NOTE

Effects of Intranasal Administration of Atrial Natriuretic Hormone on Spontaneously Hypertensive Rats

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Abstract

The effects of the intranasal administration of synthetic alpha-human atrial natriuretic polypeptide (alpha-hANP) were investigated in 14 anesthetized spontaneously hypertensive rats (SHR; Okamoto-Aoki strain). They were given intranasally synthetic alpha-hANP in distilled water at doses of 10 μg/kg, 50 μg/kg and 100 μg/kg. Intranasal application of 200 μl of distilled water as a control was also performed in 3 anesthetized SHR. Sixteen anesthetized SHR were examined for the effects of intravenous administration of alpha-hANP at doses of 4 μg/kg, 10 μg/kg, 20 μg/kg and 40 μg/kg.

Urinary volume and the urinary excretion of sodium increased 2- to 3-fold during the 50 minutes following intranasal administration of a single dose of 50 μg/kg or 100 μg/kg, although neither the urinary volume nor the urinary excretion of sodium increased after intranasal administration of 10 μg/kg of alpha-hANP or 200 μl of distilled water. There were no significant changes in arterial pressure or heart rate after the intranasal administration of synthetic alpha-hANP or distilled water. In contrast, arterial pressure was decreased and urinary volume and urinary excretion of sodium were increased, in a dose dependent manner, within 5 minutes after intravenous bolus-injection of alpha-hANP and returned to their baseline levels within 20 minutes.

These results indicate that intranasal administration of synthetic alpha-hANP exerts its diuretic effect without concomitant changes in arterial pressure or heart rate in SHR.

Since de Bold et al. (1981) discovered the natriuretic action of rat atrial extracts, several polypeptides of a potentially physiological importance have been isolated from mammalian atrial tissue (Needleman et al., 1985, Palluk et al., 1985).

Kangawa and Matsuo (1984) isolated 3 polypeptides from human atria; alpha-, beta- and gamma-human atrial natriuretic polypeptide (hANP). One of these peptides, alpha-hANP, has been synthetized, and its
natriuretic and vasodepressor actions have been studied by intravenous administration in experimental animals as well as man (Kangawa and Matsuo, 1984, Richards et al., 1985). It is also reported that either the depressor action or natriuretic effect of intravenous administration of alpha-hANP in spontaneously hypertensive rats (SHR) was greater than in normotensive rats.

Thus SHR were used in this study and the depressor and natriuretic effects of the intranasal administration of alpha-hANP were observed in anesthetized SHR.

Materials and Methods

Synthetic alpha-hANP, a 28 amino-acid polypeptide, was purchased from Peptide Institute Inc. (Osaka, Japan). The alpha-hANP was dissolved in distilled water at a concentration of 0.5 mg/ml immediately before intranasal administration.

Thirty-three male SHR, aged 10 to 14 weeks (12.2 ± 0.3, mean ± SD) and weighing 190 to 260 g (223 ± 4.2), were used in this study. These SHR were anesthetized with intraperitoneal sodium pentobarbital (40 mg/kg body weight). The carotid artery was cannulated for measurement of arterial pressure (AP) via a pressure transducer and heart rate was recorded on a polygraph. The femoral vein was cannulated for 280 µl/min infusion of saline. A bladder catheter was placed to collect timed urine. The urine volume (UV) was measured by weight. The concentration of urinary sodium was measured with a flame photometer.

After 3 control measurements of UV and UNaV, a single dose of alpha-hANP was administered with a microsyringe into the nasal cavities of each anesthetized animal at a dose of 10 µg/kg (n = 4), 50 µg/kg (n = 5) or 100 µg/kg (n = 5). The intranasal administration of 200 µl of distilled water as a control was also performed in 3 anesthetized SHR, and their UV, UNaV, AP and heart rate (HR) were measured as described above. The 16 anesthetized SHR were examined to verify the effects of an intravenous administration of alpha-hANP at a single dose of 4 µg/kg, 10 µg/kg, 20 µg/kg or 40 µg/kg (n = 4 for each group). Their UV, UNaV, AP and HR were also measured as described above.

Statistical analysis of UV and UNaV compared with the control values after distilled water and after alpha-hANP administration were evaluated by Student’s t-test. The statistical differences in AP and HR between baseline values and values after alpha-hANP administration were assessed by one-way analysis of variance. A p value of less than 0.05 was considered significant. All data are presented as the mean ± SE.

Results

Figure 1 represents the time course of diuretic and natriuretic responses after each intranasal administration of alpha-hANP and/or distilled water. Both UV and UNaV increased significantly between 20 and 50 minutes after an intranasal administration of alpha-hANP at a dose of 50 µg/kg and 100 µg/kg. However, the UV and UNaV did not change after the intranasal administration of a single dose of 10 µg/kg of alpha-hANP or 200 µl of distilled water. The AP (mean AP 163.0 ± 1.0 mmHg, n = 17) and HR (mean 378.7 ± 1.6 bpm, n = 17) did not change appreciably during the study period after the intranasal administration of each dose of alpha-hANP or distilled water (Table 1). In contrast, the intravenous administration of alpha-hANP produced a dose-dependent decrease in the mean AP (MAP) between the doses of 40 µg/kg and 10 µg/kg, whereas MAP did not change after the intravenous injection of 4 µg/kg of alpha-hANP or 200 µl of distilled water (Figure 2). The UV and UNaV increased dose-dependently after the intravenous injection of alpha-hANP in doses between 4 µg/kg and 40 µg/kg (Figure 2). Increases in UV and UNaV occurred within 5 minutes after the intravenous administration of alpha-hANP and returned to the baseline values within 15 minutes.
Fig. 1. Effects on urinary volume (UV) and excretion of urinary sodium (UNaV) after the intranasal administration of alpha-hANP in anesthetized SHR.

Both UV and UNaV increased significantly after an intranasal administration of alpha-hANP at a dose of 50 µg/kg and 100 µg/kg. However, the UV and UNaV did not change after the intranasal administration of a dose of 10 µg/kg of alpha-hANP(∗∗) or 200 µl of distilled water (D. W.∗).

† p<0.05 and ‡ p<0.01 compared to the D. W. value.

Discussion

Atrial natriuretic polypeptides are one of a group of endogenous natriuretic hormones that have been recognized as important endocrine mediators of renal and cardiovascular homeostasis (de Bold et al., 1984, Borenstein et al., 1983, Camargo et al., 1984, Oshima et al., 1984, Kangawa and Matsuo 1984, Koike et al., 1984). Alpha-hANP is a 28 amino-acid peptide which has been isolated from human atrial tissue by Kangawa and Matsuo (1984). The peptide has been shown to cause diuresis-natriuresis and hypotension when injected intravenously into experimental animals (Kangawa and Matsuo 1984). A recent study by Richards et al. (1985a, 1985b) has demonstrated that the intravenous administration of alpha-hANP at a dose of 100 µg/body produces a diuresis with a duration of 30 minutes and lowers blood pressure for a period of 10 to 175 minutes in healthy volunteers and hypertensive patients.

The data in the present study demonstrate that the intranasal administration of alpha-hANP in anesthetized SHR at a dose
Table 1. The changes in arterial pressure and heart rate after the intranasal administration of alpha-hANP to anesthetized spontaneously hypertensive rats.

<table>
<thead>
<tr>
<th>Control Period</th>
<th>Time after Intranasal Administration of a-hANP</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>−30 min</td>
</tr>
<tr>
<td>D. W.</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>163.3</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>385.0</td>
</tr>
<tr>
<td>a-hANP</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>164.5</td>
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<tr>
<td>10 µg/kg</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>±3.1</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>±6.3</td>
</tr>
<tr>
<td>50 µg/kg</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>±3.2</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>±8.0</td>
</tr>
<tr>
<td>100 µg/kg</td>
<td></td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>±3.4</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>±9.1</td>
</tr>
</tbody>
</table>

The mean arterial pressure (MAP) and heart rate (HR) did not significantly change during the study period after the intranasal administration of each dose of alpha-hANP or distilled water (D. W.).

Fig. 2. Responses in UV, UNaV and MAP within 5 minutes after the intravenous injection of alpha-hANP to anesthetized SHR.

The UV and UNaV increased dose-dependently after intravenous injection of alpha-hANP, and the MAP decreased dose-dependently after the intravenous injection except at a dose of 4 µg/kg of alpha-hANP.

† p<0.05 and ‡ p<0.01 compared to the D. W. value.
over 50 μg/kg produces a long-lasting diuresis and natriuresis without changes in arterial pressure and heart rate. The results also confirm that the intravenous administration of alpha-hANP produces a dose-dependent decrease in arterial pressure without changes in heart rate in anesthetized SHR. However, an intravenous administration of 4 μg/kg of alpha-hANP shows an interesting result in that the natriuresis after alpha-hANP injection increases significantly without a decrease in arterial pressure. It has already been demonstrated that a small dose of alpha-hANP or atrial extract produces a significant diuresis and natriuresis with little change in systemic arterial pressure (Trippodo et al., 1983, Yukimura et al., 1984). Thus, it can be speculated that a small increase in the plasma alpha-hANP concentration will produce a significant increase in natriuresis without a decrease in arterial pressure. It can also be speculated that if a small amount of alpha-hANP is absorbed slowly after intranasal administration, then the plasma concentration of alpha-hANP may increase only slightly even after a large amount of alpha-hANP is administered intranasally.

We have also studied the intranasal administration of alpha-hANP in healthy normal human volunteers. The intranasal administration of alpha-hANP produced a sustained increase in natriuresis of long duration without changes in arterial pressure and creatinine clearance (Shionoiri and Kaneko 1986). Our recent study has demonstrated that the plasma concentration of alpha-hANP was increased after the intranasal administration of alpha-hANP to healthy human volunteers, and the natriuresis and diuresis were confirmed (Oda et al., 1986).

Thus, it is suggested that intranasally administered alpha-hANP may be absorbed gradually, and alpha-hANP might be used as diuretics by intranasal administration. Further studies are needed before it is used by intranasal application in clinical situations.

References


Richards, A. M., M. G. Nischols, H. Ikram, M. W. I. Webster, T. G. Yandle and E. A. Es-


