Opioids in the Systemic Hemodynamic and Renal Responses to Stress in Conscious Spontaneously Hypertensive Rats

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Endogenous opioid peptides have been implicated in the regulation of cardiovascular and renal function. We tested this hypothesis by examining whether the opioid antagonist naloxone alters the cardiovascular or renal responses produced by environmental stress (air stress) in conscious spontaneously hypertensive rats (SHR). Before naloxone administration, air stress produced significant increases in heart rate, mean arterial pressure, and renal sympathetic nerve activity, and it caused a decrease in urinary sodium excretion. After intravenous and intracerebroventricular administration of naloxone, the air stress–induced pressor and antinatriuretic responses were inhibited. Subsequent studies with a different opioid antagonist, the quaternary compound naltrexone methylbromide, also showed inhibition of the air stress–induced pressor and antinatriuretic responses and demonstrated opioid receptor specificity of this inhibition. Furthermore, since only intracerebroventricular and not intravenous administration of naltrexone methylbromide inhibited the pressor and antinatriuretic responses to air stress, a central nervous system site of action was established. The opioid antagonists caused inhibition of the pressor and antinatriuretic responses to air stress without affecting the air stress–induced increase in renal sympathetic nerve activity. Our investigations indicate that central endogenous opioid peptides contribute to the pressor and antinatriuretic responses that occur in conscious SHR during acute environmental stress. (Hypertension 1989;13:808–816)

Exogenous administration of opioid peptides has been shown to alter various parameters of cardiovascular function such as systemic arterial pressure, heart rate, and baroreceptor reflex function.1–4 Furthermore, synthetic opioid agonists produce changes in the urinary excretion of water and sodium.5–8 On the basis of these findings, it has been suggested that endogenous opioid peptides participate in the regulation of cardiovascular and renal function.

To determine whether endogenous opioids participate in regulation of cardiovascular function, investigations have focused on examining changes in heart rate and arterial pressure that result from opioid receptor blockade produced by stereospecific opioid antagonists (i.e., naloxone and naltrexone). With this approach, however, an endogenous opioid mediated influence on cardiovascular function may not be readily apparent because of the possibility that various opioidergic systems remain quiescent until activated by a particular stimulus or condition that alters the mechanisms regulating opioid peptide synthesis and release. In this regard, administration of naloxone to normotensive rats produces no or minimal effects on cardiovascular function.4,9–12 In contrast, the changes in mean arterial pressure and heart rate that occur in rats subjected to different forms of stress (short-term isolation, intense light and sound, cold, and foot shock)13,14 are significantly influenced by naloxone administration. Thus, an association between the cardiovascular responses to stress and the release of opioid peptides is suggested.

Together with changes (a pressor response with tachycardia and regionally specific changes in vascular resistance) in cardiovascular function that occur on presentation of a stressor, mechanisms regulating renal hemodynamic and excretory function are also altered. With acute exposure to air stress as an environmental stimulus, conscious spon-
taneously hypertensive rats (SHR) manifest antidiuretic and antinatriuretic responses that are mediated by an increase in renal sympathetic nerve activity.\textsuperscript{15-17} Since air stress does not alter glomerular filtration rate or renal plasma flow, the antidiuretic and antinatriuretic responses are mediated by an increase in renal tubular reabsorption.\textsuperscript{15,16}

Although increases in renal sympathetic nerve activity augment the renal tubular reabsorption of sodium under stressful conditions, it is possible that other mechanisms operate simultaneously to influence the resultant renal excretory responses observed. In light of evidence suggesting an association between the cardiovascular responses to stress and the release of opioid peptides, it may be hypothesized that activation of opioidergic systems contributes to the changes in renal function during stress. This activation is exemplified by studies demonstrating that naloxone significantly increases the urinary excretion of sodium in conscious rats stressed by fasting, a manipulation that activates endogenous opioid systems.\textsuperscript{18}

Thus, the purpose of the present study was to investigate whether endogenous opioid peptides contribute to the systemic cardiovascular and renal responses to environmental stress (air stress) in conscious SHR. To examine this question, we studied changes in systemic cardiovascular and renal function evoked by air stress before and after opioid receptor blockade with naloxone. In addition, a central versus peripheral site of opioid action was investigated with the use of the quaternary opioid antagonist naltrexone methylbromide, a compound with limited ability to cross the blood-brain barrier.\textsuperscript{19}

We measured renal sympathetic nerve activity to assess whether the influence of endogenous opioid peptides on renal function during air stress was mediated by affecting the air stress–induced increase in renal sympathetic nerve activity.

Materials and Methods

Subjects

We used male SHR (Taconic Farms Inc., Germantown, New York) weighing 250–350 g in our studies. All rats were fed normal sodium diets (Na content 163 meq/kg) and allowed tap water ad libitum. All experimental procedures were in accordance with the University of Iowa and National Institutes of Health guidelines for the care and use of animals.

Surgery

On the day of the experiment, rats were anesthetized with methohexitol sodium (Brevital, 20 mg/kg i.p. supplemented with 10 mg/kg i.v. as needed, Eli Lilly, Indianapolis, Indiana) and instrumented with catheters (Tygon, Fisher Scientific International, Chicago, Illinois) in the left carotid artery and jugular vein. The catheters were tunneled to the back of the neck, flushed, and filled with heparinized saline (100 units/ml; Elkins-Sinn, Cherry Hill, New Jersey) and plugged with stainless steel pins. Through a suprapubic incision, a polyethylene urinary bladder catheter (PE-240), modified from that of Gellai and Valtin,\textsuperscript{20} was flanged and sutured into the urinary bladder, exteriorized and secured by suturing to adjacent muscle, tissue, and skin. For some experiments, a stainless steel cannula was also implanted into the right lateral cerebral ventricle 2–3 days before experimentation. The coordinates used for cannula implantation were derived from the atlas of the rat brain by Paxinos and Watson:\textsuperscript{21} 0.3 mm posterior to the bregma, 1.3 mm lateral to the midline, and 4.0 mm below the skull surface. The cannula was fixed into position by jeweler’s screws and cranioplastic cement. We verified cannula position by observing leakage of cerebrospinal fluid from the cannula after removal of the obturator.\textsuperscript{16,17}

After implantation of these catheters, some rats were also implanted with a renal sympathetic nerve activity recording electrode. The latter implantation was performed by exposing the left kidney through a left flank incision via a retroperitoneal approach. With the use of a dissecting microscope (×25), a renal nerve branch from the aorticorenal ganglion was isolated and carefully dissected free. The renal nerve branch was then placed on a bipolar platinum wire electrode (Cooner Wire Co., Chatsworth, California). Renal sympathetic nerve activity was amplified (×10,000–50,000) and filtered (low, 30; high, 3,000 Hz) with a Grass P511 bandpass amplifier (Grass Instr. Co., Quincy, Massachusetts). The amplified and filtered signal was channeled to a Tektronix 5113 oscilloscope (Tektronix Inc., Beaverton, Oregon) and Grass Model 7DA polygraph for visual evaluation, to an audio amplifier–loudspeaker (model AM8 Audio Monitor, Grass Instr. Co.) for auditory evaluation, and to a rectifying voltage integrator (model 7P10, Grass Instr. Co.) and a frequency discharge counter (Scope Raster/Stepper model 140A, W-P Instruments, Inc., New Haven, Connecticut). The integrated voltage, frequency discharge, and renal neurogram signals were displayed on the Grass polygraph. We assessed the quality of the renal sympathetic nerve activity signal by its pulse-synchronous rhythmicity and by examining the magnitude of decrease in recorded renal sympathetic nerve activity during sinoaortic baroreceptor loading with an intravenous injection of 3 μg norepinephrine. The renal sympathetic nerve activity remaining after maximum inhibition following norepinephrine administration was similar to the background noise observed approximately 30 minutes postmortem; this value was subtracted from all experimental values of renal sympathetic nerve activity. When an optimal renal sympathetic nerve activity signal was observed, the recording electrode was fixed to the renal nerve branch with a silicone cement (Wacker Sil-Gel 604, Wacker-Chemie, Munich, FRG). We then secured the electrode cable in position by suturing it to the abdom-
inal trunk muscles. Finally, the electrode cable was exteriorized, and the flank incision was closed in layers.

For certain experiments, rats were subjected to bilateral renal denervation 5–7 days before experimentation. We performed bilateral renal denervation via bilateral flank incisions and by stripping the renal arteries and veins of adventitia, cutting the renal nerve bundles, and coating the vessels with a solution of 10% phenol in absolute ethanol as previously described. This renal denervation procedure prevents the renal vasoconstrictor response to suprarenal lumbar sympathetic nerve stimulation, prevents the antinatriuretic response to environmental stress, reduces renal catecholamine histofluorescence to nondetectable levels, and reduces renal tissue norepinephrine concentrations to less than 5% of control for up to 15 days postdenervation.

After surgical preparation, rats were placed in rat holders that permitted forward and backward movement and collection of steady-state urine and allowed effective delivery of the air jet to the rat’s head. An intravenous infusion (58 μl/min) of isotonic saline containing sufficient quantities of insulin and p-aminohippurate (PAH) for determination of insulin and PAH clearance, respectively, was then started and allowed to continue during surgical recovery and throughout the duration of the experimental protocol. Four to 6 hours after habituation and the start of isotonic saline infusion, the arterial catheter was flushed and attached to a pressure transducer (model P23Db, Statham, Oxnard, California), and the urinary bladder catheter was led to a collection beaker. The quality of the renal sympathetic nerve activity recording was again tested with intravenous injection of norepinephrine (3 μg) as previously described to ensure the absence of noise due to mechanical movement, respiration, or heart rate. If the quality of the renal sympathetic nerve activity recording was the same as that observed when the electrode was implanted, then the experiment commenced.

Experimental Protocols

After stabilization of urinary flow rate, arterial pressure, and heart rate, urine was collected for renal clearances during two consecutive sets of experimental periods (control, air stress, and recovery; 10 minutes each). Five minutes was allowed after the start of air stress before the collection period began; similarly, 5 minutes was allowed after discontinuation of air stress before the recovery collection began. Immediately after the completion of the first recovery period, one group of SHR received 1 mg/kg i.v. naloxone (Sigma Chemical Co., St. Louis, Missouri). Naloxone was dissolved in isotonic saline and injected as a bolus in a volume of 0.2 ml followed by a 0.2-ml isotonic saline flush. After allowing 10 minutes for equilibration, we repeated the same sequence of experimental periods (control, air stress, and recovery). Venous blood samples (200 μl) were taken at the end of each urine collection period. Stressful environmental stimulation consisted of an air jet delivered to the top of the rat’s head through a tube located 4–5 cm in front of the rat. Repeated applications of air stress in the same SHR result in similar increases in heart rate, mean arterial pressure, and renal sympathetic nerve activity and in decreases in urinary flow rate and sodium excretion. In addition to examining the opioid antagonist-mediated changes in systemic cardiovascular and renal function evoked by air stress in SHR with an intact renal innervation, we also repeated experiments in SHR that had undergone prior bilateral renal denervation. In some experiments, drugs were injected intracerebroventricularly (2-μl injection volume through a 10-μl Hamilton syringe) rather than intravenously. For each drug protocol, we used separate groups of SHR. Drugs used for intracerebroventricular administration were naloxone (100 μg/kg dissolved in isotonic saline vehicle) and naltrexone methylbromide (5 μg total, 18.7 μg/kg, dissolved in isotonic saline vehicle). In the absence of air stress (time control), the effects of 100 μg/kg naloxone i.c.v. were examined on baseline parameters of systemic cardiovascular and renal function. The 1 mg/kg i.v. naloxone dose was used for initial evaluation; the 100 μg/kg i.v. and i.c.v. doses were matched in an attempt to localize the site of action (i.e., peripheral vs. central) of naloxone. The dose of naltrexone methylbromide was derived from the 100 μg/kg i.c.v. naloxone dose and preliminary trials. We demonstrated the efficacy of the naloxone by showing that naloxone 100 μg/kg i.v. bolus blocked the diuretic and natriuretic responses to d-Ala-2-methionine enkephalinamide but had no effect of its own on renal function.

Urine samples (10 minutes each) were collected during control (two consecutive periods) and sequentially, beginning 10 minutes after intracerebroventricular microinjection of naloxone for a total duration of 70 minutes. For experiments with renal sympathetic nerve activity recordings, we again assessed the quality of the renal sympathetic nerve signals with 3-μg i.v. injections of norepinephrine after completion of the protocol. The rat was then killed, and postmortem renal sympathetic nerve activity was continuously recorded for 30 minutes as a measure of background noise. The kidneys were removed, decapsulated, drained, and weighed.

Miscellaneous

Urine volume was determined gravimetrically. Urine sodium concentration was measured by flame photometry (model 143, Instrumentation Laboratories, Lexington, Massachusetts). Urine and plasma insulin and PAH concentrations were determined by the anthrone23 and ethylenediamine24 methods, respectively. Glomerular filtration rate was measured as inulin clearance:

\[ C_{IN} = \frac{(V)(U_{IN})}{P_{IN}} \]
where \( U_N \) and \( P_N \) are urine and plasma inulin concentrations, respectively, and \( V \) is urine flow rate. Effective renal plasma flow was determined by PAH clearance:

\[
(V)(U_{PAH}/P_{PAH})
\]

where \( U_{PAH} \) and \( P_{PAH} \) are urine and plasma PAH concentrations, respectively. Heart rate was determined with a linear cardiotachometer (Grass 7P4) driven by the arterial pressure waveform. Data acquisition was performed with a commercially available software package (Labtech Notebook, version 4.2, Lab. Technol. Corp., Wilmington, Massachusetts). Integrated renal sympathetic nerve activity is expressed as \( \mu V \cdot \sec/1 \sec \) interval. Because of the limitations of comparing values for multifiber renal sympathetic nerve activity between rats, the data are expressed as percentage of control with the control values for each rat defined as 100%.

**Statistical Analysis**

Statistical analysis was conducted with repeated-measures analysis of variance for main effects and interactions and Scheffe’s test for pairwise comparisons among means. \( p<0.05 \) was considered statistically significant in each case.

**Results**

Figure 1 illustrates the systemic cardiovascular and renal effects evoked by air stress before and after intravenous administration of the opioid antagonist naloxone (1 mg/kg) in nine conscious SHR. Before naloxone administration, air stress significantly increased heart rate from 435±8 to 489±7 beats/min, mean arterial pressure from 163±4 to 172±4 mm Hg, and renal sympathetic nerve activity 36±7% and decreased urinary sodium excretion from 3.4±0.8 to 1.7±0.4 \( \mu eq/min/g \) kidney wt. After intravenous naloxone, air stress elicited similar increases in heart rate and renal sympathetic nerve activity. In contrast, the pressor (160±3-165±3 mm Hg) and antinatriuretic (3.9±0.8-4.0±0.7 \( \mu eq/min/g \) kidney wt) responses to air stress were abolished. Glomerular filtration rate and renal plasma flow were not altered by air stress before or after intravenous naloxone.

To investigate the site of action (peripheral vs. central nervous system) of naloxone after its intravenous bolus administration, a similar experimental protocol was repeated with intracerebroventricular naloxone in nine conscious SHR. As shown in Figure 2, administration of 100 \( \mu g/kg \) naloxone i.c.v. prevented both the air stress-induced rise in mean arterial pressure (from 165±5 to 175±5 mm Hg and from 166±5 to 169±5 mm Hg after naloxone) and reduction in urinary sodium excretion (from 4.06±0.3 to 2.0±0.3 before and 5.3±0.5 to 4.6±0.5 \( \mu eq/min/g \) kidney wt after naloxone). Intracerebroventricular naloxone did not, however, alter the heart rate or renal sympathetic nerve activity responses to air stress. Moreover, in the absence of air stress, Figure 3 illustrates that 100 \( \mu g/kg \) naloxone i.c.v. did not alter any baseline parameter of systemic cardiovascular or renal function measured during time control in seven conscious SHR.

Illustrated in Figure 4 are the results obtained when the same dose of naloxone (100 \( \mu g/kg \) i.c.v.) was administered intravenously to seven conscious SHR. In a similar manner as observed when given intracerebroventricularly, 100 \( \mu g/kg \) i.v. bolus naloxone inhibited the air stress-evoked rise in mean arterial pressure, prevented the reduction in urinary sodium excretion, but did not alter the increase in heart rate. In an analogous manner, after intravenous administration of this same dose of naloxone to rats that had undergone prior bilateral renal denervation, air stress failed to evoke a significant increase in
mean arterial pressure (from 165±6 to 177±6 mm Hg before and from 159±5 to 163±4 mm Hg after administration). However, in contrast to rats with an intact renal innervation, air stress did not evoke a significant change in urinary sodium excretion before (from 3.5±0.4 to 4.0±0.4 μeq/min/g kidney wt) or after (from 4.4±0.5 to 4.7±0.7 μeq/min/g kidney wt) naloxone administration. Similar increases in heart rate were produced by air stress before and after antagonist administration in these renal denervated SHR.

To further examine the receptor specificity and site of action (peripheral vs. central) of an endogenous opioid peptide-mediated influence on systemic cardiovascular and renal function during air stress, we used naltrexone methylbromide, a quaternary opioid antagonist incapable of permeating the blood–brain barrier. Shown in Figure 5 are the systemic cardiovascular and renal responses to air stress before and after intracerebroventricular naltrexone methylbromide (5 μg) in nine conscious SHR. Naltrexone methylbromide abolished the rise in mean arterial pressure (from 161±6 to 171±5 before and from 165±5 to 164±4 mm Hg after naltrexone methylbromide) and the decrease in urinary sodium excretion (from 3.1±0.6 to 1.5±0.3 before and from 3.3±0.6 to 2.8±0.6 μeq/min/g kidney wt after naltrexone methylbromide) produced by air stress. Naltrexone methylbromide had no effect on the air stress–induced increases in heart rate and renal sympathetic nerve activity. More-
Discussion

Our study examined whether endogenous opioid peptides contribute to the changes in systemic cardiovascular and renal function that occur during acute environmental stress (air stress) in conscious SHR. After blockade of endogenous opioid peptides with the opioid antagonist naloxone, the increase in mean arterial pressure and decrease in urinary sodium excretion that result from air stress were prevented. Blockade of the air stress-induced pressor and antinatriuretic responses occurred regardless of route of naloxone administration (i.v. or i.c.v.) and were not associated with any alteration in the renal sympathoexcitatory response to air stress. In contrast, intracerebroventricular, but not intravenous, administration of the quaternary opioid antagonist naltrexone methylbromide was effective in abolishing the air stress–induced pressor and antinatriuretic responses, again, without affecting the stress–induced increase in renal sympathetic nerve activity. Together, these findings suggest that endogenous opioid systems are activated during conditions of environmental stress and contribute to the changes in arterial pressure and urinary sodium excretion that result from this stimulus. Our studies demonstrate that opioid modulation of these systemic cardiovascular and renal responses occurs at a location within the central nervous system.

Opioid peptides have been thought to be involved in the regulation of cardiovascular function. In support of this hypothesis, administration of exogenous opioids produces variable changes in mean arterial pressure and urinary sodium excretion. However, glomerular filtration rate and renal plasma flow were not affected by air stress before or after intracerebroventricular naltrexone methylbromide.

Figure 6 illustrates the systemic cardiovascular and renal responses to air stress before and after 5-μg i.v. bolus injection of naltrexone methylbromide in five conscious SHR. Intravenous administration of naltrexone methylbromide did not alter the changes in systemic cardiovascular or renal function caused by air stress. Equivalent increases in heart rate, mean arterial pressure, and renal sympathetic nerve activity and decreases in urinary sodium excretion resulted from air stress before and after intravenous naltrexone methylbromide.
arrest, heart rate, and baroreceptor reflex function. To elucidate whether endogenous opioids participate in cardiovascular regulation, investigations have been performed to examine changes in these cardiovascular parameters that result from administration of opioid antagonists such as naloxone. In spite of these efforts, a number of studies failed to demonstrate a role for endogenous opioids in cardiovascular function. In part, this may be due to the possibility that endogenous opioid systems remain silent until activated by specific stimuli. In this manner, the arterial hypotension of endotoxic, circulatory, and hemorrhagic shock have been shown to be antagonized by blockade of opioid receptors with naloxone. Although the mechanism by which opioids are involved in these shock models is not completely defined, the models serve to illustrate that endogenous opioid systems may contribute to the changes in mean arterial pressure and heart rate when normal cardiovascular function is altered.

As an alternative approach to studying the involvement of opioid peptides in cardiovascular regulation, the present study used environmental stress (air stress) as a means to activate opioidergic pathways. A clear association between alterations in circulating peripheral and central nervous system levels of opioid peptides and stress has been established. During air stress, significant increases in both mean arterial pressure and heart rate occur in conscious SHR. These studies demonstrate that administration of naloxone inhibits the pressor response to air stress without altering the increase in heart rate. Furthermore, these findings indicate that endogenous opioid peptides released during air stress contribute to the increase in mean arterial pressure observed with this environmental stimulus. In related studies in conscious rats, naloxone has also been shown to reverse the pressor responses induced by a variety of stressful environmental stimuli such as intense light and sound, cold, foot shock, and brief isolation thus supporting a role for opioid peptides in the pressor responses to acute environmental stressors. These results are different from those of McCubbin et al who showed that during psychological (mental) stress in human subjects naloxone increased mean arterial pressure in persons with low basal mean arterial pressure but had no significant effect on responses in people with high basal mean arterial pressure. These contrasting findings may reflect differences in species or responses that occur from different types of acute stressors (environmental vs. mental).

The mechanisms by which naloxone alters the arterial pressure response during air stress may be multiple. During air stress, opioid peptides may be released into discrete brain regions known to be involved in arterial pressure regulation. In these regions, opioid blockade may prevent the normal expression of the pressor response that occurs during stress. In this regard, a functioning opioid system is required for angiotensin II to mediate its pressor response. Naloxone suppresses the release of renin and inhibits the rise in plasma concentrations of adrenocorticotropic hormone and corticosterone that normally occurs in response to stress. Moreover, naloxone may inhibit the secretion of epinephrine by the adrenal medulla evoked by central opioid receptor stimulation. Since naloxone in the low doses used in this study is primarily a μ opioid receptor antagonist, the results suggest that the pressor response to air stress is dependent on the μ opioid receptor. Furthermore, studies with naltrexone methylbromide indicate a central nervous system location, which is supported by the finding that only intracerebroventricular administration of naltrexone methylbromide was effective in preventing the increase in arterial pressure to air stress. Similarly, although peripheral administration of naloxone attenuated the hypertension induced by brief isolation in rats, peripheral administration of naltrexone methylbromide was without effect.

In addition to inhibiting the pressor response to air stress, naloxone also prevented the antinatriuretic response that normally occurs to this stressor. Furthermore, naloxone produced this effect

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**FIGURE 6. Effect of intravenous administration of 5 μg naltrexone methylbromide in conscious spontaneously hypertensive rats. SHR, spontaneously hypertensive rats; HR, heart rate; MAP, mean arterial pressure; RSNA, renal sympathetic nerve activity; UNaV, urinary sodium excretion; C, control; A, air stress; R, recovery; NMBr, naltrexone methylbromide. ** **p<0.01; *p<0.05 compared with control values.**
without evoking changes in renal hemodynamic variables or alteration of the air stress–induced increase in renal sympathetic nerve activity. This latter finding is of particular interest since previous investigations have demonstrated the importance of the renal sympathetic nerves in mediating the increase in renal tubular reabsorption of sodium during air stress. In this respect, prior bilateral renal denervation prevents the air stress–induced decrease in urinary sodium excretion in conscious SHR. Similarly, since bilateral renal denervation prevents the antinatriuretic effect of intravenous morphine administration, it has been suggested that this opioid response depends in part on a mechanism involving intact renal nerves. In contrast, in previous studies from our laboratory, the renal excretion of water and sodium were influenced by intravenous infusion of the opioid agonists methionine enkephalin (natural) and D-Ala2-methionine enkephalinamide (synthetic analogue) without producing changes in renal sympathetic nerve activity. Thus, it may be suggested from these studies that endogenous opioids may affect the renal tubular reabsorption of sodium by a mechanism independent of changes in renal sympathetic nerve activity.

Although it is apparent from our studies that central opioidergic pathways must be functional for an increased renal tubular sodium reabsorption response to acute environmental stress, our results also confirm that intact renal innervation is also required for a stress-induced antinatriuretic response to occur. This is supported by the finding that air stress did not alter the urinary excretion of sodium before or after naloxone administration in rats that had undergone prior bilateral renal denervation. Thus, naloxone’s inability to affect urinary sodium excretion during air stress in these renal-denervated animals suggests that these two mechanisms, an intact renal innervation and a functional central opioid system, interact in the regulation of renal tubular sodium reabsorption during environmental stress.

The manner by which naloxone prevents the increase in renal tubular sodium reabsorption in the face of an increase in renal sympathetic nerve activity is currently unknown, and further studies are needed to elucidate the nature of this complex interaction. Our data do demonstrate that blockade of opioid actions, evoked by air stress, is responsible for the abolition of the antinatriuretic response to air stress since, in time control studies in the absence of air stress, baseline parameters of renal function were not altered by naloxone. Furthermore, the site of action is localized to the central nervous system since only intracerebroventricular and not intravenous naltraxone methylbromide abolished the antinatriuretic response to air stress. During air stress, the central release of opioids may have a secondary influence on the secretion of various substances (e.g., antidiuretic hormone, atrial natriuretic factor, renin-angiotensin-aldosterone, or γ-melanocyte-stimulating hormone) capable of influencing the renal handling of sodium. Contribution of these and other mechanisms may thereby collectively influence the net urinary sodium excretion during the acute environmental stimulus of air stress.

In summary, the present data demonstrate that the release of endogenous opioid peptides during air stress contributes to the changes in mean arterial pressure and urinary sodium excretion observed as a result of this acute environmental stimulation. Moreover, since this modulating influence of the central opioid peptide system on the renal sodium excretion response occurred without affecting the renal sympathoexcitatory response to air stress, it appears that additional mechanisms can interact with the renal sympathetic nerves in the control of renal sodium handling during acute environmental stress.

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References


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