doi: 10.22201/fmvz.24486760e.2025.1287
Vol. 12 | 2025

Veterinaria México OA
Publicación Digital de la Facultad de Medicina Veterinaria y Zootecnia https://veterinariamexico.fmvz.unam.mx/

Effect of lipopolysaccharide on body physiological responses

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Abstract

Lipopolysaccharide (LPS) is an important compound with pathogenic properties. LPS is considered a bacterial endotoxin, and the body induces widespread inflammation responses by stimulating the immune system through blood cells and synthesizing proinflammatory cytokines. After entering the circulation, these proinflammatory cytokines affect different body organs and induce systematic inflammation. Proinflammatory cytokines also enter the brain through the periventricular hypothalamus (PeVH) and by affecting microglia and astrocytes; they stimulate the brain's immune response. After the induction of systemic and central inflammation, the animal sickness behavior appears. In this review, we are going to investigate the peripheral and central effects of LPS-induced inflammation on different animal species.

Keywords: Animal sickness behaviors; Lipopolysaccharide; Periventricular hypothalamus; Inflammation; Proinflammatory cytokines.

Submitted: 2023-11-04
Accepted: 2024-08-05
Published: 2025-01-31

Additional information and declarations can be found on page 15

Cite this as:

Yousefvand S, Hamidi F, Parham A. Effect of lipopolysaccharide on body physiological responses. Veterinaria Mexico OA. 2025;12. doi: 10.22201/fmvz.24486760e.2025.1287.

doi: 10.22201/fmvz.24486760e.2025.1287
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Note to readers:

For your convenience, this article includes an alphabetical list of abbreviations. Please refer to this list if you encounter any abbreviations that you are unsure of while reading the article.

List of abbreviations

AA: Arachidonic acid.
Ach: Acetylcholine.
AchE: Acetylcholinesterase.
APR: Acute phase response.
ARC: Arcuate nucleus.
BBB: Blood-brain-barrier.
CBF: Cerebral blood flow.
CNS: Central nervous system.
CRF: Corticotropin-releasing factor.
HPA: Hypothalamic-pituitary-adrenal.
ICV: Intracerebroventricular.
IDO: Indoleamine 2,3-deoxygenase.
ILs: Interleukins.
IP: Intraperitoneal.
IV: Intravenous.
LHA: Lateral hypothalamus area.
LPS: Lipopolysaccharide.
LTP: Long-term potentiation.
LTs: Leukotrienes.
NF-kβ: Nuclear factor-kβ.
NO: Nitric oxide.
NOS: Nitric oxide synthesis.
NPY: Neuropeptide Y.
PeVH: Periventricular hypothalamus.
PGE2: Prostaglandin E2.
PVN: Paraventricular nucleus.
ROS: Reactive oxygen species.
sPLA2-IIA: Secretory phospholipase A2-IIA.
TL1A: TNF-like ligand 1A.
TNF-α: Tumor necrosis factor-α.
WBC: White blood cell.

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Study contribution

LPS endotoxin is used to investigate the body's immune response to harmful pathogens, especially pathogens that are normally associated with living organisms. Then the body's peripheral and central response to it is measured. By entering the body, LPS causes the release of environmental proinflammatory cytokines into the systemic circulation. Then these cytokines enter the central nervous system through blood circulation and periventricular hypothalamus nucleus. After that, by affecting different brain areas, including the hypothalamus nuclei, it causes inflammation, infection, and widespread central responses in the body.

Introduction

Inflammation is the body's natural response to pathological disorders or changes in the physiological state of the body.[1, 2] Inflammation caused by a wide range of pathogens has almost the same central reactions.[3] These central reactions include changes in behavioral patterns. These behavioral patterns are considered *animal sickness behavior*. Animal sickness behavior includes decreased food and water intake, body weight,[3] fever induction, sleep deprivation, inactivation, deficits in memory and learning,[4] and neuroendocrine changes.[5] Animal sickness behavior patterns also include changes in blood parameters,[6] induction of neuroinflammation,[7] effect on the level of different brain neurotransmitters,[8] and behavioral changes such as depressive-like behavior,[9] fatigue,[10] anxiety-like behavior,[11] anhedonia,[12] and lethargy.[13]

These animal sickness behaviors reduce energy consumption to perform activities, and store energy for defending the body and recovering from the disease.[4] Thus, anorexia is beneficial early in the disease, but prolonged anorexia delays recovery.[14] Identifying these animal sickness behaviors in animals helps to diagnose and treat inflammation promptly.[15] Systematically and centrally applied lipopolysaccharide (LPS) induces acute phase response (APR), and animal sickness behavior (Figure 1).[16, 17] APR occurs in the liver and brain and induces the expression of proinflammatory cytokines in these two organs. The response of the liver and brain to proinflammatory mediators is different.[18, 19] The liver is directly exposed to LPS, and Kupffer cells respond to LPS-induced inflammation by secreting proinflammatory cytokines.[20] The brain is not directly exposed to LPS due to the presence of the blood-brain-barrier (BBB). The periventricular hypothalamus (PeVH) does not have a BBB, but it has receptors for leukotrienes (LTs), and interleukins (ILs). Therefore, proinflammatory cytokines in this way induce infection in the brain and especially the hypothalamus.[21, 22] LPS reaction in mammalian species related to species and individual dependent. Birds' responses to inflammation and infection are nearly identical to mammals'.[23, 24] The central effect of inflammation on behavioral changes is conducted by the central nervous system (CNS) microglia, and astrocytes.[2, 25]

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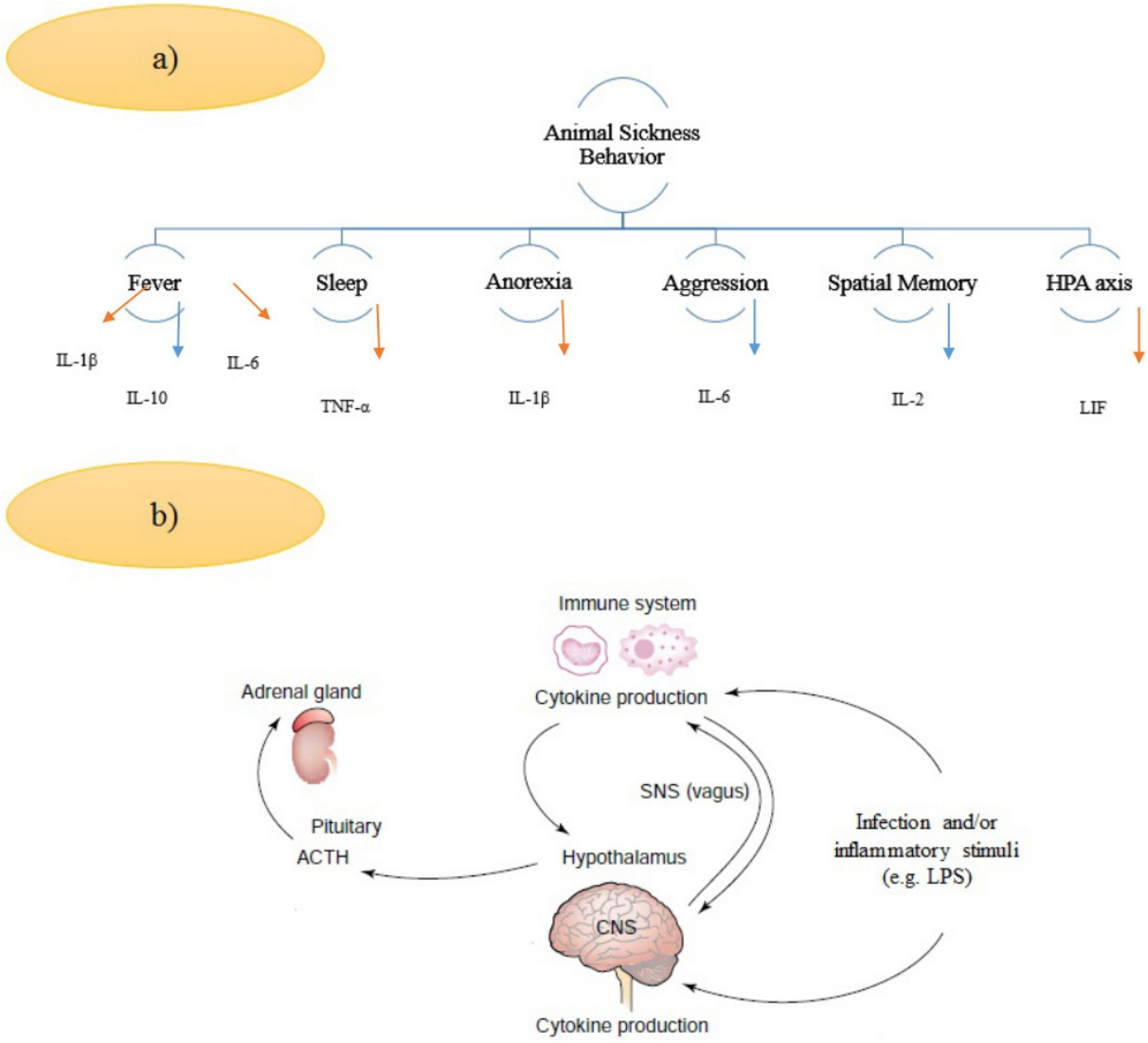

Figure 1. a) Animal sickness behavior patterns caused by proinflammatory, and anti-inflammatory cytokines. b) Pathways related to the immune system and central nervous system (CNS) in inflammation state. Leukemia inhibitory factor (LIF) is required for hypothalamic stress response which is related to interleukin 6 (IL-6)[26]. The nerve vagus is the link between the immune system and the CNS. Proinflammatory. Anti-inflammatory.

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Lipopolysaccharide is a component of the gram-negative bacteria's wall.[27] It is released as a result of bacterial lysis or the rapid proliferation of bacteria.[28] In the structure of LPS, there are O side chains, core, and lipid A.[29] The immunologically active component of LPS is lipid A. Lipid A binds to the toll-like receptor 4 and starts transcriptions. After that, nuclear factor-ƙβ (NF-ƙβ) excitation and the expression of inflammatory genes occur.[30] Then, proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-α (TNF-α) enter the circulation. So, these factors affect CNS-induced animal sickness behavior.[31]

IL-1β and IL-6 responses to inflammation are different, as well as the different signaling cascades effects. IL-1β acts through the NF-ƙβ pathway,[32] while IL-6 acts as, and signal transducer and activator of the transcription three pathway.[33] Proinflammatory cytokines and their receptors are distributed in different parts of the digestive tract, as well as in various parts of the brain, including the hypothalamus. During general inflammation, the body's immune system passages respond related to CNS inflammation through the vagus nerve and the circumventricular organ. Then CNS issues the necessary response by synthesis of proinflammatory cytokines.[34] The effects of LPS on laboratory animals are different [35–38]. These effects are influenced by drug dose, number of injected doses, bacterial source, and injection methods (Table 1).[39, 40]

LPS is the most available compound for investigating sickness behavior in different animal models;[35–38] of LPS-induced systemic and central inflammation.

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Table 1. The effects of lipopolysaccharide on central and peripheral physiological responses

Substance	Type organism	Administration type	Dosage	Action (s)	Action mechanism (s)	Ref
Escherichia coli LPS	Chicken	IV	1 500 000 ug/kg	Hypotension	NO	(6)
Escherichia coli LPS	Chicken	IV	1 500 000 ug/kg	Hypotension	NO	(6)
Escherichia coli LPS	Rat	ICV	5 µg/5 µL	Learning disorder	Induced oxidative stress, and neuroinflammation	(7)
Salmonella typhimurium LPS	Chicken	IV	5 mg/kg	Diarrhea	Increased IL-6	(24)
Escherichia coli LPS	Pigs	IV	1.2 µg/kg	Hypophagia	IL-1, IL-6, IL-8, and TNF-α	(31)
Escherichia coli LPS	Pigs	IV	1.2 µg/kg	Depression	Dopamine, and noradrenalin	(31)
Escherichia coli LPS	Chicken	IV	5 mg/kg body weight	Hyperthermia	Increased IL-1 synthesis in liver	(41)
Escherichia coli LPS	Chicken	IV	5 mg/kg	Decreased body weight	Increased IL-1	(41)
Escherichia coli LPS	Rat	IV	100 µg/kg	Hyperthermia	NOS synthesis induction	(42)
Escherichia coli LPS	Chicken	ICV	20 ng/10 µL	Hypophagia	c-FOS expression increased, and NPY decreased	(43)
Escherichia coli LPS	Rats	IP	5 mg/kg	Anxiety	Increasing the level of tau proteins, and decreasing BDNF	(44)
Escherichia coli LPS	Mice	IP	0.33 mg/kg	Anhedonia	Increased proinflammatory cytokine, and indoleamine 2,3 dioxygenase	(45)
Escherichia coli LPS	Rat	ICV	50 µg/20 µL	Neuroinflammation	Increased AchE activity	(46)

IV: Intravenous. ICV: Intracerebroventricular. IP: Intraperitoneal.

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This inflammation affects different organs, and symptoms of animal sickness behavior appear.[47] So far, a comprehensive study on the effects of LPS on different organs, animal sickness behavior, and body physiological responses has not been done. Therefore, the current review article examines this response to LPS-induced inflammation.

Study design

This review article studied multiple credible papers from electronic sources. Authentic papers indexed in the Web of Science, Scopus, PubMed, SID, Google Scholar, and ISI databases via the keywords below: lipopolysaccharide, inflammation, animal sickness behavior, food intake, body temperature, body weight, memory, learning, central nervous system, depressive-like behavior, fatigue, anxiety-like behavior, anhedonia, and lethargy.

Central lipopolysaccharide effects on food intake

The central control of feeding is a complex process in which different parts of the brain, especially the hypothalamus, are involved. The hypothalamus plays a unique role in regulating food intake and energy balance through various neurotransmitters and specialized nuclei.[48–55] The nervous, immune, and neuro-endocrine systems are involved in the central control of feeding. Therefore, substances and compounds that disrupt the balance of these systems also interfere with food intake.[56] Anorexia is a clinical symptom associated with pathological conditions such as inflammation and infection.[57]

Anorexia is part of APR. The main target organ for proinflammatory cytokines to induce anorexia is the brain. Proinflammatory cytokines play an essential role in inflammation-induced anorexia.[14, 57] These substances are synthesized both in glial cells and neurons[58] and enter the brain through the BBB, and periventricular organs.[59] LPS is one of the compounds that induce inflammation and subsequently anorexia, and hypophagia in pigs, mammals, and birds.[31, 60] This reduction can be due to the appetite-reducing effects of proinflammatory cytokines such as IL-1, IL-6, IL-8, IL-10, and TNF-α.[61]

LPS in the brain stimulates glial cells through TLR4. Then IL-1, IL-1β, IL-6, IL-10, IL-8, and TNF-α are released from glial cells. These ILs express enzymes that decompose arachidonic acid (AA) into prostaglandin and thromboxane. Therefore, these compounds affect CNS-expressed animal sickness behavior such as decreased feeding.[60, 62, 63] Centrally and peripheral administration of LPS reduced feeding.[26, 64] The results of several studies have shown that LPS exerts its central reducing effect on food intake through two pathways.[14] LPS stimulates the release of proinflammatory cytokines in different brain regions,[65] especially the arcuate nucleus (ARC).[66]

The ARC is the most important nucleus in controlling food consumption and energy balance.[67] In this nucleus, through IL receptor-1, LPS stimulates the expression of c-FOS in proopiomelanocortin neurons,[68] and corticotropin in corticotropin-releasing factor (CRF) neurons in the ARC, and paraventricular nucleus (PVN). Also, prostaglandin E2 (PGE2) inhibits the release of neuropeptide Y (NPY) through the NPY1 receptor and finally reduces food intake.[26, 64] Also during stress and sickness state, CRF secreted from the PVN causes the release of adrenocorticotropin hormone from the anterior pituitary. This hormone mediates the hypophagia effects of LPS by acting on the adrenal gland and secreting corticosteroids.[28, 69] Nitric oxide (NO) is a neuromodulator that plays a role in LPS-induced central anorexia. NO induces anorexia during LPS-induced inflammation by inhibiting ghrelin orexigenic neurons of the ARC.[70]

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Lipopolysaccharide effects on body weight

The effects of LPS on the animal's body weight can be different according to the species and even the breed of the animal. IV injection of LPS in laying chickens induced weight loss in the first 6–24 hours, and animal weights returned to the normal range 48 hours after the injection. Also, minor changes in the growth of organs (spleen, heart, adrenals, and liver) were observed.[41] Liver enlargement can result from increased metabolic activity induced by LPS. In endotoxemia, the liver synthesizes and releases IL-1 in birds. After that LPS exerts its harmful effects on the body.[24, 41] This LPS-induced weight loss could be due to reduced food intake.[71]

Central lipopolysaccharide effects on body temperature

Behavioral patterns of temperature changes in response to LPS vary among different animals.. LPS in laying chickens caused hypothermia in the first six hours after injection, primary hyperthermia in twelve hours after injection, and secondary hyperthermia in 24–48 hours after injection.[72] Broilers have a biphasic temperature response: hypothermia, and hyperthermia. Laying chicks experience hypothermia, hypothermia followed by hyperthermia, and hyperthermia without hypothermia.[7, 43, 72] Chickens are very resistant to the effects of LPS, and they show different temperature behaviors depending on the dose of LPS. Low doses of LPS only produce hyperthermia. Moderate doses cause hypothermia and hyperthermia. High doses of LPS cause high and persistent hypothermia,[46,72] before inducing fever.[6, 72] Indicated that IV injection of LPS in pigs first induced hypothermia, and then hyperthermia.[73]

LPS increases the expression of IL-I mRNA in chicken liver. The liver is the primary source of ILs in endotoxemia. LPS has increased the metabolic activity of the liver by affecting it. The liver secretes inflammatory acute phase proteins and proinflammatory cytokines including IL-1 which cause animal sickness behavior such as fever. In birds, IL-1 functions similarly to IL-1β in mammals.[42, 74, 75] In chickens, 3 hours after receiving LPS, IL-6 serum level elevated. This elevation is just before the induction of fever.[76] Proinflammatory cytokines such as IL-1 via sending a signal to the brain cause an increase in the level of PGE2. PGE2 is one of the important factors inducing fever.[6] PGE2 induces fever by stimulating cold-sensitive neurons in the preoptic area of the brain.[77]

NO plays a key role in body temperature regulation. NO exerts this role through control of the vasomotor center, thermogenesis through brown fat tissue, and neuroendocrine control.[74] In addition to this direct effect, NO exerts its effect on body temperature control during endotoxemia through its effect on the release of proinflammatory cytokines such as TNF-α, IL-1β, and IL-1. NO exerts its effect on the central control of body temperature regulation through the PeVH, PVN, and supraoptic nuclei which contain nitric oxide synthesis (NOS) enzyme. NO production in these regions during endotoxemia is associated with fever and neuroendocrine changes.[42]

When a fever-causing pathogen (such as LPS) enters the body, white blood cells (WBC) with compounds such as TNF-α placed against it. Chickens don't have TNF-α, but they have TNF-like ligand 1A (TL1A). TNF-α in mammals and TL1A in chickens cause IL-1β and IL-6 production.

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Then, these proinflammatory cytokines, by affecting the CNS, increase the level of PGE2 in the brain and fever. TNF-α, IL-1β, and IL-6 are the key blood factors responsible for inducing fever.[75] TL1A also increases the level of α1 acid glycoprotein, ceruloplasmin, and NO. These compounds develop the inflammation process.[76]

LPS-induced hypothermic phase reduces tissue hypoxia.[6] It has a protective function in septic shock and protects vital organs of the body.[78] The relationship between hypothermia and tissue hypoxia indicates a decrease in heat generation in the tissue. Blood pressure also decreases during hypothermia. LPS increases NO production by stimulating the activation of NOS.[79, 80] NO reduces the temperature by dilating blood vessels. After some time, the arterial blood pressure returns to normal, and tissue perfusion decreases. As a result, the body temperature gradually increases, and fever is induced. Therefore, NO is responsible for lowering blood pressure and hypothermia.[73, 81]

Central lipopolysaccharide effects on blood parameters

During inflammation induced by LPS, leukocytes are isolated from the circulation and attach to the post-capillary venules endothelium to migrate to the damaged tissue. In most cases, leukocytes become trapped in the lung tissue, and unable to re-enter circulation.[82, 83] LPS-induced reduction in circulating granulocytes via hypothermia. A decrease in blood neutrophils has also been observed in dogs and pigs.[6] LPS increases WBC in circulation.

Additionally, apoptosis increases, and apoptotic cells enter the circulation by binding to LPS, reducing its serum concentration and proinflammatory cyto–kines.[84] So, this increases protective effects against LPS-induced endotoxemia, septic shock, and even reduced diffusion of proinflammatory cytokines.[84] As well, LPS increased the number of eosinophils heterophils, and other WBCs in broilers. The increase in the number of heterophils is due to their important role in the normal healing of cells. An increase in the level of leukocytes is also a reason for adaptive immunity.[24]

Central lipopolysaccharide effect on the central nervous system

Neuroinflammation is the process of CNS involvement with pathogens. This process causes disorders in behavioral patterns such as depressive-like behavior, cognitive disorders, and social diseases.[34] Different compounds, including LPS, cause neuroinflammation and disorders in behavioral patterns. The most important mechanisms of the CNS in the face of neuroinflammation are the increase of reactive oxygen species (ROS) and activation of proinflammatory cytokines, particularly IL-1β, IL-6, and TNF-α.[85]

Also, neuroinflammation reduces cerebral blood flow (CBF). This reduction in CBF induces cellular stress and eventually cognitive disorders. The mechanism of cell stress induction is as follows: neuroinflammation and disruption of the neurovascular unit reduce CBF. Decreased CBF leads to the accumulation of cellular metabolites and the reduction of the release of toxic substances. As a result, the amount of ROS increases and leads to the induction of cellular stress. Cellular stress can lead to cognitive disorders.[85, 86]

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Also, neuroinflammation is associated with the degradation of membrane phospholipids via secretory phospholipase A2-IIA (sPLA2-IIA). This degradation resulted in the synthesis, and release of AA, lysophospholipids, and predecessors of proinflammatory mediators including prostaglandins and LTs.[87, 88] sPLA2-IIA activation resulted in membrane permeability alternations and interruption of membrane construction.[89] This process caused dysfunctions in CNS and cognitive disorders. These dysfunctions are related to proinflammatory cytokine activation in microglia[90] and astrocytes such as TNF-a, IL-1β, and IL-6.[91]

LPS activates the NF-B pathway by accumulating amyloid-beta plaques in the hippocampus.[92] Activating this pathway increases the accumulation of proinflammatory cytokines and stimulates the activity of microglia cells. Then, cell death occurs in the hippocampus and pathogenic behaviors and cognitive disorders arise.[92] The effects of LPS on neuroinflammation and neurotransmitter release are mediated by IL-1, IL-6, and TNF-α.[8] In addition to the role in the synthesis and release of proinflammatory cytokines, microglia also play a role in the synthesis of nitrogen free radicals and ROS. Microglia promote inflammation through these pathways.[93]

Acetylcholine (Ach) is a parasympathetic neurotransmitter; that inhibits the release of proinflammatory cytokines from macrophages and microglia.[46] Cholinergic system activity by reducing the production of proinflammatory cytokines plays a protective role against the neuroinflammatory process. AchE quickly metabolizes Ach. It has been shown that LPS via increasing AchE activity, reduces the activity of the cholinergic system. Therefore, removes Ach's inhibitory effect on neuroinflammation, and promotes neuroinflammation.[46, 94–96]

Also, dopamine is a neurotransmitter that LPS affects and reduces its concentration.[93] In addition to affecting the brain's reward system, dopamine also affects the stress control centers, including the hypothalamic-pituitary-adrenal (HPA) axis. Therefore, the lack of dopamine by affecting the brain's reward system can cause depressive-like behavior and reduce social activities.[97, 98] Moreover, LPS reduces noradrenaline in the CNS through proinflammatory cytokine mediators. The nucleus secreting noradrenaline in the brain is the locus coeruleus. This nucleus sends many inputs to the hippocampus.[99, 100]

The hippocampus plays an important role in the HPA axis response to stress and behavior. As a result, LPS reduces dopamine and noradrenaline through IL-1, leukemia inhibitory factor (LIF),[26] IL-6, and TNF-α. Subsequently, by affecting the reward system and the HPA axis, it causes fear, stress, mood changes, the reduction of social behaviors, and the appearance of animal sickness behaviors.[31, 101, 102] LPS activates the indoleamine 2,3-deoxygenase (IDO) enzyme through TNF-α to affect social behaviors, especially depressive-like behavior. This enzyme transforms tryptophan into kynurenine. So, the kynurenine level in the circulation and brain increased.[9]

Kynurenine and IDO enzymes are the mediators of cognitive disorders, including depressive-like behavior, mood, and behavior.[103, 104] Peripheral[103] and central[105] injections of LPS induce depressive-like behavior by activating proinflammatory cytokine, and IDO receptors.

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Central lipopolysaccharide effect on memory

LPS induces oxidative stress[106] through activation of microglia, synthesis of proinflammatory cytokines, and release of ROS.[25, 107] Furthermore, oxidative stress induces the production of the 1 κβ inhibitory subunit of the NF- κβ transcription factor which correlates to the neuro-inflammatory cluster in the pathogenic mechanisms of cognitive and behavioral malformations and neuronal damage. Ultimately, these factors decline the endogenous antioxidant system.[108] As well, the level of neurotrophic factors in the brain is reduced, especially in the hippocampus. Damage to the hippocampus induces numerous psychological and neurological disorders such as reduced long-term potentiation (LTP), and behavioral patterns.[1, 109–111] This effect on LTP is mediated by IL-1β and TNF-α.[112] Furthermore, LPS causes major neurological deficits in this way.

LPS causes dysfunction of mitochondria, increases the amount and function of AchE, induces oxidative stress,[1] and reduces NO levels in the brain.[113] Oxidative stress induced by ROS causes mitochondrial dysfunction. This disorder in mitochondrial function is due to damage to mitochondrial membrane lipids via a change in the mitochondrial membrane potential.[114] The cholinergic system in the brain is essential in the process of memory formation. In inflammation induced by LPS, by increasing the activity of the AchE enzyme, neurodegeneration occurs in the cholinergic system, and by causing a decrease in the level of Ach in the hippocampus, it causes memory formation disorders.[85, 115] NO contributes to learning by facilitating LTP. In LPS-induced inflammation in the brain, the activity of the NOS enzyme is reduced, as a result, reducing the level of NO in the hippocampus, causes impairment in learning.[85, 113]

Central lipopolysaccharide effects on behavior

Inflammation diseases in animals affect different aspects of behavior. This change in different aspects of behavior is induced by immune-stimulating substances such as LPS. The main mediators of these responses are proinflammatory cytokines including IL-1β, IL-6, TNF-α (mammals),[116] and TL-1A (birds).[117] These behavioral changes can include depressive-like behavior,[9] fatigue,[10] anxiety-like behavior,[11] anhedonia,[12] lethargy,[13] and anorexia.[57] It is indicated that LPS in laying chickens caused behavioral changes including prolonged sitting and inactivity, hyperthermia, reduced duration of standing, feeding, drinking, movement, and preening.[41, 72] Animals that receive LPS show animal sickness behaviors in loneliness. These animals do not show any animal sickness behaviors in their colonies despite receiving LPS, and IL-6 increased. Animals living in social conditions do not exhibit sickness behaviors in order to maintain their survival.[4]

Fatigue

Infections are associated with numerous systemic symptoms, including fatigue and pseudo-fatigue behaviors.[10] Fatigue is divided into four types: physical fatigue, mental fatigue, environmental fatigue, and immunological fatigue. Immune-induced fatigue is related to the CNS and endocrine system. LPS is usually used to induce this type of fatigue.[118–120] These behaviors are associated with the disruption of the CNS.

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Fatigue and pseudo-fatigue behaviors have symptoms such as headaches, muscle weakness, weakness and reflex slowness, impaired motion coordination, reduced cognitive abilities, and decreased motivation and rewarding behaviors. Most of these behaviors appear after a rest period.[121] The main and precise causes of fatigue are not clear. Researchers suspect that prolonged activation of the immune system during disease and inflammation may be one of the causes of fatigue.[122] In the activation of the immune system during the inflammation, the concentration of proinflammatory cytokines, including IL-2,[123] IL-1β, and TNF-α is high. Also during this period, body temperature decreases.[124] These proinflammatory cytokines can induce fatigue by entering the brain, disrupting the BBB, and damaging serotonergic neurons, the basal ganglia, and the HPA axis.[125–127]

Anhedonia

Anhedonia is a characteristic of various neurological diseases, including major depressive disorder that affects humans.[12] Anhedonia means loss of interest and motivation to perform pleasurable activities and behaviors related to the reward system.[128, 129] In patients with anhedonia, motivational behaviors such as appetite and consumption behavior including food intake are affected and disrupted.[130] In animal models, reduced sensitivity to reward, and inability to enjoy pleasurable experiences are considered anhedonia.[131]

Inflammation is the immune system's response to harmful stimuli. Inflammatory responses in the body aim to preserve tissue and ensure the survival of the organism.[132] LPS-induced systemic inflammation destroys the BBB and causes neuroinflammation.[133] In neuroinflammation, microglia, glial, and astrocytes are activated, and exert their inflammatory and anti-inflammatory effects[134, 135] Microglia (M) cells are of two types: M1 and M2. M1 promotes inflammation by producing proinflammatory cytokines. M2 is anti-inflammatory.[136] Activation of proinflammatory cytokines released by microglia, and astrocytes causes cognitive impairment and depressive-like behavior symptoms including anhedonia.[137]

The increase of proinflammatory cytokines in neuroinflammation causes changes in the secretion and release of brain neurotransmitters including dopamine in the basal ganglia.[12, 138] Decreased dopamine secretion causes decreased motivation,[139] depressive-like behavior, and mood changes including anhedonia.[140] In addition to dopamine, which induces anhedonia in neuroinflammation, endocannabinoids also play a role in this relationship. In neuroinflammation, the brain level of endocannabinoid decreases and may induce anhedonia.[141] In animals, the increase of inflammatory mediators is related to the occurrence of anhedonia behaviors.[142]

IDO increases in response to inflammation and plays a critical role in sickness behaviors such as depressive-like behavior and anhedonia.[45, 103] IDO enzyme in the CNS metabolizes tryptophan to L-kynurenine. As the level of tryptophan decreased, the level of serotonin reduced.[137] This reduction leads to the synthesis and release of neuroregulators including 3-hydroxykynurenine, and quinolinic acid.[143] Increasing the level of these metabolites by affecting N-methyl-D-aspartate receptors causes nerve damage and behavioral changes.[144] Proinflammatory cytokines in LPS-induced inflammation cause anhedonia by increasing serotonin

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transporter enzyme activity and inhibiting serotonin reuptake.[145] Systemic administration of LPS in rats[131] and mice induces anhedonia.[146, 147]

Anxiety-like behavior

Anxiety-like behavior is a vague feeling of fear and worries with an unknown origin which is considered the individual's response to risks. anxiety-like behavior symptoms include uncertainty, helplessness, and physiological arousal; which is sometimes accompanied by increased heart rate and blood pressure.[44] LPS binds to TLR4 in glial cells and releases proinflammatory cytokines.[148, 149] So, LPS via proinflammatory cytokines increases the level of tau proteins and amyloid accumulation. Proinflammatory cytokines subsequently impact the BDNF signaling pathway by reducing the phosphorylation of the BDNF receptor (TrkB) and increasing tau protein levels. As a result, BDNF levels decrease in the hippocampus and cerebral cortex. As a result, it causes anxious behavior.[44] Oxidative stress plays an important role in the induction and pathophysiology of anxiety-like behavior.[150] LPS induces oxidative stress in the brain. Oxidative stress in the brain causes increased production of ROS and induces neuroinflammation in the brain.[150] So, induced behavioral abnormalities including anxiety-like behavior.[11]

Lethargy

Lethargy is a disorder characterized by drowsiness, an unusual lack of energy and mental alertness. It can be caused by a variety of things, including an inflammatory disease, an injury, or medications. Orexin neurons in the lateral hypothalamus area are associated with motivational and reward-based behaviors. These neurons are involved in LPS-induced lethargy. Following inflammation, the activity of orexin neurons is suppressed via GABAergic neurons in the lateral hypothalamus area (LHA).[13] Following inflammation, this activity decreases. Decreased activity of these neurons is associated with lethargy.[151, 152]

Neurons sensitive to inflammation in the brain receive messages related to inflammation from the dorsal complex of the vagus nerve and IL-1. These neurons then integrate the received messages and issue the final response to inhibit the orexin neurons. These neurons might therefore also be involved in lethargy.(77) Melanocortin regulates LHA activity through the melancocortin 4 receptor. GABAergic neurons in the LHA inhibit the activation of orexin neurons.[77] As well, LPS exerts its central effects in the brain through NO. LPS via NO induces behavioral responses such as hypothermia, inactivity, and lethargy.[153]

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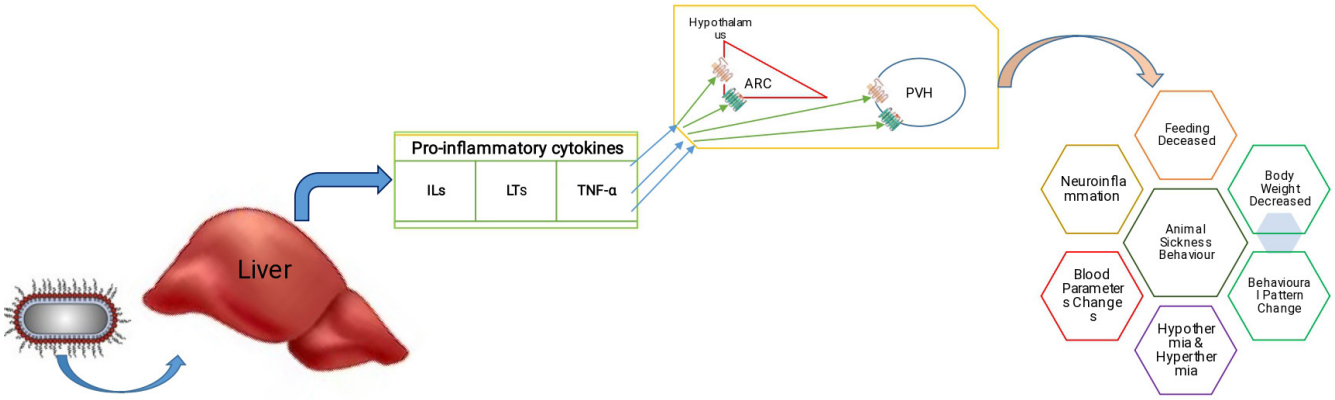

Graphical abstract. Effect of LPS on body physiological responses. CD14: Cluster of differentiation 14. NF-ƙβ: Nuclear factor-ƙβ. TNF-α: Tumor necrosis factor-α. O_2: Superoxide. IL-R: Interleukin-Receptor. LT-R: Leukotriene-Receptor. ARC: Arcuate Nucleus. PVH: Paraventricular Nucleus.↑ : Receptor Stimulating (Own authorship).

Conclusion

Inflammation is the body's physiological response to harmful stimuli. This response is caused by many pathogenic compounds that enter the body. LPS is one of the most common pathogens inducing systemic and central inflammation. Inflammation through the effect on hematopoietic blood cells causes the synthesis and release of proinflammatory cytokines from the liver Kupffer cells. These cytokines include IL-1β, IL-6, IL-10, IL-8, and TNF-α. Then, these proinflammatory cytokines induce neuroinflammation by passing through the BBB and affecting the PVN via LTs, and IL receptors. Neuroinflammation causes animal sickness behavior such as fever, decreased food intake, and body weight, increased circulating WBC, increased apoptosis, memory loss, cognitive disorders, depressive-like behavior, lethargy, fatigue, anhedonia, and anxiety-like behavior (Graphical abstract). Knowing the sequence of behaviors will lead to better identification of inflammation and help to treat it.

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Data availability

All relevant data are included in the document.

Acknowledgments

The authors thank the Ferdowsi University of Mashhad for cooperation.

Funding statement

This review article has not been funded.

Conflicts of interest

The authors have no conflict of interest.

Author contributions

Conceptualization: SH Yousefvand, A Parham, F Hamidi.
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