INFLUENCE OF ATRIAL NATRIURETIC PEPTIDE, BRAIN NATRIURETIC PEPTIDE AND URODILATIN ON THE HISTAMINE-INDUCED BRONCHOCONSTRICTION IN THE CONSCIOUS GUINEA PIG

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ABSTRACT


The influence of human atrial natriuretic peptide (ANP) and of two related peptides, human brain natriuretic peptide (BNP) and urodilatin (URO) on the bronchoconstriction induced by inhalation of histamine in conscious, non-anaesthetized guinea pigs was tested.

Changes in lung function were registered using two independent methods, one operating in a closed body-plethysmographic system, the other in an open system based on the time lag of air flow curves. The peptides were infused (0.25 ml/min) into the jugular vein for a period from 10 min before until 15 min after the histamine inhalation.

ANP displayed virtually no effect on the bronchoconstriction. URO showed some inhibition at 1280 ng kg⁻¹ min⁻¹, but not at lower doses. BNP (640 ng kg⁻¹ min⁻¹) inhibited the bronchoconstriction markedly for the total registration period.

It can be concluded from these results that BNP exerts bronchoprotective effects in the conscious guinea pig, which are superior to those of ANP or URO.

Keywords: Natriuretic peptides, lung function, guinea pig, histamine bronchoconstriction

INTRODUCTION

In recent years, a possible role in the physiological regulation as well as in the pharmacological modulation of the airways has been attributed to a novel family of endogenous peptide hormones, the atrial natriuretic peptides.

De Bold et al. [1] postulated the existence of a natriuretic factor from the rat heart atrium (ANF) involved in the blood volume homeostasis. This finding led to the isolation of a new family of peptides from rat and human heart atria, capable of evoking smooth muscle relaxation and natriuresis [2–5].

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Atrial natriuretic peptides were later found to influence the physiological regulation of the circulatory system at many levels. They were shown to reduce the circulating blood volume by enhancing natriuresis and diuresis [6–8], relax vascular smooth muscle directly [9], lower the cardiac output [10] and inhibit renine, aldosterone and vasopressin secretion [11–13]. All these effects lead to a reduction in blood pressure and circulating blood volume [11].

The brain natriuretic peptide (BNP), another new member of the atrial peptide family, was originally isolated from porcine brain [14,15]. However, the cardiac atrium of various species has since been identified as the main site of synthesis, storage and secretion of the peptide, which, like the ANP, seems to play a role as circulating hormone [14–24]. A number of effects similar to those of the ANP have been found in animals and humans [14,15,25–28] but species differences in the biological actions have also been postulated [29].

Urodilatin was originally isolated from human urine by Schulz-Knappe et al. [30]. It is an ANP variant extended by 4 N-terminal residues (ANP95–126). Although it has not been found in human plasma, some of its systemic pharmacological effects were found to be stronger than those of ANP99–126 [31,32].

Dose-dependent relaxing effects of several variants of ANP on isolated trachea and pulmonary vasculature, first reported by O’Donnell et al. [33], were later confirmed by several authors [34–37]. The activity on human tissue preparations seemed to depend upon the bronchoconstrictory agent [38,39].

An in-vivo protective effect against a bronchoconstrictive agent was also shown for sheep and guinea pigs, but could not be demonstrated in dogs and rats [36,40–44]. In rabbits, an indirect effect of ANP on the airways has been postulated [45,46], and evidence for central nervous modulation of the tracheal tone of anaesthetized cats by ANP has also been reported [47].

In humans, intravenously applied ANP relaxed the basal tone of normal and asthmatic airways. It also displayed a protective potency against bronchoconstriction evoked by histamine or distilled water inhalation in asthmatic patients [48–52]. Asthmatic airways were also dilated and protected against histamine and methacholine by higher doses of inhaled ANP [53–56].

The other members of the ANP family also displayed actions on airways. In contrast to ANP, urodilatin infusions protected rats against stimulated bronchoconstriction. This peptide was also able to lower the resting tone of human asthmatic airways [45,57–59].

Effects of BNP on airways remained unknown until relaxing and protective effects of this peptide against histamine preconstriction of guinea pig tracheal muscle preparations were reported by Takagi and Araki [60]. A comparison of the effective doses (EC50) of ANP [61] and BNP makes a superior relaxing action of BNP probable [60].

Results of tests of ANP on histamine bronchoconstriction in guinea pigs are not uniform [36,41], and no reports about actions of urodilatin on guinea pigs airways or in-vivo respiratory effects of BNP have come to our knowledge so far.

Here we report the effects of three different peptides (ANP, BNP and urodilatin) on histamine-induced bronchoconstriction in the conscious guinea pig.