

Role of Inflammation in Suicide: From Mechanisms to Treatment

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Suicidal behavior is complex and manifests because of a confluence of diverse factors. One such factor involves dysregulation of the immune system, which has been linked to the pathophysiology of suicidal behavior. This review will provide a brief description of suicidality and discuss the contribution of upstream and downstream factors in the etiology of suicidal behavior, within the contextual framework of inflammation. The contribution of inflammatory conditions such as traumatic brain injury, autoimmune disorders, and infections to neuropsychiatric symptoms and suicidality is only beginning to be explored. We will summarize studies of inflammation in the etiology of suicide, and provide a neurobiological basis for different mechanisms by which inflammation might contribute to the pathophysiology. Finally, we will review treatments that affect upstream and downstream pathways related to inflammation in suicidality.

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INTRODUCTION

Death by suicide is the second leading cause of mortality among the 15–29 age group worldwide (WHO, 2012). It is estimated that 40 000 people die of suicide every year in the United States, and the global death toll is estimated to be at ~800 000 (WHO, 2014). The World Health Organization predicts close to one million deaths by the year 2030, contributing to a projected 1.4% of all deaths worldwide (World Health Organization, 2011). The actual numbers may be far higher, as suicidal deaths tend to be typically under reported because of societal taboos and criminalization of suicide in certain societies.

Suicide attempts may, likewise, be grossly underestimated because of poor reporting and insufficient data collection. Twenty or more suicide attempts occur for every one death by suicide, suggesting that suicide attempts are more frequent than suicide itself (Bertolote *et al*, 2010). Suicide attempts are currently the best predictor of completed suicide, which indicates that proper reporting and close monitoring of the individuals who attempt suicide may serve to prevent future suicides. To this effect, Da Cruz *et al* determined that over 40% of individuals who died by suicide visited the emergency department at least once in the

12 months before death; with 28% of them visiting on more than three occasions. Death by suicide followed soon after the last emergency department visit in the group of frequent attempters compared with other attenders (Da Cruz *et al*, 2011). This critically underscores the insufficiency of existing methods of suicide risk assessment, demonstrated by failure to identify high-risk individuals despite repeated visits to the emergency department before death.

There are also some consistent gender differences in suicidal behavior that are important to note. In many countries, including the United States, male-completed suicides outnumber females-completed ones with a ratio ~3 : 1, although women are more likely to experience suicidal ideation to a higher degree than men (SAMHSA, 2013). Men are also likely to employ more violent methods of suicide than women (Canetto and Sakinofsky, 1998). Both suicide deaths and attempts are acts of extreme psychological despair, and constitute a profound emotional burden to both the family and relatives of the victims. In essence, there is a great need to develop diagnostic methods, which include behavioral and biological indicators for reliable and timely identification of risk factors that may lead to suicidal behavior.

CLINICAL ASPECTS OF SUICIDALITY

Suicide is defined as an intentional act of taking one's life by engaging in self-directed injurious behavior. Suicidal ideation and suicide attempts are suicidal behavior that may manifest as standalone events or precipitate a completed suicide (Crosby *et al*, 2011). Several theories have been

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proposed to model suicide risk, each taking into account etiological and phenotypic variability that is associated with suicide. They are categorized into risk factors that predispose (distal factors) and precipitate suicidal event (proximal factors). Proximal factors are typically associated with neuropsychiatric pathology and may be precipitated by stressful life events (Mann, 2003). Psychiatric disorders and the risk for suicidal behavior has been a topic of intense study given that ~90% of suicide completers are diagnosed with some form of psychiatric illness including major depressive disorder (MDD) and substance abuse disorders (Arsenault-Lapierre *et al*, 2004). Behavioral traits such as impulsivity and aggressive behavior may also contribute to the risk of suicidal behavior, specifically in adolescents or young adults. These traits are often co-morbid with different psychiatric disorders such as bipolar disorders and substance abuse disorders (Brent *et al*, 1994; Cuomo *et al*, 2008; McGirr *et al*, 2008).

Familial transmission and early life adversity (ELA) are distal events associated with suicide risk (Mann, 2003; Moscicki, 1994). Physical or sexual abuse and parental neglect are significantly associated with suicidal risk (Brezo *et al*, 2008). The association between ELA and suicide risk in these individuals is strongly supported by the changes in several downstream factors, including epigenetic changes, hypothalamic–pituitary–adrenal (HPA) axis activation and neuronal plasticity, informed to a large extent by animal studies and post-mortem studies (Labonte *et al*, 2013; Labonte *et al*, 2012; McGowan *et al*, 2009; Roth *et al*, 2011).

Family history of suicidal behavior has also been identified as a risk factor. In a registry-based study, Tidemalm *et al* (2011) assessed suicides in probands of individuals who died by suicide, and determined that the risk does run in families and is influenced by both genetic and shared environmental factors. Given that suicidal behavior is strongly associated with psychiatric disorders, Brent *et al* examined suicidal behavior and psychopathology among probands of adolescent suicide victims. They observed that the rates of suicide attempts were higher in relatives of adolescent suicide victims even after controlling for familial rates of psychopathology, suggesting that familial transmission of suicide is discrete from psychopathology (Brent *et al*, 1996).

Substance abuse is also considered a risk factor for suicidal behavior. The risk for suicide is much higher in individuals with substance abuse disorder compared with general population (Wilcox *et al*, 2004). However, the majority of individuals with substance abuse issues are often diagnosed with other psychiatric conditions, a confounding factor which must be kept in perspective (Treatment. CfSA, 2009). Conditions, such as early childhood trauma and post-traumatic stress disorders (PTSDs), often co-occur with substance abuse and their ability to confer suicide risk has also been explored. Roy (2003) assessed the association between childhood trauma and suicide attempts in individuals with substance abuse and determined that in these individuals, suicide attempts were associated with childhood trauma. Furthermore, Price *et al* (2004) found that drug dependence was associated with PTSD and suicidal behavior

in a cohort of Vietnam veterans assessed over a period of 25 years. Overall, suicidal behavior may manifest as a consequence of interaction between early life events, traits such as aggression and impulsivity, and psychiatric illness.

INFLAMMATION AND SYMPTOMS OF SUICIDALITY

Aberrations in inflammatory cytokines have been reported in several neuropsychiatric conditions, including MDD, schizophrenia, and bipolar disorders (Dowlati *et al*, 2010; Miller *et al*, 2011; Munkholm *et al*, 2013). Mechanistically, it is known that inflammation can trigger depressive symptoms and is associated with suicidality based on studies involving patients who receive interferon (IFN)-based or interleukin-2 (IL-2) immuno-therapy (Buter *et al*, 1993; Capuron *et al*, 2004; Dieperink *et al*, 2004; Janssen *et al*, 1994; Renault *et al*, 1987). It is well established that ~30–45% of patients receiving IFN treatment develop depressive-like symptoms during the course of therapy, with a proportion of them experiencing these symptoms long after therapy has ceased (Meyers *et al*, 1991; Miyaoka *et al*, 1999). Moreover, healthy volunteers who receive injections of lipopolysaccharide (LPS), a bacterial endotoxin, which induces a strong inflammatory response in the periphery as well as in the central nervous system, experience depressive symptoms (Yirmiya *et al*, 2000). However, questions arise as to whether inflammation contributes to symptoms of suicidality or merely exists as an epiphenomenon in patients who are considered ‘primary psychiatric patients’. Moreover, are there individuals in whom inflammation is particularly pronounced and is associated with a specific symptom profile? Several studies indicate that inflammation may be particularly pronounced in patients who experience suicidality (Figure 1; Table 1). An early study found that patients with a history of suicide attempts have increased blood levels of the soluble IL-2 receptors compared with healthy controls (Nassberger and Traskman-Bendz, 1993). This was followed by two post-mortem studies, which independently provided evidence of increased inflammation in the brains of suicide victims. First, Tonelli *et al* (2008) reported elevated mRNA transcripts of IL-4 and IL-13 in the orbitofrontal cortex of suicide victims. Subsequently, Steiner *et al* (2008) demonstrated increased microgliosis, indicative of an enhanced inflammation, in suicide victims with a diagnosis of depression and schizophrenia. These initial findings were supported by a study from our group, showing elevated levels of IL-6 in the cerebrospinal fluid (CSF) of recent suicide attempters. In addition, we observed that IL-6 levels in these patients correlated with the severity of depression as assessed by Montgomery–Asberg Depression Rating Scale (Lindqvist *et al*, 2009). A previous study had found lower CSF levels of neuroprotective IL-8 levels in suicide attempters compared with healthy controls, confirming dysregulation of the immune system in suicidal patients (Isung *et al*, 2012). Since then, we found that decreased IL-8 levels were specific

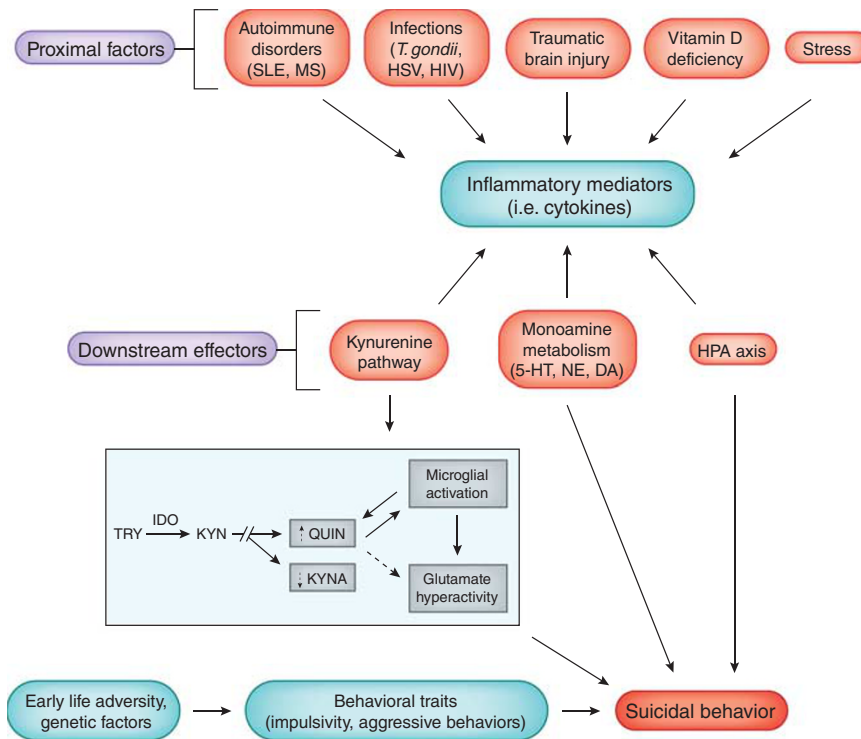


Figure 1. Contributing factors to suicidal behavior etiology. Genetic factors can predispose individuals to behavioral traits that predispose them to exhibit suicidal behavior. Proximal factors with an underlying immune component can induce a sustained immune response, which, then, is known to modulate a variety of downstream effectors including modifying monoamine metabolism, increasing tryptophan metabolism via the kynurenine pathway, and dysregulating the hypothalamic–pituitary axis. KYN, kynurenine; KYNA, kynurenic acid; MS, multiple sclerosis; NE, norepinephrine; QUIN, quinolinic acid; SLE, systemic lupus erythematosus; 5-HT, serotonin.

to patients with anxiety and identified the presence of a single-nucleotide polymorphism in the promoter region of the IL-8 gene, which predicted more severe anxiety in the suicide attempters (Janelidze *et al*, 2015). Interestingly, O'Donovan *et al* (2013) demonstrated that increased inflammation correlated with the degree of suicidal ideation in patients with depression, even after controlling for active suicide attempts and degree of depressive symptoms. Limited post-mortem data on teenage suicide victims also points to the association between inflammation and suicide. Pandey *et al* (2012) reported that post-mortem brain tissue from teenage suicide victims had increased mRNA and protein levels of IL-1 β , IL-6, and tumor necrosis factor alpha (TNF- α) in certain cortical regions (Brodmann area 10). More studies are clearly needed to support the relationship between inflammation and suicidality in youth, as suggested by a recent meta-analysis (Kim *et al*, 2014). Together, these studies suggest that suicidal individuals may have an inflammatory signature irrespective of their primary diagnoses and other underlying conditions. However, there are studies that also report a decrease in cytokine levels in suicidal individuals (Clark *et al*, 2016; Gabbay *et al*, 2009). Although some of these discrepancies may be attributed to differences in sample size, study design, and relevant controls, it is critical to acknowledge the complexity of drawing definitive conclusions, while controlling for diverse confounding factors such as medication history, post-mortem tissue integrity, past

psychiatric and substance abuse history, and previous suicide attempts. In this context, meta-analyses provide a formal, qualitative assessment of previously published studies, which can then be used to derive conclusions. In one such meta-analysis study that assessed changes in inflammatory cytokines in blood, CSF, and post-mortem tissue of suicidal individuals, Black *et al* found a robust association between increased suicidality and plasma levels of IL-1 β and IL-6. These changes were significant to distinguish psychiatric patients with suicidality from psychiatric patients without suicidality and healthy controls. They also found increased IL-1 β and IL-6 in post-mortem brain tissue from suicide completers and reported that reduced CSF levels of IL-8 were associated with suicidal behavior (Black and Miller, 2015).

In an interesting study, Torres-Platas *et al* (2014) showed that depressed individuals who committed suicide have a greater proportion of activated microglia in the anterior cingulate cortex white matter compared with subjects without psychiatric disorders who died from other causes. The same group also had specific microglial phenotypes that were associated with concurrent increases in vascular density and increased expression of perivascular macrophage markers. Schnieder *et al* (2014) reported similar findings, where they observed increased density of perivascular cells in prefrontal cortex white matter of suicide victims. It is known that peripheral cytokines can be trafficked into the CNS either through regions with limited blood–brain barrier (BBB)

TABLE 1 Clinical Studies Connecting Inflammatory Mediators and Effectors with Suicidal Behavior and Predisposing Behavioral Traits

Study reference	Population	Type of patients	Type of control participants	Type of biological sample	Study outcomes in patients compared with controls
Nassberger and Traskman-Bendz, 1993	Adults	Suicide attempters	Healthy controls	Plasma	Elevated soluble IL-2 receptors levels
Coccaro, 2006	Adults	Personality disorder subjects with higher CRP levels	Personality disorder subjects with lower CRP levels	Plasma	Elevated TNF- α and CRP levels are associated with aggressive traits
Steiner et al, 2008	Adults	Suicide completers with a diagnosis of depression and schizophrenia	Non-suicides without psychiatric disorders	Post-mortem brain	Increased microgliosis in cortical and subcortical regions
Tonelli et al, 2008	Adults	Suicide completers	Non-suicides without psychiatric disorders	Post-mortem brain	Elevated IL-4 (females) and IL-13 (males) mRNA in orbitofrontal cortical regions
Gabbay et al, 2009	Adolescents	MDD patients with suicidality	Non-suicidal MDD patients	Plasma	Decreased TNF- α levels
Lindqvist et al, 2009	Adults	Suicide attempters	Healthy controls	CSF	Elevated IL-6 levels (correlates with the depression severity)
Janelidze et al, 2011	Adults	Suicide attempters	Non-suicidal depressed patients	Plasma	Elevated levels of IL-6 and TNF- α ; decreased IL-2 levels
Steiner et al, 2011	Adults	Suicide completers	Non-suicides without psychiatric disorders	Post-mortem brain	Increased density of QUIN reactive microglia in anterior cingulate cortex
Sublette et al, 2011	Adults	Depressed suicide attempters	Non-suicidal depressed patients	Plasma	Increased kynurenine levels
Isung et al, 2012	Adults	Suicide attempters	Healthy male controls	CSF	Lower IL-8 levels
Pandey et al, 2012	Adolescents	Suicide completers	Non-suicides without psychiatric disorders	Post-mortem brain	Increased mRNA and protein levels of IL-1 β , IL-6, and TNF- α in Brodmann area 10
Erhardt et al, 2013	Adults	Suicide attempters	Healthy controls	CSF	Increased QUIN levels, which positively correlate with IL-6 levels and suicidal intent; increased QUIN/KYNA ratio
O'Donovan et al, 2013	Adults	MDD patients with high suicidal ideation	MDD patients with low suicidal ideation	Plasma	Elevated IL-6 and CRP levels but not TNF- α
Coccaro et al, 2014	Adults	Healthy individuals with intermittent explosive disorder	Non-aggressive individuals with or without psychiatric disorders	Plasma	CRP and IL-6 levels are associated with aggressive behaviors compared with psychiatric or healthy controls
Isung et al, 2014	Adults	Suicide attempters	No control group	Plasma and CSF	Plasma IL-6 levels positively correlate with impulsivity trait and with violent suicide attempt methods
Pandey et al, 2014	Adults	Depressed and non-depressed suicide completers	Non-suicidal depressed patients and healthy controls	Post-mortem brain	Irrespective of psychiatric diagnoses, increased mRNA and protein levels of TLR3 and TLR4 in dorsolateral prefrontal cortex
Schnieder et al, 2014	Adults	Suicide completers	Non-suicides	Post-mortem brain	Activated microglia in ventral prefrontal white matter
Torres-Platas et al, 2014	Adults	Depressed suicide completers	Non-suicides without psychiatric disorders	Post-mortem brain	Elevated activated microglia and circulatory macrophages in the dorsal anterior cingulate white matter
Bay-Richter et al, 2015	Adults	Suicide attempters	Healthy controls	CSF	QUIN levels remain elevated over a period of 2 years; KYNA levels are decreased over this time period and correlate with more severe depressive and suicidal symptoms
Busse et al, 2015	Adults	Suicide completers	Non-suicides without psychiatric disorders	Post-mortem brain	Decreased density of QUIN reactive microglia in hippocampal regions
Janelidze et al, 2015	Adults	Suicide attempters	Healthy controls	Plasma and CSF	Lower IL-8 levels are specific to patients with anxiety; a SNP in IL-8 gene promoter predicts more severe anxiety
Clark et al, 2016	Adults	Individuals with depressive disorder who died of suicide, natural causes, homicide, and accident	Non-suicides without psychiatric disorders	Post-mortem brain	Lower IFN- γ and TNF- α levels, decreased KYN/TRY ratio, IDO-1/2, TDO, and QUIN

Abbreviations: CRP, C-reactive protein; CSF, cerebrospinal fluid; IDO-1/2, indoleamine 2,3-dioxygenase; IFN- γ , interferon- γ ; IL-1 β , interleukin-1 β ; IL-2, interleukin-2; IL-4, interleukin-4; IL-6, interleukin-6; IL-8, interleukin-8; IL-13, interleukin-13; KYN, kynurenine; KYNA, kynurenic acid; MDD, major depressive disorder; QUIN, quinolinic acid; SNP, small nucleotide polymorphism; TDO, tryptophan 2,3-dioxygenase; TLR3, Toll-like receptor 3; TLR4, Toll-like receptor 4; TNF- α , tumor necrosis factor- α ; TRY, tryptophan.

permeability, such as the circumventricular organs and the choroid plexus, or through a compromised BBB (Dantzer *et al*, 2008), which has been reported to be leaky in suicidal individuals (Bayard-Burfield *et al*, 1996; Falcone *et al*, 2010; Ventorp *et al*, 2016). In line with these findings, Wohleb *et al* demonstrated increased peripheral myeloid cell trafficking into perivascular spaces and specific brain regions using a repeated social defeat stress model. These changes were further accompanied by microglial activation and induction of anxiety-like behavior. This suggests an active role for peripheral myeloid cells in altering neuroimmune response and behavior (Wohleb *et al*, 2013).

Certain behavioral traits, such as impulsivity and aggression, have been found to confer a greater degree of suicide risk (Brent *et al*, 1994; McGirr *et al*, 2008). Clinical studies also indicate a relationship between inflammation and traits of aggression and impulsivity (Coccaro *et al*, 2014; Isung *et al*, 2014; Mommersteeg *et al*, 2008; Suarez *et al*, 2002). For example, in individuals with personality disorders, elevated TNF- α and C-reactive protein (CRP) are associated with aggressive traits (Coccaro, 2006). Recently, the same group demonstrated that plasma CRP and IL-6 levels are associated with aggressive behavior in individuals diagnosed with intermittent explosive disorders (Coccaro *et al*, 2014). A study on suicide attempters by Isung *et al* (2014) found that plasma IL-6 levels were positively correlated with impulsivity trait and with violent suicide attempt methods.

The above-mentioned studies provide evidence that suicidal behavior is associated with the changes in cytokine profiles in peripheral blood as well as in the brain. In addition, it is important to determine whether such changes are specific for suicidal behavior, independent of underlying psychiatric diagnosis. It is also of interest to assess whether similar or different degrees of inflammatory changes are found among individuals with suicidal ideation as well as among suicide attempters and completers. Addressing this, Janelidze *et al* (2011) observed plasma IL-6 and TNF- α levels to be elevated in suicidal depressed individuals compared with non-suicidal depressed individuals and healthy controls, suggesting that suicidal individuals may have a unique cytokine profile among depressive patients. Supporting this, O'Donovan *et al* (2013) found that a higher degree of suicidal ideation was associated with an increased inflammatory index in patients independent of the degree of depressive symptoms. These findings are in line with an early hallmark study, showing increased microglial density in schizophrenic and depressed suicide completers, although not in patients from the same diagnostic groups that died from other causes, stressing that the inflammatory changes might be specific to suicidality across diagnostic boundaries (Steiner *et al*, 2008).

NEUROIMMUNOLOGICAL MECHANISMS INVOLVED IN SUICIDAL BEHAVIOR

Inflammatory cytokines can be synthesized in the central nervous system or enter the brain from the periphery via

different mechanisms, including compromised BBB. We have previously shown that suicide attempters have an increased BBB permeability, which is associated with increased CSF levels of glycosaminoglycan hyaluronic acid, which is a ligand for CD44 and is indicative of increased neuroinflammation (Ventorp *et al*, 2016).

One of the mechanisms, which could be responsible for the observed increase in inflammatory cytokine levels, is activation of the Toll-like receptors (TLRs). TLRs have a critical role in regulating innate immune response and facilitating immune function in the event of infection (Hanke and Kielian, 2011). They are widely expressed in different cell types of the CNS and are identified to have diverse functions, from cognition to memory (Okun *et al*, 2010; Okun *et al*, 2011). In the only study to date on suicidal subjects, Pandey *et al* (2014), concluded that, irrespective of psychiatric diagnoses, mRNA and protein levels of TLR3 and TLR4 were consistently dysregulated in suicide victims (depressed and non-depressed). Although preliminary, this study, for the first time, demonstrated the role of TLRs in suicide.

Inflammatory cytokines may promote suicidal behavior by several mechanisms. Additional mechanisms by which cytokines may contribute to the pathophysiology of suicidal behavior include activation of the kynurenine pathway of tryptophan catabolism, dysregulation of the HPA axis and alterations in monoamine metabolism, as described below.

The kynurenine pathway consists of a series of enzymes involved in the metabolism of the essential amino acid, tryptophan. The pathway is active in the periphery as well as in the central nervous system. The initial step in metabolism of tryptophan into kynurenine is catalyzed by indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO). Kynurenine is further broken down into highly neuroactive compounds such as quinolinic acid (QUIN) and kynurenic acid (KYNA). Inflammatory cytokines such as IFN- γ , IL-6, IL-1 β , and TNF- α are potent activators of IDO and/or TDO (Kim *et al*, 2012; Mandi and Vecsei, 2012; Schwieler *et al*, 2015; Taylor and Feng, 1991; Urata *et al*, 2014). QUIN is one of the neuroactive metabolite that is synthesized in microglia. QUIN is a selective N-methyl-D-aspartic acid (NMDA) receptor agonist and acts via activation of the NR1+NR2A and NR1+NR2B NMDA receptor subunits (de Carvalho *et al*, 1996). In addition to NMDA receptor activation, QUIN also inhibits astrocytic uptake of glutamate by inhibiting glutamine synthetase and increases neuronal glutamate release (Tavares *et al*, 2002). KYNA, on the other hand, blocks the cholinergic $\alpha 7$ nicotinic receptor and antagonizes the glycine site of the NMDA receptor (Hilmas *et al*, 2001; Stone, 1993). KYNA also antagonizes α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptor, which has been implicated in the pathophysiology of depression and in the mechanism of action of several antidepressant drugs (Freudenberg *et al*, 2015; Schwarcz *et al*, 2012). We found QUIN levels in CSF of suicide attempters to be two to three times higher than in healthy controls with no change in KYNA levels. Interestingly, in the same study, QUIN levels positively correlated

with IL-6 in CSF, indicating that the activation of the kynurenine pathway in these patients was associated with an active inflammatory state. The increase in QUIN was also correlated with the suicidal intent in this cohort of patients (Erhardt *et al*, 2013). Furthermore, to determine whether QUIN levels remain elevated over time, we measured CSF QUIN for two continuous years after an initial suicide attempt. Not only did we find QUIN to be elevated over 2 years, we also observed that high levels of IL-6 and lower KYNA in the same patient group correlated with the severity of suicidal ideation and depressive symptoms (Bay-Richter *et al*, 2015). Interestingly, a post-mortem study found increased QUIN immunoreactivity in suicidal depressed patients seemingly in agreement with our findings (Steiner *et al*, 2011). In the same study, certain regions of the anterior cingulate cortex in suicide victims reportedly contained higher density of QUIN-positive microglia. However, a follow-up study found a decrease in the number of QUIN reactive microglia in the hippocampi from the same suicide victims (Busse *et al*, 2015). These findings suggest that certain brain regions may be more sensitive to inflammatory insult, which might have contributed to specific differences in the localization of QUIN reactive microglia in the brains of suicide victims. On the other hand, plasma KYNA has been previously shown to be reduced in depressed patients, although neither QUIN nor cytokine levels were profiled in these patients (Myint *et al*, 2007). Interestingly, we found a twofold increase in CSF QUIN/KYNA ratio in suicide attempters compared with healthy controls. KYNA, being an NMDA receptor antagonist, may induce a net positive effect on NMDA receptor signaling leading to aberrant glutamate signaling (Erhardt *et al*, 2013).

Evidence suggests that the dysregulation of the kynurenine pathway might be more pronounced in depressed individuals with suicidality than depressed patients without suicidal behavior. Sublette *et al* (2011) were the first to demonstrate that blood kynurenine levels are elevated in suicide attempters compared with a depressed-only control group. Interestingly, Dahl *et al* (2015) also reported that depressive episodes in MDD patients are not associated with an increase in plasma kynurenine metabolite levels, despite the presence of elevated cytokine levels in these individuals. In addition, it should be noted that certain metabolites do not freely cross the BBB, and it might, therefore, be of importance to study the CSF levels of metabolites when determining their correlation to neuropsychiatric symptoms (Schwarcz *et al*, 2012).

So far, only a few studies have compared suicidal depressed individuals with non-suicidal depressive individuals, trying to assess whether the biological changes of these two groups are different or, perhaps, similar but differing in magnitude. Indeed, a multitude of papers have shown that patients with depression display inflammation (Dowlati *et al*, 2010; Howren *et al*, 2009; Liu *et al*, 2012; Valkanova *et al*, 2013) and the exact same mechanisms (inflammation and activation of the kynurenine pathway) are proposed as the mechanism of depression (particularly of inflammation-induced depression) (Dantzer and Walker, 2014; Maes *et al*,

2011; Myint *et al*, 2012; Reus *et al*, 2015). Evidence at this point is scarce, but indicates that the inflammatory changes and generation of kynurenine neurotoxic metabolites are, at least, more pronounced in suicidal individuals (Janelidze *et al*, 2011; O'Donovan *et al*, 2013; Sublette *et al*, 2011). It is difficult to determine from the available studies whether these changes are actually unique to patients with suicidal ideation or behavior. The reason is that studies on depressive patients frequently do not attempt to distinguish between suicidal and non-suicidal patients. Patients with a certain degree of suicidal ideation are often included among the non-suicidal depressive individuals. Additional studies on this topic are highly warranted in the future.

In addition to the kynurenine pathway activation, inflammatory cytokines can also induce the changes in monoamine metabolism as well as in the HPA axis (Oquendo *et al*, 2014). Cytokine administration in both animals and humans is known to activate the HPA axis (Dunn, 2000). IFN- α used in the treatment of hepatitis C is a potent activator of the HPA axis as it causes increases in cortisol and adrenocorticotropic hormone levels within several hours of the treatment. HPA axis activation also correlates with the onset of depressive symptoms in patients who undergo interferon therapy compared with those who do not (Capuron *et al*, 2003). The serotonin system is one of the most widely studied neurotransmitter systems in depressive disorders (Vaswani *et al*, 2003) and its dysregulation by inflammatory cytokines could be one of the mechanisms underlying suicidal ideation and behavior (Oquendo *et al*, 2014). IL-1 β and TNF- α have been shown to enhance the expression and activation of serotonin transporters in cell lines via a p38 mitogen-activated protein kinase pathway (Mossner *et al*, 1998; Ramamoorthy *et al*, 1995; Zhu *et al*, 2006; Zhu *et al*, 2005). Acute IL-6 administration is also known to increase serotonin release in rat striatum (Zhang *et al*, 2001). Alterations in cytokine-induced serotonin metabolism have also been reported. 5-hydroxyl indole acetic acid (5-HIAA), a metabolic product of serotonin, has been shown to be elevated following LPS injections in rodent models of depression (O'Connor *et al*, 2009). Thus, inflammatory cytokines can influence a variety of neurotransmitter functions, ranging from synthesis to inducing changes directly at the receptor level.

UPSTREAM TRIGGERS OF SUICIDALITY

The rates of suicidal behavior in individuals affected by conditions that involve the immune system are generally higher than in individuals with somatic conditions that do not increase inflammation. For example, ~1% of adolescents with hemophilia, a genetic condition that does not involve inflammation, have previously attempted suicide compared with 7% of adolescents with thalassemia major, a condition that is often characterized by the presence of chronic vascular inflammatory state (Ghanizadeh and Baligh-Jahromi, 2009; Ghanizadeh *et al*, 2006). Furthermore, causal

effects of inflammation contributing to depression and suicidal behavior are highlighted by studies showing increased incidence following IFN-based treatment in cancer and hepatitis patients (Capuron *et al*, 2000; Capuron *et al*, 2004; Dieperink *et al*, 2004; Janssen *et al*, 1994; Miyaoka *et al*, 1999). It is also known that MDD is more prevalent in patients afflicted with conditions characterized by chronic inflammation (such as cardiovascular diseases, type 2 diabetes, and rheumatoid arthritis) than in the general population (Steptoe, 2007).

AUTOIMMUNE DISORDERS

Multiple sclerosis (MS) is a chronic inflammatory neurological disorder characterized by sensory and motor loss, cognitive impairment, blindness, and fatigue. Patients with MS report high rates of depression reaching ~40% in these patients (Chwastiak *et al*, 2002). In a subset of MS patients with no history of psychiatric illness, treatment with IFN- γ worsens depressive symptoms and induces suicidal ideation or attempts (Benros *et al*, 2011; Chwastiak *et al*, 2002; Fragoso *et al*, 2010). Death by suicide may account for at least 15% of mortality in MS populations (Sadvnick *et al*, 1991). Another study determined an increased risk for suicide completion in a Swedish cohort of MS patients (Fredrikson *et al*, 2003). A similar study in a smaller cohort of Danish MS patients identified a twofold increase in risk of death by suicide compared with the general population, with the greatest risk in the first year following diagnosis (Bronnum-Hansen *et al*, 2005). Systemic lupus erythematosus (SLE) is another autoimmune disorder predominantly affecting women of reproductive age. About 17–71% of SLE patients present with psychiatric symptoms (Wekking, 1993). Prevalence of depression is estimated to be fourfold higher in SLE patients compared with non-SLE patients with at least 75% of SLE patients being diagnosed with depression during their lifetime (Palagini *et al*, 2013). Interestingly, the presence of anti-NR1 antibodies has been consistently reported in the CSF of SLE patients and correlates positively with their neuropsychiatric symptoms (Arinuma *et al*, 2008; Fragoso-Loyo *et al*, 2008; Gono *et al*, 2011; Lapteva *et al*, 2006; Yoshio *et al*, 2006). As mentioned above, NR1 is a subunit of the ionotropic glutamate NMDA receptor (Perez-Otano *et al*, 2001). Examining a Chinese population of SLE patients, Pan *et al* reported a 34% prevalence of suicidal ideation, with lower estimates ranging from 8 to 12% reported in other SLE populations across the world (Ishikura *et al*, 2001; Xie *et al*, 2012; Zakeri *et al*, 2012). It is unclear if suicidal thoughts in these patients manifest as a consequence of the disease or from an underlying psychiatric condition or both.

INFECTIONS

Infections induce inflammation, and, as such, may activate the above-mentioned neuroinflammatory mechanisms

leading to depression and suicidal symptoms. Certain infections may be particularly strong triggers of neuroinflammation, as they invade the central nervous system, and such neurotrophic pathogens include herpes viruses, human HIV, and possibly hepatitis C virus. The prevalence of MDD, suicidal ideation, and attempted suicides in HIV patients is reported to be up to 27.2%, 31%, and 32.7%, respectively (Serafini *et al*, 2015). Chronic hepatitis C patients also display a higher prevalence of depression and suicide risk compared with the general population (Lucaciu and Dumitrascu, 2015). Alavi *et al* (2012) found that, before treatment, 36% of chronic hepatitis C patients suffer from major depression and 18% endure a moderate-to-severe suicide risk. A study by Okusaga *et al* (2011) found higher seropositivity for influenza B virus in patients with a history of suicide attempt, whereas seropositivity for all three types of viruses (influenza A, B, and coronaviruses) was associated with the history of mood disorders. Recently, the onset of *de novo* depression has been associated with the higher levels of cytomegalovirus IgG antibodies with the odds of incident depression being three times greater in individuals with antibody levels in the highest quartile (Simanek *et al*, 2014). Certain neurotrophic pathogens are not only capable of inducing inflammation but might manipulate the host neurons in very specific ways to trigger a behavioral response. *Toxoplasma gondii* is a common protozoan parasite that establishes latency in the muscle and brain (Henriquez *et al*, 2009). Infection in humans is frequently asymptomatic and can occur, for example, after consumption of undercooked meat infected with parasitic oocysts. The host immune response CD4⁺ and CD8⁺ T cells are responsible for keeping the parasite under control and relatively quiescent in the central nervous system (Gazzinelli *et al*, 1992). Interestingly, latent *T. gondii* infection has been identified as a risk factor for suicide and suicide attempts (Arling *et al*, 2009; Ling *et al*, 2011). Reactivation of infection has also been associated with traits such as aggression and impulsivity, two behavioral endophenotypes associated with suicidal behavior (Cook *et al*, 2015).

Proposed mechanisms underlying *T. gondii*-associated behavioral changes include alterations in immune response as well as dysfunction associated with dopaminergic neurotransmission. In rodents, for example, infection with *T. gondii* elicits release of IFN- γ , IL-12, IL-8, and TNF- α primarily by cells of the innate immune system (Miller *et al*, 2009). Recently, using a rodent model of *T. gondii* infection, Notarangelo *et al* (2014) showed that brain kynurenine and QUIN levels are persistently elevated in infected animals. Moreover, the *T. gondii* genome encodes for tyrosine hydroxylase, a rate-limiting enzyme in the synthesis of dopamine, wherein it catalyzes the conversion of tyrosine into L-DOPA (Gaskell *et al*, 2009). Using *T. Gondii*-infected mice, Prandovsky *et al* showed that increased dopamine staining was restricted to tissue cysts containing the parasite. They also observed increased dopamine release in response to *T. gondii* infection (Prandovszky *et al*, 2011). Together, the biological effects of *T. gondii* might include increases in

the levels of pro-inflammatory cytokines, QUIN, and dopamine, thus altering both glutamatergic and dopaminergic neurotransmission.

TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) results from sudden trauma to the brain. Immune system activation following TBI usually occurs as a secondary event and further worsens existing neuro-degeneration and other neurological impairments following initial trauma. The neuroinflammation is characterized by microglial activation and release of inflammatory factors such as IL-1 β , TNF- α , and IFN- γ (Block and Hong, 2005). In a study involving the largest cohort of TBI patients (two million controls and 200 000 Swedish TBI patients), it was determined that those with TBI are three times more likely to die of suicide than controls (Fazel *et al*, 2014). To determine whether increases in inflammatory mediators are associated with TBI, Jeungst and colleagues measured TNF- α levels in serum and CSF of TBI patients 6 and 12 months following initial injury. Not only did elevated TNF- α levels correlate with TBI but they also found positive correlations between TNF- α levels and disinhibition (a behavioral proxy for impulsivity), as well as disinhibition and suicidal ideation at various time points. Thus, they found an alternative rationale for the etiology of TBI, involving immune activation and increase in cognitive deficits associated with impulse control and suicidal behavior (Jeungst *et al*, 2014). A study by Mackay *et al* (2006) found an increase in activation of the kynurenine pathway, which was sustained for at least 1 year (and possibly longer) following TBI. Meanwhile, another study determined that during the first year after mild-to-severe TBI, suicidal ideation was present in 25% of patients (Mackelprang *et al*, 2014). These long-lasting effects of the TBI could be, in part, responsible for the increased risk of suicidality observed in veterans (Brenner *et al*, 2011).

VITAMIN D DEFICIENCY

Low levels of vitamin D have been linked with MDD and other psychiatric illnesses (Kjaergaard *et al*, 2011), and recent studies have begun to explore its role in suicidal behavior. Umhau *et al* (2013) investigated vitamin D status in a cohort of active duty military service professional and found that low levels of vitamin D correlate with increased suicide risk. Although it is still unclear how vitamin D is associated with suicidal behavior, it is plausible that its immune-modulatory functions might have a role. 1,25-dihydroxyvitamin D₃ attenuates immune response by suppressing the effects of IL-2 and IFN- γ , produced by Th1 cells, subsequently preventing the activation and proliferation of T-cell populations (Cippitelli and Santoni, 1998). Furthermore, vitamin D also inhibits the release of cytokines such as IL-6 and TNF- α from human monocytes (Zhang *et al*, 2012). Grudet *et al* compared vitamin D levels in suicide attempters, non-suicidal depressed patients, and

healthy individuals, and found that suicidal patients had significantly lower levels of vitamin D, compared with the other groups, and that 58% of the suicide attempters were severely vitamin D deficient. Lower vitamin D levels also correlated with elevated levels of inflammatory cytokines in the suicidal and depressive patients (Grudet *et al*, 2014).

THERAPY

Several clinical trials have found that ketamine robustly decreases depressive and suicidal symptoms in as little as 40 min with effects lasting for several weeks (DiazGranados *et al*, 2010; Larkin and Beautrais, 2011; Price and Mathew, 2015; Price *et al*, 2009; Zarate *et al*, 2012). Animal studies also showed that ketamine is capable of reducing depressive effects in LPS-injected mice, which exhibit activation of the kynurenine pathway in the brain through IDO induction (O'Connor *et al*, 2009; Walker *et al*, 2013). As ketamine is an NMDA receptor antagonist, its observed beneficial effects could be due to its competing action with neurotoxic QUIN, an NMDA receptor agonist. In addition, ketamine can be metabolized *in vivo* via P450 enzymes to produce various metabolites, some of which are biologically active, such as (2R, 6R)-hydroxynorketamine (HNK), and mediate antidepressant effects by activation of AMPA receptors (Zanos *et al*, 2016). Currently, there are several ongoing clinical trials investigating whether repeated administration or different doses of ketamine are able to increase its efficacy in various psychiatric disorders (US National Institute of Health, 2016).

Another drug with therapeutic potential to treat MDD and suicidal behavior includes 4-chloro-kynurenine (4-Cl-KYN), which is a brain-penetrating prodrug of 7-chloro-kynurenic acid, and works by blocking the glycine co-agonist site of the NMDA receptor. 4-Cl-KYN exerts similar antidepressant effects of ketamine, but not side effects in animal models (Zanos *et al*, 2015). Interestingly, these beneficial mood-altering effects are contingent on the activity of AMPA receptors, suggesting an important relationship between NMDA and AMPA receptors in generating antidepressant response. There is, currently, an ongoing clinical trial testing the antidepressant effects of 4-Cl-KYN in MDD patients (US National Institute of Health, 2016).

Another potentially promising pharmacological target is glycogen synthase kinase-3 (GSK3), which raises the levels of pro-inflammatory cytokines and, thus, is thought to promote the development of aggression and depressive symptoms, which are closely linked to development of suicidality (Beurel and Jope, 2014). Administration of lithium, which exhibits anti-inflammatory effects through inhibition of GSK3, has been found effective in decreasing depressive-like and aggressive behavior in animal models (Beurel and Jope, 2014) and reducing suicidal attempts and suicide completion in patients with bipolar as well as unipolar depression (Baldessarini *et al*, 2006; Guzzetta *et al*, 2007).

Other potential drug targets include cyclooxygenase-2 (COX-2) inhibitors, which are selective nonsteroidal

anti-inflammatory drugs. Several recent meta-analyses of randomized controlled trials (RCTs) have found a COX-2 inhibitor celecoxib to be an effective add-on treatment for unipolar depression as celecoxib decreases depression severity and increases remission rates (Faridhosseini *et al*, 2014; Na *et al*, 2014). A RCT conducted by Nery *et al* (2008) has found that adjunctive treatment with celecoxib is able to produce a rapid antidepressant effect in bipolar disorder patients during depressive or mixed phases.

Infliximab, which is a monoclonal antibody against TNF- α , has also shown some antidepressant effects, as it is able to decrease depressive symptoms in patients with treatment-resistant depression and elevated levels of plasma inflammatory biomarkers (Raison *et al*, 2013). A new, recently started RCT will evaluate the effect of adjunctively administered infliximab on bipolar I and II depression (US National Institute of Health, 2016). Other clinical studies have shown that infliximab and etanercept, another TNF- α blocker, are capable of improving symptoms of depression in patients with various inflammatory conditions (Ersozlu-Bozkirli *et al*, 2015; Ertenli *et al*, 2012; Gelfand *et al*, 2008; Minderhoud *et al*, 2007; Tookman *et al*, 2008).

Minocycline, which is a broad-range tetracycline antibiotic capable of decreasing microglial activation, is another promising treatment for depressive symptoms. Preliminary data from an open-label study of patients with MDD suggest that adjunctive minocycline treatment is able to reduce the severity of depressive and psychotic symptoms (Miyaoaka *et al*, 2012). Currently, ongoing RCTs are investigating the effect of minocycline add-on treatment for the management of depressive symptoms in patients with treatment-resistant depression (Husain *et al*, 2015), MDD (Dean *et al*, 2014), and bipolar depression (Savitz *et al*, 2012).

Other anti-inflammatory drugs with therapeutic promise in the treatment of depressive and suicidal symptoms include those targeting cytokine IL-6 and its biological function. An example of such drug is tocilizumab, a monoclonal anti-IL-6 receptor antibody that works by preventing the IL-6 ligand from binding to the IL-6 receptors. Previous studies have found that tocilizumab is able to effectively treat several inflammatory and autoimmune diseases (Choy *et al*, 2002; Fonseka *et al*, 2015; Ito *et al*, 2004) and a recently initiated RCT will assess the ability of tocilizumab to decrease depressive symptomatology in treatment-resistant depression (US National Institute of Health, 2016). A more recently developed drug is the human anti-IL-6 monoclonal antibody—sirukumab. In previous studies, sirukumab was able to decrease inflammatory symptoms in patients with rheumatoid arthritis (Smolen *et al*, 2014; Tanaka and Martin Mola, 2014). An ongoing RCT will assess the efficacy and safety of an add-on sirukumab treatment in MDD patients (US National Institute of Health, 2016).

Pentoxifylline is a phosphodiesterase inhibitor, which, among other effects, decreases the expression of pro-inflammatory cytokines such as TNF- α , IL-1, and IL-6 in blood cells (Ferrari *et al*, 2010; Gonzalez-Espinoza *et al*, 2012; Neuner *et al*, 1994; Pollice *et al*, 2001). Although it has also

been shown to decrease depressive-like behavior in animal models (Bah *et al*, 2011; Elgarf *et al*, 2014), whether it can be replicated in humans has not yet been determined. A recently started RCT will attempt to shed some light, as it will explore whether pentoxifylline is able to reduce depressive symptoms, as well as improve artery function, in older primary care patients (US National Institute of Health, 2016).

Most of the above-mentioned anti-inflammatory treatments are in the process of being tested for their effectiveness as anti-depressive action. As discussed in the above sections of this review, irrespective of psychiatric condition, suicidal patients and those at increased suicidal risk often display pronounced inflammatory changes and, therefore, might benefit from anti-inflammatory therapies. Unfortunately, suicidal patients are frequently excluded from the initial phase of investigation due to the safety concerns. Thus, whether the mentioned anti-inflammatory treatments could be additionally used as effective therapies for suicidal behavior remains to be studied in well-designed clinical trials.

CONCLUSIONS

Mounting evidence implicates dysregulation of the immune system in pathophysiology of suicidality. The potential upstream triggers of suicidal behavior include various inflammatory conditions (TBI, vitamin deficiency, autoimmune disorders, and infections), which, through raised levels of inflammatory mediators, can cause dysregulation of the kynurenine pathway of tryptophan catabolism, hyperactivation of the HPA axis, and alterations in monoamine metabolism in the patients. These neurobiological effects might cause profound changes in emotion and behavior, which could ultimately lead to suicide in vulnerable individuals. More studies are needed to further characterize the interconnection between upstream triggers of inflammation, downstream mediators, and predisposition factors, which, in the presence of inflammation, confer resilience or vulnerability towards development of suicidality.

Currently, anti-inflammatory treatments, initially approved for other conditions, are being tested in depressive individuals. Although for safety concerns, actively suicidal individuals and those at increased suicide risk are excluded from such clinical trials, it may be of key importance to include suicidal individuals in the future as this patient group exhibits the most pronounced inflammatory changes, likely to respond to treatment. Ketamine, an NMDA receptor antagonist, which might counteract some of the actions of the kynurenine pathway metabolites, is being specifically tested in suicidal individuals.

In the future, it may prove to be advantageous to target additional signaling and regulatory mechanisms involved in neuroinflammation. Such targets could include TLRs, activation of which regulates the production of pro-inflammatory cytokines, as some studies have found some abnormalities in brain and blood TLRs' levels in depressed

and suicidal patients (Pandey *et al*, 2014; Wu *et al*, 2015). Another target could be regulation of the balance between Th1 and Th2-type T-cell populations, as several studies have found an imbalance of these cell types and their corresponding cytokines in the blood of MDD patients with suicidality (Huang and Lee, 2007; Kim *et al*, 2008; Mendlovic *et al*, 1999).

Altogether, as neuroinflammation is gradually becoming more accepted as a cause of behavioral symptoms in suicidal individuals, a wide range of novel treatment options, targeting either upstream or downstream factors in the inflammatory cascade, are showing promise to help affected patients. As such, the future for development of novel therapies in psychiatry looks brighter than in decades.

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