $\alpha_1$-agonist methoxamine (MX) (Fig. 1).

The ratio of the magnitude of $\alpha_2$-induced contractions to that of $\alpha_1$-induced contractions in human specimens was remarkably lower than that in the canine tissue [8] (Fig. 2). The imidazoline derivatives (tramazoline and oxymetazoline) produced a greater response than B-HT 920 or CLO, but less than MX or NA (Fig. 1). This imidazoline derivative response was antagonized, for the most part, but the $\alpha_1$-antagonist prazosin, even though these derivatives were considered to be relatively specific for $\alpha_2$ adrenoceptors. Simulation of both $\alpha_1$- and $\alpha_2$-receptors by NA also mediated vasoconstriction. Figure 2 shows that NA produced a slightly lower maximum contractile response in human nasal mucosa compared with MX. This was contrary to the results obtained in the blood vessels of the dog [7].

Although an increase in free intracellular $Ca^{2+}$ is essential for muscle contraction, $10^{-5} M$ NA-induced contraction in the human nasal mucosa was resistant

**Fig. 1.** Contractile responses induced by various $\alpha$-agonists compared with NA as the standard (100%) [$n = 5$ (NA), $n = 3$ (others)]. NA, noradrenaline; MX, methoxamine; TM, tolazoline; OM, oxymetazoline; CL, clonidine

**Fig. 2.** Comparisons of dose-response curves obtained with $\alpha$-agonists between human and canine nasal mucosa. Left: human turbinate [$n = 5$ (NA), $n = 3$ (MX, CL)]. Right: canine septum [$n = 10$ (NA), $n = 4$ (MX, CL)]

**Fig. 3.** The effect of $Ca^{2+}$ on NA-induced mucosal contractions. Upper: human specimen; lower: canine specimen