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Lipopolysaccharide reduces sodium intake and sodium excretion in dehydrated rats

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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.

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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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 ± 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

burettes (0.1 ml divisions) fitted with stainless steel spouts, 1 h after the FURO/CAP injection. Water and 0.3 M NaCl intake was then recorded at 15, 30, 60, 120, 180, 240 and 300 min. Rectal body temperature was measured immediately before injecting LPS, before offering water and 0.3 M NaCl, and at 120 and 300 min, after fluid intake recordings.

2.10. Effect of LPS on the hypotension induced by FURO/CAP

A group of animals (n = 14) received an intra-arterial catheter by surgery, as described above. Immediately after recovery from the surgery the rats were moved to individual polypropylene cages with wood-chip bedding, and given free access to food and water for 24 h, after which they were transferred to the cardiovascular recording room. After half an hour in this room, food and water were removed and the catheter connected to the pressure transducer, while the animal remained in its cage. Basal MAP and HR were recorded for 10 min. Next, half the group received 0.6 mg/kg of LPS ip and the other half a control injection of saline. The cardiovascular recordings proceeded without interruption for another 60 min, when each animal received a FURO/CAP injection and the recordings persisted for a final 90 min.

2.11. Effects of LPS on urine excretion and blood biochemistry in rats treated with FURO/CAP

A group of animals (n = 15) was transferred to individual metabolic cages, without access of food or fluid. They were subdivided into two groups, one that received 0.6 mg/kg LPS ip and another that received saline. One hour later, all animals received a suprapubic massage to induce urine void; urine collected during this first hour was discarded. Next, all animals received a FURO/CAP treatment and urine was collected for another hour, to measure sodium and potassium concentration. All animals received a final suprapubic massage to induce urine void, and were transferred to another room for immediate blood collection. Trunk blood was collected as described above, for biochemical analysis.

2.12. Effect of LPS on thirst induced by acute treatment with furosemide or by gavage with 2 M NaCl

Furosemide alone induces massive natriuresis (about 1.5–2.0 mEq in 1 h) and diuresis, followed by thirst within two hours [17,19,25]. On the day of the test, food and fluids were removed and the animals (n = 35) randomly received an intraperitoneal injection of LPS (0.3, 0.6, 1.25 and 5.0 mg/kg) or saline. One hour later, all animals received a subcutaneous injection of the natriuretic and diuretic furosemide (10 mg/rat). Water was offered from graduated burettes (0.1 ml division) fitted with stainless steel spouts, 1 h after the furosemide injection. Water intake was then recorded at 15, 30, 60, 120 and 180 min.

Animals in another group (n = 33) were trained for the gavage test. On the day of the test, food and fluids were removed and the animals randomly received an intraperitoneal injection of LPS (0.3, 0.6, 1.25 and 5.0 mg/kg mg/kg) or saline. One hour later, all animals received 2 ml of 2 M NaCl by gavage, which induces hypernatremia and hyperosmolality, with no signs of hypovolemia, within 1 h [21]. Water was offered from graduated burettes (0.1 ml division) fitted with stainless steel spouts, 1 h after the gavage. Water intake was then recorded at 15, 30, 60, 120 and 180 min.

2.13. Effects of LPS on sodium excretion and blood biochemistry after 2 M NaCl gavage

One group of animals (n = 13) was transferred to individual metabolic cages, without access to food or fluid. They were subdivided into two groups, one that received 1.0 mg/kg LPS ip and another that received saline. One hour later all animals received a suprapubic massage to induce urine void; urine collected during this first hour was discarded. Next, all animals received 2 M NaCl by gavage and urine was collected for another hour to measure sodium and potassium concentrations. All animals then received a last suprapubic massage for urine void and trunk blood was immediately collected, as described, for biochemical analysis.

3. Results

3.1. Effect of LPS on 0.3 M NaCl and water intake induced by FURO/CAP

There was a difference between treatments for the non-cumulative 0.3 M NaCl intake induced by FURO/CAP [$F(6, 36) = 4.0$; $p = 0.003$] (Fig. 1, left). All (0.3–5 mg kg) but the smallest dose (0.15 mg/kg) of LPS inhibited the 0.3 M NaCl intake compared to saline at 15 min. There were no differences in time [$F(4, 24) = 1.9$, $p = 0.135$]. There was no interaction between treatment and time [$F(24, 144) = 1.2$, $p = 0.203$].

There was a difference between treatments for the non-cumulative water intake induced by FURO/CAP [$F(6, 36) = 3.6$; $p = 0.006$] (Fig. 1, right). Only the highest doses of LPS (2.5 and 5 mg/kg) reduced the water intake from 80 to 100% compared to saline at 15 min. There was an effect for time [$F(4, 24) = 8.5$, $p < 0.001$]. There were no interaction between treatment and time [$F(24, 144) = 1.5$; $p = 0.062$].

There was a difference between treatments for rectal temperature [$F(6, 36) = 3.9$; $p = 0.045$]. LPS (2.5 and 5 mg/kg) produced a drop in rectal temperature (35.2 ± 0.1 and 34.4 ± 0.3 °C, respectively) compared to saline (36.6 ± 0.1 °C) at time zero, coinciding with the beginning of the ingestive test. There was effect for time [$F(3, 18) = 10.6$; $p < 0.001$]. There was an effect for interaction between treatment and time [$F(18, 108) = 2.3$; $p = 0.004$)].

The 2.5 or 5 mg/kg LPS also produced behavioral effects characterized by piloerection and the body curled with the nostrils pointing ventrally. No grooming was observed when the animals received these two doses.

3.2. Effects of LPS on the hypotension induced by FURO/CAP

The dose of 0.6 mg/kg was chosen for this test because it effectively suppressed sodium intake but did not produce hypothermia or alterations in posture.

With respect to MAP there was no significant difference between treatments (LPS 0.6 mg/kg vs saline) [$F(1, 5) = 0.1$; $p = 0.758$] (Fig. 2, top). There was a significant effect [$F(14, 70) = 4.6$; $p < 0.001$] for variations of mean arterial pressure with time. There was no effect for interaction between time and treatment [$F(14, 70) = 0.2$; $p = 0.998$]. There was also no significant difference between treatments in heart rate [$F(1, 5) = 0.8$; $p = 0.403$], but there was a significant change over time [$F(14, 70) = 5.4$; $p < 0.001$] and an interaction between time and treatment [$F(14, 70) = 2.1$; $p = 0.018$] (Fig. 2, bottom).

3.3. Effects of LPS on thirst induced by acute treatment with furosemide or 2 M NaCl gavage

There was a difference between treatments for the non-cumulative water intake induced by acute injection of furosemide [$F(4, 30) = 2.6$; $p = 0.042$]. LPS (0.3–5 mg/kg) reduced the water intake by 30 to 80% at 15 min (Fig. 3, left). There was an effect for time [$F(4, 120) = 72.4$; $p < 0.001$]. There was no interaction between treatment and time [$F(16, 120) = 1.6$; $p = 0.061$].

There was a difference between treatments for the non-cumulative water intake induced by gavage of 2 M NaCl [$F(6, 18) = 3.9$; $p = 0.011$]. LPS (0.3–5 mg/kg) reduced the water intake by 60 to 100% at 15 min (Fig. 3, right). There was an effect for time [$F(4, 12) = 4.2$; $p = 0.022$].

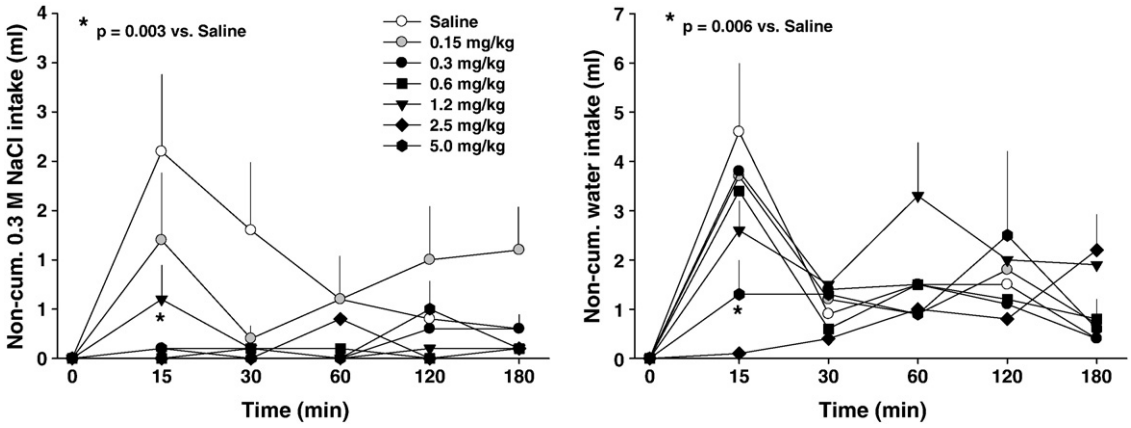

Fig. 1. Non-cumulative 0.3 M NaCl (left) and water (right) intake of rats that received LPS or saline ip 1 h prior to FURO/CAP. N = 7/group.

There was an interaction between treatment and time [$F(24, 72) = 4.4$; $p < 0.001$].

3.4. Summary of the effects of LPS on fluid intake

The results from Figs. 1 and 3 concerning water and 0.3 M NaCl intake recorded at 15 min in all tests are summarized in Fig. 4. The statistics are the same as that described for the original data from each Figure valid only within and not between groups.

LPS abolished most of water intake induced by gavage at doses (0.3, 0.6, 1.2 and 5 mg/kg) but reduced water intake induced by furosemide by only 40–80%. The same doses, excepting the highest, barely had any effect on water intake induced by FURO/CAP, although they were effective in abolishing 0.3 M NaCl intake induced by this treatment.

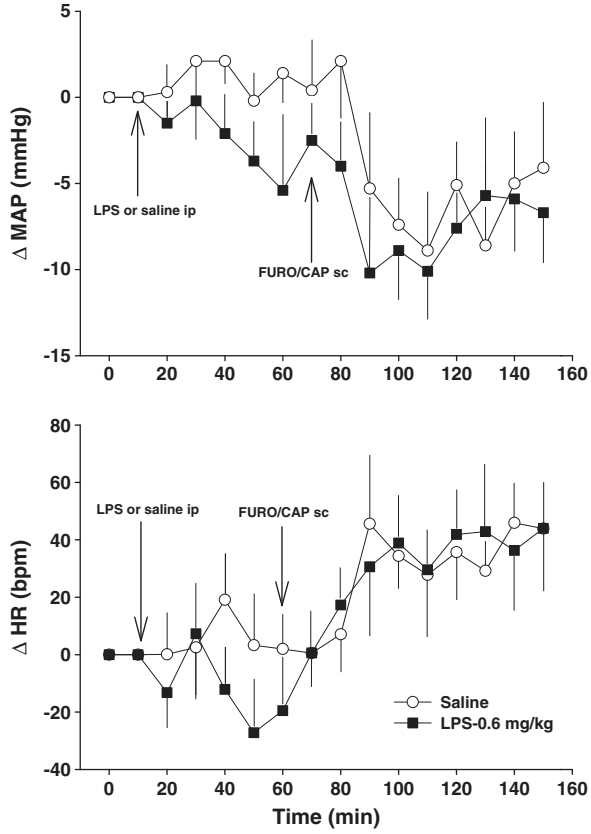

Fig. 2. Changes in mean arterial pressure (Δ MAP) and heart rate (Δ HR) of rats that received LPS (0.6 mg/kg) or saline ip 1 h prior to FURO/CAP. Arrows indicate the moments of injections. N = 7/group.

3.5. Effects of LPS on renal excretion and blood biochemistry in rats treated with FURO/CAP

LPS (0.6 mg/kg) reduced the diuresis and natriuresis by 30% ($p < 0.05$) relative to saline, without changing kaliuresis, in FURO/CAP treated rats (Table 1). However, LPS had no effect on serum sodium or potassium concentration, or on the total plasma protein concentration of these animals (Table 1).

3.6. Effects of LPS on sodium excretion and blood biochemistry after NaCl gavage

LPS (1.0 mg/kg) had no significant effect on natriuresis, diuresis or kaliuresis (Table 2). However, LPS reduced sodium urine concentration from 299 ± 68 to 128 ± 41 mEq/l ($n = 8$ per group, $p = 0.049$). LPS reduced serum sodium and total serum protein concentration, but had no effect on serum potassium concentration (Table 2).

4. Discussion

The lipopolysaccharide (LPS), at doses ranging from 0.3 to 5 mg/kg ip inhibited 0.3 M NaCl intake induced by FURO/CAP treatment. The same doses also reduced water intake induced by furosemide alone or by an intragastric load of 2 M NaCl, while only the highest doses (2.5 and 5 mg/kg) inhibited water intake induced by FURO/CAP. LPS also reduced urine volume and sodium excretion in rats treated with FURO/CAP without changing their mean arterial pressure or heart rate. LPS also reduced urine and serum sodium concentration and total serum protein in rats that received 2 M NaCl by gavage. Only 2.5 and 5.0 mg/kg of LPS induced postural changes and hypothermia in addition to reduction in fluid intake.

The results suggest that LPS not only inhibits water intake, but also inhibits sodium intake. However, a strong inhibitory effect on sodium intake was achieved at low doses, whereas the maximum effect of LPS on water intake was achieved only at the two highest doses. Thus, the results also suggest that the inhibitory effect may be stronger on sodium intake compared to water intake when the rat has the option of ingesting sodium solution.

The effects of LPS on thirst were not exclusive for intracellular dehydration as those of interleukin-1β given systemically [16]. The effect of LPS on FURO/CAP- and furosemide-induced water intake is

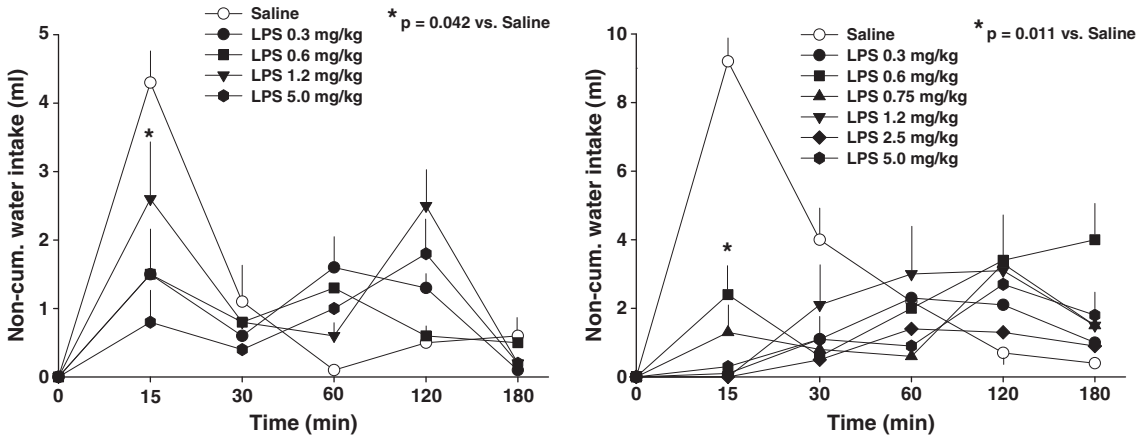

Fig. 3. Non-cumulative water intake of rats that received LPS or saline ip 1 h prior to 10 mg of furosemide ip (right) or prior to gavage of 2 M NaCl (left). N = 4–8/group.

consistent with an inhibition of thirst mediated by hypovolemia and angiotensin II [14,18,23–25]. However, doses of LPS that effectively abolished gavage-induced thirst either had no effect or only partially inhibited the FURO/CAP- or furosemide-induced thirst. The effect of LPS also interacted with time when water intake was induced by gavage. Thus, LPS can inhibit any kind of thirst, but the inhibition is stronger on intracellular than extracellular thirst.

The inhibition LPS exerted on both types of thirst and on sodium intake is consistent with the production of lethargy accompanied by fever in the rat [27], but it also suggests that the inhibition is not of the same degree for every behavior. Moreover, although LPS may elicit central mechanisms to reduce activity and ingestive behavior [28], it may also have a systemic effect, other than alteration in body temperature or arterial pressure, which attenuated the signals of dehydration and contributed to the inhibition of fluid intake. The dose of LPS that had no effect on body temperature or on arterial pressure reduced both diuresis and natriuresis induced by furosemide in the FURO/CAP tests, and reduced urine sodium concentration and serum sodium concentration in the hypertonic NaCl gavage tests.

Although the effects of LPS on renal excretion may contribute to the inhibition of fluid intake, the 30% reduction induced by LPS on the natriuresis induced by FURO/CAP does not correlate with the complete suppression of sodium intake induced by the same dose of LPS. This dissociation between the intensity of natriuresis and sodium intake is consistent with previous findings showing that the amount of sodium ingested is higher than sodium loss when rats enter the sodium appetite test 24 h after the injection of furosemide [29].

A decrease in MAP, concomitant with an increase in HR, occurred in response to FURO/CAP as expected [18,25], whether the animals were treated with LPS or not. A general inhibition of behavior was also expected if LPS had debilitated the animal by producing a strong hypotension associated with shock [4], but this did not happen in the present experiments. Therefore, we cannot attribute the inhibition of fluid intake in FURO/CAP-treated animals to the cardiovascular effects of LPS.

The LPS induced simultaneous reduction in serum sodium concentration and total protein in animals that received the hypertonic ig load. This suggests an expansion of blood volume and dilution of the extracellular fluid, which could generate inhibitory signals for thirst [14]. Yet, the serum sodium concentration after LPS is still five units above the range of normovolemic rats [21], which could still contribute to cell dehydration [20]. Therefore, we cannot rule out that the inhibition of intracellular thirst results from activation of central mechanisms, systemic dilution and expansion of extracellular fluid, or a combination of central and systemic mechanisms.

The selective inhibition on intracellular thirst, reduced sodium excretion and the expansion of blood volume is at least in part consistent with a role to increase cardiovascular performance during endotoxemia, as suggested in the Introduction [16]. However, reduced sodium absorption in the intestine, as reported in previous works [2], and the reduced sodium intake, as shown here, may have a role to protect the animal from hypernatremia. This raises the possibility that the central mechanisms that mediate LPS-induced anorexia [28] overlap those that protect the rat from excess hypertonic NaCl intake through the parabrachial and dorsal raphe nucleus [30,31].

The results do not exclude the participation of interleukin-1β, but they suggest that the effect of LPS on thirst is not mediated exclusively by this type of interleukin. This is not surprising given the several mediators activated by LPS. Recall, however, that icv injection of

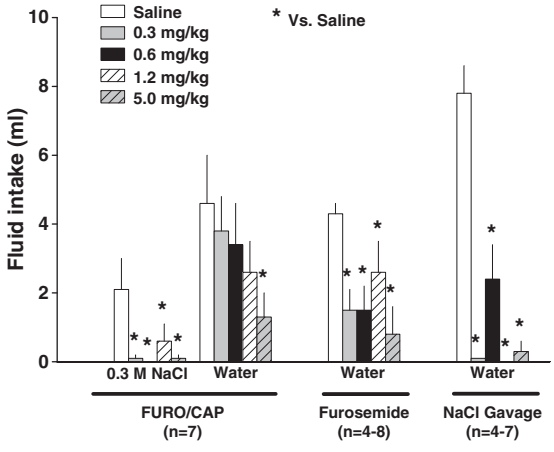

Fig. 4. Summary of the effects of LPS on fluid intake induced by different protocols at the 15 min of ingestive tests (FURO/CAP, furosemide or hypertonic NaCl gavage) according to data withdrawn from Figs. 1 and 3. Significance is based on SNK withdrawn from two-way ANOVA performed for treatment, time and interaction between treatment and time (see Figs. 1 and 3 for p values). Number of animals inside parentheses.

Table 1
Renal excretion and blood biochemistry in rats treated with FURO/CAP combined with saline or LPS (0.6 mg/kg).

Treatment	UV (ml/2 h)	$U_{Na}V$ (μEq/2 h)	U_KV (μEq/2 h)	S_{Na} (mEq/l)	S_K (mEq/l)	Tp (g/%)
LPS (8)	7.1 ± 0.8*	831 ± 10*	300 ± 28	140 ± 1	6.1 ± 0.3	6.6 ± 0.3
Saline (8)	10.3 ± 0.2	1187 ± 53	451 ± 23	141 ± 1	5.8 ± 0.2	7.2 ± 0.2

Values are means ± S.E.M.; number of animals inside parentheses. UV, urine volume; $U_{Na}V$, amount of sodium excreted; U_KV, amount of potassium excreted. S_{Na}, serum sodium concentration; S_K, serum potassium concentration; T_P, total serum protein.
* $p < 0.05$ vs. Saline.

Table 2
Renal excretion and blood biochemistry of 2 M NaCl gavage-treated rats in response to LPS (1 mg/kg).

Treatment	UV (ml/h)	$U_{Na}V$ (μEq/h)	U_KV (μEq/h)	S_{Na} (mEq/l)	S_K (mEq/l)	Tp (g/%)
LPS (8)	0.9 ± 0.3	183.6 ± 68.0	81.9 ± 32.9	141.6 ± 0.5*	4.8 ± 0.1	5.4 ± 0.1*
Saline (8)	0.8 ± 0.2	345.2 ± 146.7	72.6 ± 36.2	146.5 ± 0.6	4.9 ± 0.1	5.8 ± 0.1

Values are means ± S.E.M.; number of animals inside parentheses. UV, urine volume; $U_{Na}V$, amount of sodium excreted; U_KV, amount of potassium excreted. S_{Na}, serum sodium concentration; S_K, serum potassium concentration; T_P, total serum protein.
* $p<0.05$ vs. Saline.

interleukin-1β inhibits all types of thirst [32]. Moreover, LPS given systemically also inhibits thirst induced by icv injections of either angiotensin II or hypertonic NaCl [15]. Thus, it is possible that LPS exerts its effects on thirst by separately affecting the systemic and central production of interleukins.

In addition to the cytokines, the inhibitory effect of LPS on fluid intake could also result from the activation of inhibitory hormones and neurotransmitters. LPS induces oxytocin secretion [4] dependent on the activation of circumventricular organs and the hypothalamic paraventricular nucleus [33]. The oxytocin secreted into the circulation has been suggested as a marker for the activity of central oxytocin, which may interact with α_2-adrenoceptors to inhibit sodium intake [34,35].

Reduced sodium excretion seems an initial response to LPS that precedes renal failure in septicaemia or endotoxic shock [5,36]. However, one may speculate if reduced sodium excretion is adaptive to milder infections by contributing to spare water and electrolytes and thus compensate the predicted reduction in fluid and mineral intake. Accordingly, contrary to what was suggested in the Introduction, the effect on sodium excretion would be complemented by a stronger inhibition of sodium compared to water intake, and by preferential inhibition of intra- versus extracellular thirst. This suggestion is analogous to the ability of the sick animal to reorganize its selection of macronutrient intake according to its nutritional and energetic requirements [1]. Therefore, it is possible that the effect of LPS on sodium balance is an advantageous complement to the strategy of sickness behavior.

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