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Effects of Central Interleukin-1 on the Cardiovascular Response in Hemorrhaged Rats

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The arterial pressure is regulated by the nervous and humoral mechanisms. The neuronal regulation is mostly carried out by the autonomic nervous system through the rostral ventrolateral medulla (RVLM), a key area for the cardiovascular regulation, and the humoral regulation is mediated by a number of substances, including the angiotensin (Ang) II and vasopressin. Recent studies suggest that central interleukin-1 (IL-1) activates the sympathetic nervous system and produces hypertension. The present study was undertaken to elucidate whether IL-1 and Ang II interact in the regulation of cardiovascular responses to the stress of hemorrhage. Thus, Sprague-Dawley rats were anesthetized and both femoral arteries were cannulated for direct measurement of arterial pressure and heart rate (HR) and for inducing hemorrhage. A guide cannula was placed into the lateral ventricle for injection of IL-1 (0.1, 1, 10, 20 ng/2 μl) or Ang II (600 ng/10 μl). A glass microelectrode was inserted into the RVLM to record the single unit spike potential. Barosensitive neurons were identified by an increased number of single unit spikes in RVLM following intravenous injection of nitroprusside. I.c.v. IL-1 β increased mean arterial pressure (MAP) in a dose-dependent fashion, but HR in a dose-independent pattern. The baroreceptor reflex sensitivity was not affected by i.c.v. IL-1 β. Both i.c.v. IL-1 α and β produced similar increase in MAP and HR. When hemorrhage was induced after i.c.v. injection of IL-1 β, the magnitude of MAP fall was not different from the control. The IL-1 β group showed a smaller decrease in HR and a lower spike potential count in RVLM than the control. MAP fall in response to hemorrhage after i.c.v. injection of Ang II was not different from the control. When both IL-1 and Ang II were simultaneously injected i.c.v., however, MAP fall was significantly smaller than the control, and HR was increased rather than decreased. These data suggest that IL-1, a defense immune mediator, manifests a hypertensive action in the central nervous system and attenuates the hypotensive response to hemorrhage by interaction with Ang II.

Key Words: Angiotensin II, Interleukin-1, Hemorrhage, Cardiovascular regulation

INTRODUCTION

Interleukin-1 (IL-1) is a polypeptide produced by a large variety of cells including neurons, as a result of infection, toxic injury, trauma or antigenic challenge (Mizutani et al, 1991; Dinarello, 1992). IL-1 is present in two molecular forms, IL-1 α and IL-1 β, which are the products of different genes. They are synthesized as 31 kDa precursors and are structurally related at the three dimensional level (Dinarello, 1991). IL-1 exerts a variety of effects (Aggarwal & Pocsik, 1992), including several neural changes such as hyperalgesia that have been called illness responses (Watkins et al, 1995). Most studies of IL-1 have been carried out on its peripheral rather than the central actions, however, in addition to their peripheral action, it is present also in the central nervous system.

Numerous reports indicate that intracerebroventricular (i.c.v.) injection of IL-1 produces hypertension (Kimura et al., 1993; Kannan et al, 1996). Central IL-1 directly activates the sympathetic nervous system to elevate of the arterial pressure (Takahashi et al, 1992; Haefeli et al, 1993), which may play a role to prevent the hypotension caused by endotoxins introduced by an infection (Kaplan et al., 1993). However, others observed hypotension without a compensatory tachycardia (Weinberg et al, 1988). Some investigators reported that central IL-1 did not alter the arterial pressure on its own, but rather cause a hypotension by acting in concert with lipopolysaccharide and tumor necrosis factor (Weinberg et al, 1992), and induce a biphasic response depending on the doses used (Yamamoto et al., 1994). Thus, it is still debated whether central IL-1 has a hypertensive or a hypotensive effect.

Although it is not easy to find the hypotensive mechanism of IL-1, a number of hypotheses have also been proposed on the mechanism of arterial pressure regulation. Morimoto et al. (1992) stated that the hypertensive action

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ABBREVIATIONS: Ang II, angiotensin II; IL-1 β, interleukin-1 β; BRS, baroreflex sensitivity; MAP, mean arterial pressure; RVLM, rosral ventrolateral medulla.

of IL-1 was caused by the increased sympathetic discharge and humoral mediators like prostaglandins, and Qi et al. (2002) demonstrated that cyclooxygenase-2 (COX2) inhibitors or gene knockout animals dramatically augmented the pressor effect of angiotensin II (Ang II). Based on these reports, it is conceivable that IL-1 and Ang II may interact in the arterial pressure regulation, and it seems of a great value to investigate whether such an interaction exists at central sites. However, few works on this type of interaction have so far been done. Thus, it seems important to elucidate the central role of the interaction of IL-1 and Ang II, especially under stressed conditions such as hemorrhage. The aims of the present study were to determine the effects of IL-1 on the cardiovascular responses in the lateral ventricle and to explore the interactions of these substances with Ang II after hemorrhage.

METHODS

Animal preparation

Experiments were performed on adult Sprague-Dawley male rats, weighing 350~450 g. The rats were anesthetized with an intraperitoneal injection of urethane (0.1 g/100 g BW), and adequacy of anesthesia was assessed by monitoring the stability of arterial pressure and heart rate (HR), and the arterial pressure responses to pinching the hind paws. Anesthetics were supplemented when it was necessary.

Both femoral arteries were cannulated to measure arterial pressure and to perform hemorrhage. Femoral vein was also cannulated to administer drugs. Arterial pressure was recorded by a transducer (model P23XL, Ohmeda, USA), and HR was determined with an HR counter (model 7P4H, Grass, USA) triggered by the arterial pressure wave. All variables were recorded continuously on a direct-writing polygraph (model 79, Grass, USA) and with a computer through a CED 1401 (Cambridge Electronics Design, England).

The trachea was intubated for artificial ventilation (model 683, Harvard Apparatus, England). A minute respiratory volume was 600~780 ml/kg of oxygen-enriched room air. The animal was paralyzed with a bolus injection of pancuronium bromide (mioblock, 0.5 mg/kg) and given supplemental doses (0.1 mg/kg i.v.) as needed. Rectal temperature was kept at 38°C with a thermostatically controlled heating pad (Harvard Apparatus, England) or an infrared lamp. To check the state of rats during entire period of experiment, electrocardiogram was monitored continuously through an oscilloscope (Narco Bio-System Inc., USA).

Operation for intracerebroventricular injection

The rats were placed on a stereotaxic frame (model 1404, David Kopf Inst., USA) with the head in a horizontal position. The scalp was longitudinally incised and skull was leveled between lambda and bregma. A 22-gauge stainless steel guide cannula was placed into the lateral ventricle through a small hole drilled in the skull (1.5 mm lateral, 0.8 mm caudal to bregma and 4.0 mm deep from the bone) according to the stereotaxic atlas of Paxinos and Watson (1986). The cannula was anchored to the skull with dental cement and a jeweler's screw. A stainless steel obturator was used to seal the cannula.

The obturator was removed from the guide cannula placed into the lateral ventricle. An injector cannula connected to a 10 μl Hamilton syringe through polyethylene tube (PE-20) was inserted into the lateral ventricle. The tip of the injector cannula extended 1 mm beyond the guide cannula.

Drug administrations and hemorrhage

The i.c.v. administration of IL-1 β (0.1, 1, 10 and 20 ng/2 μl), IL-1 α (10 ng/2 μl) and Ang II (600 ng/10 μl) was carried out slowly with a syringe attached to a infusion pump (model 22, Harvard, England). Injection rate was 2 μl/min. All drugs were purchased from Sigma Chemical Co. (St. Louis, MO, USA) and dissolved in 0.9% saline.

When pressure responses to the drugs reached a maximum, 3 ml/kg of blood was hemorrhaged at a rate of 3 ml/min using a withdrawal pump (model 22, Harvard, England). In experiments where both IL-1 β and Ang II were administered, IL-1 β (10 ng/2 μl) was injected first into the lateral ventricle and, when the arterial pressure showed a maximum response, Ang II was injected. After the arterial pressure response to Ang II reached a maximum (approximately 2 min), hemorrhage was induced.

Single unit spike recordings in the rostral ventrolateral medulla (RVLM)

A glass microelectrode was used to record single unit activity in the RVLM. The rats were fixed in a stereotaxic apparatus. A micropositioner (Model 660, David Kopf, USA) was used to advance the electrode tip into the region of the RVLM (2.0 mm lateral to the midline, 12.0 mm caudal to the bregma and 6.5 mm below the skull) for recording. Barosensitive neurons were identified by increased spontaneous firing rate after a bolus intravenous injection of a vasodilator, sodium nitroprusside (5 μg/100 g).

Neural signals were amplified (CyberAmp380, Axon Inst., USA) with low and high cutoff frequencies of 100 Hz and 4 kHz, respectively, and monitored on an oscilloscope (model 2205, Tektronix, USA). Neural spikes were discriminated by a time-amplitude window discriminator (model D130, Digitimer, England) and fed into the A/D converter (model 1401plus, CED, England). The ongoing neural activity was integrated at intervals of 1 s using a CED 1401 program. A typical example of changes of mean arterial pressure (MAP), HR and neuronal firing rate after nitroprusside administration are shown in Fig. 1. An increase in HR and firing rate of barosensitive neurons in response to the nitroprusside-induced fall of arterial pressure can be seen. The baseline activity was calculated by averaging the firing rate in the 60 s period prior to administration of drugs.

Baroreceptor reflex test

To evaluate the effect of IL-1 β administration on the autonomic mechanism, baroreflex control of HR was determined in each rat by measuring the reflex tachycardia in response to transient decrease in MAP evoked by an i.v. bolus administration of nitroprusside (5 μg/100 g). The averaged ratio between changes in HR and in MAP ($\triangle$HR/$\triangle$MAP) was used as an index of baroreflex sensitivity (BRS). The BRS was assessed before and after the infusion of IL-1 β.

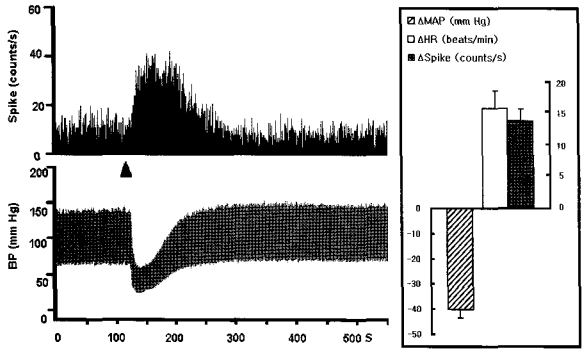

Fig. 1. A: Illustration of changes of mean arterial pressure (△MAP) and single unit spike activity obtained from barosensitive neuron in RVLM, when nitroprusside (5 μg/100 g, indicated by filled triangle) was injected. Bin width = 1 s. B: Maximum changes in MAP, HR and single unit spike activity of RVLM. Values are means ±SE.

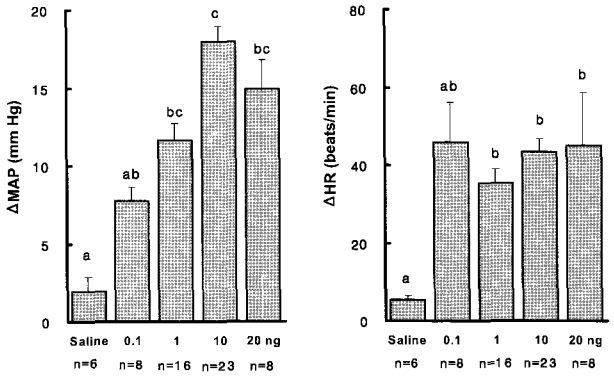

Fig. 2. Changes in mean arterial pressure (△MAP) and heart rate (△HR) in response to intracerebroventricular (i.c.v.) administration of graded doses of interleukin-1 β (IL-I β). Values are means±SE. Bars with different alphabet are significantly different at $p<0.05$ by Duncan's multiple range test.

Verification of intracerebroventricular cannula location

At the end of each experiment, 5 μl of Evans blue dye (5%) was injected through the i.c.v. cannula. The position of the cannula in the lateral ventricle was confirmed by the diffusion of the dye throughout the ventricular system.

Statistical analysis

Results were expressed as mean±SE. Significant difference was considered at $p<0.05$ using the unpaired t-test or one-way analysis of variance (ANOVA) and Duncan's multiple range test.

RESULTS

The cardiovascular effects of i.c.v. injections of IL-1 β were investigated in the rat. The basal MAP in saline, 0.1, 1, 10, and 20 ng IL-1 β injection groups were 74.2±1.8, 78.1 ±4.1, 74.3±3.4, 75.9±2.4 and 79.3±10.9 mm Hg, respectively and showed no significant difference. As shown in Fig. 2, the rise of MAP induced by saline, 0.1, 1, 10, and 20 ng/2 μl IL-1 β administration was 1.9±1.0, 7.8±0.9, 11.6± 1.1, 17.9±1.0 and 14.9±1.9 mm Hg, respectively, showing a dose-dependent increase in the range of 0.1 to 10 ng. Therefore, the high response concentration was used in the following experiment. On the other hand, the corresponding increase of HR was 5.5±1.0, 46±10, 35±4, 43±3 and 45± 14 beats/min, respectively, showing a dose-independent increase.

Baroreceptor reflex sensitivity (BRS) was measured by i.v. administration of nitroprusside before (control) and after i.c.v. administration of IL-1 β (Fig. 3). BRS in IL-1 β group (−0.27±0.03 beats/min/mm Hg) was not significantly different from the control (−0.29±0.04 beats/min/mm Hg). These results indicate that the hypertensive action of IL-1 β is independent of the baroreceptor reflex.

Changes in the MAP and HR after i.c.v. administration of IL-1 β and IL-1 α are shown in Fig. 4. Increases in MAP and HR after IL-1 α injection were 14.4±2.2 mm Hg and

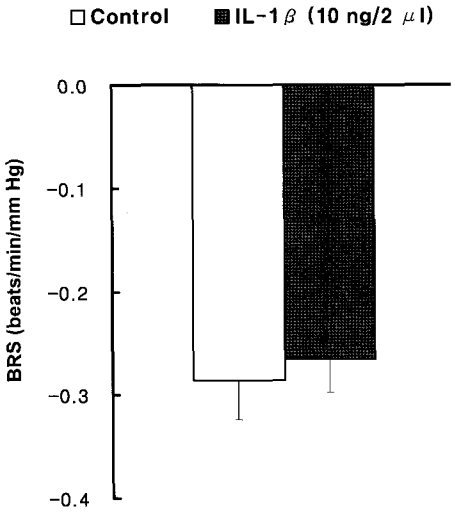

Fig. 3. Baroreceptor reflex sensitivity (BRS=△HR/△MAP) measured by intravenous injection of nitroprusside (5 μg/100 g) before (control) and after i.c.v. injection of IL-1 β. Values are means±SE (n=14).

48±6 beats/min, respectively, which were not significantly different from 17.9±1.0 mm Hg and 43±3 beats/min in the IL-1 β group. After administration of IL-1 β and IL-1 α, times required to reach maximum increase in MAP were 76.2±6.1 min and 92.2±17.9 min, respectively. Thus, i.c.v. administration of both IL-1 β and IL-1 α produced similar cardiovascular responses.

Changes in MAP, HR and single unit spike of RVLM before and after i.c.v. administration of IL-1 β in response to acute hemorrhage are shown in Fig. 5. Changes of MAP, HR and firing rates after hemorrhage were −28.4±2.8 mm Hg, −12±5 beats/min and 4.6±2.2 counts/s in the IL-1 β group and −30.0±2.1 mm Hg, −23±5 beats/min and 6.9± 2.5 counts/s in the control group, respectively. Thus, after hemorrhage, the magnitude of MAP fall was not different between the two groups. The decrease of HR in response

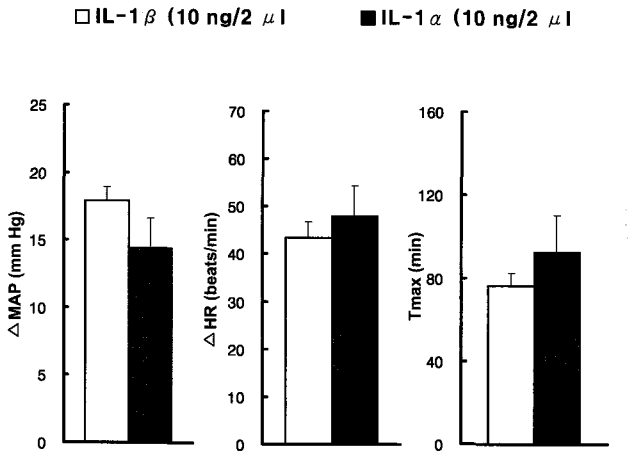

Fig. 4. Changes of mean arterial pressure (△MAP) and heart rate (△HR) caused by i.c.v. injections of IL-1β (n=23) and IL-1α (n=5). Time required to reach maximum increase (Tmax) in MAP produced by i.c.v. injections of IL-1β and IL-1α. Values are means ±SE.

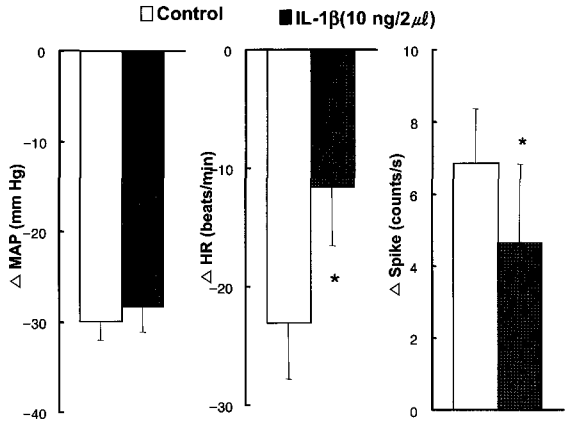

Fig. 5. Changes in mean arterial pressure (△MAP), heart rate (△HR) and single unit spike of RVLM (△spike) before (control) and after i.c.v. administration of IL-1β to rats with acute hemorrhage. Values are means±SE (n=9). * $p<0.05$ vs. control.

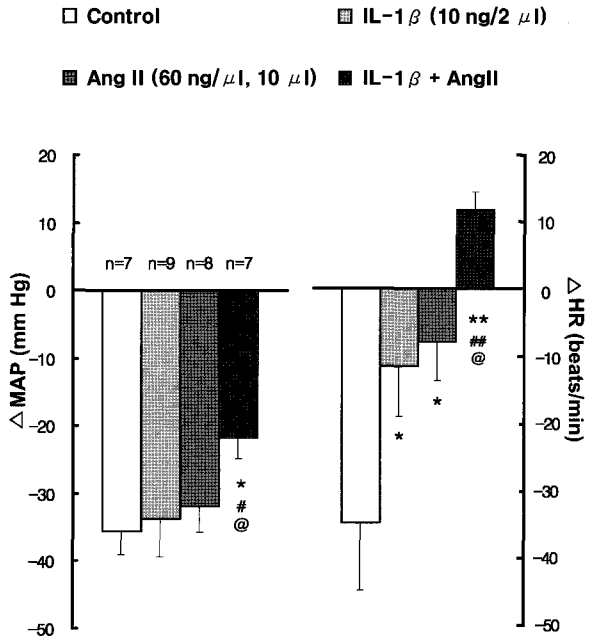

Fig. 6. Effects of i.c.v. administration of drugs (IL-1β, Ang II and IL-1β+Ang II) on the responses of mean arterial pressure (△MAP) and heart rate (△HR) to hemorrhage. Values are means ± SE. * $p<0.05$, ** $p<0.01$ vs. control; # $p<0.05$, ## $p<0.01$ vs. IL-1β; @ $p<0.05$ vs. Ang II.

to MAP fall was significantly less in the IL-1β group than the control, but the increase in zRVLM spike was also significantly less in the IL-1β group. These results do not seem to indicate a consistent change in defensive mechanisms against arterial pressure fall.

Fig. 6 shows that MAP falls in response to hemorrhage after i.c.v. administration of IL-1β or Ang II were −33.7± 5.6 and −31.9±3.8 mm Hg, respectively, and were not significantly different from −35.5±3.5 mm Hg in the control. After administration of both IL-1β and Ang II, however, MAP fall, −21.8±3.1 mm Hg, was significantly smaller than that in other three groups. The decreases in HR in response to hemorrhage after i.c.v. administration of IL-1β or Ang II were −12±7 and −8±6 beats/min, respectively, and were significantly smaller than −35±10 beats/min in the control. After administration of both IL-1β and Ang II, HR showed an increase of 12±3 beats/min in response to hemorrhage, whereas other three groups showed a decrease.

DISCUSSION

In the present study, central IL-1β within a range of 0.1 through 10 ng/2μl induced a dose-dependent increase in MAP response, but no further increase was observed beyond the range. However, HR increased dose-independently in response to i.c.v. IL-1β. Hashimoto et al. (1993) also reported that the arterial pressure rise was independent of dose at higher concentrations. In the present study, the results did not show a consistent change in defensive mechanisms against the arterial pressure fall, and the baroreceptor reflex sensitivity in the IL-1β group was found not to be different from that in the control group. This result seems to indicate that the hypertensive action of IL-1β involves not only the baroreceptor reflex pathway, but also various other sites or other mechanisms.

A number of hypotheses on the mechanism of hypertensive action of IL-1β have so far been proposed. Takahashi et al. (1992) and Hashimoto et al. (1993) stated that the hypertensive action of IL-1β was mediated by increased sympathetic discharge and by humoral factors including vasopressin and corticotropin, and Morimoto et al. (1992) proposed that increased sympathetic discharge and prostaglandins are involved in the hypertensive mechanisms of IL-1β. The involvement of prostaglandins is supported by the observation that a prior treatment with indomethacin, a blocker of the cyclooxygenase pathway, eliminates the hypertensive action of IL-1β (Takahashi et al, 1992). Moreover, i.c.v. injection of prostaglandin E_2 produces responses similar to those induced by IL-1, but with shorter latency (Kannan et al, 1996), suggesting that IL-1β augments cardiovascular and sympathetic outflow through the central action of prostaglandin E_2 in conscious rats (Kannan et al,

1996). Prostaglandins are closely associated with Ang II in various aspects. Harris & Breyer (2001) reported that prostaglandins are involved in the renin-angiotensin system in the kidneys, and other studies have demonstrated that activation of COX2 stimulates renin synthesis and increases plasma renin activity (Harding et al, 1997; Traynor et al, 1999). Furthermore, nitric oxide, prostaglandins and renin-angiotensin system interact physiologically with each other in the regulation of renal hemodynamics and excretory function (Olsen et al., 1985; Raij & Baylis, 1995). Previous studies on Ang II-dependent hypertension support a role for constrictor prostanoids and have implicated PGH_2, TXA_2, or $PGF_{2\alpha}$ as potential mediators (Mistry & Nasjletti, 1988), and other studies also suggest that PGE_2 could subserve this vasoconstrictor role (Zhang et al, 2000; Audoly et al, 2001). Nevertheless, it is also highly likely that there is an interaction between IL-1 and Ang II, and the exact mechanisms of IL-1 regulatory functions remain to be elucidated.

One would expect that the hypertensive action of IL-1β prevents the arterial pressure fall caused by hemorrhage, however, the IL-1β group in the present study showed no difference from the control. Because the RVLM plays a central role in the neural control of the circulation (Guyenet, 1990; Dampney, 1994) and many humoral factors exert their actions of arterial pressure control at RVLM, we counted the spike in the RVLM. The smaller decrease in HR and the smaller increase in the number of RVLM spikes during hemorrhage in the IL-1β group might reflect the complexity of the mechanisms of IL-1β. Thus, the protective role of IL-1β in hemorrhage needs to be further investigated. The decreased HR by hemorrhage observed in this study is in accordance with the result reported by Ullman (2000).

Assuming that a part of arterial pressure regulation by IL-1 is mediated by prostaglandins and that prostaglandins interact with Ang II, the present study was undertaken to investigate the interaction of the two substances during hemorrhage. In a preliminary experiment in which hemorrhage was induced after a prior treatment with Ang II alone, the magnitude of arterial pressure fall was not different from the control. Calapai et al. (1998) reported that i.c.v. administration of Ang II caused a marked increase in arterial pressure in conscious freely moving rats compared with that of CSF-treated animals, and Ahn et al. (1993) reported that, although i.c.v. Ang II had a hypertensive action, a prior treatment with i.c.v. Ang II did not alter the arterial pressure fall in response to hemorrhage. However, the arterial pressure fall during hemorrhage was definitely reduced by a prior i.c.v. treatment with both IL-1β and Ang II. This result indicates that an interaction of IL-1β and Ang II does play a protective role against the arterial pressure fall during hemorrhage. However, Andreis et al. (1992) observed an inhibitory effect of IL-1 on the secretion of aldosterone in response to Ang II, and suggested that IL-1 and Ang II had opposing roles in the kidney. And Bataillard & Sassard (1994) stated that the hypertensive action of IL-1 was mediated by prostaglandins and sympathetic nervous activation, but did not depend on the renin-angiotensin system. Since different observations have been made depending on the sites of action and on the methods employed, the interaction between IL-1 and Ang II appears to have not been firmly elucidated.

In summary, IL-1 administered into the lateral ventricle exerted a hypertensive action, and a prior i.c.v. administration of either IL-1 or Ang II did not prevent the arterial pressure fall in response to hemorrhage. When both substances were simultaneously injected into the lateral ventricle, however, the magnitude of arterial pressure fall was reduced during hemorrhage.

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