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Hypothalamic Mu-Opioid Receptors in Cardiovascular Control: A Review

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FEUERSTEIN, G. AND A.-L. SIRÉN. *Hypothalamic mu-opioid receptors in cardiovascular control: A review.* PEPTIDES 9: Suppl. 1, 75–78, 1988.—The endogenous opioid system includes three major families of peptides [22]: dynorphins (derived from pre-proenkephalin B); endorphins (derived from pre-proopiomelanocortin) and enkephalins (derived from pre-proenkephalin A). Multiple species of opioid peptides are derived from these major precursors and many of them possess potent cardiovascular properties. Multiple forms of opioid receptors have been defined in the central nervous system. Although the relationship of these receptors to the multiple actions of the opioid systems is not well understood, some predications can be made: *in vitro* the dynorphin-related peptides bind preferentially to kappa-opioid receptors; the enkephalins bind preferentially to delta and μ-opioid receptors and while beta-endorphin binds to mu- and delta-, but not to kappa-opioid receptors. While little is known on the role of the opioid system in normal cardiovascular regulation, it has become clear that cardiovascular stress situations substantially modify the activity of the endogenous opioid system. This review focuses on the mu-opioid system in the hypothalamus with special emphasis on its potential role in cardiovascular control of both normal and pathophysiologic states.

μ-Opioid receptors Hypothalamus Cardiovascular system Sympathetic nervous system

THE MU-OPIOID SYSTEM IN THE HYPOTHALAMUS

The regional distribution of opioid peptides and opioid receptors in the brain has been well characterized [22,29]. Morphine and various unspecific synthetic analogs of enkephalins were first used to define the mu-receptor [29]. Goodman and coworkers [16] demonstrated by autoradiographic methods that mu-receptors are present in the hypothalamus, a finding which was further confirmed by Quirion *et al.* [28] using the highly selective mu-agonist, D-ala^2-MePhe^4-Gly^5-ol-enkephalin (DAGO) [18] as the ligand. Feuerstein and others [10] also showed direct mu-receptor binding in the hypothalamus by using DAGO. In addition to the hypothalamus, mu-receptors have been demonstrated in other brain areas important for autonomic functions (e.g., brainstem) [16,28]. The endogenous opioids which bind to the mu-receptor are also found in the hypothalamus: Enkephalin containing neurons are present in many hypothalamic nuclei, while beta-endorphin containing neurons are mainly restricted to the arcuate nucleus from where they extend long axonal projections to brainstem, midbrain and limbic area [22]. The distribution of opioid mu-receptors within the hypothalamus might provide an explanation for a variety of autonomic actions (cardiovascular, respiratory, thermoregulatory) observed when morphine or other mu-receptor agonists are administered into the brain (see below). Moreover, the presence of both mu-receptors and their endogenous ligands in the hypothalamus might indicate that the mu-opioid system plays a role in the hypothalamic control of the cardiovascular system. This assumption is further supported by the findings that opioids and adrenergic neurons are closely interrelated in the brain [31].

CARDIOVASCULAR EFFECTS OF OPIOIDS IN THE HYPOTHALAMUS

Exogenous opioid peptides/opiates elicit differential effects on blood pressure and heart rate depending on the route of administration or the state of consciousness [6,14]. Generally, pressor responses and tachycardia follow lateral cerebral ventricle administration while hypotension and bradycardia follow injections into the cisterna magna or the fourth cerebral ventricle [6, 14, 24]. Therefore it was argued that two classes of opiate cardiovascular receptor exist: delta receptors located in the forebrain mediating pressor effects and mu-receptors located in the hindbrain mediating depressor responses [15,24]. However, microinjections of various opioid peptides and morphine into discrete brain nuclei have revealed specific pressor and depressor sites for opioids within the hypothalamus which are located less than 1 mm apart from each other [6,7]. In the anesthetized rat, injection of the specific mu-receptor agonist DAGO [18] into the nucleus preopticus medialis (POM) produced hypotension, tachycardia and bradypnea [7]. Injections of morphine (relative mu-agonist) and D-ala^2, D-leu^5-enkephalin (DADL, [23]) into the POM of these rats induced increments of blood pressure and heart rate, while the microinjection of these agents into the neighboring periventricular nucleus of hypothalamus (HPV) resulted in hypotension and bradypnea. The putative kappa-receptor agonist Dynorphin 1–13 elicited

hypotension and bradycardia in both POM and HPV of anesthetized rats [7]. The POM was confirmed to be a highly sensitive site for the cardiovascular actions of DAGO, DADL, morphine and morphiceptin (selective mu-agonist, [2]) in the anesthetized rat [5]. In this study dose-response relationships for the different opioid agonists were established. The mu-agonist DAGO was 10 fold more potent than the delta-agonist DADL suggesting that mu-receptors mediate the cardiovascular and respiratory effects of opioids in the POM [5]. Moreover, all the opioid effects were naloxone reversible [5,7].

In contrast to the depressor response to the mu-agonists in the anesthetized rats, microinjections of the specific mu-agonist DAGO into the anterior hypothalamus of conscious rats elicited a pressor response with a biphasic effect on the heart rate [25–27]. Pfeiffer and coworkers [27] injected selective mu-, delta- and kappa-agonists into the anterior hypothalamic and septal region of the conscious rat. They found that low doses of both the mu-agonist (DAGO) and the relative delta-agonist (DADL) caused dose-dependent increases in blood pressure and heart rate which were naloxone reversible. Higher doses of DAGO and DADL produced pressor responses but had little effect on the heart rate while the kappa-agonist was ineffective at these doses. The mu-agonist was about 10 fold more potent than the delta-agonist.

Increases in blood pressure and heart rate following low doses but decreases in heart rate following higher doses of DAGO were also reported upon intracerebroventricular or intrahypothalamic injections of this agent in the conscious rats [26]. The effects of DAGO were antagonised by a selective blockade of the mu-receptors by β-funaltrexamine [26]. Interestingly, a selective delta-agonist (dimeric tetrapeptide enkephalin) was inactive, underscoring the role of the mu-receptors in mediating the opioid effect in the hypothalamus [26].

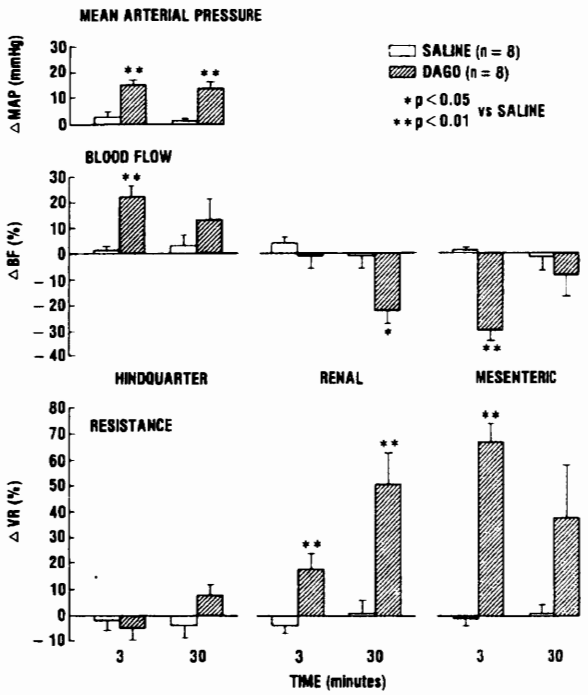

FIG. 1. Effect of DAGO microinjected into the POM on mean arterial pressure and regional blood flow in the conscious rat. DAGO (10 nmol) or saline was injected into the POM at a volume of 1 μl. MAP=mean arterial pressure, BF=blood flow and VR=vascular resistance. The BF and VR are presented as percent changes from the baseline level before drug injection. VR=MAP/BF. The analysis of variance followed by the Student-Newman-Keul test was used to calculate the statistical significance. Vertical bars denote S.E.M. The peak response for each of the peripheral organs varied as well as the nature of the response. n=Number of rats in each group.

MECHANISMS INVOLVED IN THE HEMODYNAMIC EFFECTS OF HYPOTHALAMIC MU-RECEPTORS

Preliminary studies in our laboratory [30] have shown that the pressor response of DAGO microinjected into the POM of conscious rats is mainly due to an increment of cardiac output, although a transient increase in the total peripheral resistance was also observed. By using the directional pulsed ultrasound Doppler technique, we also found distinct changes in regional blood flow and vascular resistance after POM injections of DAGO in unanesthetized rats [30]. Preliminary results of these studies still in progress in our laboratory are summarized in Fig. 1: Immediately after the DAGO injection the hindquarter (primarily skeletal muscle) blood flow increased with a concomitant decrease in the mesenteric blood flow, while there was no significant change in the renal blood flow. However, the renal blood flow gradually decreased reaching a maximum of $-22\pm5\%$ from the baseline 30 min after the injection. The mesenteric vascular resistance sharply increased briefly after the DAGO administration and the renal resistance slowly increased reaching a maximum of $+51\pm12\%$ 30 min after the injection. These findings clearly demonstrate that selective mu-receptor stimulation in the anterior hypothalamus produced distinct changes in regional blood flow that could not be observed by studying the gross hemodynamic changes only. The transient but opposite effects of DAGO on skeletal muscle and mesenteric blood flow may explain the lack of effect of DAGO on total peripheral resistance. The potent vasoconstrictor action of mu-receptor stimulation in the POM could also contribute to the detrimental effect of opioids in shock (see below). Furthermore, the POM has been reported to be involved in the cardiovascular control [1]. Since mu-receptors and their endogenous ligands are abundantly present at this brain site [10, 22, 29], the distinct effect of DAGO on organ blood flow might indicate that the mu-opioid system in the POM could have a physiological role in the regional blood flow distribution to various organs.

THE ROLE OF AUTONOMIC NERVOUS SYSTEM

Concomitantly with the pressor response, enkephalins induced increments of plasma catecholamines following injections into the anterior hypothalamus of conscious rats [9, 25, 26]. The effect was completely blocked by naloxone and again the mu-agonist was about 10 fold more potent than the delta-agonist [25,26]. Although measuring plasma catecholamines only might not be a good index for sympathetic activation, these findings suggest that the cardiovascular stimu-

lation mediated by the mu-receptors in the hypothalamus are due to an activation of sympathetic outflow. This view is further supported by the findings that adrenal demedullation attenuated the pressor and tachycardic responses of DAGO injected into the anterior hypothalamus [26]. Additional treatment of the adrenal demedullated rats with the adrenergic neuron blocking agent bretylium reversed the DAGO-effects and resulted in severe fall in blood pressure and heart rate [26]. Thus, the pressor and tachycardic responses to intrahypothalamic injections of enkephalins seem to involve an activation of adrenal medulla and sympathetic outflow, while the initial bradycardia has been shown to involve vagal pathways [26].

SHOCK

The endogenous opioid system was considered to have a detrimental role in various shock states [6,19]. This suggestion was based primarily on the fact that the opioid antagonist naloxone reversed the hypotension in several shock states [19]. However, the effect of naloxone on survival in hemorrhagic shock is at present clearly controversial [4, 17, 20, 21]. Studies in our laboratory have failed to show any beneficial effect of naloxone in different hemorrhagic shock paradigms in the rat, while morphine was found to have a detrimental effect. Hemorrhage has been shown to induce distinct changes in opioid levels in the cerebrospinal fluid [3] and in distinct brain nuclei (including hypothalamic sites) [11] as well as alterations of opioid receptors in the brain [10]. The potent depressor effect of enkephalins injected into distinct hypothalamic nuclei on the cardiorespiratory system in the anesthetized rat [5,7] and the respiratory acidosis induced by the mu-agonist in the conscious rat [27] further suggest that opioids may exacerbate shock. However, injection of the selective mu-agonist DAGO into the anteroventral hypothalamus (AV3V) of conscious rats exposed to hemorrhage improved the recovery of blood pressure and increased heart rate, while both the delta- and kappa-agonists were ineffective [12]. Lesions in the AV3V region were recently found to worsen recuperation from hemorrhagic shock [13] and it was suggested that a specific mu-receptor agonist might have a beneficial role in the treatment of shock and trauma via a centrally-mediated mechanism [12].

HYPERTENSION

Hypertension is associated with significant changes in the opioid system. For example, the levels of dynorphins and Leu-enkephalin in the pituitary gland and several hypothalamic nuclei are substantially different in the spontaneously hypertensive rats (SHR) as compared to the normotensive animals [8]. The opioid system has been implicated in the development of high blood pressure in SHR, since the pressor responses to intracerebroventricularly administered opioids in SHR are enhanced as compared to normotensive rats [9,24]. It has been shown in our laboratory that SHR also differ from normotensive rats in their response to hypothalamic administration of enkephalins [9]; the SHR showed an augmented pressor response to the mu-agonist DAGO or the delta-agonist DADL microinjected into the POM. These enkephalin analogues had little effect on heart rate in SHR, while in normotensive Wistar-Kyoto rats a pronounced tachycardia accompanied the pressor response [9]. Again, the mu-agonist was more potent than the delta-agonist. The potent vasoconstrictor action of the mu-agonist in the POM on the mesenteric and renal vasculature [30] might also indicate that mu-receptor stimulation in this brain region could play a role in the development and/or maintenance of hypertension. However, more detailed studies on the opioid effects in various models of hypertension must still be elaborated. Furthermore, a sustained release of mu-agonist into the central nervous system over a long time period (e.g., in osmotic minipumps) could further clarify the role of hypothalamic mu-receptors in the ontogenesis of high blood pressure.

SUMMARY

Opioid peptides/opiates elicit potent cardiorespiratory effects upon microinjections into discrete hypothalamic nuclei. In the anesthetized rat, injections of various enkephalins into the anterior hypothalamus induced hypotension and bradypnea but caused an increase in blood pressure accompanied with a biphasic heart rate response (an initial bradycardia followed by a long-lasting tachycardia) in conscious rats. Since the selective mu-agonist was over a tenfold more potent than the relative delta-agonist in producing cardiorespiratory changes, these effects seem to be mediated by the stimulation of mu-opioid receptors. Furthermore, the cardiovascular effects of opioids in hypothalamus are extremely site specific; morphine or synthetic enkephalins are capable of eliciting both pressor and depressor responses in neighboring hypothalamic nuclei which are less than 1 mm apart from each other. The pressor effect of mu-opioid agonists in the hypothalamus seems to be due mainly to an increment of cardiac output, although a transient increase in peripheral resistance might also contribute. Opioid mu-receptor stimulation in the anterior hypothalamus resulted in a distinct pattern of changes in regional blood flow: the blood flow to skeletal muscles increased while mesenteric and renal blood flow decreased causing a concomitant rise in vascular resistance. Since mu-opioid receptors and opioid peptides are abundantly present in the brain (including the hypothalamus), opioid mu-receptors in the hypothalamus might have a physiological role in the redistribution of organ blood flow. Moreover, the potent vasoconstrictor and pressor responses of mu-opioid analogs administered into hypothalamic nuclei might indicate that the mu-opioid system in the hypothalamus is involved in the ontogenesis of hypertension. This suggestion may further be supported by the findings that both the opioid peptides and the opioid receptors are changed in SHR as compared to normotensive animals.

The role of the opioid system in various states of shock and trauma is clearly controversial. Although systemically administered opiates are detrimental in hypovolemic shock, specific stimulation of the mu-opioid receptors in distinct hypothalamic nuclei may have a beneficial effect in hemorrhage.

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