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The role of the kynurenine pathway in suicidality in adolescent major depressive disorder

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ABSTRACT

The neuroimmunological kynurenine pathway (KP) has been implicated in major depressive disorder (MDD) in adults and adolescents, most recently in suicidality in adults. The KP is initiated by the enzyme indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan (TRP) into kynurenine (KYN) en route to neurotoxins. Here, we examined the KP in 20 suicidal depressed adolescents—composed of past attempters and those who expressed active suicidal intent—30 non-suicidal depressed youth, and 22 healthy controls (HC). Plasma levels of TRP, KYN, 3-hydroxyanthranilic acid (3-HAA), and KYN/TRP (index of IDO) were assessed. Suicidal adolescents showed decreased TRP and elevated KYN/TRP compared to both non-suicidal depressed adolescents and HC. Findings became more significantly pronounced when excluding medicated participants, wherein there was also a significant positive correlation between KYN/TRP and suicidality. Finally, although depressed adolescents with a history of suicide attempt differed from acutely suicidal adolescents with respect to disease severity, anhedonia, and suicidality, the groups did not differ in KP measures. Our findings suggest a possible specific role of the KP in suicidality in depressed adolescents, while illustrating the clinical phenomenon that depressed adolescents with a history of suicide attempt are similar to acutely suicidal youth and are at increased risk for completion of suicide.

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1. Introduction

Suicide is among the most serious health problems for children and adolescents in the United States. According to a recent report by the Centers for Disease Control and Prevention (CDC), suicide has become the second leading cause of death among children aged 12–17 years after non-intentional injuries and ahead of homicides and malignancies (Perou et al., 2013). The two most prominent risk factors for completed suicide in youth are a past suicide attempt and a diagnosis of a depressive episode, each independently representing a 10–30 fold increased risk for completed suicide (Shaffer et al., 1996). Consequently, depressed adolescents with a past suicide attempt are at high risk for completion of suicide (Brent et al., 1993).

There has been sparse research into the neurobiology of suicide. Clinical and postmortem work has mainly focused on the monoamine system, documenting serotonin (5-HT) and dopamine deficiency with limited progress on the contributory biology. Over the past decade there has been a shift in research from the monoamine system to complex mechanisms that induce neuroplasticity impairment, such as inflammation and glutamatergic excitotoxicity. The neuroimmunological kynurenine pathway (KP) is hypothesized to play a key role in such processes, linking peripheral inflammation and glutamate disturbances (Laugeray et al., 2010). The KP (illustrated in Fig. 1) is activated by the enzyme indoleamine 2,3-dioxygenase (IDO), which is induced by pro-inflammatory cytokines and is the rate-limiting enzyme of the pathway. IDO metabolizes tryptophan (TRP) into kynurenine (KYN), thereby reducing TRP availability for 5-HT synthesis. KYN by itself is not neuroactive, but crosses the blood brain barrier to generate free-radical-producing 3-hydroxykynurenine (3-HK) and 3-hydroxyanthranilic acid (3-HAA) or the glutamatergically active

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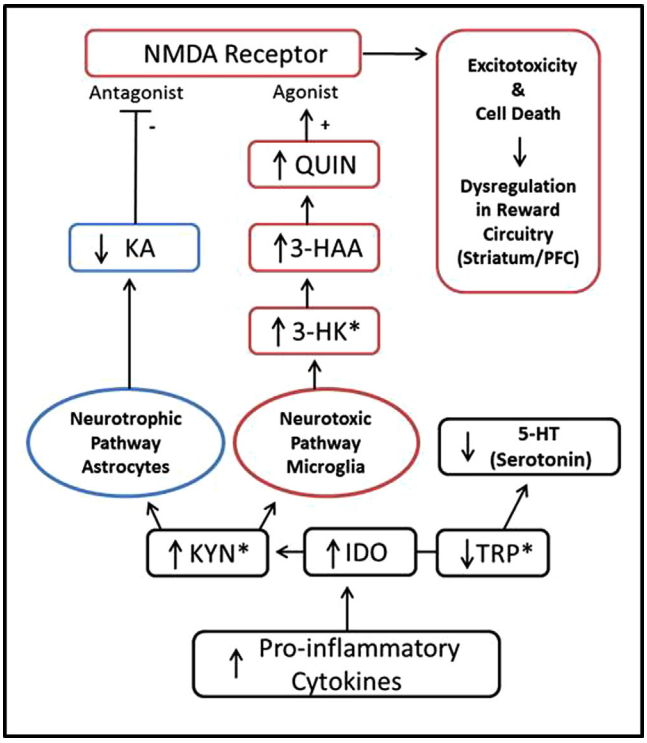

Fig. 1. Depiction of the kynurenine pathway.
*Note:**indicates metabolites that cross the blood–brain barrier.

kynurenine metabolite quinolinic acid (QUIN). Conversely, KYN can also be metabolized into kynurenic acid (KA), which is a glutamate receptor antagonist, constituting the neurotrophic branch of the KP. Converging evidence dating back to the 1970s has implicated the KP neurotoxic branch with major depressive disorder (MDD) (Curzon and Bridges, 1970; Heyes et al., 1992; Laugeray et al., 2010). Work from our laboratory documented relationships between KP activation and anhedonia (Gabbay et al., 2010a, 2012) in adolescents with MDD. More recently, the KP has been associated specifically with suicidality in adults (Sublette et al., 2011; Erhardt et al., 2013; Bay-Richter et al., 2015). Findings included elevated cerebrospinal fluid (CSF) QUIN levels in suicide attempters across psychiatric disorders compared to healthy control adults (Erhardt et al., 2013; Bay-Richter et al., 2015). However, these studies did not include a non-suicidal psychiatric group and thus, findings may be related to the psychiatric condition rather than the suicidal behavior. In a separate study, plasma KYN, TRP, and IDO (indexed by KYN/TRP) were examined, with only KYN levels elevated in depressed patients with a history of suicide attempt compared to those who had never attempted suicide (Sublette et al., 2011). However, there was no acutely suicidal subgroup.

Based on the above observations, we sought to examine the KP in depressed suicidal adolescents, composed of both past attempters and those who expressed active suicidal intent, compared to non-suicidal depressed adolescents and healthy controls (HC). Hypotheses were that depressed suicidal adolescents would exhibit increased KP activation, indexed by increased IDO (quantified by KYN/TRP), KYN and 3-HAA, and decreased TRP. Since psychotropic medications are known to have anti-inflammatory effects (Kostadinov et al., 2014; Liu et al., 2014; Obuchowicz et al., 2014), analyses were repeated while excluding medicated participants. Finally, we explored whether KP metabolites differed between subgroups of depressed adolescents who were actively suicidal and those with prior attempts, both of which were included in the suicidal group.

2. Methods

2.1. Subjects

The current sample is part of previous published studies examining a) plasma cytokine levels in suicidal depressed adolescents (Gabbay et al., 2009) and b) the KP in adolescent MDD (Gabbay et al., 2010a). Participants were 30 non-suicidal adolescents with MDD (mean age = 15.21, S.D. = 1.93, 12 females), 20 adolescents with MDD and at high risk for suicide (actively suicidal or previous attempt; mean age = 16.82, S.D. = 1.84, 15 females), and 22 healthy controls (HC; mean age = 15.96, S.D. = 2.64, 13 females). The entire MDD group (n = 50) and healthy controls (n = 22) were matched on age and gender; however, suicide subgroups were not specifically matched on these variables. Therefore, age and gender were included in statistical models.

Adolescents with MDD (both suicidal and non-suicidal) were enrolled from the New York University (NYU) Child Study Center, the NYU Tisch inpatient psychiatric unit, and the Bellevue Department of Psychiatry. The healthy controls were recruited from the New York Metropolitan area. This study received NYU School of Medicine IRB approval. Participants aged 18 and older (n = 14) provided signed informed consent; those under age 18 provided assent, and a parent or guardian provided signed consent.

2.2. Inclusion and exclusion criteria

Exclusion criteria for all subjects included: immune-affecting medications taken in the past 6 months, any immunological or hematological disorder, chronic fatigue syndrome, any infection during the month prior to the blood draw (including the common cold), significant medical or neurological disorders, and in females, a positive urine pregnancy test. For subjects with MDD, the following disorders were exclusionary: (1) schizophrenia, (2) pervasive developmental disorder, (3) posttraumatic stress disorder, (4) obsessive–compulsive disorder, (5) Tourette's disorder, (6) eating disorder, and/or (7) a substance-related disorder in the past 3 months (based on history and urine toxicology test). Due to recruitment challenges, especially of patients expressing active suicidal intent and the need to start treatment as soon as possible, psychotropic medication treatment was not exclusionary for adolescents with MDD. Healthy controls could not have any major current or past psychiatric diagnosis as per the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., text rev., DSM-IV-TR; American Psychiatric Association, 2000), and could not be taking psychotropic medications.

Adolescents with MDD were required to have a depressive episode lasting at least 6 weeks and a minimum severity score of 36 on the Children's Depression Rating Scale-Revised (CDRS-R). Adolescents at high risk for suicide all met MDD criteria and were either expressing active suicidal intent and were thus hospitalized inpatients or had a past suicide attempt. Previous suicide attempts were differentiated from self-harm behavior without suicidal intent as serious incidents that would have resulted in death if not intervened, such as hanging, overdose, and ingestion of toxic materials.

2.3. Assessments

Baseline assessment consisted of both psychiatric and medical evaluations. To determine psychiatric status, a board-certified child and adolescent psychiatrist (V.G., C.A.) interviewed subjects and parents at the NYU Child Study Center using the Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version for Children (K-SADS-PL; Kaufman et al., 1997). Additional assessments included the CDRS-R, the Children's Global Assessment Scale (CGAS), and the Beck Depression Inventory, 2nd edition (BDI-II).

2.3.1. Suicidality

Suicidal ideations were assessed by the Beck Scale for Suicidal Ideation (BSSI). The BSSI has two subscales with a subtotal maximum score of 10 for subscale 1 and of 32 for subscale 2. Per the instructions, participants who answered "0" on questions 4 and 5 of subscale 1 did not proceed to subscale 2. Therefore, only those participants who completed both parts 1 and 2 of the BSSI questionnaire were included in the correlational analyses that assessed the relation between KP metabolites and suicidality, to ensure that participants' scores were based on the same final total.

2.3.2. Medical assessments

Baseline evaluations included medical history and laboratory tests, containing complete blood count, metabolic panel, liver and thyroid function tests, a urine toxicology test (assessing amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, phencyclidine, and propoxyphene), and a pregnancy test for females.