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The Opioid System in Circulatory Control

Anna-Leena Sirén and Giora Feuerstein

Opioid peptides and multiple opioid receptors are found in brain cardiovascular nuclei, autonomic ganglia, the heart, and blood vessels, and opioids induce potent cardiovascular changes. The role of endogenous opioids in normal cardiovascular homeostasis is unclear; however, current data suggest opioid involvement in stress.

Introduction

The endogenous opioid system consists of a large family of opiate-like peptides: the enkephalins derived from preproenkephalin A, the endorphins derived from preproopiomelanocortin, and dynorphins derived from preproenkephalin B (8). The presence of several classes of opiate receptors, μ (morphine), δ ([Met^5]- and [Leu^5]enkephalin), κ (ketocyclazocine), ϵ (β-endorphin), and σ (SKF-10,047) has been well established, and the existence of multiple receptor subtypes has been proposed for μ- and κ-receptors based on pharmacological and biochemical studies (8, 10, 12).

The type and main pharmacological effects of multiple opioid receptor classes are summarized in Table 1. In brief, these opioid receptors have been implicated in extremely diverse biological actions of which modulation of pain perception is most extensively studied. However, the opioid system has been shown to be involved in food consumption, body temperature, pituitary hormone release, respiration, behavior, and cardiovascular regulation (7, 8, 10). For the purposes of this review, only the cardiovascular effects mediated through opioid receptors are analyzed.

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Distribution of opioid peptides and opioid receptors in cardiovascular structures

The regional distribution of opioid peptides and the variety of opioid receptors in the brain have been extensively investigated (8), and opiate receptors have been shown in virtually every cardiovascular nucleus (10, 11). Most notable are hypothalamic cardiovascular centers such as the preoptic nucleus, paraventricular nucleus, lateral hypothalamic nucleus, the central nucleus of amygdala, hippocampus, the periaqueductal gray, the dorsal raphe nucleus, the parabrachial nucleus, and the nucleus reticularis paragigantocellularis. They occur in particularly high densities in the caudal part of the nucleus tractus solitarii (10).

Opioid receptors have also been identified in the spinal cord, where they appear to be primarily associated with laminae II and III of the dorsal horn at least in the rat, guinea pig, and human spinal cord (10). Dense areas of κ-opioid binding are detected in the posterior pituitary and median eminence (10).

Opioid peptides and opioid receptors are also found in peripheral cardiovascular organs such as the heart, blood vessels, kidneys, and the adrenal medulla. Furthermore, cardiovascular organs might be influenced by blood-borne opioid peptides, which are markedly elevated during cardiovascular stress situations such as bleeding-induced hypovolemic hypotension (4, 7).

Cardiovascular effects of opioid peptides

The vast majority of reports that suggested a role for opioids in cardi-

Table 1. Agonists, antagonists, and proposed functions of multiple opioid receptor subtypes

Receptor	Agonist	Antagonist	Function
μ_1	DADL DAMGO Dermorphin TAPS* β-End=Enk>DynA	Naloxonazine* Naloxazone* Naloxone β-FNA	Supraspinal analgesia, euphoria, respiratory stimulation, tachycardia, sympathetic stimulation, hypertension?, cerebral blood flow regulation
μ_2	Morphine DAMGO Dermorphin β-End>DynA>Enk	β-FNA Naloxone TAPS?	Spinal analgesia, respiratory depression, bradycardia
δ	DPDPE* DADL Enk=β-End>DynA	ICI17864* Naltrindole*	Reward, spinal analgesia, tachycardia
κ_1	U69593* U50488* EKC DynA>>β-End>>Enk	Nor-BNI* Naloxone (high doses)	Analgesia, sedation, regulation of vasopressin release, hypotension, bradycardia, diuresis, inhibition of NE release, dysphoria, psychotomimetic effects
κ_2	DynA* Bremazocine* EKC		Ibid?
ϵ	β-End		
σ	Cyclazocine SKF-10,047 Phencyclidine	Haloperidol	Psychotomimetic effects

DADL, [D-Ala^2,D-Leu^5]enkephalin; DAMGO, [Tyr-D-Ala^2-Gly-NMePhe^4-ol^5]enkephalin; DPDPE, [D-Pen^2,D-Pen^5]enkephalin; DynA, dynorphin A; EKC ethylketocyclazocine; β-End, β-endorphin; Enk, enkephalin; β-FNA, β-funaltrexamine; Nor-BNI, nor-binaltorphimine; TAPS, Tyr-D-Arg^2-Phe-(NMe)Gly^4. * Selective agonists and antagonists.

ovascular regulation have been pharmacological studies in which opiates and opioid peptides were administered to anesthetized or conscious animals. Peripherally injected opiates such as morphine to normal animals consistently produce hypotension (7). However, centrally injected opiates or opioid peptides produce depressor or pressor responses; this highly productive and controversial field is the result of several inconsistencies that include *1*) species; *2*) anesthetized versus conscious subjects; *3*) the type of opiate/opioid peptide administered; 4) the size of administration; 5) the experimental condition, e.g., stressed versus resting animals; and 6) the selectivity toward specific opiate receptors (4). Furthermore, it is still unclear whether endogenous opioids play a crucial role in cardiovascular physiology.

Effective blockade of opioid receptors by naloxone in normal humans or animals does not significantly alter cardiovascular variables such as systemic blood pressure or heart rate. This lack of effect of naloxone might be due to instantaneous adjustments in the hemodynamic balance resulting from the multiple systems activated. If this were the case, an early change in some variables should be detected. The lack of even short-term changes therefore suggests that the involvement of the opioid system in cardiovascular control is more of an adaptive and regulatory system in physical and stress situations.

Cardiovascular effects of μ-selective opioids

In general, μ-selective opiates when administered centrally in the rat induce a dose-related pressor response that is accompanied by a biphasic heart rate response (4, 5, 13, 14). It is our view that in the central nervous system selective activation of the μ-opioid receptor produces cardiovascular responses in conscious animals through activation of the sympathoadrenomedullary axis. This claim is based solely on studies with highly selective μ-opioid agonists such as the [D-Ala^2-MePhe^4-Gly^5-ol]enkephalin (DAMGO) or the heptapeptide dermorphin; such highly specific and potent μ-agonists produce pressor and cardiac-accelerating effects at picomolar doses.

The role of the sympathoadrenomedullary system in mediation of the pressor and cardiac-accelerating effect of highly selective μ-opioid agonists in the brain was established by *1*) direct assay of plasma norepinephrine and epinephrine (13), *2*) direct monitoring of sympathetic outflow in peripheral postganglionic sympathetic nerves (3, 14), and *3*) blockade of the pressor effects by adrenergic blocking agents (13, 14). The biphasic pattern of cardiovascular responses to μ-opioid agonists might also concur with the hypothesis that μ-opioid effects are mediated by two subclasses of opioid receptors, μ_1-receptors mediating stimulatory responses and μ_2-receptors mediating depressant responses (12). In our recent studies the stimulatory effects on the cardiorespiratory system have been shown in response to central administration of the dermorphin analogue TAPS [Tyr-D-Arg^2-Phe-(NMe)Gly^4], a highly potent μ_1-agonist/μ_2-antagonist (Paakkari, Feuerstein, and Sirén, *Soc. Neurosci. Abstr.* 559, 1990).

Interestingly, striking similarities exist between the reflex response of systemic hemodynamic variables and blood flow redistribution (the classical defense response) produced by environmental stressors such as cold water or immobilization and those elicited by central administra-

tion of selective μ-opioid agonists (5, 14). This complex pattern of cardiovascular adaptation includes, in both cases, an abrupt increase in blood pressure and cardiac output, increase in muscle blood flow (due to vasodilation) with concomitant reduction in splanchnic organ blood flow (due to vasoconstriction), and increases in sympathetic nerve activity and circulating levels of catecholamines.

μ-Opioid interaction with the baroflex system

The continuous flow of information from the peripheral baroreceptors is processed in the nucleus tractus solitarii (NTS), dorsal motor nucleus of the vagus, and ventrolateral medullary nuclei, which are rich in opioid peptides and receptors (8, 10). The baroreceptor reflex is highly sensitive to modulation by selective μ-opioid agonists such as DAMGO (6). More specifically, μ-opioid receptors localized in the NTS seem to inhibit peripheral baroreceptor input in the NTS and thereby produce pressor responses as evidenced by the effect of DAMGO microinjected into this region (4, 5).

Indirect studies aimed at exploring the effect of opioid peptides on reflex changes of heart rate in response to pressure changes (traditionally elicited by systemic pressor or depressor events) have shown that opioids reduce the responsiveness of heart rate to acute blood pressure changes (4, 5, 7). However, such studies may not well represent baroregulation of the sympathetic nervous system.

More direct evidence of opioid effects on the baroreflex mechanism were obtained by direct stimulation of the baroreceptor afferents, whereas sympathetic activity and systemic hemodynamic variables were monitored directly (6). Such studies clearly revealed reflex reduction in arterial pressure, heart rate, and sympathetic nerve activity by the selective μ-opioid agonist DAMGO. However, it is important to note that no evidence was produced in favor of a tonic modulatory role of the endogenous opioid system, since in normal resting conditions administration of naloxone, a potent opiate/opioid peptide antagonist, failed to modify the baroreflexes (6).

Cardiovascular effects of δ-selective opioids

The cardiovascular effects resulting from stimulation of δ-opioid receptors have been difficult to evaluate because of the lack of highly selective agonists. The relative δ-selective enkephalin analogue [D-Ala^2-, D-Leu^5]enkephalin (DADL) induced similar cardiovascular responses as the μ-selective peptides but was ~10 times less potent that the selective μ-agonist DAMGO (7, 13). Since DADL exhibits high affinity to μ_1-opioid binding sites (12), the pressor and tachycardic responses elicited by DADL may be mediated primarily by μ_1- rather than δ-sites.

This view is further supported by the finding that the selective δ-agonist dimeric tetrapeptide enkephalin had no cardiovascular effects in the rat (13). In a recent study, however, the intracerebroventricular administration of the selective δ-agonist [D-Pen^2,D-Pen^5]enkephalin (DPDPE), which lacks affinity to μ_1-sites (12), was associated with increases in blood pressure and heart rate (11) in conscious rabbits. Unlike the effects of the selective μ-agonist DAMGO, the cardiovascular effects of the δ-agonist were not accompanied by increases in plasma catecholamines (11). Furthermore, the δ-agonist was >10 times less potent than the μ-agonist in increasing blood pressure (11).

Cardiovascular effects of κ-selective opioids

In general, κ-opioid peptides decrease blood pressure and heart rate in anesthetized animals after both central and peripheral routes of administration (4, 5, 7). Since the κ-opioid receptors have been identified in peripheral tissues such as the heart, blood vessels, and adrenal medulla and κ-agonist have been shown to inhibit norepinephrine release at a presynaptic site in various in vitro preparations, the cardiovascular effects of κ-agonists after systemic administration have been suggested to be mediated by peripheral receptor sites (15).

The functional importance of this κ-opioid receptor-mediated modulation of norepinephrine release and the role of peripheral κ-receptors in the cardiovascular effects of intravenous opiates are still controversial (5, 15). Thus, in the pithed rat in which the complete central nervous system and spinal reflexes are destroyed, the opioid peptides have negligible effects on the cardiovascular system (5).

The effects of κ-opioid peptides on cardiovascular variables in conscious animals differ dramatically from those reported in anesthetized animals. In the conscious rat, dynorphin A(1—13) induced transient pressor responses along with bradycardia and/or delayed tachycardia after both systemic and central administration (13). In the conscious rabbit, the highly selective κ-agonists dynorphin A(1—13) and U69593 had no effect on blood pressure or heart rate after intracerebroventricular administration (11).

κ-Opioid interactions with vasopressin

The vasopressin system seems to be important for many κ-opioid responses. κ-Agonists induce diuresis that is mediated by suppression of vasopressin release (9). This interaction, i.e., suppression of vasopressin release, suggests that κ-opioids may play a pivotal role in the regulation of hypothalamoneurohypophysial hormone excretion. This assumption is further supported by studies showing that dynorphin and vasopressin are colocalized in the magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei and in the neural lobe of the pituitary (8).

The pressor and bradycardic responses to κ-agonists in conscious animals may, on the other hand, be related to stimulation of vasopressin release. Carter and Lightman (2) injected the κ-agonist U50488 into the NTS of Sprague-Dawley, Long-Evans, and vasopressin-deficient Brattleboro rats. In the Sprague-Dawley rats, U50488 elicited a pressor response in the NTS that was blocked by a κ-antagonist (MR2266) and a vasopressin V_1 antagonist. In the vasopressin-deficient Brattleboro rats, U50488 had no effect on blood pressure or plasma vasopressin, whereas in the parent strain Long-Evans rats it induced a significant pressor response associated with an increase in the circulating levels of vasopressin (2).

The antagonism by the vasopressin antagonist was selective for κ-

agonists; the vasopressin antagonist did not modify the effects of a δ-agonist, whereas the α-adrenoceptor blocker phenoxybenzamine selectively blocked the pressor response to the δ-agonist but not that elicited by the κ-agonist (2). Lesions of the afferent noradrenergic pathways from brain stem to hypothalamic paraventricular and supraoptic nuclei, which may exert a facilitatory effect on vasopressin release in the magnocellular neurons, abolished the pressor but not the bradycardic response to U50488 microinjected into the NTS (2), further suggesting an interaction between vasopressin release and some of the cardiovascular effects of κ-opioids.

Opioids in hypertension

A role of opioid peptides in hypertension has been supported by studies demonstrating *1*) changes in peptide and receptor levels in hypertensive animals, *2*) demonstration of increased pain threshold in spontaneously hypertensive rats (SHR) and human hypertension, and *3*) enhanced pressor and vasoconstrictor responses to opioid peptides in hypertensive animals compared with normotensive animals (1, 5). Thus κ-receptor densities in the hypothalamus and cortex of SHR were increased compared with their normotensive controls (Wistar-Kyoto strain, WKY), whereas μ- and δ-opioid receptors did not exhibit a similar difference (1). This difference was shown to likely bear functional relevance, since SHR exhibited a higher analgetic and diuretic response to κ-agonists (1).

The vasoconstrictor and pressor effect of the μ-agonist DAMGO was also shown to be higher in SHR than WKY rats (5). The levels of endogenous opioid ligands [Leu^5]enkephalin, dynorphin A(1—16), and dynorphin A(1—8) were lower in the hypothalamic suprachiasmatic nucleus of SHR compared with WKY.

Reduced levels of dynorphin A(1—8) were also found in the hypothalamic paraventricular nucleus and central nucleus of the amygdala of SHR compared with WKY rats, whereas the levels of dynorphin A(1—13) in the substantia nigra were higher in SHR than WKY rats. The levels of β-endorphin in the plasma and posterior pituitary were also higher in SHR than normotensive WKY rats. These results suggest that opioids may be involved in the pathogenetic mechanisms of arterial hypertension. Whether the observed changes in receptor densities are secondarily due to the elevated blood pressure or constitute a genetic difference between these rat strains has yet to be determined.

Opioids in shock

The endogenous opioid system was suggested to play a role in the pathophysiology of cardiovascular shock, since the opioid antagonist naloxone improved cardiovascular function and survival in some experimental shock models (4, 7). Increased levels of opioid peptides are also found in plasma and cerebrospinal fluid of animals exposed to hemorrhage (4, 7). Changes in opioid peptides and receptors in brain nuclei and heart of rats have been reported after hemorrhagic shock. Thus κ- and δ-opioid binding decreased by 45–60% in the right atria and ventricle of hearts removed from rats 2 h after hemorrhage, whereas binding in the brain stem was increased. The levels of dynorphin A and vasopressin in the neurointermediate lobe of the pituitary were decreased 24 h after hemorrhage in this model of hemorrhagic shock in rats (4).

Summary: role of the opioid system in cardiovascular control

This brief review provides circumstantial evidence originating primarily from pharmacological and biochemical experiments in vivo. It is clear that several classes of opioid peptides and receptors are involved in multiple anatomic circuits controlling blood pressure and heart rate in the central nervous system, whereas opioids in peripheral cardiovascular organs may play little if any significant role. A second generalization that can be made at the present time concerns the state of the cardiovascular system; it is quite clear that in the normal, conscious resting state it is extremely hard to demonstrate cardiovascular responses to a potent opioid antagonist such as naloxone, in either humans or animals. The same opioid antagonist displays marked hemodynamic responses, however, when administered in cardiovascular stress situations such as hemorrhagic, septic, or traumatic shock (7).

In fact, the most compelling evidence on the role the opioid system might play in host adaptation to injury is derived from demonstrations showing that naloxone improves metabolic, endocrine, and cardiovascular indexes in animal models of tissue injury, including neurotrauma, endotoxemia, and hemorrhage; in several studies opioid antagonists have been shown to improve survival in lethal shock paradigm (4, 7).

It is also important to keep in mind that, at the present time, none of the available opioid antagonists has been shown to convey therapeutic effects in any clinical situation. The most intriguing new area that could significantly bear on cardiovascular disorders concerns recent data (5, 14) linking the fundamental stress responses to the μ-opioids and their receptors. These new data suggest that mental stress, aggressive responses, fear, and apprehension activate the sympathetic system via a selected opioid peptide and receptor. Since stress has been associated with many cardiovascular disorders, the potential exists that in the future the selective μ-opioid antagonist could be useful in alleviating cardiovascular disorders associated with excessive stress.

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Area Postrema: A Unique Regulator of Cardiovascular Function

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The area postrema, which does not have a blood-brain barrier, can sense changes in levels of blood-borne hormones. This circumventricular organ plays an important role in animal models of hypertension, recovery from hemorrhage, control of baroreflexes, and homeostasis of water and ions.

The area postrema has long been recognized as an important component in the vomiting reflex, serving as a chemosensor of noxious blood-borne substances for the central nervous system. Experimental findings during the last two decades indicate that this unusual region of the brain also plays a prominent role in cardiovascular functions.

The area postrema detects changes both in levels of circulating hormones, including angiotensin II and vasopressin, and in afferent neural activity from other cardiovascular centers in the central nervous system and modulates the output of other major cardiovascular centers, including medullary regions that regulate tonic and reflex vasomotor activity.

Recent experiments indicate that this circumventricular organ participates in recovery from hemorrhage, control of baroreflexes, and regulation of systemic water and ions. In animal models, development or maintenance of chronic hypertension apparently requires the area postrema, because removal of the area postrema prevents or attenuates increases in arterial pressure.

A chemical transducer with important connections

With few exceptions, neurons of the central nervous system are protected from exposure to most blood-borne agents by the blood-brain barrier. The blood-brain barrier is a key component in maintenance of a relatively stable environment for neuronal functions despite large fluctuations in blood chemistry. As a consequence of this protection, neurons in most regions of the brain that are involved in cardiovascular and endocrine regulation do not monitor blood concentrations of hormones directly. In contrast, capillaries in the area postrema and other circumventricular organs lack a blood-brain barrier. In these regions, circulating substances extravasate from the capillaries into the surrounding neuropil and thus can alter activities of neurons and glia directly.

Unique morphological characteristics support the concept that the area postrema serves as an important integrator of neural, endocrine, and cardiovascular functions (Fig. 1). The area postrema is characterized by numerous sinusoidal and fenestrated capillaries that are surrounded by a perivascular space (7, 12). Although large molecules such as albumin are confined to vessels of the area postrema, peptides and amines are much smaller and extravasate into both the perivascular space and surrounding neuropil. The area postrema has high densities of receptors for angiotensin II, vasopressin, catecholamines, acetylcholine, atrial natriuretic peptide, cholecystokinin, and opiates (4, 7), which may affect activities of neurons and glial cells in this region.

In addition, the area postrema has connections with other important cardiovascular centers of the central nervous system (7, 10). The area postrema receives inputs primarily from the paraventricular and dorsomedial nuclei of the hypothalamus and the carotid sinus and vagus nerves. Neurons of the area postrema project to the nucleus of the solitary tract, lateral parabrachial nucleus, dorsal

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