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Tryptophan, kynurenine, and kynurenine metabolites: Relationship to lifetime aggression and inflammatory markers in human subjects

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Abstract

Inflammatory proteins are thought to be causally involved in the generation of aggression, possibly due to direct effects of cytokines in the central nervous system and/or by generation of inflammatory metabolites along the tryptophan-kynurenine (TRP/KYN) pathway, including KYN and its active metabolites kynurenic acid (KA), quinolinic acid (QA), and picolinic acid (PA). We examined plasma levels of TRP, KYN, KA, QA, and PA in 172 medication-free, medically healthy, human subjects to determine if plasma levels of these substances are altered as a function of trait aggression, and if they correlate with current plasma levels of inflammatory markers. Plasma levels of C-reactive protein (CRP), interleukin-6 (IL-6), and soluble interleukin-1 receptor-II (sIL-1RII) protein were also available in these subjects. We found normal levels of TRP but reduced plasma levels of KYN (by 48%), QA (by 6%), and a QA/KA (by 5%) ratio in subjects with Intermittent Explosive Disorder (IED) compared to healthy controls and psychiatric controls. Moreover, the metabolites were not associated with any of the inflammatory markers studied. These data do not support the hypothesis that elevated levels of KYN metabolites would be present in plasma of subjects with IED, and associated with plasma inflammation. However, our data do

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point to a dysregulation of the KYN pathway metabolites in these subjects. Further work will be necessary to replicate these findings and to understand their role in inflammation and aggression in these subjects.

Keywords

Plasma; CRP; IL-6; sIL-1RII; Kynurenine pathway; Aggression

1. Introduction

A growing body of literature suggests a role for the inflammatory processes in aggression. Increased anger and aggression have been reported in subjects treated with interferon (Kraus et al., 2003; McHuthison et al., 1998) and circulating levels of inflammatory markers have been shown to correlate with various measures of aggression. For example, C-reactive protein (CRP) has been reported to correlate directly with personality (Brummett et al., 2010; Coccaro, 2005; Marsland et al., 2008; Suarez, 2004), and with life history, measures of aggression (Coccaro et al., 2014) in both healthy volunteers (Brummett et al., 2010; Graham et al., 2006; Kiecolt-Glaser et al., 2005; Marsland et al., 2008; Miller et al., 2003; Ranjit et al., 2007; Sjogren et al., 2006; Suarez, 2003) and in psychiatric patients (Coccaro, 2005; Coccaro et al., 2014). The same has been reported for interleukin-6 [IL-6; (Brummett et al., 2010; Coccaro et al., 2014; Marsland et al., 2008; Suarez, 2003)], and both CRP and IL-6 have been reported to be elevated in subjects with intermittent explosive disorder (Coccaro et al., 2014), a disorder of impulsive aggression (Coccaro, 2012). Moreover, animal studies demonstrate increased defensive aggression in cats when inflammatory cytokines, such as IL1-β and IL-2, were injected into the medial hypothalamus or periaqueductal grey (Bhatt et al., 2008; Patel et al., 2010; Zalcman and Siegel, 2006).

The relationship between inflammation and behavior of any kind is quite complex and many factors and/or endogenous substances may account for this relationship in human aggression. Proinflammatory cytokines, for example, can induce indoleamine 2,3-dioxygenase (IDO), the rate-limiting enzyme that converts tryptophan (TRP) to kynurenine [KYN (Fujigaki et al., 2006)]. Thus, increased activity of IDO could lead to a reduction in TRP, and an increase in KYN, and a reduction in the synthesis of serotonin (5-hydroxytryptamine, 5-HT). Since reduced levels, and/or function, of central 5-HT is related to aggressive behavior (Coccaro et al., 2015a,b), it is possible that elevation of circulating inflammatory markers accounts for an inflammation-aggression relationship through an indirect effect on 5-HT synthesis.

In addition to a possible reduction in 5-HT (through induction of IDO), KYN and its metabolites are also associated with depressive symptoms. For example, increased levels of plasma KYN, and KYN/TRP ratio, as observed in INF-α treated hepatitis C patients, are associated with the emergence of depressive symptoms (Bonaccorso et al., 2002). In other studies, similar treatment with INF-α increases cerebrospinal fluid (CSF) KYN (but not CSF TRP) levels and correlates with level of depressive symptoms (Raison et al., 2010; Wichers et al., 2005). In addition, KYN is further metabolized to kynurenic acid (KA) and to

quinolinic acid (QA). KYNA blocks the glycine-site of the *N*-methyl-D-aspartate (NMDA) receptor (Jhamandas et al., 2000); QA, in contrast, stimulates NMDA-R containing NR1 + NR2A and the NR1 + NR2B subunits (de Carvalho et al., 1996; Stone, 1993). Activity at NMDA glutamate receptors is relevant because CSF glutamate levels are reported to correlate with measures of aggression so that subjects with high CSF glutamate levels are more aggressive than those with low CSF glutamate levels (Coccaro et al., 2013). If, based on animal studies, activation of NMDA glutamate receptors leads to aggression (Bandler 1984; Beart et al., 1998; Beitz 1989; Duncan et al., 2004; Lu et al., 1992; Schubert et al., 1996; Shaikh et al., 1994), KYNA might act to reduce aggression while QA might act to increase aggression. Finally, while less is known about the physiologic role of PA, this KYN pathway metabolite has been reported to antagonize the neurotoxic, though not the glutaminergic agonist effects of QA (Beninger et al., 1994; Cockhill et al., 1992). If so, an interaction between QA and PA could also have effects on aggressive behavior.

In this study, we sought to test the hypothesis that the elevated levels of inflammatory markers observed in impulsive aggressive subjects with intermittent explosive disorder (IED) would be associated with induction of IDO enzymes and, thus, associated with a reduction in circulating TRP, an increase in KYN, and variable differences in KA and QA. In addition, we hypothesized that measures of life-time history trait aggression and/or trait impulsivity would correlate with TRP, KYN, KA, QA, and PA.

2. Methods

2.1. Subjects

One-hundred-seventy-two physically healthy, and medication-free, subjects with plasma levels of CRP, IL-6 and sIL-RII protein, and plasma levels of TRP, KYN, KA, QA, and PA, were included in this study. Subjects were recruited through public service announcements, newspaper, and other media advertisements seeking out individuals who: a) reported psychosocial difficulty related to personality disorder traits or, b) had little evidence of psychopathology. While plasma CRP and IL-6 data have been previously reported in all subjects (Coccaro et al., 2014), plasma levels of sIL-RII protein and plasma levels of TRP, KYN and their metabolites, have not been previously reported and are new to this report. All subjects gave signed informed consent as approved by our Institutional Review Board (IRB). Subjects with bipolar disorder, schizophrenia, or mental retardation were excluded. Medical health was documented by comprehensive medical history and exam which included a screen for drugs of abuse (all subjects tested negative).

2.2. Diagnostic assessment

Syndromal psychiatric and personality disorder diagnoses were made by DSM-5 criteria (American Psychiatric Association, 2013). Research diagnostic assessments were performed by individuals with masters/doctoral degrees in clinical psychology with inter-rater (kappa) reliability ranging from 0.79–0.93 (mean + sd: 0.84 + 0.05) across mood, anxiety, substance use, impulse control, and personality disorders. Final diagnoses were assigned by previously described best-estimate consensus procedures (Coccaro et al., 2012) as previously described.

Fifty-two subjects met criteria for current Intermittent Explosive Disorder (IED), 56 subjects for a Non-IED DSM-5 disorder (Psychiatric Controls: PC), and 64 subjects without evidence of any DSM-5 disorder (Healthy Controls: HC). Among IED/PC subjects, 90 had current history of a syndromal psychiatric disorder, 102 had lifetime history of such a disorder, and 83 had a personality disorder. About half (52%) of PC/IED subjects had prior history of psychiatric treatment or of a behavioral disturbance for which mental health care should have been sought but was not. DSM-5 diagnoses for the subjects are listed in Table 1.

2.3. Measures of aggression and related variables

Aggression was assessed with the Aggression Scale from Life History of Aggression [LHA (Coccaro et al., 1997)]. The LHA assess the number of times a person has engaged in aggressive behavior in their life. The LHA ranges from 0 to 25 with scores >12 indicating a significant history of lifetime aggression over and above what is observed in a control group of non-aggressive individuals. Other assessments included Beck Depression Scale [BDI-II (Beck and Brown, 1996)] for state depression, and Life Experiences Survey [LES (Sarason et al., 1978)] for stressful life events over the past six months. Age, sex, racial, socioeconomic (ses), and current alcohol/smoking use data were collected by the diagnostic assessors during study evaluation.

2.4. Assay of plasma CRP, IL-6, and sIL-1RII

Results of CRP and IL-6, but not sIL-RII, assays have been published previously (Coccaro et al., 2014) and are reported primarily to document elevations of inflammatory markers in IED compared with control subjects and document direct correlations with measures of aggression in all subjects. Subjects were free of all medications for at least four weeks. Whole blood, anticoagulated with EDTA, was obtained between 9 and 11 AM through venipuncture of a forearm vein. Plasma was prepared after centrifugation and stored at −80 °C until assay. CRP, IL-6, and sIL-1RII protein plasma levels were detected by commercially available (R&D Systems) enzyme-linked immunosorbent assay (ELISA) kits and assayed, undiluted, according to manufacturer's instructions (n.b., plasma IL-1β levels were undetectable in these samples and, thus, sIL-1β RII protein levels were used as an indirect assessment of IL-1β activity). Optical density at 450 nm was assessed using an automatic microplate reader (LabSystems MultiSkan), and the amount of inflammatory marker in each sample was determined using the standard curve generated with each assay according to manufacturer's instructions. All samples were run together to avoid problems with assay drift and inter-assay variability and ELISA kits from the same manufacturer's lot were used for all assays. The mean of the duplicates was the unit of analysis. Lower limit of detection was 0.02 mg/L for CRP, 0.70 pg/mL for IL-6, and 10.00 pg/mL for sIL-1RII and intra-assay variability was less than 6% for each.

2.5. Plasma TRP, KYN, KA, QA, and PA

Plasma TRP and KYN were assayed by high performance liquid chromatography (HPLC) in thje laboratory of one of the authors (DF) as previously described (Widner et al., 1997) with intra-/inter-assay CVs for TRP of 1.0%/4.5% and 4.4%/7.6% for KYN. KA was assayed by HPLC (Linderholm et al., 2012) in the laboratory of one of the authors (SE) and had intra-/inter-assay CVs of 4.1% and 4.3%. QA (Bay-Richter et al., 2015) and PA (Smythe et al.,

2002) were analyzed by gas chromatography/mass spectrometry in the laboratory of one of the authors (LB); intra-/inter-assay CVs for QA were <9% while intra-/inter-assay CVs for PA were <7.9%. The KYN/TRP ratio, a measure relevant to the reciprocal relationship between KYN and TRP, was calculated by dividing the plasma level of KYN by that of TRP. The KYN/KA ratio, a measure putatively relevant to the neuro-toxic *vs.* protective effects of these two metabolites, was calculated by dividing the plasma level of KYN by that of KA. The QA/KA ratio a measure putatively relevant to the NMDA glutamate agonist *vs.* antagonist effects of these two metabolites, was calculated by dividing the plasma level of QA by that of KA.

2.6. Statistical analysis and data reduction

Comparisons between groups were performed by *t*-test, analysis of variance and covariance followed post-hoc testing by Tukey HSD, and by X^2 tests. Correlational analyses were conducted by parametric and nonparametric methods as necessary. In addition, several analyses involved multiple regression and stepwise multiple regression in order to determine the nature of the relationships among primary outcome variables while accounting for co-variability in relevant variables such as age, sex, race, ses, BMI, depression score, recent psychosocial stress, and current alcohol/smoking usage. The sample had >80% power to detect group differences of a medium size (f = 0.25) at an alpha level of 0.05. Post-hoc analyses after ANCOVA Plasma CRP and sIL-1βRII levels were normally distributed; IL-6 levels were not and were log-transformed for analysis. None of the other plasma level variables were normally distributed and, thus, plasma levels of TRP, KYN, KA, QA, and PA were also log-transformed for analysis.

3. Results

3.1. Demographic, relevant covariates, and behavioral characteristics across subjects (Table 2)

Demographically, subjects differed only in Hollingshead socioeconomic status (SES) score but not in age, sex, race, or in years of education. Differences in SES were due to a greater proportion of subjects with higher SES scores among PC compared with HC or IED subjects. Body mass index (BMI) did not differ across groups although state depression scores were higher in IED compared with PC subjects whose depression scores were greater than that of HC subjects and stressful life experience scores were greater in IED compared with HC subjects whose scores were similar to those of PC subjects. As expected, the groups differed in LHA Aggression, scores (IED > PC > HC).

3.2. Inflammatory plasma markers in IED/PC/HC subjects and correlations with LHA aggression

As previously reported in our larger sample of 197 subjects (Coccaro et al., 2014), plasma levels of CRP (IED: 2.30 + 0.73 *vs.* PC: 1.72 + 1.43 *vs.* HC: 1.15 + 0.84 mg/dL; $F[2,169] = 17.36$, $p < 0.001$) and Log IL-6 (IED: 0.21 + 0.29 *vs.* PC: −0.86 + 0.53 *vs.* HC: −0.18 + 0.69 ng/mL; $F[2,169] = 54.94$, $p < 0.001$) were significantly higher in IED compared with PC and HC subjects. Both plasma CRP and Log IL-6 correlated with LHA Aggression score across all subjects (CRP: $r = 0.40$, $p < 0.001$; IL-6: $r = 0.34$, $p < 0.001$). While plasma levels of

sIL-1RII followed a similar linear pattern as CRP and Log IL-6 (IED: 836 + 367; PC: 764 + 282; HC: 754 + 242 ng/mL), group differences were not statistically significant ($F[2,169] = 1.24$, $p = 0.291$). Despite this, a statistically significant correlation between plasma sIL-1RII levels and LHA Aggression was observed across all subjects ($r = 0.23$; $p = 0.002$). A composite measure of all three inflammatory markers (i.e., mean of the z-values for each inflammatory marker) correlated highly with LHA Aggression ($r = 0.48$, $p < 0.001$); Fig. 1. Addition of age, sex, race, ses, body mass index, state depression, recent psychological stress, and current alcohol/smoking usage reduced the magnitude, but not the statistical significance, of this correlation (partial $r = 0.37$, $p < 0.001$).

3.3. Plasma levels of TRP, KYN, KA, QA, and PA as a function of subject group

Table 2 displays mean raw values for TRP, KYN, and KYN metabolites, and Fig. 2 depicts mean log values for these compounds in the respective groups. While statistically significant group differences were observed for all plasma levels except for KA, plasma levels for IED were similar (TRP, KA) or lower (KYN, QA) compared with HC subjects. Plasma levels for TRP and KYN were lower in PC than HC subjects and were the same as for IED subjects for KYN.

3.4. Plasma levels of TRP, KYN, KA, QA, and PA as a function of LHA aggression and BDI depression

Stepwise multiple regression analyses with KYN pathway metabolites as separate dependent variables with age, sex, race, SES, BMI, recent psychosocial stress, current alcohol/smoking, and LHA Aggression scores, and BDI Depression scores, as independent variables were performed. Higher LHA Aggression scores were associated with lower plasma levels of QA ($\beta = -0.22$, $p < 0.005$), and PIC ($\beta = -0.18$, $p < 0.02$; Overall $F[1,168] = 5.83$, $p < 0.02$). Higher BDI Depression scores ($\beta = -0.18$, $p = 0.015$) were associated with lower plasma levels of TRP (Overall $F[3,168] = 6.51$, $p < 0.001$) and with lower plasma KYN ($\beta = -0.22$, $p < 0.01$; Overall $F[1,170] = 8.20$, $p < 0.01$).

3.5. Plasma levels of TRP, KYN, KA, QA, and PA as a function of circulating inflammatory markers

Similar analysis revealed relationships between TRP and sIL-1RII plasma levels ($\beta = 0.27$, $p < 0.001$; Overall $F[5,166] = 7.25$, $p < 0.001$) and between PA and IL-6 plasma levels ($\beta = -0.40$, $p < 0.001$; Overall $F[2,167] = 16.98$, $p < 0.001$) only.

3.6. KYN/TRP, KYN/KA, and QA/KA ratios as a function of subject group, LHA aggression, BDI depression, and circulating inflammatory markers

Fig. 3 displays the mean values for KYN/TRP, KYN/KA, and QA/KA ratios as a function of subject group. A statistically significant group difference was observed only for the QUIN/KYNA between IED and HC. However, no significant correlations were observed between these ratios and LHA Aggression scores. Modest inverse correlations were observed between BDI Depression scores and KYN/TRP and KYN/KA ratio but these relationships were not statistically significant after correlating for multiple comparisons (Table 3). Finally,

no significant relationships were observed between KYN metabolite pathway metabolites and plasma levels of the inflammatory markers studied.

4. Discussion

This is the first study to examine plasma TRP, KYN, and KYN pathway metabolites in the context of elevated circulating levels of inflammatory markers in impulsively aggressive (IED) subjects compared with psychiatric and healthy controls. Despite the presence of a heightened inflammatory process among subjects with IED, plasma levels of TRP, KA, and PA were no different from that in healthy controls. In contrast, plasma levels of KYN were reduced in subjects with IED compared with HC subjects and levels of QA were reduced in IED compared with both control groups. Finally, we observed modest, but statistically significant, inverse relationships between LHA Aggression scores and plasma levels of QA and PA, though not with plasma TRP, KYN, or KA.

4.1. Inflammation and aggression

We have expanded our previous work in this area (Coccaro et al., 2014) by demonstrating a positive correlation between plasma levels of sIL-1RII protein and life history of aggressive behavior. Combining the three inflammatory measures we now report that the composite value of these markers account for no less than 13% ($r^2 = 0.137$) of the variance in life history of aggression scores after accounting for relevant covariates. Further, the positive correlation between plasma sIL-1RII levels and aggression is a confirmation of our recent finding of the same in the CSF of personality disordered subjects from a different cohort (Coccaro et al., 2015a,b). sIL-1RII was studied in place of IL-1β because our pilot studies demonstrated that IL-1β could not be detected in our CSF or plasma samples. The sIL-1RII protein is a IL-1 related protein that acts as a “decoy” receptor for IL-1 (Colotta et al., 1994). It acts to bind IL-1β, preventing it from binding to sIL-1RI receptor protein which is necessary to enable IL-1β to act as an inflammatory cytokine. While sIL-1RII also binds IL-1β, only IL-1β is readily available in the circulation and capable of entering the CNS (Gabay et al., 2010). sIL-RII is not the only protein that modulates IL-1’s pro-inflammatory activity. IL-1Ra, a competitive inhibitor of IL-1, also blocks IL-1 activity, but only when IL-1Ra is present in great excess of IL-1 (Arend et al., 1990; Fischer et al., 1991). In contrast, IL-1β binds to IL-1RII with much greater affinity than either IL-1β or IL-1Ra and, thus, sIL-1RII can serve as “proxy” for IL-1β, in turn, representing a counter-response to inflammatory activity mediated through IL-1β (Gabay et al., 2010).

4.2. TRP, KYN, and their metabolites, and IED and in aggression

Overall, our observations regarding circulating levels of TRP and KYN pathway metabolites suggest that the low levels of inflammation observed in IED subjects may not be associated with the kind of changes in the TRP and in the KYN pathway as reported in some (Kegel et al., 2014; Linderholm et al., 2012; Raison et al., 2010; Sublette et al., 2011), though not all (Dahl et al., 2015), studies of psychiatric, and related, patients. This may be due to fundamental differences in the subjects studied [e.g., Depressed Suicide Attempters (Sublette et al., 2011); Schizophrenia; (Kegel et al., 2014; Linderholm et al., 2012); Hepatitis C patients treated with IFN-α (Raison et al., 2010)] or in the body compartment

examined [e.g., plasma (Dahl et al., 2015; Sublette et al., 2011) *vs.* cerebrospinal fluid [CSF (Kegel et al., 2014; Linderholm et al., 2012; Raison et al., 2010)]. For example, patients with major depression and a recent suicide attempt, had reduced plasma levels of TRP, and elevated levels of KYN, compared with healthy controls, in one study (Sublette et al., 2011), but not in another study focusing on patients with major depression where no TRP/KYN pathway metabolite differed from healthy controls (Dahl et al., 2015). Patients with schizophrenia had elevations of CSF KYN/KA, but not CSF QA, compared with healthy volunteers, in one study (Kegel et al., 2014), as well as elevations of CSF KYN/KA, but not TRP, in another study (Linderholm et al., 2012). Patients with Hepatitis C, treated for 12 weeks with IFN-α, displayed elevated CSF levels of KYN, KA, and QA (though not CSF TRP; Raison et al., 2010). In this same study, plasma levels of TRP were reduced while plasma levels of KYN (though not QA) were elevated, and the KYN/TRP ratio was reduced (Raison et al., 2010). Accordingly, the results of the current study are in line with the results of some (Dahl et al., 2015; Hughes et al., 2012; Quak et al., 2014), but not other (Gabbay et al., 2010; Myint et al., 2007, 2013; Savitz et al., 2015) studies of depressed patients.

While speculative, it is possible that our results, as well as those in patients with major depression (Dahl et al., 2015), reflect a shift from Th1 (T-helper cell type 1: cell-mediated) to Th2 (T-helper cell type 2: antibody-mediated) immune activation in these kinds of subjects (D'Elios and Del Prete, 1998; Sperner-Unterweger and Fuchs, 2015). Specifically, the lower plasma levels of KYN observed in IED, compared with HC, subjects is consistent with a preponderance of Th2, rather than a Th1, immunity state. This is because heightened levels of inflammatory cytokines related to Th1-immunity (e.g., IFN-γ) more potently activate KYN pathway enzyme activity than cytokines related to Th2-immunity [e.g., IL-6 (Schroecksnadel et al., 2011)] the latter of which are elevated in subjects with IED (Coccaro et al., 2014). In a predominantly Th2-immunity state, then, lower KYN levels would be observed relative to TRP levels. In addition, a reduction, rather than an increase, in QA levels, in IED compared with HC subjects, is also consistent with a Th2-immunty state because Th1, rather than Th2, cytokines activate QA production (Heyes et al., 1992). That said, it is possible that the chronicity of aggression, as observed in individuals with IED, makes this disorder different from other state-dependent disorders.

The reduction in plasma QA in IED, compared with healthy and psychiatric controls, is of note because QA correlated inversely with LHA Aggression scores in these subjects and because QA has glutaminergic agonistic properties. However, both animal (Bandler, 1984; Beart et al., 1998; Beitz 1989; Duncan et al., 2004; Lu et al., 1992; Schubert et al., 1996; Shaikh et al., 1994) and human (Coccaro et al., 2013), studies suggest that increasing glutaminergic activity should increase, not reduce, aggressive behavior. Thus, it is difficult to fit the findings of reduced plasma QA into an explanatory model for behavioral aggression and further studies investigating CSF levels of the KYN pathway metabolites are needed.

The inverse correlation between LHA Aggression and plasma PA levels is a novel finding and suggests that a higher life history of aggression is associated with lower PA levels. Since PA works to block QUIN-induced NMDA receptor activation (Beninger et al., 1994), lower levels of PA should be associated with reduced blockade of QA-induced NMDA receptor activation and less anti-QA/NMDA activity. However, this state of affairs should be

associated with less aggression, not more, and we observed no relationship between aggression and the ratio of PA to QA ($r = -0.03$, $p = 0.665$). Accordingly, it is unlikely that PA's relationship with aggression is through any effect on QA. Instead, it is possible that PA may exert an effect on mechanisms involved in aggression or that this, modest, relationship between PA and aggression ($\beta = -0.18$) represents a Type 1 error. More studies in this area will be needed to answer to confirm a relationship between PA and aggression.

4.3. Strengths and limitations

The strengths of this study include a well characterized sample, validated measures of history of actual aggressive and impulsive behavior, and a standardized approach to minimize the effect of extraneous factors on inflammatory marker levels and on levels of TRP, KYN and its metabolites. Limitations include, first, the cross-sectional nature of the study and, second, that correlational analysis never can establish causality. Third, it is possible that circulating levels of tryptophan, and its metabolites, may not reflect levels of these substances in the central nervous system in all, or some, conditions. Thus, it will be important recognize the relevance of metabolomics (Kaddurah-Daouk et al., 2014) in linking peripheral metabolite data with CSF (Raison et al., 2010), genetic (Myint et al., 2013), and imaging (Savitz et al., 2015) data in future studies. Further, although we have a thorough evaluation of lifetime aggression, we did not measure current levels of aggression in this study. That said, current aggression is highly variable over short periods of time and is difficult to assess in outpatient studies. Fourth, we did not collect data relevant to nutritional intake. While we have no reason to suspect differences in this regard, it is widely known that tryptophan intake is linked to plasma and brain tryptophan levels (Schaechter and Wurtman, 1990) and that deficiency of pyridoxine (vitamin B6) can interfere with the breakdown of kynurenine (Linkswiler, 1967). Fifth, there could be differences kynurenine and its metabolites between fasting and fed state and differences due to variability in body mass index, time of sample collection, and concomitant medication intake. In this study all samples were obtained in the fasting state in the morning over a short, two-hour window, of time. Subjects were free of all medications for no less than four weeks, typically much longer if they had even been on medications at all, and body mass index (as well as other potential confounders) were included in all final analyses. Finally, while our subjects were physically healthy by history and examination, other relevant biomedical variables (e.g., hematologic, lipid, coagulation, complement measures) that might aid in fully ruling out existing medical conditions were not collected. Despite this, no subject had a plasma CRP level >5 mg/L. Given that the upper normal limit of plasma CRP is 10 mg/L, it is unlikely that these findings could be accounted for by a known medical cause.

4.4. Conclusion

In this study, we report that elevated circulating inflammatory markers in IED subjects were associated with normal levels of TRP and reduced levels of KYN and QA metabolites, opposite to our initial hypothesis. While this may be due to primary activation of Th2 immunity (D'Elios and Del Prete, 1998; Sperner-Unterweger and Fuchs, 2015), this hypothesis would need to be tested, experimentally, in another study. In the end, there was little overall association between traits of aggression and these endogenous circulating substances with the exception of modest inverse relationships between aggression scores and

plasma levels of QA and PA. This needs to be further studied in similar subjects with samples from CSF, as the relationship between peripheral and central levels of KYN pathway metabolites has not been fully elucidated. Finally, it is critical to note that these data are only suggestive of the role, or lack thereof, for KYN pathway metabolites and replication of these findings will be needed.

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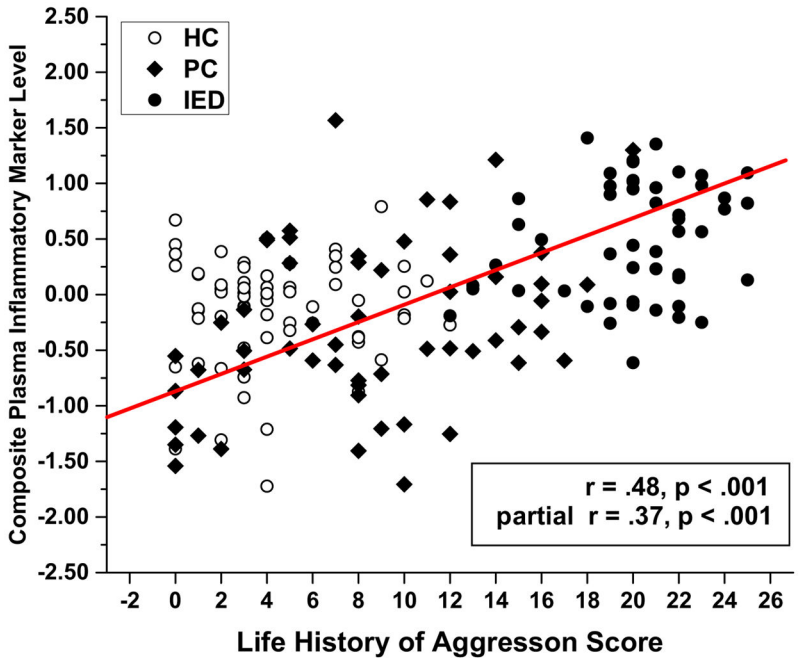

Fig. 1.

Correlation between Composite Inflammatory Markers and LHA Aggression ($r = 0.48$, $p < 0.001$; partial $r = 0.37$, $p < 0.001$ including relevant covariates; see text).

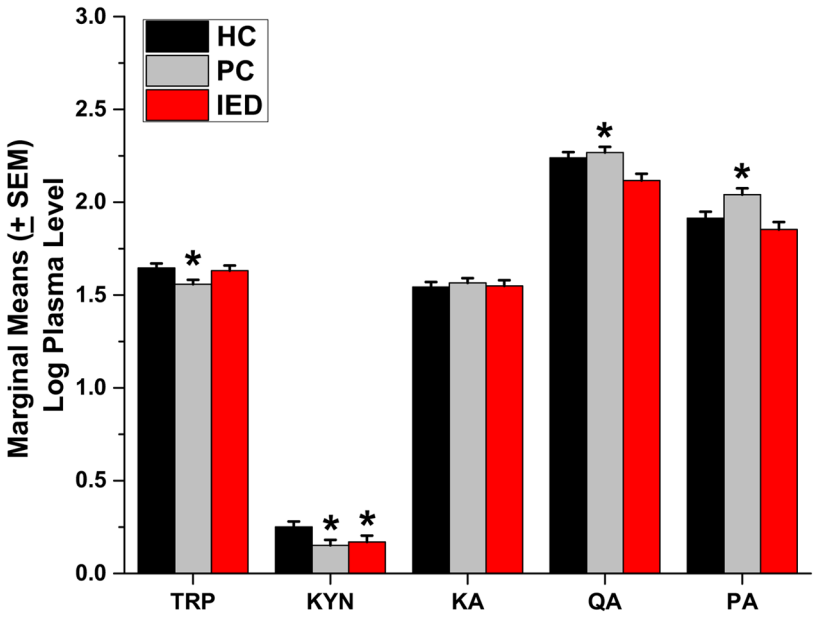

Fig. 2.

Marginal Means (+SEM), after including all relevant covariates (see text), for Log plasma levels of Tryptophan (TRP), Kynurenine (KYN), Kynurinic Acid (KA), Quinolinic Acid (QA), and Picolinic Acid (PA) in Healthy Control (HC), Psychiatric Control (PC) and IED subjects. * = $p < 0.05$ compared with HC Subjects.

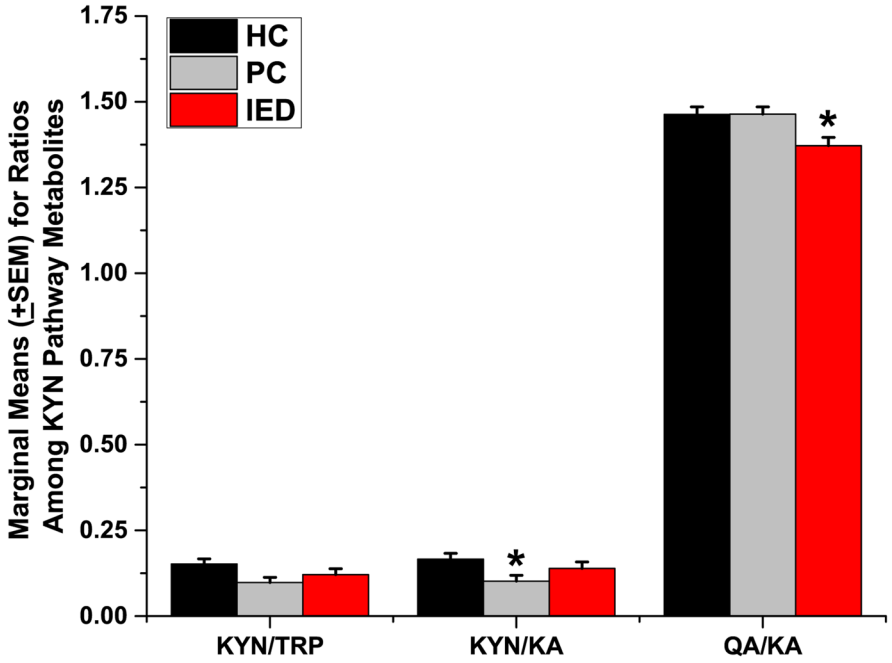

Fig. 3.

Marginal Means (+SEM), after including all relevant covariates (see text), for ratios among Kynuernine Pathway Metabolites: KYN/TRP Ratio, KYN/KA Ratio, and QAN/KA Ratio in Healthy Control (HC), Psychiatric Control (PC) and IED subjects. * = $p < 0.05$ compared with HC Subjects.

Table 1

DSM-5 syndromal and personality disorder diagnoses in PC/IED subjects.

	PC (N = 56)	IED (N = 52)	P
Current Syndromal Disorders:			
Any Depressive *or* Anxiety Disorder	26 (46.4%)	21 (40.4%)	=0.564
Any Depressive Disorder	8 (14.3%)	15 (28.8%)	=0.099
Any Anxiety Disorder	20 (35.7%)	13 (25.0%)	=0.296
Any Substance Use Disorder	0 (0.0%)	0 (0.0%)	=0.999
Any Stress and Trauma Disorder	10 (17.9%)	8 (15.4%)	=0.800
Any Eating Disorder	3 (5.4%)	4 (7.7%)	=0.709
Any Obsessive-Compulsive Disorder	2 (3.6%)	0 (0.0%)	=0.496
Any Somatoform Disorder	0 (0.0%)	1 (1.9%)	=0.481
Non-IED Impulse Control Disorder	0 (0.0%)	0 (0.0%)	=0.999
Lifetime Syndromal Disorders:			
Any Depressive *or* Anxiety Disorder	34 (60.7%)	40 (76.9%)	=0.097
Any Depressive Disorder	19 (33.9%)	37 (71.2%)	=0.001*
Any Anxiety Disorder	21 (37.5%)	17 (32.7%)	=0.688
Any Substance Use Disorder	17 (30.4%)	28 (53.8%)	=0.019
Any Stress and Trauma Disorder	15 (26.8%)	12 (23.1%)	=0.824
Any Eating Disorder	3 (5.4%)	9 (17.3%)	=0.067
Any Obsessive-Compulsive Disorder	0 (0.0%)	2 (3.5%)	=0.619
Any Somatoform Disorder	0 (0.0%)	1 (1.9%)	=0.481
Non-IED Impulse Control Disorder	0 (0.0%)	2 (3.8%)	=0.229
Personality Disorders:			
Any Personality Disorder	31 (55.4%)	52 (100.0%)	<0.001*
Personality Disorder Clusters:			
Cluster A (Odd)	2 (3.6%)	15 (28.8%)	<0.001*
Cluster B (Dramatic)	11 (19.6%)	33 (63.5%)	<0.001*
Cluster C (Anxious)	11 (19.6%)	21 (40.4%)	=0.022
PD-NOS	11 (19.6%)	12 (23.1%)	=0.815

* $p < 0.05$ after correcting for multiple comparisons.

Table 2

Demographic aggression, and relevant covariate data among the groups.

	Healthy Controls (N = 64)	Psychiatric Controls (N = 56)	Intermittent Explosive Disorder (N = 52)	p	Group Differences
Demographic Variables					
Age (Years + SD)	32.2 + 9.1	35.7 + 7.2	35.5 + 7.7	0.031	HC = PC = IED[a]
Gender (M/F)	31/33	23/33	26/26	0.602	HC = PC = IED[b]
Race (White/Non-White)	41/23	44/12	32/20	0.085	HC = PC = IED[b]
SES Score	43.0 + 12.1	47.1 + 12.0	41.3 + 11.5	0.042	HC = IED < PC[a]
Aggression Variable					
LHA Aggression	4.4 + 3.1	8.5 + 5.3	20.0 + 3.1	<0.001	HC < PC < IED[a]
Relevant Covariates					
Body Mass Index (BMI)	27.3 + 4.0	26.4 + 5.8	27.0 + 4.1	0.558	HC = PC = IED[a]
State Depression (BDI-II)	2.5 + 8.7	7.3 + 7.9	16.7 + 12.7	<0.001	HC < PC < IED[a]
Stressful Life Experiences(LES: Past Six Months)	5.4 + 5.1	6.3 + 5.7	13.2 + 11.3	0.026	HC = PC < IED[a]
Current Alcohol Use: Drinks Per Day	0.6 + 0.6	0.4 + 0.6	1.8 + 4.2	0.004	HC = PC < IED[a]
Current Smoking Use: Cigarettes Per Day	1.9 + 5.6	2.6 + 5.8	8.3 + 28.5	0.085	HC = PC = IED[a]
Raw TRP, KYN and KYN Metabolite Variables					
Tryptophan [μmol/L]	47.7 + 10.8	39.4 + 16.7	49.6 + 33.3	0.033	HC = IED > PC[c]
Kynurenine [μmol/L]	2.0 + 0.8	1.6 + 1.1	1.6 + 1.2	0.039	HC > PC = IED[c]
Kynurenic Acid [nmol/L]	38.5 + 17.3	41.6 + 1.4	37.2 + 14.9	0.490	HC = PC = IED
Quinolinic Acid [nmol/L]	197.3 + 97.8	203.1 + 84.6	148.9 + 80.9	0.005	HC = PC > IED[c]
Picolinic Acid [nmol/L]	100.3 + 85.7	127.4 + 68.6	90.6 + 94.7	<0.001	HC = IED < PC[c]

[a] By ANOVA.

[b] By Chi-Square.

[c] $p < 0.05$ by Tukey HSD after ANCOVA on log-transformed values.

Table 3

βvalues for relationships between KYN pathway ratios and LHA aggression, BDI depression, and circulating plasma inflammatory markers.

	LHA Aggression	BDI Depression	CRP	Log IL-6	sIL-1βRII
KYN/TRP Ratio	−.06	−0.21 *	−0.06	0.15	0.02
KYN/KYNA Ratio	−0.03	−0.20 *	−0.07	0.14	0.07
QUIN/KYNA Ratio	−0.07	0.03	−0.06	0.04	0.05

* $p < 0.05$ (uncorrected). No β value was $p < 0.0035$ (corrected for 15 comparisons).