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Inhibition of water intake by the central administration of IL-1β in rats: Role of the central opioid system

P.A. Luz, L. Andrade, N. Miranda, V. Pereira, J. Fregoneze, E. De Castro e Silva *

Department of Physiology, Health Sciences Institute, Federal University of Bahia, Vale do Canela s/n, 40110-100 Salvador, Bahia, Brazil

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Abstract

In the present study we investigated, the effect of third ventricle injections of IL-1β on water intake, in rats, induced by three different physiological stimuli: dehydration induced by water deprivation, hypernatremia associated with hyperosmolarity induced by intragastric salt load, and hypovolemia produced by subcutaneous polytethyleneglycol administration. Central administration of IL-1β at the doses of 4 and 8 ng reduced water intake in all three conditions studied. Third ventricle injections of IL-1β (8 ng) were unable to diminish water intake in the groups of rats pretreated with central injections of the non-selective opioid antagonist naloxone (10 μg) in the three different conditions studied. Furthermore, the central administration of IL-1β was neither able to modify the intake of a 0.1% saccharin solution when the animals were submitted to a "dessert test" nor to induce any significant locomotor deficit in the open-field test. These results suggest that the central activation of interleukin-1 receptors by IL-1β is able to impair the thirst-inducing mechanisms triggered by the physiological stimuli represented by dehydration, hyperosmolarity and hypovolemia. These results lead us to conclude that the antidipsogenic effects observed following central administration of IL-1β require the functional integrity of the brain opiatergic system.

Keywords: IL-1β; Opioids; Naloxone; Water intake; Hyperosmolarity; Hypovolemia; Dehydration

1. Introduction

Interleukin-1β (IL-1β), an immunoregulatory cytokine, is produced by activated macrophages and other immune cells during acute and chronic pathological processes. In addition, IL-1β is also synthesized and released in the central nervous system by several types of cells including neurons, astrocytes, microglia and endothelial cells (Cunningham and De Souza, 1993; Rothwell and Luheshi, 2000). Both blood-borne and brain-originated IL-1β induce a myriad of visceral and behavioral responses (Banks et al., 2002; Licinio and Wong, 1997). IL-1β actions on the central nervous system include an increase in hypothalamo-pituitary axis function, hyperthermia, changes in blood pressure, sleep induction, sickness behavior and anorexia associated with shifts in the energy balance of the organism (Turnbull and Rivier, 1999).

Peripheral and central administration of IL-1β produces a significant antidipsogenic effect and it is possible that endogenous IL-1β may play a role in the homeostatic control of water intake in circumstances in which this cytokine is naturally released from its original sources (Osaka et al., 1992; Plata-Salamán and Ffrench-Mullen, 1992; Nava et al., 1996; Sonti et al., 1997; Karádi et al., 2005).

A complex interactive network of inhibitory and stimulatory inputs, involving different brain neurotransmitters and areas, controls water intake. Central cholinergic, angiotensinergic and β-adrenergic pathways seem

* Corresponding author. Tel.: +55 71 9979 6061; fax: +55 71 3337 0591.
E-mail address: emilio@ufba.br (E. De Castro e Silva).

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to induce water intake, whilst α-adrenergic, serotonergic and opioidergic circuitries exert the opposite effect (Johnson and Thunhorst, 1997; Stricker and Sved, 2000). As far as the opiatergic system is concerned, it has been demonstrated that central opiatergic stimulation reduces water intake provoked by the activation of central angiotensinergic pathways (Summy-Long et al., 1981; Summy-Long et al., 1983) and intracerebroventricular injections of morphine decrease water intake in rats (Eidi et al., 2003).

Substantial evidence suggests that opioids may interact with the immune system modulating its function, and some immunological responses may depend on the functional integrity of the opioid system (Bodnar and Klein, 2005).

In this study, the effects of the central administration of IL-1β on water intake were investigated using three different thirst-inducing experimental protocols: water deprivation, hyperosmolarity induced by intragastric salt load and hypovolemia elicited by subcutaneous administration of polyethyleneglycol. The possible participation of the central opioid system in the antidipsogenic effects of IL-1β was also explored.

2. Materials and methods

2.1. Animals

Wistar male rats (220 ± 20 g) kept under controlled light (lights on from 7 AM to 7 PM) and temperature (22–24 °C) conditions were used in the present study. In the days immediately prior to the experimental sessions, they had free access to tap water and laboratory chow (Nuvital Nutrientes Ltd., Curitiba, Brazil). The experimental protocols were conducted according to the regulations established by the National Institutes of Health (USA) and were approved by a local committee regulating the use of animals in research laboratories. The number of animals used in each experimental set varied from 6 to 14.

2.2. Surgical procedure

Third ventricles were cannulated under sodium pentobarbital anesthesia (50 mg/kg i.p.) six days before the experimental sessions. Briefly, after positioning the rat in a stereotaxic apparatus (David Kopf Instruments, USA), a chronic 28-gauge guide cannula was implanted. The following coordinates were used: anteroposterior = 0.5 mm behind the bregma; lateral = 0.0 mm; vertical = 8.0 mm below the skull. To avoid lesions to the brain regions involved in the control of cardiovascular and body fluid homeostasis, the animals were fixed to the stereotaxic apparatus with the head inclined upwards (+2.0 mm). The cannulas were fixed to the skull bone by two screws embedded in dental acrylic. After the experimental sessions, the position of the cannulas was verified. The animals were sacrificed by CO_2 inhalation and a Blue Evans dye injection was given through the cannula in order to confirm whether its tip was in the proper place. Only the data from animals whose cannulas were strictly inside the third ventricle were considered.

2.3. Drugs and microinjections

The following drugs were used: Interleukin-1β (rhIL-1β, recombinant human – *Escherichia coli* derived) purchased from R&D Systems (catalog number 201-LB); polyethylene glycol (m.w. 15,000–20,000; PEG) and naloxone hydrochloride acquired from Sigma Chemical, Co., St. Louis, MO. All drugs were dissolved in sterile isotonic saline solution. Third ventricle injections were given using a Hamilton microsyringe connected to a Mizzy-Slide-Pak needle through polyethylene tubing. A total volume of 2 μl was slowly injected (60 s).

2.4. Experimental protocols

2.4.1. Water deprivation

After 14 h of water deprivation (from 18:00 to 08:00 the night before the experiment), different groups of naïve animals received third ventricle injections of IL-1β at various doses, or isotonic saline solution (controls). Thirty minutes after the central injections, graduated bottles containing water were reintroduced into the cages. Cumulative water intake was measured for the next 120 min. These groups of animals were also compared to an additional normohydrated group not submitted to water deprivation, who received third ventricle injections of saline.

2.4.2. Intragastric salt load

Animals were fasted for 14 h, from 18:00 to 08:00, the night before the experiment. Ten minutes after third ventricle injections of IL-1β at different doses or isotonic saline solution (controls) the animals received an intragastric salt load. This was achieved by administrating 1 ml/100 g of a hypertonic saline solution (1.5 M) via orogastric tubing. Twenty minutes after the salt load, graduated bottles containing water were reintroduced into the cages and the cumulative water intake was recorded over the next 120 min. In this experimental set, the graduated bottles were removed from the cages immediately before the intracerebroventricular (icv) injections, and were reintroduced 30 min later. These groups of animals were compared to an additional group receiving intragastric administration of isotonic saline solution followed by third ventricle injections of saline.