Physiology & Behavior 102 (2011) 164–169

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Lipopolysaccharide reduces sodium intake and sodium excretion in dehydrated rats

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ARTICLE INFO

Article history:
Received 12 October 2009
Received in revised form 14 October 2010
Accepted 18 October 2010

Keywords:
LPS
Sodium appetite
Thirst
Dehydration
Kidney
Sickness behavior

ABSTRACT

The objective of this study was to find out if lipopolysaccharide (LPS) administered intraperitoneally affects sodium and water intake and renal excretion in dehydrated rats. LPS (0.3–5 mg/kg b.w.) inhibited 0.3 M NaCl intake induced by subcutaneous injection of the diuretic furosemide (FURO, 10 mg/kg b.w.) combined with the angiotensin converting enzyme inhibitor, captopril (CAP, 5 mg/kg b.w.). Only the highest doses of LPS (2.5 and 5 mg/kg) inhibited water intake induced by FURO/CAP. LPS (0.6 mg/kg) reduced urinary volume and sodium excretion, but had no effect on mean arterial pressure or heart rate of rats treated with FURO/CAP. LPS (0.3–5.0 mg/kg) abolished intracellular thirst and reduced by 50% the urine sodium concentration of rats that received 2 ml of 2 M NaCl by gavage. LPS (0.3–5.0 mg/kg) also reduced thirst in rats treated with FURO alone (10 mg/rat sc). The results suggest that LPS has a preferential, but not exclusive, inhibitory effect on sodium intake and on intracellular thirst. The inhibition of hydro-mineral intake and the antinatriuresis caused by LPS in dehydrated rats may contribute to the multiple effects of the endotoxin on fluid and electrolyte balance and be part of the strategy to cope with infections.

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1. Introduction

“Sickness behavior” has been hypothesized as to be an adaptive syndrome of behavioral and physiological alterations of animals coping with infectious pathogens [1]. Reduced activity, feeding and drinking are some of the behavioral alterations induced by infection.

Lipopolysaccharide (LPS), an endotoxin derived from the wall of gram-negative bacteria, triggers not only a general reduction in animal activity, but also has a broad influence on body fluid balance, linked to neurohypophyseal secretion, sodium transport in the gut and renal sodium excretion [2–5]. Although the sickness behavior may have an adaptive value, reduced thirst, associated with impaired sodium balance and dehydration, plus concurrent hypotension, may lead to a general collapse of volume compartments in response to LPS [6–9]. Therefore, a complete understanding of the effects of LPS on fluid balance has important practical and theoretical consequences.

The antidipsogenesis induced by LPS in a water-deprived rat has been known for several years and it is mediated by central production of nitric oxide, prostaglandins and, perhaps, TNF-α [10–12]. Thirst in a water-deprived animal arises from double dehydration, a mechanism which comprises volume reduction in both intracellular and extracellular compartments and is mediated by a combination of osmorreception and angiotensin II [13,14]. Since LPS also inhibits thirst induced by intracerebroventricular (icv) injections of either angiotensin II or hypertonic NaCl [15] the effect of LPS on water intake seems an outcome of inhibition of both mechanisms.

However, interleukin-1β, which belongs to a network of cytokines activated by LPS [1], may selectively inhibit one type of thirst when it is produced by systemic maneuvers that produce selective dehydration on body fluid compartments. Interleukin-1β injected intraperitoneally inhibits intracellular thirst induced by intraperitoneal injection of hypertonic NaCl, but has no effect on extracellular thirst induced by subcutaneous injection of polyethylene glycol [16].

It is therefore reasonable to ask if LPS exerts a similarly selective inhibition on thirst. A selective effect on fluid intake may have important implications for the overall strategy of the sickness behavior. For example, the selective inhibition on intracellular thirst could benefit survival by maintaining blood hypertonicity and thus increasing cardiovascular performance in response to endotoxemia induced by LPS [16]. This suggests that LPS may have no effect on sodium intake.

LPS also has influences on renal sodium excretion that may affect fluid intake. For example, septicaemia induces renal failure and increased fractional sodium excretion associated with reduction in tubular sodium transporter activity [5]. However, to the best of our knowledge, it is not known whether LPS alters the sodium excretion

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doi:10.1016/j.physbeh.2010.10.014

associated with procedures to induce selective dehydration and fluid intake.

Diuretics and sodium load are used in procedures to induce extracellular and intracellular thirst respectively. The diuretic furosemide induces water intake acutely in response to extracellular dehydration when sodium appetite is still incipient [17–19] and gavage of hypertonic NaCl leads to water intake in response to intracellular dehydration [20,21]. One advantage to give a hypertonic load through intragastric route, compared to intraperitoneal or subcutaneous [22], is to avoid pain.

Procedures to induce extracellular dehydration may lead not only to water but also to sodium intake, but they require either a delay of several hours or a strong initial stimulus. Rapid hypertonic NaCl and water intake can be elicited in a two-bottle test by treating rats with a systemic injection of furosemide combined with captopril, an inhibitor of the angiotensin-converting enzyme (FURO/CAP). These effects of FURO/CAP can be explained by assuming that while furosemide induces fast, heavy extracellular dehydration – a powerful stimulus for secretion of renin which converts angiotensinogen to angiotensin I – captopril given at a low dose prevents the formation of circulating angiotensin II. The reduced conversion to angiotensin II may thus increase the delivery of angiotensin I to encephalic areas not reached by captopril [14,18,23–25]. Angiotensin I is then converted to angiotensin II in the brain and thus newly formed angiotensin II, accompanied by mild hypotension, triggers the circuits subserving sodium and water intake.

The objective of the present work was to find out, first, whether LPS inhibits the sodium and water intake induced by FURO/CAP and, second, whether it has a preferential effect on extracellular, as opposed to intracellular dehydration. Effects of LPS on the renal sodium excretion associated with each treatment were also investigated.

2. Methods

2.1. Animals

Male Holtzman rats weighing 280–320 g were used. The animals were housed in individual stainless steel cages with free access to standard laboratory chow (0.5–1.0%, Guabi Rat Chow, Paulínia, São Paulo, Brazil) with more sodium than the rat requires [26], water and 0.3 M NaCl solution. Rats were maintained in a room whose temperature was controlled at 23 ± 2 °C and humidity at in a 12 h light/dark cycle lights on 7:30 AM. The experimental protocols were approved by the Institutional Ethical Committee for Animal Care and Use (CEEA) and followed the recommendations of the Brazilian College of Animal Experimentation (COBEA).

2.2. Drugs

Lipopolysaccharide extracted from *Escherichia coli*, serotype 026: B6 (Sigma), was dissolved in sterile isotonic saline at doses of 0.15–5 mg/kg b.w.

Furosemide (diuretic) (Sigma) was dissolved in isotonic saline, adjusted to pH = 9.0 with 0.1 N sodium hydroxide solution at a dose of 10 mg/kg b.w. (FURO/CAP) or 10 mg/rat (furosemide-induced thirst).

Captopril (angiotensin converting enzyme inhibitor) (Sigma) was dissolved in sterile isotonic saline at a dose of 5 mg/kg b.w.

2.3. Body temperature measurement

Rectal temperature was measured by digital thermometer immediately before LPS injection and at the intervals described in the experiments with FURO/CAP.

2.4. Urine sample collection

The animals were housed in metabolic cages at the beginning of the test and the urine spontaneously eliminated was collected every 60 min for 2 h. Urine sodium and potassium concentrations were measured with an ion sensitive electrode (Nova 1, Nova Biomedical).

2.5. Blood biochemistry

Immediately after decapitation, trunk blood samples were collected in tubes containing a separating gel and serum was separated by centrifugation (2000 rpm for 10 min). The sodium and potassium serum concentrations were measured by ion sensitive electrode. Total plasma protein concentration was measured by refractometry (Atago).

2.6. Blood pressure and heart rate

In rats anaesthetized with ketamine (80 mg/kg b.w.) combined with xylazine (7 mg/kg b.w.), a polyethylene tube (PE-10 connected to a PE-50) was inserted into the abdominal aorta through the femoral artery to record arterial pressure. An arterial catheter was tunneled subcutaneously and exposed on the back of the rat. On the next day, pulsatile arterial pressure, mean arterial pressure (MAP), and heart rate (HR) were simultaneously recorded in unanaesthetized and unrestrained rats by connecting the arterial catheter to a Statham Gould (P23Db) pressure transducer coupled to a pre-amplifier (model ETH-200 Bridge Bio Amplifier, CB Sciences, Dover, NH, USA) that was connected to a PowerLab computer data acquisition system (model Powerlab 16SP, ADInstruments, Castle Hill, Australia).

2.7. Intragastric (ig) hypertonic NaCl load (NaCl gavage)

The animals were removed from their cages and gently trained to receive an ig load by infusing distilled water (1 ml) through a polypropylene tubing (PE-10) connected to a syringe. The length of the tubing and the effective sodium load (2 ml of 2 M NaCl) needed to induce strong hypernatremia, natriuresis, reduced plasma renin activity and thirst were based on previous work [21]. The training began after 2 days of adaptation and was prescribed for once a day for 5 days. On the 6th day, each animal received an ig load of hypertonic saline after food and every fluid was removed from the cage. Water was offered 1 h after gavage, for the drinking test.

2.8. Statistics

Two-way repeated measures ANOVA was used to analyze data from the ingestive and arterial pressure tests with treatment and time as factors. Planned comparisons were made with the Student-Newman-Keuls post-hoc test. The unpaired t-test was used to analyze data in the blood biochemistry and renal excretion tests. A probability of less than 0.05 was required for significance. Data are expressed as means $\pm$ standard error of the mean.

2.9. Effect of LPS on 0.3 M NaCl and water intake induced by a combined injection of furosemide and captopril (FURO/CAP)

The animals (n = 49) were gently manipulated to measure rectal temperature once a day, by habituation, on the days that preceded a FURO/CAP test. On the day of the test, food and fluids were removed and the animals randomly received an intraperitoneal injection of LPS (0.15, 0.3, 0.6, 1.2, 2.5 or 5.0 mg/kg) or saline. One hour later, all animals received simultaneous subcutaneous injections of the natriuretic and diuretic furosemide, FURO (10 mg/kg), and a low dose of the angiotensin-converting enzyme (ACE) inhibitor captopril, CAP (5 mg/kg). Water and 0.3 M NaCl were offered from graduated

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