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Central leukotrienes modulate fever tolerance to LPS in rats

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ABSTRACT

Leukotrienes mediate several inflammatory events such as neutrophil chemoattraction, leukocyte adhesion, and central-release of cytokines and fever. However, there is no information available about their putative role in lipopolysaccharide (LPS) tolerance. The rational of the present study was to find out if central leukotrienes are involved in the development of LPS tolerance. Thus, we inhibited central leukotriene synthesis in tolerant rats using a pharmacological tool, *i.e.*, a selective inhibitor of leukotriene synthesis MK-886 injected into the third ventricle (3V) of rats. Body core temperature (Tb) was measured using a datalogger placed inside the abdominal cavity. A low-dose of LPS (100 μg/kg ip) was given for 4 consecutive days to induce LPS tolerance. At day 4, rats received a microinjection of MK-886 into the 3V immediately before LPS, whereas control groups were treated with vehicle (saline). We observed that LPS failed to induce plasma cytokines surges, increased hypothalamic PGE_2 levels and fever 3 days post LPS treatment, aptly characterizing the tolerance. When MK-886 was given to control rats treated with saline, no significant change in Tb was observed. However, a full LPS-induced fever was observed in tolerant rats pretreated with MK-886, which was associated with an enhancement in the hypothalamic PGE_2 levels, that were not accompanied by plasma cytokines (IL-1β, and IL-6) and PGE_2 surges. These data are consistent with the notion that central leukotrienes play a role in fever tolerance to LPS.

1. Introduction

Sepsis is a life-threatening organ dysfunction induced by an inappropriate host response against pathogens. In the early phase of sepsis, a hyper-inflammatory response to infection is observed, followed by tissue damage and organ failure. At the late phase of sepsis, there is a reprogramming in the immune response causing immunoparalysis and increasing the vulnerability of the patient to other infections (Boomer et al., 2011). Despite recent progress in the knowledge of sepsis, septic patients still have high mortality rates due to the uncontrolled inflammation at the early stage or by long-term lethal secondary infections caused by the immunosuppressive state (Hotchkiss et al., 2013; Stevenson et al., 2014).

One of the ongoing methods used to study the pathophysiology of immunoparalysis to find effective therapies to restore host defense in the septic patient is lipopolysaccharide (LPS; bacterial outer membrane component) tolerance (Andrade et al., 2019; Jędrzejewski et al., 2019). LPS tolerance can be experimentally induced by repeated injections of LPS, which virtually abrogate fever (BEESON, 1946) and other pattern signals of sickness syndrome including achiness, loss of appetite, and sleepiness.

Sickness syndrome is mediated by a classical set of brain immune responses during illnesses in which prostaglandins are the main brain mediators (Saper et al., 2012). There is no doubt that the inhibition of COX, an enzyme that converts arachidonic acid (AA) into prostaglandin H_2, alleviates the symptoms of sickness. Specifically, PGE_2 produced in the preoptic area (POA) of anterior hypothalamus has been thought to play a role as the proximal, putative mediator of fever (Schiltz and Sawchenko, 2003).

There is substantial evidence that other eicosanoids, such as leukotrienes, have their synthesis significantly increased in the hypothalamus during endotoxemia (Azab and Kaplanski, 2004; Goulet et al., 1994; Kozak and Fraifeld, 2004a; Lopes et al., 2017; Paul et al., 1999). 5-lipoxygenase (5-LO) is a key enzyme in the biosynthesis of this mediator, acting directly on AA and other intermediates, that results in the synthesis of leukotrienes B4 (LTB4) and Cys-LTs (LTC4, LTD4, and LTE4) (Funk, 2001). Unlike prostaglandins, leukotrienes seem to play a cryogenic role in LPS-induced fever (Kozak and Fraifeld, 2004b; Paul et al., 1999). However, their central role in temperature control during LPS tolerance has not been investigated.

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In the present study, we investigate the central role of hypothalamic leukotrienes, specifically in LPS tolerance by analyzing body core temperature (Tb) and the hypothalamic PGE_2 levels in rats. We also investigate the role of hypothalamic leukotrienes in peripheral pyrogens production, *i.e.*, plasma PGE_2, IL-1β, and IL-6 of tolerant rats.

2. Methods

2.1. Animals

Adult male Wistar rats (290–300 g) were individually caged and maintained at a controlled temperature of 29 °C on a 12-h light/dark cycle (lights on at 6 a.m.). Regular food and water were provided ad libitum. All experiments were approved by the Animal Care and Use Committee of the University of São Paulo/Brazil at the Ribeirão Preto campus (Protocol number 2016.1.393.58.1). The present study was performed in accordance with the Guide for the Care and Use of Laboratory Animals of the National Council for the Control of Animal Experimentation (CONCEA).

2.2. Drugs

LPS tolerance was induced using a low dose of LPS (Sigma, MO, USA; serotype 0111: B4; dose: 100 μg/kg ip) administration. The dose of LPS administered was sufficient to activate febrigenic signaling in a slightly high temperature inside the thermoneutral zone (29 °C) (23). LPS was diluted in pyrogen-free saline. The dose was based on body mass measured immediately before LPS administration of each rat, since LPS induces important body weight changes. MK-886 (3-[1-(p-chlorobenzyl)-5- (isopropyl)-3-tert-butylthioindol-2-yl]-2, 2-dimethyl-propanoic acid; Sigma, MO, USA) was used as an inhibitor of leukotrienes biosynthesis. This drug selectively inhibits FLAP (5-lipoxygenase-activating protein), a protein required for leukotrienes formation. It was dissolved in pyrogen-free saline at a final concentration of 4 μg/kg and administered into the third ventricle (3V) (dos Santos et al., 2012; Martins et al., 2011).

2.3. Surgeries

Five days before the experiment, an intracerebroventricular (3V) cannula (for MK-886/vehicle administration) was implanted, and an intra-abdominal temperature datalogger (for T_b recording; SubCue, Alberta, Canada) was inserted in the peritoneum of all animals. All surgery procedures were performed under anesthesia with a mixture of 10% ketamine and 2% xylazine (1:1; 1 ml/kg of body weight) ip and anti-inflammatory flunixin meglumine (0.1 ml subcutaneously) and antibiotic pentabiotic (1.200.000 IU; 0.1 ml intramuscular) were injected subcutaneously and intramuscularly, respectively. In a surgical aseptic field, the intraperitoneal cavity was exposed for the datalogger insertion and closed at the end of this surgery. After that, the animals were fixed to a stereotaxic apparatus with the incisor bar set at −3.3 mm. The following coordinates were assigned with a reference from bregma (Paxinos and Watson, 2007): anterior-posterior: −0.4 mm; lateral: 0 mm and dorsoventral: −4.5 mm. The intracerebroventricular cannula (22-gauge; 16-mm of length) was fixed to the skull with a stainless-steel screw and dental cement.

2.4. LPS tolerance induction

The LPS tolerance protocol started by food intake and body weight measurement (7–8 am) followed by injection of LPS ip or its vehicle (saline). This procedure was conducted daily until day 3 to verify LPS tolerance by fever and anorexia attenuation (Figs. 1 and 2, respectively). At day 4, the animals received MK-886 or its vehicle (saline) icv 60 min before LPS/saline ip injection and after 5 h the animals were decapitated and brain and plasma samples were quickly collected for posterior analysis.

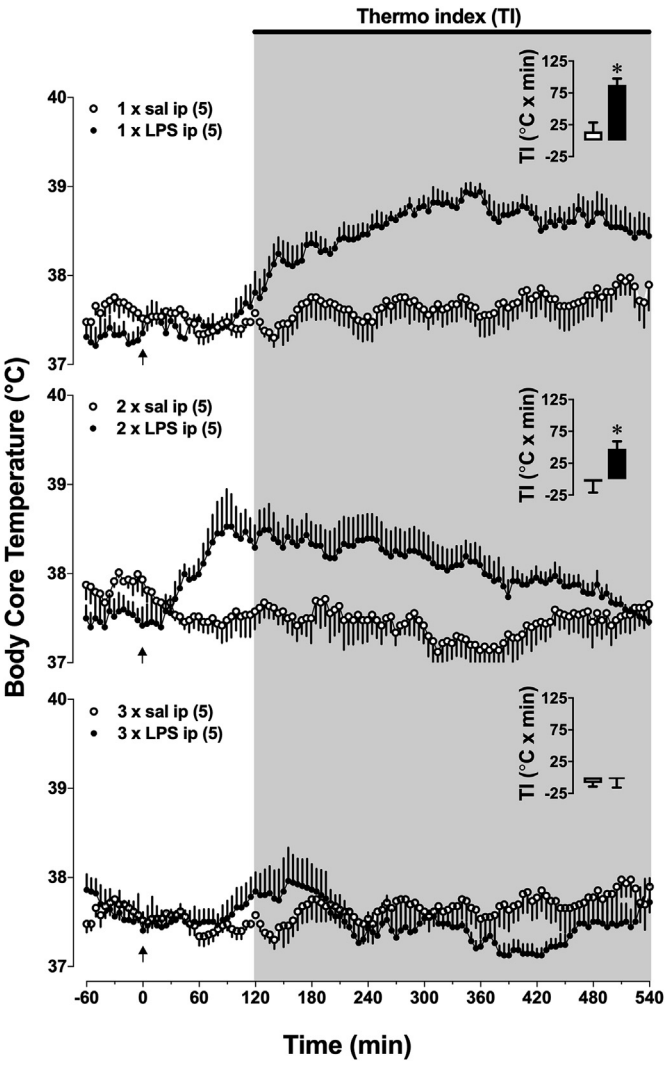

Fig. 1. Development of LPS tolerance by daily deep body temperature (Tb) measurement. Time courses of Tb of saline (sal) and LPS groups on day 1 (Fig. 1 upper graph), 2 (Fig. 1 middle graph), and 3 (Fig. 1 bottom graph). Arrow indicate the time of injection of saline or LPS intraperitoneally daily. The gray area indicates the febrile period analyzed by thermal indexes. Thermal indexes of the febrile periods between saline and LPS-treated groups are represented on the upper right corner of the time-course graph in each day. Values are means ± SEM. n = 6–8. *P < 0.05, LPS group vs. SAL group.

2.5. PGE_2 and cytokines measurements

Plasma collection was performed using EDTA as an anticoagulant, and indomethacin (at a final concentration of 10 μM) to prevent ex-vivo eicosanoids production. Samples were centrifuged (at 2,000 g/10 min/4°C), and stored for posterior analysis at - 80°C. To understand if central inhibition of leukotriene synthesis could alter the immune non-responsiveness state of LPS tolerant animals, we measured the plasma IL-1β and IL-6 levels. Additionally, we hypothesized that LPS tolerance is accompanied by changes in hypothalamic PGE_2 levels. Hypothalamus was dissected, homogenized in lysis buffer (RIPA) with a protease inhibitor cocktail, centrifuged (2,000 g/20 min/4°C) and the supernatant was separated for PGE_2 measurement. It was used the enzyme-linked immunosorbent assay technique (ELISA) following manufacturer's instructions for PGE_2, IL-1β, and IL-6 measurements.

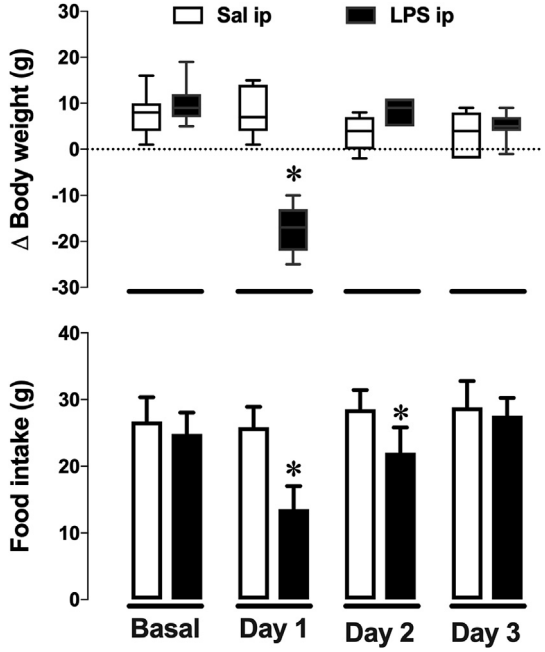

Fig. 2. Development of LPS tolerance by body weight deviation (Δ) and food intake measurements. Body weight deviation (A) and food intake (B) of saline (sal) and LPS groups on day 1, 2, and 3. Values are means ± SEM. n = 6–8. *P < 0.05, LPS group vs. SAL group.

2.6. Statistical analyzes

Thermal index (TI) from the area under the curve (AUC) of values of Tb during the febrile period (120–300 min post-LPS injection) was analyzed by one-way ANOVA test followed by the post hoc Student-Newman Keuls. Baseline was fixed in 37.2 °C. One-way ANOVA test was used to analyze hypothalamic and plasma PGE_2 levels followed by the post hoc Student-Newman Keuls. Data were expressed by means ± SEM. P < 0.05 was considered statistically significant.

3. Results

3.1. LPS-induced tolerance in rats

As shown in Fig. 1, LPS tolerance was induced by three daily consecutive injections of low doses of LPS (100 μg/kg ip) in rats. The effectiveness of the LPS tolerance was evaluated by the undetectable plasma cytokines (IL-6 and IL-1β) levels and the attenuation of two pattern symptoms of the sickness syndrome [5]: (1) fever, determined by the thermal indexes comparing Tb of LPS and saline-treated animals in the febrile phase (area under curve; indicated by the top right corner graphs in Fig. 1); and (2) anorexia, determined by the evaluation of daily body weight deviation and food intake of the groups (Fig. 2).

On the first day of LPS-injection, fever was observed (Fig. 1) as well as a decrease in body weight and food intake (Fig. 2) of LPS-treated rats compared to their control (P < 0.05). On the second day of LPS injection, an altered course-time of Tb was observed (Fig. 1, *middle graph*) along with an increase in body weight (Fig. 2) in LPS-treated animals, indicating the development of LPS tolerance. On the third day of LPS-injection, LPS tolerance was completed since we observed the absence of differences in Tb (Fig. 1, *bottom graph*), body weight deviation, and food intake (Fig. 2) between LPS-treated animals and their control (P > 0.05).

3.2. Effect of central leukotrienes inhibition on fever tolerance to LPS in rats

Pretreatment with MK-886 at a dose of 4 μg/kg icv restored the febrile response in LPS tolerant animals (Fig. 3), evidenced by the enhancement of Tb compared with LPS-tolerant animals treated with saline icv (P < 0.05). These data support the idea that the leukotrienes play a role in LPS tolerance in rats.

3.3. Central leukotrienes inhibition and hypothalamic PGE_2 production in LPS tolerant rats

To investigate the central role of leukotrienes in fever abrogation in LPS tolerant rats, we measured the hypothalamic PGE_2 levels, the proximal mediator of fever [6]. As shown in Fig. 4, LPS tolerant animals had a similar hypothalamic PGE_2 production compared to saline treated rats that was reverted by the inhibition of central leukotrienes in LPS tolerant animals (P < 0.05).

3.4. Central leukotrienes inhibition and plasma PGE_2, IL-6, and IL-1β production in LPS tolerant rats

To investigate whether central leukotrienes act only in the central development of LPS tolerance, we examined plasma production of PGE_2, IL-6, and IL-1β. We did not observe any differences in plasma PGE_2 levels between groups (Fig. 4). All the groups had undetectable plasma cytokine levels (data not shown). These data indicate that leukotrienes act only in central areas reverting fever tolerance without altering peripheral febrigenic signaling.

4. Discussion

In the present study, we investigated the potential role of central leukotrienes in fever tolerance to LPS. To address the cryogenic potential of leukotrienes in LPS tolerance, we had to validate the LPS tolerance protocol. The efficacy of the protocol was proved by the

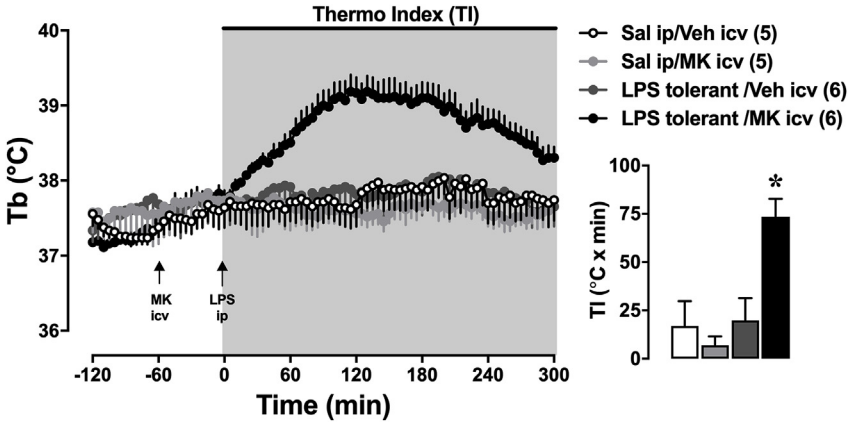

Fig. 3. Role of central leukotrienes in LPS tolerance. Time course of Tb of animals treated for 4 days with saline (sal group) or LPS (LPS tolerant group) and pre-treated with MK-886 (leukotrienes synthesis inhibitor) or its vehicle (veh) at the fourth day of saline or LPS injections. Arrow indicate the time of injection of MK-886 intracerebroventricularly, and saline or LPS intraperitoneally. Gray areas indicate the febrile period analyzed by thermal indexes. Thermal index of the febrile periods is represented on the side of its time-course graph. Values are means ± SEM. n = 6–8. *P < 0.05, LPS group vs. SAL group.

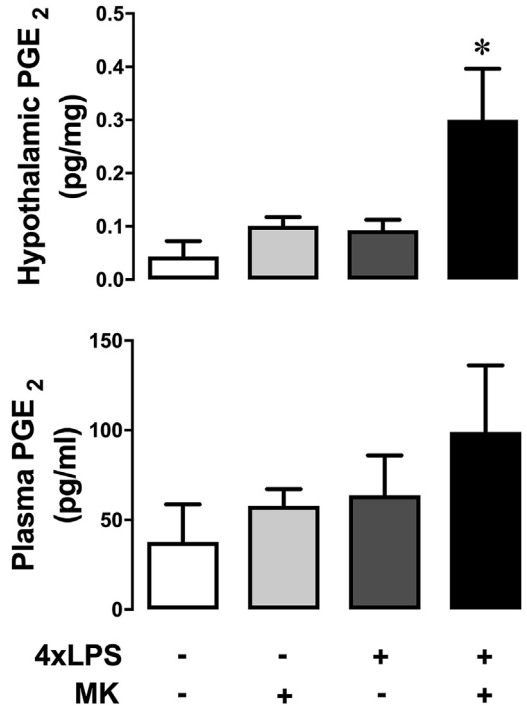

Fig. 4. Role of central leukotrienes in hypothalamic and plasma PGE_2 production in fever tolerance to LPS. Hypothalamic and plasma levels of PGE_2 at 300 min after LPS or saline administration in saline of LPS tolerant rats pretreated with MK-886 (leukotrienes synthesis inhibitor) or its vehicle (veh) at the last day of injections (day 4). Values are means ± SEM. n = 6. *P < 0.05, LPS group vs. SAL group.

absence of two indicators of sickness syndrome: fever and anorexia. The LPS tolerance protocol was performed by daily injection of a low dose of LPS (100 μg/kg ip) in rats for 3 days. The dose selected was the same utilized by another study (Kwiatkoski et al., 2013) that evokes the rise in body core temperature at the first immune challenge. As expected, first LPS-injection induced not only an increase in Tb but also a decrease in daily body weight deviation and food intake. After the third injection, we detected an abrogation of the signals analyzed, legitimizing the protocol used.

Fever is a classical signal of immune challenge. The activation of peripheral immune cells by the infectious agent increases the production of a number of inflammatory mediators. The first induced mediator by the immune challenge is TNF-α, followed by other cytokines such as IL-1β and IL-6 (Kluger et al., 1995), eicosanoids such as prostaglandins and leukotrienes (Blatteis, 2006; Ivanov and Romanovsky, 2004; Kozak and Fraifeld, 2004b), and gasotransmitters such as nitric oxide and hydrogen sulfide (Branco et al., 2014). These mediators act direct or indirectly and culminate in an increase of hypothalamic PGE_2, inducing fever. In humans, some studies have described that febrile patients had a better outcome compared to patients who did not display fever (Ahkee et al., 1997; Bryant et al., 1971). In a model of septic shock in rats, the control of Tb was correlated with a poor outcome (Su et al., 2005). Here, central inhibition of leukotrienes reverted fever tolerance by increasing PGE_2. In the literature, an increased synthesis of PGE_2 was observed in 5-LO–deficient mice after arachidonic acid inflammation in ear tissue (Goulet et al., 1994), and the pharmacological inhibition of 5-LO enhanced the production of PGE_2 in mice after LPS injection (Azab and Kaplanski, 2004; Fraifeld et al., 2000; Paul et al., 1999). The mechanisms involved in this response still need to be investigated. We speculate a possible shift induced by the higher production of leukotrienes, decreasing the availability of arachidonic acid to produce PGE_2 in the hypothalamus of tolerant animals. However, we still do not know the responsible for the shift in the production of these hypothalamic eicosanoids in LPS tolerance.

It is also important to mention that the production of hypothalamic PGE_2 in LPS tolerant rats may differ among conditions such as the dose of LPS, the rat strain, the time-course after LPS injection and the ambient temperature. Chemo et al. (1997) observed that a second exposure (48 h after the first injection) to a relatively high dose of LPS (250 μg/kg ip) caused a decrease in hypothermia and fever induced by LPS in Sprague-Dawley rats in a low ambient temperature. This response was reported to be followed by a decrease in hypothalamic PGE_2 levels 2 h after LPS re-exposure and an increase 24 h later compared to animals that received a single LPS injection. In essence, their results seem to contrast with the present study, since we observed that a fourth exposure to a low dose of LPS (100 μg/kg ip) leads to no significant changes in Tb of Wistar rats. These data are associated with decreased hypothalamic PGE_2 levels, 2 h after the fourth LPS exposure. Reconciling these data, it seems reasonable to state that LPS tolerance is a complex immune response, associated with intricate changes in hypothalamic PGE_2 production that depends upon the factors aforementioned.

Fever tolerance takes place by decreasing the production of the endogenous pyrogens. Interestingly, central leukotrienes seem to downregulate central PGE_2 (Fig. 4), without affecting peripheral pyrogens in LPS tolerance. This response might be related to the differences between peripheral and central immune activation in tolerance. For example, splenic cytokines expression is different from that observed in the central nervous system in LPS-immune challenge re-exposure (del Rey et al., 2009). Additionally, it was observed that microglial cells are dependent upon neurons and astroglia to induce tolerance (Chu et al., 2016), indicating the exceptionality of the CNS. Faggioni et al. (1995) observed that the LPS pretreatment (3 daily LPS injections given ip) does not blunt brain TNF-α production when LPS was administered centrally. These data indicate that peripheral LPS tolerance does not cause central LPS tolerance, if we consider TNF-α only as a marker of LPS tolerance. However, these results do not imply that peripheral LPS tolerance occurs independently of the CNS. Moreover, previous studies have already documented that the CNS plays a key role in peripheral LPS tolerance (Almeida et al., 1999; Navarro et al., 2007; Raffaini et al., 2006) which are in agreement with the present study. Here, we suggest that central leukotrienes are one of the central mechanisms participating in fever tolerance to LPS.

5. Conclusion

Our results indicate that central leukotrienes play a key role in fever tolerance by decreasing hypothalamic PGE_2 production without altering peripheral pyrogens.

Conflicts of interest

We have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jtherbio.2019.07.015.

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