AT₁ Receptors Mediate Excitatory Inputs to Rostral Ventrolateral Medulla Pressor Neurons From Hypothalamus

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Abstract—Angiotensin II type 1 (AT₁) receptors are located on pressor neurons in the rostral ventrolateral medulla, and their activation results in an increase in arterial pressure. However, the normal role of these AT₁ receptors in cardiovascular regulation is unknown. In this study, we tested the hypothesis that these receptors mediate synaptic excitation of rostral ventrolateral medullary pressor neurons in response to activation of the hypothalamic paraventricular nucleus. In anesthetized rats, microinjections of the γ-aminobutyric acid receptor antagonist bicuculline were made into the paraventricular nucleus; this injection causes activation of the nucleus as a consequence of disinhibition. The pressor and sympathoexcitatory responses evoked by paraventricular nucleus activation were significantly reduced (by ≈40% to 50%) after microinjection of the specific AT₁ receptor antagonists losartan or L-158,809 into the rostral ventrolateral medulla on the ipsilateral, but not contralateral, side. These responses were reduced to a similar degree after microinjections of the neuroinhibitory compound muscimol into the ipsilateral, but not contralateral, rostral ventrolateral medulla. However, bilateral microinjections of the glutamate receptor antagonist kynurenic acid into the rostral ventrolateral medulla had no effect on the responses evoked from the paraventricular nucleus. Conversely, bilateral microinjections of kynurenic acid into the rostral ventrolateral medulla virtually abolished the somatosympathoexcitatory reflex, whereas bilateral microinjections of losartan or L-158,809 had no effect on this effect on reflex. The results indicate that excitatory synaptic inputs to pressor neurons in the rostral ventrolateral medulla arising from activation of the paraventricular nucleus are mediated predominantly by AT₁ receptors. (Hypertension. 1999;34:1301-1307.)

Key Words: angiotensin II ■ blood pressure ■ brain ■ receptors, glutamate ■ bicuculline ■ blood vessels

It is well established that the rostral part of the ventrolateral medulla (RVLM) contains a group of spinally projecting sympathoexcitatory neurons that play a crucial role in the tonic and phasic regulation of sympathetic vasomotor activity and arterial blood pressure (for reviews see References 1 and 2). These neurons are a site of convergence of central pathways subserving many cardiovascular reflexes as well as responses evoked from higher brain regions.1,2

Numerous studies have demonstrated that glutamate and γ-aminobutyric acid (GABA) receptors play a major role in the synaptic regulation of RVLM sympathoexcitatory neurons.1,2 There is also evidence, however, indicating that angiotensin (Ang) receptors may also play a role in the synaptic regulation of these neurons. First, studies using in vitro autoradiography have shown that there is a high density of Ang receptors in the RVLM of several mammalian species, including humans (for review see Reference 3). These receptors are predominantly Ang II type 1 (AT₁) receptors, and their location corresponds very closely with that of sympathoexcitatory neurons in the RVLM.3 Microinjection of Ang II into the RVLM pressor region results in an increase in arterial pressure and sympathetic activity, an effect that is mediated by AT₁ receptors.4 However, Ang II does not appear to affect respiratory neurons in the RVLM,5 suggesting that AT₁ receptors are associated specifically with cardiovascular neurons in this region. Finally, studies in vitro have confirmed that the depolarizing effect of Ang II on spinally projecting RVLM neurons is mediated by AT₁ receptors and that this is a postsynaptic effect.5

Although glutamate receptors have been shown to mediate excitatory synaptic inputs to RVLM sympathoexcitatory neurons that are activated by stimulation of a variety of peripheral receptors and some supramedullary regions,1,2,7,8 there is also evidence that excitatory inputs to these neurons activated by stimulation of certain hypothalamic regions (eg, the paraventricular nucleus [PVN] and perifornical area) are nonglutamatergic.9 This raises the possibility that AT₁ receptors in the RVLM may mediate excitatory inputs to RVLM neurons originating from these hypothalamic regions. To test this hypothesis, in the present study, we have determined the effect of specific blockade of AT₁ receptors in the RVLM on the excitation of RVLM sympathoexcitatory neurons evoked by activation of the hypothalamic PVN. In addition, as a control, we have also examined the effect of blockade of AT₁ receptors in the RVLM on the somatosympathoexcitatory reflex, which is known to be mediated primarily by...
glutamatergic synaptic inputs to RVLM sympathoexcitatory neurons.7

Methods

General Procedures

Experiments were performed on male Sprague-Dawley rats (8 to 12 weeks old, 280 to 420 g, Laboratory Animal Services, University of Sydney, New South Wales, Australia) anesthetized with urethane (1.3 to 1.5 g/kg IP). All experiments were carried out in accordance with the Guidelines for Animal Experimentation of the National Health and Medical Research Council of Australia. Body temperature was monitored with a rectal probe and maintained in the range 37°C to 38°C with a thermoregulated heating pad. Catheters were placed in a femoral vein and a femoral artery, and the trachea was cannulated. The head was placed in a stereotaxic frame with the tooth bar fixed 19 mm below the interaural line. In all experiments, the dorsal surface of the medulla and the renal sympathetic nerve were exposed, as described in detail previously.10 In most animals, a small craniotomy was made near the bregma to allow for the later insertion of a micropipette into the PVN; in the remainder of the animals, the sciatic nerve was exposed on one side. After completion of all surgical procedures, neuroumucosal blockade was induced with alcuronium chloride (0.1 mg/kg IV every 1 to 2 hours) and artificially ventilated at a rate and tidal volume that maintained a arterial CO2 (measured with a Datex Engstrom CO2 monitor) in the range 4.0% to 4.5%. The effects of alcuronium chloride were allowed to wear off before each additional dose was administered. The adequacy of anesthesia without neuroumucosal blockade was verified by the absence of a withdrawal response to noiceptive stimulation of a hind paw and during neuroumucosal blockade by a stable baseline arterial pressure, heart rate (HR), and sympathetic nerve activity. Supplemental doses of urethane (0.1 g/kg IV) were administered if necessary. The mean arterial pressure (MAP), HR, and renal sympathetic nerve activity (RSNA) were recorded continuously as described previously.10

Microinjections of Drugs

Microinjections of the GABA receptor antagonist bicuculline (20 nL of 2 mmol/L solution) were made into sites in the PVN on the left side by use of a micropipette held in a micromanipulator. The tip of the micropipette was first positioned, by use of the coordinates for the PVN according to the atlas by Paxinos and Watson,11 in the track located 1.8 mm posterior and 0.5 mm lateral to the bregma and at a depth of 7.7 mm below the dura. A microinjection of bicuculline was then made into this site. Usually, this resulted in a pressor response of at least 20 mm Hg, but if it did not, the micropipette tip was repositioned, usually 0.2 mm more rostral or caudal. In all experiments, no more than 3 sites were tested in this way before a pressor response of at least 20 mm Hg was obtained. All subsequent microinjections of bicuculline were then made into this site.

Various compounds were also injected into the pressor region in the RVLM by using a micropipette held in a second micromanipulator at an angle of 20° (tip rostral). The rostrocaudal, mediolateral, and dorsoventral coordinates of the micropipette tip in the RVLM were determined with respect to the obex, midline, and dorsal surface, respectively. Microinjections of sodium glutamate (40 to 50 nL of 50 mmol/L solution) were made first into the RVLM on each side to determine the coordinates of sites at which a pressor response of at least 30 mm Hg was evoked. Usually, <3 penetrations of the medulla were required to identify the pressor region on each side. All subsequent microinjections were made into the identified pressor region. The compounds injected were kynurenic acid (100 nL of 27 mmol/L solution), losartan (100 nL of 10 mmol/L solution, gift of Merck Sharpe & Dohme, Rahway, NJ), the AT1 receptor antagonist L-158,809 (100 nL of 10 mmol/L solution, gift of Merck Sharpe & Dohme, Rahway, NJ), or the GABA receptor agonist muscimol (100 nL of 10 mmol/L solution). The vehicle solutions were 10 mmol/L phosphate-buffered saline (pH 7.4) for the glutamate microinjections and artificial cerebrospinal fluid (pH 7.4) for all other compounds.

Microinjections were made by pressure, and the volume injected was measured by determining the displacement of the meniscus in the pipette with respect to a horizontal grid viewed through an operating microscope.

Experimental Procedures

Responses Evoked From the PVN

The general strategy in these experiments was to test the effect of blockade of AT1 receptors in the RVLM on one side to the response evoked from the PVN on the ipsilateral side, because it is known that the projection from the PVN to the RVLM is almost entirely ipsilateral.12 As a control, the effect on the PVN-evoked response of blockade of AT1 receptors in the RVLM on the contralateral side was also tested. In addition, we also tested the effect on the PVN-evoked response of inhibition of neurons (by microinjection of the GABAA receptor agonist muscimol) in either the ipsilateral or contralateral RVLM.

In the first series of experiments, the control response to a unilateral injection of bicuculline into the PVN was recorded. Then, 60 minutes after the injection of bicuculline, a microinjection of losartan (1 nmol) was made into the RVLM pressor region on the side ipsilateral to the injection site in the PVN. Five minutes later, a second microinjection of bicuculline was then made into the PVN, followed by another waiting period of 60 minutes, after which a bicuculline microinjection was again made into the PVN. There was then a further waiting period of 60 minutes, after which a microinjection of losartan (1 nmol) was made into the RVLM pressor region on the contralateral side, followed 5 minutes later by a final bicuculline microinjection into the PVN. In the second series of experiments, the procedure was the same except that (1) 60 minutes after the first injection of bicuculline into the PVN, a microinjection of L-158,809 (1 nmol) was made into either the ipsilateral or contralateral RVLM, and (2) 60 minutes after the third injection of bicuculline into the PVN, an injection of muscimol (1 nmol) was made into the ipsilateral or contralateral RVLM.

In another series of experiments, we tested the effect of blockade of glutamate receptors in the RVLM on the PVN-evoked response. In these experiments, the control response to a unilateral microinjection of bicuculline into the PVN was recorded. Then, 60 minutes after the microinjection of bicuculline, microinjections of the glutamate receptor antagonist kynurenic acid (2.7 nmol) were made into the RVLM on both sides (<2 minutes between injections). Five minutes later, a second microinjection of bicuculline was made into the PVN, but no further procedures were performed.

Somatosympathoexcitatory Reflex Responses

It is well established that the central pathways mediating the somatosympathoexcitatory reflex include an essential synapse in the RVLM and that this synapse is glutamatergic.7 Therefore, the purpose of this series of experiments was 2-fold: (1) to test whether the dose of kynurenic acid used in the experiments described above on the PVN-evoked sympathoexcitatory response was sufficient to block glutamatergic transmission in the RVLM and (2) to test whether the dose of the AT1 receptor antagonists used in the experiments on the PVN-evoked response may have affected glutamatergic transmission in the RVLM. Thus, in this series of experiments, the average sympathoexcitatory response evoked by repeated stimulation of the sciatic nerve was measured (according to the procedure described previously19 ) before and after injections of either kynurenic acid (2.7 nmol), losartan (1 nmol), or L-158,809 (1 nmol) into the RVLM pressor region. Injections of all these compounds were made bilaterally (<2 minutes between ipsilateral and contralateral injections), and the somatosympathoexcitatory reflex was tested 5 minutes after the second injection. In an additional series of experiments, the effects of unilateral injection of kynurenic acid into the RVLM on the side contralateral to the site of sciatic nerve stimulation was also tested, because it has been shown that the somatosympathoexcitatory reflex is mediated primarily via the contralateral RVLM.13
Baseline Cardiovascular Variables

The Table shows the baseline MAP and HR just before microinjections of bicuculline into the PVN before and after microinjections of losartan, L-158,809, muscimol, or kynurenic acid into the ipsilateral, contralateral, or bilateral RVLM pressor region. It was not possible to compare accurately the baseline level of RSNA at these times because of technical factors, such as changes in the position of the nerve on the electrodes during the waiting time between microinjections of bicuculline (at least 60 minutes), which sometimes affected the magnitude of the recorded signal. The results show that the baseline MAP and HR were not significantly different before and after microinjection of losartan or L-158,809 into the ipsilateral or contralateral RVLM or of kynurenic acid bilaterally into the RVLM. In contrast, after muscimol injection into the ipsilateral or contralateral RVLM, there was a small but statistically significant decrease in both MAP and HR (Table).

Results

Baseline Cardiovascular Variables

The Table shows the baseline MAP and HR just before microinjections of bicuculline into the PVN before and after microinjections of losartan, L-158,809, muscimol, or kynurenic acid into the ipsilateral, contralateral, or bilateral RVLM pressor region. It was not possible to compare accurately the baseline level of RSNA at these times because of technical factors, such as changes in the position of the nerve on the electrodes during the waiting time between microinjections of bicuculline (at least 60 minutes), which sometimes affected the magnitude of the recorded signal. The results show that the baseline MAP and HR were not significantly different before and after microinjection of losartan or L-158,809 into the ipsilateral or contralateral RVLM pressor region. In contrast, after microinjection of bicuculline into the PVN in one experiment, before any injections of losartan into the RVLM pressor region, the magnitudes of the evoked increases in MAP, HR, and RSNA (Figure 1). Usually, these variables began to increase gradually within 10 seconds after microinjection, reaching a peak value within 5 to 10 minutes, followed by a gradual decrease back to the preinjection levels (within 20 to 40 minutes). When microinjections of bicuculline were made into the RVLM pressor region, the magnitudes of the evoked increases in MAP, HR, and RSNA were significantly reduced compared with the control responses (Figures 1 and 2A), by 38 ± 5%, 36 ± 5%, and 44 ± 5%, respectively (n = 6). The evoked responses returned to the control levels when the bicuculline microinjection was repeated 60 minutes later (Figures 1 and 2A). In contrast to the effects of microinjection
into the ipsilateral RVLM, microinjection of losartan into the contralateral RVLM pressor region had no significant effect on the evoked response from the PVN (Figures 1 and 2A). Similarly, 5 minutes after microinjection of L-158,809 into the ipsilateral RVLM pressor region, the increases in MAP, HR, and RSNA evoked by bicuculline injection into the PVN were reduced by 39±5%, 37±5%, and 50±4% (n=7) compared with their respective control responses but returned to the control values when tested again 60 minutes later (Figure 2B). In contrast to the effects of microinjection into the ipsilateral RVLM, microinjection of L-158,809 into the contralateral RVLM pressor region had no significant effect on the evoked response from the PVN (Figure 2B).

The increases in MAP, HR, and RSNA evoked by bicuculline injection into the PVN were also greatly reduced, by 45±5%, 26±6%, and 56±1% (n=6) compared with their respective control responses, after microinjection of muscimol into the ipsilateral RVLM pressor region (Figure 2C). However, microinjections of muscimol into the contralateral RVLM pressor region or of microinjections of kynurenic acid into the RVLM pressor region bilaterally had no effect on the magnitudes of the evoked responses from the PVN (Figure 2C).

Histological analysis demonstrated that the centers of all injection sites in the hypothalamus were located either within or on the border of the PVN, extending from the level 1.4 mm to 2.1 mm caudal to bregma (Figure 3).

**Evoked Somatosympathoexcitatory Reflex**

In contrast to the lack of effect on the evoked response from the PVN, bilateral injections of kynurenic acid into the RVLM pressor region greatly reduced the increase in RSNA, reflexly evoked by stimulation of the sciatic nerve, to 14±4% (n=6) of the control response, as illustrated in Figure 4A. When tested 60 minutes after injections of kynurenic acid, however, the reflex response had returned to the control level (Figure 4A). A very similar effect was also observed when a unilateral injection of kynurenic acid was made into the RVLM pressor region on the contralateral side (data not shown).

In contrast to the effects of kynurenic acid, after bilateral injections of either losartan (n=6) or L-158,809 (n=3) into the RVLM pressor region, the magnitude of the somatosympathoexcitatory reflex was virtually unchanged (90±3% and 99±3% of the control response, respectively), as illustrated in Figure 4B.
Discussion

The present study has demonstrated that blockade of AT₁ receptors in the RVLM reduces the pressor and sympathoexcitatory response evoked by activation of neurons in the hypothalamic PVN. Moreover, the reduction of this response was very similar to that resulting from injection of muscimol into the RVLM, which is believed to cause complete or nearly complete inhibition of RVLM neurons (see below). In contrast, blockade of ionotropic glutamate receptors in the RVLM had no effect on this response. Thus, the results indicate that excitatory synaptic inputs to the RVLM sympathoexcitatory neurons arising from activation of the PVN are mediated predominantly or exclusively by AT₁ receptors. To our knowledge, this is the first demonstration of a role of AT₁ receptors in the synaptic excitation of RVLM neurons by inputs arising from the hypothalamus or any other brain region.

Previous studies have reported that microinjection of neuroexcitatory amino acids into the PVN results in alterations in arterial pressure, HR, and sympathetic activity, although there is considerable variability in the observed responses (for review see Reference 1). The reason for such variability may be that neuroexcitatory amino acids directly excite pressor neurons as well as interneurons within the PVN that inhibit the pressor neurons, so that the net effect depends on the balance between these 2 opposing factors. In the present study, therefore, we have used the method of microinjection of bicuculline, which activates PVN neurons as a consequence of the removal of tonic GABAergic inhibition. In agreement with previous studies, bicuculline microinjection consistently evoked increases in MAP, HR, and RSNA. Moreover, these responses were found to be highly reproducible in control experiments, when bicuculline microinjections were made into the PVN before and after injections of losartan, L-158,809, or muscimol into the contralateral RVLM, which is not part of the descending pathway from the PVN to the spinal sympathetic outflow. Thus, the fact that the pressor and sympathoexcitatory response to microinjections of bicuculline were consistently reduced only after microinjection of losartan, L-158,809, or muscimol into the ipsilateral RVLM indicates that this reduction was specifically due to an action of these compounds on the synaptic transmission of signals to RVLM neurons originating from the PVN.

Previous studies have demonstrated that both losartan and L-158,809 are highly specific antagonists of AT₁ receptors. In view of the fact that L-158,809 has an affinity for AT₁ receptors in the brain and other tissues that is 10 to 100 times greater than that of losartan, it is likely that microinjection of 1 nmol L-158,809, as used in the present study, also blocked these receptors. At the same time, microinjections of these doses of losartan or L-158,809 into the RVLM had no effect on the somatosympathoexcitatory reflex, which is known to be mediated by glutamate receptors. This, therefore, rules out the possibility that the reduction of the sympathoexcitatory response evoked from the PVN was due to an inhibitory effect of losartan or L-158,809 on glutamatergic transmission. This was further demonstrated by the fact that microinjection of kynurenic acid into the RVLM, at a dose that abolished the somatosympathoexcitatory reflex, had no effect on the evoked response from the PVN.

Figure 3. Distribution of the centers of injection sites in the PVN, mapped onto standard sections from the atlas of Paxinos and Watson. The distance of each section caudal to the bregma is indicated. 3V indicates third ventricle; AH, anterior hypothalamic area; f, fornix; and RCh, retrochiasmatic area.

Figure 4. Examples of the average sympathoexcitatory response evoked by 30 consecutive stimulations of the sciatic nerve. A, One experiment before (control) and 5 and 60 minutes after bilateral microinjections of kynurenic acid (Kyn) into the RVLM pressor region. B, Another experiment before (control) and 5 minutes after bilateral microinjections of L-158,809 into the RVLM pressor region.
It is also most unlikely that losartan or L-158,809 had a nonspecific inhibitory effect on RVLM neurons, because unilateral or bilateral injections of these compounds had no effect on resting blood pressure or, as stated above, on glutamatergic neurotransmission in the RVLM. Therefore, we conclude that the effects of these compounds in reducing the evoked response from the PVN is due to a specific action on AT1 receptors. This conclusion is further strengthened by the fact that the 2 compounds have different chemical structures, and that their only known common pharmacological property is their antagonism of AT1 receptors.16,17 AT1 receptors mediate the actions of Ang II; therefore, it follows that Ang II is likely to be the endogenous neurotransmitter to RVLM neurons mediating excitatory inputs originating from the PVN. Consistent with this, application of Ang II to single spinaly projecting RVLM neurons in vitro elicits a depolarizing effect that is due to a reduction in resting K+ conductance, an effect that is blocked by losartan.6 Furthermore, Ang II has been convincingly demonstrated to be an excitatory neurotransmitter in other central autonomic pathways, such as the pathway from the subfornical organ to the PVN.18

As mentioned above, injection of muscimol into the ipsilateral RVLM attenuated the pressor and sympathoexcitatory response evoked from the PVN by approximately one half. The dose of muscimol injected (1 nmol) was 10 times greater than that which has previously been shown to result in a profound fall in arterial pressure when injected bilaterally into the RVLM,9 indicating that it was sufficient to produce complete or nearly complete inhibition of RVLM neurons. Thus, the fact that the pressor and sympathoexcitatory response evoked from the PVN was reduced but not abolished after injection of muscimol into the ipsilateral RVLM supports the finding of Kiely and Gordon9 that this response is mediated partly by a descending pathway that includes a synapse within the RVLM and partly by a separate descending pathway that is independent of the RVLM. The latter pathway may be the direct projection from PVN neurons to sympathetic preganglionic neurons in the spinal cord that has been demonstrated anatomically.19

The source of endogenous Ang II that acts on AT1 receptors in the RVLM in response to activation of the PVN is unknown. Ang II–like immunoreactivity has been demonstrated in nerve fibers within the RVLM,20 but the source of these fibers has not been determined. It has been shown, however, that both the PVN and the lateral parabrachial nucleus in the pons contain neurons that are immunoreactive for Ang II.20 The PVN projects directly to the RVLM,12 whereas the lateral parabrachial nucleus projects to the RVLM11 but also receives afferent inputs from the PVN.19 Thus, activation of the PVN could lead to the release of Ang II from the terminals of axons originating from Ang II–containing cell bodies in the PVN itself or in the lateral parabrachial nucleus (or other relay nucleus). Alternatively, it has been proposed that Ang II in the brain can be formed in the extracellular fluid from angiotensinogen, which itself is produced in astrocytes.22 Thus, it is conceivable that Ang II could be formed in this way in the RVLM and then taken up into nerve terminals from which it is subsequently released.

Clearly, further studies are needed to determine the source of endogenous Ang II that is released in the RVLM as a consequence of PVN activation.

Although the present study demonstrated that the sympathoexcitatory and pressor response evoked by disinhibition of the PVN was not altered after blockade of glutamate receptors in the RVLM, it is still possible that glutamate may act as a cotransmitter in the excitatory pathway from the PVN to the RVLM and play a functionally important role under particular circumstances, eg, mediating synaptic excitatory responses to short-term rather than prolonged activation of PVN neurons. There is much evidence for colocalization of putative neurotransmitters in central cardiovascular neurons,1 and it has been suggested that glutamate may be a cotransmitter with Ang II in other central pathways, such as that from the subfornical organ to the PVN.18 Therefore, further studies are also needed to test whether glutamate may act as a cotransmitter with Ang II within the PVN-RVLM pathway.

In a previous study, Hirooka and Dampney23 found that the somatosympathoexcitatory response reflexly evoked by sciatic nerve stimulation was significantly reduced after microinjection of the Ang receptor antagonist [Sar1,Thr8]Ang II into the RVLM. In contrast, the results of the present study showed that this reflex was unaffected after microinjection of losartan and L-158,809 into the RVLM. However, unlike losartan and L-158,809, [Sar1,Thr8]Ang II is a nonselective antagonist that blocks not only AT1 receptors but also other receptors, such as those that mediate the actions of Ang-(1–7).24 Furthermore, bilateral microinjections of [Sar1,Thr8]Ang II into the RVLM results in a profound fall in resting MAP,25 whereas bilateral microinjections of losartan do not result in a decrease in resting MAP.4 Thus, the present results, together with those of previous studies, indicate that the effects of [Sar1,Thr8]Ang II in the RVLM in reducing sympathetic vasomotor tone and the somatosympathoexcitatory reflex is due to an action on receptors other than AT1 receptors.

Although the present study has focused on inputs to RVLM sympathoexcitatory neurons originating from the PVN, it is possible that inputs to these neurons from other regions may also be mediated by AT1 receptors. For example, there are Ang II–immunoreactive neurons in the lateral hypothalamus,20 a region that also projects to the RVLM.1 Furthermore, the lateral parabrachial nucleus receives inputs from many hypothalamic and other forebrain regions,19 so that AT1 receptors on RVLM neurons may play an important role in mediating inputs from several brain regions apart from the PVN.

In conclusion, the present study has demonstrated a critical role for AT1 receptors in generating excitation of RVLM sympathoexcitatory neurons in response to activation of the PVN. Because the PVN is believed to have a major role in generating cardiovascular responses to stressful stimuli,26 the AT1 receptors in the RVLM could be an important component of the central pathways mediating such responses.

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References
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