Hypertension

Brief Review

The Opioid Peptides
A Role in Hypertension?
Giora Feuerstein and Anna-Leena Siren

SUMMARY This review is an attempt to highlight evidence that may implicate the endogenous opioid system in the pathogenesis of hypertension in humans. The evidence raised includes biochemical, physiological, pharmacological, and behavioral studies conducted in vitro and in vivo systems, experimental models of hypertension, and humans with essential hypertension. While the compelling biochemical and pharmacological evidence in experimental animals clearly shows the presence of opioid peptides and their receptors in strategic sites of cardiovascular control and potent cardiovascular response to opioid peptides, opioid antagonists show no consistent blockade or reversal of hypertension in experimental animals or humans. One possible explanation for this phenomenon could be the vast redundancy in systems regulating blood pressure (i.e., the blockade of one system still leaves many other systems fully able to rapidly offset the eliminated system). Regarding the opioid system, the situation is much more complex, since some opioid receptors (μ-type) mediate pressor responses, while other receptors (κ-type) mediate depressor responses. Therefore, nonselective opioid receptor antagonists (e.g., naloxone), which block both types of receptors, can be devoid of any cardiovascular activity, while a selective μ-receptor antagonist or a selective and potent κ-receptor agonist may produce the desired antihypertensive effect. A combination of both actions (i.e., a drug that is both a μ-antagonist and a κ-agonist) might be even more advantageous. Until such compounds are developed, this hypothesis will be hard to prove. (Hypertension 9: 561-565, 1987)

KEY WORDS • μ-opioid receptors • κ-opioid receptors • naloxone • blood pressure • vascular resistance

Numerous neurally localized peptides are now known to exist within the central nervous system (CNS). Many of these peptides originally were found in the hypothalamus and pituitary gland and later were shown to be widely distributed in the CNS and to possess diverse autonomic functions through modulation of sympathetic and parasympathetic tone and the baroreceptor reflex mechanism.

Neuropeptides like vasopressin, angiotensin, bradykinin, neurokinins (e.g., substance P and thyrotropin-releasing hormone) have long been a subject of discussions in reference to cardiovascular regulation. The opioid peptides, discovered in the past decade,1-2 have drawn immediate attention as potential participants in central cardiovascular control, since opiates (e.g., morphine) have been known for almost two centuries to have potent effects on cardiorespiratory variables.3-5 The opioid system is especially complex because of the multiple species of opioid peptides and multiple forms of receptor subtypes (Table 1). The purpose of the present report is to provide a critical review of the evidence supporting a role of the endogenous opioid peptides in the development and maintenance of high blood pressure.

The Endogenous Opioids and the Cardiovascular System

The Central Opioid Peptide System

Opioid peptides (β-endorphin, enkephalins, dynorphins) and multiple opioid receptors are present in brain nuclei involved in cardiovascular control.6 These opioid peptides exert potent cardiovascular actions when injected into the cerebral ventricles (i.c.v.) or...
discrete brain nuclei. Microinjections of opioids into brain nuclei such as the hypothalamic paraventricular, medial preoptic, nucleus ambiguus, or the nucleus tractus solitarii elicit potent cardiovascular changes in various experimental animals. Generally, low to medium doses of μ-opioid agonists such as morphine, morphiceptin, dermorphin, and D-Ala²-MePhe⁴-Gly⁵-ol-enkephalin (DAGO) induce a pressor effect with biphasic changes in heart rate (bradycardia, tachycardia); high doses of μ-receptor agonists cause cardiovascular collapse and death. Since D-Ala²-Leu-enkephalin (DADL), a relatively selective δ-receptor agonist, is about 10 times less potent than the μ-agonist DAGO in eliciting cardiovascular responses, μ-opioid receptors rather than δ-receptors seem to be the primary receptors in the mediation of the central pressor actions of opioid peptides. Opposite to the responses elicited by μ-opioid receptor activation, stimulation of the κ-opioid receptors in the paraventricular nucleus, medial preoptic nucleus, nucleus tractus solitarii, nucleus ambiguus, or dorsal motor nucleus of the vagus produces depressor and bradycardic responses in the anesthetized rat. The μ-opioid receptor might also have a role in hypertension, since hypothalamic μ-opioid receptor stimulation activates the sympathoadrenomedullary system and further elevates the blood pressure of spontaneously hypertensive rats (SHR). 

The Peripheral Opioid System
Besides their presence in the CNS, opioid peptides are present in the heart, blood vessels, sympathetic nerves, and adrenal gland. The peripheral opioid system has been shown to inhibit norepinephrine release at a presynaptic site in various in vitro preparations. Also, intravenous injection of opioid peptides decreased, whereas the opioid antagonist naloxone increased, sympathetic nerve activity and blood pressure in anesthetized cats. However, the effect of i.v. administered opioids and opioid antagonists might be due to an action of the sympato-inhibitory centers in the brain, since in the pithed rat, in which the entire CNS and spinal reflexes have been destroyed, opioid peptides are devoid of any cardiovascular actions of their own and have no influence on the pressor and tachycardic responses elicited by sympathetic stimulation. 

The Opioid System and the Baroreceptor Reflex Mechanism
Most commonly, the effects of opioids on baroreceptor reflexes have been assessed by measuring heart rate changes in response topressor or hypotensive stimuli. However, sensitivity of the baroreceptor-heart rate reflex does not always reflect the gain of the baroreceptor-blood pressure reflex. Dashwood and Feldberg showed that the pressor response of naloxone in anesthetized cats after bilateral vagotomy and stellate ganglion removal was enhanced when these animals were further exposed to sinoaortic denervation. However, in a recent study in anesthetized rats in which the aortic nerve baroreceptor afferents were electrically stimulated, naloxone had no effect on the reflex hypotension. Although naloxone failed to modify baroreceptor reflexes in this study, intracerebral injection of the μ-agonist DAGO or the δ-agonist DADL attenuated the decreases in blood pressure, heart rate, and sympathetic nerve activity produced by the aortic nerve stimulation. Again, μ-receptors seem to be involved in the opioid-mediated action. 

Central Opioids in Experimental Hypertension
Biochemical Evidence
Important changes have been described in the central opioid system in several models of experimental hypertension. Hypertension-prone Sabra rats have significantly higher levels of endogenous opioids in their cerebral spinal cord, hypothalamus, and pituitary gland as compared with levels in their normotensive controls. Similar, renal hypertensive rats (two-kidney, one clip) have higher levels of opioid peptides in their cerebral cord as compared with levels in normotensive controls. Dynorphin A (1–13), dynorphin A (1–8), and leu²-enkephalin are lower in the suprachiasmatic nucleus of SHR than in those of Wistar-Kyoto rats (WKY). Furthermore, SHR had lower levels of dynorphin A (1–8) in paraventricular nuclei and central amygdala and higher dynorphin A (1–13) levels in the substantia nigra. The levels of β-endorphin immunoreactivity in the plasma and neurointermediate lobe of SHR were also shown to be higher than those found in normotensive controls. The levels of this potent endorphin were the same in the anterior lobe of the pituitary gland in both strains. 

Opioid receptor numbers in particular fractions from brains of 8-week-old SHR are about twice those measured in normotensive WKY, while there are no differences in receptor density before the development of hypertension. Significant decrease in [H]naloxone binding in the spinal cord of hypertension-prone rats as compared with normal rats has also been described. Interestingly, the difference in the opioid receptors between SHR and WKY totally disappeared in SHR with established hypertension. Up-regulation of opioid receptors caused by reduced levels of endogenous opioids was suggested to underlie the increased receptor binding in adult SHR compared with that in

<table>
<thead>
<tr>
<th>Opioid Peptides and Receptor Subtypes</th>
<th>Endogenous opioid peptide</th>
<th>Receptor subtype</th>
<th>Endogenous precursor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leu-enkephalin</td>
<td>δ</td>
<td>Preproenkephalin A</td>
<td></td>
</tr>
<tr>
<td>Met-enkephalin</td>
<td>μ, δ</td>
<td>Preproenkephalin A</td>
<td></td>
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<tr>
<td>Dynorphin (1–17)</td>
<td>κ</td>
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<tr>
<td>β-endorphin</td>
<td>ε</td>
<td>Preproopiomelanocortin</td>
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<tr>
<td>Unknown</td>
<td>σ</td>
<td>Endogenous phenerydine receptor binding protein</td>
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TABLE 1.
young prehypertensive SHR. The significance of these findings in relation to the ontogenesis of hypertension is still obscure.

Behavioral Evidence
Cardiovascular centers and pathways share anatomical, biochemical, and pharmacological properties with the pain system (for a review, see Reference 34). Recent studies indicate a diminished responsiveness to noxious stimuli in genetically and experimentally hypertensive rats. Naloxone normalized the increases in pain threshold in SHR, suggesting a relationship between the central opioid system and cardiovascular regulation in this model. In one study, the pain sensitivity was reduced in SHR but not in rats with other forms of experimental hypertension. The analgesic effect of morphine was enhanced in SHR as compared with WKY; however, the relationship of the change in pain perception to the ontogenesis of hypertension remains obscure.

Pharmacological Evidence
The opioid system has been implicated in the development of high blood pressure in SHR, since the pressor responses to i.c.v. administered opioid peptides are enhanced in SHR as compared with those in normotensive rats. SHR differ from normotensive rats in their response to hypothalamic administration of enkephalins; the SHR showed an augmented pressor response to the µ-agonist DAGO or the δ-agonist DADL microinjected into medial preoptic nucleus. In normotensive WKY, unlike the SHR, pronounced tachycardia accompanied the pressor response. Studies still in progress in our laboratory have shown that the SHR also differ from WKY in their sensitivity to the distinct regional blood flow changes mediated by µ-receptors (Figure 1). The renal and mesenteric vasoconstriction produced by DAGO (0.1–10 nmol per rat i.c.v.) were significantly potentiated in SHR compared with WKY.

The partial opioid antagonist diprenorphine was also shown to produce a more pronounced hypotensive response in SHR than in WKY. The opioid antagonist naloxone has been reported to lower blood pressure in stress-induced hypertension. Intravenous infusion of the opioid antagonists naloxone and naltrexone was shown to produce transient decreases in blood pressure and heart rate in SHR but not in WKY. However, in several other studies conducted in normotensive or hypertensive animals, naloxone had no effect on blood pressure. Also, infusion of naloxone over 2 weeks to young SHR failed to prevent the development of hypertension. These studies may suggest no crucial role for the endogenous opioids in blood pressure regulation. However, during blockade of the pressor µ-opioid receptors, other pressor systems, such as the vasopressin or angiotensin systems, might become more important for cardiovascular homeostasis. This mechanism was suggested to underlie the failure of a long-term infusion of vasopressin to alter blood pressure in conscious rats. Further studies are necessary to explore this question.

The Opioid System and Antihypertensive Drugs
A role for the endogenous opioids in blood pressure control in hypertension has also been suggested on the basis of interactions of opioid peptides and opioid antagonists with centrally acting antihypertensive drugs. First, the opioid antagonist naloxone reversed the hypotensive action of the centrally acting antihypertensive drugs clonidine and α-methyldopa in SHR but not in WKY. However, in more recent studies naloxone had no influence on the cardiovascular responses or changes in circulating catecholamines induced by

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**Figure 1.** Effect of intracerebroventricularly (i.c.v.) administered D-Ala²-MePhe⁴-Gly⁵-ol-enkephalin (DAGO) on mean arterial pressure (MAP) and regional blood flow in conscious SHR and WKY. Increasing doses of DAGO (0.1–10 nmol per rat) were injected i.c.v. at 45-minute intervals. Changes in the hemodynamic variables are presented as changes from the baseline before DAGO administration. Statistical significance was calculated by analysis of variance followed by the Student-Newman-Keul test. Vertical bars denote SEM. S = saline i.c.v.
clonidine in either SHR or WKY. Second, i.e.v. infusion of antibodies to β-endorphin abolished the hypotensive action of clonidine in various forms of experimental and genetic hypertension. The decreases in blood pressure, heart rate, and sympathetic nerve activity induced by intrathecal injection of clonidine in normotensive Wistar rats were also prevented by pretreatment with a dynorphin antiserum. Furthermore, morphine was reported to suppress the rebound hypertension occurring after clonidine withdrawal in SHR. Third, clonidine and α-methyladrenalin increased the release of opioid peptides from the brainstem of SHR as well as their concentrations in plasma and cerebrospinal fluid of normotensive rats. Met-enkephalin levels and opioid receptors in cardiovascular nuclei (nucleus tractus solitarii and dorsal medial nucleus) of SHR were also increased by clonidine and α-methyladrenalin. However, more recent studies have shown that clonidine depresses the plasma levels of β-endorphin immunoreactivity in SHR but not in WKY; consequently, the concentration of β-endorphin immunoreactivity in the neurointermediate lobe of SHR only increases after clonidine administration. These studies strongly suggest a role for α₂-adrenergic receptors in the neurointermediate lobe in the regulation of β-endorphin release in hypertension. The increase in opioid peptides in the brain might not be specific to centrally acting antihypertensive drugs but instead may reflect the change in systemic blood pressure, since the peripheral acting vasodilator hydralazine produced the same changes in brain opioid levels and receptors.

The Opioid System in Human Hypertension

In agreement with the animal studies, reduced sensitivity to pain in humans with essential hypertension has also been reported. Other investigators recently confirmed this finding in established hypertensive as well as in borderline hypertensive patients. However, naloxone was not used to reverse the increase in pain sensitivity in these studies, and, therefore, mechanisms other than an increase in opioid tone cannot be excluded.

A role for the central opioid system in the pathogenesis of hypertension in humans has also been suggested based on the interactions of naloxone with the centrally acting antihypertensive drugs. Thus, transient pressor responses have been described in essential hypertensive patients receiving clonidine therapy or in severe clonidine overdosage. In normotensive subjects, naloxone does not reverse the effects of clonidine. Also, a more recent study reported that naloxone had no effect on the clonidine-induced reduction in blood pressure and plasma catecholamines in hypertensive patients. Furthermore, naloxone had no effect on blood pressure in either normotensive or hypertensive humans, although it significantly increased plasma epinephrine levels in essential hypertensive patients. These studies taken together make it difficult to draw conclusions on the potential role of the central opioid system in human hypertension.

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