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Lipopolysaccharide administration induces sex-dependent behavioural and serotonergic neurochemical signatures in mice

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ABSTRACT

Challenging the innate immune machinery with the pro-inflammatory agent lipopolysaccharide (LPS) results in the development of a sickness syndrome characterized by numerous depressive-like behavioural and physiological manifestations, most of which overlap with the clinical symptoms of major depression. Although women are known to mount stronger pro-inflammatory responses during infections and being at higher risk to develop depressive disorders compared to men, the vast majority of experimental studies investigating the neurobiological effects of LPS administration have been conducted in males. Herein, we investigated the behavioural effects of LPS administration (0.83 mg/kg) in male and female C57BL/6J mice subjected to tests screening for alterations in locomotor activity (open field test), *anorexia* (food consumption), *anhedonia* (sucrose preference test), behavioural despair (forced swim test) and grooming behaviour (splash-test). We further mapped the brain's serotonergic and dopaminergic activity in five limbic brain regions implicated in the pathophysiology of major depression (i.e., prefrontal cortex, hippocampus, striatum, amygdala, and hypothalamus) at two critical time-points post-LPS treatment; at 6 h when depression of behavioural activity is maximal, and at 24 h when depressive-like symptoms develop independently of obvious locomotor performance impairments associated with acute LPS administration. Our findings indicate that the two sexes present with differential behavioural sensitivity to this immune stressor, as impairment of grooming behaviour in the splash test was more persistent in female mice, and anorexia lasted longer in their male counterparts. Notably, LPS affects the brain's serotonergic neurochemistry in a sex-specific manner, as it induced sustained serotonergic hyperactivity in females at 24 h post-LPS administration in all the brain regions examined. Moreover, the kinetics of dopaminergic activation appeared to be sex-differentiated upon LPS challenge. Given the higher prevalence of affective disorders in women, a focus of basic science on sex differences that underlie neuroinflammatory processes is imperative in order to elucidate the neuroimmunological substrate of major depression.

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1. Introduction

According to the World Health Organization (WHO), major depressive disorder (MDD) affects 350 million people worldwide, and by 2030 is expected to be the leading cause of disease burden globally (Collins et al., 2011; WHO, 2011). Strikingly, women experience MDD at roughly twice the rate of men (Grigoriadis and Robinson, 2007; Holden, 2005; Marcus et al., 2005). Still, most discoveries on the neurobiology and the pharmacotherapy of MDD rely on studies conducted in male subjects. Data accumulated largely during the last two decades advocate the innate immune response as a mechanism that may be implicated in the pathophysiology of MDD, mainly due to the documented elevations in circulating levels of leukocytes and pro-inflammatory cytokines observed in depressed patients (Dantzer et al., 2008; Hodes et al., 2015; Pitychoutis and Papadopoulou-Daifoti, 2010).

The notion that activation of the immune system is implicated in the pathophysiology of MDD has its roots in clinical observations in inflammatory disorders, such as rheumatoid arthritis, multiple sclerosis, diabetes and coronary artery disease, that were associated with increased prevalence of MDD (Elenkov, 2008). Lipopolysaccharide (LPS, endotoxin) is a prototypical microbial-associated molecular pattern (MAMP) which specifically ligates Toll-like receptor (TLR) 4, a pattern recognition receptor expressed on the surface of innate immune cells. TLR4-

Abbreviations: 5-HIAA, 5-hydroxy-indoleacetic acid; 5-HT, serotonin, 5-hydroxytryptamine; ANOVA, analysis of variance; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; DOPAC, dihydroxyphenylacetic acid; FST, forced swim test; GR, glucocorticoid receptor; HPLC, high performance liquid chromatography; HVA, homovanillic acid; HPA, hypothalamus-pituitary-adrenal; IDO, indolamine 2,3-dioxyenase; IL-6, interleukin-6; IQ, interquartile range; LPS, lipopolysaccharide; MAMP, microbial-associated molecular pattern; MDD, major depressive disorder; OFT, open field test; TST, tail suspension test; TLR, Toll-like receptor; TNF-α, tumor necrosis factor-α; VEH, vehicle; WHO, World Health Organization.

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mediated recognition of LPS initiates intracellular signaling cascades ultimately leading to the production and release of pro-inflammatory cytokines (Lu et al., 2008). Experimentally, challenging the innate immune machinery with LPS results in a mild state of *nosothymia*, termed as sickness behaviour (Pitychoutis and Papadopoulou-Daifoti, 2010). Despite its limitations, LPS-induced sickness behaviour is a syndrome conceptualized through numerous depressive-like behavioural and physiological manifestations, most of which overlap with the clinical symptoms of depression (e.g., *anhedonia*, fatigue, reduction in food intake, and alterations in the brain's monoaminergic systems) (Dantzer et al., 2008). Depressive-like symptoms following LPS administration in rodents have been typically assessed shortly (i.e., 1–6 h) following the immune challenge (Dantzer et al., 2008). Thus, assessment of LPS-induced depressive-like behaviours was confounded by the profound depression of motor activity that occurs shortly following LPS administration (Frenois et al., 2007). However, Frenois et al. (2007) confirmed that depressive-like behaviour following treatment with a slightly higher dose of LPS (0.83 mg/kg) in male mice develops over a background of sickness, and also that its neurobiological mechanisms can be dissociated from acute sickness associated with impairment of locomotor activity (Frenois et al., 2007). Indeed, specific depressive-like behaviour (i.e., behavioural despair assessed in the forced swim test; FST and the tail suspension test; TST) develops in immune-stimulated animals independently of obvious impairments associated with locomotor performance (i.e., depressed locomotor activity that peaks at 6 h), and is still apparent at 24 h post-LPS administration when locomotor activity has returned to baseline (Dantzer et al., 2008; Frenois et al., 2007).

It is well established that LPS administration results in enhanced peripheral pro-inflammatory cytokine secretion. During an inflammatory episode a "*replica*" of the peripheral immune response is created within the central nervous system (CNS) by cytokines and inflammatory mediators that signal the brain via different routes, and consequently stimulate the in situ production of prostaglandins and cytokines (Pitychoutis and Papadopoulou-Daifoti, 2010). Induction of pro-inflammatory mediators by glial cells affects neurotransmitter metabolism (e.g., serotonin; 5-HT and dopamine; DA) and the hypothalamus-pituitary-adrenal (HPA) axis reactivity, as well as neuronal integrity and synaptic plasticity in stress-sensitive brain regions, such as the hippocampus. Overall, neural inflammatory activation causes a wide spectrum of neuroimmune, neurochemical and neuroendocrine effects that ultimately lead to the induction of depressive symptomatology (Pitychoutis and Papadopoulou-Daifoti, 2010). Notably, a battery of evidence shows that stimulation of the innate immune system by peripheral LPS administration induces profound central monoaminergic alterations in rodents (Dantzer et al., 2008). Of note, elegant *in vivo* microdialysis studies have shown that LPS administration boosts extracellular concentrations of 5-HT and 5-hydroxindoleacetic acid (5-HIAA) in the medial prefrontal cortex and hippocampus, two brain regions heavily implicated in the pathophysiology of MDD (Linthorst et al., 1995; Linthorst and Reul, 1998). In their landmark study, O'Connor et al. (2009) demonstrated that LPS-induced alterations in serotonergic activity may be attributed to LPS-induced activation of the tryptophan-degrading enzyme indolamine 2,3-dioxyenase (IDO) within the brain (O'Connor et al., 2009). Given that tryptophan is the rate-limiting precursor molecule in 5-HT biosynthesis, it is hypothesized that alterations in its metabolism may account for precipitation of depressive symptoms (Dantzer et al., 2008). Furthermore, LPS administration has also been shown to enhance DA metabolism in most regions of the male rodent brain in a non-selective manner (Dunn, 1992; Dunn et al., 2005).

Although women are known to mount stronger pro-inflammatory responses during infections (Bouman et al., 2005; Darnall and Suarez, 2009; Marriott and Huet-Hudson, 2006) and being at higher risk to develop depressive disorders compared to men (Grigoriadis and Robinson, 2007; Holden, 2005; Marcus et al., 2005), the vast majority of studies investigating the neurobiological effects of LPS administration in humans and in rodents have been conducted solely in males (Pitychoutis et al., 2009; Darnall and Suarez, 2009; Engler et al., 2016). So far, only few studies have directly addressed sex-related differences in inflammatory and behavioural responses to LPS with inconsistent results. For instance, in a most recent study conducted in humans profound sex differences were reported in acute pro-inflammatory and

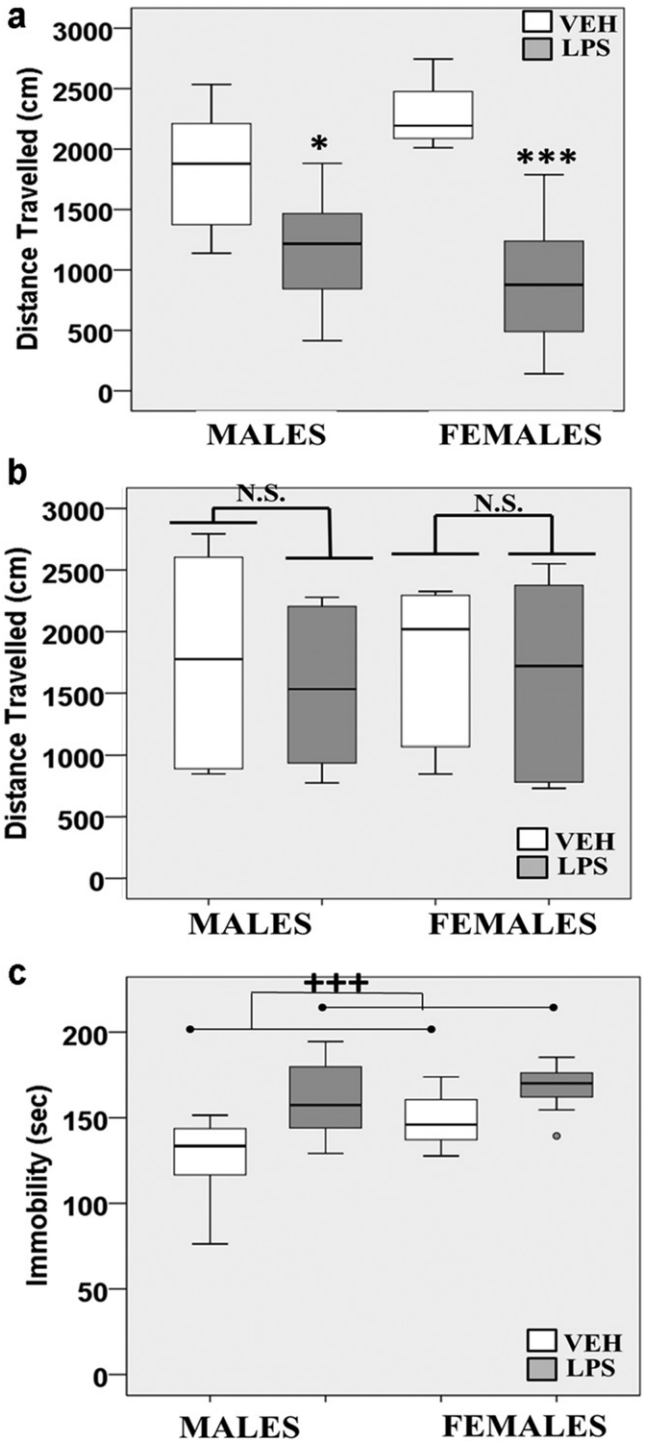

Fig. 1. Box-whisker plots showing the effects of LPS administration (0.83 mg/kg; i.p.) on spontaneous horizontal locomotor activity at a) 6 h (N = 8 per group) and at b) 24 h post-administration (N = 6 per group); c) LPS-induced behavioural despair was assessed by measuring immobility duration in the FST at 24 h post-injection in the absence of apparent deficits in locomotor activity (Males: N = 7 VEH; N = 8 LPS, and females: N = 7 VEH; N = 9 LPS). *p < 0.05; ***p < 0.001 differences between LPS- and VEH-treated mice of the same sex; $^{+++}$p < 0.001 main effect of LPS treatment in 2-way ANOVAs.

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