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IMPACT OF STRESS IN INFLAMMATION ASSOCIATED WITH DEPRESSION

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ABSTRACT
Interpersonal loss and social rejection are key proximal risk factors for major depression. The two principal stress response systems namely the sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis are responsible. Both systems enable the brain to communicate with the rest of the body. Data from several lines of research converge to demonstrate that stress is associated with elevated inflammatory activity. It is reported that depression is associated with a chronic, low-grade inflammatory response and activation of cell-mediated immunity, as well as activation of the compensatory anti-inflammatory reflex system. It is similarly accompanied by increased oxidative stress, which contributes to neuroprogression in the disorder. Patients with depression exhibit increased inflammatory markers and administration of cytokines and other inflammatory stimuli can induce depressive symptoms. Mechanisms by which cytokines access the brain and influence neurotransmitter systems relevant to depression have also been studied. However, antagonizing inflammatory pathways may improve depressive symptoms.

KEYWORDS: Stress, depression, inflammation, cytokines.

INTRODUCTION
Depression is a common disorder, which occurs in all genders, ages, in all social backgrounds and also in animals. According to the World Health Organization, depression is the leading cause of disability as measured by disability adjusted live years and the 4th leading contributor to the global burden of disease in 2000, with tendency to rise up to 2020.[1] Clinical and subsyndromal depression adversely affect physical health, relationships and cognitive performance.[2, 3] Depression produces the greatest decrement in personal health when compared with chronic physical diseases such as angina, arthritis, asthma and diabetes.[4] The link between stress and depression is not novel and there are functional link with stress exposure and depression.[5] Stress is one of the best-studied mediators by which genetic vulnerabilities are translated into mood disorder pathology through the process of neuroprogression.[6] Stress is defined as a state of disturbed homeostasis including somatic and mental adaptive reactions, universally defined as "stress response" aiming to reconstitute the initial homeostasis or a new level of homeostasis after successful adaption, i.e., allostasis.[7] We summarize the literature demonstrating that how stress produces inflammation and that is responsible for the depression.

STRESS IN INFLAMMATION
Stress is usually defined as a state of disturbed homeostasis inducing somatic and mental adaptive reactions, globally defined as "stress response," aiming to reconstitute the initial homeostasis or a new level of homeostasis after successful adaptation, i.e., allostasis.[8-11] There is wide consensus and support from preclinical and clinical data that stress exposure conceivably plays a causal role in the etiology of MD (major depression) and depression-like disorders.[8,11-13] Growing evidence indicates several classical candidates, including neurotransmitters and neuropeptides, as well as immune and inflammatory mediators, as likely intermediate links between stress exposure, depressive symptoms and MD.[14,15] The two principal stress response systems in both humans and other animals are (1) a part of the nervous system called the sympathetic nervous system and (2) a hormone system called the hypothalamic-pituitary-adrenal (HPA) axis. Both systems enable the brain to communicate with the rest of the body. Activation of the sympathetic nervous system produces several physiological responses within seconds, such as an accelerated heart rate, increased respiration and blood flow redistribution from the skin to the skeletal muscles. These responses facilitate the "fight or flight" behavioral response. Activation of the HPA axis induces glucocorticoid secretion, which in turn affects a wide range of physiological responses, such as changes in blood sugar levels and blood pressure, fat redistribution, muscle breakdown and immune system modulation.[16] The HPA axis consists of three groups of hormone producing cells. They reside, respectively, in the brain

region called the hypothalamus; in a hormone-secreting gland called the pituitary gland (located just below the hypothalamus); and in the adrenal glands, which are situated on top of the kidneys. These groups of cells act in a coordinated fashion to control the secretion of glucocorticoid hormones from the adrenal gland into general circulation.

Glucocorticoid secretion from the adrenal glands depends directly on the release of the adrenocorticotropic hormone (ACTH) from the pituitary gland and indirectly on the release of the corticotropin-releasing hormone (CRH) from the hypothalamus. This hormone "cascade" becomes activated whenever CRH-producing nerve cells (i.e., neurons) in the hypothalamus are stimulated by neural input from other brain regions, usually in response to a stressful situation. As a result of this stimulation, these hypothalamic neurons secrete CRH into specific blood vessels located at the junction of the hypothalamus and the pituitary gland. CRH then is transported through these blood vessels to the pituitary gland (i.e., the anterior pituitary), where it stimulates specialized cells (i.e., corticotrope cells) to secrete ACTH into the bloodstream. Through the blood, ACTH is transported to the adrenal glands, where it induces certain cells to release glucocorticoids into the bloodstream.

Glucocorticoid hormones have a wide range of regulatory effects on virtually every organ system in the body, including the central nervous system (i.e., the brain and spinal cord). Cortisol's ability to affect many body systems allows this hormone to be an effective mediator of a generalized stress response. At the same time, however, the extensive range of cortisol's effects necessitates tight regulation of the hormone's levels. This control is achieved largely through a negative feedback mechanism.[17] Thus, cortisol itself either directly or indirectly inhibits the CRH-producing neurons in the hypothalamus and the ACTH-producing cells in the anterior pituitary that control cortisol secretion, thereby blunting overall HPA axis activity and subsequent cortisol secretion.

Over- activity of this system has been attributed to glucocorticoid receptor (GR) resistance, secondary to either reduced expression of GR or decreased functionality of GR. Functional inhibition is induced by preventing the entry of the cortisole GR receptor complex into the nucleus (by inducing Jun amino-terminal kinase) and also by preventing the binding of the complex to the DNA (by inducing nuclear factor kB).[18] This in turn leads to altered expression of GR in cells. Change in expression and functionality of the system can be measured with TNF-α blockers. Recent work has been done to establish links between glucocorticoid mechanisms to neurogenesis (a process thought to be key in mediating the action of antidepressants). They suggest that activation of GR is necessary for the antidepressant induced modulation of neurogenesis in humans.[19] Early life stress can be particularly deleterious because of its potential to influence the programing of the hypothalamic pituitary adrenal (HPA) axis[20] to induce persistent sensitization of neuroendocrine, autonomic, oxidative, and immune responses to stress. All these cumulatively contribute to the cellular and synaptic alterations underlying neuroprogression.[21,22] Specific examples include changes in reactivity of inflammatory cytokines [e.g., interleukin 6 (IL-6)][22], alterations in markers for lipid peroxidation [e.g., 8-iso-prostaglandin F (2α)], oxidative damage to DNA (8-hydroxy-20 deoxy-guanosine) and RNA (8-hydroxyguanosine)[21], as well as altered cortisol, adrenocorticotropic hormone, and corticotrophin releasing factor responses.[22] Stress during earlier life is not only associated with disruption of the HPA axis, but may also serve to sensitize proinflammatory responses to future insults.[23-25] Of specific interest are proinflammatory mediators, such as cytokines [i.e., interleukin 1, IL-6 and tumor necrosis factor alpha (TNF-α)] and C-reactive protein (CRP). Cytokines are thought to influence neurodevelopment during key stages, such as adolescence, interacting with biological systems including those of stress hormones and gonadal hormones.[26] As such, perturbation of inflammatory balance in adolescents may significantly contribute to neuroprogression and development of psychiatric illness.[26-28] For example, elevated serum levels of TNF-α, IL-6 and interleukin-10 (IL-10) have been reported during the early stages of bipolar disorder[29] and CRP appears to be a biomarker of de novo depression risk.[30]

As the mood disorder pathology progresses, an increasing number of proinflammatory cytokines are observed, including elevated levels of interferon gamma (IFN-γ).[27, 29, 31] Increases in IFN-γ are associated with dysregulation of the tryptophan metabolite pathway via direct role in indoleamine 2, 3-dioxygenase (IDO) activation. Activation of IDO is commonly found in later stages of mood disorders and is a biomarker of depression-like behavior mediated by neural inflammation in animal models.[24] Proinflammatory cytokines activate IDO, resulting in depletion of serotonin and augmentation of quinolinic acid (QUIN) metabolism over kynurenicacid (KYNA). Tryptophan metabolites (kynurenine, KYNA, 3-hydroxykynurenine and QUIN) act as neuromodulators to influence behavioral, neuroendocrine and neurochemical aspects of depression.[32-35] Consequently, this accumulation of QUIN facilitates neurodegeneration over neuroprotection, impacting mood disorder neuroprogression and resultant disability.[36] Thus stress is associated with elevated inflammatory activity. These effects are apparent for both early life stress and adulthood life stress and they have been demonstrated at the protein level (i.e., proinflammatory cytokines), intracellular signaling level (i.e., transcription factors).

INFLAMMATION IN DEPRESSION

Empirical evidence of bidirectional communication between peripheral cytokine activity and the brain is

provided by basic studies of inflammation and behavior. Cytokine to brain communication is occurred when, in response to inflammatory signaling in the periphery, certain classes of cells in the brain specifically, microglial cells and astrocytes begin secreting proinflammatory cytokines that bind to cytokine receptors throughout the brain.[37]

The proinflammatory cytokines in the peripheral blood go through the weak region of blood-brain barrier or by their specific transport proteins on the brain endothelial cells and exhibit higher circulating levels of several proinflammatory cytokines including IL-1, IL-6 and TNF-α, as well as higher levels of the systemic inflammatory biomarker CRP.[38] In the brain, proinflammatory cytokines alter the metabolic processes of neurotransmitters, such as serotonin and dopamine whose secretion suppression and the reuptake block take a role in the pathogenesis of depression and provide advices to the therapy. Then, the proinflammatory cytokines activate the CRH of the PVN and upregulate ACTH and cortisol. Besides, the proinflammatory cytokines disrupt synaptic plasticity through altering the relevant growth factors, such as brain-derived neurotrophic factor (BDNF). Many evidences come from clinical treatment for infectious diseases, in which they present the IFN-α-induced depressive symptom and IFN-α is the inducer of IL-6, TNF-α and IL-1β.[39] One study has shown that long term administration of IFN-α is associated with reduced neural responses to a hedonic reward task in the bilateral ventral striatum, a brain region that is involved in reward related responding. Reduced activation of the ventral striatum, in turn, was significantly correlated with greater symptoms of anhedonia, depression and fatigue.[40] Thus research point of view inflammation plays a prominent role in depression, particularly when somatic or neurovegetative symptoms are present.

In turn, these cytokines promote the release of the neurotransmitters norepinephrine, dopamine and serotonin[37,41], implicating central inflammatory cytokines in the initiation or modulation of neurochemical cascades that directly affect behavior. Via these interactions, central cytokine activation leads to disturbances in sleep wake activity, as characterized by alterations in measures of sleep continuity and architecture. These interactions also evoke decreases in daytime activity, as well as decreased interest in feeding, grooming, socializing, and mating and hedonic behaviors. These behaviors have been collectively called sickness behaviors and they are thought to facilitate an organism's recuperation and recovery from injury or infection.[42] The fact that inflammatory cytokines can induce sickness behaviors is highly relevant for depression since these behaviors are strikingly similar to somatic and behavioral symptoms of depression.[43,44] These effects thus argue for the possibility that cytokines may be able to induce major depression in humans by altering the activity of neurotransmitters and neural systems that regulate cognition, mood, and behavior.

Action on neurotransmitters

Monoamine neurotransmitters

Monoamine pathways have been implicated in the aetiology of depression for a number of years. SSRI antidepressants have been reported to be effective in inducing and sustaining remission of inflammation in patients with RA.[45] There seems to be a bidirectional relationship between serotonergic systems and inflammation. A key site of action of antidepressants is the serotonin transporter (SERT) which regulates serotonergic neurotransmission.[46] Proinflammatory cytokines, including TNF-α, induce glial indoleamine dioxygenase. This activates the kynurenine pathway, thus channelling the available dietary tryptophan (the substrate for serotonin synthesis) to form kynurenine (Kyn), 3 hydroxy kynurenine (3HK) and quinolinic acid (QUIN), rather than serotonin (5HT). Accumulation of 3HK and QUIN-both N-methyl-D-aspartate (NMDA) receptor agonists-contribute to excitotoxicity and calcium mediated cell death.[47]

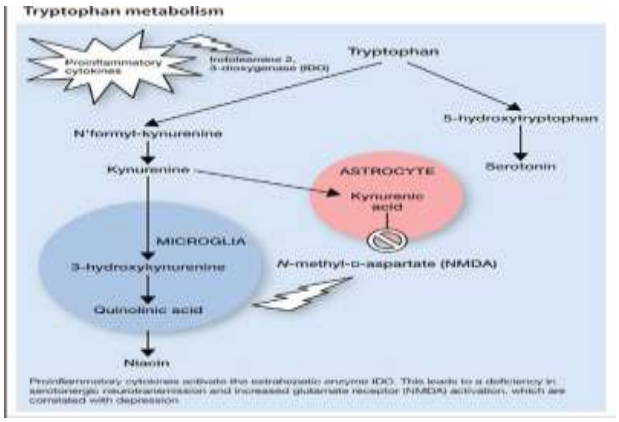

Fig. 1 5-HT metabolism pathway.

Recent findings suggest that antidepressants have anti-inflammatory and analgesic properties. One study showed that CRP levels were decreased following treatment with antidepressant.[48] Also evidence that raised proinflammatory biomarkers in patients with MDD showed a decrease in response to treatment with venlafaxine (a serotonin and norepinephrine reuptake inhibitor, exhibiting serotonin reuptake inhibition at lower doses and norepinephrine reuptake inhibition at higher doses) at the serotonergic (lower) dose range rather than the norepinephrine (higher) dose range, suggesting that sertonergic pathways mediate the anti-inflammatory response to antidepressants.[49] Peripheral activation of 5-HT_{2A} receptors in primary aortic smooth muscle cells leads to an extremely potent inhibition of TNF-α mediated inflammation, another possible mechanism of action of SSRIs in mediating the anti-inflammatory action. SSRIs, including escitalopram, are thought to increase extracellular serotonin concentrations at these receptors.[50] Another monoamine that has been implicated in major depression is dopamine, particularly

in symptoms associated with anhedonia and sickness behaviour. As with serotonin, proinflammatory cytokines influence the synthesis and reuptake of dopamine.[51,52]

Glutamate neurotransmission

Glutamate induced excitotoxicity-excess activation of neuronal glutamate receptors that ultimately leads to cell death has been implicated in mediating neuronal death in many disorders, including stroke and neurodegenerative disorders. Glutamate induced excitotoxicity has also been implicated in psychiatric disorders such as depression.[53] Excessive accumulation of intracellular calcium is thought to be the major step that leads to neuronal cell death. The type of receptor that has been most implicated in glutamate excitotoxicity is the NMDA subtype. It is thought that over stimulation of these receptors leads to an overload of calcium and in turn, neuronal death. Other receptors, such as a-amino-3-hydroxy-5-methyl-4-isoxa- zolepropionic acid (AMPA) and kaininate receptors, are also thought to play a role in excitotoxicity as their ion channels are partially permeable to calcium.[54] Inflammatory processes have been found to be associated with an increase in glutamate induced neurotoxicity. Proinflammatory cytokines are thought to mediate this process. Mechanisms by which these inflammatory mediators cause an increase in glutamate neurotransmission include: Upregulation and augmentation of NMDA function, Increased release and reuptake inhibition of glutamate, Action on AMPA receptors, Activation of kynurenine pathway.

Upregulation and augmentation of glutamatergic pathway: It has been recognised that hippocampal neurons exposed to IL-1b and TNF-α intensify the excitotoxic neuronal damage induced through NMDA and AMPA receptors.[55] The action of IL-1b on the glutamatergic system is thought to be through its action on the IL-1 R1 receptor. These receptors colocalise with NMDA receptors on hippocampal neurons. NMDA receptors consist of two subunits, NR1 and NR2. NR2 subunits have further isoforms. It is proposed that IL-1b induces phosphorylation of the NR2B isoform, which leads to upregulation of NMDA receptor function. This leads to an increase in Ca2+ influx into the neuron and consequent cell death.[56]

Increased release and reuptake inhibition of glutamate: IL-1b has also been found to inhibit the reuptake of glutamate by glial cells. This is thought to be mediated through the action of these proinflammatory cytokines on expression of the glutamate transporter. This malfunction of the transporter leads to an increase in extracellular glutamate and further NMDA mediated excitotoxicity. In addition to this, IL-1b has been found to activate nitric oxide synthase which leads to an increase in production of nitric oxide and hence an increase in glutamate release.[57]

Action on AMPA receptors

TNF-α has been shown to influence the trafficking of AMPA glutamate receptors in inflammatory conditions. Normally AMPA receptors have four subunits, GluR1e4. The presence of TNF-α leads to production of AMPA receptors lacking the Glu R2 subunit. This receptor conformation is said to facilitate calcium influx into the neuron. This predisposes the neuron to glutamate induced excitotoxicity.[58]

Kyneurenine pathway

The impact of the Kyn pathway on excitotoxicity was described above. This activation of the Kyn pathway by proinflammatory cytokines thus channels the available tryptophan to form Kyn, 3HK and QUIN. 3HK and QUIN are NMDA receptor agonists. High concentrations of these compounds are thought to contribute to excitotoxicity and calcium mediated cell death.[59]

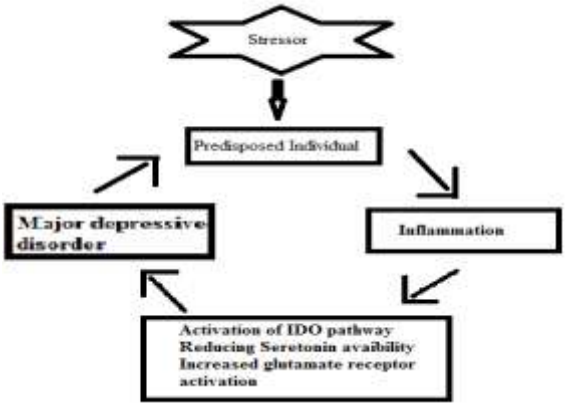

Fig. 2 Pathway linking stress, inflammation and depression.

CONCLUSION

In conclusion, we know that adverse social environmental conditions that typically precipitate depression and about cognitive and emotional processes that mediate these effects. With the advent of new neuroimaging, immunological, and genome wide profiling techniques a detail set of biological mechanisms that link stress with depression has been identified. Inflammation is undoubtedly a key player in this link.

Based on existing data, we conclude that stress likely increases risk for depression in a substantial number of people by up-regulating inflammatory activity and by altering social, cognitive and affective processes that are known to promote this disorder. These insights are important because they can help update contemporary theories of depression with information about biological mechanisms that are involved in the pathogenesis of depression. The hope is that by targeting these and other dynamics, we may one day be able to reduce the prevalence of depression and the substantial financial burden and personal suffering associated with this common and costly disorder.

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