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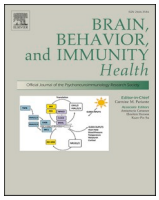

Inflammatory processes in the prefrontal cortex induced by systemic immune challenge: Focusing on neurons

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ABSTRACT

Peripheral immune challenge induces neurobiological alterations in the brain and related neuropsychiatric symptoms both in humans and other mammals. One of the best known physiological effects of systemic inflammation is sickness behavior. However, in addition to this depression-like state, there are other cognitive outcomes of peripherally induced neuroinflammation that can be linked to the dysfunction of higher-order cortical areas, such as the prefrontal cortex (PFC). As the physiological activity of the PFC is largely based on the balanced interplay of excitatory pyramidal cells and inhibitory interneurons, it may be hypothesized that neuroinflammatory processes result in a shift of excitatory/inhibitory balance, which is a common hallmark of several neuropsychiatric conditions. Indeed, many data suggest that peripherally induced neuroinflammation is strongly associated with molecular and functional changes in PFC neurons leading to disturbances in their synaptic networks. Different experimental approaches may cause some incongruence in the reviewed data. However, it is commonly agreed that acute systemic inflammation leads to changes in the excitatory/inhibitory balance in the PFC by proinflammatory signaling at the brain borders and in the brain parenchyma. These cellular changes result in altered local and brain-wide network activity inducing disturbances in the top-down control of goal-directed behavior and cognition regulated by the PFC. Lipopolysaccharide (LPS)-treated rodents are the most widely used experimental models of peripherally induced neuroinflammation, so the majority of the reviewed data come from studies utilizing the LPS model. This may limit their general interpretation regarding the neuronal effects of peripheral immune activation. In addition, several biological variables (e.g., sex, age) can influence the PFC effects of systemic immune challenge, not only the nature and severity of immune activation. Therefore, it would be desirable to investigate inflammation-related neuronal changes in the PFC using other models of systemic inflammation as well, and to focus on the targeted fine-tuning of the affected cell types *via* common molecular mechanisms of the immune and nervous systems.

1. Introduction

Neuroinflammation induced by peripheral immune activation (e.g., infections, injuries) causes diverse neuropsychiatric symptoms in individuals with otherwise normal central nervous system (CNS) functions. Despite the biomedical importance of the CNS effects of peripheral immune challenge, the related neurobiological mechanisms are only partially elucidated. This is especially true for brain regions that play a crucial role in the regulation of behavior and cognition, such as the prefrontal cortex (PFC). The purpose of this short review is to summarize the most important data of recent years describing neuronal changes in the PFC caused by systemic immune activation without claim to completeness. The first three sections highlight three considerations that shape the basic logic of the review: (i) peripheral immune activation induces behavioral and cognitive symptoms, (ii) PFC functions basically rely on the balanced synaptic communication of excitatory and inhibitory neurons, the disturbances of which can also cause neuropsychiatric symptoms, and (iii) peripheral immune activation leads to complex proinflammatory changes at the brain borders and in the CNS parenchyma that potentially influence neuronal functions. The fourth section aims to review how these proinflammatory processes cause changes in the functioning of PFC neurons, which may contribute to the behavioral consequences of systemic inflammation. Lipopolysaccharide (LPS)-treated rodents belong to the most widely used animal models of

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peripherally induced neuroinflammation (Catorce and Gevorkian, 2016), thus the findings reviewed here mainly come from experiments using the LPS model. This may limit the general interpretation of the reviewed data regarding the neuronal effects of peripheral immune activation. Behavioral alterations associated with systemic immune activation are together called sickness behavior, which is an evolutionarily conserved adaptive response in vertebrate species (Lopes et al., 2021) and shows several phenomenological similarities with clinical depression (Maes et al., 2012). However, in addition to the core symptoms of sickness behavior (behavioral suppression, increased somnolence, reduced food and water intake), other cognitive effects of systemic inflammation can be associated with functional disturbances in the CNS, especially in higher-order cortical areas, such as the PFC. Learning and memory impairments, abnormal motor coordination, increased anxiety, and deficits of exploratory behavior have been revealed in rodent models of neuroinflammation-associated diseases (Zhao et al., 2019). Low mood, anxiety, and delirium have been described in the acute phase of COVID-19 infection, while psychosis and catatonia have been reported in the minority of COVID-19 cases (Butler et al., 2020). Cerebral dysfunctions ranging from mild delirium to deep coma have been observed in patients with sepsis-associated encephalopathy (Gofton and Young, 2012), while impairments of associative learning, visual perception, and working memory have been reported in sepsis survivors (Calsavara et al., 2018). Similarly, mnemonic dysfunctions have been described in rodents subjected to systemic immune challenge, e.g. aversive memory impairment in a sepsis model (Mina et al., 2014) and impaired contextual fear conditioning after treatment with bacterial endotoxin (Cunningham and Sanderson, 2008). These neuropsychiatric abnormalities develop mostly in the absence of direct CNS infection or injury (Gofton and Young, 2012; Cosentino et al., 2021), which highlights the complex cellular and molecular mechanisms of neuroimmune communication that are reviewed elsewhere (e.g., Dantzer, 2018; Reardon et al., 2018; Chu et al., 2020). As the majority of cognitive functions impaired by peripherally induced neuroinflammation can be associated with the PFC, the aim of this review is to summarize the recently described neurobiological, especially neuronal processes in the PFC that may contribute to the behavioral and cognitive symptoms of systemic immune activation. However, it should be emphasized that several biological variables can influence the PFC effects of peripheral immune challenge, the detailed discussion of which is beyond the scope of this short review. Perhaps, the most relevant of these variables are sex and age, since it is well established that these factors affect physiological PFC functions (Baena et al., 2010; Knouse et al., 2022) and several aspects of immune responses (Yung, 2000; Klein and Flanagan, 2016). As a result, the CNS effects of neuroimmune interactions may also depend significantly on the sex and age of the individual. Among others, it has been shown that LPS treatment induced sickness behavior in an age- and sex-dependent manner in mice (Cai et al., 2016), and experimental myocardial infarction led to different degrees of depression-like behavior and cytokine production in the PFC in male and female rats (Najjar et al., 2018). Thus, for a holistic overview of the PFC effects of peripherally induced acute neuroinflammation, the nature and severity of immune activation should be taken into account, as well as other fundamental biological variables.

2. The basics of PFC organization and its functional aspects

The PFC plays a central role in the regulation of goal-directed behavior and higher brain processes (Kesner and Churchwell, 2011; Friedman and Robbins, 2022), and its dysfunctions are involved in the pathophysiology of many neuropsychiatric diseases (Murray et al., 2011; Smucny et al., 2022). Different subregions of the PFC developed at different stages of the mammalian evolution. The agranular parts (i.e., lacking cortical layer 4) of the PFC evolved earlier, thus these can be found both in rodents and primates. On the other hand, rodents do not have homologues of the granular subregions of the PFC that evolved later and form the largest part of the primate PFC (Preuss and Wise, 2022). The extensively studied rodent PFC covers the medial wall of the frontal lobe (medial PFC, mPFC), and is thought to be homologous with the agranular medial frontal cortex of primates (Anastasiades and Carter 2021; Preuss and Wise, 2022). The mPFC regulates higher brain functions *via* its long-range connections and local network activity, which is driven by the balanced synaptic communication of excitatory pyramidal cells and inhibitory interneurons (Ferguson and Gao, 2018; Anastasiades and Carter 2021). This dynamically regulated balance between excitatory and inhibitory neurotransmission is a general principle of cortical network organization, and profound evidence suggests its crucial role in the maintenance of PFC-regulated cognitive functions (Jocham et al., 2012; Bicks et al., 2015; Selimbeyoglu et al., 2017). Excitatory/inhibitory imbalance in the PFC has been widely associated with different neuropsychiatric conditions accordingly (Legon et al., 2016; Page and Coutellier, 2019; Voineskos et al., 2019). The main subtypes of mPFC pyramidal cells are distributed across layer 2/3 and layer 6, where they form local excitatory circuits and maintain widespread afferent and efferent connections with many other brain regions (e.g., basolateral amygdala, mediodorsal thalamus, ventral hippocampus, ventral tegmental area, contralateral mPFC) (Anastasiades and Carter 2021; Le Merre et al., 2021). Synaptic integration and output of these projection neurons are accurately regulated by local inhibitory interneurons, which form well-defined circuit motifs (e.g., feedforward and feedback inhibition, disinhibition) in each layer of the mPFC supporting the computational capacity and plasticity of excitatory networks (Ferguson and Gao, 2018; Anastasiades and Carter 2021). The heterogeneous interneuron population of the mPFC is also innervated by subcortical structures (e.g., thalamus, amygdala, raphe nuclei), which is crucial for the precise gating and transmission of the incoming long-range inputs (Sun et al., 2019; Yang et al., 2021). Thus, the neurophysiological substrate of proper PFC function is the balanced interplay of glutamatergic and GABAergic neurons, which is fine-tuned by the long-range inputs targeting both cell populations. The resulting local network activity shapes the output of projection neurons to cortical and subcortical regions enabling the top-down control of goal-directed behavior and cognition by the PFC according to sensory signals and internal cues (Zhang et al., 2016; Otis et al., 2017; Paneri and Gregoriou, 2017).

3. CNS processes related to peripherally induced acute neuroinflammation

Systemic immune activation leads to molecular, cellular, and circuit-level changes in the brain parenchyma with the involvement of resident CNS cells (neurons, glial, and vascular cells) and brain-invading immune cells (e.g., leukocytes and perivascular macrophages) (Fig. 1). If the four hallmarks of CNS inflammation (elevated levels of proinflammatory cytokines, microglial activation, immune cell infiltration, and local tissue damage) can be identified, then the tissue response can be termed as neuroinflammation (Estes and McAllister, 2014). Peripheral immune activation signals to the CNS mainly *via* the blood-brain barrier (BBB) and other brain borders (meninges, choroid plexus) (Matsumura and Kobayashi, 2004; Frederick et al., 2022), however, BBB-independent pathways (e.g., circumventricular organs and vagal afferents) also contribute to the neuroimmune communication (Quan, 2008). Inflammatory signaling at the BBB requires all cell types of the neurovascular unit (NVU), and involves both physiological (e.g., cytokine, chemokine, and prostaglandin E_2 signaling) and pathological (e.g., BBB disruption and leakage during severe inflammation) mechanisms leading to a proinflammatory tissue environment in the brain parenchyma (Matsumura and Kobayashi, 2004; Banks et al., 2015; Tohidpour et al., 2017).

Immune-to-brain communication at the BBB during systemic inflammation involves all cellular (endothelial cells, pericytes, astrocytes, and in a broader sense, microglia as well) and noncellular components (endothelial glycocalyx, endothelial and astrocytic basement membrane) of the NVU, which has been thoroughly reviewed elsewhere

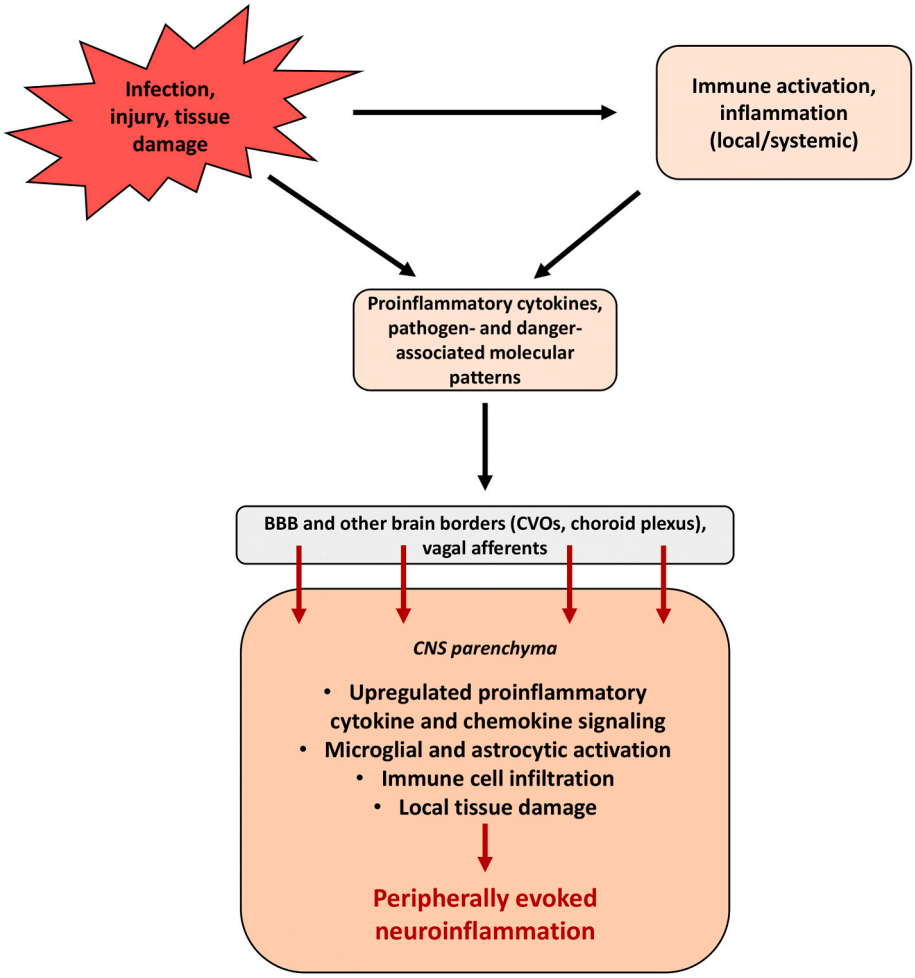

Fig. 1. Peripheral immune activation signals to the brain *via* different mechanisms and induces proinflammatory tissue response in the CNS parenchyma. Peripheral infections and injuries trigger immune responses leading to local and/or systemic inflammation with enhanced proinflammatory processes. Proinflammatory mediators, especially cytokines, reach the brain through the blood circulation and induce inflammatory signaling at the brain borders resulting in the activation of CNS immune response. The mechanisms of immune-to-brain communication at the blood-brain barrier (BBB) involve all cell types of the neurovascular unit. In addition, signaling in the circumventricular organs (CVOs) and choroid plexus can also contribute to the transmission of peripheral inflammatory signals to the CNS parenchyma. The afferent fibers of the vagus nerve can be directly stimulated by proinflammatory mediators in peripheral tissues, which underlies the major neural mechanism of neuroimmune interactions. Once inflammatory signals of peripheral origin are transferred to the CNS parenchyma, they induce secondary neuroinflammation being manifested in cytokine signaling, microglial and astrocytic activation, immune cell infiltration, and consequently in local tissue damage.

(e.g., Galea, 2021; Huang et al., 2021). BBB endothelial cells express cytokine receptors so they can efficiently respond to immune activation by enhancing inflammatory gene expression and signaling *via* soluble mediators and extracellular vesicles acting on other NVU and parenchymal cells (Pan et al., 2011; Lopez-Ramirez et al., 2012; Yamamoto et al., 2015). Under more severe inflammatory conditions, endothelial cells coordinate the passage of leukocytes into the brain, and the disruption of their tight junctions leads to solute leakage across the BBB (Galea, 2021; Huang et al., 2021). Pericytes are the mural cells of the BBB taking part basically in the adjustment of capillary diameter and in the regulation of cerebral blood flow at the microcirculation level (Muoio et al., 2014; McConnell and Mishra, 2022). However, these cells also respond to immune activation by proinflammatory mechanisms, like enhanced expression of cyclooxygenase-2, production of reactive oxygen and nitrogen species, enhanced phagocytic activity, activated NF-κB pathway, and expression of chemokines and cytokines (Jansson et al., 2014; Pieper et al., 2014). The immune response of the CNS is mainly mediated by microglia that show molecular and morphological changes in response to immunogenic effects (Rodríguez et al., 2022). At the same time, it should be emphasized that the proinflammatory signaling at the brain barriers is at least as important as microglial activation and in some cases (e.g., in depression with mild peripheral inflammation) may play a more significant role than microglial cells (Turkheimer et al., 2023). The exact mechanism and result of microglial activation depend on the nature and severity of stimuli. However, amoeboid morphology, increased phagocytic activity and migration, enhanced cytokine signaling, recruitment of peripheral immune cells, and the engulfment of dying cells and cellular debris are strongly related to the immune functions of activated microglia (Woodburn et al., 2021). Astrocytes are also immune-competent cells that substantially contribute to neuroinflammation with similar mechanisms, such as enhanced proinflammatory gene expression, upregulated cytokine and chemokine signaling, direct cell contacts with peripheral immune cells, and altered regulation of BBB permeability (Dong and Benveniste, 2001; Colombo and Farina, 2016; Diaz-Castro et al., 2021). Microglia and astrocytes are also integrant components of the NVU, and they cooperatively contribute to BBB inflammatory signaling induced by peripheral immune activation. Depending on the nature of the immune challenge, both cell types can produce anti- or proinflammatory mediators. Their proinflammatory processes discussed above largely influence BBB permeability mainly through interactions with endothelial cell tight junctions and BBB transporters, production of reactive oxygen species,

and promotion of peripheral immune cell infiltration (Liu et al., 2020; Huang et al., 2021). The inflammatory activity of oligodendrocytes seems to be more limited due to their special role in myelin sheath formation. These cells may participate in neuroinflammation indirectly by the secretion of signaling molecules acting on other glial and immune cells (Yang and Zhou, 2019; Nutma et al., 2020). These neuroimmunological processes related to glial and immune cells may have both protective (acute, low-level inflammation) and detrimental (chronic inflammation) effects on neuronal functions depending on the nature and duration of activating stimuli (Colombo and Farina, 2016; DiSabato et al., 2016; Liu et al., 2016). Several of these proinflammatory changes have already been observed in the PFC using rodent models of systemic immune activation (Ji et al., 2020; Jiang et al., 2022). Thus, their effects on neuron-specific processes (e.g., intrinsic excitability, synaptic communication) should be investigated for a better understanding of CNS symptoms of systemic inflammation. Some data suggest that peripheral inflammation induces disturbances in neuronal excitability and synaptic transmission leading to an abnormal (mostly increased) ratio of excitation/inhibition. Experimental gut inflammation was shown to increase clonic seizure susceptibility *in vivo* and to enhance burst firing after 4-aminopyridine treatment in hippocampal slices (Riazi et al., 2008). These effects appear to depend on microglial tumor necrosis factor-alpha (TNF-α) signaling (Riazi et al., 2008), which may be related to the ability of this cytokine to increase the expression of glutamate receptors and to decrease the expression of GABA receptors on neurons (Olmos and Lladó, 2014). Other mechanisms may also contribute to the excitatory/inhibitory imbalance induced by systemic immune activation as it was found in the murine hippocampus that peripheral LPS treatment leads to inhibitory synapse-related protein loss *via* complement C3/C3a receptor signaling (Li et al., 2020). Ultimately, the interactions of these inflammation-related effects, especially in the case of chronic inflammation, can induce secondary pathological changes in the brain, e.g., altered cerebral blood flow and metabolism, perturbed mitochondrial dynamics and energy production, altered pH regulation, excitotoxicity, reactive gliosis, neurodegenerative processes, and oxidative stress (Morimoto et al., 2002; Semmler et al., 2008; Sankowski et al., 2015; Tyrtyshnaia et al., 2016; Harland et al., 2020; Gu et al., 2021). Oxidative stress is a major mechanism involved in several CNS pathologies related to neuroinflammation and cognitive decline. This is also supported by the observation that reducing oxidative stress by cholinergic agonists with significant antioxidant potential improves scopolamine-induced cognitive deficits in mice (Srivastava et al., 2019; Tripathi et al., 2019). In conclusion, systemic immune activation results in an inflammatory tissue milieu in the CNS leading to widespread changes at all levels of neural functioning. Subsequently, this inflammatory response induces compensatory mechanisms in all CNS cell types in order to restore tissue homeostasis and brain functions.

4. Neuronal alterations in the PFC related to peripherally induced acute neuroinflammation

The neuronal effects of peripheral immune activation require the transmission of proinflammatory signals to neurons, which can be achieved directly by immune-specific molecular signals and/or by secondary stress signals related to the proinflammatory tissue milieu in the CNS. Direct contacts between immune cells and neurons have been associated mainly with severe neuroinflammatory conditions (Nitsch et al., 2004; Liblau et al., 2013; Brummer et al., 2022), while paracrine communication mechanisms (e.g., signaling by cytokines, chemokines, and kynurenine metabolites) may play a more significant role in physiological neuroimmune interactions and moderate neuroinflammation (Stone et al., 2022). In each case, neurons need to express the proper immune-related proteins (receptors, coreceptors, adaptor proteins, signaling proteins, transcription factors, etc.) enabling the detection of inflammatory signals and the adequate cellular response. Indeed, it has long been observed that neurons express genes and proteins classically linked to immunological functions both under physiological and pathological conditions, e.g., MHC class I genes (Lv et al., 2015), complement components (Thomas et al., 2000), chemokines (De Haas et al., 2007), cytokines (Cavanaugh et al., 2015), and their corresponding receptors (Sawada et al., 1993; Callewaere et al., 2007). The bioinformatics analysis of our single-cell transcriptomic data also revealed that PFC neurons express several genes associated with immune functions, such as antimicrobial activity and communication process between lymphocytes (Mittli et al., 2021). The single-cell harvesting was performed on pyramidal cells and fast-spiking interneurons in PFC slices of wild-type male mice (Ravasz et al., 2021), suggesting that the neuronal expression of these immune-related genes may contribute to physiological brain processes. The vast majority of the immune genes were expressed by small number of neurons with low copy numbers. However, more than 85% of the investigated transcripts could be identified in the transcriptome of PFC neurons, which does not differ remarkably from sequencing data from immune cells. The next step in understanding the neuronal expression of immune genes should be performed at the level of functional proteins to show that they are indeed synthesized based on their mRNAs and to investigate their function in CNS neurons. Therefore, we focused on interleukin-1 beta (IL-1β) signaling because its role in neuroinflammatory processes is well established (Basu et al., 2004; Mendiola and Cardona, 2018). Our transcriptomic data showed that the gene encoding the receptor of IL-1β (IL-1R1) was similarly expressed in excitatory and inhibitory PFC neurons, however, the gene encoding the coreceptor of IL-1β (IL-1RAcP) was expressed predominantly by pyramidal cells. As both proteins are necessary for the cellular effects of IL-1β (Dinarello, 2009), we chose a simple method to investigate the functional effect of this transcriptomic difference. We recorded the electrophysiological activity of the two cell types in acute PFC slices of mice and found that the intrinsic excitability of pyramidal cells was enhanced by IL-1β in a concentration-dependent manner, which could be abolished by the antagonist of IL-1R1. Contrarily, fast-spiking interneurons did not show any electrophysiological changes during IL-1β treatment (Mittli et al., 2023). Thus, we did not demonstrate the different distribution of the IL-1RAcP protein in the two cell types, but our functional data seem to confirm the transcriptomic results and suggest that IL-1β may induce excitatory/inhibitory imbalance in the PFC. Other interleukins can also cause disturbances in the synaptic networks of the PFC. Interleukin-6 (IL-6) was found to reduce the amplitude of inhibitory postsynaptic currents of pyramidal cells in rat and mouse brain slices (Garcia-Oscos et al., 2015). Since we aimed to study the potential network-level effects of the IL-1β-related neuronal changes, mice were treated with bacterial LPS and fronto-occipital electroencephalographic (EEG) recordings were performed (Mittli et al., 2023). It is well known that peripheral immune challenge increases the brain levels of proinflammatory cytokines (Tonelli and Postolache, 2005), and we also demonstrated it in our model. The EEG recordings revealed an altered neural oscillation in the frontal cortex and changes in fronto-occipital functional connectivity during peripherally induced acute neuroinflammation (within 24 h after LPS treatment). As synaptic processes largely contribute to field potentials and related brain functions, we prepared synaptosomes from the PFC and analyzed the LPS-induced protein changes by proteomic methods. The synaptosome samples were prepared 4 h after LPS administration, i.e., we evaluated the short-term synaptic changes related to acute sickness behavior. The proteomic data suggest that systemic inflammation leads to widespread molecular changes in PFC synapses related to synaptic signaling, cytoskeletal organization, carbohydrate/energy metabolism, and redox state regulation (Mittli et al., 2023). Wang et al. (2016) reported similar proteomic changes (altered energy metabolism, neurogenesis, cytoskeleton, and signal transduction) in the PFC of LPS-treated mice 6–24 h after LPS injection. However, this experiment was performed on whole tissue samples, thus the observed alterations cannot be linked directly to certain cellular or subcellular components. Other studies have also revealed functionally relevant changes in PFC neurons

associated with neuroinflammatory conditions (Garcia-Oscos et al., 2015; Ji et al., 2020; Diaz-Castro et al., 2021; Feng et al., 2021; Jiang et al., 2022). LPS treatment increased the levels of GABA signaling-related proteins in the mPFC and enhanced the inhibitory postsynaptic currents in mPFC pyramidal cells as measured by patch clamp recordings in acute brain slices (Jiang et al., 2022). The reported molecular and synaptic changes were associated with altered oscillatory activity in the mPFC, which could be attenuated by minocycline treatment (an inhibitor of microglial activation) (Jiang et al., 2022). These data suggest that peripherally evoked neuroinflammation increases the

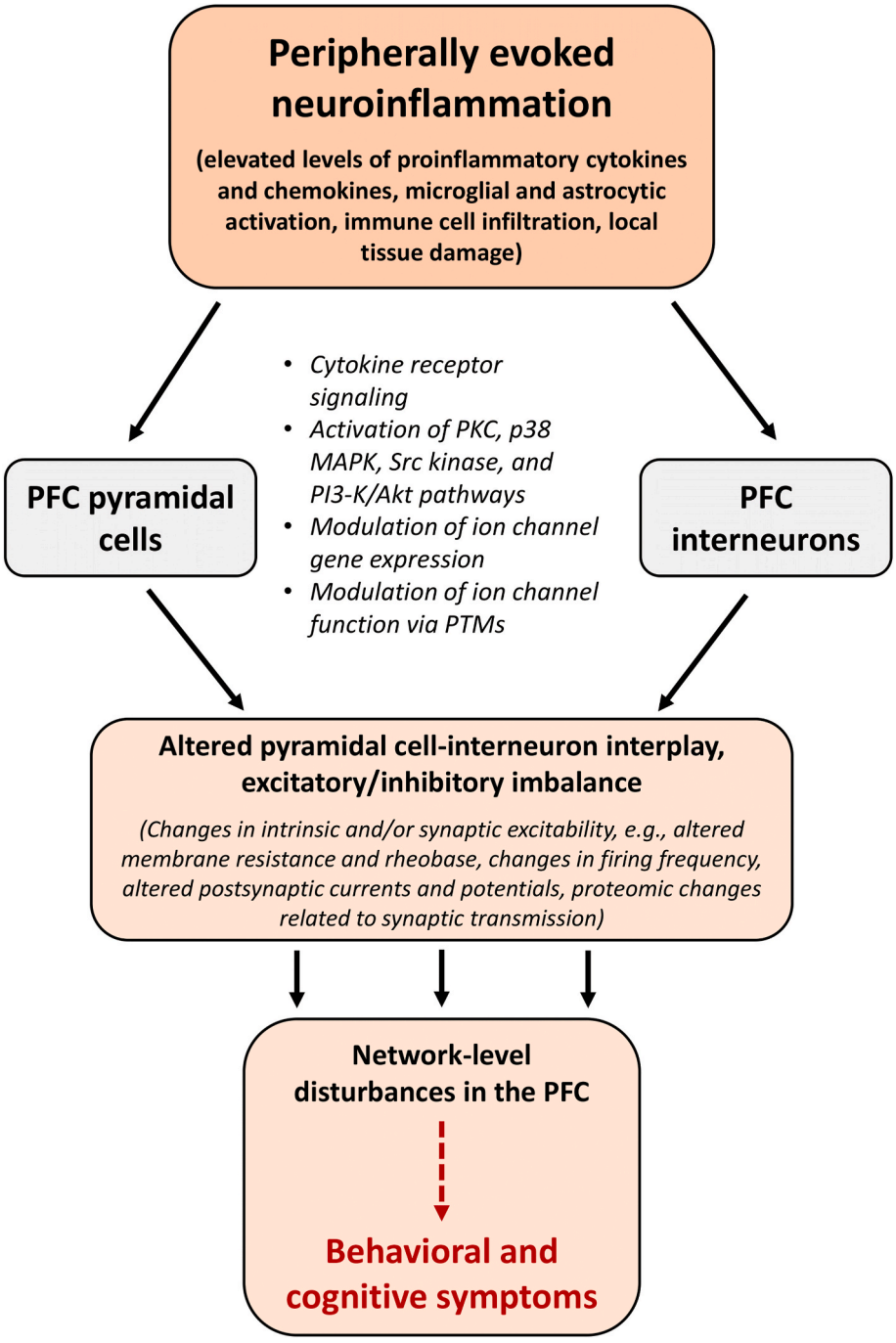

Fig. 2. Peripherally evoked neuroinflammation leads to altered neuronal function in the PFC through various molecular and cellular mechanisms. Proinflammatory signaling at the brain borders during systemic inflammation activates the immune response of the CNS, one of the most important factors of which is cytokine production by glial cells. However, other cell-to-cell communication mechanisms may also contribute to the inflammatory interactions between glial cells, brain-invading immune cells, and neurons. Neurons express several cytokine and chemokine receptors so these proinflammatory mediators can activate intracellular signaling pathways leading to altered intrinsic and/or synaptic excitability of PFC pyramidal cells and interneurons. Transcriptome and proteome differences between neuron types presumably contribute to the cell type-specific effect of certain proinflammatory molecules. The molecular mechanisms of inflammation-induced electrophysiological changes can mainly be linked to the altered expression of voltage- and ligand-gated ion channel genes and to the modulation of ion channel function by posttranslational modifications (PTMs). The altered electrophysiological and synaptic properties of PFC neurons lead to excitatory/inhibitory imbalance in the synaptic networks of PFC and to disturbances in oscillatory synchronization between the PFC and other brain regions. These network-level changes can ultimately contribute to the behavioral and cognitive symptoms of acute peripheral immune activation.

inhibitory neurotransmission in the mPFC (i.e., induces excitatory/inhibitory imbalance), which is predominantly mediated by microglial activation. The results of Feng et al. (2021) also support this idea. The authors found in acute brain slices of LPS-treated mice that fast-spiking parvalbumin (PV) interneurons in the prelimbic cortex enhanced their intrinsic excitability, whereas pyramidal cells did not show any measurable electrophysiological changes. In addition, the hyperexcitable state of PV interneurons was associated with an enhanced recruitment of these cells during novel object recognition, as shown by the LPS-induced increase in the percentage of c-fos immunoreactive interneurons 1.5 h after the behavioral test (Feng et al., 2021). Regarding the electrophysiological activity of PFC pyramidal cells during systemic immune activation, other data also show that these cells do not change significantly their intrinsic and synaptic activity in brain slices of LPS-treated mice (Diaz-Castro et al., 2021). However, our results revealed a moderate enhancement of pyramidal cell excitability, which appeared to partially reflect the excitatory effect of *ex vivo* IL-1β-treatment (Mittli et al., 2023). Thus, multiple data suggest that peripherally induced neuroinflammation results in increased GABAergic activity in the PFC. At the same time, Ji et al. (2020) reported reduced expression of PV and glutamate decarboxylase and decreased intensities of vesicular GABA transporter and PV buttons in the mPFC of LPS-treated rats, which indirectly implies the weakening of GABAergic neurotransmission. Similarly, it was shown in rat and mouse brain slices that LPS treatment reduces the synaptic ratio of inhibitory and excitatory currents in mPFC pyramidal cells, which can be prevented by an IL-6 antagonist and by the activation of the cholinergic anti-inflammatory reflex (Garcia-Oscos et al., 2015).

The molecular pathways connecting inflammation and altered cellular electrophysiology are only partially understood. Nevertheless, the activation of neuronal cytokine receptors and the subsequent post-translational modifications of voltage- and ligand-gated ion channels by PKC, p38 MAPK, and Src kinases and by the PI3–K/Akt pathway seem to be strongly involved (Diem et al., 2003; Viviani et al., 2003; Zhou et al., 2011; Ghosh et al., 2016) (Fig. 2). The modulation of ion channel expression and function by inflammatory mediators and the related molecular pathways are thoroughly reviewed elsewhere (Eisenhut and Wallace, 2011). In conclusion, several studies utilize the LPS model to induce neuroinflammation in laboratory animals (for details see Table 1). The differences in the dose and batches of LPS, the number of treatments, and the time after administration may contribute to the heterogeneity of the reported results. On the other hand, it can be seen that peripheral immune activation induces molecular and electrophysiological changes in PFC neurons, which can be detected at the synaptic,

Table 1
Neurobiological changes in the PFC related to peripherally induced neuroinflammation. Only those results are highlighted from the reviewed publications that could be linked to neuronal cells (EPSC: excitatory postsynaptic current, GAD67: glutamate decarboxylase 1, IPSC: inhibitory postsynaptic current, PV: parvalbumin, SST: somatostatin, VGAT: vesicular GABA transporter).

Publication	Animals	Neuroinflammation model	Time between treatment and data collection	Main results
Diaz-Castro et al. (2021)	C57BL/6J mice (female, 8–9 weeks old)	a single dose of LPS (5 mg/kg, i.p.)	48 h	no differences in neuron numbers in the PFC; no differences in PFC pyramidal cell excitability parameters; unaltered spontaneous EPSCs; slightly increased frequency of miniature EPSCs; unaltered amplitude of miniature EPSCs
Feng et al. (2021)	GAD67-GFP mice and PV-Cre mice on C57BL/6J background (male, 8–10 weeks old)	a single dose of LPS (0.3 mg/kg, i.p.)	6 h	increased intrinsic excitability of fast-spiking interneurons in the mPFC (increased input resistance and decreased rheobase, higher firing frequency); specifically, PV interneurons in the prelimbic mPFC showed enhanced intrinsic excitability; no differences in the excitability of non-fast-spiking interneurons and pyramidal cells; increased recruitment of PV interneurons during novel object recognition
Garcia-Oscos et al. (2015)	C57BL/6J mice and Sprague Dawley rats (25–50 days old, sex not reported)	acute brain slices treated with IL-6 (10 ng/ml)	acute experiment	decreased IPSC amplitude in mPFC pyramidal cells
		a single dose of LPS (10 mg/kg, i.p.)	<3.5 h	decreased synaptic ratio between inhibitory and excitatory synaptic currents (sI/E) in mPFC pyramidal cells; decreased IPSC saturation current
Ji et al. (2020)	Sprague Dawley rats (male, 10–12 weeks old)	repeated LPS treatment for three consecutive days (1 mg/kg, i.p.)	6 days (after the first LPS injection)	decreased intensities of GAD67 and PV in the mPFC, while no differences in SST intensity; decreased intensities of VGAT and PV buttons in the mPFC; no differences in baseline neural oscillations in the mPFC, while decreased field potential power during novel object recognition test
Jiang et al. (2022)	C57BL/6J and GAD67$^{+/GFP}$ knock-in mice (male and female, 1–2 months old)	a single dose of LPS (0.5 mg/kg, i.p.)	2 h	increased amplitude and frequency of miniature IPSCs in mPFC pyramidal cells, while no differences in miniature EPSCs; increased number of dendritic spines in the same cells; no differences in the synaptic currents of mPFC GABAergic interneurons; increased expression of GABA signaling proteins in the mPFC; increased evoked IPSC amplitude in mPFC pyramidal cells; increased probability of presynaptic GABA release; increased GABA concentration in the mPFC; altered oscillatory activity in the mPFC
Mittli et al. (2023)	C57BL/6N mice (male, 1–6 months old)	acute brain slices treated with IL-1β (0.05–20 ng/ml)	acute experiment	enhanced intrinsic excitability of mPFC pyramidal cells; unaltered excitability of fast-spiking interneurons
		a single dose of LPS (2 mg/kg, i.p.)	2–24 h	slightly enhanced excitability of mPFC pyramidal cells in brain slices; altered neural oscillation in the frontal cortex; altered fronto-occipital functional connectivity; proteomic changes of PFC synapses (signaling, cytoskeletal organization, carbohydrate metabolism)
Wang et al. (2016)	CD-1 mice (male, 10–14 weeks old)	a single dose of LPS (0.83 mg/kg, i.p.)	6–24 h	proteomic changes in the PFC (energy metabolism, neurogenesis, cytoskeleton, signal transduction, redox homeostasis, nucleic acid metabolism, molecular chaperones)[a]

[a] This proteomic experiment was performed on whole tissue samples from the PFC, thus the reported changes cannot be directly linked to certain PFC cell types.

cellular, and network levels and presumably lead to excitatory/inhibitory imbalance in the local networks of PFC. In most cases, the observed neuronal changes are associated with glial activation, suggesting that peripherally induced neuroinflammation affects neuronal functions indirectly *via* the proinflammatory processes of other CNS-resident and invading cell types.

5. Conclusions and future directions

It has long been observed that neuroinflammatory processes and PFC dysfunctions play major role in the pathomechanism of several CNS disorders. Both acute inflammatory and chronic neuropsychiatric conditions appear to share a common neurophysiological mechanism, namely the disturbed balance of excitatory and inhibitory neurotransmission in cortical circuits. A more thorough understanding of these processes could be facilitated by studies on appropriate animal models using omics and classical approaches, as unbiased omics data are particularly suitable for identifying new mechanisms and potential drug targets. Since most of the available data related to the effects of systemic inflammation on PFC neurons are based on the LPS model of Gram-negative bacterial infection and on the application of proinflammatory cytokines, it would be relevant to investigate neuronal changes using other models of peripheral immune activation as well. For instance, the systemic administration of Gram-positive bacterial toxins (e.g., peptidoglycan, lipoteichoic acids) and heat-killed bacteria, infection with various live bacteria, the cecal ligation and puncture model, local inflammation models (e.g., paw inflammation, experimental periodontitis), or viral infection models (e.g., the administration of double-stranded RNA from viruses). Emphasis should also be placed on the nervous system application of drugs that affect the immune system in a well-known manner, as numerous data suggest that there are many common molecular mechanisms in the physiological and pathological functioning of the immune and nervous systems. The selective fine-tuning of the affected CNS cell types is particularly desirable, which could be performed *via* brain area- and cell type-specific manipulations (e.g., focusing on PFC pyramidal cells or interneurons). Currently, methods partially based on *in vivo* molecular mechanisms seem to be the most suitable for this purpose, such as mRNA-based therapeutics or drug delivery by modified extracellular vesicles. To conclude, several clinical and experimental observations have provided insight into how acute immune activation can have remarkable effects on PFC-related behavioral and cognitive processes. This review aimed to address neuronal changes in the PFC associated with acute systemic inflammation based on publications of recent years mainly utilizing LPS or cytokine treatment to induce immune activation in rodents. Most of the reviewed data suggest that peripherally evoked neuroinflammation causes widespread molecular changes in PFC neurons leading to altered intrinsic excitability and synaptic transmission and thus to changes in excitatory/inhibitory balance in PFC circuits. These molecular and cellular alterations may contribute to the inflammation-related disturbances of goal-directed behavior and cognition regulated by the PFC.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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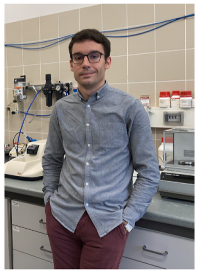

Dániel Mittli is a PhD candidate in Molecular Cell and Neurobiology and part-time researcher at the Institute of Biology, ELTE Eötvös Loránd University and InnoScience Ltd. He completed his BSc in Biology (2017) and his MSc in Neuroscience and Human Biology (2019) also at ELTE under the supervision of Dr. Katalin Adrienna Kékesi in the laboratory of Dr. Gábor Juhász (Laboratory of Proteomics). His graduate research focused on the bioinformatics analysis of single-cell mRNA sequencing data obtained from prefrontal cortical pyramidal cells and interneurons, with particular attention to genes that were traditionally associated with immune functions. Then, he applied for a PhD student position in the same lab and continued his work in collaboration with the ELTE NAP Neuroimmunology Research Group as well as with other Hungarian and foreign laboratories (University of Pennsylvania, Institute of Biochemistry of the Romanian Academy, Babeș-Bolyai University). During his PhD, he was studying neuroinflammatory processes in the prefrontal cortex related to the neuropsychiatric symptoms of peripheral immune activation (e.g., sickness behavior, delirium) using *ex vivo* and *in vivo* electrophysiological methods, as well as omics and bioinformatics approaches. Besides, he was supervising the graduate research of biophysics and biology students. Recently, he is working on the functional effects of systemic inflammation on the visual system, since it is well known from human clinical data that severe inflammatory conditions (e.g., COVID-19 infection, sepsis-associated encephalopathy) cause disturbances not only in higher-order cognitive processes, but also in basic sensory functions. His work has been supported by the National Research, Development and Innovation Office of Hungary and by the Gedeon Richter Plc. Centenarial Foundation, Budapest, Hungary.