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Review article

Comparison of bacterial lipopolysaccharide-induced sickness behavior in rodents and humans: Relevance for symptoms of anxiety and depression

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ABSTRACT

Increasing evidence from animal and human studies suggests that inflammation may be involved in mood disorders. Sickness behavior and emotional changes induced by experimental inflammatory stimuli have been extensively studied in humans and rodents to better understand the mechanisms underlying inflammation-driven mood alterations. However, research in animals and humans have remained compartmentalized and a comprehensive comparison of inflammation-induced sickness and depressive-like behavior between rodents and humans is lacking. Thus, here, we highlight similarities and differences in the effects of bacterial lipopolysaccharide administration on the physiological (fever and cytokines), behavioral and emotional components of the sickness response in rodents and humans, and discuss the translational challenges involved. We also emphasize the differences between observable sickness behavior and subjective sickness reports, and advocate for the need to obtain both subjective reports and objective measurements of sickness behavior in humans. We aim to provide complementary insights for translational clinical and experimental research on inflammation-induced behavioral and emotional changes, and their relevance for mood disorders such as depression.

1. Introduction

In this mini-review, we provide a short historical introduction of the concept of sickness behavior and of the links between sickness behavior and symptoms of depression in the past 30 years (part 1.1), and introduce the model of LPS-induced experimental inflammation (part 1.2). Then, we provide a comparison of LPS-induced physiological changes, such as cytokine production and fever induction (part 2), LPS-induced sickness behavior, focusing on reduced activity/increased fatigue, lowered food consumption and appetite, and social withdrawal (part 3), and LPS-induced mood-related changes, such as depressive-like and anxiety-like behaviors (part 4) between animals and humans. We end with the conclusion that, in spite of difficult points of comparison, there are many similarities between animal and human sickness behavior (Fig. 1) and recommendations for future research (part 5).

1.1. Sickness behavior and symptoms of depression

The idea that systemic inflammation can modify behavior, as for example during severe bacterial infections, was suggested already in the nineteenth century when William Osler proposed apathy as a diagnostic criterion of 'progressive septicaemia' (Osler, 1892). In the 1960s, Ned Miller observed that the peripheral administration of bacterial endotoxin lowered rodents' efforts to receive a reward, and related this to his own "paralysis of initiative" when he had the flu (Miller, 1964). The bacterial endotoxin was later discovered to contain lipopolysaccharide (LPS), a cell wall component of Gram-negative bacteria (Beutler, 2002). Twenty-four years later, Benjamin Hart described "sickness behavior" by stating that "the sleepy or depressed or inactive animal is less motivated to move about using energy that could fuel metabolic increases associated with fever" (Hart, 1988). In his review, Hart provides a table "of the common viral, bacterial, rickettsial and protozoan diseases of domestic animals and people which were stated to be characterized by fever, anorexia and depression (or similar signs)", indicating that sickness behavior is common to many mammals,

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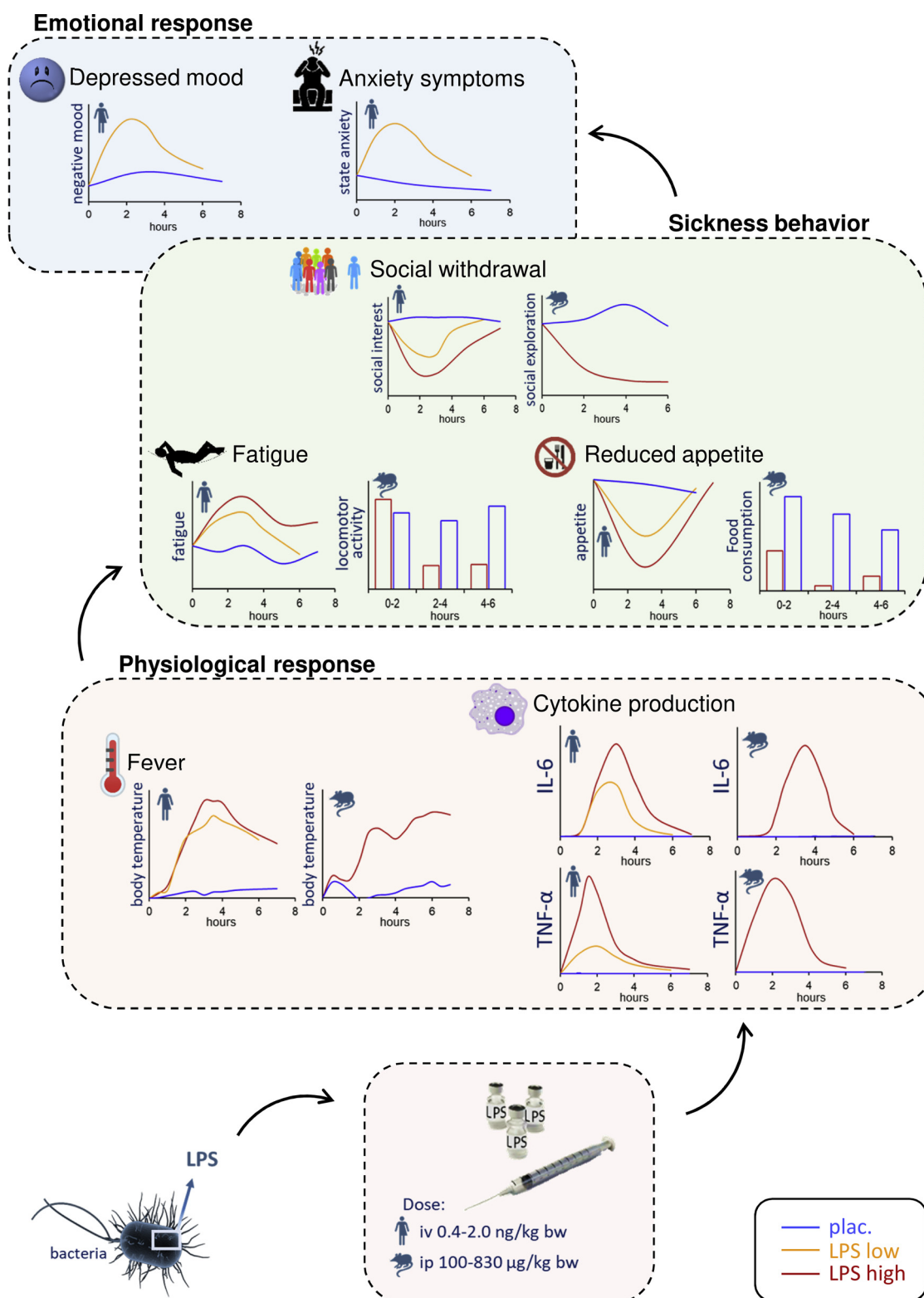
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including humans. He further wrote: “This picture of the lethargic, depressed, anorexic, and febrile individual is not specific to any particular animal species, but is seen in humans and a variety of animals, and the behavioral signs are seen with a variety of systemic diseases as well as with some more localized infections.”

Beyond Hart’s use of the word “depressed”, several authors have indicated links between sickness behavior and depression. One of the

first was Smith’s “macrophage theory of depression”, indicating “the significant association of depression with coronary heart disease, rheumatoid arthritis, stroke and other diseases where macrophage activation occurs” (Smith, 1991). A more articulate formulation regarding sickness behavior was put forward by Raz Yirmiya a couple of years later, when he linked the “behavioral and psychological effects of immune activation” to the DSM diagnostic entity of “depression due to a

Fig. 1. Physiological and behavioral response to LPS in rodents and humans.

Illustration of the physiological and behavioral changes observed in rodents and humans after administration of LPS. In humans, 0.4–2.0 ng/kg body weight of LPS is typically administered intravenously (iv), while in animals studies of sickness behavior, 100–833 µg/kg body weight of LPS is (mostly) injected intraperitoneally (ip), which result in about ten times lower circulating LPS concentration compared to iv administration. The graphs shown were obtained based on our own collected data, except IL-6 and TNF-α in rodents, which were based on data available in the literature. For the human studies, approvals were obtained from the respective ethical committee (reference numbers: regional ethical review board in Stockholm 2015/1415-32, local ethic review board of the University of Duisburg-Essen 15-6503-BO) and volunteers signed an informed consent form after a complete oral and written explanation of the study. All relevant animal experiments complied with European (EU Directives) and North-American (NIH Publications) recommendations on animal research.

The X-axis represents the time after the LPS injection (in hours). Note that the figure is intended to compare the kinetic of the responses, and not for quantitative comparison; thus the Y-axes should not be compared between humans and animals. In humans, the effect of a lower dose (iv 0.8 ng/kg body weight) and a higher dose (iv 2.0 ng/kg body weight) of LPS is reported. In animals (rats), one dose-range of LPS was used for the different panels (ip 200–250 µg/kg). Sickness behavior as defined in part 3 and mood-related changes were assessed. Measures of mood-related changes in animals are per definition secondary interpretations (see part 4) and are thus not depicted here.

Abbreviations: LPS: lipopolysaccharide; plac.: placebo; iv = intravenous; ip = intraperitoneal; bw: body weight; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α. **Pictures credit:** Macrophage: <https://commons.wikimedia.org/wiki/File:Macrophage.svg>; Anxiety: adapted from <https://commons.wikimedia.org/wiki/File:ANXIETY.jpg>.

medical condition” (Pollak and Yirmiya, 2002; Yirmiya, 1996). This idea and further research indicating that the behavioral and emotional changes induced by pro-inflammatory cytokines, including fatigue, social withdrawal, motivational changes, and reduced appetite, are similar to that of clinical depression (Dantzer, 2001; Dantzer et al., 2008; DellaGioia and Hannestad, 2010; Dooley et al., 2018), and that cytokine therapy in the treatment of cancer or chronic viral infections increases the risk of clinical depression (Capuron and Miller, 2004), suggested that inflammatory cytokines could be involved in the development of depression. These findings gave rise to the idea that major depression could be related to elevated peripheral concentrations of cytokines. A meta-analysis found indeed higher concentrations of the cytokines tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in clinically depressed patients compared with healthy controls (Dowlati et al., 2010). Research further suggests that inflammatory pathways may play a role in mood disorders (Arnold et al., 2018; Miller and Raison, 2016), and a recent meta-analysis suggests that inflammatory processes alter brain functions, predisposing patients with inflammatory diseases to mood disorders (Kraynak et al., 2018). Moreover, observations that conditions such as obesity and post-traumatic stress disorder, known to be associated with increased incidence of depression, are accompanied by so called low-grade inflammation, are also in accordance with the idea that inflammation contributes to clinical depression (Castanon et al., 2014; Passos et al., 2015). Finally and interestingly, inflammation has also been proposed as one core mechanism mediating the negative effects of stress and life adversity on health over time (Olvera Alvarez et al., 2018).

Since its initial description by Benjamin Hart, sickness behavior has been described in birds (Owen-Ashley and Wingfield, 2006), fish (Kirsten et al., 2018) and insects (Adamo, 2006; Kazlauskas et al., 2016), suggesting that sickness behavior, like fever, is an evolutionary conserved response. The finding that the manifestation of sickness behavior, experimentally-induced by the administration of bacterial LPS, is moderated by external conditions, such as temperature and food availability (Aubert et al., 1997a,b), subsequently indicated that sickness behavior is the expression of a motivational state (Dantzer and Kelley, 2007). This, along with the observation that mortality is increased in force-fed infected animals (Murray and Murray, 1979), indicated that behavioral changes observed during infection are host responses which, together with physiological changes, contribute to pathogen elimination. Animal research has subsequently focused on unraveling how peripheral pro-inflammatory cytokine signals reach the central nervous system (CNS) and alter brain functions to elicit fever and sickness behavior (Konsman et al., 2002; Quan and Banks, 2007). More recently, human imaging studies have described cytokine- and LPS-induced changes in brain activity (Felger, 2017; Harrison, 2017; Kraynak et al., 2018), and shown substantial overlap with the brain regions activated following LPS administration in animals (Dantzer et al., 2008). This has laid the groundwork for a better understanding of

the mechanisms underlying inflammation-induced behavioral and emotional alterations (Dooley et al., 2018; Schedlowski et al., 2014) and led to propose potential treatment targets of inflammation-associated depression (Miller and Raison, 2016). However, investigations to understand the mechanisms responsible for these inflammation-associated depression-like symptoms have been predominantly performed in experimental animals. This raises the question of whether and to what extent inflammation-induced behavioral and emotional alterations of relevance for depression are indeed comparable between humans and animals. Therefore, we here aim to compare sickness behavior, including specific behavioral alterations such as social withdrawal, fatigue, and reduced appetite, as well as depressive-like and anxiety-like behavior, during experimental inflammatory episodes induced by the peripheral administration of bacterial LPS between rodents and humans.

1.2. Translational issues of the model of LPS-induced experimental inflammation

The peripheral administration of LPS is the most widely used experimental model to induce inflammation and sickness behavior, both in animals and humans. The translational issues to consider are not only if LPS administration in animals is an adequate model of bacterial infection, but also whether and how well the behavioral effects of LPS injection in animals “translate” and compare to LPS-induced sickness behavior in humans. To address these issues, it is useful to consider the criteria that have been put forward to animal models, namely, construct, face and predictive validities (Belzung and Lemoine, 2011; Willner, 1984). Thus, in order to address the “translational trajectory” of interest, one would at least need to address the three following questions: first, is LPS administration a valid model for bacterial infectious diseases (construct validity), second, how well do measures of LPS-induced sickness behavior translate between rodents and humans (face/ethological validity), and third, is LPS-induced sickness behavior in rodents and humans responsive to anti-inflammatory drugs (predictive/remission validity).

Peripheral administration of bacterial LPS mimics important aspects of Gram-negative bacterial infections such as activating the same pattern recognition receptor (i.e. Toll-like receptor 4) (Suffredini and Noveck, 2014). In addition, one of the most reliable host responses to Gram-negative bacterial infection, namely the increase in the circulating concentrations of the acute phase proteins C-reactive protein, is also observed after peripheral LPS injection both in animals and in humans (Engler et al., 2017; Iraz et al., 2015; Kyvelidou et al., 2018). LPS administration thus possesses important construct validity as a model for Gram-negative bacterial infection.

Regarding face validity, it is important to note that we are primarily interested in the question of whether LPS administration is an appropriate model for sickness behavior, which is relevant to understand how

pro-inflammatory cytokines can contribute to symptoms of depression, and only secondarily in the question of whether LPS administration is a good model for human depression. Readers interested mainly in the latter issue are referred to several other reviews: De La Garza, 2005; DellaGioia and Hannestad, 2010; Dooley et al., 2018. In terms of face validity of sickness behavior, it has been shown that LPS administration reproduces the behavioral changes observed after inoculation of bacteria in animals, for example the reduction in water and food intake and the choice of preferred ambient temperature (Lagerspetz and Vaatainen, 1987; Moore et al., 1977; Schaedler and Dubos, 1961). Some of these behavioral changes (in particular decreased general activity, food intake and social interactions) seem, like fever, to be evolutionary conserved from insects to mammals (see above), and resemble those commonly observed in ill humans. They have therefore been considered to reflect an array of behavioral changes that develop in sick individuals, including humans, during infection-induced inflammation (Dantzer, 2001). However, the assumed face validity of the model of LPS administration has been based on the fact that LPS-induced behavioral characteristics in animals *resemble* those in sick humans, but no direct comparison has been made. It is also important to note that, although animal models of CNS and mood disorders are typically modeled after human conditions, the study of sickness behavior has started in animals. One of the main questions to address is therefore to what extent the symptoms and signs that develop in humans after an inflammatory challenge correspond to animal sickness behavior.

Finally, concerning predictive/remission validity, anti-inflammatory drugs, such as dexamethasone, have been shown to reduce the behavioral effect of LPS in animals (De La Garza et al., 2004; Fishkin and Winslow, 1997; Johnson and Von Borell, 1994; Wyns et al., 2015), but this has not been investigated in humans. However, not all NSAIDs reduce LPS-induced behavioral changes (Teeling et al., 2010). Further investigations are therefore needed to validate the predictive validity of this model.

In this review, we do not intend to focus on the construct, face and predictive validities of the model of LPS administration in other domains than that of sickness behavior. In particular, we would like to focus on the issue of face validity of the LPS model as model of inflammation-induced sickness behavior, which is now assumed based only on the fact that behavioral modifications of sick animals resemble those of sick humans, but without direct comparison. Here, we thus want to provide a comprehensive comparison of inflammation-induced changes between animals and humans regarding three aspects: first, LPS-induced physiological changes, such as cytokine expression and fever induction; second, LPS-induced sickness behavior proper, here focusing on reduced activity/increased fatigue, food consumption and appetite, and social withdrawal; third, LPS-induced mood-related changes, such as depressive-like and anxiety-like behaviors. Of note, only behavioral manifestations linked to symptoms of depression and anxiety will be considered here. This is because many depression or anxiety symptoms can be reformulated in simpler concepts/explanations such as behavioral despair or passive coping, and can be operationalized and compared at the behavioral level in animals and humans (Maier and Seligman, 2016; Roelofs, 2017). Other behavioral manifestations such as cognitive changes will not be included here, as many of the cognitive tasks typically used for humans are hard to implement in animals, and the effects of LPS on cognitive functions are not yet fully characterized. We will also discuss some issues that remain to be solved with respect to the concept of LPS-induced sickness behavior in rodents and humans. These are the necessary steps to further characterize the LPS model and will help to make the best use of this model in understanding the mechanisms underlying inflammation-induced mood disorders.

2. LPS-induced cytokine and fever responses in rodents and humans

To be able to compare inflammation-induced behavioral responses in rodents and humans, it is important to first examine the non-behavioral components of the systemic inflammatory response, i.e. the production of cytokines and fever.

In rodents, the systemic pro-inflammatory cytokine response to intravenous (iv) or intraperitoneal (ip) administration of commonly used, sublethal, doses of LPS typically starts with an early rise in the plasma concentration of tumor necrosis factor (TNF)- α that peaks at about 2 h, closely followed by a peak in interleukin (IL)-1 β , and a subsequent maximum rise of IL-6 approximately one hour later (Degre, 1996; LeMay et al., 1990; Waage, 1987; Zuckerman et al., 1989) (Fig. 1). In comparison, after iv administration of LPS to humans, TNF- α peaks at about 1.5–2 h followed by IL-6 peaking 2–3 h after the injection (Benson et al., 2017; Calvano and Coyle, 2012; Coyle et al., 2006; Ferguson et al., 2013; Grigoleit et al., 2011; Kox et al., 2014) (Fig. 1). However, in contrast to rodents, there seems to be no substantial increase in plasma IL-1 β in humans at least for LPS doses up to 2.0 ng/kg (Dorrestijn et al., 2010; Engler et al., 2017). This may partly be related to assay sensitivity, as IL-1 β is typically undetectable in 50–80 % of the cases. Apart from this, and the magnitude of the TNF- α and IL-6 increases, the temporal dynamics of the pro-inflammatory cytokine responses to bacterial LPS in rodents closely resembles those observed in humans (Fig. 1).

The LPS-induced rise in body temperature in humans typically starts 1 h and peaks 3–4 h after the injection (Benson et al., 2017; Calvano and Coyle, 2012; Coyle et al., 2006; Grigoleit et al., 2011; Kox et al., 2014). Importantly, all human studies consistently show a monophasic rise in body temperature after LPS administration, while reports in rodents often describe a pattern with two or more phases of fever (Fig. 1) (Romanovsky et al., 1998; Rudaya et al., 2005). Monophasic fevers can be observed in rodents also, but with lower doses of LPS (1 μ g/kg administered intravenously) (Romanovsky et al., 1996). Moreover, in rodents, low doses of LPS that induce similar increases in circulating concentrations of pro-inflammatory cytokines as in humans are not sufficient to elicit the physiological responses (i.e. fever, tachycardia and hypotension) typically observed in humans (Copeland et al., 2005). In addition, the magnitude of plasma cytokine production observed during comparable LPS-induced physiological responses is much higher in rodents (Degre, 1996; LeMay et al., 1990; Waage, 1987; Zuckerman et al., 1989) than in humans (Benson et al., 2017; Calvano and Coyle, 2012; Coyle et al., 2006; Ferguson et al., 2013; Grigoleit et al., 2011; Kox et al., 2014). Altogether, these data suggest, based on fever as a functional readout, that relatively low doses of LPS are typically used in humans. The doses of LPS used to induce a sickness response in mice or rats (10–1000 μ g/kg body weight, often injected intraperitoneally) are indeed about 10,000–100,000 times higher than those administered to humans (0.4–2.0 ng/kg body weight administered intravenously). This is likely due to inherent differences in the immune system of laboratory rodents and humans (Mestas and Hughes, 2004; Seok et al., 2013). It is also important to keep in mind that wild and pet store mice show much more robust immune responses than specific-pathogen-free lab mice (Abolins et al., 2017; Beura et al., 2016), suggesting that part of the reasons why higher doses of LPS have been used in laboratory rodents is that their immune systems responds less readily than that of their wild counterparts and human volunteers.

Another interesting point of comparison could be the relationships between the levels of cytokines in the blood and sickness behavior. Significant associations between LPS-induced cytokine blood concentrations and sickness behavior have been reported in humans (e.g. Cho et al., 2016; Eisenberger et al., 2009; Grigoleit et al., 2011; Karshikoff et al., 2015; Lasselín et al., 2020a; Moieni et al., 2015; Reichenberg et al., 2001), although such correlations are not always found for all aspects of sickness behavior (e.g. Draper et al., 2017;

Grigoleit et al., 2011; Hannestad et al., 2011; Moieni et al., 2015). These non-significant results could be due to lack of statistical power, but also to the fact that peripheral cytokine concentrations do not exactly reflect inflammatory changes in the brain (Engler et al., 2017). However, blood is often the only tissue that can be obtained from humans for ethical reasons. In animal studies, cytokines levels have been studied in different tissues, and these have indicated that the (patho) physiological relevance of circulating cytokine concentrations is questionable. Cytokines indeed often act locally (Foster, 2001), and the local production of cytokines in proximity to a sensory afferents or within the nervous system may be more relevant for some components of sickness behavior under certain circumstances (Konsman et al., 2002). Some authors have hence questioned the idea that sickness following immune activation is mediated by circulating cytokines (Poon et al., 2013). Thus, it is highly likely that, at least in animals, circulating cytokines are neither relevant nor correlate neatly with LPS-induced sickness behavior. This does not, however, preclude the translational relevance of the LPS model.

Considering that the increase in body temperature involves pro-inflammatory cytokine action on the CNS (Konsman et al., 2002), it is interesting to determine how the fever response concurs with the behavioral sickness response, such as reduced locomotor activity. Interestingly, while decreased activity is indeed observed in rodents during the second phase of biphasic fever after iv administration of higher doses of LPS, increased locomotor activity is encountered when LPS induces a monophasic fever (i.e. at low doses) in rodents (Romanovsky et al., 1996; Tkacs and Li, 1999; Tkacs et al., 1997). Furthermore, reduction in social interactions in rodents typically occur in the presence of biphasic fevers (Konsman et al., 2000). Nevertheless, species-specific sickness behaviors, like food burrowing in mice, have been shown to be already affected by non-pyrogenic doses of LPS (Teeling et al., 2007). Thus, the type of behavioral effects observed in rodents after LPS injection might depend on the level and progression of the inflammatory response, while the doses of LPS used in humans are likely to induce one particular pattern of sickness response.

The observed differences in LPS-induced cytokine and fever responses between rodents and humans urge caution in comparison of rodent and human sickness behavior. Nevertheless, and in spite of the differences in the doses of LPS used and the magnitude of pro-inflammatory cytokine responses induced, similar kinetics of rises in circulating cytokine concentrations and body temperature (+1–2 °C) can be observed in rodents and humans after LPS administration at doses typically used in the respective models Fig. 1. This could indicate that the mechanisms underlying sickness physiology are, at least, in part comparable in rodents and humans.

3. LPS-induced sickness behavior in rodents and humans

Sickness behavior has been defined as the “coordinated set of behavioral changes that develop in sick individuals during the course of an infection” (Dantzer, 2001). It has first been described in rodents that were administered bacterial LPS, and is characterized by changes in sleep patterns (Kadlecova et al., 1972; Krueger et al., 1986; Lancel et al., 1995), a reduction of food intake (Arnold et al., 1989; Aubert et al., 1997b; Holmes and Miller, 1963; McCarthy et al., 1984), of locomotor and exploratory activities (Kozak et al., 1994; Linthorst et al., 1995; Yirmiya, 1996), and of social, maternal and sexual behaviors (Aubert et al., 1997a; Bluthé et al., 1996; Yirmiya, 1996), which typically does not exceed 24 h (Fig. 1).

In humans, reduction in food intake (Reichenberg et al., 2002) and alterations of sleep patterns (Besedovsky et al., 2019; Korth et al., 1996; Mullington et al., 2000; Pollmacher et al., 1993) have also been observed during experimental LPS-induced sickness. However, the majority of studies investigating sickness behavior in humans use self-report assessments. This approach attempts to assess sickness behavior subjectively by addressing, for instance, fatigue, reduced appetite and

social disengagement. For example, the recently developed Sickness Questionnaire (SicknessQ) allows the acute and repeated assessment of subjective ratings of sickness behavior (Andreasson et al., 2019, 2016; Lasselin et al., 2018). Although self-report assessments are usually performed at a lower frequency than for cytokine and body temperature measurements, a clear peak in fatigue, reduction in appetite and reduced social interest can be observed 2–3 h after LPS injection (Fig. 1) (DellaGioia et al., 2013; Draper et al., 2017; Eisenberger et al., 2010; Hannestad et al., 2011; Hermann et al., 1998; Moieni et al., 2015; Lasselin et al., 2020). Six to eight hours after LPS administration, the inflammation-induced malaise is usually back to pre-injection baseline levels.

While LPS-induced signs of sickness in rodents and humans appear to follow similar patterns (Fig. 1), direct comparison between observable sickness behavior in animals and subjective sickness reports in humans must be made with caution. While feeling tired, having lost one's appetite and a decreased interest for social activities is part of the motivational drive to change behavior, subjective experiences of sickness may not necessarily give rise to the kind of overt behavioral changes observed in LPS-injected animals. As it reflects a motivational reorganization of priorities (Dantzer and Kelley, 2007), sickness behavior is moderated by internal and external conditions (Aubert, 1999; Dantzer, 2001; Irwin and Eisenberger, 2017). Thus, the subjective sickness feeling would not necessarily translate into objectively measurable behavioral changes, as objective behavioral changes would be more affected by the context. For instance, sick and tired individuals can overcome a feeling of fatigue and maintain similar physical activity, or even increase it, depending on the motivational priorities (Aubert et al., 1997a; Lasselin et al., 2017; Miller, 1964). Conversely, inferring “feelings” from objective behavioral changes in animals is difficult and reflects a problematic anthropomorphic perspective.

Objective behavioral assessments should not replace subjective assessments in human studies, but studying both reported feelings and observable behavioral changes in studies of sickness in humans is crucial for the comparison of sickness behavior between humans and rodents. Sickness feelings are obviously not directly assessable in rodents and it is thus important to understand whether objective changes correlate with subjective sickness feelings in humans. One example is the feeling of fatigue, which has been modelled using certain physical tasks in rodents (Zhang et al., 2016). However, the notion of fatigue involves several dimensions beyond physical fatigue, such as mental fatigue (e.g. difficulties to concentrate) and altered motivation (Dantzer et al., 2014; Karshikoff et al., 2017) and thus would require several behavioral measures. Moreover, spontaneous fatigue is foremost a feeling and is not always correlated with objective measures of reduced physical or mental performance (Leavitt and DeLuca, 2010). Understanding what type(s) of objective changes (e.g. reduced performance in physical tasks, altered concentration in mental tasks, redirection of expended effort) associate with fatigue intensity after LPS administration would thus help to model the feeling of fatigue during sickness in animals. However, objective overt behavioral changes during experimental sickness in humans is relatively unusual, and have included for instance reduced food consumption (Reichenberg et al., 2002), increased frequency of moans and sighs (Lasselin et al., 2018), increased yawning (Marraffa et al., 2017), reduced walking speed (Lasselin et al., 2020b; Sundelin et al., 2015), and changes in the willingness to expend effort to get a reward (Draper et al., 2017; Lasselin et al., 2017).

The studies on reward have used behavioral tasks analog to the rodent effort-based decision-making tasks, but with conflicting results: one showed reduced incentive motivation during sickness (Draper et al., 2017) and the other increased incentive motivation when the reward was deemed worthwhile (Lasselin et al., 2017). This discrepancy might be explained by differences in task designs. The main difference between the two tasks was that subjects in the former study chose to spend effort to get a reward when the stake was “worth the effort”, while subjects in the latter study had to choose between a low

or high effort tasks and could not rest. Interestingly, a study using a similar effort-based decision making task after LPS administration in rodents found an overall reduced incentive motivation, and a redirection of the remaining effort towards the more valuable reward (Vichaya et al., 2014). It is thus possible that sickness behavior is characterized by reduced incentive motivation, but that, when required, effort will be directed towards rewards with higher value (Vichaya and Dantzer, 2018).

Altogether, these observations highlight the complexity of sickness behavior, but also indicate that sickness behavior likely translates between animals and humans. Objective measurements of sickness behavior in humans, in addition to reports of subjective feelings, would be highly valuable to obtain a more complete picture of sickness behavior. Indeed, sickness behavior was originally investigated in animals, and later studied in humans, however without using comparable measures, i.e. by assessing feelings in humans. Although there is no doubt that sickness feelings largely shape sickness behavior, it is essential to establish links between sickness feelings and objective measures of sickness behavior, in particular if we are to promote translation between humans and animals.

4. LPS-induced depressive-like and anxiety-like behavior in rodents and humans

The majority of studies investigating sickness behavior in humans use self-report assessments of fatigue, reduced appetite and social disengagement, but also mood. Depressive-like and anxiety-like symptoms are aspects of sickness behavior that have been proposed to be of particular relevance for understanding the pathophysiology of inflammation-associated depression (Dantzer, 2018; DellaGioia and Hannestad, 2010; Dooley et al., 2018; Lasselin et al., 2016; Schedlowski et al., 2014).

The first indications in animals that anxiety may be caused by inflammatory stimuli were that sick rodents spent less time in the open arms of an elevated plus maze and in the illuminated part of a light-dark box as well as in exploring a novel object in an open field (Lacosta et al., 1999; Lyte et al., 1998). However, it has been argued that these test could reflect a “natural preference for unlit and/or enclosed spaces” rather than anxiety-like behavior (Ennaceur and Chazot, 2016). In addition, injection of LPS or IL-1 β also results in less exploration of other areas of these devices (Swiergiel and Dunn, 2007), suggesting that the observed effects may reflect reduced locomotion. Nevertheless, LPS-injected rodents also show more immobility and alarm vocalization calls, which support the notion that this immune challenge favors anxiety-like behaviors (Bassi et al., 2012).

Descriptions of behavioral changes after LPS administration in rodents (Bluthe et al., 1994; Johnson et al., 2005; Konsman et al., 2000, 2008; Marvel et al., 2004; Romanovsky et al., 1996; Segreti et al., 1997; Swiergiel et al., 1997; Tollner et al., 2000; Watanabe et al., 2004) often seem to follow dictionary definitions of depression as “a lowering of physical or mental vitality or of functional activity” (e.g. <https://www.merriam-webster.com/dictionary/depression>). Based on the findings that chronic, but not acute, administration of the antidepressant imipramine in rats attenuated the LPS-induced reduction in food intake, social interaction, activity and anhedonia, a link was proposed between sickness behavior and clinical depression (Yirmiya, 1996). However, a subsequent study in mice showed that chronic antidepressant treatment did not alter the reduction in sweetened milk or food intake after administration of LPS or IL-1 β (Dunn and Swiergiel, 2001). In addition, it has been argued that LPS increases aversive properties and decreases appetitive properties of mixed tastes without necessarily affecting the capacity to experience pleasure (Aubert and Dantzer, 2005). Moreover, food-restricted mice trained to nose-poke for food display a proportionally greater reduction in pokes for regular grains as compared to chocolate pellets 24 h after peripheral LPS administration (Vichaya et al., 2014). This finding suggests that LPS-induced inflammation

alters the willingness to work for reward (incentive motivation) rather than reduce the sensitivity to reward (anhedonia), as also indicated by human data (Draper et al., 2017; Lasselin et al., 2017). This may also explain how LPS and pro-inflammatory cytokines reduce rodents' highly reinforcing self-stimulation of the medial forebrain bundle (Anisman et al., 1998; Borowski et al., 1998; van Heesch et al., 2013). Of relevance for depression, both animal and human studies thus indicate that LPS alters incentive motivation.

Employing animal tests, such as the Porsolt forced swim test (FST) or the tail suspension test (TLT), to assess so-called helplessness or behavioral despair as features of depression is complicated by the fact that administration of LPS or IL-1 β leads to a general reduction in locomotor activity (Biesmans et al., 2013; Dunn and Swiergiel, 2005). Nevertheless, the idea that LPS-induced behavioral changes would be related to depressive symptoms, independently from sickness behavior as defined in the prior section, emerged from work showing that ip injection of high doses of LPS increased immobility of mice in the FST or TLT one day and up to one month later, when typical sickness behaviors, like reduced locomotor activity and food intake, had waned (Anderson et al., 2015; Frenois et al., 2007). The depressive-like effect of LPS appears however more complex, as lower doses of LPS that reliably induce sickness behavior were not found to increase immobility in the FST, even 24 h later (Deak et al., 2005). Furthermore, Renault and Aubert (2006) showed that mice display more active climbing 1.5 h after injection, although they did confirm the increased immobility during the FST one day after an ip injection of a moderate dose of LPS. More generally, some authors consider increased immobility in the FST an adaptive passive coping strategy rather than a measure of behavioral despair (Commons et al., 2017; Molendijk and de Kloet, 2015). It would therefore be intellectually honest to indicate alternative interpretations, such as passive coping, rather than depressive-like behavior, when employing such tests, without precluding the relevance of such models for inflammation-associated depression.

Animal studies of depressive- and anxiety-like behavior after LPS administration are thus confronted to the difficulty to capture feeling-based features of human behaviors associated with emotion and mood. Indeed, the question of anxiety-like and depressive-like behavior in animals depends on which behavioral changes are considered to reflect depression and anxiety. As a consequence, it seems that only studies on LPS administration in human volunteers can solve the question if and, if so, which behavioral changes reflect depression and anxiety. To this aim, and as for sickness behavior, assessment of both feelings and observable behavioral changes in humans are thus important to better understand inflammation-induced anxiety- and depressive-like behavior.

In humans, negative mood and anxiety symptoms after administration of LPS are clearly present as measured by self-reports. Individuals receiving LPS report an increase in negative mood as well as in state anxiety within hours after the injection (see Fig. 1 and Benson et al., 2017a, Benson et al., 2017b; Eisenberger et al., 2010, 2009; Engler et al., 2016, 2017; Lasselin et al., 2016; Moieni et al., 2015; Reichenberg et al., 2001; Wegner et al., 2014). These symptoms are acute responses to the internal detection of pathogen-associated molecules patterns and do not meet clinically-used diagnostic criteria for anxiety and depression. However, these studies collectively present compelling evidence demonstrating the ability of inflammatory mediators to potentiate negative emotions (Lasselin et al., 2016). However, contrary to the behavioral changes observed in the FST and TLT in rodents administered high doses of LPS (Dantzer et al., 2008), negative mood and anxiety do not persist 24 h after LPS administration in humans and occur at the same time as sickness feelings. In addition, depressive-like behavior in rodents appears to relate to changes in serotonin biosynthesis (O'Connor et al., 2009) and CNS transporters (Zhu et al., 2010), but the (plasma) kynurenine pathway did not appear to mediate the relationship between LPS-induced cytokines and depressed mood in a recent study in humans (Kruse et al., 2019). Furthermore,

pre-treatment with a selective serotonin reuptake inhibitor anti-depressant appear not to fully prevent LPS-induced depressive-like behavior, particularly negative mood symptoms, in humans (Hannestad et al., 2011). Further characterization of depressive- and anxiety-like features induced by inflammation is thus needed in humans. This is crucial to determine which tests can be used in animals to capture the emotional features of sickness behavior (Monteggia et al., 2018).

Overall, it seems that LPS-induced depressive- and anxiety-like behaviors cannot be compared in a straightforward manner between humans and animals. Although both animal (Dantzer et al., 2008; De La Garza, 2005) and human (Dooley et al., 2018) studies using LPS administration have allowed to characterize inflammation-induced brain changes of potential relevance for depression, it is unclear whether the molecular mechanisms of depressive- and anxiety-like behavior observed in rodents are similar to those underlying negative mood and state anxiety symptoms in humans after LPS administration. One crucial aspect of animal studies is the fact that depressive-like behavior in animals can often only be assessed once reduced locomotor activity has subsided. So far, and to the best of our knowledge, only high, sepsis-like, doses of LPS appear to induce long-term depressive-like behavior, but not milder doses that would allow a comparison with humans' depressive-like behavior, unless the comparison would be the long-term consequences of severe bacterial sepsis on mood (which is a highly relevant, but much more circumscribed question).

5. Conclusion

In the present review, we have compared LPS-induced behavioral changes in animals and humans using circulating pro-inflammatory cytokines and fever as potential points of comparison. Sickness behaviors (reduced activity/fatigue, reduced food consumption/reduced appetite, and social withdrawal) and mood-related changes (depressive-like and anxiety-like behavior) after LPS administration in humans and animals were compared, revealing many similarities (Fig. 1). However, several considerations to promote the translation of LPS-induced sickness behavior between animals and humans should be considered. First, there is a clear lack of objective measurements of sickness behavior in humans. Although sickness feelings are an essential part of sickness behavior, measuring objective changes that occur and correlate with sickness feelings and mood alterations in controlled experimental human studies would allow to further understand LPS-induced behavioral changes observed in animals. Along these lines, it is important to determine the effect of various contexts on LPS-induced behavioral changes to unravel the complexity of sickness behavior. Second, animal studies could derive tests of depressive- and anxiety-like behaviors during sickness from the objective changes observed in humans and that are linked to symptoms of depression and anxiety, and translate back to animal models. Interestingly enough, this would close the loop of the translation of sickness behavior from rodents to humans back to rodents. Finally, studies in animals need to determine whether depression-like behavior only occurs at relatively high doses of LPS, as indicated by findings obtained in the FST, or whether such behavior can be observed in other tests after administration of lower doses of LPS. A better understanding of the effects of mood-targeting therapies on inflammation-induced depressive- and anxiety-like behavior, in particular in humans, would also be valuable. Depressive-like behavior was found to be blocked by antidepressants targeting serotonin (Dong et al., 2016; Ohgi et al., 2013; Yirmiya et al., 2001) as well as by ketamine (Ji et al., 2019; Verdonk et al., 2019) in rodents. This remains however unclear in humans. Pre-treatment with a serotonin-reuptake inhibitor was found to reduce LPS-induced fatigue, but not mood symptoms (Hannestad et al., 2011), while a norepinephrine-dopamine reuptake inhibitor did not have any effect on LPS-induced sickness behavior (DellaGioia et al., 2013). However, only two studies using pre-treatment with antidepressants have been conducted and further studies are needed. Consideration of these points would create improved conditions for

translational research in which both animal and human research can fully take their part, and would put the scientific community in a better position to understand the neuroimmune dysregulation that may be a part of mood disorders, such as clinical depression.

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Declaration of Competing Interest

None.

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