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Review Article

SCI and depression: Does inflammation commandeer the brain?

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ABSTRACT

The incidence of depression is almost twice as high in the spinally injured population compared to the general population. While this incidence has long been attributed to the psychological, economic, and social burdens that accompany spinal cord injury (SCI), data from animal studies indicate that the biology of SCI may play an important role in the development of depression. Inflammation has been shown to impact stress response in rodents and humans, and inflammatory cytokines have been associated with depression for decades. The inflammation inherent to SCI may disrupt necessary mechanisms of mental homeostasis, such as serotonin production, dopamine production, and the hypothalamic pituitary adrenal axis. Additionally, gut dysbiosis that occurs after SCI can exacerbate inflammation and may cause further mood and behavior changes. These mediators combined may significantly contribute to the rise in depression seen after SCI. Currently, there are no therapies specific to depression after SCI. Elucidation of the molecular pathways that contribute to SCI-specific depression is crucial for the understanding of this disease and its potential treatments.

1. Introduction

While paralysis or loss of limb function is the most recognizable consequence of a spinal cord injury (SCI), SCI also affects psychological wellbeing. In a recent meta-analysis, Williams and Murray (2015) estimated that 22.2% of patients with SCI suffer from major depressive disorder (MDD), an incidence nearly three times greater than the 8.1% in the general US population (Brody et al., 2018). An additional 16-34% of SCI patients report significant clinical symptoms of depression but do not meet the criteria for MDD (Bombardier et al., 2012; Krause et al., 2000; Migliorini et al., 2009). Depression affects a significant portion of people living with SCI.

The impact of depression on both physical and psychological health after SCI is also significant. Depression is associated with an increased risk of suicide (Cao et al., 2014; Craig et al., 2015; DeVivo et al., 1991; Soden et al., 2000), an increased incidence of urinary tract infections and pressure ulcers, longer hospitalization stays, less adherence to rehabilitation protocols, lower community involvement, and greater unemployment (Elliott and Frank, 1996; Fuhrer et al., 1993; Herrick et al., 1994). Yet, despite its prevalence and its significant impact on quality of life, there has been relatively little research on the etiology of depression after SCI.

Injury characteristics *per se* do not appear to affect mental health scores (Abrantes-Pais et al., 2007; Charlifue et al., 2011; Leduc and Lepage, 2002; Tramonti et al., 2014), but psychosocial changes are associated with the development of depression. As in the general population, individuals with poor social relationships are more likely to experience mental health problems than those with satisfaction in relationships (de la Vega et al., 2018; Dodd et al., 2015; Kraft and Dorstyn, 2015; Müller et al., 2012; Tough et al., 2017; Zürcher et al., 2019). Environmental (physical and structural) and assistance (e.g., health care and home caregiver services) barriers are significant obstacles for social participation after SCI (Hammel et al., 2015; Tsai et al., 2017). Loss of employment, insurance, and income after SCI, together with the high costs of ongoing medical care and accommodations necessary to adapt with disability, can also lead to a decline in socioeconomic status (Fyffe et al., 2011; Paul et al., 2013). In the United States, even among people with SCI that do return to work, women, minorities, and those with less than a college degree earn less, further contributing to financial strain (Krause and Broderick, 2004; Krause and Pickelsimer, 2008; Krause and Saunders, 2009; Krause and Terza, 2006). Not surprisingly, individuals with financial strain are also more likely to report general mental health problems and depressive symptomatology after SCI (Fekete et al., 2014; Krause et al., 2000; Lim et al., 2017; Zürcher et al., 2019). Susceptibility to depression after SCI is impacted by personal and environmental changes.

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Using scales such as the Connor-Davidson Resilience Scale (Connor and Davidson, 2003) and the Snyder's Hope Scale (Snyder et al., 1991), researchers have shown that low resilience is also significantly associated with depression after SCI (Catalano et al., 2011; Dodd et al., 2015; Min et al., 2014). Resilience is defined as the process of positive behavioral and psychological adaptation in the context of significant adversity (Todd and Worell, 2000) and has been associated with personality traits, such as openness to experience, conscientiousness, and extraversion (Oshio et al., 2018; Riolli et al., 2002). Resilience is also associated with more active, versus passive, coping strategies including problem solving, seeking support, exercising, and engaging in adaptive processes (Cairns et al., 2014). Although stress resilience is likely affected by psychosocial factors, work in animal models suggests that it is also mediated through active neurobiological processes (Gardner et al., 2009; Hodes et al., 2014; Maldonado-Bouchard et al., 2016; Menard et al., 2017; Wood et al., 2015). Human studies also suggest that there is an interaction between resilience and inflammatory processes. For example, when compared with individuals that adopt active coping strategies, individuals with passive coping strategies have greater plasma concentrations of interleukin 6 (IL-6) following a 3 min simulated public speaking challenge (Carroll et al., 2011). Kiecolt-Glaser et al. (2009) found that feelings of helplessness and anxiety during the Trier Social Stress Test (Kirschbaum et al., 1993) were associated with sensitized immune responses to common allergens (e.g. house dust mite, ragweed, tree mix, grass mix) and greater release of IL-6 from stimulated primary blood leucocytes. Further, Maes and colleagues found that psychological stressors increase the production of IL-6, IL-1ra, and IFN-γ from cells in the peripheral blood of a student population, particularly those who identified as stressed (Maes et al., 1997; Maes et al., 1995; Maes et al., 1993; Maes et al., 1998). Biological and psychological processes clearly interact to influence affect after injury.

Inflammation has been implicated in susceptibility to stress and may be causal for depression. Inflammation is a hallmark of spinal cord injury, and this review will focus on the role of inflammation in depression. First, we will discuss the evidence for inflammation after injury and its relation to depression in humans and animal models. Next, we will review the molecular mechanisms that have been proposed to underlie inflammation-mediated susceptibility to depression. We will discuss how increases in inflammation and HPA-axis hyperactivity may lead to depression after SCI, describing data collected from both animal models and humans.

2. SCI and inflammation

Inflammation resulting from SCI has been well described (Davies et al., 2007; Popovich et al., 1997). Immediately following SCI, peripheral macrophages infiltrate into the cord, and resident microglia transform into activated microglia (Popovich et al., 1997). Inflammation persists as neutrophils, microglia, and macrophages are attracted to the injury site, where they attempt to remove dead cells and promote healing. While acute inflammation can have beneficial effects, the chronic inflammation that develops with SCI has serious negative outcomes, including neuropathic pain, metabolic disorders, and even, ironically, immune system impairment (Allison and Ditor, 2015a; Sun and Jones, 2016).

Importantly, inflammation is not confined to the primary site of injury, or even the spinal cord. After SCI, the brain also expresses pro-inflammatory cytokines associated with activated microglia, which release cytotoxic and pro-inflammatory agents, producing neurotoxicity in their surroundings and accounting for behavioral changes related to cell death (Takeuchi, 2010; Wu et al., 2014a). Activated microglia have been identified in the thalamus, hippocampus, and frontal cortex in a rodent model of SCI, becoming activated as soon as 7 days post-SCI and remaining for at least 10 weeks (Wu et al., 2014a; Wu et al., 2014b). These changes are also associated with cognitive deficits, indicating that they are likely to be functionally significant.

Further, the inflammatory response after SCI is not limited to the central nervous system. SCI can lead to gut dysbiosis and bacterial translocation across the gut wall. Bacterial translocation, in turn, results in heightened immune activity in gut-associated lymphoid tissue and, subsequently, more systemic immune activity and inflammation (Kigerl et al., 2016). A subset of patients also develops persistent peripheral inflammation. In fact, 1 year after injury, over half of SCI patients display elevated serum IL-2 and tumor necrosis factor-α (TNF-α) levels, while exhibiting no differences in anti-inflammatory cytokine levels (Hayes et al., 2002). SCI causes rates of chronic inflammation significantly higher than those found in the able-bodied population (Hayes et al., 2002).

Interestingly, even among healthy, able-bodied controls and SCI patients who were asymptomatic for any complications (pressure ulcers, pain, or urinary tract infections), a subset of individuals (smaller in able-bodied control subjects) have IL-6 levels about equal to those of the symptomatic patients (Davies et al., 2007). These data indicate that some members of the population have elevated inflammatory cytokine levels, regardless their injury status. However, we do not currently know if there are any clinically significant outcomes for these uninjured or complication-free individuals with high pro-inflammatory cytokine profiles. Given the association between depression and inflammation, as discussed below, it would be important to know whether high inflammatory profiles affect psychological wellbeing.

3. Inflammation and depression after SCI

3.1. Inflammatory cytokines are associated with depression

As we learn more about depression, we have begun to realize that it is not merely a disease of the brain or the mind. In the past few decades, considerable evidence has suggested a connection between inflammation and depression; pro-inflammatory cytokine upregulation has been described in both peripheral tissue and the central nervous systems of depressed individuals (Lindqvist et al., 2009; Liu et al., 2012; Loftis et al., 2010; Maes et al., 1997; Maes et al., 1995; Maes et al., 1993; Myint et al., 2005; Pandey et al., 2012). Chronic inflammation has been noted in many cases of major depression, and depression itself is often comorbid with diseases characterized by chronic inflammation or injury to the CNS. For example, there can be up to 50% lifetime prevalence of depression among patients with multiple sclerosis, and patients with psoriasis, inflammatory bowel disease, and arthritis have increased likelihoods of developing depression (Jensen et al., 2016; Marrie et al., 2017; Olivier et al., 2010; Siegert and Abernethy, 2005). Further, interferon-α (IFN-α) immunotherapies for diseases such as cancer and hepatitis C cause a significant increase in depressive symptoms in patients, with up to 50% developing major depression (Capuron et al., 2009; Capuron et al., 2002). In animal models, central or systemic administration of pro-inflammatory cytokines produces a "sickness" behavior that is characterized by behavioral and physiological changes associated with depression (Anisman et al., 2005). These depressive-like symptoms can last for several weeks after administration (Anisman and Merali, 2003; Schmidt et al., 2003), long after the levels of exogenously applied cytokines would have subsided, and symptoms are attenuated by the clinically-relevant antidepressant, fluoxetine (Merali et al., 2003). These data indicate a causative, rather than merely a correlative, relationship between pro-inflammatory cytokines and depression.

Animal studies have also found that depression after SCI is associated with increased inflammation. A clip compression injury resulted in elevated pro-inflammatory cytokines (TNF-α, IFN-γ, IL-1β, and IL-6) in both blood plasma and the spinal cord of spinally injured rats with depression-like symptoms (decreased sucrose preference and social interaction), compared to sham and injury-naïve rats, for up to 28 days post injury (Do Espírito Santo et al., 2019). Others have found signs of an activated immune response in the brain, accompanied by behavioral

deficits after SCI in mice. In a comprehensive evaluation of cerebral inflammation after SCI, Wu et al. (2014b) analyzed cognition, depressive-like behaviors (as measured by tail suspension test and sucrose preference test), cerebral microglial activation, and cell cycle activity in spinally injured mice. They found that spinally injured mice showed more depressive-like activity than their uninjured counterparts and that administration of CR8, a cyclin-dependent kinase inhibitor and cell-cycle inhibitor, reduced neuronal cell death, decreased microglial activation, and reversed the depressive behaviors. Using behavior to phenotype subjects, Maldonado-Bouchard et al. (2016) found that "depressed" and "not-depressed" SCI rats differ in their molecular responses. They found increased inflammatory cytokines in both the serum and the hippocampi of depressed SCI rats, compared to both the intact controls and the not-depressed SCI rats. By 24 days post-injury, SCI rats exhibiting depression-like behaviors had higher IL-1β and IL-17A in their serum and higher IL-1α and TNFα in their hippocampi, indicating that depression after SCI is associated with increased inflammation, even relative to not-depressed SCI subjects. These studies show that even in the absence of psychological stressors, inflammation is associated with depression after SCI.

One of the few studies examining the interaction between inflammation and depression after SCI in humans investigated the therapeutic impact of an anti-inflammatory diet (Allison and Ditor, 2015b). Participants eliminated inflammation-inducing foods, such as refined wheat and sugar, from their diets and introduced anti-inflammatory supplements, such as curcumin, omega-3 fatty acids, and antioxidants. One month after the start of treatment, patients on the diet had lower IL-1β and lower scores on the Center for Epidemiological Studies Depression Scale than they did before the start of treatment. Though the treatment itself did not target a specific mechanism of depression, this study measured kynurenine and tryptophan levels in patients' serum, which are products of an inflammation-driven alternative tryptophan pathway, and they found that the change in depression score was positively correlated to the changes in kynurenine and the tryptophan/kynurenine ratio in these patients. These findings support both the inflammatory theory of depression and the tryptophan/kynurenine pathway as a mechanism of action, which will be discussed below.

3.2. Pre-existing inflammation increases susceptibility to depression

While SCI *per se* increases inflammation, we know that only a subset of people with SCI develop depression. Multiple studies investigating inflammation after SCI have shown that, while SCI patients as a whole exhibit higher inflammatory cytokines for weeks to months after the injury, only a subset of patients drive that difference. However, little work has been done to elucidate why, biologically, these subsets develop depression.

It is important to create models capable of identifying individual differences that produce susceptibility to depression. Using a comprehensive behavioral ethogram and statistical analyses, our laboratory was one of the first to describe depression behavior in a subset of SCI rats (Luedtke et al., 2014). Using hierarchical clustering we are able to identify specific subjects that show depressive behavioral changes after SCI, allowing us to more effectively explore individual differences between depression susceptible and resilient animals. Luedtke et al. (2014) found that 35% of spinally injured rats developed depression symptoms in the month following a T12 contusion injury, a percentage concomitant with the human population (Williams and Murray, 2015). We have since shown that the subset of SCI rats that exhibit depression also have higher peripheral inflammation, higher heart rates and lower heart rate variability than non-depressed counterparts (Maldonado-Bouchard et al., 2016; Brakel et al., 2019). These are physiological symptoms that are also found in humans with depression and anxiety (Appelhans and Luecken, 2006). These data support the idea that there are physiological differences between subjects that are susceptible to depression after SCI and those that are not.

An individual's susceptibility to depression after SCI may be determined, at least in part, by their level of pre-existing inflammation. Mice that are vulnerable to developing depressive behaviors 10 days after experiencing repeated social defeat stress have elevated levels of plasma IL-6 immediately after their first defeat, whereas resilient animals do not (Hodes et al., 2014). This indicates that minor stressors can expose pre-existing differences in individuals. The immune system is at least partly responsible for these differences, because whole blood monocyte cultures, collected from susceptible rats before social defeat, produce more IL-6 when exposed to an immune stressor (lipopolysaccharides) than do cultures from resilient mice (Hodes et al., 2014). This immune system action even affects previously-resilient mice: transplanting bone marrow from a stress-susceptible mouse causes susceptibility in the recipient as well, after even a mild stressor (Hodes et al., 2014). In our own lab, we have seen that rats susceptible to depression after SCI have higher levels of pre-existing serum IL-6 before the injury, and pre-treating rats with IL-6 via intraperitoneal injection for one week leading up to injury predisposes them to develop depression after SCI (Brakel, unpublished data). Because SCI is a physical stressor that creates an immune response and increases inflammation, it likely activates the same mechanisms seen in other stress models.

Pre-existing inflammation as a predictor of depression susceptibility has also been seen in humans. In white collar workers with no serious health complications, serum IL-6 and C-reactive protein (CRP) levels predicted symptoms of depression that developed 12 years after the serum samples were collected (Gimeno et al., 2009; Zalli et al., 2016). Similarly, Khandaker et al. (2014) measured serum IL-6 and CRP levels in 9-year-old children and found that those with the top-third of IL-6 values were more likely to be depressed at 18 years of age. In an aging population (> 55 years old), these same inflammatory markers predicted depression 5 years after sample collection (Gimeno et al., 2009; Zalli et al., 2016). Interestingly, others have shown that baseline inflammatory biomarkers correlate with the effectiveness of antidepressant treatments: patients with high baseline levels of CRP respond better to the TNF-α inhibitor infliximab or the selective serotonin reuptake inhibitor (SSRI) escitalopram, while those with lower CRP respond better to the tricyclic nortriptyline (Raison et al., 2013; Uher et al., 2014). These results indicate that a patient's inflammatory profile not only impacts their susceptibility to depression, but also their response to treatment. This makes sense, because inflammation affects a variety of molecular mechanisms involved in depression, modulating serotonin, BDNF, dopamine, and the glucocorticoid response system.

4. Molecular mechanisms of inflammation-driven depression

Pharmacological studies have shown that interventions that target inflammatory pathways significantly alter the expression of neurotransmitters implicated in depression. Peripheral inflammatory signals may impact brain function in several ways. Transmitted to the brain via humoral, cellular, or neural routes (Fig. 1), peripheral inflammatory signals modulate serotonin (5-HT), brain-derived neurotrophic factor (BDNF), and dopamine (DA) pathways, as well as potentiating the activity of the hypothalamic-pituitary-adrenal (HPA) axis (Anisman, 2009; Audet and Anisman, 2013; Maes et al., 2011; Miller and Raison, 2016; Raison et al., 2010; Zhu et al., 2010). The link between decreased serotonin and depression is well-established, and this system is typically targeted with antidepressants (Coppen and Doogan, 1988; Fakhoury, 2016; Kambeitz and Howes, 2015). More recent data, however, have shown that BDNF and DA are also associated with depression. BDNF levels are reduced in depressed patients, are inversely correlated with the degree of clinical impairment and with reductions of hippocampal volume, and normalize with successful antidepressant treatment (Huang et al., 2008; Shimizu et al., 2003). BDNF expression and protein levels, are also lower in the prefrontal cortex and hippocampus of individuals who die by suicide than in age- and sex-matched controls (Dwivedi et al., 2003). Research using neuroimaging, pharmacological,

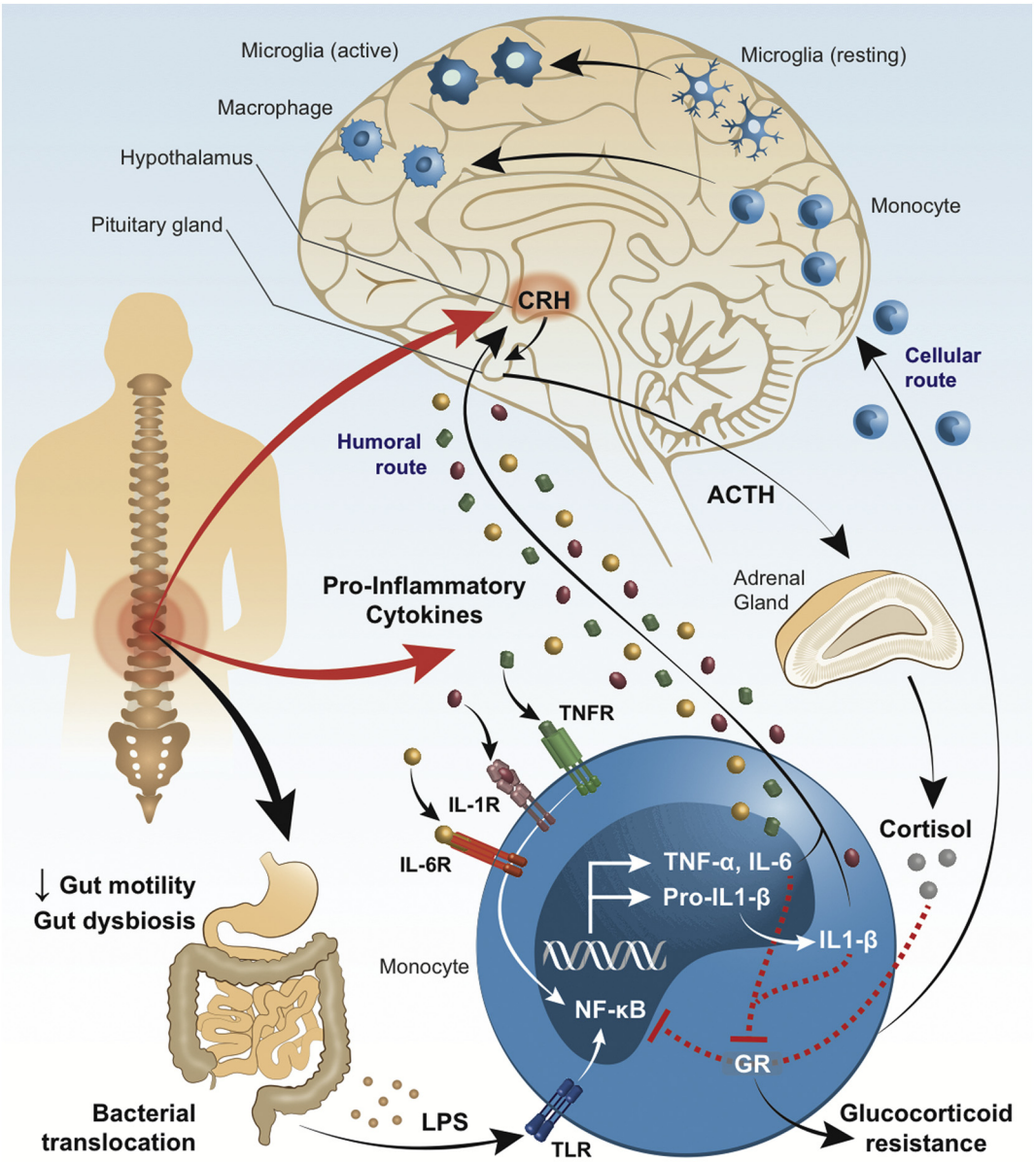

Fig. 1. Spinal cord injury (SCI) has major effects throughout the body and influences the inflammatory response in multiple systems. Under normal conditions, the hypothalamus creates corticosterone releasing hormone (CRH), which causes adrenocorticotropic hormone (ACTH) release in the pituitary gland, which acts on the adrenal gland to release cortisol. In immune cells, cortisol binds to the glucocorticoid receptor (GR) to inhibit nuclear factor-κB (NF-κB) and promote negative feedback of the stress response. Inflammation or gut dysbiosis from SCI disrupts the HPA axis and initiates an immune response in monocytes via cytokine receptors or toll-like receptors (TLR), increasing NF-κB production, which prevents transcription of anti-inflammatory factors and promotes transcription of pro-inflammatory cytokines. Pro-inflammatory cytokines can travel directly to the brain, where they continue to stimulate the HPA axis. Monocytes also travel to the brain via circulation and then release inflammatory factors that activate resting microglia into their active, inflammatory state.

and electrophysiological methods in humans and animal models of depression has also provided support for the presence of DA dysfunctions (for review, see Yadid and Friedman, 2008). In depressed patients with anhedonia, PET imaging studies have shown significantly lower DA transporter (DAT) binding compared with healthy subjects (Meyer et al., 2001; Sarchiapone et al., 2006). The following sections review the molecular mechanisms that may underlie the development of depression in conditions characterized by inflammation, such as SCI.

4.1. Effects of cytokines on 5-HT and BDNF via the kynurenine cycle

The kynurenine pathway of tryptophan metabolism has been heavily implicated as a causal factor in the development of inflammation-induced depression. As shown in Fig. 2, cytokine-induced activation of the enzyme indoleamine 2,3-dioxygenase (IDO) decreases serotonin and BDNF levels, in part by diverting the metabolism of tryptophan (the primary precursor of serotonin) into kynurenine, decreasing serotonergic availability (Maes et al., 2011; Müller, 2016; Raison et al., 2010). Cytokines, like IL-1β and IFN-γ, can also increase kynurenine 3-monooxygenase (KMO) levels in microglia and neurons (Connor et al., 2008; Corona et al., 2010; Gonzalez-Pena et al., 2016; Guillemin et al., 2003; Laumet et al., 2017). KMO is a key enzyme for the metabolism of kynurenine into 3-hydroxy-kynurenine (3-HK). 3-HK is then transformed into quinolinic acid (QUIN) by kynureninase and 3-hydroxyanthralinic acid dioxygenase (Schwarcz and Stone, 2017). QUIN is excitotoxic. It produces excessive activation of the N-methyl-D-

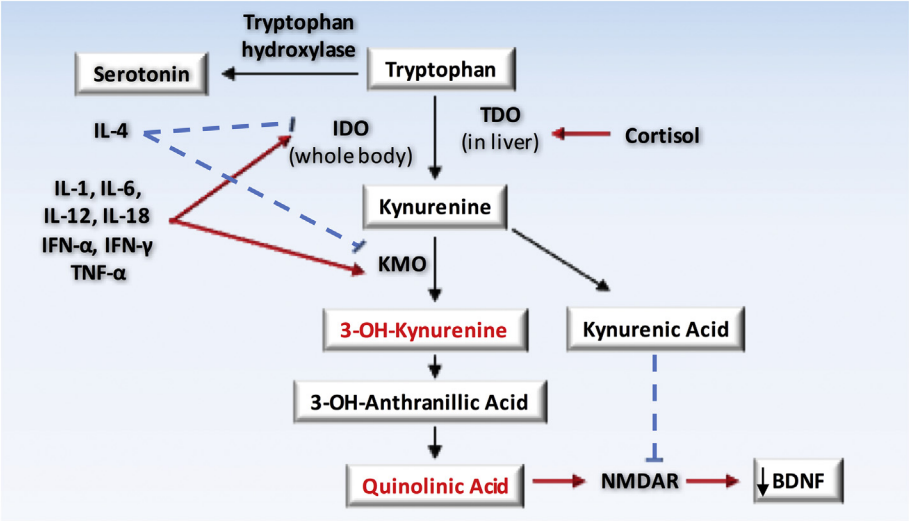

Fig. 2. Kynurenine Pathway: The amino acid tryptophan is an essential precursor to serotonin. However, it can also be converted to kynurenine, most commonly in the liver, through tryptophan 2,3-dioxygenase (TDO), or, throughout the rest of the body and especially the central nervous system, through indolamine 2,3-dioxygenase (IDO). Kynurenine is further metabolized into kynurenic acid, an N-methyl-D-aspartate receptor (NMDAR) antagonist or into quinolinic acid, an NMDAR agonist, which can produce neurotoxicity and decrease brain derived neurotrophic factor (BDNF) in the brain. Cortisol can activate TDO, while IFN-γ and other proinflammatory cytokines, working in conjunction, activate both IDO and kynurenine monooxygenase (KMO). Anti-inflammatory cytokines, such as IL-4, can inhibit IDO. *Red text: neurotoxic, red arrows: activation, blue dashes: inhibition.*

aspartate (NMDA) receptor (Heyes et al., 1992; Heyes et al., 1991; Schwarcz et al., 1983), and, together with cytokine-induced reductions in astrocytic glutamate reuptake and stimulation of astrocyte glutamate release, can lead to excessive glutamate both within and outside the synapse (for review see Bryleva and Brundin, 2016). Excessive glutamate binding to extrasynaptic NMDA receptors can, in turn, lead to increased excitotoxicity and decreased BDNF (Santana-Martínez et al., 2018).

Dysregulation of kynurenine metabolism is linked to depression at multiple levels. In rodents, lipopolysaccharide (LPS) administration induces expression of IDO, IFN-γ, TNF-α, and IL-1β, while also decreasing sucrose preference and increasing immobility in the forced swim and tail suspension tests. O'Connor and colleagues found that administration of 1-methyltryptophan, a competitive IDO inhibitor, blocked the development of depression after LPS administration (O'Connor et al., 2009a; Salazar et al., 2012). Similarly, Bacillus Calmette-Guerin (BCG) produces depression-like behavior and increased expression of IDO, IFN-γ, and TNF-α in the brain (Moreau et al., 2008). O'Connor et al. (2009a, 2009b) showed that the depressive phenotype and kynurenine dysregulation produced by BCG is absent in IDO and IFN-γ KO mice. IDO is the rate-limiting step of kynurenine production, and its upregulation leads to decreased serotonin and increased neurotoxic factors.

Parrott et al. (2016b) also showed that KMO activity is significantly increased following a peripheral immune challenge with LPS. Targeted deletion of the KMO gene, prevented the expression of depression-like behaviors on the tail suspension test and spontaneous alterations on the Y-maze (a measure of working memory) after LPS administration, suggesting that hippocampal-dependent behaviors may be particularly vulnerable to neurotoxic dysregulation of kynurenine metabolism (Parrott et al., 2016a). Similarly, Laumet et al. (2017) showed that KMO activity is necessary for the development of depression after a spared nerve injury. They found that inhibition of KMO activity reverses depression-like behavior in forced swim test after injury. Interestingly, Wang et al. (2017) also found an association between polymorphisms of the *KMO* gene and the incidence of postpartum depression symptoms in women. Heightened KMO activity, arising from KMO rs1053230 G/A genetic variations, was associated with a higher serum 3-HK/KYN ratio and increased susceptibility to develop depression. KMO appears to be a pivotal mediator of hippocampal-dependent depressive-like behaviors.

Increased KMO activity leads to elevations in neurotoxic metabolites including 3HK and QUIN. 3HK is capable of inducing oxidative stress, mitochondrial stress, and cell death (Colín-González et al., 2013), while QUIN, which is produced by microglia and macrophages, exerts neurotoxic effects through multiple different mechanisms, including activation of the NMDA receptor (Guillemin, 2012). Suicide victims have increased levels of QUIN in their brains, and patients with major depression have increased microglial production of QUIN in the subgenual anterior cingulate cortex, a brain region implicated in the neurobiology of depression and often targeted for deep brain stimulation therapy (Harrison et al., 2009; Steiner et al., 2011).

Additionally, QUIN can decrease BDNF in the brain by activating the inflammatory Jun N-terminal kinase (JNK) pathway (Santana-Martínez et al., 2018). Importantly, following SCI, decreased BDNF levels are observed both in spinal tissue (Garraway et al., 2011; Hajebrahimi et al., 2008; King et al., 2000; Liebl et al., 2001) and in the hippocampus (Fumagalli et al., 2009). Depression after SCI may depend on cytokine-mediated decreases in BDNF expression. Notably, current anti-depressants do not target BDNF. It has been proposed, however, that the rapid action of ketamine, an NMDAR antagonist which acts as an antidepressant in treatment-resistant patients (Murrough, 2012), may be mediated by the release of BDNF in the prefrontal cortex (Lepack et al., 2014).

4.2. Cytokines disrupt dopamine activity

Quinolinic acid and the kynurenine pathway demonstrate how cytokines can disrupt the synthesis of serotonin, but cytokines can also inhibit dopamine synthesis. Single injections of septic doses of LPS (5 mg/kg) cause progressive neurodegeneration of the nigrostriatal dopaminergic system (Qin et al., 2007; Reinert et al., 2014), which can be blocked by inhibition or genetic deletion of inflammatory cytokines such as TNF (Qin et al., 2007; Tian et al., 2006; Van Heesch et al., 2014). Cytokines disrupt tetrahydrobiopterin (BH4), which is an important cofactor for tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis, and ultimately decrease dopamine production (Miller et al., 2013). IFN-α treatment results in decreased levels of downstream products of BH4 in rats' CSF (Miller et al., 2013). High levels of CSF IL-6 also correlate with low levels of CSF BH4, further demonstrating the link between cytokines and monoamine production (Felger et al., 2013a). Finally, multiple cytokines have also been shown to impact monoamine reuptake in the brain. The mitogen-activated protein kinase (MAPK) kinase, which is activated by many cytokines (Fig. 3), increases the activity of dopamine reuptake transporters (Miller et al., 2013). These findings support the hypothesis that inflammation has downstream effects that contribute to the development of depression.

Although not studied as extensively as the kynurenine pathway, cytokine-induced changes in dopamine expression are associated with the expression of depression-like behaviors. Using *in vivo* microdialysis,

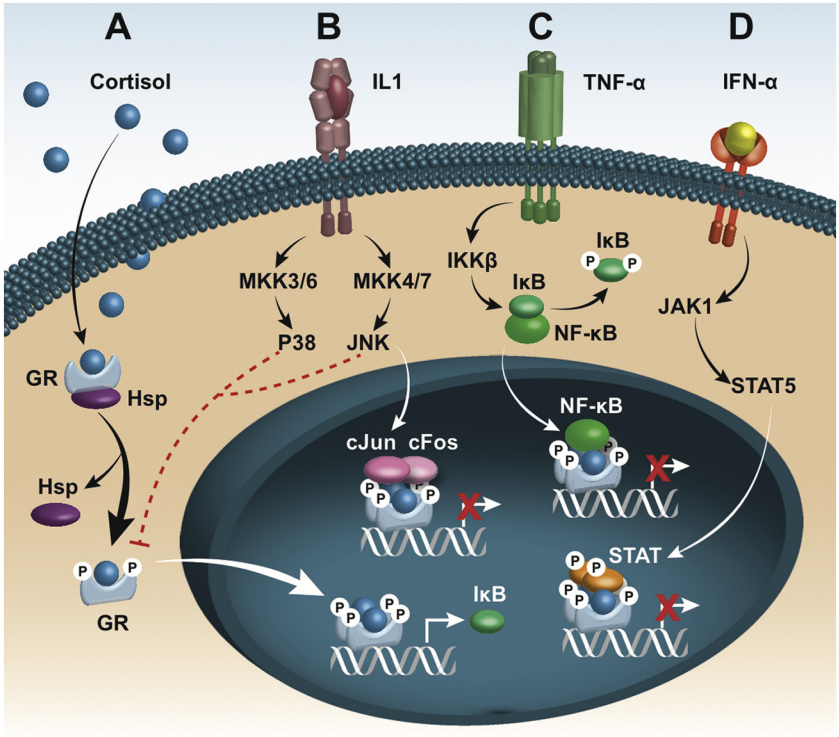

Fig. 3. A) Cortisol binds to the glucocorticoid receptor (GR), which causes dissociation of the heat shock protein and phosphorylation of GR. GR then translocates into the nucleus, where it dimerizes and acts as a transcription factor for a number of genes, such as inhibitor κB (IκB), and directly binds to and inactivates NF-κB. B) TNF-α binds to its receptor and activates IκB kinase β, which phosphorylates IκB and allows NF-κB to enter the nucleus and bind to GR, inactivating both molecules. C) IL-1 binds to its receptor and activates mitogen activated protein kinase (MAPK) kinases (MKK), which results in the activation of Jun amino-terminal kinase (JNK) and p38 kinase, both of which can phosphorylate GR further and inactivate it. JNK can also phosphorylate cJun, allowing it to create a heterodimer with cFos and interact with the GR. D) IFN-α binds to its receptor and causes Janus kinase (JAK) phosphorylation, which then phosphorylates signal transducers and activators of transcription (STAT) proteins, which inhibit GR activity in the nucleus.

Felger et al. (2013b) showed that DA release was decreased in the striatum of monkeys after chronic administration of IFN-α, which correlated with reduced effort-based sucrose consumption. Gentile et al. (2015) investigated depressive-like behavior in mice with experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis. They showed that mice with mild EAE displayed depression-like behavior in the forced swim and tail-suspension tests, despite no generalized motor deficits, as measured with the rotarod and cat walk tasks. The EAE mice also had increased striatal expression of IL-1β and reduced DA release, relative to controls. Supporting the hypothesis of causal IL-1β effects on the dopaminergic system, IL-1ra treatment increased DA levels in the striatum of the EAE mice (Gentile et al., 2015). Central administration of IL-1ra also blocks depression-like behaviors (anhedonia) in EAE mice (Pollak et al., 2003). Capuron et al. (2012) showed that there was increased uptake and decreased turnover of [^{18}F]fluorodopa (FDOPA) in the caudate, putamen, and ventral striatum of IFN-α-treated patients who develop MDD. Baseline and percent change in FDOPA uptake was correlated with IFN-α-induced depression and fatigue (Capuron et al., 2012). Like the DA precursor l-DOPA, FDOPA is taken up by dopaminergic neurons, converted by DA decarboxylase to DA, and then stored in vesicles for release. The increased FDOPA uptake after IFN-α administration suggests that neuronal loss is minimal, and dopamine should be synthesized. However, the decreased turnover suggests that release is impaired. Notably, intrastriatal administration of kynurenic acid to rats has been shown to lead to marked reductions in extracellular dopamine that can be reversed by the allosteric alpha-7 nicotinic acetylcholine receptor agonist galantamine (Wu et al., 2007). Kynurenic acid produces these effects by blocking the alpha-7 nicotinic acetylcholine receptor, which inhibits glutamate release and, subsequently, dopamine release (Borland and Michael, 2004; Wu et al., 2007). Activation of the kynurenine pathway may not only affect serotonin and BDNF levels, it may also affect dopamine.

To our knowledge, very little is known about the effects of spinal cord injury on dopamine expression in the brain. Recently, Voulalas et al. (2017) showed that 21 days after a lesion of the anterolateral quadrant of the spinal cord, both mice and rats display a remarkable decline in the expression of D1 receptors in the periaqueductal gray. These changes were associated with a significant reduction in hindpaw withdrawal thresholds in lesioned animals compared to sham-operated controls. While depression was not assessed, changes in dopamine receptor expression in other areas of the brain, particularly those affecting the mesolimbic pathway, would affect susceptibility to depression. Further research on the effects of SCI on dopamine levels and receptor expression, as well as the role of dopamine in depression is needed.

4.3. Hypothalamic pituitary adrenal (HPA) axis hyperreactivity

Acute spinal cord injury not only increases inflammation, it also increases the expression of glucocorticoids. In humans, urinary cortisol remains elevated for months after SCI (Campagnolo et al., 1999; Cruse et al., 2000). Similarly, after thoracic contusion injuries, rats and mice have elevated serum corticosterone levels (Gaudet et al., 2018; Gezici et al., 2009; Lucin et al., 2007; Popovich et al., 2001). Popovich et al. (2001) found that circulating corticosterone is elevated for 24 h after SCI and remains above control levels for up to 1 month postinjury in a rodent T8 contusion model.

Typically, corticosteroids act as part of a homeostatic mechanism designed to control inflammation and regulate cell stress responses (Fig. 1). Glucocorticoids bind to glucocorticoid receptors (GR) in the cell cytosol, causing a morphological change, phosphorylation of the receptor, and translocation into the cell nucleus, where the receptor regulates the expression of target genes (Fig. 3). GR translocation is necessary for the inhibition of nuclear factor-kappaB (NF-κB) and the transcriptional repression of inflammatory genes controlled by NF-κB (Bekhbat et al., 2017). Transactivation of anti-inflammatory genes by the GR, such as the IκB proteins, also suppresses the nuclear translocation of NF-κB and inflammation (Newton et al., 2007). Activation of the GR plays a significant role in modulating the effects of stress on the immune system.

Depression, however, has been associated with glucocorticoid resistance, which undermines the glucocorticoid-mediated inhibition of inflammatory processes. Under stressful conditions, the hypothalamus

releases corticotropin releasing hormone (CRH), which induces the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH subsequently travels to the adrenal glands and causes them to release glucocorticoids (cortisol in humans or corticosterone in rodents). Binding to their receptors in the HPA axis, endogenous glucocorticoids serve as potent negative regulators of HPA axis activity (De Kloet et al., 1998). When the HPA axis fails to induce negative feedback, however, it continues producing cortisol. In patients with major depression, numerous studies have shown loss of the negative feedback of glucocorticoids (Gold et al., 1988; Heuser et al., 1994; Holsboer and Barden, 1996). For example, Heuser et al. (1994) found that while administering dexamethasone, an exogenous glucocorticoid, lowered levels of circulating cortisol and ACTH in healthy controls, it had no effect in depressed patients. A significant percentage of depressed individuals also have higher levels of cortisol throughout their bodies, in urine, cerebrospinal fluid, plasma, and serum (Pariante and Miller, 2001), as well as increased activity and size of the pituitary and adrenal glands (for review see Nemeroff and Vale, 2005).

Several mechanisms have been identified as contributors to the development of glucocorticoid resistance. Depressed patients and people subject to early childhood stress (a predictor for future depression) tend to have mutations in their GR genes, and they have decreased levels of the active GR isoform (GRα) compared to non-depressed controls (Alt et al., 2010; Bet et al., 2009; Carvalho et al., 2014). Inflammatory cytokines also have a direct impact on GR function. A number of studies have demonstrated that treatment with pro-inflammatory cytokines, like IL-1 and IL-6, decreases GR function, causing decreased sensitivity to the functional effects of glucocorticoids and decreased GR affinity for the ligand (Maddock and Pariante, 2001; Miller et al., 1999; Pariante et al., 1999). Additionally, stimulating IL-2, IL-4, IL-6, IL-10, IFN-α/β, or IFN-γ activates the Jak-STAT pathway, and IL-1 or TNF-α activates the mitogen-activated protein kinase (MAPK) pathway. Both pathways ultimately produce more inflammatory products and phosphorylate the GR at key residues to prevent its action in the nucleus (Fig. 3) (Pace et al., 2007). The large body of work indicating GR inhibition upon the addition of inflammatory molecules, such as IL-1 and TNF-α, link cytokine activity with glucocorticoid resistance.

Interestingly, it has recently been proposed that dysfunctional glucocorticoids not only signal less effectively, they may also produce a pro-inflammatory response (Frank et al., 2011; Horowitz and Zunszain, 2015). Glucocorticoid signaling has been demonstrated to enhance inflammation under both stress (Blandino Jr et al., 2009; Frank et al., 2010; Frank et al., 2012; Kelly et al., 2018; Munhoz et al., 2006; Smyth et al., 2004) and central nervous system injury conditions (Dinkel et al., 2002; Sorrells et al., 2013). Glucocorticoids can upregulate the expression of the TLR2 and TLR4, which are activated by pathogen-associated molecular pattern molecules (PAMPS) and damage-associated molecular pattern molecules (DAMPS), and initiate signaling cascades that lead to the synthesis and release of inflammatory mediators (Hermoso et al., 2004; Weber et al., 2013). Busillo et al. (2011) also showed that glucocorticoids positively regulate the expression of NLRP3 in macrophages, sensitizing macrophages to extracellular ATP and increasing the secretion of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6. Therapies that address glucocorticoid resistance will be pivotal in the treatment of depression, and particularly in decreasing vulnerability to relapse of depression when exposed to a stressor.

The switch from anti- to pro-inflammatory effects of glucocorticoids has also been linked to other molecules besides cytokines that are upregulated after SCI. Frank et al. (2015) suggested that stress-induced increases in central glucocorticoids results in activation of GRs and, through an unknown mechanism, increases the secretion of High-Mobility Group Box 1 (HMGB1), which then primes the NLRP3 inflammasome. HMGB1 is significantly increased in both the acute and chronic phases of SCI (Chen et al., 2011; Kigerl et al., 2018a; Papatheodorou et al., 2017). HMGB1 is a potent systemic inflammatory cytokine that can selectively bind multiple receptors (e.g., RAGE and TLRs) to activate many cell types, including macrophages (He et al., 2012) and monocytes (Andersson et al., 2000), to produce cytokines (for review see Tang et al., 2014). After injury, elevations of HMGB1 may not only increase inflammation and susceptibility to depression, but may maintain the inflammatory response. Further, macrophage migration inhibitory factor (MIF), which is also elevated in rodent models and in humans in the acute and chronic stages of SCI (Bank et al., 2015; Koda et al., 2004; Stein et al., 2013; Su et al., 2017), can counter-regulate the effects of glucocorticoids (Aeberli et al., 2006; Calandra et al., 1995; Pariante et al., 1999). Intriguingly, CRH, which induces pituitary ACTH secretion, also stimulates MIF secretion from the anterior pituitary (Calandra et al., 1995; Nishino et al., 1995; Tierney et al., 2005; Waeber et al., 1999). Calandra et al. (1995) showed that MIF then dose-dependently decreases the glucocorticoid inhibition of TNF-α, IL-1β, IL-6 and IL-8 secretion by LPS-stimulated human monocytes. Once secreted, MIF exhibits a broad range of immune and inflammatory activities, including the induction of inflammatory cytokines (Calandra and Roger, 2003). Elevated levels of MIF have also been associated with depressive symptoms (Bay-Richter et al., 2015; Edwards et al., 2010; Musil et al., 2011; Xu et al., 2018). These data suggest that the molecular changes induced by SCI may increase susceptibility to depression via glucocorticoid dysregulation and an increase in inflammation.

The apparent need for GRs to regulate inflammation after SCI, and the prevalence of glucocorticoid system dysfunction in a portion of the depressed population, presents a unique explanation for depression after SCI. SCI acts as an acute and chronic stressor that activates the immune response and engages the glucocorticoid system. Individuals with pre-existing glucocorticoid dysfunction or inflammation-induced glucocorticoid resistance, resulting in increased cytokine expression, will be more susceptible to depression that results from inflammation.

4.4. Changes in the microbiome

Another emerging element in the depression and SCI story is gut dysbiosis. Bacteria in the gut can communicate with the rest of the body via immune cells and secreted metabolites that cross the blood brain barrier. Gut dysbiosis occurs when pathogenic bacteria outnumber beneficial bacteria. It can cause bacterial translocation out of the gut ("leaky gut"), which further activates the immune system. Gut dysbiosis is associated with inflammation in many diseases and disease models (Gómez-Hurtado et al., 2011; Jiang et al., 2015; Li et al., 2014; Yamashiro et al., 2017), including SCI (Gungor et al., 2016; Kigerl et al., 2018b; Zhang et al., 2018). Patients or subjects with these disease conditions tend to have more circulating pro-inflammatory cytokines than controls (Gómez-Hurtado et al., 2011; Jiang et al., 2015; Li et al., 2014; Shaw et al., 2016; Yamashiro et al., 2017). SCI-induced changes in the microbiome population and intestinal permeability (Gungor et al., 2016; Kigerl et al., 2016), may contribute to depression post injury through these inflammatory outcomes. Indeed, gut dysbiosis has been shown to significantly impact recovery and immune function in human patients and animal models of SCI. Mice with pre-established gut dysbiosis recover less completely and have larger spinal cord lesions one month post-injury than mice with normal guts (Kigerl et al., 2016). Butyrate-producing bacteria are also decreased in the intestines of patients with complete SCIs, potentially increasing inflammation and microglial activation, as butyrate is anti-inflammatory (Gungor et al., 2016). Mice treated with probiotics after SCI recovered immune function and locomotion better than those that received no probiotics, and trials have started for the use of probiotics in treating urinary tract infections and diarrhea in humans after SCI (Anukam et al., 2009; Kigerl et al., 2016; Wong et al., 2014).

There is also mounting evidence to suggest that the gut microbiota influences stress and depression. Depressed patients exhibit dysbiosis or

altered fecal counts of several types of gut bacteria (Aizawa et al., 2016;Jiang et al., 2015; Naseribafrouei et al., 2014; Zheng et al., 2016). Moreover, fecal transplants of microbiota from patients with major depressive disorder, but not from healthy controls, into germ-free mice or microbiota-depleted rats produces depression-like behaviors in the transplanted rodents (Naseribafrouei et al., 2014; Zheng et al., 2016). In animal models, considerable data show that disrupting the gut microbiota can cause cognitive and affective deficits, reduce BDNF production in the brain, and alter tryptophan metabolism (Bercik et al., 2011; Desbonnet et al., 2015; Gareau et al., 2011; Sudo et al., 2004). Further, fecal transplants from stress-susceptible rats into naïve subjects produces depression-like behaviors and higher levels of IL-1β in the hippocampus, compared to transplants from stress-resilient mice or unstressed controls (Pearson-Leary et al., 2019).

Reconstitution of normal gut bacteria can also decrease inflammation-induced depression behaviors in animal models (Lyte et al., 2006). For example, Hao et al. (2019) showed that administration of *Faecalibacterium prausnitzii* (ATCC 27766) during or after exposure to chronic unpredictable stress prevented and reversed symptoms of depression and anxiety, assayed with the forced swim test, the elevated plus maze, and open field. *F. prausnitzii* treatment also lowered blood plasma levels of corticosterone, IL-6, and CRP, while elevating the expression of IL-10. In humans, Rudzki et al. (2019) found that augmentation of SSRI treatment with *Lactobacillus Plantarum 299v* improved cognitive performance and decreased KYN concentration in MDD patients, although it did not affect depression. These preclinical data suggest that psychobiotics (probiotics that yield positive psychiatric effects in psychopathology, Dinan et al., 2013), may be novel therapeutics for the treatment of inflammation-associated depression and anxiety.

In addition to changes in the composition of the microbiome, gut dysbiosis can cause increased permeability of the intestinal barrier. Increased bacterial translocation and increased expression of LPS-respondent IgM and IgA has been associated with the pathophysiology of depression (Maes et al., 2012; Maes and Leunis, 2008). Maes et al. (2012) found that depressed patients have significantly larger IgA and IgM responses to gram-negative enterobacteria, when compared to healthy controls. In mesenteric lymph nodes and peripheral blood, the translocated Gram-negative bacteria and LPS, which is a component of cell walls of Gram-negative bacteria, may cause immune activation, binding to TLR-2/4 complexes and causing increased production of pro-inflammatory cytokines (Slyepchenko et al., 2017). Reducing intestinal permeability may reduce depression symptoms by decreasing any ongoing inflammation induced by elevations in systemic LPS. Ait-Belgnaoui et al. (2012) showed that administration of *Lactobacillus farciminis* for 2 weeks prior to partial restraint stress reduced circulating ACTH and corticosterone levels, decreased pro-inflammatory cytokine expression in the hypothalamus, and prevented stress-induced colonic hyperpermeability and LPS upload in the portal blood. In untreated rats, acute restraint stress impaired the intestinal epithelial barrier, resulting in increased portal blood LPS concentration and IL-1β, IL-6, and TNF-α mRNA expression in the hypothalamus (Ait-Belgnaoui et al., 2012). Preventing the translocation of gram negative bacteria into the portal blood will reduce peripheral inflammation and may be effective for the treatment of depression.

Changes in gut bacteria and intestinal permeability may also influence the availability serotonin, GABA, and BDNF in both the periphery and the central nervous system (Bercik et al., 2011; Bravo et al., 2011; Desbonnet et al., 2015; Yano et al., 2015; Waclawiková and El Aidy, 2018). Inflammatory-induced altered levels of kynurenine in the gut may transfer to the blood circulation and ultimately to the brain, resulting in altered levels of kynurenine and its metabolites, kynurenic acid and quinolinic acid, with concomitant decreases in serotonin and BDNF (Waclawiková and El Aidy, 2018). Higher levels of ACTH and corticosterone with lower levels of BDNF have been found in germ-free mice exposed to stress (Sudo et al., 2004). These changes were reversible through monocolonisation by *B. infantis*. Frank et al. (2018) have also shown that immunization with *Mycobacterium vaccae* blocks stress-induced increases in mRNA for *Nlrp3* and *Il1b* gene expression in the hippocampus, and decreases the protein expression of the alarmin HMGB1. There are still no definitive mechanisms through which the gut influences behavior, but these preclinical studies highlight the potential therapeutic opportunity of targeting inflammation and HPA axis activity with psychobiotics.

5. Therapeutic strategies for depression after SCI

Despite the prevalence of depression after SCI, very little research has been published on therapeutic strategies for these patients. One literature review, published in 2004, only found nine empirical articles addressing treatments specific to patients experiencing depression after SCI (Elliott and Kennedy, 2004). Disappointingly, more recent years have not produced many more empirical studies. This dearth of information is distressing, because depression is so widely reported in the SCI community.

Currently, there are no specific treatments for depression after SCI, beyond those available to the general population. In 1999, a case study reported increased spasticity in an SCI patient after the administration of various standard antidepressant SSRIs (Stolp-Smith and Wainberg, 1999). Three different SSRIs were tried: trazadone, fluoxetine, and sertraline, and, though they effectively reduced depressive symptoms in the patient, they were also associated with a rise in spasticity to such an extent that treatment had to be discontinued. Since then, few antidepressant trials have been published in this field, and many people have expressed concern that standard and effective antidepressants may continue to cause spasticity. Indeed, 5-HT plays a critical role in the maintenance of motoneuron stability (Elbasiouny et al., 2010; Harvey et al., 2006; Murray et al., 2010). After SCI, 5-HT receptor distribution is disrupted, and the delicate balance of excitatory and inhibitory receptors is pushed towards excitation. Thus, SSRIs, which increase 5-HT in neuron terminals, could overload the motoneuron system, causing unwanted spasticity, though this has not been vigorously investigated.

However, SSRIs and serotonin-norepinephrine reuptake inhibitors still seem to be the most prescribed antidepressants for the depressed SCI population. A study of over 940 SCI patients found that SSRIs were the most used antidepressant, and the researchers suggested that spasticity did not create meaningful difficulty; it was certainly overruled by the benefits of higher adherence to the antidepressant treatment regimen that accompanied SSRI use (Fann et al., 2011). However, concern for the lack of empirical studies in this field prompted these same researchers to conduct their own clinical trial (Fann et al., 2015). They administered venlafaxine hydrochloride extended release, a selective serotonin-norepinephrine reuptake inhibitor, or placebo to depressed SCI patients. After 12 weeks, patients in the treatment group showed slightly more improvement on the Maier subscale, a subset of the Hamilton Depression Rating Scale (HAM-D), popularly used by clinicians for the diagnosis of depression. The Maier subscale excludes somatic items, which are often altered after SCI (energy, appetite, sexual dysfunction, weight loss, sleep, headache, and bodily concern), which may make it a more appropriate measure of depression in these patients. The impact on depression was small, and clinically was only considered partial remission, but, patients on venlafaxine also reported greater improvement in SCI-related disability, especially in family and social life and home responsibilities (Fann et al., 2015). These results indicate that modern SSRIs may be an effective treatment for depression after SCI, with less fear of side-effects than was once thought. However, the efficacy for these drugs is still suboptimal. In a large study in 2011, 29% of depressed SCI patients were taking an antidepressant, with 12% on SSRIs (Fann et al., 2011). Given that these individuals were still scoring as “depressed” on the Patient Health Questionnaire while taking these drugs, it follows that they were not effective at eliminating depression.

Other treatments for depression after SCI focus on psychotherapy

strategies. Dorstyn et al. (2010) reported that cognitive behavior therapy (CBT) helped reduce depression symptoms in 50% of treated patients and anxiety symptoms in 66%, but only during a 12-week rehabilitation phase, while the patient was going to therapy. Three months after the discontinuation of therapy, depression scores were actually worse than baseline. Other studies have had similar success. Empirical studies of psychological treatments after SCI primarily cover CBT, coping methods, and psychoeducation (Mehta et al., 2011; Perkes et al., 2014). As a whole, these studies show that psychotherapy is effective during treatment but that the effects do not necessarily persist after the patient exits treatment. In an effort to bridge the post-treatment gap in mental care, some clinicians are investigating the efficacy of telecounselling, with moderate success (Dorstyn et al., 2013). The results, while difficult to generalize, do suggest that in the absence of access to in-person counselling, tele- or e-counselling may be a viable alternative. These data underscore the fact that well-defined treatment options for depression after SCI are lacking, as are effective mental health follow-up for individuals no longer in a clinical treatment facility.

Because of these difficulties in treatment after SCI, the scientific community would benefit from both rigorous, empirical comparisons of antidepressants for the spinally injured patient and investigation of alternative treatments. Standard antidepressants still seem to have a remarkably low success rate, indicating that SCI makes depression more complicated than it already is. One solution to this problem could lie in the inflammatory pathways already well-characterized separately in both depression and SCI. Some people have already seen success in managing depression in the general population with anti-inflammatory drugs or cytokine inhibitors (Abbasi et al., 2012; Akhondzadeh et al., 2009; Brunello et al., 2006; Johansson et al., 2012; Maciel et al., 2013; Makunts et al., 2018). Given the high levels of baseline inflammation after SCI, this may be an effective strategy. Additionally, it may be a viable solution for patients who have little access to mental health services.

6. Summary and conclusions

Depression after SCI is a prevalent problem in need of careful investigation. It can be difficult to diagnose, but it continues to persist at a much higher rate in the injured population. While some elements of depression after SCI might be similar to those found in depression in the general population, depression after SCI is complicated and exacerbated by the altered inflammatory response in the central nervous system following injury. Data suggest that inflammatory cytokines and the glucocorticoid system play an important role in the propagation of depressive symptoms after CNS trauma, but conclusive evidence has yet to elucidate a mechanism. Further research is needed to explore outcomes and inform clinical treatments.

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