AT$_1$ Receptors in the RVLM Mediate Pressor Responses to Emotional Stress in Rabbits

Dmitry N. Mayorov, Geoffrey A. Head

Abstract—In this study, we examined the role of angiotensin type 1 (AT$_1$) receptors in the rostral ventrolateral medulla (RVLM) in mediating the pressor action of emotional stress in conscious rabbits. Rabbits were chronically instrumented with guide cannulas for bilateral microinjections into the RVLM and an electrode for measuring renal sympathetic nerve activity (RSNA). Airjet stress evoked increases in arterial pressure, heart rate, and RSNA, which reached a maximum ($+9 \pm 1$ mm Hg, $+20 \pm 5$ beats/min, and $+93 \pm 17\%$, respectively) in the first 2 minutes of stress exposure. Then RSNA rapidly returned to prestress values, while arterial pressure and heart rate remained close to the maximal level until the conclusion of the 7-minute airjet exposure. Microinjections of the nonselective angiotensin receptor antagonist sarile (0.5 nmol, n=8) or AT$_1$ receptor antagonists losartan (2 nmol, n=6) or candesartan (0.2 nmol, n=6) into the RVLM did not alter resting cardiovascular parameters. By contrast, the antagonists attenuated the sustained phase (4 to 7 minutes) of the pressor stress response by 55% to 89%. However, only sarile decreased the onset of this response. The antagonists affected neither the stress-induced tachycardia nor the pressor response to glutamate microinjections. Microinfusion of angiotensin II (4 pmol/min, n=8) into the RVLM did not change the pressor response to airjet stress but attenuated tachycardic response by 47%. Microinjections of vehicle did not alter the cardiovascular stress response. Sarile, losartan, and angiotensin II did not affect the sympathoexcitatory response to baroreceptor unloading. These results suggest that AT$_1$ receptors in the RVLM are important in mediating the pressor effects of emotional stress in conscious rabbits. (Hypertension. 2003;41:693-699.)

Key Words: receptors, angiotensin II, stress, blood pressure, brain, rabbits

The excessive blood pressure responses to psychoemotional challenges, particularly in combination with the aversive effects of increased life stress, are believed to be a precursor of hypertension, coronary heart disease, and atherosclerosis. However, remarkably little is known about the mechanisms that modulate the cardiovascular susceptibility to psychoemotional stress. In view of the primary importance of activating the sympathetic nervous system in blood pressure stress responses, these mechanisms are likely to include neural imbalance at the level of the brain stem presympathetic nuclei. The critical neurons appear to be the cell group in the rostral ventrolateral medulla (RVLM). This cell group plays a key role in the generation and maintenance of sympathetic vasomotor outflow and also is the anatomic site of convergence of excitatory inputs from higher brain structures, primarily conveying stressor environmental stimuli. However, until recently, experimental evidence for the importance of the RVLM in cardiovascular reactions to psychoemotional stress was elusive because of the difficulty in accessing this area in conscious, freely behaving animals. A short time ago, we developed, in conscious rabbits, a method for bilateral microinjections into the RVLM. We found that blockade of ionotropic excitatory amino acid (EAA) receptors in this region by kynurenic acid markedly reduced the onset of the pressor response to a jet of air.

To our knowledge, this was the first direct evidence that the RVLM is a critical relay in mediating the cardiovascular response to acute environmental stress in conscious animals. Remarkably, in this study, the pressor response recovered after several minutes of airjet stress, prompting us to investigate whether the RVLM is essential in the maintenance of elevated blood pressure during stress exposure, and if so, which receptor subtypes mediate the sustained phase of the pressor stress reaction. In the present study, we sought to establish the role of angiotensin II (Ang II) type 1 (AT$_1$) receptors in the RVLM in mediating the cardiovascular reactions to acute emotional stress in conscious rabbits. Ang II has been recognized recently as a major stress mediator in the brain, whereas the RVLM has a high density of AT$_1$ receptors and is a major site of the sympathoexcitatory action of Ang II in various species. We determined whether bilateral administration of selective AT$_1$ receptor antagonists, losartan and candesartan, or the nonselective Ang II receptor antagonist sarile into the RVLM alters the acute hypertension evoked by airjet stress. In addition, as a control, we evaluated the effects of...
Figure 1. Top, Schematic representation of the coronal view of the rabbit medulla with shaded areas showing injection site evaluated by pontamine sky blue diffusion into the RVLM from 1 rabbit. IO indicates inferior olive; NA, nucleus ambiguous. Bottom, Original recordings of MAP responses to unilateral injections of glutamate (10 nmol in 100 nL) into the left and right RVLM of the same rabbit. Arrows mark injection of glutamate.

these antagonists on the pressor response to glutamate microinjections into the RVLM and on the sympathoexcitatory response to baroreceptor unloading.

Methods

General Procedures

The experiments were performed in conscious rabbits of either sex, weighing 2.7 to 3.2 kg, bred and housed at the Baker Heart Research Institute, in accordance with the Australian Code of Practice for the Care and Use of Animals for Scientific Purposes. Three weeks before the experiments, rabbits were implanted with guide cannulas for bilateral microinjections into the RVLM, and 2 weeks later, a bipolar electrode for recording renal sympathetic nerve activity (RSNA).6 On the day of the experiment, the animal was placed in a standard rabbit box (15×40×18 cm, width×length×height), and mean arterial pressure (MAP), heart rate (HR), and RSNA were recorded continuously, as described previously.6

Experimental Protocol

In each rabbit, the location of injection sites was initially identified functionally by using microinjections of glutamate (Figure 1). Only those rabbits in which glutamate (5 to 10 nmol in 50 to 100 nL bilaterally) evoked a pressor response >20 mm Hg were included in the studies. During the experiment, the cardiovascular responses to airjet stress were determined before and after bilateral administration into the RVLM of sarile (0.5 nmol in 200 nL, n=8), losartan (2 nmol in 100 nL, n=6), or Ang II (4 pmol/20 nL per minute for 25 minutes, n=8). In each rabbit, the RSNA and HR baroreflexes were assessed before and 20 to 25 minutes after drug administration.6 In each experiment, the RSNA values were normalized to the upper plateau of the control baroreflex curve, which was taken to equal 100 normalized units (nu). Because both sarile13,14 and losartan10 can exert Ang-unrelated actions in the RVLM, in additional series of experiments, the MAP and HR responses to airjet stress were evaluated before and after bilateral microinjections of the highly specific AT1 receptor antagonist candesartan (0.2 nmol in 100 nL, n=6) or vehicle (100 nL). Also, the pressor responses to microinjections of glutamate into the RVLM were determined before and 10 to 30 minutes after local injections of sarile, losartan, or candesartan.

The selected doses of the drugs were based on previous experiments.10,13,15,16 Glutamate, sarile (Sar8Ile9-Ang II), Ang II (all obtained from Sigma), losartan (a gift of DuPont, Wilmington, Del), and candesartan (a gift of Astra Zeneca, Australia) were dissolved in sterile Ringer’s solution (Baxter). Each rabbit was subjected to 1 to 2 different treatments per experiment in 2 experiments 2 days apart. In the case of 2 treatments during the same experiment, a 2- to 3-hour period was allowed between treatments, and full functional recovery of the cardiovascular response to airjet stress was observed before proceeding to the next treatment. The airjet stress was induced by directing a fine stream of compressed air to the face of the rabbit at a rate of 20 L/min for 7 minutes.7 The microinjections into the RVLM were made through a stainless steel injector (outer diameter, 315 μm), which extended 7.0 mm beyond the guide cannula. On completion of the experiment, each animal was euthanized with sodium pentobarbionate, and the injection sites were marked with 100 nL of 2% pontamine sky blue. Brains were removed, fixed in 10% formaldehyde solution, then frozen, sectioned at 30 μm, and examined under the microscope for dye distribution.

Statistical Analysis

Values are expressed as mean±SE. A 1-way ANOVA was used to compare the resting values between treatment groups. A multifactor repeated-measures ANOVA was used to determine the effect of drug treatment, stress (onset, plateau), and their interaction. The between-animal sum of squares (SS) as well as the treatment SS were removed from the total SS to obtain a within-animal SS.11 Effects were considered significant, and the null hypothesis was rejected when P<0.05.

Results

Basal MAP, HR, and RSNA and Their Responses to Stress

Resting values of MAP, HR, and RSNA were not different before or after the bilateral administration of sarile, losartan, or Ang II into the RVLM in conscious rabbits (Table). Airjet stress evoked sustained increases in MAP and HR, which typically reached a maximum within 2 minutes (+9±1 mm Hg and +20±5 beats/min, respectively, P<0.001) and did not change thereafter (Figure 2). By contrast, airjet stress induced only a transient increase in RSNA, which was greatest in the first minute (+22±4 nu, P<0.001) but rapidly returned to prestress levels as a more gradual pressor response developed. This return was presumably mediated by the arterial baroreflex, as we found that airjet stress evoked a stable RSNA increase in chronically sinoaortic-denervated rabbits (n=3; data not shown). There was no difference in hemodynamic or RSNA responses to airjet stress before treatments with sarile, losartan, or Ang II (F2,19 between groups<0.8, P>0.05).

Sarile

Microinjections of sarile (0.5 nmol, n=8) into the RVLM markedly attenuated the pressor response to airjet stress, producing a similar relative decrease during initial (−59±14%, P<0.01) and sustained (−55±15%, P<0.05) phases of the response (Figure 2). By contrast, the tachycardia evoked by airjet stress was unaltered by the antagonist (Figure 2). Microinjections of sarile did not alter the RSNA or HR baroreflex (Table). The pressor response to glutamate (5 nmol, n=3) was not different before (+24±3 mm Hg) and 10 to 30 minutes after (+25±6 mm Hg) administration of sarile. In 3 control rabbits instrumented for microinjections 1.5 mm rostral to the
RVLM, microinjections of sarile did not alter resting MAP and HR or their responses to airjet stress (data not shown).

**Losartan**

Microinjections of losartan (2 nmol, n=6) into the RVLM did not change the onset of the pressor response to airjet stress (Figure 2). However, the maintenance of this response, estimated as the average increase in MAP during 4 to 7 minutes of stress exposure, was abolished by losartan (+9±2 mm Hg and +1±1 mm Hg before and after injection, respectively). By contrast, the tachycardic response to airjet stress remained unaltered (Figure 2). The pressor response to airjet stress recovered 2.5 to 3 hours after injection of losartan. At that time, the average increase in MAP was +10±2 mm Hg and +8±2 mm Hg during the onset and plateau of the response, respectively. In contrast to sarile and candesartan, microinjections of losartan evoked transient (3 to 5 minutes) increases in MAP (+12±2 mm Hg, P<0.01, Figure 3) and RSNA (+12±4 nu, P<0.05). Microinjections of losartan into the RVLM did not affect RSNA and HR baroreflexes (Table, Figure 3) nor the pressor responses to glutamate (Figure 3).

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### Table 1: Resting and Baroreflex Parameters Before and After Bilateral Administration of Sarile, Losartan, or Ang II Into the RVLM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sarile (n=8)</th>
<th>Losartan (n=6)</th>
<th>Ang II (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MAP, mm Hg</strong></td>
<td>Control</td>
<td>Δ</td>
<td>Control</td>
</tr>
<tr>
<td></td>
<td>82±2</td>
<td>−1±2</td>
<td>80±2</td>
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<td></td>
<td>86±2</td>
<td>+4±2</td>
<td>76±2</td>
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<td></td>
<td>84±2</td>
<td>+2±2</td>
<td>72±2</td>
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<td><strong>RSNA, nu</strong></td>
<td>23±5</td>
<td>+2±1</td>
<td>26±3</td>
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<td></td>
<td>25±2</td>
<td>−2±5</td>
<td>25±2</td>
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<tr>
<td></td>
<td>27±2</td>
<td>+1±4</td>
<td>26±2</td>
</tr>
<tr>
<td><strong>HR, bpm</strong></td>
<td>214±12</td>
<td>−2±3</td>
<td>195±6</td>
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<td></td>
<td>193±8</td>
<td>+5±6</td>
<td>193±8</td>
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<tr>
<td></td>
<td>202±8</td>
<td>+8±6</td>
<td>219±6</td>
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<td><strong>RSNA baroreflex parameters</strong></td>
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<td></td>
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<tr>
<td>Lower plateau, nu</td>
<td>11±2</td>
<td>+0±1</td>
<td>13±2</td>
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<td></td>
<td>14±3</td>
<td>+1±1</td>
<td>15±3</td>
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<td></td>
<td>16±4</td>
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<td>17±6</td>
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<td><strong>Range, nu</strong></td>
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<td>87±3</td>
<td>+7±7</td>
<td>87±3</td>
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<tr>
<td><strong>Gain, −nu/mm Hg</strong></td>
<td>5.4±0.8</td>
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<td>5.3±0.5</td>
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<td></td>
<td>5.4±0.6</td>
<td>+0.9±0.6</td>
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<td><strong>HR baroreflex parameters</strong></td>
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<td>Lower plateau, nu</td>
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<td><strong>Gain, −bpm/mm Hg</strong></td>
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<td>8.5±1.3</td>
</tr>
<tr>
<td></td>
<td>8.0±0.5</td>
<td>+0.9±1.9</td>
<td>8.0±0.5</td>
</tr>
</tbody>
</table>

Values are mean±SE. F indicates F ratio between control values with 2,19 degrees of freedom; Δ, change from control.

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**Figure 2.** Left, Average responses to airjet stress before (white circles) and after (black circles) bilateral administration of sarile (0.5 nmol, n=8) or losartan (2 nmol, n=6) into the RVLM. Each dot represents value, averaged over a 30-second period. Dashed lines mark the beginning and conclusion of airjet stress. Right, Average changes in MAP and HR during the onset and plateau of the response before (white bars) and after (black bars) treatment. Onset of MAP and HR responses to airjet stress was measured as the average change during the second minute; plateau of the response was determined as the average change during 4 to 7 minutes of airjet stress. Values are mean±SE. *P<0.05 vs control responses.

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**Figure 3.** Top, Effects of microinjections of losartan (2 nmol, n=6) into the RVLM on RSNA and HR baroreflexes. Circles on curves represent resting values. White circle and dashed line indicate control; black circle and solid line, losartan. Error bars are average SE calculated from ANOVA, indicating variation within animals. Bottom, Average MAP responses to injections of glutamate (5 nmol, n=6) into the RVLM before and 10 to 30 minutes after local injection of losartan. SE values are omitted for clarity. Arrows mark injection of glutamate and losartan.
Angiotensin II

Microinfusion of Ang II (4 pmol/min, n=8) into the RVLM did not alter the pressor response to airjet stress (overall change, −17±15%, P>0.05). However, Ang II attenuated the stress-evoked tachycardia by 36±13% and 48±18% during the onset and plateau of the response, respectively (P<0.05). The RSNA and HR baroreflexes were not different before and after Ang II microinfusion (Table).

Candesartan

Resting values of MAP (78±3 mm Hg) and HR (180±6 beats/min) before microinjections of candesartan (0.2 nmol, n=6) were not different from those before administration of sarile, losartan, or Ang II. Microinjections of candesartan into the RVLM did not change resting MAP (+3±2 mm Hg) or HR (+7±7 beats/min). The onset of the pressor response to airjet stress was not different before (+11±2 mm Hg) or after (+11±2 mm Hg) microinjections of candesartan (Figure 4). However, the plateau of the response was decreased by candesartan, from +11±1 mm Hg to +5±1 mm Hg (P<0.01). By contrast, the tachycardic response to airjet stress remained unaltered. Microinjections of vehicle did not affect the MAP and HR responses to airjet stress (Figure 4). The pressor responses to glutamate (5 nmol, n=5) were not different before (+25±6 mm Hg) and after (+27±7 mm Hg) candesartan microinjections.

Discussion

The major finding of the present study is that blockade of AT1 receptors in the RVLM decreases the pressor response to emotional stress in conscious rabbits. These results extend earlier findings that Ang II receptor antagonists, given intracerebroventicularly, attenuate the pressor response to environmental stressors in conscious animals to provide, to our knowledge, the first evidence that the AT1 receptor in the RVLM is a major target in action of endogenous Ang II as a stress mediator. The current results are also consistent with recent findings in anesthetized rats that AT1 receptors in the RVLM mediate the pressor responses to stimulation of the hypothalamus.

The present data show that microinjections of the selective AT1 receptor antagonists, losartan and candesartan, as well as the nonselective antagonist sarile into the RVLM did not change resting arterial pressure, apart from a transient pressor response to losartan. However, this transient response contrasted to the long-lasting effect of losartan on the circulatory stress reaction and also was previously shown to be independent of AT1 receptors in the RVLM. The lack of sustained changes in arterial pressure after microinjections of AT1 antagonists into the RVLM is in accord with previous findings in anesthetized rats and rabbits. Similarly, Fontes and colleagues have shown that local injections of AT1 receptor antagonists evoked only transient (~5 minutes) increases in blood pressure in conscious normotensive rats. Together, these findings suggest that AT1 receptors play a limited role in tonic excitation of the vasomotor RVLM neurons in normotensive animals at resting conditions. By contrast, the AT1 receptors appear to be important in the tonic support of blood pressure in hypertension, because microinjections of AT1 receptor antagonists into the RVLM evoke depressor responses in hypertensive rats. The present results extend these findings, indicating that AT1 receptor antagonists in the RVLM can also be involved in maintaining acute, stress-induced hypertension in conscious animals.

In the current study, the effects of the antagonists were unlikely to be due to a nonspecific inhibitory action on the RVLM vasomotor neurons, because both sarile and losartan did not alter the sympathoexcitatory response to baroreceptor unloading. To our knowledge, this is the first report on the influence of an AT1 receptor antagonist in the RVLM on baroreflexes in conscious animals. The lack of effect of sarile and losartan on the baroreflex, which is known to be mediated by γ-aminobutyric acid (GABA) receptors in the RVLM, rules out the possibility that attenuation of the pressor stress response was due to facilitation of GABAergic transmission. Furthermore, it also argues against a nonspecific inhibition of glutamatergic transmission, as we recently found that the baroreflex gain is also controlled by EAA receptors in the RVLM in conscious rabbits. The lack of a nonspecific interaction with EAA receptors is further supported by the current finding that none of the antagonists changed the pressor response to local microinjections of glutamate. The lack of effect of sarile on the pressor response to glutamate is also consistent with previous findings. By contrast, losartan was shown to attenuate the pressor response to glutamate in anesthetized rats. Apart from differences in experimental preparations, the dissimilarity between the current and previous study can be attributed to the time at which the glutamate response was determined. In the former study, glutamate was always injected 10 minutes after losartan. It is possible that,
at this time, losartan might still exert a nonspecific action associated with its initial pressor action in rats.

Another new observation of this study is that the AT₁ receptor antagonists were less effective than sarile in attenuating the initial phase of the acute stress–evoked hypertension. It is possible that the initial pressor response in the case of AT₁ receptor–only blockade could be due to unmasking actions at other receptors in the RVLM. In particular, we have recently shown that ionotropic EAA receptors in this region play a role in mediating the onset of the pressor stress reaction. Another possibility is that the effect of sarile was mediated via actions on another receptor(s), as the hypotensive action of the sarile-related peptides in the RVLM was found to be independent of Ang receptors in anesthetized rabbits and rats. However, in the current study, sarile did not affect resting blood pressure, indicating that this inhibitory action might be less prominent in the absence of anesthesia. Either way, the present experiments strongly suggest that AT₁ receptors in the RVLM play a critical role in the maintenance, but not in initiation, of the stress-evoked hypertension. These results warn against the use of mental stress models with short duration for estimating the influence of Ang II on cardiovascular stress reactions, because during a short-term stress exposure, this influence might not be fully developed. This might also explain why earlier clinical studies, which used short-lasting (3-minute) stressful tasks, failed to demonstrate that angiotensin-converting enzyme (ACE) inhibitors diminish the cardiovascular response to mental stress. By contrast, it has recently been shown that an ACE inhibitor attenuated the pressor stress response to a more long-lasting (20-minute) challenge.

In this study, microinfusion of Ang II into the RVLM did not alter blood pressure and RSNA, in accord with our previous results in conscious rabbits, but in contrast to earlier findings in conscious rats. The lack of effect of Ang II was unlikely to be due to a low dose used, because the same microinfusion into the fourth cerebral ventricle increased blood pressure and facilitated the RSNA baroreflex. The inability of Ang II to produce pressor effects in the present study might be due to spread into the caudal ventrolateral medulla, where Ang II can decrease arterial pressure and thus, offset its excitatory action in the RVLM. However, this is also unlikely, because we found recently that Ang II microinfusion into the intermediate ventrolateral medulla did not affect cardiovascular parameters in conscious rabbits. Studies in anesthetized animals also demonstrated both hypertension and no change in blood pressure in response to Ang II microinjections into the RVLM. Although the reason for such complexity is not clear, one possibility is that both excitatory and inhibitory Ang-sensitive inputs to the presympathetic neurons coexist within the RVLM and might be unequally activated under different experimental conditions. The finding in rats that exogenously applied Ang II both excites and inhibits activity of the barosensitive RVLM neurons supports this possibility.

Another important finding of this study is that administration of Ang II receptor antagonists into the RVLM did not change the stress-evoked tachycardia, indicating that AT₁ receptors in the RVLM play little role in modulating cardiac stress reactions. Considering our earlier finding that blockade of EAA receptors in the RVLM does not alter the stress-induced tachycardia, it appears that the RVLM is not a critical relay synapse in the cardiac response to emotional stress in rabbits. This is supported by recent findings in rats that the cardiac component of the defense-like response to activation of the dorsomedial hypothalamus is mediated by neurons in the medullary raphe pallidus, but not in the RVLM. Nevertheless, it is likely that the RVLM may indirectly influence, possibly via ascending projections or baroreflex mechanisms, cardiac stress reactions, because local microinfusion of Ang II in conscious rabbits or glutamate attenuated the airjet stress–evoked tachycardia, without altering the pressor response in rabbits. It is possible that this inhibitory influence specifically relates to stress-evoked cardiac stimulation, because, in the current study, Ang II did not affect the baroreflex-induced tachycardia.

In conclusion, the results of the present study suggest that AT₁ receptors in the RVLM play a key role in mediating the pressor reaction to acute emotional stress in conscious rabbits. The lack of effect of the Ang II antagonists on resting cardiovascular parameters or on the sympathoexcitatory response to baroreceptor unloading indicates that the excitatory action of endogenously released Ang II in the RVLM may be intrinsically linked to stress exposure in conscious animals.

**Perspectives**

In this study, we found that AT₁ receptors in the RVLM are important in mediating the acute stress–evoked hypertension in conscious rabbits. Consequently, these findings indicate that the abnormalities in Ang-sensitive inputs to the vasomotor RVLM neurons are likely to contribute to excessive cardiovascular response to psychoemotional stressors, which is believed to play a role in the development of various cardiovascular disorders. These results warrant further clinical investigation, as they suggest that AT₁ receptor antagonists, which have successfully completed clinical development in recent years, might also be beneficial in diminishing the excessive blood pressure responses to psychoemotional stressors, frequently observed in hypertensive patients. We are not aware of any publication on the effect of AT₁ receptor antagonists on the human circulatory stress reactions. However, to date, most antihypertensive agents, including ACE inhibitors and β-blockers, which reliably lower resting blood pressure, failed to diminish the pressor responses to psychoemotional stressors.

**Acknowledgments**

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