Effects of adrenomedullin and PAMP on adrenal catecholamine release in dogs

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Effects of adrenomedullin and PAMP on adrenal catecholamine release in dogs. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R1118–R1124, 1999.—We examined the effects of proadrenomedullin-derived peptides on the release of adrenal catecholamines in response to cholinergic stimuli in pentobarbital sodium-anesthetized dogs. Drugs were administered into the adrenal gland through the phrenicoadominal artery. Splanchnic nerve stimulation (1, 2, and 3 Hz) and ACh injection (0.75, 1.5, and 3 µg) produced frequency- or dose-dependent increases in adrenal catecholamine output. These responses were unaffected by infusion of adrenomedullin (1, 3, and 10 ng·kg⁻¹·min⁻¹) or its selective antagonist adrenomedullin (22–52) (5, 15, and 50 ng·kg⁻¹·min⁻¹). PAMP-derived 20 peptide (PAMP; 5, 15, and 50 ng·kg⁻¹·min⁻¹) suppressed both the splanchnic nerve stimulation- and ACh-induced increases in catecholamine output in a dose-dependent manner. PAMP also suppressed the catecholamine release responses to the nicotinic agonist 1,1-dimethyl-4-phenylpiperazinium (0.5, 1, and 2 µg) and to muscarine (0.5, 1, and 2 µg), although the muscarine-induced release response was relatively resistant to PAMP. These results suggest that PAMP, but not adrenomedullin, can act as an inhibitory regulator of adrenal catecholamine release in vivo.

proadrenomedullin-derived peptides; acetylcholine; splanchnic nerve stimulation; adrenal gland

ADRENOMEDULLIN (AM), consisting of 52 amino acids, is a potent and long-lasting hypotensive peptide that was first isolated from human pheochromocytoma (15). The hypotensive effect of AM is considered to result from activation of adenylate cyclase and production of nitric oxide [as reviewed by Richards et al. (24)]. Proadrenomedullin, the precursor of AM, contains a unique 20-residue sequence termed proadrenomedullin NH₂-terminal 20 peptide (PAMP; see Ref. 14). PAMP also causes transient and potent hypotension, the mechanism of which is supposed to involve suppression of sympathetic neurotransmission (24). These peptides are detectable not only in tissues of the adrenal gland, right atrium, kidney, and brain but also at considerable concentrations in arterial blood (24). The pharmacological profile and systemic distribution of these peptides indicate that they have physiological roles in cardiovascular homeostasis.

AM and PAMP are abundant in adrenal medullary cells and are cosecreted with catecholamines in response to nicotinic receptor stimulation (10, 11). There are specific binding sites for AM (9) and PAMP (8) in the adrenal gland. It has been demonstrated that, in bovine cultured adrenomedullary cells, AM does not affect basal catecholamine release but increases Ca²⁺ efflux probably through accelerating Na⁺/Ca²⁺ exchange (7), and PAMP suppresses carbachol-evoked synthesis and release of catecholamines with inhibition of Ca²⁺ influx (10, 23). However, little is known about the effects of these proadrenomedullin-derived peptides on adrenal medullary catecholamine release evoked by endogenous and exogenous ACh.

In the present study, we examined the effects of AM, the AM antagonist AM-(22–52), and PAMP on adrenal catecholamine release in response to splanchnic nerve stimulation and intra-arterial injection of cholinergic agonists in anesthetized dogs.

MATERIALS AND METHODS

Animal preparation. The experiments were performed in mongrel dogs of either sex weighing 7–14 kg. After initial anesthesia with pentobarbital sodium (30 mg/kg iv), a constant level of anesthesia was maintained throughout the experiments by intravenous infusion of pentobarbital sodium (4–6 mg·kg⁻¹·h⁻¹) with an infusion pump (model 1015; Atom, Tokyo, J apan). Artificial respiration was performed with a ventilator (model SN-480-4; Shinano, Tokyo, J apan) with room air at 18 strokes per minute (20 ml/kg tidal volume). The surgical procedure used in this study was described previously (12). The left adrenal gland was exposed by a retroperitoneal flank incision, and a polyethylene catheter was inserted into the left adrenolumbar vein for collection of venous effluent blood from the adrenal gland. A thread was placed around the junction of the adrenolumbar vein with the abdominal vena cava. Adrenal blood samples were obtained by pulling the thread, thus occluding the adrenolumbar vein and causing retrograde flow of blood. Blood samples of 1 or 2 ml were collected in chilled test tubes containing 6 or 12 mg EDTA. When not being sampled, adrenal venous blood was returned directly to the vena cava. Coagulation of blood was prevented by an initial intravenous injection of sodium heparin (250 U/Kg). Systemic blood pressure and heart rate were measured with a polygraph (model RPM-6008M; Nihon Kohden, Tokyo, J apan) from the signal converted by a pressure transducer (model MPU-0.5; Nihon Kohden) simultaneously and were recorded on a heat-writing recticorder (model RJG-4128; Nihon Kohden).

Administration of drugs into the adrenal gland. The procedure for intra-arterial administration of drugs into the adrenal
groups. In groups 1 and 3 Hz at 2-min intervals during a 6-min stimulus period. Delivered by an electronic stimulator (model SEN-1101; Nihon Kohden) and an isolation unit (model SS-101J; Nihon Kohden). Stimulus frequency was raised stepwise from 1 to 2 and 3 Hz at 2-min intervals during a 6-min stimulus period.

Experimental protocol. The dogs were divided into nine groups. In groups 1 (n = 6) and 2 (n = 7), the effects of AM on splanchnic nerve stimulation- and ACh-induced increases in catecholamine output were examined, respectively. Splanchnic nerve stimulation (1, 2, and 3 Hz) was repeated four times at 30-min intervals. The first set of splanchnic nerve stimulation during saline infusion in the adrenal gland was regarded as a control. A set of ACh injections (0.75, 1.5, and 3 µg) into the adrenal gland was repeated four times at 30-min intervals. Each dose of ACh in a volume of 100, 200, or 400 µl was injected for 3 s at 5-min intervals. The first set of ACh injections during saline infusion was regarded as a control. AM infusion (1, 3, and 10 ng·kg⁻¹·min⁻¹) was started 10 min before the start of the second, third, and fourth sets of splanchnic nerve stimulation or ACh injections, respectively. Groups 3 (n = 7) and 4 (n = 8), the effects of AM-(22–52) (5, 15, and 50 ng·kg⁻¹·min⁻¹) on the splanchnic nerve stimulation- and ACh-induced increases in catecholamine output were examined, respectively, with the same protocol as used in groups 1 and 2. In groups 5 (n = 7) and 6 (n = 7), the effects of PAMP (5, 15, and 50 ng·kg⁻¹·min⁻¹) on the splanchnic nerve stimulation- and ACh-induced increases in catecholamine output were examined, respectively, with the same protocol as used in groups 1 and 2. In groups 7 (n = 8) and 8 (n = 7), the effects of PAMP (5, 15, and 50 ng·kg⁻¹·min⁻¹) on the DMPP (0.5, 1, and 2 µg)- and muscarine (0.5, 1, and 2 µg)-induced increases in catecholamine output were examined, respectively, with the same protocol as used in the ACh experiment.

In an additional five dogs (group 9), we also examined the effects of AM at a higher dose (100 ng·kg⁻¹·min⁻¹) on the splanchnic nerve stimulation-induced increases in catecholamine output in a similar manner as in group 1.

Blood sampling and determination of adrenal catecholamine output. In all groups, venous blood was sampled before and during splanchnic nerve stimulation or agonist injection to determine basal catecholamine output and stimul-induced increases in catecholamine output, respectively. Sampling during the basal state (during saline, AM, AM-(22–52), or PAMP infusion) was performed 2 min before splanchnic nerve stimulation or each series of drug injections. The time required to collect 1 ml (during basal state or splanchnic nerve stimulation) or 2 ml (during cholergic drug injection) of blood served to estimate adrenal venous flow rate. Adrenal blood samples were centrifuged to obtain plasma samples. Catecholamines were extracted from plasma by the alumina adsorption method, and plasma epinephrine and norepinephrine concentrations were determined by HPLC with electrochemical detection (model LC-304; Bioanalytical Systems), as described previously (12). Adrenal catecholamine (sum of epinephrine and norepinephrine) output (ng·min⁻¹) was calculated by multiplying plasma catecholamine concentration (ng/ml) by adrenal plasma flow rate (ml/min). Adrenal plasma flow rate was determined from the adrenal venous blood flow and the hematocrit of adrenal venous blood. The basal catecholamine output was determined from samples collected before splanchnic nerve stimulation or injection of agonists. The splanchnic nerve stimulation- and the agonist-induced increases in catecholamine output were calculated by subtracting the basal catecholamine output from that obtained during stimulation.

Data analysis. All data are expressed as means ± SE. Multifactor repeated-measures ANOVA was applied to evaluate overall statistical significance of the effects of cholinergic stimulation and the peptide in each experimental group. The significance of differences between the control values and those during infusion of AM, AM-(22–52), or PAMP at each dose were evaluated by single-factor repeated-measures ANOVA and Dunnett's test. Two-way ANOVA with replication was used to compare percentage inhibition by PAMP of the catecholamine output responses. Differences at P < 0.05 were considered statistically significant.

Drugs. The drugs used were AM, AM-(22–52), and PAMP (Peptide Institute, Osaka, Japan), ACh chloride (Daichi Seiyaku, Tokyo, Japan), DMPP iodide (Aldrich, Milwaukee, WI), and muscarine chloride (Sigma, St. Louis, MO). All drugs were dissolved in 0.9% saline.

RESULTS

Effects of AM, AM-(22–52), and PAMP on catecholamine output in response to splanchnic nerve stimulation and ACh. Splanchnic nerve stimulation (1, 2, and 3 Hz) or intra-arterial injection of ACh (0.75, 1.5, and 3 µg) into the adrenal gland produced frequency- and dose-dependent increases in adrenal venous plasma catecholamine concentration (data are not shown). ACh injection, but not splanchnic nerve stimulation, increased adrenal plasma flow rate (data are not shown). Catecholamine output, calculated from the catecholamine concentration and the adrenal plasma flow rate, was increased by splanchnic nerve stimulation and ACh injection (Figs. 1 and 2).

Infusion of AM (1, 3, and 10 ng·kg⁻¹·min⁻¹; Fig. 1) or AM-(22–52) (5, 15, and 50 ng·kg⁻¹·min⁻¹; Fig. 2) into the adrenal gland did not affect the splanchnic nerve stimulation- or ACh-induced increases in catecholamine output. Infusion of PAMP (5, 15, and 50 ng·kg⁻¹·min⁻¹) attenuated the splanchnic nerve stimulation- and ACh-induced increases in catecholamine output in a dose-dependent manner (Fig. 3). Figure 3 also shows percentage inhibition by PAMP of the catecholamine output responses (calculated for each frequency of nerve stimulation and each dose of ACh injection, and then averaged). There were no significant differences between the values obtained with splanchnic nerve stimulation and ACh.

Effects of PAMP on catecholamine output in response to DMPP and muscarine. PAMP also attenuated the increases in catecholamine output induced by DMPP and muscarine in a dose-dependent manner (Fig. 4). The percentage inhibition values of the DMPP- and muscarine-induced catecholamine output responses
(Fig. 4), calculated in a similar manner as described above, showed that the inhibitory effect of PAMP on the muscarine-induced response was smaller than the effect on the DMPP-induced response.

Effects of peptides on basal catecholamine output, adrenal plasma flow rate, blood pressure, and heart rate. The results obtained are presented in Table 1. Basal catecholamine output was not affected by AM, AM-(22—52), or PAMP. Basal adrenal plasma flow rate slightly increased during AM infusion (10 ng·kg\(^{-1}\)·min\(^{-1}\)) and decreased during AM-(22—52) infusion (15 and 50 ng·kg\(^{-1}\)·min\(^{-1}\)) but remained unaffected during PAMP infusion. AM (10 ng·kg\(^{-1}\)·min\(^{-1}\)) and AM-(22—52) (50 ng·kg\(^{-1}\)·min\(^{-1}\)), but not PAMP, slightly reduced mean blood pressure. A slight reduction in heart rate was observed during AM-(22—52) infusion (50 ng·kg\(^{-1}\)·min\(^{-1}\)).

Effects of high dose of AM on catecholamine output in response to splanchnic nerve stimulation. AM at 100 ng·kg\(^{-1}\)·min\(^{-1}\) reduced basal mean arterial pressure from 116 ± 4 to 107 ± 6 mmHg (P < 0.05) and increased basal adrenal plasma flow from 1.8 ± 0.1 to 2.2 ± 0.2 ml/min (P < 0.05) and catecholamine output from 7.7 ± 2.5 to 12.6 ± 2.6 ng/min (P < 0.05). However, AM (100 ng·kg\(^{-1}\)·min\(^{-1}\)) did not affect the splanchnic nerve stimulation-induced increases in catecholamine output; the values were 101 ± 21, 229 ± 53, and 622 ± 136 ng/min during 1-, 2-, and 3-Hz nerve stimulation, respectively, in the control period and 78 ± 16, 255 ± 62, and 575 ± 115 ng/min during 1-, 2-, and 3-Hz nerve stimulation, respectively, in the AM infusion period.

Finally, it should be noted that effects of the three peptides on epinephrine output and norepinephrine output were the same. For this reason, total output of epinephrine and norepinephrine was expressed as catecholamine output.

**DISCUSSION**

A previous study in our laboratory demonstrated that the intra-arterial administration method allowed evaluation of the direct action of drugs on adrenal catecholamine release under in vivo conditions (13). In the present study, we examined whether proadrenomedullin-derived peptides modified the release of adrenal catecholamines. Adrenal catecholamine release was evoked by splanchnic nerve stimulation and by injection of cholinergic agonists into the adrenal gland through the phrenicoabdominal artery. The catecholamine release responses induced by the nerve stimulation and the agonist injection had been confirmed to be reproducible throughout the experimental periods (19, 21).

The peptides infused into the adrenal gland over a wide dose range (except the highest doses) did not affect blood
pressure or heart rate. The changes produced by the highest doses were only slight. Thus hemodynamic influence of the peptides on adrenal catecholamine release was negligible.

AM in the dose range of 1–10 ng·kg$^{-1}$·min$^{-1}$ did not alter either basal catecholamine output or the increases in catecholamine output in response to splanchnic nerve stimulation and ACh injection. The doses of AM used seem to be sufficient to produce its action, because AM at the highest dose increased adrenal plasma flow rate and reduced blood pressure. The former response may have been due to the vasodilatory action in the adrenal gland, and the latter response indicated that intra-arterially administered AM enters the systemic circulation in an amount sufficient to produce systemic vasodilation. AM thus does not seem to affect basal adrenal catecholamine release, as demonstrated by Houchi et al. (7) in cultured adrenal chromaffin cells, or to interact with the catecholamine release...
Table 1. Effects of AM, AM-(22—52), and PAMP on MAP, HR, CA output, and APF under basal conditions

<table>
<thead>
<tr>
<th>AM, ng·kg⁻¹·min⁻¹</th>
<th>n</th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>CA Output, ng·min⁻¹</th>
<th>APF, ml·min⁻¹</th>
</tr>
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<tbody>
<tr>
<td>Control</td>
<td>13</td>
<td>129 ± 6</td>
<td>137 ± 10</td>
<td>3.7 ± 1.3</td>
<td>2.3 ± 0.2</td>
</tr>
<tr>
<td>1</td>
<td>128 ± 6</td>
<td>134 ± 10</td>
<td>3.8 ± 1.3</td>
<td>2.5 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>126 ± 6</td>
<td>133 ± 10</td>
<td>3.5 ± 1.2</td>
<td>2.5 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>124 ± 7*</td>
<td>132 ± 10</td>
<td>3.5 ± 1.4</td>
<td>2.6 ± 0.2†</td>
<td></td>
</tr>
<tr>
<td>AM-(22—52), ng·kg⁻¹·min⁻¹</td>
<td>15</td>
<td>113 ± 4</td>
<td>137 ± 5</td>
<td>4.6 ± 0.7</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>5</td>
<td>113 ± 4</td>
<td>134 ± 5</td>
<td>5.4 ± 1.2</td>
<td>1.9 ± 0.2</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>114 ± 4</td>
<td>133 ± 6</td>
<td>4.7 ± 1.2</td>
<td>1.8 ± 0.2†</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>108 ± 4†</td>
<td>130 ± 6*</td>
<td>5.3 ± 1.7</td>
<td>1.8 ± 0.2†</td>
<td></td>
</tr>
<tr>
<td>PAMP, ng·kg⁻¹·min⁻¹</td>
<td>29</td>
<td>122 ± 5</td>
<td>146 ± 6</td>
<td>3.7 ± 2.0</td>
<td>2.7 ± 0.3</td>
</tr>
<tr>
<td>5</td>
<td>120 ± 5</td>
<td>145 ± 6</td>
<td>3.7 ± 1.2</td>
<td>2.8 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>120 ± 5</td>
<td>144 ± 7</td>
<td>3.7 ± 1.2</td>
<td>2.5 ± 0.3</td>
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<tr>
<td>50</td>
<td>119 ± 5</td>
<td>142 ± 7</td>
<td>3.7 ± 1.5</td>
<td>2.5 ± 0.3</td>
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</tr>
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</table>

Values are means ± SE; n, no. of dogs. Effects of adrenomedullin (AM) (groups 1 and 2), AM-(22—52) (groups 3 and 4) and proadrenomedullin NH₂-terminal 20 peptide (PAMP; groups 5–8) on mean arterial pressure (MAP), heart rate (HR), catecholamine (CA) output, and adrenal plasma flow rate (APF) under basal conditions. *P < 0.01 and †P < 0.05 compared with the corresponding control value.

evoked by endogenous or exogenous ACh. We also confirmed that AM, even at the high dose (100 ng·kg⁻¹·min⁻¹) that substantially reduced blood pressure and increased adrenal plasma flow, failed to suppress the nerve stimulation-induced catecholamine output response. Although an increase in basal catecholamine output was observed during the AM infusion (100 ng·kg⁻¹·min⁻¹), the change was very small when compared with the nerve stimulation- or ACh-evoked response, and it should be noted that the data were obtained by application of the pharmacologically high dose that caused systemic hypotension. However, the possibility remains that endogenous AM maximally affects the adrenal catecholamine release under physiological conditions and thereby masks the effects of exogenous AM, since the concentration of AM in the adrenal medulla was demonstrated to be >30-fold higher than that in other organs (24). We therefore examined the effects of AM-(22—52), a selective AM antagonist (3), to evaluate the participation of endogenous AM in adrenal catecholamine release. AM-(22—52) in the dose range of 5, 15, and 50 ng·kg⁻¹·min⁻¹ failed to affect basal catecholamine output and the cholinergic stimuli-induced increases in catecholamine output. Adrenal plasma flow rate, blood pressure, and heart rate were reduced by AM-(22—52), indicating that the doses used were sufficient to produce its action. These findings suggest that AM does not modulate catecholamine release from adrenal medullary cells in vivo, although it participates in the control of adrenal blood flow through a vasodilatory action as demonstrated in the renal vasculature of anesthetized dogs (2).

PAMP attenuated the splanchnic nerve stimulation-induced increases in catecholamine output in a dose-dependent manner. This suggests that PAMP inhibits the release process by acting on a presynaptic site rather than on a postsynaptic site of the adrenal medullary cells. PAMP also produced dose-dependent suppression of the catecholamine release induced by injection of ACh, indicating that PAMP acts on the adrenal medullary cells. The extent of the inhibitory effect of PAMP on the ACh-induced catecholamine release response was the same as its effect on the splanchnic nerve stimulation-induced response. These results suggest that PAMP has little or no effect on the presynaptic site.

Previous studies in our laboratory suggested that the catecholamine release induced by splanchnic nerve stimulation is mainly mediated by nicotinic receptors, with a muscarinic mechanism being only a subsidiary factor, whereas the release induced by exogenous ACh is mediated by both nicotinic and muscarinic receptors in anesthetized dogs (13, 25). Therefore, it may be reasonable to assume that PAMP inhibits catecholamine release by interfering with the process mediated by nicotinic receptors. Nabe et al. (17) recently reported that PAMP suppresses nicotinic inward current in neurons of rat locus ceruleus. However, it is not clear whether PAMP inhibits the release process mediated by muscarinic receptors. No information is available dealing with the effects of PAMP on the muscarinic catecholamine release. To clarify the inhibitory effect of PAMP on nicotinic and muscarinic catecholamine release, we examined its effects on catecholamine release in response to DMPP, a selective nicotinic agonist, and to muscarine. PAMP attenuated both the DMPP-induced catecholamine release and the muscarine-induced catecholamine release in a dose-dependent manner, although the inhibition of the latter response was relatively small. PAMP was reported to inhibit the nicotinic responses in cultured bovine adrenal medullary cells (10, 18). Our present results are consistent with these observations and indicate further that PAMP can also inhibit muscarinic catecholamine release.

The elevation of intracellular Ca²⁺ is an essential step in the process of catecholamine release. PAMP has been suggested to suppress nicotinic ion currents and thereby reduce Ca²⁺ influx through voltage-dependent Ca²⁺ channels in cultured bovine adrenal medullary cells (10, 18). Takano et al. (26) reported that PAMP inhibits N-type Ca²⁺ channels via a pathway mediated by pertussis toxin-sensitive G protein in PC-12 cells. These mechanisms may be involved in the inhibitory action of PAMP on the cholinergic stimulation-induced adrenal catecholamine release observed in the present study.

The inhibitory effect of PAMP on the muscarine-induced catecholamine release was smaller than that on DMPP-induced release, which may have been due to a difference in the contribution of Ca²⁺ influx to catecholamine release between nicotinic and muscarinic activation. Activation of nicotinic receptors produces Ca²⁺...
influx through voltage-dependent Ca\(^{2+}\) channels (1, 5), and in this case the elevation of intracellular Ca\(^{2+}\) was entirely dependent on Ca\(^{2+}\) influx. Activation of muscarinic receptors elevates intracellular Ca\(^{2+}\) both by mobilizing Ca\(^{2+}\) from intracellular Ca\(^{2+}\) stores (16, 27) and stimulating Ca\(^{2+}\) influx through voltage-dependent Ca\(^{2+}\) channels (4, 6). Thus the elevation of intracellular Ca\(^{2+}\) by muscarinic stimulation is partially dependent on Ca\(^{2+}\) influx. This may explain why the muscarine-induced catecholamine release response was relatively resistant to PAMP compared with that induced by DMPP.

In summary, the present study demonstrates that, in anesthetized dogs, PAMP, but not AM, can attenuate the adrenal catecholamine release induced by endogenous and exogenous ACh and that nicotinic catecholamine release is more susceptible to PAMP than muscarinic catecholamine release. PAMP may play an inhibitory role in the control of catecholamine release from the adrenal gland in vivo.

The present study demonstrates different roles of the proadrenomedullin-derived peptides AM and PAMP in the adrenal gland in vivo; AM slightly contributes to maintaining adrenal blood circulation but does not participate in the control of adrenal catecholamine release, whereas PAMP has an ability to regulate adrenal catecholamine release evoked by cholinergic stimulation. We hypothesize that mechanisms by which PAMP attenuates the cholinergic catecholamine output response involve suppression of voltage-dependent Ca\(^{2+}\) channels (10, 18), which may be mediated by the pertussis toxin-sensitive G protein (26). A series of in vivo studies performed in our laboratory have demonstrated that the cholinergic adrenal catecholamine release is modulated by N-type Ca\(^{2+}\) channels (21), K\(_{\text{A}}\) channels (one type of voltage-dependent K\(^{+}\) channels (20)), and nitric oxide (19). It is of interest that the inhibitory action of nitric oxide on the adrenal catecholamine release seems to depend on activation of high-conductance Ca\(^{2+}\)-activated K\(^{+}\) channels (22). PAMP may also interact with these modulation mechanisms of the adrenal catecholamine release. Although the in vivo experiments cannot clarify the precise pathways, combination of drugs with high selectivity for each mechanism would reveal the interaction and may be able to provide further information on physiological aspects of this peptide in the cardiovascular homeostasis.

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