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Review article

Neuroinflammation and depressive disorder: The role of the hypothalamus

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ABSTRACT

Data accumulated over the last two decades has demonstrated that hypothalamic inflammation plays an important role in the etiopathogenesis of the most prevalent diseases, such as cardiovascular diseases, metabolic syndrome, and even cancer. Recent findings indicate that hypothalamic inflammation is also associated with stress exposure and certain psychiatric diseases, such as depressive disorder. Mechanistic studies have shown that intense and/or chronic stress exposure is accompanied by the synthesis of inflammatory molecules in the hypothalamus, altered hypothalamic–pituitary-adrenal axis activity, and development of glucocorticoid resistance. Consequently, these factors might play a role in the etiopathogenesis of psychiatric disorders. We propose that hypothalamic inflammation represents an interconnection between somatic diseases and depressive disorder. These assumptions are discussed in this mini-review in the light of available data from studies focusing on hypothalamic inflammation.
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1. Hypothalamic inflammation

The hypothalamus plays a crucial role in systemic homeostatic regulation [1]. In support of this, both experimental and clinical data have shown that various stimuli, such as peripheral inflammation [2], or increased intake of saturated fatty acids [3] might disrupt hypothalamic homeostatic regulation via induction of inflammation in this brain structure [2,4]. In addition to the well-described association between hypothalamic inflammation and somatic diseases (e.g. cancer cachexia, hypertension, obesity, type II diabetes) [4–6], recent studies indicate that hypothalamic inflammation might also be associated with stress exposure and psychiatric diseases, including depressive disorder [7–10].

Indeed, current data support the hypothesis that stress-related neuroinflammation might contribute to the development of psychiatric diseases. As such, the hypothalamus, a central component of the neuroendocrine stress response, might be affected by these changes [9,10] and thus play a role in the etiopathogenesis of psychiatric diseases.

2. Stress-related hypothalamic inflammation: Potential contributing factors

Multiple factors might play a role in stress-related hypothalamic inflammation. Most studies on stress and hypothalamic inflammation focus on the effect of glucocorticoids in the development of neuroinflammatory processes [11]. The hypothalamus contains a high concentration of glucocorticoid and mineralocorticoid receptors which, among other factors, serve to regulate hypothalamic–pituitary-adrenal (HPA) axis activity. However, long-term stress exposure may lead to the development of glucocorticoid resistance in corticoliberin (CRH) neurons of the hypothalamic paraventricular nucleus, which in turn disrupts the negative feedback loop regulating activity of the HPA axis. As a result, a chronically activated HPA axis and hypercorticoidism lead to an

Abbreviations: ACTH, adrenocorticotropic hormone; ATP, adenosine triphosphate; BDNF, brain derived neutrophic factor; CNS, central nervous system; CRH, corticoliberin; FA, fatty acids; FGF, fibroblast growth factor; GR, glucocorticoid receptor; HPA axis, hypothalamic–pituitary-adrenal axis; Iba1, calcium-binding adapter molecule 1; ICAM-1, intracellular cell adhesion molecule 1; IDO, indoleamine 2,3-dioxygenase; IFN-α, interferon α; IL-1β, interleukin 1β; IL-2, interleukin 2; IL-6, interleukin 6; IL-10, interleukin 10; ISC, immune system cells; MAT, metabolically active tissue; NCAM, neural cell adhesion molecule; NF-κB, nuclear factor kappa B; NLRP3, NOD-like receptor 3; NMDA, N-methyl-D-aspartate; TLRs, toll-like receptors; TNF-α, tumor necrosis factor α; Trp, tryptophan; VCAM-1, vascular cell adhesion molecule 1; SSRIs, selective serotonin reuptake inhibitors.

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alteration of the physiologic function of glucocorticoids and cause an inadequate response of various tissues and cells to these hormones [12,13].

In the hypothalamus, chronically elevated levels of glucocorticoids induce expression of ionized calcium-binding adapter molecule 1 (Iba1, a marker of microglial activity) [14–16]. Rather than immediately produce inflammatory factors, the glucocorticoid-activated microglia are put into a primed state [17]. The primed microglia then increase number of cell surface receptors, such as toll-like receptors (TLRs) [18,19], which makes the activated microglia especially prone to further stimuli. A subsequent challenge (such as lipopolysaccharide administration), may induce an exaggerated microglial response accompanied by excessive production of inflammatory factors [17,20]. Moreover, glucocorticoids might enhance production of NOD-like receptor 3 (NLRP3) protein – a part of the inflammasome and increase maturation as well as release of interleukin 1β (IL-1β) in response to extracellular adenosine triphosphate (ATP) in human macrophages [21]. Therefore, stress itself might trigger expression of inflammatory factors.

Increased expression of inflammatory markers in the brain has also been detected after a single stress exposure in various animal models [10,22]. These data indicate that besides glucocorticoid resistance, other mechanisms might also be responsible for induction of inflammatory changes in the central nervous system (CNS). Moreover, in the hypothalamus, IL-1β induces CRH secretion from the paraventricular nucleus and activates the HPA axis [23].

Stress exposure might induce expression of IL-1β in the hypothalamus, which in turn activates the HPA axis and elevates circulating glucocorticoid levels. Glucocorticoid resistance might further potentiate expression of inflammatory cytokines in the hypothalamus, forming a vicious cycle of central IL-1β expression and HPA axis hyperactivity [24]. In support of this, a previous study has proved that sustained exposure to IL-1β might play a role in glucocorticoid resistance with decreased expression of specific anti-inflammatory markers regulated via glucocorticoid receptors [25].

2.1. Psycho-social stress and hypothalamic inflammation

Increased expression of IL-1β has been found in the hypothalamus following acute exposure to electric foot shock [10] and immobilization [22]. Moreover, other studies have shown that there is increased expression of various inflammatory markers (including IL-1β) in multiple brain structures after chronic psychosocial stress exposure [14–16,26]. In rodents, various psychosocial stressors increased expression of inflammatory markers such as vascular cell adhesion molecule 1 (VCAM-1), intracellular cell adhesion molecule 1 (ICAM-1), and Iba1 in the prefrontal cortex, hippocampus, amygdala, and hypothalamus, including the paraventricular nucleus [9,14–16].

3. The role of inflammation in etiopathogenesis of depressive disorder

Depressive disorder is one of the most commonly diagnosed mental disorders in adult patients as well as in children and adolescents. The key symptoms are sadness and anhedonia, accompanied by other, more variable symptoms such as sleep disorders, exhaustion, weight loss, or various cognitive deficits [27].

Many of depression-related symptoms exhibit a striking resemblance to the symptoms that appear in the acute phase of the immune response characterized by sickness behavior. Along with the observation that immunotherapy with pro-inflammatory cytokines such as interferon α (IFN-α) [28], or interleukin 2 (IL-2) [29] induces depressive symptomatology in a high percentage of the population, these findings led to the hypothesis that inflammation may be involved in the development of depressive disorder. Evidence showing that patients with chronic peripheral inflammatory diseases have a higher incidence of depressive disorders when compared to a healthy population, also favor this hypothesis [30]. Findings of increased concentrations of pro-inflammatory cytokines in the plasma of depressed patients when compared to healthy subjects also indicate a relationship between depressive disorder and peripheral inflammation [31,32]. Moreover, increased expression of several pro-inflammatory cytokines in the frontal cortex of depressed people has also been reported [33].

However, even if administration of pro-inflammatory cytokines increases the frequency of depressive disorders, this behavior does not occur in all patients. In a group of patients with hepatitis C who were treated long-term with IFN-α, depressive disorder occurred in 39% of cases [28]. Similarly, in some individuals with progressive metastatic melanoma, administration of IL-2 induced severe depressive symptoms that led to temporary discontinuation of the treatment. Furthermore, 24 – 48 h after discontinuation, these symptoms disappeared [29].

3.1. Potential role of the hypothalamus and HPA axis

The unanswered question is why pro-inflammatory cytokines do not induce depressive disorder in all patients, but only in some individuals and what characteristics of this vulnerable part of the population determine its increased susceptibility to depressive disorders. Previous studies have proved that glucocorticoid resistance as well as inflammation might play an important role [7,8,34–36], however the specific mechanisms were unclear until recently.

Several studies have shown increased HPA axis activity in depressed patients [37,38]. In addition, some authors believe that dysregulation of the HPA axis is not only a frequent accompanying phenomenon of depressive disorder, but also a factor that may arise as a result of various life events (e.g. stressful experiences in early-life or during in utero development) or pathologies (e.g. Cushing's syndrome) and consequently may be responsible for increased susceptibility to this psychiatric disorder [7,8]. This is in accordance with the two-hit hypothesis of depression which assumes that early-life/prenatal stress exposure might prime microglia. Further stressful events in adolescence or early adulthood activate these primed microglia and trigger production of inflammatory factors, which may lead to HPA axis hyperactivity and glucocorticoid resistance [20]. Therefore, the two-hit hypothesis might explain increased vulnerability of some patients to immune challenges.

Hyperactivity of the HPA axis also seems to have a crucial role in chronic stress-associated depressive disorder. Studies on mice exposed to chronic mild stress have found that brain IL-1β may act as a mediator of depressive symptoms via activation of the HPA axis and suppression of neurogenesis in the hippocampus. In addition, the effect of chronic mild stress was mimicked by exogenous administration of IL-1β [34]. Moreover, elevated concentrations of IL-1β were found in the cerebrospinal fluid of acutely depressed patients [39]. Together with studies reporting hypothalamic expression of IL-1β under various stress conditions, [10,26] these data suggest that chronic stress might play a significant role in the etiopathogenesis of depressive disorder, possibly even without microglial priming during early-life development (Fig. 1).

3.2. Negative impact of glucocorticoid resistance on depressive disorder

People with a hyperactive HPA axis respond differently to immune stimuli when compared to the healthy population. These patients suffer from glucocorticoid resistance of the circulating

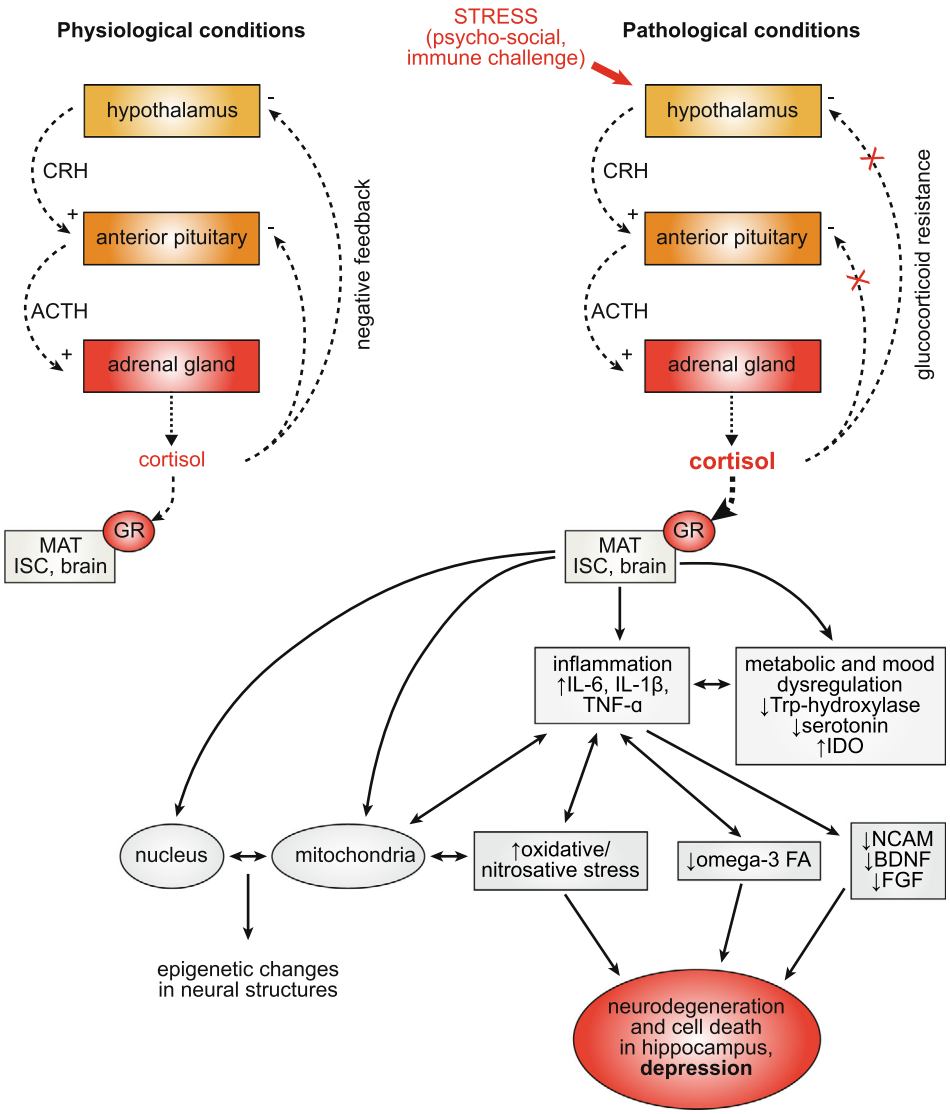

Fig. 1. Function of the HPA axis during physiological conditions and chronic stress. Under physiological conditions, glucocorticoid levels are regulated by the HPA axis' negative feedback loop. Chronic stress alters HPA activity, disrupts the negative feedback loop, and leads to glucocorticoid resistance. Glucocorticoid resistance decreases availability of neuroprotective factors and increases expression of inflammatory molecules, which in turn lead to subcellular stress and elevated activity of IDO. Similarly, decreased levels of omega-3 fatty acids might contribute to inflammation. Moreover, glucocorticoids might cause epigenetic modulations of neuronal DNA. All of these changes might lead to alterations in neurotransmission, neurodegeneration, nerve cell death, and ultimately depression. ACTH – adrenocorticotropic hormone, BDNF – brain derived neurotrophic factor, CRH – corticoliberin, FA – fatty acids, FGF – fibroblast growth factor, GR – glucocorticoid receptor, IDO – indoleamine dioxygenase, IL-1β – interleukin 1β, IL-6 – interleukin 6, ISC – immune system cells, MAT – metabolically active tissue, NCAM – neural cell adhesion molecule, TNF-α – tumor necrosis factor α, Trp – tryptophan.

immune cells, which leads to their inability to adequately terminate the immune response and thus causes an increase in pro-inflammatory cytokine production [40]. Moreover, an in vitro study using human cancer cell cultures has shown that elevated levels of pro-inflammatory cytokines induce expression of the inactive form of the glucocorticoid receptor, which may lead to a potentiation of glucocorticoid resistance [41]. It is well known that peripheral glucocorticoid resistance and associated elevated levels of pro-inflammatory cytokines activate indoleamine 2,3-dioxygenase (IDO – an enzyme of serotonin metabolism) and lead to a worsening of depressive symptoms [42] (Fig. 2).

Increased levels of glucocorticoids might also have a negative impact on various brain structures. Interestingly, it has been demonstrated that there is a reduction in functional connectivity between the hypothalamus and the subgenual cortex in depressed patients. This part of the cerebral cortex has bi-directional connections with the hypothalamus (including the paraventricular nucleus) and is responsive to cortisol. Therefore, changes in the functional connectivity of these structures may be related to dysregulation of the HPA axis in depressed patients [36]. Moreover, high glucocorticoid levels may induce neurotoxicity and subsequent atrophy in the hippocampus, a structure crucially involved in the etiopatogenesis of depressive disorder [43].

3.3. Neuroinflammation in monoamine hypothesis of depressive disorder

Expression of pro-inflammatory cytokines might interact with brain neurotransmitter systems. For example, tryptophan (a precursor molecule for serotonin synthesis) levels are reduced in the plasma of patients receiving IL-2 and/or IFN-α, correlating with the appearance of depressive symptoms [35]. Pro-inflammatory cytokines might also directly modulate serotonergic neurotransmission in the brain. In support of this, administration of IL-1β

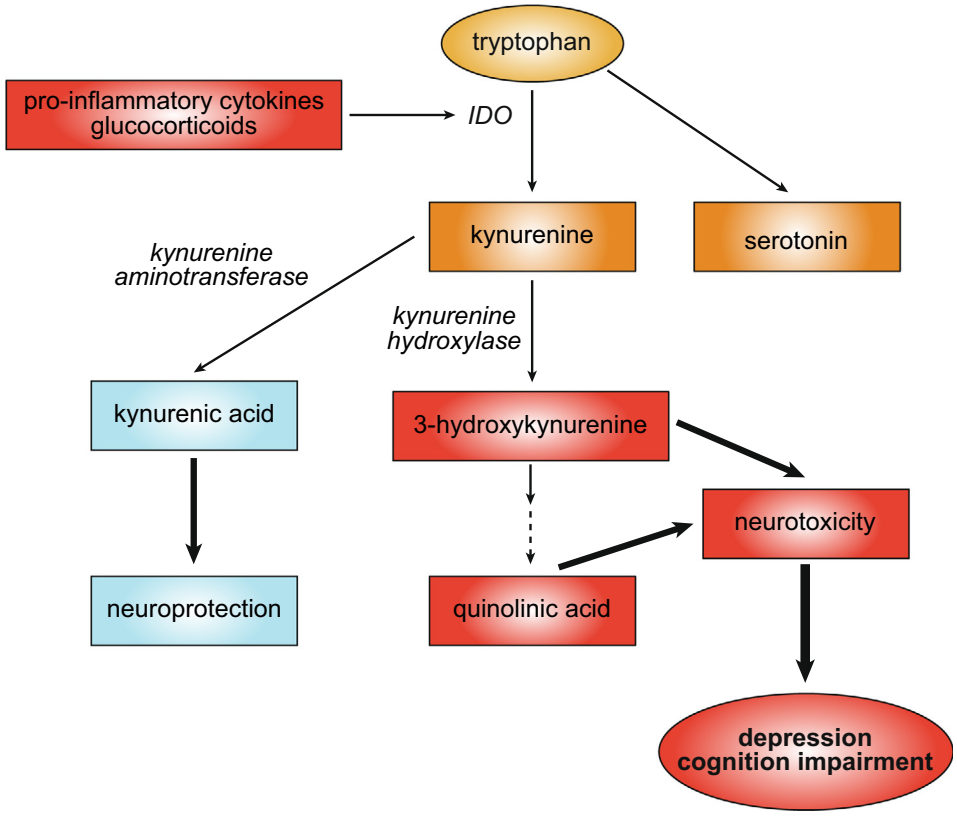

Fig. 2. Kynurenine pathway. Under physiological conditions, the neurotransmitter serotonin is synthetized from the amino acid tryptophan. During inflammation, pro-inflammatory cytokines activate the kynurenine pathway via stimulation of IDO, leading to the formation of kynurenine. Kynurenine can be metabolized by kynurenine hydroxylase to 3-hydroxykynurenine and then to quinolinic acid, or with kynurenine aminotransferase to kynurenic acid. 3-hydroxykynurenine and quinolinic acid actions are neurotoxic and might lead to cell death. Kynurenic acid is an antagonist of neuroprotective glutamatergic NMDA receptors. IDO – indoleamine dioxygenase, NMDA – N-methyl-D-aspartate.

increases serotonergic neurotransmission in the hippocampus and hypothalamus of experimental rats [44,45]. Moreover, exposure to IL-1β increases the release of norepinephrine and dopamine in the anterior hypothalamus [45].

However, current data indicate that inflammation-related depressive disorder is associated with activation of enzymes that result in tryptophan degradation and creation of multiple metabolites that may indirectly affect serotonergic neurotransmission rather than conversion of tryptophan to serotonin. For example, the key metabolite kynurenine is produced from tryptophan in the kynurenine pathway [46]. This reaction might be catalyzed by a number of enzymes, with IDO having a key role. IDO is found in various immune cells, including cells of the CNS. Kynurenine can either be metabolized to 3-hydroxykynurenine and then to quinolinic acid, or within another metabolic pathway to kynurenic acid [47]. All of these agents affect the main excitatory system in the mammalian brain – the glutamatergic neurotransmitter system. To ensure optimal excitatory neurotransmission and limit excitotoxic damage, the glutamatergic system has developed complex regulatory mechanisms. Some components of this regulatory system are directly related to IDO and kynurenine pathway activity [48]. However, while the actions of 3-hydroxykynurenine and quinolinic acid are neurotoxic and might lead to cell death, kynurenic acid is an antagonist of glutamatergic N-methyl-D-aspartate (NMDA) receptors and has a neuroprotective function [46]. Indeed, decreased levels of kynurenic acid and increased levels of quinolinic acid have been found in patients with depressive disorder [49] (Fig. 2). Therefore, these compounds may indirectly affect serotonergic neurotransmission by interfering via the glutamatergic system of the brain.

3.4. Role of hypothalamic inflammation in depressive disorder

Stress and depressive disorder are associated with various comorbidities. Recent research links the inflammatory basis of chronic stress exposure to cardiovascular and metabolic diseases, as well as certain cancer types [50]. Similarly, depressive disorder is frequently associated with various comorbidities including autoimmune disorders, metabolic syndrome, and cardiovascular diseases [51,52]. Previously, it has been proven that many of the above-mentioned disorders are associated with hypothalamic inflammation [4–6]. Therefore, it is possible that chronic stress induces hypothalamic inflammation, which in turn leads to disruption of homeostasis and development of associated somatic diseases. On the other hand, somatic diseases might induce hypothalamic inflammation on their own (for review see [53]). Moreover, hypothalamic inflammation might modulate HPA axis activity [2], lead to glucocorticoid resistance, and cause depressive symptoms in some patients. Either way, hypothalamic inflammation represents an interconnection between depressive disorder and somatic diseases. Therefore, we assume that anti-inflammatory treatment might be beneficial in patients with somatic disorders and associated psychiatric comorbidities.

4. Possible clinical implications

Despite significant progress in research of the neuroinflammatory basis of stress, as well as psychiatric and somatic diseases, many aspects of hypothalamic inflammation need to be determined. To date, it is not clear whether management of glucocorticoid resistance might be beneficial in the treatment of depressive

disorders. Similarly, the detailed epigenetic mechanisms by which early-life and in utero events contribute to increased inflammation in later years are not fully understood. However, there are already some potential treatments focusing on reducing neuroinflammation in hypothalamic inflammation-related disorders.

Although stress, depressive disorder, and various somatic conditions associated with hypothalamic inflammation represent serious problems for society, a healthy life-style still seems to be one of the most efficient approaches in reducing their negative impacts. Regular physical activity increases production of anti-inflammatory cytokines, such as interleukin 10 (IL-10) and reduces hypothalamic inflammation in rats fed a high-fat diet [54]. Similarly, endurance training has reduced hypothalamic inflammation in a murine model of cancer cachexia [55]. In addition, some of the current studies suggest a positive effect of stress relieving techniques (such as mindfulness meditation and yoga) on inflammation, immunity, as well as biological aging [56–58]. These techniques might be especially suitable for stressed patients and patients with depressive disorder.

Current data indicate that the ratio of omega-6/omega-3 fatty acids is also involved in the pathogenesis of depressive disorder. Increased levels of omega-6 fatty acids in membranes might play a role in the etiopathogenesis of depressive disorder via several mechanisms, such as altered membrane fluidity and increased production of pro-inflammatory cytokines with subsequent activation of the HPA axis [59]. Conversely, omega-3 fatty acids seem to have a protective effect [60,61].

The detrimental effect of inflammatory stimuli can be reversed by antidepressants, particularly selective serotonin reuptake inhibitors (SSRIs), which seem to be very effective in reducing inflammation, as well as restoring HPA axis activity [62]. Potentially, also other medicaments, such as nuclear factor kappa B (NF-κB) inhibitors, inhibitors of the kynurenine pathways, antioxidants, and mitochondrial modulators (e.g. polyphenolic compounds from natural sources) might be effective in reducing hypothalamic inflammation [63,64].

5. Conclusion

Findings from the last decades have proved that many somatic diseases, such as metabolic disorders and cardiovascular diseases, are associated with neuroinflammatory changes in the hypothalamus. Based on the available data, we hypothesize that hypothalamic inflammation induced by stress exposure modifies HPA axis activity and consequently plays a role in the development of depressive disorder. Therefore, hypothalamic inflammation may represent a node that interconnects stress, somatic diseases, and depressive disorder. Suppression of hypothalamic inflammation should be considered as a treatment that could benefit psychiatric patients, as well as patients with certain somatic diseases.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2020.03.005.

References

[1] Goldstein DS, Kopin IJ. Homeostatic systems, biocybernetics, and autonomic neuroscience. Auton Neurosci 2017;208:15–28.
[2] Burfeind KG, Michaelis KA, Marks DL. The central role of hypothalamic inflammation in the acute illness response and cachexia. Semin Cell Dev Biol 2016;54:42–52.
[3] de Git KCG, Adan RAH. Leptin resistance in diet-induced obesity: the role of hypothalamic inflammation. Obes Rev 2015;16:207–24.
[4] Rahman MH, Bhusal A, Lee WH, Lee IK, Suk K. Hypothalamic inflammation and malfunctioning glia in the pathophysiology of obesity and diabetes: translational significance. Biochem Pharmacol 2018.
[5] Pimentel GD, Ganeshan K, Carvalheira JB. Hypothalamic inflammation and the central nervous system control of energy homeostasis. Mol Cell Endocrinol 2014;397:15–22.
[6] Valdearcos M, Xu AW, Koliwad SK. Hypothalamic inflammation in the control of metabolic function. Annu Rev Physiol 2015;77:131–60.
[7] Tafet GE, Nemeroff CB. The links between stress and depression: psychoneuroendocrinological, genetic, and environmental interactions. J Neuropsychiatry Clin Neurosci 2016;28:77–88.
[8] Heim C, Newport DJ, Mletzko T, Miller AH, Hemeroff CB. The link between childhood trauma and depression: insights from HPA axis studies in humans. Psychoneuroendocrino 2008;33:693–710.
[9] Sawicki CM, Mckim DB, Wohleb ES, Jarrett BL, Reader BF, Norden DM, et al. Social defeat promotes a reactive endothelium in a brain region-dependent manner with increased expression of key adhesion molecules, selectins and chemokines associated with the recruitment of myeloid cells to the brain. Neuroscience 2015;302:151–64.
[10] Blandino P, Barnum CJ, Solomon LG, Larish Y, Lankow BS, Deak T. Gene expression changes in the hypothalamus provide evidence for regionally-selective changes in IL-1 and microglial markers after acute stress. Brain Behav Immun 2009;23:958–68.
[11] Duque ED, Munhoz CD. The pro-inflammatory effects of glucocorticoids in the brain. Front Endocrinol 2016;7.
[12] McEwen BS. Physiology and neurobiology of stress and adaptation: central role of the brain. Physiol Rev 2007;87:873–904.
[13] Merkulov VM, Merkulova TI, Bondar NP. Mechanisms of brain glucocorticoid resistance in stress-induced psychopathologies. Biochem-Moscow+. 2017;82:351–65.
[14] Kopp BL, Wick D, Herman JP. Differential effects of homotypic vs. heterotypic chronic stress regimens on microglial activation in the prefrontal cortex. Physiol Behav 2013;122:246–52.
[15] Wohleb ES, Fenn AM, Pacenta AM, Powell ND, Sheridan JF, Godbout JP. Peripheral innate immune challenge exaggerated microglia activation, increased the number of inflammatory CNS macrophages, and prolonged social withdrawal in socially defeated mice. Psychoneuroendocrino 2012;37:1491–505.
[16] Wohleb ES, Hanke ML, Corona AW, Powell ND, Stiner LM, Bailey MT, et al. beta-adrenergic receptor antagonism prevents anxiety-like behavior and microglial reactivity induced by repeated social defeat. J Neurosci 2011;31:6277–88.
[17] Frank MG, Hershman SA, Weber MD, Watkins LR, Maier SF. Chronic exposure to exogenous glucocorticoids primes microglia to pro-inflammatory stimuli and induces NLRP3 mRNA in the hippocampus. Psychoneuroendocrino 2014;40:191–200.
[18] Lehnardt S, Cameron J, Massillon L, Follett P, Jensen FE, Ratan R, et al. Activation of innate immunity in the CNS triggers neurodegeneration through a toll-like receptor 4 dependent pathway. Mol Biol Cell 2002;13:537a–8a.
[19] Olson JK, Miller SD. Microglia initiate central nervous system innate and adaptive immune responses through multiple TLRs. J Immunol 2004;173:3916–24.
[20] Calcia MA, Bonsall DR, Bloomfield PS, Selvaraj S, Barichello T, Howes OD. Stress and neuroinflammation: a systematic review of the effects of stress on microglia and the implications for mental illness. Psychopharmacology 2016;233:1637–50.
[21] Busillo JM, Azzam KM, Cidlowski JA. Glucocorticoids sensitize the innate immune system through regulation of the NLRP3 inflammasome. J Biol Chem 2011;286:38703–13.
[22] Minami M, Kuraishi Y, Yamaguchi T, Nakai S, Hirai Y, Satoh M. Immobilization stress induces interleukin-1 beta mRNA in the rat hypothalamus. Neurosci Lett 1991;123:254–6.
[23] Silverman MN, Pearce BD, Biron CA, Miller AH. Immune modulation of the hypothalamic-pituitary-adrenal (HPA) axis during viral infection. Viral Immunol 2005;18:41–78.
[24] Goshen I, Yirmiya R. Interleukin-1 (IL-1): A central regulator of stress responses. Front Neuroendocrin 2009;30:30–45.
[25] Escoll P, Ranz I, Munoz-Anton N, van-den-Rym A, Alvarez-Mon M, Martinez-Alonso C, et al. Sustained interleukin-1 beta exposure modulates multiple steps in glucocorticoid receptor signaling, promoting split-resistance to the

transactivation of prominent anti-inflammatory genes by glucocorticoids. Mediat Inflamm 2015.
[26] Audet MC, Jacobson-Pick S, Wann BP, Anisman H. Social defeat promotes specific cytokine variations within the prefrontal cortex upon subsequent aggressive or endotoxin challenges. Brain Behav Immun 2011;25:1197–205.
[27] Kennedy SH. Core symptoms of major depressive disorder: relevance to diagnosis and treatment. Dialogues Clin Neurosci 2008;10:271–7.
[28] Lotrich FE, Rabinovitz M, Gironda P, Pollock BG. Depression following pegylated interferon-alpha: Characteristics and vulnerability. J Psychosom Res. 2007;63:131–5.
[29] Eton O, Rosenblum MG, Legha SS, Zhang WH, East MJ, Bedikian A, et al. Phase I trial of subcutaneous recombinant human interleukin-2 in patients with metastatic melanoma. Cancer 2002;95:127–34.
[30] Murray CJL, Lopez AD. Global mortality, disability, and the contribution of risk factors: global burden of disease study. Lancet 1997;349:1436–42.
[31] Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, et al. A meta-analysis of cytokines in major depression. Biol Psychiat 2010;67:446–57.
[32] Diniz BS, Teixeira AL, Talib L, Gattaz WF, Forlenza OV. Interleukin-1beta serum levels is increased in antidepressant-free elderly depressed patients. Am J Geriatric Psychiatry: Off J Am Assoc Geriatric Psychiatry 2010;18:172–6.
[33] Shelton RC, Claiborne J, Sidoryk-Wegrzynowicz M, Reddy R, Aschner M, Lewis DA, et al. Altered expression of genes involved in inflammation and apoptosis in frontal cortex in major depression. Mol Psychiatr 2011;16:751–62.
[34] Goshen I, Kreisel T, Ben-Menachem-Zidon O, Licht T, Weidenfeld J, Ben-Hur T, et al. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenocortical activation and hippocampal neurogenesis suppression. Mol Psychiatr 2008;13:717–28.
[35] Capuron L, Ravaud A, Neveu PJ, Miller AH, Maes M, Dantzer R. Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy. Mol Psychiatr 2002;7:468–73.
[36] Sudheimer K, Keller J, Gomez R, Tennakoon L, Reiss A, Garrett A, et al. Decreased hypothalamic functional connectivity with subgenual cortex in psychotic major depression. Neuropsychopharmacol 2015;40:849–60.
[37] Varghese FP, Brown ES. The hypothalamic-pituitary-adrenal axis in major depressive disorder: a brief primer for primary care physicians. Primary Care Companion J Clin Psychiatry 2001;3:151–5.
[38] Martinac M, Babic D, Bevanda M, Vasilj I, Glibo DB, Karlovic D, et al. Activity of the hypothalamic-pituitary-adrenal axis and inflammatory mediators in major depressive disorder with or without metabolic syndrome. Psychiat Danub. 2017;29:39–50.
[39] Levine J, Barak Y, Chengappa KNR, Rapoport A, Rebey M, Barak V. Cerebrospinal cytokine levels in patients with acute depression. Neuropsychobiology 1999;40:171–6.
[40] Cohen S, Janicki-Deverts D, Doyle WJ, Miller GE, Frank E, Rabin BS, et al. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. P Natl Acad Sci USA 2012;109:5995–9.
[41] Webster JC, Oakley RH, Jewell CM, Cidlowski JA. Proinflammatory cytokines regulate human glucocorticoid receptor gene expression and lead to the accumulation of the dominant negative beta isoform: A mechanism for the generation of glucocorticoid resistance. P Natl Acad Sci USA 2001;98:6865–70.
[42] Hestad KA, Engedal K, Whist JE, Farup PG. The relationships among tryptophan, kynurenine, indoleamine 2,3-Dioxygenase, depression, and neuropsychological performance. Front Psychol 2017;8.
[43] Tatomir A, Micu C, Crivii C. The impact of stress and glucocorticoids on memory. Clujul Med. 2014;87:3–6.
[44] Linthorst ACE, Flachskamm C, Holsboer F, Reul JMHM. Local-administration of recombinant human Interleukin-1-beta in the rat hippocampus increases serotonergic neurotransmission, hypothalamic-pituitary-adrenocortical axis activity, and body-temperature. Endocrinology 1994;135:520–32.
[45] Shintani F, Kanba S, Nakaki T, Nibuya M, Kinoshita N, Suzuki E, et al. Interleukin-1-Beta augments release of norepinephrine, dopamine, and serotonin in the rat anterior hypothalamus. J Neurosci. 1993;13:3574–81.
[46] Myint AM, Kim YK, Verkerk R, Scharpe S, Steinbusch H, Leonard B. Kynurenine pathway in major depression: evidence of impaired neuroprotection. J Affect Disorders 2007;98:143–51.
[47] Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat Rev Neurosci 2008;9:46–57.
[48] Niciu MJ, Kelmendi B, Sanacora G. Overview of glutamatergic neurotransmission in the nervous system. Pharmacol Biochem Be 2012;100:656–64.
[49] Ogyu K, Kubo K, Noda Y, Iwata Y, Tsugawa S, Omura Y, et al. Kynurenine pathway in depression: A systematic review and meta-analysis. Neurosci Biobehav R 2018;90:16–25.
[50] Liu YZ, Wang YX, Jiang CL. Inflammation: the common pathway of stress-related diseases. Front Hum Neurosci 2017;11.
[51] Slavich GM, Irwin MR. From stress to inflammation and major depressive disorder: a social signal transduction theory of depression. Psychol Bull 2014;140:774–815.
[52] Zhang YX, Chen YJ, Ma LN. Depression and cardiovascular disease in elderly: current understanding. J Clin Neurosci 2018;47:1–5.
[53] Mravec B, Horvathova L, Cernackova A. Hypothalamic inflammation at a crossroad of somatic diseases. Cell Mol Neurobiol 2019;39:11–29.
[54] Ropelle ER, Flores MB, Cintra DE, Rocha GZ, Pauli JR, Morari J, et al. IL-6 and IL-10 Anti-Inflammatory Activity Links Exercise to Hypothalamic Insulin and Leptin Sensitivity through IKK beta and ER Stress Inhibition. Plos Biol. 2010;8.
[55] Lira FS, Yamashita AS, Rosa JC, Tavares FL, Caperuto E, Carnevali LC, et al. Hypothalamic inflammation is reversed by endurance training in anorectic-cachectic rats. Nutr Metab 2011;8.
[56] Black DS, Slavich GM. Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. Spec Issue: Adv Meditation Res 2016;1373:13–24.
[57] Kiecolt-Glaser JK, Christian L, Preston H, Houts CR, Malarkey WB, Emery CF, et al. Stress, inflammation, and yoga practice. Psychosom Med. 2010;72:113–21.
[58] Mooventhan A, Nivethitha L. Evidence based effects of yoga in neurological disorders. J Clin Neurosci 2017;43:61–7.
[59] Husted KS, Bouzinova EV. The importance of n-6/n-3 fatty acids ratio in the major depressive disorder. Medicina-Lithuania. 2016;52:139–47.
[60] Durackova Z, Trebatickỳ B, Trebatická J, Muchová J. Targeting mitochondria with natural antioxidants. 2018. p. 293-323.
[61] Trebaticka J, Hradecna Z, Bohmer F, Vavakova M, Waczulikova I, Garaiova I, et al. Emulsified omega-3 fatty-acids modulate the symptoms of depressive disorder in children and adolescents: a pilot study. Child Adol Psych Men 2017;11.
[62] Galecki P, Mossakowska-Wojcik J, Talarowska M. The anti-inflammatory mechanism of antidepressants – SSRIs, SNRIs. Prog Neuro-Psychoph 2018;80:291–4.
[63] Bremner P, Heinrich M. Natural products as targeted modulators of the nuclear factor-kappa B pathway. J Pharm Pharmacol 2002;54:453–72.
[64] Viatour P, Merville MP, Bours V, Chariot A. Phosphorylation of NF-kappa B and I kappa B proteins: implications in cancer and inflammation. Trends Biochem Sci 2005;30:43–52.