Published in final edited form as:
J Neural Transm. 2012 February ; 119(2): 253–260. doi:10.1007/s00702-011-0685-7.

The possible role of the kynurenine pathway in anhedonia in adolescents

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Abstract

To address the heterogeneous nature of adolescent major depression (MDD), we investigated anhedonia, a core symptom of MDD. We recently reported activation of the kynurenine pathway (KP), a central neuroimmunological pathway which metabolizes tryptophan (TRP) into kynurenine (KYN) en route to several neurotoxins, in a group of highly anhedonic MDD adolescents. In this study, we aimed to extend our prior work and examine the relationship between KP activity and anhedonia, measured quantitatively, in a group of MDD adolescents and in a combined group of MDD and healthy control adolescents. Thirty-six adolescents with MDD (22 medication-free) and 20 controls were included in the analysis. Anhedonia scores were generated based on clinician- and subject-rated assessments and a semi-structured clinician interview. Blood KP metabolites, collected in the AM after an overnight fast, were measured using high-performance liquid chromatography. The rate-limiting enzyme of the KP, indoleamine 2,3-dioxygenase (IDO), was estimated by the ratio of KYN/TRP. Pearson correlation tests were used to assess correlations between anhedonia scores and KP measures while controlling for MDD severity. IDO activity and anhedonia scores were positively correlated in the group psychotropic medication-free adolescents with MDD ($r = 0.42$, $P = 0.05$) and in a combined group of MDD subjects and healthy controls (including medicated patients: $r = 0.30$, $P = 0.02$; excluding medicated patients: $r = 0.44$, $P = 0.004$). In conclusions, our findings provide further support for the role for the KP, particularly IDO, in anhedonia in adolescent MDD. These results emphasize the importance of dimensional approaches in the investigation of psychiatric disorders.

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Keywords

Indoleamine 2,3-dioxygenase; Anhedonia; Adolescents; Major depressive disorder; Kynurenine pathway

Introduction

Progress in understanding the neurobiology of major depressive disorder (MDD) in adolescents and adults has been hampered by the disorder's heterogeneous nature. The major challenge has been that the *categorical diagnosis of MDD*: (a) relies on a syndromal definition that comprises a cluster of symptoms most likely derived from different etiologies, and (b) does not capture the continuum of symptoms ranging from lesser to greater severity. For this reason, investigating symptoms within the disorder may enhance the likelihood of success in neurobiological investigations of MDD. Anhedonia—the reduced capacity to experience pleasure—is a core symptom of MDD and highly variable among depressed adolescents; can be quantitatively measured and is tied to the reward circuitry; and as such an ideal candidate for a targeted biological investigation in adolescent MDD.

Mounting data suggest a role for the immune system in MDD (Miller 2009; Irwin and Miller 2007). Evidence includes multiple reports of increased levels of pro-inflammatory cytokines in the blood as well as in the cerebrospinal fluid (CSF) of depressed and suicidal adult and adolescent patients (Gabbay et al. 2009a, b; Levine et al. 1999; Lindqvist et al. 2009; Hayley 2011). Other data from animal and human studies have demonstrated that peripheral immunotherapy frequently induces depressive symptoms, particularly anhedonia, as well as leads to concurrent changes in the neural reward circuitry (Eisenberger et al. 2010; Miller 2009; Shuto et al. 1997; Capuron et al. 2007; Majer et al. 2008). These observations suggest that peripheral and brain inflammatory processes are tightly linked and can affect brain function.

The kynurenine pathway (KP) is a central neuroimmunological branch which has been hypothesized to play a key role in linking peripheral inflammation and brain function via production of oxygen radicals and highly potent neurotoxins (Schwarcz and Pellicciari 2002; Amori et al. 2009). The KP is activated by the rate-limiting enzyme indoleamine 2,3-dioxygenase (IDO), which metabolizes tryptophan (TRP) into kynurenine (KYN). KYN is further metabolized to several neurotoxins including 3-hydroxy-kynurenine (3-HK), 3-hydroxyanthranilic acid (3-HAA), and quinolinic acid (QUIN). Of these, 3-HK and 3-HAA generate reactive radicals which induce oxidative stress and neuronal apoptosis (Goldstein et al. 2000). QUIN is a specific *N*-methyl-D-aspartate (NMDA) receptor agonist and potent excitotoxin (Schwarcz et al. 1983). Converging evidence indicates that peripheral induction of IDO plays a key role in initiating the KP cascade that leads to neurotoxicity and depressive symptoms (Wichers et al. 2005; Bonaccorso et al. 2002; Capuron et al. 2002, 2003a; Myint et al. 2007). IDO is a cytoplasmatic enzyme which is expressed mainly in antigen-presenting cells such as dendritic cells (Boasso et al. 2005). Two other enzymes, tryptophan 2,3-dioxygenase (TDO) and IDO2, have similar activity but differ in their expression patterns; the former is primarily expressed in the liver while the latter, which was first reported in 2007 (Murray 2007), is predominantly expressed in the kidneys, epididymis, testis, and liver (Ball et al. 2009). IDO is induced by proinflammatory cytokines, particularly by interferon (IFN)-γ, and the IFN-γ pathway is required for the normal upregulation of IDO expression during infection (Kwidzinski and Bechmann 2007).

We have examined the KP and its associated neurotoxicity in adolescent MDD and reported decreased blood TRP and increased IDO activity in highly anhedonic MDD adolescents compared to both controls and non-anhedonic MDD adolescents, along with significant associations between both KYN and neurotoxic load with severity of MDD episode in the anhedonic MDD subgroup (Gabbay et al. 2010a). Additionally, using proton magnetic resonance spectroscopy, we documented associations between KYN and 3-HAA blood levels and striatal total choline (tCho, membrane turnover biomarker) in the subgroup of anhedonic MDD adolescents (Gabbay et al. 2010b). Our findings suggest a specific role for the KP in anhedonia, classified categorically.

Here, we extended our prior work while adopting a dimensional investigative approach and examined the relationship between the KP and anhedonia severity, measured quantitatively. To our knowledge, the specific relationships between KP metabolites and/or IDO activity and anhedonia have not been investigated in adult or in adolescent MDD. Based on the notion that anhedonia is a continuous symptom ranging from normal to pathological, we hypothesized that anhedonia scores would be positively correlated with IDO activity (estimated by KYN/TRP) and KP neurotoxicity (indexed by 3-HAA/KYN and 3-HAA) and negatively correlated with TRP levels in the blood in the MDD group as a whole. We also explored these relationships in the full sample of MDD adolescents and controls.

Methods

Study subjects

Study subjects were the same as previously reported (Gabbay et al. 2010a), excluding individuals missing the necessary assessments to generate anhedonia scores (see below).

The MDD subjects were recruited from the New York University (NYU) Child Study Center, the Bellevue Hospital Department of Psychiatry, and through local advertisements in the New York Metropolitan area. The healthy control (HC) subjects were recruited from the greater New York Metropolitan area by means of advertisements and through families of NYU staff. The study was approved by the NYU School of Medicine Institutional Review Board and the New York City Health and Hospital Corporation. Prior to the baseline clinical evaluation, study procedures were explained to subjects and parents. Participants age 18 and over ($N = 10$) provided signed informed consent; those under age 18 provided signed assent and a parent provided signed informed consent.

Inclusion and exclusion criteria—Exclusion criteria for all subjects consisted of 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, a positive urine toxicology test, and in females, a positive urine pregnancy test.

Inclusion criteria for adolescents with MDD were DSM-IV-TR diagnosis of MDD with current episode duration ≥6 weeks and a severity score ≥37 on the Children's Depression Rating Scale-Revised (CDRS-R). Exclusionary diagnoses included a lifetime psychiatric history of bipolar disorder, schizophrenia, pervasive developmental disorder, post-traumatic stress disorder, obsessive-compulsive disorder, Tourette's disorder, eating disorder, and a substance-related disorder in the past 12 months. HC subjects did not meet criteria for any major current or past DSM-IV-TR diagnoses and had never received psychotropic medication.

Clinical assessments—All subjects were assessed by a child and adolescent psychiatrist or psychologist at the NYU Child Study Center. Diagnoses were established using the

Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (K-SADS-PL) (Kaufman et al. 1997), a semi-structured diagnostic interview completed with subjects and parents. Additional assessments included the CDRS-R and the Beck Depression Inventory, 2nd edn (BDI-II) (Beck et al. 1997). Baseline medical assessments included medical history and laboratory tests, constituting complete blood count, metabolic panel, liver and thyroid function tests, urine toxicology tests (assessing amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, opiates, phencyclidine, and propoxyphene), and a urine pregnancy test for females.

Anhedonia—Anhedonia scores were computed by summing the equally weighted responses associated with anhedonia on: (a) the self-rated BDI-II (item 4: “Loss of Pleasure” and item 12: “Loss of Interest”); (b) the clinician-rated CDRS-R (item 2: “Difficulty Having Fun”); and (c) the K-SADS-PL diagnostic interview (p. 8, “Anhedonia, Lack of Interest, Apathy, Low Motivation, or Boredom” and Affective Disorders Supplement page 1, “Lack of Reactivity of Depressed or Irritable Mood to Positive Stimuli”). Such an approach has been used in several investigations that assessed anhedonia severity (Pizzagalli et al. 2005; Joiner et al. 2003), and scores were shown to correlate with other anhedonia assessments (e.g., Snaith–Hamilton Pleasure Scale) (Leventhal et al. 2006).

Determination of kynurenine pathway metabolite concentrations

All blood samples (10 ml) were drawn between 08:00 and 09:00 a.m. after an overnight fast (≥12 h), processed within 20 min of collection, and stored at −80°C. All analyses were conducted while blind to the clinical status of subjects.

Calibration curves were prepared from stock solutions (100 μg/ml) to yield the respective levels of TRP (1, 2, 4, 8, 12, and 14 μg/ml), KYN (0.05, 0.1, 0.2, 0.4, 1, 2, 4, and 5 μg/ml), and 3-HAA (0.1, 0.2, 0.4, 0.8, 2, and 3 μg/ml) in double-distilled-grade water and human plasma. The internal standard (3-nitro-L-tyrosine, 1 mg/ml) was also added to all calibration standards for recovery purposes.

Plasma (0.20 ml) was combined with 5 μl of 1 μg/μl 3-nitro-L-tyrosine followed by the addition of 0.20 ml of 0.05 M KH_2PO_4 (pH 6.2). Subsequently, 50 μl of cold 2 M trichloroacetic acid was added, followed by vigorous vortexing. The mixture was centrifuged at 9,500 rpm for 10 min, and the supernatant was transferred into auto-sampler vials for analysis by high-performance liquid chromatography (HPLC). Aliquots of 200 μl of the supernatant were injected into the chromatographic system using a WISP model 717 autosampler (Waters Associates, Milford, MA, USA).

The eluted components of interest were detected as follows: (1) KYN and 3-nitro-L-tyrosine by tandem monitoring with UV absorption at 360 nm; (2) TRP and 3-HAA by fluorescence monitoring at 340 nm (with UV excitation at 285 nm). A gradient elution was used for development of the chromatography in the following manner: the gradient consisted of a combination of two buffers, A (40 mM citrate buffer/0.1 mM succinic acid, disodium salt/0.05% sodium azide) and B (60% methanol/40 mM citrate buffer/0.1 mM succinic acid, disodium salt/0.05% sodium azide). The following sequence of steps was employed: 0–3 min, 0% B; 3–12 min, 0% B–65% B (linear gradient); 12–18 min, 65% B; 18–20 min, 65% B–100% B; 20–24 min 100% B; 24–26 min, 100% B–0% B (linear gradient); 26–30 min 0% B. A flow rate of 0.8 ml/min was used during the 30 min elution sequence of the analytical HPLC C18 column (4.6 × 150 mm, 5 μm, Luna C18, Phenomenex, Torrance, CA, USA).

Data analysis

Pearson correlation coefficients were used to characterize the association of KP metabolite plasma levels with anhedonia scores for the MDD subjects alone as well as for the combined MDD and healthy control groups. To control for the possible confounding effect of MDD severity, analyses were carried out while controlled for CDRS-R scores. Since psychotropic medications can affect the KP, analyses were repeated while excluding medicated subjects. Statistical significance was defined as two-sided $P \leq 0.05$, while trends toward significance were defined as $P \leq 0.1$.

Results

Subjects

Study subjects consisted of 36 adolescents with MDD (ages 13–19, mean 15.9 ± 1.7, 21 female) and 20 HC (ages 11–20, mean 16.1 ± 2.7, 12 female). Subject groups did not significantly differ with respect to age or gender. Clinical and demographic information for all subjects, including medication use and anhedonia scores, are described in Table 1. Of the 36 adolescents with MDD, 22 (61%) were psychotropic medication-free (20 were psychotropic medication-naïve). All 14 patients on medication had failed to respond to treatment at the time of blood draw.

Association between KP metabolite plasma levels and anhedonia scores

MDD group—We observed a trend toward a significant correlation between anhedonia scores and IDO activity for the MDD group while controlling for severity ($r = 0.31$, $P = 0.06$, Fig. 1a). When medicated subjects were excluded, a significant correlation between IDO activity and anhedonia scores was observed in the medication-free MDD group ($r = 0.42$, $P = 0.05$, Fig. 1b).

Whole group (MDD and HC)—A significant positive correlation between IDO activity and anhedonia scores was observed in all subjects ($r = 0.30$, $P = 0.02$, Fig. 2a). This correlation remained significant when medicated patients were excluded ($r = 0.44$, $P = 0.004$, Fig. 2b).

No significant correlations or trends toward significance were found between TRP, KYN, 3-HAA, or 3-HAA/KYN blood levels and anhedonia scores in either the whole sample or the MDD group alone.

Discussion

This is the first study to examine the relationship between KP activity and anhedonia as assessed dimensionally. We found a significant positive correlation between IDO activity (reflected by the ratio KYN/TRP) and anhedonia scores in psychotropic-free depressed adolescents as well as in a combined group of depressed adolescents and healthy controls.

The present findings are consistent with our previous studies implicating the KP in adolescent MDD, where increased IDO activity and neurotoxicity were present only in the subgroup categorized as highly anhedonic, as well as studies by other research groups reporting increased urinary excretion of KYN and 3-HK in anhedonic depressed women (Curzon and Bridges 1970) and decreased plasma TRP/competing amino acids ratios in several studies of highly anhedonic MDD subjects (Cowen et al. 1989; Anderson et al. 1990; Maes et al. 1996). The correlation we established between IDO activity and anhedonia, assessed quantitatively, supports the view that psychiatric symptoms should be studied as dimensions ranging from normal to pathological in addition to their traditional binary/

categorical classification. Such an approach provides greater power as well as insight into the underlying biological mechanisms of psychiatric symptoms. Notably, our correlation between IDO activity and anhedonia scores was more significant when medicated patients were excluded and may be explained by the anti-inflammatory properties of antidepressants (Maes et al. 1999; Kubera et al. 2001).

Another important observation is the relatively narrow range of IDO activity in the healthy control group versus the wide range in MDD patients. This phenomena is not uncommon in biological research of psychiatric illness, which by itself suggests the heterogeneous nature of MDD and supports our dimensional investigative approach.

Our finding of a relationship between anhedonia and IDO may be related to IDO being the rate-limiting enzyme of the KP and its role in initiating the KP cascade and subsequent neurometabolic alterations. Clinical trials in patients with hepatitis C who underwent immunotherapy support this perspective. Findings include increased plasma IDO activity (reflected by KYN/TRP ratios) coupled with parallel increases of KYN, QUIN, and kynurenic acid (KA) in the CSF in response to treatment with IFN-α (Raison et al. 2009). Since metabolites other than KYN and 3-HK do not cross the blood–brain barrier, these findings suggest that peripheral activation of IDO leads to parallel activation of the KP in the brain. Preclinical data confirm this notion. For example, O'Connor et al. reported that a peripheral immunological challenge with lipopolysaccharides (LPS) in mice resulted in elevated brain expression of IDO and cytokine mRNAs along with depressive symptoms (i.e., increased duration of immobility in forced-swim and tail suspension tests). Authors also documented that direct and indirect peripheral inhibition of IDO blocked the central transcription of IDO in the brain and the development of depressive-like behaviors in mice following LPS (O'Connor et al. 2008). Importantly, the direct inhibition of IDO (with the antagonist 1-methyltryptophan) did not affect cytokines but still prevented depressive symptoms (O'Connor et al. 2008). Moreover, several studies in mice have specifically linked peripheral and central IDO activation to anhedonic behaviors assessed by decreased preference for sucrose (Henry et al. 2008; Moreau et al. 2008).

At the same time, Raison et al. (2009) also reported significant correlations between KYN, QUIN and KA with specific immunological variables (e.g., IFN-α, TNF receptor) in the CSF and with depressive symptoms. Similarly, immune system stimulation with LPS has also been shown to induce cytokine production in the mouse brain, particularly the pro-inflammatory cytokine IL-1β, with concurrent production of IDO mRNA in microglia (Henry et al. 2008). This suggests that the KP is only one player in the generalized inflammatory response associated with depression (McNally et al. 2008).

As illustrated in Fig. 3, activation of the KP neurotoxic branch can contribute to dopaminergic alterations within the neural reward circuitry via several linked processes. The KP neurotoxin, QUIN, directly alters the mesolimbic dopaminergic system and induces dopaminergic and GABAergic neuronal death (Kurachi et al. 2000; Sumiyoshi et al. 2004; Beskid and Finkiewicz-Murawiejska 1992; Araujo et al. 2000) while KA, another KP metabolite, tightly controls the firing of midbrain dopaminergic neurons, with decreased endogenous KA resulting in decreased dopamine release (Erhardt et al. 2009; Wu et al. 1994). Additionally, animal studies suggest that 3-HK and 3-HAA toxicity is dependent upon transporter-mediated cellular intake with brain region selectivity; striatal and cortical neurons (key regions within the neural reward circuitry) are particularly vulnerable to these toxins (Okuda et al. 1998; Heyes et al. 2001).

Clearly, the KP is one of the players in the cascade in which peripheral activation of the immune system results in alterations in the mesolimbic dopamine system, with cytokines

and the hypothalamic–pituitary–adrenal (HPA) axis being tightly linked as well (illustrated in Fig. 3). Cytokines initiate the KP via induction of IDO. At the same time, considerable evidence indicates that cytokine therapy induces alterations in the mesolimbic dopaminergic system and in reward processing (Eisenberger et al. 2010; Miller 2009). Similarly, immune system activation is strongly connected to HPA axis activity (Capuron et al. 2003b), with alterations in the latter being one of the most consistent findings in anhedonic depressed patients (Tremblay et al. 2005).

Several limitations should be noted. Our estimates of IDO activity are based on KYN/TRP ratio rather than directly assessing the enzyme activity. The ratio of KYN/ TRP is a commonly used and widely accepted method of estimating IDO activity (Schrocksnadel et al. 2006). There are, however, several issues to this method. TRP in blood is highly labile and easily changed, and as such can affect our estimates of IDO activity (Badawy 2009). TRP is partly bound to albumin, with competitive binding by thyroxine and fatty acids (Badawy 2009), while brain uptake of TRP is dependent on free blood TRP levels (Kema et al. 2000). Further, since TRP is also metabolized to KYN by TDO, the ratio KYN/TRP indirectly indicates the sum of IDO + TDO activities. Diet and processes that influence the equilibrium between free TRP and protein-bound TRP modify is availability for uptake in the brain (Kema et al. 2000). However, addressing this concern, all subjects had to fast for at least 12 h before the blood draw. Additionally, we did not measure the major neurotoxins of the KP such as QUIN and 3-HK.

In summary, the results of the present study support a role for the KP in anhedonia. Future studies should involve different patient populations as well as measure KP enzyme activity directly.

Acknowledgments

This study was supported by grants from NIH (AT002395, MH077072, AT004576), the American Foundation for Suicide Prevention, the NYU School of Medicine General Clinical Research Center grant (M01-RR00096), the Leon Levy Foundation, and generous gifts from the Anita Saltz Foundation and from Bruce and Claude Wasserstein.

Statement regarding human subjects: All procedures described in this manuscript have been approved by the NYU Institutional Review Board and New York City Health and Hospital Corporation; procedures comply with the ethical standards established in the 1964 Declaration of Helsinki. All subjects involved in the study provided informed consent prior to inclusion.

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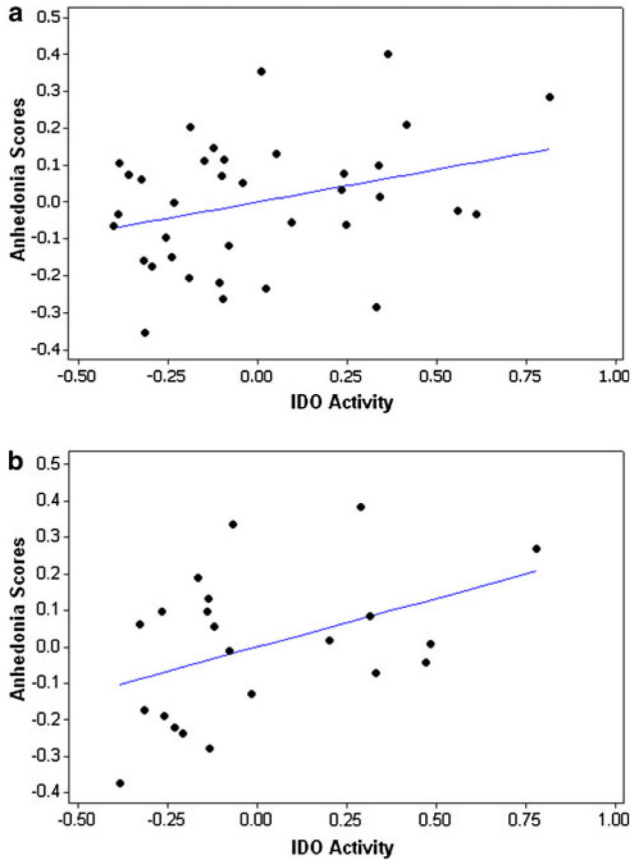

Fig. 1.

Scatter plots indicating partial correlations between IDO activity and anhedonia scores, controlling for CDRS-R scores. **a** (*top*) all MDD subjects, $r = 0.31$, $P = 0.06$. **b** (*bottom*) medication-free MDD subjects, $r = 0.42$, $P = 0.05$

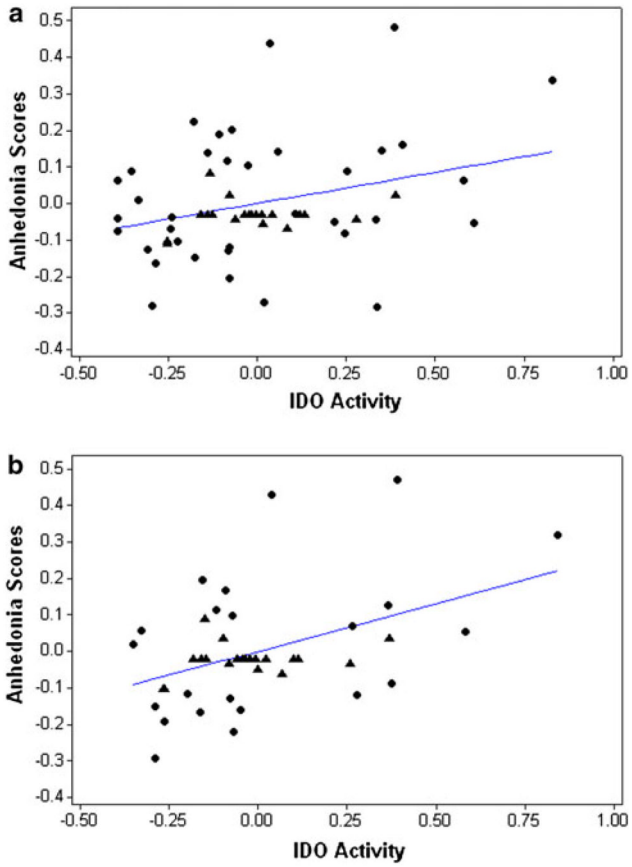

Fig. 2.

Scatter plots indicating partial correlations between IDO activity and anhedonia scores, controlling for CDRS-R scores. **a** (*top*) all subjects, $r = 0.30$, $P = 0.02$. **b** (*bottom*) all subjects excluding medicated MDD patients, $r = 0.44$, $P = 0.004$. Control subjects are indicated by *triangles* while MDD subjects are indicated by *circles*. Note that the range of anhedonia scores in HC group was relatively small (0.0–0.14), so the HC subjects appear clustered together in the plots. The appearance of lower IDO activity and anhedonia scores in the MDD group than in the HC group is a consequence of the statistical control for depression severity and does not reflect the uncontrolled range of either measure

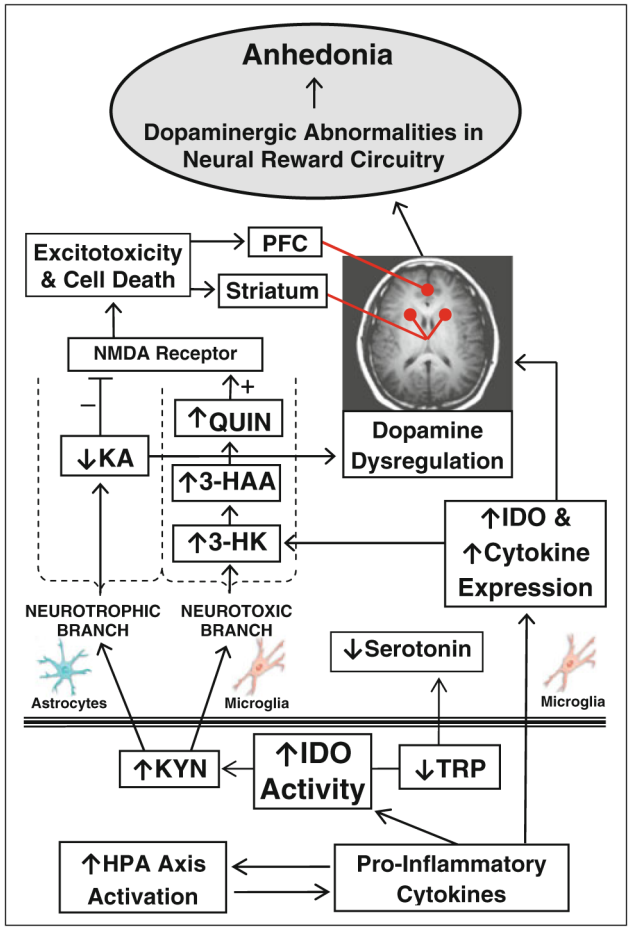

Fig. 3.

Overview of the proposed model of the kynurenine pathway in anhedonia. Plasma levels of tryptophan (*TRP*), kynurenine (*KYN*), 3-hydroxyanthranilic acid (*3-HAA*), and KYN/TRP ratio (*IDO*) were assayed in blood samples from depressed and control adolescents. TRP, KYN, and 3-hydroxykynurenine (*3-HK*) can cross the blood–brain barrier. *PFC* prefrontal cortex

Table 1

Clinical and demographic characteristics of adolescents with major depressive disorder (MDD) and healthy controls

Characteristic	MDD *N* = 36	Healthy controls *N* = 20
Age (years)	15.9 ± 1.7	16.1 ± 2.7
Gender (female/male)	21/15 (58/42%)[a]	12/8 (60/40%)[a]
Ethnicity (Caucasian/African American/Hispanic/Asian/other)	16/5/11/4/0 (44/14/31/11/0%)[a]	11/2/1/4/2 (55/10/5/20/10%)[a]
Illness history		
Duration of Illness (months)	18.8 ± 17.6 (3–84)[b]	0
History of suicide attempts	0.6 ± 0.8 (0–3)[b]	0
Medication-naïve/medication-free/medicated	20/2/14 (56/6/39%)[a]	0
CDRS-R[c]	58.4 ± 14.0 (37–97)[b]	18.3 ± 2.6 (17–27)[b]
BDI-II[d]	23.0 ± 10.6 (8–53)[b]	1.9 ± 2.8 (0–11)[b]
Anhedonia scores	0.578 ± 0.218 (0.083–1.00)[b]	0.015 ± 0.036 (0.00–0.014)[b]
Current comorbidity		
ADHD[e]	1 (3%)[a]	0
Any anxiety disorder	9 (25%)[a]	0
Any comorbidity	10 (28%)[a]	0

[a] Respective percentages

[b] Range

[c] Children's Depression Rating Scale-Revised

[d] Beck Depression Inventory, 2nd edn

[e] Attention Deficit Hyperactivity Disorder