Opiate Receptor–Mediated Decrease in Renal Nerve Activity During Hypotensive Hemorrhage in Conscious Rabbits

Hironobu Morita, Yasuhiro Nishida, Hiroyuki Motochigawa, Nobuhisa Uemura, Hiroshi Hosomi, and Stephen F. Vatner

Effects of hemorrhage on renal nerve activity and of subsequent opiate receptor blockade with naloxone were studied in conscious rabbits. Mean arterial pressure remained constant at 77 ± 2 mm Hg through 17 ± 2 ml/kg hemorrhage, while renal nerve activity increased by 159 ± 16%. After 25 ± 1 ml/kg hemorrhage, mean arterial pressure fell by 42 ± 3 mm Hg, and renal nerve activity decreased below the prehemorrhagic control level by 41 ± 15%. Bolus injection of naloxone (3 mg/kg i.v.) increased mean arterial pressure to 79 ± 2 mm Hg, not significantly different from the prehemorrhagic control level. Renal nerve activity increased by 171 ± 28%, comparable to the peak increase during nonhypotensive hemorrhage. On a different day, hemorrhage was repeated, and phenylephrine was infused during the subsequent hypotension. Phenylephrine increased mean arterial pressure to the prehemorrhagic control level. With increasing mean arterial pressure, renal nerve activity increased from its level during hypotensive hemorrhage and recovered toward the prehemorrhagic control level (—26 ± 11%), but it did not return to the peak value reached during nonhypotensive hemorrhage. To further examine the blocking effects of naloxone on changes in mean arterial pressure and renal nerve activity induced by exogenous opiate peptides, methionine-enkephalin was injected both in the control state and after treatment with naloxone. A bolus injection of methionine-enkephalin (10 μg/kg) decreased mean arterial pressure (—8.1 ± 2.0 mm Hg) and renal nerve activity (—95 ± 1%). Pretreatment with naloxone (0.5 mg/kg) effectively blocked this depressor effect and reduction in renal nerve activity. These results indicate that in conscious rabbits, hemorrhage elicits a biphasic effect on renal nerve activity that rises initially during nonhypotensive hemorrhage and then falls during hypotensive hemorrhage. This decrease in renal nerve activity is reversed by naloxone. Therefore, one mechanism by which renal nerve activity decreases during hypotensive hemorrhage appears to involve opiate receptors. (Circulation Research 1988;63:165-172) 

Hemorrhage increases sympathetic tone by unloading the arterial baroreceptors and cardiopulmonary receptors. Recently, we have observed in conscious dogs that hemorrhage increases renal nerve activity as long as mean arterial pressure remains within a normal range.1 However, during hypotensive hemorrhage, renal nerve activity falls.1 The reduction in renal nerve activity during hypotensive hemorrhage in conscious dogs still occurs after arterial baroreceptor denervation, cardiac denervation, or combined arterial baroreceptor and vagal denervation.1 Another potential mechanism for cardiovascular control during hemorrhage involves opiate receptors, and several studies have suggested a role for opiate peptides in hemorrhagic hypotension.2-11 Several studies have demonstrated that the pituitary and adrenal glands release opiate peptides in response to hemorrhage.12-14 Recently, Schadt and Gaddis10 demonstrated that hemorrhagic hypotension limits plasma norepinephrine and that naloxone increases plasma norepinephrine. Their results suggest that hemorrhagic hypotension limits sympathetic outflow from the central nervous system and that this effect is mediated by opiate receptors.

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The major goal of the present study was to determine whether naloxone could reverse the decrease in renal nerve activity during hypotensive hemorrhage in the conscious animal. Conscious rabbits were selected for the study because stable renal electroneurograms can be obtained for longer periods of time (1–2 weeks) in conscious rabbits than can be routinely accomplished in conscious dogs. Because opiate receptors are activated by acute stress such as anesthesia or surgical trauma and because the response of renal nerve activity is modified by anesthesia, it was important to conduct this study in chronically instrumented conscious animals. To further examine the effects of enkephalin on renal nerve activity and the blocking effects of naloxone, renal nerve activity was studied in response to intravenous injection of methionine-enkephalin with and without pretreatment with naloxone.

Materials and Methods

All experiments were conducted in 20 chronically instrumented conscious rabbits weighing 2.0–3.2 kg. All surgical procedures were conducted in rabbits anesthetized with sodium pentobarbital (30 mg/kg) administered intravenously via the ear vein. A venous catheter was placed into the inferior vena cava via the right jugular vein for hemorrhage and administration of drugs. An arterial catheter was placed into the subclavian artery for measuring arterial pressure. The left kidney was exposed retroperitoneally through a left flank incision. Renal sympathetic nerves along the renal artery were isolated, and two stainless-steel electrodes (model 7935, A-M system, Everett, Washington) were placed around the nerve. The nerves and electrodes were covered and fixed with a silicone gel (silicone 604A and 604B, Wacker) before closure. The electrocardiographic signals were recorded from the renal nerves using a cardiotachometer (model 1321, San-ei, Tokyo) triggered by pulse pressure. An electronic R-C filter with a 2-second time constant was used to derive mean arterial pressure. Electrical activity recorded from the renal nerves was amplified using a 50 Hz–1 kHz bandpass filter (model AVB-10, Nihonkohden, Tokyo) and was monitored by an oscilloscope (model VC-10, Nihonkohden) and audiospeaker. The output from the amplifier was passed through a gate circuit to subtract baseline noise. The noise level was determined when renal nerve discharge was eliminated reflexly following acute hypertension induced by intravenous bolus injection of phenylephrine (10 μg/kg). The output from the gate circuit was rectified by an absolute value circuit. The rectified signal was integrated by an R-C filter with a 2-second time constant. Because the integrated output was a function of renal nerve activity dependent on the area of the pulses received and their frequency, the output signal from the integrator was taken as a measure of overall renal nerve activity. To quantitate renal nerve activity, the values just before hemorrhage or drug injection were considered 100%.

Hemorrhage Experiments (n=10)

After at least a 1-hour stabilization period, the rabbit was heparinized (2,000 units/body), and then hemorrhage (3–5 ml/kg/min) was carried out. Blood was withdrawn from the previously implanted venous catheter until mean arterial pressure decreased to a level of 40–50 mm Hg. One to two minutes after cessation of hemorrhage, either naloxone was administered as bolus (3 mg/kg) or phenylephrine was infused (38 μg/min). Phenylephrine was infused until mean arterial pressure reached the prehemorrhagic control level. Ten minutes after administration, the shed blood was reinfused to the animal. These protocols were conducted in the same animals at least 24 hours apart. The order of experiments on each individual animal was randomized.

To examine the effects of naloxone alone on arterial pressure, heart rate, and renal nerve activity in the control condition (i.e., without previous hemorrhage), a bolus dose of naloxone hydrochloride (3 mg/kg i.v.; Sigma Chemical, St. Louis, Missouri) was injected, and all variables were monitored. This experiment was not conducted on the same day as that of the hemorrhage experiments.

Enkephalin Experiments (n=10)

To examine the blocking effects of naloxone on changes in mean arterial pressure, heart rate, and renal nerve activity induced by exogenous enkephalin, methionine-enkephalin (Wako Pure Chemical Industries, Osaka, Japan) was injected both in the control state and after treatment with naloxone. While arterial pressure, heart rate, and renal nerve activity were monitored, a bolus dose of methionine-enkephalin (10 μg/kg) was injected intravenously. Fifteen minutes after the injection, a bolus dose of naloxone (0.1 mg/kg) was administered. One minute after the naloxone injection, another bolus dose of methionine-enkephalin (10 μg/kg) was injected intravenously. Fifteen minutes after the first dose of naloxone, another bolus dose of methionine-enkephalin (10 μg/kg) was administered. One minute after this naloxone injection, another bolus dose of methionine-enkephalin (10 μg/kg) was injected intravenously and blocking effects of naloxone (0.5 and 2.0 mg/kg) were examined in the same manner.

Data Analysis

All data were continuously measured and recorded on an FM magnetic tape recorder (model SR-30,
TABLE 1. Effects of Hemorrhage and Subsequent Administration of Phenylephrine or Naloxone on Hemorrhaged Volume, Mean Arterial Pressure, Heart Rate, and Renal Nerve Activity

<table>
<thead>
<tr>
<th>Hemorrhaged volume (ml/kg)</th>
<th>Prehemorrhagic control</th>
<th>Nonhypotensive hemorrhage</th>
<th>Hypotensive hemorrhage</th>
<th>Phenylephrine or naloxone administration</th>
<th>5–7 minutes after administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>0</td>
<td>18 ± 1</td>
<td>26 ± 1</td>
<td>26 ± 1</td>
<td>26 ± 1</td>
</tr>
<tr>
<td>NA</td>
<td>0</td>
<td>17 ± 2</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
<td>25 ± 1</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>81 ± 4</td>
<td>74 ± 3</td>
<td>43 ± 1</td>
<td>79 ± 4†</td>
<td>77 ± 3†</td>
</tr>
<tr>
<td>NA</td>
<td>85 ± 3</td>
<td>77 ± 2</td>
<td>43 ± 1</td>
<td>79 ± 2†</td>
<td>77 ± 2†</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>239 ± 14</td>
<td>327 ± 6</td>
<td>301 ± 8</td>
<td>276 ± 8†</td>
<td>298 ± 8</td>
</tr>
<tr>
<td>NA</td>
<td>248 ± 14</td>
<td>322 ± 9</td>
<td>294 ± 11</td>
<td>246 ± 14†</td>
<td>250 ± 13*†</td>
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<tr>
<td>Renal nerve activity (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>100</td>
<td>252 ± 20</td>
<td>59 ± 11</td>
<td>74 ± 11</td>
<td>234 ± 21†</td>
</tr>
<tr>
<td>NA</td>
<td>100</td>
<td>259 ± 16</td>
<td>59 ± 15</td>
<td>271 ± 28†</td>
<td>233 ± 18†</td>
</tr>
</tbody>
</table>

PE, phenylephrine; NA, naloxone.

*p<0.05, significantly different from PE-treated group.

†p<0.05, values during PE or NA administration or 5–7 minutes after administration significantly different from values during hypotensive hemorrhage.

Results

Hemorrhage Experiments (n=10)

While all variables were recorded continuously during hemorrhage, the data presented here were sampled at the following five points: 1) just before hemorrhage (prehemorrhagic control), 2) just before the fall in mean arterial pressure (nonhypotensive hemorrhage), 3) just after a sustained reduction in mean arterial pressure to 40–50 mm Hg was obtained (hypotensive hemorrhage), 4) 1–2 minutes after the administration of naloxone or phenylephrine, and 5) 5–7 minutes after the administration of naloxone or phenylephrine.

In the phenylephrine group shown in Table 1, mean arterial pressure remained essentially at control levels of 74 ± 3 mm Hg until 18 ± 1 ml/kg blood had been withdrawn (nonhypotensive hemorrhage). When 26 ± 1 ml/kg blood had been withdrawn, mean arterial pressure fell to 43 ± 1 mm Hg (hypotensive hemorrhage). Heart rate increased to 327 ± 6 from 239 ± 14 beats/min during nonhypotensive hemorrhage and decreased slightly to 301 ± 8 beats/min during hypotensive hemorrhage, still significantly elevated from the prehemorrhagic control level. Renal nerve activity increased gradually and reached a maximum during nonhypotensive hemorrhage (+ 152 ± 20%). When mean arterial pressure began to fall, renal nerve activity also started to fall.

During hypotensive hemorrhage, renal nerve activity was significantly less than the prehemorrhagic control level (~ 41 ± 11%). One to two minutes after the cessation of hemorrhage, phenylephrine was infused continuously until mean arterial pressure reached 79 ± 4 mm Hg, which was close to the prehemorrhagic control level. At this time heart rate decreased from its level during hypotensive hemorrhage, but it was still elevated from the prehemorrhagic control level. With increasing mean arterial pressure, renal nerve activity recovered slightly from its level during hypotensive hemorrhage but still remained depressed (~ 26 ± 11%). When mean arterial pressure was maintained at the prehemorrhagic control level for 5.6 ± 0.4 minutes with phenylephrine infusion, renal nerve activity gradually increased to around its peak level (+ 134 ± 21%). Figure 1 shows a representative response to hemorrhage and phenylephrine infusion in this group.

In the naloxone group, responses of mean arterial pressure, heart rate, and renal nerve activity to hemorrhage were similar to those in the phenylephrine-treated group (Table 1). Mean arterial pressure remained essentially at control levels (77 ± 2 mm Hg) at 17 ± 2 ml/kg hemorrhage, while heart rate (322 ± 9 beats/min) and renal nerve activity (259 ± 16%) attained their peak values. After 25 ± 1 ml/kg of hemorrhage mean arterial pressure fell to 43 ± 1 mm Hg, heart rate slightly decreased from the level of nonhypotensive hemorrhage, and renal nerve activity decreased below the prehemorrhagic control level (~ 41 ± 15%). Bolus injection of naloxone (3 mg/kg i.v.) increased mean arterial pressure to 79 ± 2 mm Hg, not significantly different from the prehemorrhagic control level. Heart rate decreased from its level during hypotensive hemorrhage to 246 ± 14 beats/min, not significantly different from
FIGURE 1. Original record illustrating responses of arterial pressure (AP), mean arterial pressure (MAP), heart rate (HR), renal nerve activity (RNA), and mean renal nerve activity (MRNA) to hemorrhage and subsequent phenylephrine infusion (38 μg/min). Despite the recovery of arterial pressure, renal nerve activity does not show a rapid increase.

Without previous hemorrhage, bolus injection of naloxone (3 mg/kg i.v.) did not significantly alter mean arterial pressure (+1 ± 1 mm Hg), heart rate (-5 ± 2 beats/min) or renal nerve activity (-5 ± 6%).

Enkephalin Experiments (n=10)

Figure 3 shows a typical response of arterial pressure, heart rate, and renal nerve activity to bolus injection of methionine-enkephalin (10 μg/kg) with and without previous bolus injection of naloxone (0.5 mg/kg). Figure 4 summarizes these experiments. Methionine-enkephalin (10 μg/kg) decreased mean arterial pressure, the minimum (-8.1 ± 2.0 mm Hg) occurring at 15 seconds after the injection. It had gradually returned to the preinjection control level by 60 seconds. Renal nerve activity fell significantly, the minimum of -95 ± 1% occurring at 10 seconds after the injection, which was earlier than the minimum of mean arterial pressure. Then renal nerve activity gradually returned toward the preinjection control level. At 60 seconds after injection renal nerve activity had recovered to -1 ± 4%, not significantly different from the preinjection control level. Pretreatment with naloxone (0.1 mg/kg) was sufficient to block the depressor effect of methionine-enkephalin (10 μg/kg), but 0.5 mg/kg was not enough to block the decrease in renal nerve activity. A high dose of naloxone (0.5 mg/kg) was sufficient to block both the depressor effect and the reduction in renal nerve activity (Figure 4). Intravenous bolus injection of methionine-enkephalin (30 μg/kg) elicited similar changes in mean arterial pressure and renal nerve activity. However, pretreatment with naloxone (0.5 mg/kg i.v.) was not sufficient to block the reduction in renal nerve activity. Even after as much as 2.0 mg/kg of naloxone, 30 μg/kg of methionine-enkephalin decreased renal nerve activity by 28 ± 8%.

Discussion

The results of the present investigation conducted in conscious rabbits indicate that hemorrhage increases renal nerve activity until mean arterial pressure falls and then reduces renal nerve activity significantly below the prehemorrhagic control level during the subsequent hypotension. A reduction in renal nerve activity during hypotensive hemorrhage has been observed previously in conscious dogs. However, in that study in intact dogs, renal nerve activity fell below peak values reached...
during nonhypotensive hemorrhage but did not fall significantly below the prehemorrhagic control level. Sinoaortic baroreceptor denervation or cardiac denervation attenuated the increase in renal nerve activity during nonhypotensive hemorrhage, and sinoaortic baroreceptor denervation plus vagotomy completely blocked the increase in renal nerve activity. However, neither of these denervation procedures blocked the decrease in renal nerve activity during hypotensive hemorrhage. Thus, in that study, the reduction in renal nerve activity was not due to either sinoaortic or cardiopulmonary baroreflexes.1

The results of the present study further demonstrate that opiate receptor blockade with naloxone reverses the reduction in renal nerve activity during hypotensive hemorrhage in conscious rabbits. In rabbits treated with phenylephrine, renal nerve activity did not rapidly return to the peak level that occurred during nonhypotensive hemorrhage, in spite of a restoration of mean arterial pressure. Thus, the reduction in renal nerve activity during hypotensive hemorrhage is not predominantly due to the reduction in mean arterial pressure. However, when mean arterial pressure was maintained at the prehemorrhagic control level by continuous infusion of phenylephrine, renal nerve activity gradually increased and returned to its peak level. One possible explanation is that hemorrhagic hypotension increases the release of endogenous opiate peptides into the blood stream and that they depress the autonomic nervous system, while the elimination of hypotension with continuous phenylephrine infusion returns the rate of release of opiate peptides to normal. Naloxone injection to rabbits during hypotensive hemorrhage caused renal nerve activity to rapidly return to its peak value. These results strongly support the hypothesis that hemorrhagic hypotension activates a mechanism involving endogenous opiate peptides, limiting sympathetic drive to peripheral vascular beds resulting in generalized cardiovascular depression. Thus, the sudden drop in mean arterial pressure, as shown in Figures 1 and 2, is more likely due to an active event such as withdrawal of sympathetic tone to resistance and capacitance vessels of vascular beds. This concept is compatible with a recent study by Schadt et al9 reporting that total peripheral resistance gradually increased to 125% of control during nonhypotensive hemorrhage and then fell sharply below the control level during hypotensive hemorrhage. Rothe19 also suggested that vasodilation in peripheral vascular beds occurred during hemorrhagic shock, resulting from loss of neural control of vascular tone.

**Figure 2.** Original record illustrating responses of arterial pressure (AP), mean arterial pressure (MAP), heart rate (HR), renal nerve activity (RNA), and mean renal nerve activity (MRNA) to hemorrhage and subsequent bolus injection of naloxone (3 mg/kg). Note the dramatic reduction in renal nerve activity during hypotensive hemorrhage and the rapid recovery of arterial pressure and renal nerve activity after injection of naloxone.
In the present study, intravenous bolus injection of naloxone (3 mg/kg) without previous hemorrhage had no significant effect on the basal level of mean arterial pressure, heart rate, or renal nerve activity. Rutter et al. also found that unless there had been blood loss, naloxone elicited no pressor response in conscious rabbits. These results indicate that endogenous opiate peptides have no significant influence on these variables in intact and conscious rabbits.

For naloxone to have a pronounced pressor action, the circulation needs to have been primed by some form of stress. However, in anesthetized cats, intravenous injection of naloxone (2.0 mg/kg) produced significant increases in mean arterial pressure, pulse pressure, and preganglionic splanchnic nerve activity. Thus, under anesthetized or acute surgical conditions, hemodynamics and the autonomic nervous system are already modified by endogenous opiate peptides. These differences may contribute to the difference between conscious and anesthetized animals in response to the autonomic nervous system to hemorrhage. In anesthetized rabbits, a reduction in renal nerve activity was not observed even when mean arterial pressure fell below 50 mm Hg. In this context, it should be noted that acute stress such as anesthesia or surgical trauma causes secretion of opiate peptides.

We used 3 mg/kg naloxone, a dose 100 to 1,000 times greater than the dose necessary to reverse the effects of exogenous opiate peptides in humans. One might conjecture that other side effects rather than the antagonizing effects on opiate receptors elicited the pressor effect and increase in renal nerve activity. This is unlikely for several reasons. First, unless there had been blood loss, 3 mg/kg naloxone elicited neither a pressor response nor an increase in renal nerve activity. On the other hand, during hemorrhagic hypotension, naloxone elicited both a marked pressor response and an increase in renal nerve activity. Furthermore, it is known that hemorrhagic hypotension or hypovolemia activates the release of endogenous opiate peptides from the pituitary and adrenal gland. Thus, naloxone exerts its effect only in stressful conditions when opiate receptors are activated. These results strongly support the conclusion that the pressor response and increase in renal nerve activity are more likely due to the antagonizing effects of naloxone on opiate receptors than to other side effects.

Second, the exogenous methionine-enkephalin elicited depressor response and decrease in renal nerve activity, which were completely blocked by pretreatment with naloxone. However, a dose five times the dose that blocked the depressor effect was required to block the decrease in renal nerve activity. Methionine-enkephalin (30 μg/kg) decreased mean arterial pressure by 9 mm Hg and renal nerve activity by 95%. Pretreatment with 0.5 mg/kg naloxone was sufficient to block the depressor effect, while more than 2.0 mg/kg naloxone was required.
METHIONINE-ENKEPHALIN (10 µg/kg)

![Graph showing effects of intravenous bolus injection of methionine-enkephalin (10 µg/kg) on mean arterial pressure (MAP), heart rate (HR), and renal nerve activity (RNA) during control state (●), after pretreatment with naloxone 0.1 mg/kg (▲), and after pretreatment with naloxone 0.5 mg/kg (■). Lower panel: Effects of intravenous bolus injection of methionine-enkephalin (30 µg/kg) on MAP, HR, and RNA during control state (●), after pretreatment with naloxone 0.5 mg/kg (▲), and after pretreatment with naloxone 2.0 mg/kg (■).]

There are conflicting reports on the site of naloxone’s action and the origin of endogenous opiate peptides involved in the decrease in renal nerve activity during hypotensive hemorrhage. There are two apparent candidates for the origin of endogenous opiate peptides: the pituitary gland and the adrenal medulla. Both of these organs can increase their secretion of opiate peptides in response to hemorrhagic hypovolemia and/or hypotension. Furthermore, either hypophysectomy or adrenalectomy abolishes the beneficial pressor effect of naloxone. A study by Rutter et al suggests that low doses of intravenous naloxone (threshold 0.3 mg/kg) may exert pressor effects by acting

to block the decrease in renal nerve activity. Thus, 3.0 mg/kg naloxone may have been necessary to reverse the effects of opiate peptides on renal nerve activity in conscious rabbits.

Third, β-endorphin is found in the anterior pituitary gland and can gain access to the systemic circulation. The plasma concentration of β-endorphin in anesthetized and laparotomized dogs rises to four times the basal level immediately after severe hemorrhage. Hypophysectomy abolishes the posthemorrhage pressor action of naloxone, suggesting that the pressor effect of naloxone during hypotensive hemorrhage is predominantly due to blocking of the opiate peptides released in response to hemorrhage.
within the central nervous system, while large doses of intravenous naloxone (threshold 0.6 mg/kg) may act on the postganglionic neurons. Furthermore, their recent study demonstrated that in conscious rabbits, sympathetic noradrenergic nerves and adrenal medulla each contributed approximately equally to the pressor response to 6 mg/kg naloxone. However, the precise mechanism, origins of endogenous opiate peptides, and targets of opiate peptides that decrease renal nerve activity are still unclear. Thus, future studies in this area should consider whether the reduction in renal nerve activity during hypotensive hemorrhage is mediated in the central nervous system or at the ganglion.

In conclusion, in conscious rabbits renal nerve activity increased during nonhypotensive hemorrhage and then fell below the hypotensive control levels when mean arterial pressure fell during hypotensive hemorrhage. Bolus injection of naloxone increased mean arterial pressure to the prehemorrhagic control level and restored renal nerve activity toward its peak level reached during nonhypotensive hemorrhage. Thus, in conscious rabbits, decreases in renal nerve activity observed during hypotensive hemorrhage may be mediated by endogenous opiate peptides, suggesting that blockade of this mechanism by naloxone may be of therapeutic value in the defense against hemorrhagic hypotension.

References


Key Words • renal nerve activity • hemorrhage • naloxone • opiate receptor • methionine-enkephalin
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