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β-Endorphin in the median preoptic nucleus modulates the pressor response induced by subcutaneous hypertonic sodium chloride

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Abstract

Considerable evidence has been gathered involving the endogenous opioid system in blood pressure regulation. In the present study, we investigated the effect of administering β-Endorphin into the median preoptic nucleus (MnPO) on blood pressure (BP) and heart rate (HR) and whether this administration was capable of modulating the pressor response observed after an acute increase in plasma osmolality.

In urethane-anaesthetized Wistar rats, different doses of β-Endorphin (1, 10, 25 ng) were microinjected into the MnPO to elucidate a putative role for β-Endorphin in BP and HR regulation. Additionally, we evaluated the modulatory effect of the β-Endorphin injection (25 ng) into the MnPO on the pressor response to subcutaneous sodium chloride solution administration (2 M NaCl, 0.1 ml/10 gbw).

The MnPO-β-Endorphin microinjection resulted in a dose-dependent hypotensive and bradycardic effect and pre-treatment with the opioid antagonist, naloxone (100 ng), injected in the same nucleus, significantly antagonized the cardiovascular response to β-Endorphin administration in the MnPO.

On the other hand, a microinjection of β-Endorphin (25 ng) into the median preoptic nucleus abolished the pressor response to a subcutaneous injection of hypertonic saline.

It is concluded from these results that β-Endorphin-MnPO administration produces a decrease in BP and HR in normotensive animals and also inhibits the pressor response evoked by an acute increase in plasma osmolality.

Keywords: Median preoptic nucleus; β-Endorphin; Pressor response; Plasma osmolality

Introduction

A large number of studies suggest that the endogenous opioid system plays a significant regulatory role in the modulation of sympathetic activity and cardiovascular functions at both the central and peripheral levels (Kunos et al., 1991; Loughlin et al., 1995).

β-Endorphin has been implicated as a candidate peptide in blood pressure regulation based on several lines of evidence, i) central or systemic administration of β-Endorphin can profoundly alter blood pressure (Dunbar and Lu, 2000), ii) low plasma concentrations of β-Endorphin have been observed in several patient groups with essential hypertension (Kraft et al., 1987; Zheng et al., 1995) and iii) the antihypertensive agent, clonidine, induces hypotension, in part due to induced β-Endorphin release (Kraft et al., 1987; Kunos et al., 1981; Yasunari et al., 1987; Zheng et al., 1995). Additionally, previous results from our laboratory showed new evidence for the contribution of the β-Endorphinergic system to the compensatory mechanisms triggered in response to sodium overload. In these studies, β-Endorphin knockout mice that were kept during 2 weeks on a high sodium diet showed a significant increase in systolic blood pressure, urinary epinephrine levels as well as enhanced median preoptic nucleus (MnPO) neural activity,

Abbreviations: Ang II, angiotensin II; Arc, arcuate nucleus; βE, β-Endorphin; BP, blood pressure; HR, heart rate; LT, lamina terminalis; MAP, mean arterial pressure; MnPO, median preoptic nucleus; NTS, nucleus of the solitary tract; OVLT, organum vasculosum of the lamina terminalis; PVN, paraventricular nucleus; RVLM, rostral ventrolateral medulla; s.c., subcutaneous; SFO, subfornical organ; veh, vehicle.

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compared with heterozygous and wild-type mice (Caeiro et al., 2006).

Increased plasma osmolality has been associated with an increase in water intake and blood pressure (BP), accompanied by a variety of neurohumoral changes, including the activation of the sympathetic nervous system, an increase in vasopressin release, suppression of the peripheral renin–angiotensin system and expanded extracellular fluid volume (Akins and Bealer, 1990; Chiu and Sawyer, 1974; Crofton and Share, 1989; Garcia-Estan et al., 1989; Kawano and Ferrario, 1984; Morita et al., 1991; Peskind et al., 1993; Weiss et al., 1996). Changes in osmolality and Na^+ content are sensed at both peripheral and central levels. In the brain, studies indicate that the most sensitive and crucial osmo- and sodium-receptors are in the lamina terminalis (LT). This structure contains three forebrain nuclei: the MnPO, the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT). The OVLT and SFO are two circumventricular organs that contain cells which are sensitive to humoral signals such as changes in plasma and cerebrospinal fluid sodium concentration, osmolality and angiotensin II (ANG II) levels (Ferguson and Bains, 1997; Simpson et al., 1978; Sladek and Johnson, 1983; Vivas et al., 1990). Such unique features make the SFO and OVLT key brain regions for sensing the status of body fluids and electrolytes. Humoral signals are passed on from the SFO and OVLT to other structures in the central nervous system including the MnPO which has been shown to play a major role in many aspects of body fluid homeostasis. (Johnson and Loewy, 1990; Johnson et al., 1996; McKinley et al., 1991; Simon, 2000). Additionally, the MnPO has afferent connections with areas known to receive visceral input from arterial baroreceptors as well as other neurons involved in neuroendocrine regulation and hydromineral balance that participate in cardiovascular modulatory responses (Oldfield et al., 1992). In this regard recent evidence indicates that individual neurons of the MnPO with axonal projection to the paraventricular nucleus of the hypothalamus (PVN) respond to changes in osmolality, circulating angiotensin II and baroreceptor stimulation, suggesting that this nucleus is a key neural substrate through which neurohumoral inputs are integrated within the LT (Stocker and Toney, 2005). Lesion or inactivation of the MnPO attenuates drinking behavior, neurohypophyseal secretion of vasopressin, and centrally mediated pressor response stimulated by hyperosmolality and Angiotensin II (Ang II) (Cunningham et al., 1991; Cunningham et al., 1992; Mangiapane et al., 1983; O'Neill and Brody, 1987) and thus results in profound alterations in body fluid homeostasis and cardiovascular regulation.

Taking into account previous data that suggest that the MnPO is a terminal field for β-Endorphin arcuate neuronal projections and that, in the absence of β-Endorphin, an increase in sodium diet is accompanied by an increase in blood pressure and MnPO-neuronal activity (Caeiro et al., 2006), we hypothesized that β-Endorphin in the MnPO would modulate blood pressure and heart rate.

On the other hand, considering that i) the intracerebroventricular administration of β-Endorphin inhibits the pressor response stimulated by an acute elevation in CSF sodium chloride concentration (Summy-Long et al., 1981), that ii) the pressor response to hypertonic saline depends on the activation of the MnPO, that iii) the lesion of this nucleus evokes the suppression of this response during an increase in plasma osmolality (O'Neill and Brody, 1987; Yasuda et al., 2000), and previous data that strongly suggest that iv) the MnPO may serve as a forebrain integration site for both humoral and visceral afferent information related to body fluid homeostasis and autonomic function (Stocker and Toney, 2005), we proposed that β-Endorphin-MnPO administration would alter the cardiovascular response observed after an acute increase in plasma osmolality.

Materials and methods

Animals

Male adult Wistar-derived rats, born and reared in the breeding colony of the Instituto de Investigación Médica Mercedes y Martin Ferreyra (INIMEC-CONICET, Córdoba, Argentina) were used in the present experiments. Animals weighing 315–345 g were maintained in a temperature-controlled environment, with a 12-h light/dark cycle, with food and water *ad libitum*. Each animal was used in only one experimental condition. All the experimental protocols were approved and carried out in accordance with the guidelines of the Ferreyra Institute Ethical Committee for the use and care of laboratory animals, and the guidelines of the International Public Health Service Guide for the Care and Use of Laboratory Animals were followed.

Surgical procedures

Cannulation of vessels

On the day of the study each animal was anaesthetized with urethane (1.5 g/kg ip) and placed on a pad heated to maintain the body temperature at 37±0.1 °C. The rats were implanted with heparin–saline (50 U/ml)-filled polyethylene catheters (PE-50: 0.039 in. OD, 0.023 in. ID) in the left femoral artery and vein, in order to record blood pressure and administer when needed an additional dose of anaesthetics, respectively. The arterial catheter was connected to a blood pressure transducer and PowerLab data-acquisition system (ADInstruments, Sydney, Australia). Blood pressure was continuously recorded, and heart rate was calculated by an internal rate-meter in the data-acquisition system.

Microinjections into the MnPO

After surgical procedures for blood pressure recordings, the anaesthetized rats were mounted in a stereotaxic frame (David Kopf instruments). The dorsal surface of the skull was exposed and leveled between lambda and bregma. A hole was centered on bregma and drilled through the skull. After carefully incising the dura and gently retracting the sagittal sinus, a glass micropipette was downloaded in the injecting site. The coordinates used were 0.2 mm caudal to bregma, 0.0 lateral to the midline, and 6.0 ventral from cortical surface.