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CARDIOVASCULAR EFFECTS OF ENKEPHALINS

Enkephalins and their receptors are found in neurons and nerve terminals known to be involved in central cardiovascular control as well as the peripheral sympathetic and parasympathetic systems. Enkephalins and opioid receptors were also identified in the heart, kidneys, and blood vessels. The enkephalins interact with several specific receptors, of which μ, δ, and κ have been best characterized. Enkephalins administered to humans or animals produce cardiovascular effects which depend on the species, route of administration, anesthesia, and the selectivity for receptor subtype. While little information exists on the role of enkephalins in normal cardiovascular control, current data suggest that enkephalins might have a role in cardiovascular stress responses such as in shock and trauma.

BACKGROUND

Introduction

The endogenous opioid system includes three major families of peptides (1): enkephalins (derived from pre-proenkephalin A), endorphins (derived from pre-proopiomelanocortin), and dynorphins (derived from pre-proenkephalin B). The opioid peptides possess diverse autonomic functions through modulation of the sympathetic and parasympathetic nervous system and baroreflexes. These actions are mediated by multiple forms of opioid receptors (2). Since multiple forms of opioid peptides and multiple receptor subtypes exist, the opioid effects on the cardiovascular system are complex. This article focuses on the endogenous enkephalin system and its potential role in cardiovascular regulation in normal and shock states.

Distribution of Enkephalins in the Body

The distribution of enkephalins and their receptors in the central nervous system has been extensively studied. Enkephalin-containing neurons are found throughout the brain and spinal cord (1). Proenkephalin-containing perikarya and fibers are found in most forebrain regions, including the cerebral cortex, amygdala, hippocampus, septum, preoptic area, and most hypothalamic and thalamic nuclei. In the pons, enkephalin neurons are found in the parabrachial, dorsal tegmental, vestibular, and raphe nuclei; in the medulla oblongata, they are found in the nucleus reticularis gigantocellularis, nucleus tractus solitarius, and spinal cord dorsal gray (1). In addition to these areas, numerous other brain regions contain varying densities of enkephalinergic fibers and nerve terminals (1). Opioid receptors have also been identified in these brain areas (2).

Outside the central nervous system enkephalins are found in plasma (3), to which they are released from the pituitary and the adrenal gland (4). In addition, enkephalins are present in cardiovascular organs including the heart (5,6), blood vessels (7), adrenal medulla, and autonomic nerves (7). The enkephalins found in the heart are located in nerve endings (5).

Opioid receptors have also been identified in peripheral organs such as the heart (8–10), blood vessels (11), and kidney (9). In the heart, opiate receptor concentration in the atria is twice as much as in the ventricles (8). Characterization of the opioid-binding sites in the atria suggests the presence of δ and κ but not μ receptors in the rat atrium (8).

CURRENT STATUS

Enkephalins and Central Cardiovascular Control

Exogenous enkephalins produce different effects on blood pressure and heart rate depending on the route of administration, species, and the presence of anesthesia (for review, see 12). Pressor responses and tachycardia follow the lateral cerebral ventricle administration, but hypotension and bradycardia are observed after systemic injections of methionine-enkephalin and leucine-enkephalin in anesthetized rats (13). However, in the conscious rat, methionine or leucine-enkephalins produce pressor responses (14). The differences in opioid effects after systemic versus central administration are often used to indicate a lack of penetration in sufficient quantities to the cardiovascular sites in the brain. However,

the contrast between these routes of administration can be the result of opposite effect of the peptide in different brain nuclei, resulting in summation response with little or no effect on the gross cardiovascular variables. For example, in the hypothalamus, pressor and depressor sites for morphine and D-Ala^2,D-Leu^5-enkephalin were found in neighboring nuclei, which were less than 1 mm from each other (15). Injections of the enkephalin analog D-Ala^2-Met^3-enkephalin into the pressor area of the rostral ventrolateral medulla induced hypotension and bradycardia responses (16), while injections of this analog into the ventrolateral vasodepressor areas increased blood pressure and heart rate (17). Opposite blood pressure responses can be produced by injections of various enkephalin analogs into the anterior hypothalamus of pentobarbitone-anesthetized rats versus conscious rats: hypotension and bradycardia in the anesthetized versus increases in blood pressure and heart rate in the conscious animals (18,19).

Development of new selective agonists and antagonists for the multiple opioid receptors has made it possible to study the effects of different opioid receptor stimulation in discrete brain nuclei. For example, D-Ala^2-MePhe^4-Gly^5-ol-enkephalin (DAGO) and dermorphin (20) are highly selective ligands for the μ opioid receptor; D-Ala^2,D-Leu^5-enkephalin is a relatively selective agonist to δ opioid receptors ($\delta > \mu$), and dynorphin A species and the benzomorphans (bremazocine) act mainly on the κ opioid receptor. Microinjections of low to median doses of the μ agonists DAGO, dermorphin, morphiceptin, and morphine produce a pressor effect with bradycardic/tachycardic responses in the hypothalamic paraventricular or medial preoptic nuclei (15,18,19,21); high doses of μ receptor agonists ultimately lead to cardiovascular collapse and death. Pressor and tachycardic responses to DAGO have also been described after application into nucleus ambigus or nucleus tractus solitarius of anesthetized rats (22,23). In the rat, μ opioid receptor stimulation in the nucleus tractus solitarius also attenuates baroreflexes (23,24). Blood pressure and heart rate responses similar to those produced by DAGO can also be induced by the relatively selective δ agonist D-Ala^2,D-Leu^5-enkephalin. However, the δ agonist is about 10-fold less potent than the μ agonist in eliciting cardiovascular effects (15,18,19). Thus, the μ opioid receptors rather than δ receptors seem to be the primary receptors in mediating the pressor and tachycardic actions of enkephalins in the brain. Interestingly, microinjection of various κ opioid receptor agonists into the paraventricular nuclei, medial preoptic nuclei, nucleus ambigus, or nucleus tractus solitarius results in decreases in blood pressure and heart rate (25,26). Thus, two opioid systems opposing each other seem to exist: a μ opioid receptor dependent pressor system versus a κ opioid receptor related depressor system.

In addition to hemodynamic changes, enkephalins in the brain activate the sympatho-adrenomedullary system (19,27,28). Again, this effect seems to be mediated by the μ opioid receptors. However, activation of the parasympathetic system has also been suggested (19) although controversy exists in this matter (23).

Peripheral Cardiovascular Effects of Enkephalins

Recent studies have shown the presence of enkephalins and opioid receptors in heart, blood vessels, autonomic nerves, and adrenal medulla (see above). In isolated perfused heart preparations, enkephalins have been found to antagonize the effects of adrenergic agonists by a calcium-dependent mechanism (29). In vitro, opioid peptides acting on κ opioid receptors have been shown to inhibit norepinephrine release in rabbit and guinea pig hearts (10,30). However, no evidence for the endogenous opioid peptides in modulation of epinephrine release was found in these studies.

In rabbit ear artery preparation, [Leu]-enkephalin was found to depress the vasoconstrictor responses to field stimulation by a δ and κ opioid receptor mediated mechanism (11). In vitro, opiates cause contraction of rat aortic strips by a calcium-dependent mechanism (31,32) but induce vasodilation in rat mesenteric artery (31). Though enkephalins have various actions in isolated cardiovascular organs, the role of the peripheral opioid system in regulation of blood pressure and cardiac function in vivo is controversial. In the pithed rabbit, enkephalins have been reported to inhibit norepinephrine release in response to sympathetic stimulation (33). However, extensive studies conducted on the pithed rat (where the central nervous system and all reflexes are destroyed) failed to demonstrate cardiovascular responses to intravenous injections of various enkephalins selective for μ, δ, or κ opiate receptors (34,35). Furthermore, these studies also failed to show any role for enkephalins in modulation of the sympatho-adrenomedullary system stimulated through an electrode placed in the spinal cord. Thus, although opiate receptors seem to be present in peripheral organs, the role of these receptors in modulation of heart, kidney, and blood vessel function is still unclear.

Enkephalins in Shock

The endogenous opioid system has been implicated in the pathophysiology of shock. This suggestion was initially based on studies demonstrating that the opioid antagonist naloxone improves cardiovascular function and survival in some experimental shock models (36). Increased levels of enkephalins and beta-endorphin have been found in plasma and cerebrospinal fluid of animals exposed to hemorrhagic shock (13,37). Hemorrhagic shock was also shown to be associated with changes in opioid peptides and opioid receptors in specific brain nuclei of rats (38,39) which include selective up regulation of δ and κ opiate receptors in the brain stem (38).

FUTURE DIRECTIONS

A major question left unanswered to date is: do enkephalins play a crucial role in any particular physiological process? This question stems from observations showing that effective blockade of opioid receptors in vivo in normal humans or animals produces no appreciable cardiovascular responses. However, the lack of cardiovascular responses to naloxone (a potent opiate antagonist) might be the result of instantaneous adjustments in the hemodynamic balance due to the multiple systems involved in cardiovascular regulation and therefore may not necessarily represent lack of enkephalin involvement. Nevertheless, it seems at this time that the enkephalin system is activated as part of the general response to stress. However, the exact role of the enkephalins in the stress response is still unknown. Some reports indicate a depressor and detrimental outcome to the enkephalin activation, but these views have been widely challenged. It is equally unknown which receptors are actually activated by endogenous enkephalins which show poor selectivity for the various opioid subtypes.

More selective and potent enkephalin agonists and especially antagonists must be developed in order to examine the specific role of each opioid receptor subtype in cardiovascular functions of normal and pathophysiological states.

KEY PLAYERS

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