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ORIGINAL ARTICLE

What Animal Models Can Tell Us About Long-Term Psychiatric Symptoms in Sepsis Survivors: a Systematic Review

Felipe Dal-Pizzol[1] · Gabriela Ferreira de Medeiros[2] · Monique Michels[1] · Aurélien Mazeraud[3] · Fernando Augusto Bozza[4] · Cristiane Ritter[1] · Tarek Sharshar[2,3,5]

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Abstract

Lower sepsis mortality rates imply that more patients are discharged from the hospital, but sepsis survivors often experience sequelae, such as functional disability, cognitive impairment, and psychiatric morbidity. Nevertheless, the mechanisms underlying these long-term disabilities are not fully understood. Considering the extensive use of animal models in the study of the pathogenesis of neuropsychiatric disorders, it seems adopting this approach to improve our knowledge of postseptic psychiatric symptoms is a logical approach. With the purpose of gathering and summarizing the main findings of studies using animal models of sepsis-induced psychiatric symptoms, we performed a systematic review of the literature on this topic. Thus, 140 references were reviewed, and most of the published studies suggested a time-dependent recovery from behavior alterations, despite the fact that some molecular alterations persist in the brain. This review reveals that animal models can be used to understand the mechanisms that underlie anxiety and depression in animals recovering from sepsis.

Key Words Sepsis · long-term sequelae · psychiatric symptoms · animal models · anxiety · depression

Introduction

Although the number of deaths associated with sepsis has decreased in recent decades [1–3], sepsis is still a major health problem worldwide [4]. Lower mortality rates imply that more patients are discharged from the hospital, but sepsis survivors often experience sequelae, such as functional disability, cognitive impairment, and psychiatric morbidity [5, 6]. Few interventions have been designed to improve quality of life among survivors of sepsis [7–11], often with poor results. Nevertheless, the mechanisms that result in these long-term disabilities are not fully understood [12–15]. In this context, animal models are often important to use in understanding the mechanisms of these long-term disabilities and to develop new therapeutic strategies for these patients.

Psychiatric syndromes are often observed in sepsis survivors. Patients discharged from an intensive care unit (ICU) report a high prevalence of anxiety, depression, and posttraumatic stress disorder (PTSD) symptoms [5]. Recent meta-analyses indicate that one-third of ICU survivors develop anxiety and depressive symptoms, and one-fifth experience clinical

Felipe Dal-Pizzol and Gabriela Ferreira de Medeiros contributed equally to this work.

✉ Felipe Dal-Pizzol
fdpizzol@gmail.com

[1] Laboratório de Fisiopatologia Experimental, Programa de Pós-Graduação em Ciências da Saúde, Universidade do Extremo Sul Catarinense, 88806-000 Criciúma, Brazil

[2] Laboratoire de Neuropathologie Expérimentale, Institut Pasteur, 75015 Paris, France

[3] Laboratory of Experimental Neuropathology, Institut Pasteur, 75015 Paris, France

[4] Laboratório de Medicina Intensiva, Instituto Nacional de Infectologia Evandro Chagas (INI), Fundação Oswaldo Cruz (FIOCRUZ), 21040-360 Rio de Janeiro, Brazil

[5] Department of Neuro-Intensive Care Medicine, Sainte-Anne Hospital, Paris-Descartes University, 75015 Paris, France

PTSD symptoms [16–18]. All of these psychiatric disorders can persist for 1 year or more and are more prevalent in patients who had preexisting psychopathologies, presented psychological disorders at ICU admission, and had memories of delusional experiences during their ICU stay [16–18]. Interestingly, most ICU-related factors—such as severity of illness, diagnosis, and length of stay—have a slight impact on long-term psychiatric outcomes [16–18]. However, some observational studies have pointed out sepsis as an independent risk factor for stress disorders after critical illness [19–21].

It seems clear that sepsis elicits long-term psychiatric symptoms/syndromes that worsen a patient's quality of life, and it is still not clear whether their mechanisms are the same as those of the depressive and anxiety disorders of psychiatric patients. The effectiveness of classic treatments in the sepsis survivor population is also still in question. For example, a retrospective study showed that the *de novo* initiation of antidepressant medications in patients who were in treatment before ICU admission did not substantially decrease the prevalence of post-ICU depression [22].

Considering the extensive use of animal models in the study of the pathogenesis of neuropsychiatric disorders [23–25], it seems relevant to adopt this approach to improve our knowledge on postseptic psychiatric symptoms. This could also lead to the identification of effective therapies to preemptively prevent or treat candidates for post-ICU psychiatric symptoms. With the purpose of gathering and summarizing the main findings of studies using animal models of sepsis-induced psychiatric symptoms, we performed a systematic review and a critical appraisal of the literature on this topic.

Methods

We searched the PubMed and Medline databases for papers published between 1975 and December 2018 using combinations of words or terms that included "sepsis[MeSH Terms] OR sepsis-associated encephalopathy[MeSH Terms] OR systemic inflammatory response syndrome [MeSH Terms] OR endotoxemia[MeSH Terms] OR lipopolysaccharides (LPS) [MeSH Terms] OR cecal ligation[MeSH Terms]" AND "mental disorders[MeSH Terms] OR anxiety[MeSH Terms] OR anxiety disorders[MeSH Terms] OR mental health[MeSH Terms] OR depression[MeSH Terms] OR depressive disorder[MeSH Terms] OR affective disorder[MeSH Terms] OR stress disorder[MeSH Terms] OR mood disorder[MeSH Terms] OR attention[MeSH Terms]" limited in species to "other animals." Two independent investigators identified relevant articles by reading their titles and abstracts and included any article that used as an outcome a task that measures affective domains (for example, anxiety, depression, PTSD). Tasks that overlapped cognitive and affective domains were not included. If there was no agreement between the 2 investigators, a third researcher gave the final decision. Abstracts and articles that were not written in English were excluded. The selected publications were then read, and the pertinent publications were identified. Among these criteria, 6279 publications were identified, 284 of which were selected based on their titles and 140 of which were chosen based on the manuscripts. From these 140 articles, 7 used a low-LPS dose to investigate acute (few minutes/hour after LPS injection) sickness behavior, and therefore, these were not included in the analyses.

Results

Different animal models usually look at different behavioral domains, such as locomotion/exploration, defensive responses, anhedonia, and attempt to escape. In this sense, the use of different models is usually necessary to fully characterize a behavioral phenotype or the effect of a specific intervention. In addition, acknowledging the influence of environmental and animal-related aspects—such as species, age, sex, diet, housing situation, and stress levels—is of great importance when working with animal models. It is important to note that most models of rodent behavior have been optimized for the rat. Yet, due to the not-so-recent expansion of the mouse model, mainly due to its success in the genetic engineering field, these models were adapted to mice testing.

Anxiety

Anxiety and fear produce similar behavioral responses, including increased vigilance, freezing and/or hypoactivity, elevated heart rate, and suppressed food consumption [26]. These traits are crucial to survival and are therefore highly conserved throughout evolution, facilitating the recognition and extrapolation of anxiety-related behavior from rodents to humans. Overall, the literature suggests that the amygdala mediates fear-like behaviors to short, discrete, and proximal aversive cues, whereas the bed nucleus of the stria terminalis (BNST) mediates anxiety-like or worry-like behaviors [27], but area specificity could also be influenced by the specificity of each anxiety task. Over a dozen different tasks are available for studying anxiety and drug discovery for anxiety treatment [28], in addition to several adaptations of these tasks. Among these, 3 anxiety-related defense behavior assays that specifically aim to measure rodent anxiety have been widely adopted, which are also referred to as "approach-avoidance conflict tests": the elevated plus maze (EPM), the light–dark box (LDB), and the open field (OF) [28]. All 3 tests measure unconditioned responses based on the innate conflict between the animals' natural drive to explore novelty and their aversion toward elevated, bright, and open zones, respectively [29]. A recent meta-analysis investigated the effects of diazepam on these 3 anxiety paradigms and revealed a large effect of this drug on these tests [25], most

consistently observed in EPM and LDB [25]. It is important to note that there is strong EPM-LDB and OF-LDB assay concordance, but EPM and OF do not reproduce each other's evaluation of anxiety [25]. Other less frequently used models of unconditioned responses linked to anxiety include the predator odor aversion, measures of ultrasound vocalization (after maternal separation, for example), novelty suppressed feeding, the hole-board test, and the marble burying test. Furthermore, some models of conditioned responses have also been developed. They usually involve the pairing of a previously neutral stimulus with an aversive one, and the resulting avoidance/defense behavior is the output associated with anxiety. These tests are not the first choice for the study of anxiety due to confounding effects of motivational and perceptual states arising from interference with learning/memory, hunger/thirst, or nociceptive mechanisms intrinsic to these models [30].

It has been empirically suggested that inconsistencies between anxiety tests may result from the influence of environmental factors, including animal suppliers, handling experimenters, apparatus structure and color, illumination and light/dark cycle, and even the size of the water bottle orifice, although the extent of their contributions is controversial [30, 31]. Some vigorous environmental stressors, such as bodily restraint, social isolation, and pain, have indeed been shown to exert physiological effects on animals and lead to anxiety-like states [30, 31]. Some authors have claimed that these tasks can be considered, at best, tests of natural preference for unlit and/or enclosed spaces because even the sensitivity to the anxiolytic effects of benzodiazepines was shown to vary among strains of mice and among anxiety tests [25, 30]. Furthermore, given that these tasks cannot be performed simultaneously with the same animal, instant sources of variation can influence them and even overrule other a priori robust effects [25]. To minimize some of these influences, several alternative anxiety-related tasks, such as the 3D maze [32], the elevated platform [33], and an integrative platform using EPM, LDB, and OF [33], have been proposed. Still, there is no ideal animal model of anxiety, and each existing test has important limitations. It seems like the best choice to study anxiety in animal models is to use multiple tests so that different facets of this same trait are assessed. Additionally, combining these tests with different pharmacological treatments, modulating their aversiveness, and testing animals with different genetic backgrounds might help obtain a clearer picture of the mechanisms underlying anxious behaviors in rodents [33].

Assuming the small overlap between the emotional aspects reflected by each different anxiety test, another relevant question is which anatomic sites each of these tasks activate. Overall, the literature suggests that the amygdala mediates fear-like behaviors to short, discrete, and proximal aversive cues, whereas the BNST mediates anxiety-like or worry-like behaviors [34], but area specificity could be also influenced by the specificity of each anxiety task. Acute activation of mPFC excitatory neurons evoked a significant decrease in anxiety-like behavior selectively in EPM but not in the OF, enhancing activation of the infralimbic, prelimbic, and cingulate subdivisions of the mPFC [34]. This was also accompanied by the activation of downstream circuits, namely the claustrum, lateral septum, bed BNST, amygdala, and hippocampus CA1 [34]. There were no changes in the nucleus accumbens, CA2, or DG [35]. IL-33 knockout mice, which naturally exhibit reduced anxiety-like behaviors (evaluated in the EPM and OF), display increased activation in the mPFC and amygdala after being submitted to the EPM [36]. Other differences between EPM and OF were observed when testing kisspeptin receptor-deleted (KISS1R-KO) male mice [37], which present behavioral alterations in the EPM but not in the OF [37]. It was suggested that GABAergic control over nigrostriatal and mesolimbic dopamine levels influenced the behavior observed in the OF test [25]. Additionally, the central amygdala, hippocampus, globo palidus, and prelimbic cortex are important for the anxiogenic effect in the OF [25]. Differences between EPM and LDB are also widely described [25, 33]. Regardless of the different zones influencing these tests, the amygdala plays a central role in anxiogenic symptoms, integrating information from cortical and thalamic sensory inputs to generate fear and anxiety-related behavioral outputs. Among its multiple subdivisions, the basolateral amygdala (BLA) and the central amygdala (CeA) are particularly important in anxiety processing [38]. More complete reviews on anxiety tasks have been published elsewhere [32–34].

Depression

In humans, depression is diagnosed based on a complex cluster of highly variable symptoms. In addition to depressed or irritable mood, depression includes cognitive, emotional, homeostatic, and psychomotor symptoms, and only a subset of these symptoms can objectively be measured in rodents [39]. There are many behavioral paradigms for the study of depression, and these models usually rely on behavioral readouts that can be assessed through simple behavioral tasks and that can be extrapolated as an index of the animal's emotional state. Some models originated from the observation that stress and adverse psychosocial experiences often precede the onset or predict the recurrence of depressive episodes. The resignation latency in "despair" tests has been extensively shown to be delayed or normalized by antidepressants [40, 41]. Reductions in "positive affect" and hedonic capacity, features commonly observed in depression and that contribute to the complex construct of anhedonia, have also been modeled [42]. Finally, a trait that is often assessed as a depression-related index is the socioaffective function [43]. The 2 behavioral tests most commonly used to study depression in rodents are the forced swim test (FST) and the tail suspension test (TST), which were originally designed to predict antidepressant efficacy [44, 45]. Although it is argued by some that these tests

have some face validity—the behavioral despair exhibited in response to an inescapable stressor—whether this aligns with the human condition is not clear [46, 47]. Alternative approaches modeling different traits present in depressive disorders are also used, such as tests assessing "positive affect" and hedonic capacity, features commonly observed in depression and that contribute to the complex construct of anhedonia. In fact, the preference of rodents for sweetened solutions has long been explored in science, and the first reports of decreased sucrose preference associated with depressive states date from the last century [42]. Paradigms such as the social defeat and chronic stress procedures are known to induce deficits in sucrose consumption [48]. However, it is not clear whether the form of anhedonia seen in depressed patients is the same deficit recorded in animals [46, 47, 49]. The splash test evaluates the amount of grooming performed by rodents, which can have different meanings according to the stress status of the animal. It has been shown that spray-induced grooming is negatively correlated with the duration of immobility in the FST [50] and would hence reflect an index of depressive-like behavior in the form of "self-care." Some new tests are being developed to fill other aspects of human depression that are not covered by the aforementioned tests. The affective bias test (ABT) uses associative learning between a specific cue and a reward to test the influence of the affective state at the time of learning on the subsequent relative valuation of that reward [51]. Moreover, the judgment bias task (JBT) tests affective biases linked to decision-making behavior by evaluating the animals' interpretation of information within the context of positive or negative associations [52]. Finally, another trait that is often studied as a depression-related index is the socioaffective function, mainly assessed through the animals' vocalizations in different experimental settings [53].

As far as neuroanatomy is concerned, the FST shares some common neuroanatomic sites with human depression [54]. The activity of specific mPFC and mesolimbic dopaminergic circuits is important for the transition between active and passive behavioral states [54]. The ventral tegmental area (VTA) and its dopaminergic projections are also implicated in immobility in the FST [55], and pathways from the ventral hippocampus and basolateral amygdala regulate VTA dopamine neurons controlling the coping response [55]. FST also activates neurons (determined by the induction of FOS and glucose uptake) in relevant brain regions, mainly in the limbic cortical regions, lateral septum, medial amygdala, and paraventricular nucleus of the hypothalamus [54–56]. However, imipramine was only shown to block FOS and glucose uptake in the lateral septum but not in the cortical regions [57]. Similarly to the FST, the TST also shares some neuroanatomic similarity with human depression. TST exposure significantly activates a number of brain regions within the limbic telencephalon, hypothalamus, and brain stem, including the amygdala, but not in the hippocampus [58]. Pretreatment with antidepressants modulated neuronal activation mainly in the infralimbic cortex, lateral septal nucleus, ventrolateral preoptic nucleus, and solitary nucleus [58]. Finally, converging evidence from both rodent and human studies supports that alterations in the brain reward system underlie the anhedonia observed in rodents and humans. Mice that were exposed to social defeat developed anhedonia [59]. This phenotype was associated with increased neural activity in the prefrontal cortex, cingulate cortex, hippocampal formation, septum, amygdala, and hypothalamic nuclei [59]. The VTA and its dopaminergic projections are also relevant to sucrose preference [60], and the amygdala seems to play a central role in this behavior [61]. Additionally, the hippocampus seems to modulate sucrose preference in a SIRT6-dependent pathway [62].

Discussion

Endotoxins were described over a hundred years ago as toxins released by bacteria into their surrounding environment, but their role in the development of septic shock was only suggested halfway through the twentieth century [63]. Ever since, several studies have addressed the consequences of the exogenous administration of endotoxin via several routes—mostly intraperitoneal but also intravenous and intratracheal—and on different species, from rodents to humans. Endotoxin models are the most widely used, are the easiest to perform, and produce the greatest homogeneity among all *in vivo* models of sepsis [64]. In these models, the overwhelming innate immune response triggered by the administration of endotoxins has some similarities with human sepsis, although some noteworthy differences exist, such as hemodynamic alterations (low cardiac output and high vascular resistance) and the cytokines kinetics [64].

Most of the studies evaluated here induce sepsis by a single LPS injection in different mice strains (ICR, BALBc, C57BL/6, Swiss, and CD-1). Less than 15% of the studies injected LPS in rats. Additionally, in more than 95% of the studies, LPS was obtained from *E. coli* (0127:B8, 0111:B4, and 055:B5), and the dose range was generally from 0.1 to 0.83 mg/kg (about 90%), mostly delivered intraperitoneally (about 90%). Few studies used an LPS dose high enough to induce mortality (only 3 described mortality rate), a feature that could be expected in sepsis studies. Depressive- or anxious-like behaviors were measured mostly within the 24 h following LPS administration (in more than 90% of the studies), and this is another strong limitation if one intends to study the long-term effects of systemic inflammation. Table 1 summarizes the studies that use LPS as a model of sepsis.

The vast majority of the studies investigated both anxiety and depressive behavior 24 h after LPS administration. The effect of LPS administration in inducing anxiety- and depressive-like behavior at this time point was robust, regardless of the species (rat or mice), strain, or gender. It seems

Table 1 Studies that administered 1 single LPS dose in adult animals

Author	LPS dose	Time after LPS behavior evaluation (days)	Evaluated task	Result	Mechanisms
Semmler et al. 2007 [65]	10 mg/kg	84	OF	Worse performance	Reduction of density of neurons the CA1, CA2 region and prefrontal cortex
Anderson et al. 2015 [66]	5 mg/kg	30 to 60	Marble burying	Not altered	Microglia activation in the hippocampus
		30 to 60	Hiponeophagia	Not altered	
		30 to 60	EPM	Worse performance	
		30 to 60	FST	Not altered	
		30 to 60	TST	Worse performance	
		30 to 60	Sucrose	Worse performance	
Bossú et al. 2012 [67]	5 mg/kg	7	EPM	Not altered	TNF-α persistent with contribution of IL-18
		7	OF	Not altered	
		280	EPM	Not altered	
		280	OF	Not altered	
Zhu et al. 2017 [68]	5 mg/kg	25	Sucrose	Worse performance	NRLP3 activation
		28	TST	Worse performance	
		29	FST	Worse performance	
Yamawaki et al. 2017 [69]	5 mg/kg	7	FST	Worse performance	Microglial activation and increase of IL-1β and TNF-α levels
Aguilar-Valles et al. 2014 [70]	2.5 mg/kg	1	FST	Worse performance	Brain neutrophil transmigration and increase of IL-1β levels
		2	FST	Worse performance	
		3	FST	Not altered	
		4	FST	Not altered	
Sekio et al. 2015 [71]	2.4 mg/kg	1	FST	Worse performance	Downregulation of α1-adrenoceptor and inflammation
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
		2	Sucrose	Worse performance	
Jeon et al. 2017 [72]	1.8 mg/kg	1	TST	Worse performance	NRLP3 activation
Ismail et al. 2013 [73]	1.5 mg/kg	1	FST	Worse performance	Hormonal alterations
		2	TST	Worse performance	
Yu et al. 2018 [74]	1.2 mg/kg	1	FST	Worse performance	Activation of p38/JNK signaling pathway
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
Ming et al. 2015 [75]	1 mg/kg	140	TST	Not altered	Increase in acetylcholinesterase activity
Sriram et al. 2016 [76]	1 mg/kg	0.12	EPM	Worse performance	Increase of PARP-1 expression and decrease of BDNF in hippocampus
		0.12	LD	Worse performance	
		0.12	OF	Worse performance	
		1	FST	Worse performance	
		2	TST	Worse performance	
Zhang et al. 2016 [77]	1 mg/kg	0.6	FST	Worse performance	Increased of IL-1β and HO-1 in the hippocampus
		0.6	TST	Worse performance	
		1	FST	Worse performance	
		1	TST	Worse performance	
Li et al. 2017 [78]	1 mg/kg	2	EZM	Worse performance	Peripheral inflammatory, mainly IL-1β
		5	Sucrose	Worse performance	
		3	FST	Worse performance	
Bhatt et al. 2017 [79]	0.83 mg/kg	7	EPM	Worse performance	Kynenurine pathway

Table 1 (continued)

Author	LPS dose	Time after LPS behavior evaluation (days)	Evaluated task	Result	Mechanisms
		7	LD	Worse performance	
Camara et al. 2015 [80]	0.83 mg/kg	1	E0M	Worse performance	NFκB activation, subsequent production of TNF-α, and microglial activation
Campos et al. 2016 [81]	0.83 mg/kg	1	FST	Worse performance	Activation of proinflammatory cytokines within the hippocampus
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
Frenois et al. 2007 [82]	0.83 mg/kg	1	FST	Worse performance	IDO activation and cytokines
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
		2	Sucrose	Not altered	
		3	Sucrose	Not altered	
		4	Sucrose	Not altered	
Gawali et al. 2016 [83]	0.83 mg/kg	1	FST	Worse performance	Increase in IL-1β, TNF-α, and oxidative stress
		1	TST	Worse performance	
Ge et al. 2015 [84]	0.83 mg/kg	1	FST	Worse performance	Overproduction of proinflammatory cytokines
		1	TST	Worse performance	
		2	Sucrose	Worse performance	
Hall et al. 2016 [85]	0.83 mg/kg	1	FST	Worse performance	PARP-1 overexpression and increase of proinflammatory cytokines and oxidonitrosative stress in the hippocampus
		1	TST	Worse performance	
Jangra et al. 2016 [86]	0.83 mg/kg	0.12	EPM	Worse performance	Oxidonitrosative stress, neuroinflammation, and reduced level of neurotrophins
		0.12	LD	Worse performance	
		0.12	OF	Worse performance	
		1	FST	Worse performance	
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
Jangra et al. 2014 [87]	0.83 mg/kg	0.12	LD	Worse performance	Oxidonitrosative stress, neuroinflammation, and reduced level of neurotrophins
		0.12	EPM	Worse performance	
		1	FST	Worse performance	
		1	TST	Worse performance	
		1	Social interaction	Worse performance	
		1	Sucrose	Worse performance	
Jiang et al. 2017 [88]	0.83 mg/kg	1	FST	Worse performance	Neuroinflammatation and oxidative stress
		1	TST	Worse performance	
Kang et al. 2017 [89]	0.83 mg/kg	1	FST	Worse performance	mRNA expression of proinflammatory cytokines and IDO
		1	TST	Worse performance	
Lawson et al. 2013 [90]	0.83 mg/kg	1	FST	Worse performance	Expression of TNF-α and CD11b in the brain
		1	Sucrose	Worse performance	
O'Connor et al. 2009 [91]	0.83 mg.kg	1	FST	Worse performance	IDO activation
		1	TST	Worse performance	
Painsipp et al. 2011 [92]	0.83 mg/kg	1	FST	Worse performance	Stimulus of HPA axis and increase of IL-6
		28	FST	Worse performance	
Painsipp et al. 2010 [93]	0.83 mg/kg	0.12	FST	Worse performance	Stimulus of HPA axis and increase of IL-6
		0.12	OF	Not altered	
		28	FST	Not altered	

Table 1 (continued)

Author	LPS dose	Time after LPS behavior evaluation (days)	Evaluated task	Result	Mechanisms
		28	OF	Not altered	
Park et al. 2011 [94]	0.83 mg/kg	1	FST	Worse performance	IDO activation
		1	Sucrose	Worse performance	
Sulakhiya et al. 2016 [95]	0.83 mg/kg	0.12	EPM	Worse performance	Inflammation and oxidonitrosative stress
		012	OF	Worse performance	
		1	FST	Worse performance	
		1	TST	Worse performance	
Sulakhiya et al. 2014 [96]	0.83 mg/kg	1	FST	Worse performance	Inflammation and oxidonitrosative stress
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
		2	Sucrose	Worse performance	
Salazar et al. 2012 [97]	0.83 mg/kg	1	LD	Worse performance	IDO activation
		1	OF	Worse performance	
		1	Sucrose	Worse performance	
Walker et al. 2013 [98]	0.83 mg/kg	1	FST	Worse performance	IDO activation
		1	Sucrose	Worse performance	
Wang et al. 2016 [99]	0.83 mg/kg	1	FST	Worse performance	Changes in energy metabolism and neurogenesis in prefrontal cortex
		1	TST	Worse performance	
Wang et al. 2014 [100]	0.83 mg/kg	1	FST	Worse performance	Overproduction of IL-1β and TNF-α
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
Wu et al. 2016 [101]	0.83 mg/kg	1	FST	Worse performance	Perturbations in neurotransmitter metabolism, energy metabolism, oxidative stress, and lipid metabolism
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
Yang et al. 2017 [102]	0.83 mg/kg	1	FST	Worse performance	Neuroinflammation and oxidonitrosative stress
		1	TST	Worse performance	
		2	Sucrose	Worse performance	
Yu et al. 2016 [103]	0.83 mg/kg	0.35	FST	Worse performance	Neuroinflammation and oxidative stress
		0.35	TST	Worse performance	
		0.5	FST	Worse performance	
		0.5	TST	Worse performance	
		1	FST	Worse performance	
		1	TST	Worse performance	
Zhu et al. 2016 [104]	0.83 mg/kg	1	FST	Worse performance	Activation of NF-κB pathway and elevated levels of IL-6, IL-1β, and TNF-α in the hippocampus
		1	TST	Worse performance	
Jiang et al. 2017 [105]	0.83 mg/kg	1	FST	Worse performance	Activation of NF-κB pathway
			TST	Worse performance	
			Marble burying	Not altered	
			EPM	Not altered	
Barua et al. 2017 [106]	0.83	1	TST	Worse performance	Inflammatory cytokines and oxidonitrosative stress
		1	FST	Worse performance	
		1	Sucrose	Not altered	
Hao et al. 2013 [107]	0.8 mg/kg	1	FST	Worse performance	Proinflammatory cytokines and kynurenine pathway dysfunction
		1	TST	Worse performance	

Table 1 (continued)

Author	LPS dose	Time after LPS behavior evaluation (days)	Evaluated task	Result	Mechanisms
		2	FST	Worse performance	
		2	TST	Worse performance	
Medeiros et al. 2015 [108]	0.8 mg/kg	1	FST	Worse performance	Overexpression of TNF-α and IL-6
Wu et al. 2015 [109]	0.8 mg/kg	1	TST	Worse performance	Activation of HMGB1 pathway
Zhang et al. 2014 [110]	0.8 mg/kg	1	FST	Worse performance	NLRP3 inflammasome involvement
		1	Sucrose	Worse performance	
Deyama et al. 2018 [111]	0.8 mg/kg	1	TST	Worse performance	Inflammatory response (no specific cytokines)
Deyama et al. 2017 [112]	0.8 mg/kg	1	TST	Worse performance	Inflammatory response (no specific cytokines)
		1	FST	Worse performance	
Savignac et al. 2016 [113]	0.75 mg/kg	1	LD	Worse performance	Overexpression of IL-1β
Fischer et al. 2015 [114]	0.6 mg/kg	1	FST	Worse performance	Increase of IL-1β and IFN-γ
Adzic et al. 2015 [115]	0.5 mg/kg	1	FST	Worse performance	Neuroendocrine (increased corticotrophin-releasing hormone) and neurotrophic processes (decreased BDNF) and NFkB pathway activation
		1	Sucrose	Worse performance	
Araki et al. 2016 [116]	0.5 mg/kg	1	FST	Worse performance	Oxid nitric production and inflammatory response (IL-1β, IL-6, and TNF-α)
Bassi et al. 2012[§] [117],	0.5 mg/kg	0.15	EPM	Worse performance	Excessive and prolonged production of proinflammatory cytokines
		0.15	LD	Worse performance	
		0.15	Sucrose	Worse performance	
Corona et al. 2013 [118]	0.5 mg/kg	3	FST	Worse performance	Persistent neuroinflammation, microglial and IDO activation
Corona et al. 2010 [119]	0.5 mg/kg	0.5	Social interaction	Worse performance	Persistent neuroinflammation, microglial and IDO activation
		1	Social Interaction	Not altered	
		2	TST	Not altered	
		3	TST	Not altered	
Couch et al. 2016[‡] [120],	0.5 mg/kg	1	E0M	Not altered	Induces 5-HT genes and IL1β levels
	0.5 mg/kg	2	E0M	Worse performance	
Dong et al. 2016 [121]	0.5 mg/kg	1	FST	Worse performance	Persistent inflammation (TNF-α)
		1	TST	Worse performance	
Ji et al. 2014 [122]	0.5 mg/kg	1	FST	Worse performance	Increase of IL-6 and TNF-α levels and decreased 5-HT in the prefrontal cortex
		1	TST	Worse performance	
Li et al. 2015 [123]	0.5 mg/kg	1	FST	Worse performance	Overexpression of IL-6 and TNF-α levels
		1	TST	Worse performance	
Mello et al. 2013 [124]	0.5 mg/kg	1	FST	Worse performance	Increase of L1β levels and oxidative stress
Ohgi et al. 2013 [125]	0.5 mg/kg	1	TST	Worse performance	Inflammatory response (TNF-α)
Parrot et al. 2016 [126]	0.5 mg/kg	1	TST	Worse performance	Kynenurine pathway
		1	Sucrose	Worse performance	
		1	OF	Worse performance	
Su et al. 2016 [127]	0.5 mg/kg	1	FST	Worse performance	Persistent inflammation (IL-6 and TNF-α) in serum and hippocampus
		1	TST	Worse performance	
Tao et al. 2016 [128]	0.5 mg/kg	1	FST	Worse performance	Inflammation (IL-6 and TNF-α) and decrease of 5-HT and norepinephrine in the hippocampus
		1	TST	Worse performance	
Tomaz et al. 2014 [129]	0.5 mg/kg	1	FST	Worse performance	Inflammation (IL-1β), oxidative and nitrosative stress
		1	Sucrose	Worse performance	

Table 1 (continued)

Author	LPS dose	Time after LPS behavior evaluation (days)	Evaluated task	Result	Mechanisms
Yang et al. 2016 [130]	0.5 mg/kg	0.25	EPM	Worse performance	Astrocyte activation by CXCL12/ CXCR4 pathway
		0.25	OF	Worse performance	
Yao et al. 2015 [131]	0.5 mg/kg	1	FST	Worse performance	Inflammatory response (TNF-α levels)
		1	TST	Worse performance	
Zhang et al. 2017 [132]	0.5 mg/kg	1	FST	Worse performance	Inflammatory response (TNF-α levels) and microglial activation
		1	TST	Worse performance	
Zhang et al. 2016 [133]	0.5 mg/Kg	1	FST	Worse performance	Inflammatory response (IL-6, IL-1β, and TNF-α) in serum and hippocampus
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
Zhang et al. 2014 [134]	0.5 mg/kg	1	FST	Worse performance	Inflammatory response (TNF-α) altering BDNF and spine density in the CA3, DG, PFC, and NAc
		1	TST	Worse performance	
Zhe et al. 2017 [135]	0.5 mg/kg	1	FST	Worse performance	Inflammatory response (TNF-α and IL-6)
		1	TST	Worse performance	
		1	Sucrose	Worse performance	
Zhu et al. 2015 [136]	0.5 mg/kg	1	FST	Worse performance	Inflammatory response (TNF-α and IL-6) and decrease of NE and 5-HT levels in the prefrontal cortex
		1	TST	Worse performance	
Li et al. 2015 [137]	0.5 mg/kg	1	FST	Worse performance	Inflammatory response (TNF-α and IL-1β)
		1	Sucrose	Worse performance	
		1	EZM	Worse performance	
Li et al. 2017 [138]	0.5 mg/kg	1	TST	Worse performance	Neuroinflammation and oxidative stress
		1	FST	Worse performance	
Viana et al. 2010 [139]	0.45 mg/kg	1	TST	Worse performance	Microglial activation and TNF-α production
		1	Sucrose	Worse performance	
		2	TST	Not altered	
Godbout et al. 2008[¶] [140],	0.33 mg/kg	1	FST	Worse performance	Exaggerated neuroinflammatory response (IL-6 and IL-1β)
		3	FST	Not altered	
		3	TST	Not altered	
Henry et al. 2008 [141]	0.33 mg/kg	1	Sucrose	Worse performance	Excessive production of cytokines (IL-6 and IL-1β) and microglial activation
Yang et al. 2016 [142]	0.33 mg/kg	0.25	OF	Worse performance	Neuroinflammation mediated by cytokines (TNF-α, IL-6, and IL-1β)
		0.4	FST	Worse performance	
		0.4	TST	Worse performance	
		0.8	FST	Worse performance	
		0.8	TST	Worse performance	
		1	FST	Worse performance	
		1	TST	Not altered	
Elgarf et al. 2014 [143]	0.25 mg/kg	1	FST	Worse performance	Kynurenine/tryptophan ratio and astrocyte activation
		42		Not altered	
An et al. 2015 [144]	0.2 mg/kg	1	FST	Worse performance	Inflammatory response (TNF-α and IL-1β)
		1	TST	Worse performance	
Avitsur et al. 2017 [145]	0.2 mg/Kg	1	Sucrose	Worse performance	Inflammatory response (TNF-α and IL-1β)
Dinel et al. 2015 [146]	0.2 mg/kg	1	TST	Worse performance	Inflammatory response (TNF-α and IL-1β) and IDO activation

Table 1 (continued)

Author	LPS dose	Time after LPS behavior evaluation (days)	Evaluated task	Result	Mechanisms
Haba et al. 2012† [147],	0.2 mg/kg	0.3	FST	Worse performance	Cytokines, prostaglandins, and brain c-Fos expression
		1	FST	Worse performance	
		2	FST	Worse performance	
Renault et al. 2006 [148]	0.2 mg/kg	1	FST	Worse performance	HPA axis activation in response to cytokines
Wang et al. 2011 [149]	0.2 mg/kg	1	Sucrose	Worse performance	Glucocorticoid receptor dysfunction and increase of cytokines (TNF-α, IL-1β, and IFN-γ)
		3	Sucrose	Worse performance	
		7	Sucrose	Worse performance	
Lieberknecht et al. 2017 [150]	0.1 mg/kg	1	FST	Worse performance	Persistent inflammation (IL-1β) in hippocampus
		1	Splash test	Worse performance	
Prager et al. 2013* [151],	0.1 mg/kg	0.12	EPM	Worse Performance	Amygdaloid neuronal activation and cytokines production (IL-1β and TNF-α)
Pitychoutis et al. 2009 [152]	0.1 mg/kg	1	Sucrose	Worse performance	Neuroinflammation mediated by cytokines (TNF-α, IL-6, and IL-1β)
		1	Social interaction	Not altered	
Yeh et al. 2015 [153]	0.1 mg/kg	1	Sucrose	Not altered	Neuroinflammation (TNF-α) and loss of dopaminergic neurons in the substantia nigra

* The same effect observed using staphylococcal enterotoxin B 1 mg/kg

† Doses less than 1 mg/kg induce transitory alterations in FST at 10 h after LPS. Doses less than 0.5 mg/kg did not induce any alteration even as early as 10 h after LPS administration

‡ 0.1-mg/kg doses did not alter E0M, FST, TST, and sucrose from 1 to 2 days

§ Doses from 0.01 to 0.25 mg/kg did not alter any of the tests at 4 h

¶ Aged animals had worse performance until 3 days after LPS administrations, differently from adult animals

clear from these studies that a nonlethal single systemic stimulus is able to transiently induce symptoms of anxiety and depression in rodent models. The duration of these symptoms is variable, but they generally persist until the second day after LPS administration. For example, when administering a single dose of 2.5 mg/kg IP, changes in depressive-like behavior (FST) were observed up to the second day post-LPS but not after 3 or 4 days [70]. This increase in depressive-like behavior was also seen in the sucrose preference test when using an LPS dose of 0.83 mg/kg [82]. On the other hand, using a dose of 0.83 mg/kg, anxiety symptoms (EPM and LD) could be observed until 7 days after LPS administration [79]. In 2 different studies from the same group, it was possible to observe depressive symptoms at 28 days after 0.83 mg/kg LPS administration in one [92] but not in the other [93] using the same mice strain. Additionally, long-term depressive behavior was dependent on mice strain and social environment [92]. Thus, it is not possible to truly know whether these low LPS doses induce sustained alterations in the brain that mimic long-term psychiatric symptoms observed in sepsis survivors or even if the molecular alterations that occurred in this early phase are comparable to those involved in brain dysfunctions afterward.

Few studies have investigated the interaction between some comorbidities and systemic inflammation. Couch et al. (2016) [120] demonstrated that the combination of a low dose of LPS and chronic stress (CS) resulted in an enhanced depressive-like phenotype. A dose of 0.1 mg/kg LPS was not sufficient to alter EOM behavior, sucrose preference, and FST, but a prior CS potentiates LPS effects mainly by inducing 5-HT genes and IL1-β levels. The same pattern was seen using repeated very low doses of LPS (50 μg/kg) and CS. Depressive behavior combining both stimuli could be observed after 6 weeks and is related to the hippocampal kynurenine/tryptophan ratio, TNF-α levels, and astrocyte activation [143].

The largest LPS dose that was found in the literature search was LPS 10 mg/kg [65], with a reported mortality rate of 16%. Twelve weeks after a single LPS injection, animals presented anxiety-like behavior observed in the OF. This was associated with a reduced density of NeuN-immunoreactive neurons in CA1 and CA2 and in the prefrontal cortex. Additionally, acetylcholine neurons were found in parietal association and in somatosensory cortical areas. Taking a more detailed description of models that used large LPS doses, it was observed that using a dose of LPS (5 mg/kg) in C57BL/6 and a mortality of 15%, it was possible to have deficits in 3 different depressive components 28 days after LPS administration. These alterations are secondary at least to acute NRLP3 activation [68]. Using the same 5 mg/kg dose and an observed mortality of around 10%, Anderson et al. (2015) [66] observed consistent anxiogenic and depressive behaviors in different tasks (sucrose preference, TST, EPM) between 30 and 60 days after LPS. Reinforcing these findings, depressive symptoms were reversed by fluoxetine. Mechanistically, these findings were related to microglia activation in the hippocampus [66]. The only exception to these results was presented by Bossú et al. (2012) [67]. Using a dose of 5 mg/lg LPS, they did not show increased anxiety (EPM and OF), either at 7 or 280 days after LPS injection; however, the authors speculated that persistent participation of TNF-α accompanied by a contribution of IL-18 can lead to behavioral alteration. Of note, from all studies that used higher LPS doses, this was the only one that did not report any mortality and was performed in rats. Using doses of less than 5 mg/kg, long-term deficits (i.e., more than 10 days) were barely observed (Table 1).

There is a subgroup of studies that are based on neonatal sepsis. Generally, LPS was administered in a low dose (~ 50 μg/kg) at postnatal 3 to 5, and behavioral changes (both depression and anxiety) were determined at adult life [154–162]. Usually, adult animals more frequently developed protracted anxiety or depressive symptoms when compared to controls. Additionally, some studies injected repeated LPS doses [163–174].

The mechanisms of action of how a single LPS injection can induce acute anxiety-/depressive-like symptoms were explored. Some studies use behavioral tolls to understand how systemic inflammation interferes in brain regions and how this could induce acute anxiety-/depressive-like symptoms. For example, after a small systemic LPS injection (0.5 mg/kg), astrocytes are activated early in both the hippocampus and the amygdala and produce CXCL12 in response [130]. Microinjection of CXCL12 into the amygdala is sufficient to induce anxiety-like behaviors in mice. Both systemic LPS and amygdala CXCL12 injection-induced anxiety were blocked by an antagonist of the CXCL12 receptor (CXCR4). Additionally, the formation of quinolinic acid from tryptophan seems to be relevant because KO mice exposed to kynurenine 3-monooxygenase (KMO) or 3-hydroxyanthranilic acid dioxygenase (HAAO) are specifically protected from LPS-induced immobility in the TST [126]. Furthermore, the direct administration of 3-hydroxykynurenine, the metabolic product of KMO, caused a dose-dependent increase in depressive-like behaviors [126]. This was also true when an indoleamine 2,3-dioxygenase (IDO) inhibitor was administered [118]. Apparently, not only brain resident cells are responsible for the depressive phenotype after LPS administration because the administration of an antipolymorphonuclear antibody abolished LPS- and CLP-induced depressive behavior, brain neutrophil transmigration, and brain IL-1β levels [70, 169].

However, most of the studies have only associated different alterations related to the kynenurine pathway [79, 82, 89, 91, 94, 97, 98, 107, 118, 119, 126, 143, 146], microglial activation [66, 69, 80, 118, 119, 132, 139, 141], or astrocytic activation by the CXCL12/CXCR4 pathway [130]. The region

most affected is always the hippocampus and/or the prefrontal cortex. Prager et al. (2013) report that the amygdala is affected too [151].

Most of the included studies (72%) report persistent inflammation mediated by IL6, TNF-α, and IL-1β levels as mechanisms of action. Some authors [70, 77, 78, 113, 114, 124, 129, 150] emphasize only IL-1β as the cytokine mediator of inflammation, whereas others report only TNF-α [67, 80, 90, 121, 125, 131, 132, 134, 139, 153], and still others, only IL6 [92, 93]. NF-kB is the pathway most mentioned as the route in activating cytokines after LPS injection, but only Yu et al. [74] reported that the p38/JNK pathway is activated during the LPS challenge.

Oxidative [83, 88, 101, 103, 124, 129, 138] and nitro-oxidative stress [76, 86, 87, 95, 96, 102, 106, 129] parameters are too related in some studies (12%) as the main mechanism of action of LPS injection. Besides this, alterations in neurotrophic factors have been mentioned in some studies [76, 86, 115, 134], as well as deregulation on the HPA axis [75, 92, 93, 115, 148] (Fig. 1).

Another relevant tool that helps prove the concept of whether certain animal behavior is really showing anxiety- or depressive-like symptoms is the pharmacological demonstration that the anxious phenotype can be reversed using benzodiazepines or that the depressive phenotype can be reversible by an antidepressant. Unfortunately, these strategies are scarcely used in the selected articles. Additionally, when drugs are tested, they are generally administered for days before the LPS challenge and, in very few situations, after LPS administration, when the physiological alterations in the brain are already installed. However, it is not the aim of this review to describe in detail the molecular mechanisms determined from these studies.

In summary, LPS-induced systemic inflammation could be useful as a model of postsepsis anxiety and depression. One should keep in mind that anxiety disorders, depressive symptoms, and PTSD are observed in sepsis survivors [3–6], and most of the studies using LPS (mainly at doses lower than 1 mg/kg) showed 1 to 2 days of limited anxiety and depressive symptoms that resolved spontaneously. Generally, short-term septic patients present encephalopathy that is clinically characterized by impaired consciousness ranging from delirium to coma [175]. Thus, it is uncertain if an acute dose of LPS mimics what is observed in septic patients, but it is reasonable to suppose that this model could be a useful tool to understand the initial mechanisms that drive long-term psychiatric symptoms. It seems relevant when using this model that the LPS dose should be associated with some mortality (as do sepsis and septic shock) and that brain structures involved in a given behavior should be assessed. Additionally, to increase consistency, it is suggested that more than one anxious or depressive behavior should be measured and that classic drugs that reverse these behaviors should be used to double-check the specificity of the phenotype observation (i.e., benzodiazepines and antidepressants). A clear advantage of this model is the rapid timeframe between LPS administration and phenotype and molecular correlates observations. Whenever possible, long-term observation of the animal (for more than 10 days) with the use of a larger LPS dose (higher than 5 mg/kg) that elicits as 15 to 20% mortality should better mimic the clinical scenario of sepsis survivor patients and open the perspective to develop drugs to be used after the brain pathophysiological alterations have already been in course.

The cecal ligation and perforation (CLP) model was developed in the 1970s and is considered by many as the gold standard for animal models of sepsis [64]. In this model, anesthetized rats or mice are subjected to a midline laparotomy and have their cecum isolated, ligated, and perforated before having it returned to the abdominal cavity, which is then closed. This technique induces inflammatory, immune, hemodynamic, and biochemical alterations similar to human sepsis. For example, contrary to endotoxin administration, CLP induces a slower but more consistent increase in plasma cytokines that resembles human sepsis [64]. The degree of severity associated with the procedure can vary greatly according to factors such as the aseptic practices adopted, the resuscitation protocol, the site of ligation, the number of punctures, and needle size used. As a consequence, it is of great importance that the procedure is performed with high consistency and reproducibility [64].

Due to intrinsic characteristics, the acute evaluation of anxiety and depressive behavior is almost impossible in the CLP model. The influence of anesthesia, analgesia, and pain is nonnegligible, limiting the CLP model to a tool for the study of the late phases of sepsis recovery. Thus, the CLP model seems more useful for studying long-term anxiety and depressive behavior in survivors. The vast majority of CLP studies describe mortality after the procedure, generally around 30 to 50%. These experiments also systematically comprise antibiotic treatment and fluid administration. These factors support the argument that the CLP model is more closely related to human sepsis.

Within our search, only 4 studies assessed anxiety and depression after CLP in mice [176–179]. All these studies were performed in young adult male mice, mostly from the C57BL/6 strain (3 out of 4). During CLP, the number of punctures performed varied greatly (from 1 to 3), whereas the size remained constant (22G). The mortality was described for 3 of these studies and ranged from 0 to 50%. Only anxiety-related traits were evaluated in these studies, either at 10 days post-CLP (2 studies) or at a longer term (29 and 35 days, 2 studies). Only one of the studies evaluating the effect of CLP on anxious-like behavior found a significant increase in this behavior 10 days after CLP.

Behavioral assessment after CLP has been relatively more frequently performed in rats. For this group, we identified 8

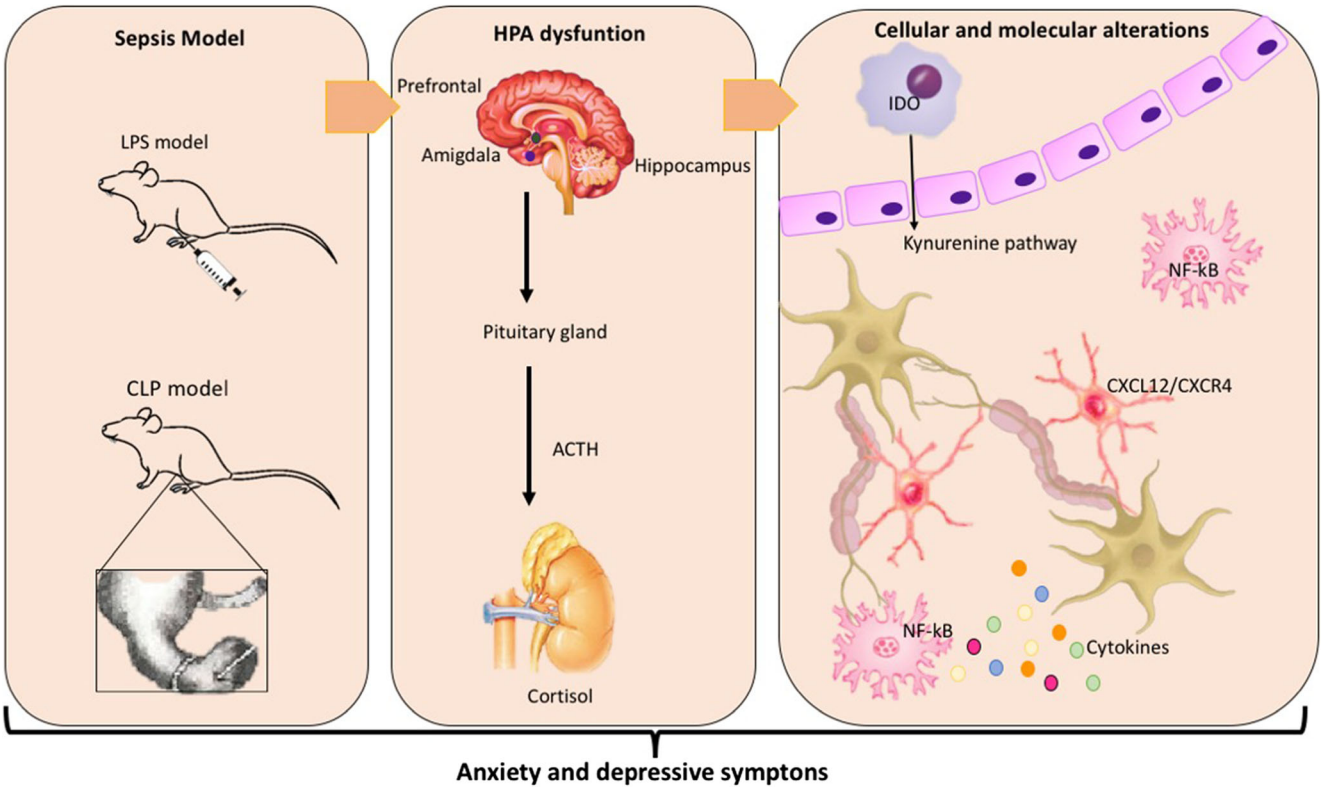

Fig. 1 Animal models of sepsis have been used in the study of the pathogenesis of neuropsychiatric disorders. LPS-induced systemic inflammation could be a useful tool to study anxiety and depressive symptoms in the context of sepsis. The CLP model consistently induces a depressive-like phenotype, making it an interesting model of the long-term mood disorders observed in human sepsis survivors. In both LPS and CLP models, basically the same molecular targets are altered: microglial activation and cytokines are frequently reported and generally affect the hippocampus; blood–brain barrier permeability is mentioned as one of the first mechanisms induced by the CLP model; besides this, oxidative stress, apoptosis, and HPA alterations are related

studies, all performed in male Wistar rats, mostly adults (7 out of 8) [179–185]. The procedures always included one puncture of the same size (14G) and led to a mortality rate varying between 30 and 60%. All these studies evaluated the long-term consequences of CLP on behavior between 7 and 10 days post-CLP, and one of these studies also included a 30- and a 60-day post-CLP evaluation for both anxiety- and depression-related behaviors. All but 1 of the 7 studies that evaluated the impact of CLP on depression-related behaviors found a negative influence of this procedure up to 30 days post-CLP, regardless of the behavioral test used (FST, sucrose preference, or sweet food consumption). Among the 3 studies that evaluated anxiety-related behaviors, only 1 found an influence of CLP on this trait, with increased anxiety-related behavior in the elevated plus-maze 7 days post-CLP. Interestingly, despite the different results, all 3 studies investigating the effect of CLP on anxiety-related behaviors used readouts from the elevated plus-maze as anxiety indexes. It is noteworthy, however, that those that did not find an effect of CLP on anxiety evaluated this behavior at a longer term (from 10 to 60 days post-CLP), which might explain the variability among these results.

Overall, it seems that the CLP model consistently induces a depressive-like phenotype, although this effect needs to be confirmed in the mouse model. This effect seems to last for at least 30 days, making it an interesting model of the long-term mood disorders observed in human sepsis survivors. Although only assessed in one study, the apparent improvement of depressive-like behavior at 60 days post-CLP should be taken into account when planning long-term experiments and should be confirmed with more experiments investigating the behavioral consequences of CLP at longer terms. On the other hand, the results observed for anxiety-related behavior are not robust. Only 2 out of 7 studies found an influence of the CLP of this trait, which seems to depend greatly on the timing of the evaluation (only observed at early times) and of the behavioral task used (only observed in the EPM).

Paradigms to study depressive behavior are similar to the LPS model. Depression is generally evaluated by FST or sucrose preference and generally could demonstrate depressive behavior in sepsis survivor animals. In the vast majority of the studies during the first 10 days after CLP depression is observed in these animals, and at longer times (30-60 days), animals tend to return to sham-operated behavior (Table 2).

Table 2 Studies that induced sepsis by cecal ligation and perforation (CLP)

Author	Puncture number/size	Mortality (%)	Time after CLP behavior evaluation (days)	Evaluated task	Result	Mechanism
Anxiety						
Gao et al. 2017 [176]	2/22	20	10	OF	Not altered	Hippocampal IBA1-positive cells, IL-1β and IL-6 levels, and decreased NRG1 and ErbB4 expressions
Ozcan et al. 2015 [186]	2/18	50	10	OF	Not altered	Inflammation, cerebral endothelial activation, and blood–brain barrier breakdown
			30	OF	Not altered	
			60	OF	Not altered	
			10	EPM	Worse performance	
			30	EPM	Not altered	
			60	EPM	Not altered	
Wu et al. 2013 [177]	2/22	50	29	OF	Not altered	Inflammation (TNF-α, IL-6, IL-1β)
Leite et al. 2013 [180]	1/14	50	7	EPM	Worse performance	Production of several proinflammatory cytokines
Calsavara et al. 2013 [178]	3/22	Sublethal	10	EPM	Worse performance	Brain cytokines TNF-α, IFN-γ, IL-1β, and IL-6 levels increase
Chavan et al. 2012 [179]	1/22	30	35	Black–white alley	Not altered	Increase of high mobility group box 1 (HMGB1) levels in serum
Tuon et al. 2008 [184]	1/14	50	10	EPM	Not altered	Brain inflammation, oxidative stress, and neuron apoptosis
			30	EPM	Not altered	
			60	EPM	Not altered	
Barichelo et al. 2007 [187]	1/14	60	10	EPM	Not altered	Brain inflammation and apoptosis, mainly in the hippocampus
Depression						
Steckert er al 2017 [188]	1/14	50	10	Splash test	Worse performance	Systemic inflammation (TNF-α, IL-1β, and IL-6) and oxidative stress
				FST	Not altered	
He et al. 2016 [169]	1/NI	0	2	Sucrose	Worse performance	Brain neutrophil transmigration
			4	Sucrose	Worse performance	
			7	Sucrose	Not altered	
Ozcan et al. 2015 [186]	2/18	50	10	FST	Worse performance	Inflammation, cerebral endothelial activation and blood–brain barrier breakdown
			30	FST	Not altered	
			60	FST	Not altered	
Petronilho et al. 2012 [181]	1/14	50	10	FST	Worse performance	Oxidative stress
Cassol-Jr et al. 2010 [182]	1/14	50	10	Sucrose	Worse performance	Systemic inflammatory response and HPA axis dysfunction
Comim et al. 2010 [183]	1/14	32	10	Sucrose	Worse performance	Systemic inflammatory response, HPA axis dysfunction and decreases of BDNF
Tuon et al. 2008 [184]	1/14	50	10	FST	Worse performance	

Table 2 (continued)

Author	Puncture number/size	Mortality (%)	Time after CLP behavior evaluation (days)	Evaluated task	Result	Mechanism
			30	FST	Worse performance	Brain inflammation, oxidative stress and neuron apoptosis
			60	FST	Not altered	
Tuon et al. 2007 [185]	1/14	60	10	FST	Worse performance	Brain inflammation, oxidative stress
Barichello et al. 2007 [187]	1/14	60	10	FST	Worse performance	Brain inflammation and apoptosis, mainly in hippocampus

The differences in mainly anxiety-related behaviors are intriguing. First, in both LPS and CLP models, basically the same molecular targets are altered: Cytokines are more frequently reported and generally affect the hippocampus [169, 176–178, 180, 183–188]; microglial activation is reported by Gao et al. (2017); blood–brain barrier permeability is mentioned by Ozcan et al. (2015) as one of the first mechanisms induced by the CLP model; and a decrease of neurotrophic factors is related by Gao et al. (2017). Besides this, oxidative stress [181, 184, 188], apoptosis [184, 185, 187], and HPA alterations [182, 183] are related (Fig. 1).

Generally, treatments are able to completely reverse both phenotypic and molecular alterations. It seems that both models provide a time-limited dysfunction (inflammatory, metabolic, neurotransmitters) that varies secondary to characteristics of the models. A more sharp but transient increase in cytokines is achieved by LPS, contrasted with a slower, more consistent increase in CLP. These time differences are consistent with differences observed in the duration of anxiety and depressive symptoms when using these models. As for LPS models, the CLP model is useful in understanding acute molecular alterations that occur acutely in the brain, despite it being more difficult to access neurological function (see above). Probably, its great advantage is a more reliable toll to study long-term brain alterations. However, even in this context, one should interpret the data with caution. Most of the published studies suggested a time-dependent recovery from behavior alterations, despite the fact that some molecular alterations persist in the brain. So this model should probably be improved by adding some second hit to make alterations more sustained (for example, a second inflammatory hit after CLP, induce CLP in aged animals, or animals with some comorbid condition) and thus more reliable to understand the mechanisms that underlie anxiety and depression in septic survivor animals. Another limitation that should be observed is the necessity to develop a model to study PTSD in these animals.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no competing interests.

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