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REVIEW ARTICLE

Mutual relations between the amygdala and pro-inflammatory cytokines: IL-1β and IL-6

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Abstract

Interleukin 1 (IL-1) and interleukin 6 (IL-6) are typical examples of multifunctional pro-inflammatory cytokines involved in the regulation of the immune response, hematopoiesis, and inflammation. Both peripheral and intraventricular administration of these cytokines causes acute phase symptoms, e.g. fever, activation of the hypothalamic-pituitary-adrenal axis and psychological depression. The amygdala belongs to the strucxtures of the limbic system involved in the regulation of the immune response. Increased activity of immune system may lead to changes in the role of amygdala, medial prefrontal cortex, anterior cingulate cortex or insula. The aim of the study was to present the mutual interactions between the amygdala and pro-inflammatory cytokines such as interleukin 1β (IL-1 beta) and interleukin 6 (IL-6). Most of the data included in this review comes from animal studies.

Keywords: amygdala · inflammation · IL-1β · IL-6

Citation

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Introduction

Interleukin 1 (IL-1) and interleukin 6 (IL-6) are typical examples of multifunctional pro-inflammatory cytokines involved in the regulation of the immune response, hematopoiesis, and inflammation. Both peripheral and intraventricular administration of these cytokines causes acute phase symptoms, fever, activation of the hypothalamic-pituitary-adrenal axis and depression. The amygdala belongs to the structures of the limbic system involved in the regulation of the immune response. Increased activity of immune system may lead to changes in the role of amygdala, medial prefrontal cortex, anterior cingulate cortex or insula [1-4].

Many authors demonstrate that excessive inflammatory responses play an essential role in the pathophysiology of anxiety disorders and depression. Increased serum levels of inflammatory cytokines were observed in patients with depressive disorders. Neuroinflammation is caused by the activation of microglial cells, which stimulate nuclear factor-kappa B (NF-κB) and produces inflammatory cytokines. Systemic inflammation caused by peripheral injection of lipopolysaccharide (LPS) mobilizes the innate immune system, which in turn creates neuroinflammatory responses in the brain.

The aim of this study was to present the mutual interactions between the amygdala and pro-inflammatory cytokines such as interleukin 1-beta (IL-1 beta) and interleukin 6 (IL-6).

Materials and methods

We searched the Medline and Google Scholar databases for articles published in English language, in the years 2015-2020 using the following keywords: amygdala IL 1-beta, IL6, inflammation. The inclusion criteria was that the article focused on the role of amygdala in the inflammatory process, particularly in the context of anxiety disorders.

Results

The search retrieved 294 articles, 45 of which were included in the review. Most of the data included in this review comes from animal studies.

Characteristics of the amygdala

The amygdala (*corpus amygdolideum*) is a group of nuclei deep in the abdominal part of the temporal lobes of the brain. In terms of functional division, the amygdala is included in the limbic system, the part of the central nervous system that is heavily involved in regulating autonomic, secretory and behavioral emotional responses [5].

The amygdala is a heterogeneous structure in terms of morphology, histochemistry and anatomy. It has a rich system of afferent and efferent connections, both subcortical and cortical. It was proposed to divide the amygdala into two parts: phylogenetically older cortico-medial region and phylogenetically younger basolateral-lateral region [6]. According to this division, the cortico-medial part consists of the following nuclei: the middle, medial, cortical and the nucleus of the lateral olfactory tract. On the other hand, the posto-lateral area consists of the basal nucleus, which includes the large and small-cell nucleus and the lateral nucleus. The medial cortex has a stronger connection with the lower levels of the nervous system, which are mainly responsible for triggering autonomic and emotional responses. The basolateral part has stronger links with the higher parts of the nervous system with a rather inhibitory or modulating effect on the motivational behavior of animals [7-8].

Within the amygdala, the nuclei receiving the afferent fibers are located mainly laterally and are usually referred to as the lateral nuclei. Thus, afferent fibers can be divided into cortical and subcortical. The subcorticals are especially important in infancy and childhood, when the amygdala grows faster than the hippocampus. All the associative sensory regions have direct access to the lateral amygdala nucleus. These regions are also connected to the prefrontal cortex by long bundles of associative fibers, giving conscious sensations and objects a cognitive assessment. The activity of the visual association cortex is particularly important in connection with the clinical problem of phobias and anxiety states. The V4 field is connected to the object and face recognition path. The V5 field leads to the motion detection path. Both contact the amygdala via the hippocampus, and therefore current events can evoke fearful memories. The orbital part of the prefrontal cortex of the right hemisphere is usually active along with the right amygdala in stressful situations. The back of the insula has direct access to the amygdala and is likely to be associated with emotional pain assessment. The activity of the Meynert's nucleus increases during the feeling of anxiety, influencing the increase in the autonomic activity that involves the amygdala [7-8].

The afferent fibers from the amygdala run in the form of an marginal line. The second exit projection is the medial discharge pathway, which runs medially and ends in the nucleus accumbens. The amygdala sends projections to the periaqueductal gray (PAG), which is the source of spinal pain suppression [7-8].

An important part of the research on the functional organization of the amygdala concerned the role of the central nucleus and the basolateral part in the mechanisms of classical conditioning of fear reactions. Based on the work on selective damage to the amygdala, it was noted that it is the main recipient of sensory information in the amygdala [9-10] in the area of auditory and contextual stimuli [11-15] The results obtained with the use of selective injury techniques and with the use of electrophysiological methods showed that the basolateral part of the amygdala, espe-

cially the lateral nucleus, is the site of association formation between conditioned and unconditional stimuli during the acquisition of the classic fear response [16-18].

Limbic structures such as the interventricular septum area and the amygdala [1] are particularly associated with emotionally colored behaviors. Damage to the interventricular septum causes the emotional hyperactivity syndrome [19-20]. In humans, stimulation of the amygdala results in fear, depression, feelings of sadness, and disgust, while complete removal of the amygdala reduces fear and aggression. In animals, cortico-medial lesions of the amygdala lead to apathy accompanied by aphagia and adipsia, and basolateral lesions of the lateral amygdala counteract hyperphagia and an increased level of fear [21].

Cytokines as a humoral "feedback" pathway for the immune system to influence the central nervous system

PAMPS (pathogen-associated molecular patterns on infectious C) are a small molecular motifs conserved within a class of microbes that can be found present on the outside (bacterial flagellin) or inside (unmethylated CpG motifs) [22]. They are associated with specific areas recognized on the surface of neutrophils, dendritic cells or macrophages [23]. In this reaction, pro-inflammatory cytokines are released, often referred to as "immuno-transmitters" [24], and they play an important role in initiating the peripheral acute phase of the response [25-26] and activating subsequent immune cells. Toll-like receptors (TLRs) belong to a class of pattern recognition receptors (PRRs), that identify microbes, which infect human organisms by recognizing PAMPs [22]. TLRs are the most studied PPRs. They are significant modulators of the innate immune response, as they explore the intracellular and extracellular space. The localization of TLRs explain their important role in recognizing potential danger [22].

The pro-inflammatory cytokines entering the brain include interleukin 1 alpha and beta (IL-1 α and β), interleukin 6 (IL-6), and tumor necrosis factor alpha (TNF-α). Dinarello [26] proved that administration of IL-1 β causes an increase in body temperature, while the blockade of this molecule and its receptors significantly reduces fever induced by administration of LPS. The action of IL-1 β is likely crucial in communication between the immune system and the brain [26]. The transmission of signals from the blood to the brain takes place humoral, which is indicated by the increased level of pro-inflammatory cytokines in the blood, induced by the presence of antigen. However, according to some researchers, the problem may be the relatively large size of cytokines (e.g. IL-1 β - 17.5 kDa), as well as their hydrophilic nature, which makes the passage of these molecules through the blood-brain barrier unlikely by passive diffusion [26].

Possible sites for the transition of cytokines to the parenchyma of the brain are places where the blood-brain barrier is weakened, especially in the periventricular area: the endplate vascular organ, the subfornical organ, the median prominence, the distal field and the vascular plexus. The presence of receptors for pro-inflammatory cytokines, especially IL-1, IL-6 and TNF-α, has been confirmed in many structures of the brain, mainly in the hypothalamus, pituitary gland, amygdala, septum, bed nucleus of the stria terminalis, hippocampus, thalamus, as well as in the ventral and dorsal striatum, pons and cerebellum [27-30] IL-1 β, crossing the blood-brain barrier in the periventricular area or the vascular plexus, stimulates the macrophage-like cells present there to produce IL-1 β, which again can induce the transcription of IL-1 β mRNA in nearby brain cells, e.g. glial and thus spread to further regions of the brain with the possibility of activating other neurons [26, 31]. In addition, it has been shown that IL-1 β produced in the brain can pass into the cerebrospinal fluid or travel through the interstitial space and along fiber bundles [26, 32].

IL-6 plays an important role in physiological homeostasis of neural tissue and in the pathogenesis of inflammatory disorders such as multiple sclerosis, Alzheimer's and Parkinson's disease [33]. It is significant in the regeneration of peripheral nerves and differentiation of oligodendrocytes. IL-6 acts on B-cells, T-cells, hepatocytes, hematopoietic progenitor cells. It can be also secreted by immune system cells - B-cells, T-cells, macrophages, microglia and non-immune cells, e.g. adipocytes, fibroblasts, endothelial cells, neurons [33]. Absence of IL-6 may cause reduced glial activation in traumatic brain injury and changes in sleeping behavior. Overproduction of this cytokine in brain leads to neurodegeneration [33].

In the central nervous system (CNS) pattern-recogntion receptors are expressed by microglia, macrophages and astrocytes [34]. Microglia and macrophages in CNS include multimolecular complexes called inflammasomes. This important protein complex "send a massage" from innate immune system to pathogenic stimuli. An inflammasome causes the activation of caspase 1 and consequently to release of pro-inflammatory cytokines, that lead to inflammatory response [34].

The answer to the LPS in blood-brain barrier (BBB) is available thanks to presence of TLR-4 and other toll-like receptors, which they occur on the membranes of the cells BBB [35]. These particular cells have receptors for chemokines, cytokines and other molecules connected with immune system [35]. The most studied effect of LPS on the BBB after disruption is that of alterations in BBB transport system. Many substances with alterations in their brain/blood ratio is thought to be caused by alterations in the transporters for those substances [35].

Another behavioral role is observed in patients with neoplastic diseases as well as those of viral or bacterial origin.

This set of behavior typical of disease errors is commonly referred to as "sickness behavior" [32]. Subjective feeling of impending illness manifested by malaise, weariness, feeling of cold and numbness, pain in joints and muscles, lack of appetite are very well known to everyone who has experienced a viral or bacterial infection. The psychological and behavioral elements of "behavioral disease" together with the onset of fever and neuroendocrine optimization present an outstanding strategic strategy in the struggle with the disease. Due to their prevalence, these symptoms are often ignored by doctors. These symptoms are often perceived as bothersome, but rather trivial processes with special pathogens affecting the sick person. Peripheral immune activation induces the synthesis of pro-inflammatory cytokines in microglia and macrophages: IL-1 α and IL-1 β, IL-6 and TNF-α. Both peripheral and intraventricular administration of these cytokines causes acute phase symptoms, fever, activation of the hypothalamic-pituitary-adrenal axis and depression.

The "sickness behaviour" syndrome unquestionably proves the relationship between the neuroendocrine and immune systems. This interaction plays a key role in maintaining homeostasis. Understanding the relationship between the neuroendocrine and immune systems is an interstate psychosomatic as well as pathophysiological and pathological basis.

Knowledge of neuroimmunomodulation is extremely important in immunotherapy. Behavioral changes must be made when cytokine therapy is used, e.g. in response to long-term IFN-α, human behavior is "depressed" and hyperalgesic.

Influence of cytokines on amygdala

It is known, that cytokines have impact on affecting fear and anxiety-related structures: amygdala, insula, anterior cingulate cortex [2]. The effects of inflammation and cytokines on previously mentioned regions produce adaptative and beneficial behavioral responses. Researchers suggest that not only does inflammation increase amygdala responses to stress are connected with increased production of inflammatory cytokines [2].

Harrison et al. showed that administration of typhoid vaccination increased IL-6 and also induced behavioral changes and intensify activation of amygdala [36]. High sensitivity in amygdala regarding stress may result in higher inflammatory cytokine production. It is important, when we think about anxiety and post traumatic stress disorder (PTSD) symptoms if amygdala activity is able to create a feed-forward effect of inflammation on neural circuitry [36, 3]. The medial prefrontal cortex is connected to the amygdala. It is said, that these structure is involved in fear extinction and emotional regulation in PTSD. A study using typhoid vaccine as an trigger of inflammation, reported reduced task-related functional connectivity of the subgenual anterior cingulate cortex to the amygdala, nucleus accumbens and superior temporal sulcus, which correlated with the IL-6 concentration in the peripheral blood. Insula is also associated with amygdala and play significant role in emotional distress in anxiety disorders and PTSD [2-3, 36] It is thought that enhanced sensitivity of the insula to the inflammatory cytokines in the periphery, especially in the presence of emotional stimuli may cause altered neural circuitry involving amygdala, medial prefrontal cortex, anterior cingulate cortex to show symptoms of anxiety, fear, emotional disturbance [2-3, 36].

Munshi et al. [37] studied, how repeated social stress impacted the peripheral immune balance. The experiments were performed on Long-Evans and Sprague-Daweley rats. Authors indicated, that chronic stress increased pro-inflammatory cytokines in serum. They indicated, that activated microglia secreted pro-inflammatory cytokines, that generated immune signals within brain [37]. It could then precipitate in the physiological and behavioral responses to neuroimmune activation. Authors highlight, that acute peripheral immune activation by IL-1β lead to increase of the basolateral amygdala neuronal activity. IL-1β can increase electroencephalographic activity in amygdala [37]. This cytokine influence on spontaneous action potential-independent transmission of central amygdala GABAergic neurons via pre- and post-synaptic mechanism. Munshi et al. observed significant increase in the basolateral amygdala neuronal firing after the stress, that correlated positively with severity of the stress. It was reduced by blockade of microglia activation [37].

Yang et al. [38] showed the effect of exogenous insulin-like grow factor 1 (IGF-1) on the cognitive dysfunctions caused by acute ischemic stroke in the rat model. IGF-1 regulates postnatal growth thought mediating effects of growth hormone. It also take part in axon guidance, cell adhesion, differentiation, plasticity. Their study showed [38] that intravenous injection of IGf-1 essentially enhanced the reduced IGF-1 concentrations in the plasma and ischemic brain tissues, hippocampus, amygdala, cortex of ischemic rats in a dose-dependent manner compared with no injection model rats. The results of the Yang's team [38] indicated that intravenous IGF-1 injection decreased cerebral infraction and brain edema in ischemic rats. ELISA assays demonstrated that IL-6, IL-1β and TNF-α in ischemia serum was higher than in sham group, while the administration of IGF-1 decreased the levels of this cytokines in comparison to the model group. These data [38] showed that supplementation of IGF-1 could exert anti-inflammatory effects on ischemic rats. Researchers [38] indicated that, IGF-1 support the neuroprotective effects trough inhibiting the neuroinflammation. They demonstrated [38] that the exogenous administration of IGF-1 improved the neurological dysfunction and cognitive deficits, decreased cerebral infraction and brain edema. It also relieved the systemic and cerebral inflammatory response.

Li et al. [39] showed, that treatment of combined Traumatic Brain Injury (TBI) and hemorrhagic shock and resusci-

tation rat model (HSR) with CORM-3 (a water-soluble carbon monoxide), reduced the impairments of depressive and anxiety-like behaviors post- trauma trough activation of PKG-ERK1/2 signal pathway. The animal model proposed in this study [38] induced depression and anxiety-like behaviors – TBI+HRS rats showed reduced center entries, lower rearing/leaning scores, less time in grooming in open field test compared to sham-treated groups. Researchers indicated [39], that the mean cerebral blood flow arterial spin labeling in the amygdala of the TBI+HRS treated rats was significantly downregulated relative to the Sham group. Their study [39] demonstrated, that trauma significantly attenuated cerebral blood flow and induced vasogenic edema in the amygdala. Animals treated with TBI+HSR showed exposure perturbed the amygdala by induction of significant neuronal apoptosis and pyroptosis in this region of the brain. Authors [39] indicated that neuropsychiatric alterations and neurological dysfunctions post TBI+HRS could be induced by neuronal pyroptosis and apoptosis. The administration of CORM-3 improved the results of TBI+HRS rats than control group in the open field test and elevated plus-maze. Animal from the test group showed improved vasogenic edema and cerebral blood flow in the amygdala. CORM-3 could improved neurological dysfunctions and the mechanism could be involved with improvements of neuronal degeneration in the amygdala. Protein kinase G (PKG) pathway caused the induction of antiapoptic proteins – ERK1/2. It is known that activated PKG promoted an elevation of phosphorylated ERK1/2 in ischemic disorder and neurological degradation. Authors [39] showed that CORM-3 increased levels of phospho-ERK1/2 while KT5823 - pharmacological inhibitor partially reversed the upregulation of phospho-ERK1/2 induced by CORM-3. Scientists demonstrated, that PKG-ERK1/2 signaling pathway could mediate the neuroprotective effects of CORM-3 in rats with TBI+HRS damage [39].

Anesten et al. [40] studied possible interactions between IL-6 and glucagon-like peptide 1 (GLP-1) in central amygdala (CeA). GLP-1 is a post-translational proglucagon product. It is a neuropeptide produced peripherally in ileal L-cells of the intestine and preproglucagon neurons of the nucleus of the solitary tract [40]. Production of GLP-1 is responsible for increase of insulin release and also decrease of glucagon release. Researchers proved that IL-6 was present in approximately 40% of GLP-1R cells in CeA. PPG-fibers appear to synapse with IL-6-immunoreactive cells in this nucleus [40]. In their study about 50% of the neurons in the CeA expressed the ligand binding receptor IL-6Rα. Anesten et al. proved that treatment with IL-6 to CeA overnight fasted mice reduced food intake [40].

Xu et al. [41] indicated that resistant stress mediated time-dependent alterations in the permeability of the BBB, with the modifications in the expressions of the proteins from tight junctions and adherens junctions and also ultrastructural changes in brain microvascular endothelial cells. They indicated showed that resistant stress could induced damage of the BBB in the amygdala [41]. Ultrastructural findings demonstrated detached endothelial cells, defective tight junctions, edematous astrogial endfeet, malformed capillary lumen in the resistant-stressed animals, it proved that resistant stress could induce morphological changes of the BBB in the amygdala [41].

Mehta et al. [42] showed that inflammation negatively correlates with amygdala-ventromedial prefrontal functional connectivity in association with anxiety in patients with depression. The right amygdala is more involved in fear conditioning. They claimed that patients with PTSD during the experiment had higher amygdala reactivity and also decreased right amygdala to left vmPFC functional connectivity in association with symptoms of hyperarousal [42]. They suggest that inflammation might play a role in behavioral symptoms of patients who are more reactive to stress or trauma. At the same time prolonged and exaggerated release of interleukins may feedback on and cause weakness of circuits that drive the symptoms of PTSD, anxiety, depression [42].

Munshi et al. [43] in their studies demonstrated how peripheral inflammatory state affects the activity of the basolateral amygdala (BLA). They showed a link between BLA neuronal firing and triggering of behavioral result of peripheral inflammation. It lead to production and release of IL-1 beta, IL-6, TNF-α [43]. Pro-inflammatory cytokines created features of sickness behavior and depressed mood. Some of these symptoms might be generated by BLA. Sickness behavior may be reason of the emergence of depressive disorders in vulnerable subjects. Hyperactivation of BLA is often observed in patients with depression.

Conclusions

Behavior and immune system, mediated by the endocrine and nervous system create a psychoneuroimmunology. From fever to stress, the impact one system on the other allow to help sense danger and to mount an appropriate adaptive response [44].

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Conflicts of interest

None.

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