Differential Actions of Angiotensin II and Angiotensin-(1–7) on Transmitter Release

Debra I. Diz and Nancy T. Pirro

The central cardiovascular and dipsogenic effects of angiotensin II involve interactions with norepinephrine, dopamine, and serotonin. Our findings that angiotensin II receptors and substance P immunoreactivity show a parallel distribution in the dorsal medulla and that angiotensin II releases substance P from perfused rat medulla slices revealed the potential for a functional relation between these peptidergic systems as well. Additional evidence suggests that the heptapeptide angiotensin-(1–7) exerts its biological activities via selective angiotensin receptor subtypes. Thus, we compared the effects of these two peptides on release of substance P and monoamines in perfused slices of medulla and hypothalamus from 77 male Sprague-Dawley rats. Transmitter levels were determined in 6-minute collections of perfusate before (basal), during (experimental), and after (recovery) perfusion with either angiotensin-(1–7), angiotensin II, or Krebs’ solution alone (control). Substance P was measured by radioimmunoassay and monoamines and their metabolites by high-performance liquid chromatography with electrochemical detection. In the medulla, 2 μM angiotensin II but not angiotensin-(1–7) significantly increased efflux of substance P (221 ± 87% of basal) and norepinephrine (130 ± 17% of basal) during the experimental period. The effect of angiotensin II on substance P was sustained into the recovery period. Dopamine and its metabolite 3,4-dihydroxyphenylacetic acid were not detected in this brain region. In the hypothalamus, both angiotensin-(1–7) and angiotensin II increased substance P (169 ± 30% and 141 ± 35% of basal, respectively); the effect of angiotensin II was sustained throughout the recovery period. In addition, angiotensin II increased norepinephrine (300%), dopamine (270%), and 3,4-dihydroxyphenylacetic acid (200%) efflux during the experimental period. Although angiotensin-(1–7) was not effective during the experimental period, an increase in all three amines (200–500%) occurred during the recovery period after the low dose. Neither peptide significantly altered serotonin as assessed by hydroxyindoleacetic acid. These data support the concept that the central nervous system actions of angiotensin peptides are mediated by interactions with specific transmitter systems. Moreover, the differential actions of angiotensin-(1–7) and angiotensin II are consistent with our previous demonstrations that angiotensin-(1–7) selectively activates subpopulations of angiotensin receptors. (Hypertension 1992;19[suppl II]:II-41–II-48)
neither serotonin all produce depressor and bradycardic effects when injected into this region.

We have additional evidence that the heptapeptide angiotensin-(1-7) [Ang-(1-7)] produces some of the same effects as Ang II in the hypothalamus and medulla and failure of Ang-(1-7) to produce the entire complement of actions attributed to Ang II may be a result of selective actions at subpopulations of Ang II receptors. Because differential activation of specific transmitter systems would be further confirmation for the selective actions of Ang-(1-7), we compared the effects of the two angiotensin peptides on the release of SP-ir and monoamines in brain slices from the medulla oblongata and hypothalamus of rats.

Methods

The brains from 77 male Sprague-Dawley rats (253±3 g body weight; Harlan Sprague Dawley, Inc., Indianapolis, Ind.) were removed after decapitation and placed in ice-cold Krebs' bicarbonate buffer. The medulla oblongata (from 1 mm caudal to 2 mm rostral to the calamus scriptorius) and the hypothalamus (from 1 mm rostral to the optic chiasm to 1 mm caudal to the infundibular stalk, 1 mm lateral to the median eminence on each side, and ventral to the thalamus) were chopped into 0.5x0.5-mm pieces using a tissue chopper (Gel Slicer, Brinkmann Instruments, Inc., Westbury, N.Y.) and placed in a chamber with an internal volume of 1 ml. The tissue was perfused at a flow rate of 0.42 ml/min with 37°C oxygenated Krebs' bicarbonate solution containing (mM) NaCl 135, KCl 3.5, MgSO4 1, NaHCO3 20, CaCl2 2.5, and 0.5% bovine serum albumin, 20 μM bacitracin, 3.3 mM dextrose, and 6 μM dithiothreitol as originally published by Pang and Vasko. Perfusion chambers were gently shaken throughout the incubation period as recommended for better diffusion of buffers and recovery of released substances. The solution was continuously bubbled with 95% O2–5% CO2 to achieve a pH of 7.4. In the high (25 mM) potassium buffer, isotonicity was maintained by lowering the amount of NaCl. After a 16-minute equilibration, samples were collected every 6 minutes for the next 24 minutes. The first sample was used for determination of basal release (basal). The second 6-minute sample (experimental) was collected during continued perfusion with the Krebs' solution containing 0.2 or 2 μM Ang II or Ang-(1-7) or the Krebs' solution alone as a time control (control). The next two 6-minute samples were collected during perfusion with the Krebs' solution alone (recovery 1 and 2).

Samples were collected on ice. SP samples (1 ml of the perfusate) were acidified with 0.14 ml glacial acetic acid and 0.1 ml of a 10% l-cysteine solution before storage at −80°C for subsequent radioimmunoassay according to the method of McGregor and Bloom using antisera No. 4892 kindly provided by V.L.W. Go. The antibody cross-reacts 100% with SP-NH2 (amide), SP-(2-11)-NH2, and SP-(4-11)-NH2; 1% with physalaemin; 0.3% with kassinin; less than 0.1% with eledoisin or substance K; and less than 0.002% with SP-OH (free acid), SP-(1-9), or the angiotensin peptides. Intra-assay and interassay variabilities were 9% and 10%, respectively. Monamine samples (1.5 ml of the perfusate) were acidified with 0.1 ml perchloric acid and analyzed by high-performance liquid chromatography with electrochemical detection either by direct injection or after Bond Elute C18 extraction according to the procedure of Crowe and Jacobsen. Values (mean±SEM) are expressed as percent of basal (spontaneous) release, where basal was defined as the amount present in the first 6-minute sample. Analyses of variance followed by least significant difference between two means. A value of p<0.05 was used as the criterion for a significant difference among means.

Results

Basal Levels

Table 1 lists average basal values obtained during the first 6-minute collection for each of the transmitters. Dopamine and its metabolite 3,4-dihydroxyphenylacetic acid (DOPAC) were detected in the perfusate only from the hypothalamus. Because monoamine oxidase inhibitors were not added to the perfusion buffer, serotonin was not consistently detected in any of the samples. Therefore, the 5-hydroxyindoleacetic acid (5-HIAA) metabolite was used as an indirect index of serotonin in these studies.

Angiotensin Peptide–Evoked Transmitter Levels in Perfusion From Medulla

When compared with the control group, Ang II (2 μM) significantly (p<0.05) increased both SP-ir (400%) and norepinephrine (167%) efflux during the experimental period (Figures 1 and 2A, top panels). The effect of Ang II on SP-ir was sustained, as elevated levels were still observed in the first recovery period. Although 2 μM Ang-(1-7) did not alter SP-ir or norepinephrine efflux during the experimental period (Figures 1 and 2A, top panels), there was an increase in norepinephrine (272% above control; p<0.05) in the recovery period (Figure 2A, top panels).

<table>
<thead>
<tr>
<th>Transmitter/metabolite</th>
<th>n</th>
<th>Medulla</th>
<th>Hypothalamus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance P (pg/ml)</td>
<td>37</td>
<td>13.9±2.9</td>
<td>7.4±0.9</td>
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<tr>
<td>Norepinephrine (ng/ml)</td>
<td>46</td>
<td>0.9±0.1</td>
<td>1.9±0.3</td>
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<td>Dopamine (ng/ml)</td>
<td>37</td>
<td>...</td>
<td>2.2±0.5</td>
</tr>
<tr>
<td>DOPAC (ng/ml)</td>
<td>37</td>
<td>...</td>
<td>2.4±0.5</td>
</tr>
<tr>
<td>5-HIAA (ng/ml)</td>
<td>32</td>
<td>2.3±0.4</td>
<td>3.4±0.3</td>
</tr>
</tbody>
</table>

Values are spontaneous (basal) efflux during the first 6-minute collection period. Average tissue weight was 0.11±0.003 g for medulla and 0.19±0.006 g for hypothalamus (n=75). Number of rats; DOPAC, 3,4-dihydroxyphenylacetic acid; 5-HIAA, 5-hydroxyindoleacetic acid.
**FIGURE 1.** Line graphs show angiotensin (Ang) II (2 μM) added during experimental (Exp) period increased substance P immunoreactivity (SP-ir) in perfusate from both medulla and hypothalamus (230–400% above the same period in control animals. SP-ir remained elevated 400–500% during recovery (Rec) periods after exposure to Ang II. In contrast, 2 μM Ang-(1–7) significantly increased SP-ir release (282%) in hypothalamus only. *p<0.05 when compared with value obtained during the same period in the control group. Number of animals in each group is shown in parentheses.

panel). 5-HIAA was not significantly altered by either angiotensin peptide (Figure 2B).

**Angiotensin Peptide-Evoked Transmitter Levels in Perfusate From Hypothalamus**

Both Ang-(1–7) and Ang II (2 μM) significantly increased SP-ir (~250% above that observed in the control group; p<0.05) during the experimental period (Figure 1, bottom panel). SP-ir levels remained elevated 350–450% over control during the two recovery periods after exposure to Ang II (p<0.05). Ang II also increased release of norepinephrine (300%), dopamine (270%), and DOPAC (200%) during the experimental period (p<0.05) when compared with the control group (Figure 2A, bottom panel, and Figure 2C). In contrast, Ang-(1–7) had no effect on these amines. Again, 5-HIAA was not significantly altered by either angiotensin peptide (Figure 2B, bottom panel).

**Effects of Angiotensin Peptides on Potassium-Evoked Transmitter Levels**

We also assessed the effects of a moderate potassium stimulus (25 mM) alone or in combination with a lower dose (0.2 μM) of Ang II or Ang-(1–7). Table 2 summarizes the data for responses in the experimental period. In the medulla, 25 mM potassium significantly enhanced release of norepinephrine and SP-ir in the experimental period (p<0.05), whereas the low dose of either angiotensin peptide had no significant effect when compared with the control group (Table 2). Moreover, when compared with the potassium stimulus alone, there was no further increase in the release of norepinephrine or SP-ir as a result of perfusion with 25 mM potassium plus either 0.2 μM Ang II or Ang-(1–7). Although 5-HIAA release was not increased by low doses of the angiotensin peptides or by 25 mM potassium alone, the combined treatment of potassium plus Ang-(1–7) caused a small but significant increase in release in the experimental period when compared with the control group (Table 2). This effect was sustained into the recovery period (162±50%; p<0.05). However, neither response was significantly different from the potassium stimulus alone.

In the hypothalamus, the 25 mM potassium stimulus did not significantly increase release of any of the transmitters (Table 2). Furthermore, neither 0.2 μM Ang II nor Ang-(1–7) alone resulted in significant stimulation of release of any of the transmitters in the experimental period (Table 2). However, 0.2 μM Ang-(1–7) significantly increased norepinephrine (158±46%), dopamine (398±244%), and DOPAC (508±380%) during the recovery period (p<0.05 when compared with the same period in the control group). This effect was not seen with Ang II. When 25 mM potassium was combined with either Ang II or Ang-(1–7), SP-ir efflux increased significantly compared with the control group (Table 2). In addition, the ability of Ang-(1–7) plus potassium to increase SP was now sustained into the recovery period (340±148% as compared with 115±18% for potassium alone during this period; p<0.05), similar to what was described above with the higher dose of Ang II alone. However, efflux of norepinephrine, dopamine, DOPAC, or 5-HIAA was not further enhanced with the combined treatment of potassium plus either Ang II or Ang-(1–7). In fact, in the experimental period, many of the values after the combined potassium plus peptide treatment tended to be lower than with either stimulus alone (Table 2), and the ability of Ang-(1–7) to enhance transmitter release in the recovery period was no longer seen.

**Discussion**

In the medulla, Ang II enhanced the efflux of both norepinephrine and SP-ir. From anatomic studies, we learned that the majority of Ang II receptors are associated with presynaptic vagal afferent fibers containing SP-ir. Moreover, the magnitude of the Ang II-induced increase in SP-ir release in the medulla was comparable to that seen with capsaicin, indicating that vagal afferent fibers may indeed be one source of released
FIGURE 2. Panel A: Line graphs show angiotensin (Ang) II (2 μM) increased norepinephrine release 150% in medulla and 300% in hypothalamus during the experimental (Exp) period when compared with the control group. The same dose of Ang-(1-7) had minimal effects during this time period but did cause a delayed increase in norepinephrine during the recovery (Rec) period. Panel B: Line graphs show neither Ang peptide significantly altered 5-hydroxyindoleacetic acid (5-HIAA) efflux. Panel C: Line graphs show Ang II but not Ang-(1-7) increased dopamine and 3,4-dihydroxyphenylacetic acid (DOPAC) in perfusate from hypothalamus during the experimental period (200-300% above the same period in control). *p<0.05 when compared with the same period in the control group.

SP. Because Ang II, norepinephrine, and SP each produce depressor effects when given into the dorsal medulla,\textsuperscript{3,19-21,37} it is possible that the cardiovascular actions of Ang II are a result of both direct and indirect actions. For example, SP-ir released from vagal afferent fibers in response to Ang II could exert

<table>
<thead>
<tr>
<th>Region/stimulus</th>
<th>n</th>
<th>Substance P</th>
<th>Norepinephrine</th>
<th>Dopamine</th>
<th>DOPAC</th>
<th>5-HIAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medulla</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Potassium (25 mM)</td>
<td>7</td>
<td>198±36*</td>
<td>174±31*</td>
<td>...</td>
<td>...</td>
<td>119±39</td>
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<tr>
<td>Ang II (0.2 μM)</td>
<td>6</td>
<td>88±10</td>
<td>102±13</td>
<td>...</td>
<td>93±6</td>
<td>...</td>
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<tr>
<td>Ang II+potassium</td>
<td>6</td>
<td>160±33</td>
<td>168±61*</td>
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<td>134±30</td>
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<tr>
<td>Ang-(1-7) (0.2 μM)</td>
<td>6</td>
<td>127±24</td>
<td>122±39</td>
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<td>...</td>
<td>124±14</td>
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<tr>
<td>Ang-(1-7)+potassium</td>
<td>6</td>
<td>177±52*</td>
<td>98±16</td>
<td>...</td>
<td>...</td>
<td>146±53*</td>
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<tr>
<td>Hypothalamus</td>
<td></td>
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</tr>
<tr>
<td>Potassium (25 mM)</td>
<td>7</td>
<td>163±31</td>
<td>151±36</td>
<td>153±28</td>
<td>142±17</td>
<td>116±38</td>
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<tr>
<td>Ang II (0.2 μM)</td>
<td>6</td>
<td>103±14</td>
<td>166±29</td>
<td>137±16</td>
<td>132±22</td>
<td>109±11</td>
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<tr>
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<td>6</td>
<td>205±30*</td>
<td>140±20</td>
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<td>6</td>
<td>80±21</td>
<td>90±14</td>
<td>121±26</td>
<td>167±82</td>
<td>81±17</td>
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<td>6</td>
<td>249±66*</td>
<td>92±36</td>
<td>246±100</td>
<td>69±20</td>
<td>83±30</td>
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</table>

Values represent efflux during perfusion with the listed stimuli in the experimental period and are expressed as percent of basal values. Basal values were determined in the collection period immediately before the experimental period. Values obtained during the recovery period are included in "Results" where appropriate. n, Number of rats; DOPAC, 3,4-dihydroxyphenylacetic acid; 5-HIAA, 5-hydroxyindoleacetic acid; Ang, angiotensin. *Significant increase when compared with values obtained during the same period in control group (p<0.05). There were no differences when potassium alone was compared with potassium plus peptide for any of the variables listed.
effects at intrinsic NTS neurons, vagal motor neurons, or the A2 catecholamine region, because SP receptors have been localized within each of these regions. Recent studies by Barnes et al also found separate populations of neurons responding either to Ang II or SP but not to both peptides. This finding implies the additional presence of Ang II receptors located postsynaptically on intrinsic neurons of the NTS and dorsal motor nucleus, possibly containing norepinephrine or SP. Earlier functional studies investigating the acute cardiovascular effects of Ang II microinjections into the dorsal motor nucleus of the vagus revealed that the heart rate component of the response is related to efferent vagal motor control of the heart, suggesting activation of vagal motor neurons. Ang II, SP, and norepinephrine receptors are reported on vagal motor neurons, consistent with direct actions of each of the substances. However, the blood pressure effects of Ang II in the dorsal and ventral medulla also appear to involve a sympathetic component. Norepinephrine-containing cells in the medulla are located in the A1 and A2 regions, with interconnections to descending vasomotor centers. Therefore, the effects on norepinephrine release may be the result of postsynaptic actions of Ang II in these regions. Anatomic evidence exists for Ang II receptors in close proximity to the catecholamine cell groups in both the dorsal and ventral medulla, and both endogenous and exogenous Ang II exert cardiovascular effects at these sites.

Serotonin is present in many vagal afferent fibers, and previous studies showed that Ang II enhances serotonin release in some brain regions. Therefore, we were surprised that Ang II had no effect on the release of 5-HIAA in the medulla. However, the reported effects of Ang II on serotonin were dose dependent (i.e., increases in serotonin with low doses of Ang II and decreases with higher doses). Thus, the dose range used in the present study may not have been appropriate. In addition, although parallel changes in serotonin and 5-HIAA are reported, it is also possible that 5-HIAA is not a sensitive indicator of serotonin release. Thus, we cannot exclude completely an action of Ang II on this transmitter as well. Recently, we showed that both Ang II and Ang-(1-7) exert similar cardiovascular and excitatory neuronal actions in the medulla oblongata. The cardiovascular effects of the two peptides could be blocked by the nonselective classical Ang II receptor antagonist [Sar^1, Thr^3]Ang II, suggesting actions at an Ang II receptor. However, additional evidence suggested that the receptors sensitive to Ang-(1-7) may represent a subset of those recognized by Ang II, because Ang-(1-7) was a potent displacer only in the rostral aspect of the dorsal medulla. Interestingly, the receptors most sensitive to Ang-(1-7) were in a region of the medulla containing the least amount of SP-ir. In the present study, release of norepinephrine and SP-ir in the medulla increased during the experimental period in response to Ang II but not to Ang-(1-7). Because unilateral sinoaortic denervation differentially altered the cardiovascular responses to Ang II and Ang-(1-7) and some medial NTS neurons were responsive to only Ang II or Ang-(1-7), our findings suggest that Ang-(1-7) and Ang II have functionally and anatomically different actions. This is further supported by studies revealing that many of the cardiovascular effects of Ang II may be presynaptic or indirect (i.e., mediated by SP or norepinephrine), as discussed above. In contrast, the acute effects of Ang-(1-7) appear to be postsynaptic and largely direct. Further studies, however, are necessary to differentiate clearly between the possibilities.

In the hypothalamus, both Ang II and Ang-(1-7) caused release of SP-ir. Although the functional consequences of this SP release are not known, recent reports suggest that tachykinins are involved in modulation of thirst and fluid balance in this brain area, and interactions with the brain angiotensin system are reported. Interestingly, eledoisin but not SP elicits an increase in plasma vasopressin after intraventricular administration, an effect apparently mediated by Ang II. Thus, tachykinins other than SP may be involved, although SP is present in the predominant tachykinin throughout the medulla oblongata and hypothalamus. Both angiotensin peptides have been shown to produce neuronal excitation in the paraventricular nucleus, and Schiavone et al reported that both Ang II and Ang-(1-7) stimulate release of vasopressin from isolated hypothalamo-neurohypophysial explants. Initial studies showed that the vasopressin-releasing effects of both peptides were inhibited by [Sar^1, Thr^3]Ang II. More recently, the effects of Ang II on vasopressin release were shown to be blocked by the AT1-selective antagonists PD123177 or CGP42112A. Although the effect of these inhibitors on the vasopressin release in response to Ang-(1-7) has not been tested, Ang-(1-7)-induced neuronal excitation in the paraventricular nucleus was inhibited by CGP42112A. Thus, an AT2 receptor may be linked to vasopressin release. In addition, we have shown that the effects of Ang-(1-7) on prostaglandin release in human astrocytes are blocked by the CYP42112A antagonist but not by the DuP 753 antagonist. In contrast, the effects of Ang II on prostaglandin release were attenuated by either CYP42112A or DuP 753, suggesting that both AT1 and AT2 angiotensin receptors are involved in the response to Ang II but that Ang-(1-7) is selective for the AT2 receptor in these cells. Moreover, these data
strengthen the concept for differential actions of the two angiotensin peptides and emphasize the importance of the enzymatic processing pathways involved in their formation.

As further indication of the potential differences between the two peptides, the high dose of Ang II caused a rapid and significant stimulation of norepinephrine and dopamine release in the hypothalamus as reported by others in brain tissue. In contrast, low but not high doses of Ang-(1-7) caused a delayed increase in norepinephrine and dopamine. Functionally, the observed effect of Ang II on norepinephrine and dopamine is consistent with previous reports by us and others that these amines mediate a portion of the central cardiovascular and neuroendocrine effects of intracerebroventricular administration of the peptide. Because the hypothalamic actions of Ang-(1-7) in the whole animal are not identical to those of Ang II, that is, Ang-(1-7) has no dipogenic or pressor effects, differences in the characteristics of the transmitter responses to the two peptides might be expected. Nonetheless, the delayed increase in norepinephrine and dopamine in the hypothalamic perfusate after prior exposure to Ang-(1-7) suggests a possible modulatory effect. Although this may again reflect the ability of the peptide to selectively activate angiotensin receptor subtypes, the actions appear distinct from those of Ang II, and future studies will attempt to document the functional significance of this latter finding.

Interestingly, with the possible exception of SP-ir release in the hypothalamus, neither Ang II nor Ang-(1-7) facilitated a potassium-evoked release of transmitters. Previous studies of the effects of Ang II on evoked release of norepinephrine in normotensive rats are inconsistent, with no effect, increases, or decreases reported. However, low doses (0.1 μM) of Ang II did facilitate potassium-evoked norepinephrine release in the hypothalamus of spontaneously hypertensive rats. Thus, in pathophysiological states, differences in the interactions among these transmitters may exist. Interestingly, Balla et al recently reported that Ang II inhibits potassium-stimulated increases in cytosolic calcium in adrenal glomerulosa cells, even though potassium-stimulated aldosterone production was not altered. The complexities of such interactions are underscored by the observed tendency for a lower release value with combined angiotensin peptide plus potassium treatment in spite of the ability of higher doses of angiotensin peptides to evoke release in the present study. In fact, a similar finding has been reported in that high doses of cholecystokinin increase basal dopamine release, whereas lower doses cause a slight reduction (20-40%) in potassium-stimulated release. It is tempting to speculate that such a phenomenon can explain several characteristics of the cardiovascular responses to angiotensin peptides. For example, when equal low doses (range of 10-1,000 fmol) of either Ang II or Ang-(1-7) are microinjected into the dorsal medulla oblongata of the rat, decreases in blood pressure and heart rate occur. In contrast, higher doses (50-250 pmol) of either angiotensin peptide produce increases in blood pressure and heart rate at the same site. Similar biphasic dose-response curves are reported for SP in the medulla, where low doses cause decreases and high doses cause increases in pressure. In addition, the acute effects of the low doses of all three of these peptides mimic activation of the baroreceptor reflex. However, endogenous angiotensin peptides appear to exert a tonic inhibitory influence when the baroreceptor reflex is activated, because the angiotensin antagonist [Sar^Thr^]Ang II facilitates the reflex. Although these findings exemplify the neuromodulatory effects attributed to neuropeptides in general, other potential direct and indirect interactions among the systems may occur. For example, SP and norepinephrine produce opposite electrophysiological actions in a number of areas, and each exerts a negative influence on release of the other. Nonetheless, our studies provide initial evidence of mechanisms for selective release of particular transmitters by members of the angiotensin peptide family. Furthermore, the different pathways activated may explain the different physiological responses observed with central administration of the two angiotensin peptides.

Acknowledgments

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II-47


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**Key Words**: angiotensin II • angiotensin-(1–7) • hypothalamus • medulla oblongata • norepinephrine • dopamine • serotonin • substance P
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