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Invited review

Kynurenine pathway metabolites and suicidality

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ABSTRACT

Suicide is a major global problem, claiming more than 800,000 lives annually. The neurobiological changes that underlie suicidal ideation and behavior are not fully understood. Suicidal patients have been shown to display elevated levels of inflammation both in the central nervous system and the peripheral blood. A growing body of evidence suggests that inflammation is associated with a dysregulation of the kynurenine pathway in suicidal patients, resulting in an imbalance of neuroactive metabolites. Specifically, an increase in the levels of the NMDA receptor agonist quinolinic acid and a simultaneous decrease in neuroprotective metabolites have been observed in suicidal patients, and may contribute to the development of suicidality via changes in glutamate neurotransmission and neuroinflammation. The cause of the dysregulation of kynurenine metabolites in suicidality is not known, but is likely due to differential activity of the involved enzymes in patients. As knowledge in these areas is rapidly growing, targeting the kynurenine pathway enzymes may provide novel therapeutic approaches for managing suicidal behavior.

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1. Introduction

Suicide is the 14th cause of years of life lost (Mortality and Causes of Death, 2015) with over 800,000 deaths reported globally every year (World Health Organization, 2014). This high death toll is still likely to be under-reported, due to the fact that suicide is stigmatized and illegal in some countries (Varnik, 2012). It is estimated that suicide attempts are 10–20 times more frequent than the number of completed suicides. Both suicide attempts and deaths by suicide result in a great psychological and economic burden for individuals, families and countries. The World Health Organization has recently declared suicide a major public health problem worldwide (World Health Organization, 2014). In the US alone, the economic cost of death by suicide is estimated to be more than $44 billion annually (Centers for Disease Control and

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Prevention, 2010).

Despite an increase in available clinical treatment options for suicidality, including pharmacological agents as well as electroconvulsive treatment, the incidence rate of suicide is increasing in many countries (World Health Organization, 2014). Even though almost half of the suicidal patients make contact with mental health and primary care providers within one month of their suicide, the health care system fails to accurately detect the risk and prevent suicide (Da Cruz et al., 2011). A difficulty in this area is to correctly identify patients with a clear suicidal intent among patients exhibiting suicidal ideation; not the least because patients with a definite intent may ultimately hide this from family and health care providers. Consequently, there is a critical need to improve suicide risk detection by means of identifying biological risk markers, as well as to develop effective, novel pharmacological interventions.

Suicidal behavior is not confined to a particular diagnostic group of patients, and as such is a transnosological phenomenon (Leenaars, 1992). The majority of patients who complete suicide have an underlying psychiatric disorder, which can range from psychotic disorders, such as schizophrenia, to mood disorders, including depression and bipolar disorder, as well as anxiety and posttraumatic stress disorders. Importantly, it is plausible that the underlying pathological molecular mechanisms, associated with suicidal ideation and behavior, are shared across these diagnostic boundaries. The current treatment options for suicidality tend to depend on the psychiatric diagnosis and often consist of antidepressants and anxiolytics (Wasserman et al., 2012). However, the first-line of choice antidepressant treatments, including SSRIs, and SNRIs, have drawbacks since it can take weeks to develop beneficial mood-enhancing effects, and the risk for suicidality has been reported to increase during the first weeks of treatment, especially in children and adolescents (Wasserman et al., 2012). Pharmacological treatment with lithium in mood disorders (Baldessarini et al., 2006; Guzzetta et al., 2007), clozapine in schizophrenia (Meltzer and Baldessarini, 2003), and electroconvulsive therapy in treatment-resistant depression (Kennedy et al., 2009) have proven effective in decreasing suicidal behavior. In addition, a robust and rapid (within hours) antidepressant and anti-suicidal effect is produced by intravenous injection of ketamine, which is an NMDA-receptor antagonist (Fond et al., 2014; Zarate et al., 2013). The biological mechanisms behind the beneficial effects of these treatments on suicidal behavior are not completely understood.

2. Risk factors of suicide

Suicidal behavior is thought to be triggered by an intricate interplay between genetic predispositions and environmental factors (Roy et al., 2009). The genetic component of suicidal behavior, including attempts and suicide completion, is estimated to be around 40% (McGuffin et al., 2010). Recently, epigenetic changes, including hypermethylation of the brain-derived neurotrophic factor (BDNF) promoter (Kang et al., 2013; Kim et al., 2014), have been proposed to be important in depression and suicidality and may provide the platform for some of the gene-environment interactions (Lockwood et al., 2015). The single most important predictor of death by suicide is previous self-harm (Hawton and van Heeringen, 2009). Psychiatric disorders, especially Major Depressive Disorder (MDD) and bipolar disorder, are present in 90% of individuals who complete suicides (Harris and Barraclough, 1997). Certain personality traits have been proposed to act as additional risk factors in individuals with and without psychiatric disease. These include higher levels of impulsivity and aggression, especially in younger suicide victims (Dumais et al., 2005; Perroud et al., 2011) and hopelessness (David Klonsky et al., 2012). The neurobiological changes implicated in suicidal behavior are not fully understood. Dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Mann, 2003) and serotonergic neurotransmission (Bach and Arango, 2012) are frequently detected in individuals exhibiting suicidal behavior. Inflammation is thought to be a contributing factor as inflammatory mediators, such as cytokines, closely and reciprocally interact with both the HPA axis and serotonin system. Inflammation also causes activation of the kynurenine pathway of tryptophan (TRP) degradation. As is the topic of this review, accumulating evidence suggest that a dysregulation of the enzymes in the kynurenine pathway may contribute to the neurobiological changes observed in suicidal patients.

3. Kynurenine pathway and inflammation

The kynurenine pathway is initiated by the conversion of TRP to N-formylkynurenine by any of these enzymes: indoleamine 2,3-dioxygenase 1 (IDO1), IDO2, or tryptophan 2,3-dioxygenase (TDO) (Fig. 1). The resulting N-formylkynurenine is further degraded to kynurenine (KYN), which is a precursor of bioactive compounds, including quinolinic acid (QUIN), kynurenic acid (KYNA), picolinic acid (PIC), and 3-hydroxyanthranilic acid (3-HAA) (Schwarcz et al., 2012). The kynurenine pathway is responsible for over 90% of TRP degradation in the periphery (Leklem, 1971) and many organs and cell types, including liver, intestine, brain and immune cells, express several of the enzymes in this pathway. Pro-inflammatory cytokines, including interferon-γ (IFN-γ), interleukin-1β (IL-1β) and IL-6, can further induce IDO-1 and TDO, and thus activate this pathway (Schwieler et al., 2015; Urata et al., 2014). Since TRP is also a precursor for neurotransmitter serotonin, it has been hypothesized that induction of the kynurenine pathway by inflammation may reduce the availability of TRP and consequently lead to reduced serotonin synthesis (Maes et al., 2011). This could theoretically contribute to the decreased levels of 5-hydroxyindoleacetic acid, a main metabolite of serotonin, that has been observed in the cerebrospinal fluid (CSF) of suicide attempters (Asberg et al., 1976). However, currently there is no clear evidence demonstrating that inflammation causes a decrease in brain serotonin levels through induction of the kynurenine pathway in depressed and suicidal patients.

4. Kynurenine pathway metabolites in psychiatric disorders and suicidal behavior

In 2011, the first report was published on the relationship between dysregulation of the kynurenine pathway and suicidal behavior (Sublette et al., 2011). In that study, Sublette et al. detected elevated plasma KYN levels in suicide attempters with depression, compared to patients with depression but no history of suicidality. A more recent study by Bradley et al. found a 40% decrease in plasma TRP levels and a 40% increase in KYN/TRP ratio in suicidal adolescents with MDD, compared to non-suicidal individuals with MDD and healthy controls (Bradley et al., 2015). KYN, like TRP, is able to pass through the blood brain barrier (BBB) into the brain (Schwarcz et al., 2012). In the brain, KYN can be differentially processed by either astrocytes or microglia to produce distinct neuroactive compounds. While the synthesis of 3-hydroxykynurenine (3-HK) and its downstream metabolites, including 3-HAA and QUIN, takes place in microglia and other cells of monocytic origin (Guillemin et al., 2003), the synthesis of KYNA occurs in astrocytes, neurons and oligodendrocytes (Du et al., 1992; Guillemin et al., 2001; Wejksza et al., 2005).