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Role of the kynurenine pathway and the endocannabinoid system as modulators of inflammation and personality traits

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ABSTRACT

Background: Kynurenine pathway metabolites and endocannabinoids both exert potent regulatory effects on the immune system, but the relationship between these molecules is unknown. The role of these immunobiological mediators in emotionality and personality traits is not previously characterized.

Methods: Interleukin-6 (IL-6), 2-arachidonoylglycerol (2-AG) and picolinic acid (PIC) were measured in the plasma of physically healthy individuals who had history of mood, anxiety, and personality disorders (n = 96) or who had no history of any psychiatric disorder (n = 56) by DSM-5 Criteria. Dimensional assessments of personality were performed using the Eysenck Personality Questionnaire (EPQ) and the Tridimensional Personality Questionnaire (TPQ).

Results: Plasma IL-6 levels were significantly associated with plasma 2-AG levels and plasma PIC levels across all subjects. PIC levels were also negatively associated with 2-AG levels across all subjects, independent of IL-6 levels. In our analysis of the biological determinants of personality factors, we identified significant associations between IL-6 and novelty seeking assessment, and between PIC and neuroticism assessment.

Conclusions: These data provide evidence of a biological link between metabolites of the kynurenine pathway, the endocannabinoid system and IL-6 and suggest that these factors may influence personality traits.

1. Introduction

Considerable data suggests that inflammation influences several important neurobiological processes, including affect and emotionality. IL-6 is a cytokine that consistently has been associated with psychiatric illness. For example, meta-analyses have concluded that the levels of IL-6 are robustly increased in blood, CSF and brains of suicidal individuals (Black and Miller, 2015) and IL-6 is also generally increased in individuals with depression (Dowlati et al., 2010). We have also shown that IL-6 in CSF is increased in suicidal individuals compared to healthy controls, and that IL-6 is specifically associated with aggression in subjects with impulsive-aggressive disorder (Coccaro et al., 2014; Lindqvist et al., 2009). Animal models have provided a potential mechanistic path through which IL-6 may specifically regulate aggression and impulsivity (Zalcman and Siegel, 2006), through neuronal receptors for IL-6 in the periaqueductal grey matter. However, inflammatory processes in the brain are complex and influenced by other central neuromodulators and neurotransmitters. These mechanisms are not fully characterized, although accumulating data indicates that both kynurenine pathway (KP) metabolites and endocannabinoids (ECs) are likely important regulators of CNS inflammatory responses.

The KP is the primary route of tryptophan degradation and an imbalance of its bioactive metabolites, such as kynurenic-, quinolinic-, and picolinic- acids, have been detected together with inflammatory changes in suicidal patients (Brundin et al., 2016; Erhardt et al., 2013; Steiner et al., 2011). While there is a large body of evidence showing pro-inflammatory cytokines influence the production of KP metabolites by activating specific KP enzymes (Kim et al., 2012; Mándi and Vécsei, 2012; Schwieler et al., 2015; Taylor and Feng, 1991; Urata et al., 2015), KP metabolites can also reciprocally modulate inflammation. As an example, kynurenine, the first metabolite, is an endogenous agonist of the Ahr-receptor, regulating tolerance induction in T-cells.(L., S., & M.

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2017) 3-hydroxyanthranilic acid also exerts anti-inflammatory effects, reducing the release of TNFα and IL-6 in dendritic cells (Lee et al., 2013). Kynurenic acid (KYNA) also modulates inflammatory responses, anti-inflammatory in some studies (Małaczewska et al., 2016) and pro-inflammatory in others (DiNatale et al., 2010). In contrast, quinolinic acid (QUIN) is able to influence inflammation by increasing the production of certain cytokines, including IL-6, and the monocyte chemoattractant protein 1 (MCP-1) in glial cells (Block and Schwarz, 1994; Guillemin et al., 2003; Schiefer et al., 1998). Quinolinic acid (QUIN) might also induce apoptosis and suppress cytokine production in T-cell populations, possibly contributing to a shift in the inflammatory response from acquired towards innate immune functions (Fallarino et al., 2002; Orihara et al., 2018). Picolinic acid (PIC), an end product of KP metabolism, is able to block the neurotoxic properties of QUIN in cell culture and animal models (Beninger et al., 1994; Cockhill et al., 1992; Jhamandas et al., 1998) and, thus, may also be behaviorally important as its KP metabolic cousins.

Another important biological factor linked with inflammation are ECs, endogenous, lipid-based neurotransmitters that are part of the endocannabinoid system, which regulate homeostasis through a broad range of functions including sleep, blood pressure, memory, cognition, emotionality, pain perception, drug addiction, and reproduction (Martin et al., 1999; Stella et al., 1997). The ECs are increasingly recognized as important modulators of the immune system, due to mounting evidence of their involvement in several chronic inflammatory diseases, including multiple sclerosis, Alzheimer's Disease and Amyotrophic Lateral Sclerosis (Chiurchiu et al., 2015a; Chiurchiù et al., 2015b; De Petrocellis et al., 2000). It has been observed that 2-arachidonoylglycerol (2-AG) and anandamide (AEA), the two most widely investigated ECs, are released from the immune cells in response to inflammation, and growing evidence suggests that they are capable of affecting the immune response at both the innate and adaptive immune levels. AEA has potent anti-inflammatory effects, capable of inhibiting the release of nitric oxide and other pro-inflammatory cytokines, including IL-6 (Chiurchiù, 2016; Hernangómez et al., 2012). In contrast, data have shown that 2-AG can exert both anti- and pro-inflammatory responses, depending on the cell type (Chiurchiù, 2016; Oka et al., 2004). Interestingly, two recent studies indicate that the ECs and the KP metabolites are capable of reciprocally influencing each other (Colín-González et al., 2016; Nagy-Grócz et al., 2017).

To summarize, the KP metabolites and ECs both exert potent regulatory effects on the immune system. However, the interactions between these two types of modulators in the brain are still unknown; as well as if they are linked to certain emotional traits in healthy subjects, or in patients with psychiatric conditions. In this study we tested the hypothesis that KP and ECs would be associated with the circulating levels of interleukin-6 (IL-6) and that both would be involved in accounting for significant variance in emotionality, as assessed by assessments of classic personality dimensional traits.

2. Methods and materials

2.1. Subjects

One-hundred-fifty-two physically healthy subjects were recruited through public service announcements seeking out individuals who reported psychosocial difficulty related to mood, anxiety, or personality disorder or who had little evidence of psychopathology. 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 and personality disorder diagnoses were made according to DSM-5 criteria(American Psychiatric Association, 2013). Diagnoses were made using information from: (a) the Structured Clinical Interview for DSM Diagnoses (SCID-I; First et al., 1997) for syndromal disorders and the Structured Interview for the Diagnosis of DSM Personality Disorder (SIDP; Pfohl et al., 1997) for personality disorders; (b) clinical interview by a research psychiatrist; and, (c) review of all other available clinical data. This process resulted in good to excellent inter-rater reliabilities (mean kappa of 0.84 $\pm$ 0.05; range: .79 to .93) across anxiety, mood, substance use, impulse control, and personality disorders. Final diagnoses were assigned by team best-estimate consensus procedures involving research psychiatrists and clinical psychologists as previously described (Coccaro et al., 2016a,b). Participants with a current history of a substance use disorder or of a life history of any bipolar disorder, schizophrenia (or other psychotic disorder), or mental retardation, were excluded from the study. After diagnostic assignment, 56 study participants had no evidence of any psychiatric diagnosis (Healthy Study Participants: HSP) and 96 had a current or lifetime diagnosis of a depressive mood, anxiety, and/or a personality disorder (Psychiatric Study Participants: PSP). Of the latter group, a majority (58%) reported: a) history of formal psychiatric evaluation and/or treatment (54%) or, b) history of behavioral disturbance during which the participant, or others, thought they should have sought mental health services but did not (4%). Syndromal and personality disorder diagnoses are listed in Table 1.

2.3. Personality trait measures

Two assessments of core personality traits were included in this study: the Eysenck Personality Questionnaire (EPQ; Eysenck and Eysenck, 1991) and the Tridimensional Personality Questionnaire (TPQ; Cloninger et al., 1991). The EPQ includes Neuroticism (EPQ-N: "Are your feelings easily hurt?" or "Are you a worrier?), Psychoticism (EPQ-P: "Do you have enemies who want to harm you?" or "Do people tell you a lot of lies"?), and Extraversion (EPQ-E: "Are you rather lively?" or "Do you like mixing with people"?) while the TPQ includes Harm Avoidance (TPQ-HA: "Things often go wrong for me unless I am very careful"), Novelty Seeking (TPQ-NS: "I like to explore new ways to do things"), and Reward Dependence (TPQ-RD: "I like to please people

Table 1
Syndromal and Personality Disorder Diagnoses.

Current Syndromal Disorders:	
Any Depressive Disorder	20 (20.8%)
Any Substance Use Disorder	1 (1.0%)
Any Anxiety Disorder	40 (41.7%)
Intermittent Explosive Disorder	41 (42.7%)
Non-IED Impulse Control Disorder	2 (2.1%)
Stress and Trauma Disorders	17 (17.7%)
Obsessive Compulsive Disorders	2 (2.1%)
Eating Disorders	6 (6.3%)
Lifetime Syndromal Disorders:	
Any Depressive Disorder	47 (49.0%)
Any Substance Use Disorder	23 (24.0%)
Any Anxiety Disorder	45 (46.9%)
Intermittent Explosive Disorder	41 (42.7%)
Non-IED Impulse Control Disorder	5 (5.2%)
Stress and Trauma Disorders	27 (28.1%)
Obsessive Compulsive Disorders	4 (4.2%)
Eating Disorders	10 (10.4%)
Personality Disorder:	
Any Personality Disorder	72 (75.0%)
Cluster A	14 (14.6%)
Cluster B	38 (39.6%)
Cluster C	27 (28.1%)
Personality Disorder-NOS	21 (21.9%)

as much as I can"). Both EPQ and TPQ have been widely studied and have documented good psychometric properties.

2.4. Assessment of circulating KP metabolites, endocannabinoids, and interleukin-6

Study participants were free of all medications for at least four weeks. Whole blood, anticoagulated with EDTA, was obtained between 9–11 AM through venipuncture of a forearm vein with participants at rest. Samples were processed within 15 min and stored at −80 °C until assays were performed. We analyzed plasma kynurenine (KYN) and kynureninc acid (KYNA) by high performance liquid chromatography (HPLC) as previously described (Linderholm et al., 2012; Widner et al., 1997). We analyzed quinolinic acid (QUIN) and Picolinic Acid (PIC) by gas chromatography/mass spectrometry as previously described (Coccaro, Lee, et al. 2016) we measured plasma 2-arachidonoylglycerol (2-AG) and anandamide (AEA) levels using liquid chromatography and tandem mass spectrometry (LC–MS/MS) as described previously (Qi et al., 2015). IL-6 plasma levels were performed using a commercially available enzyme-linked immunosorbent assay kit (R&D Systems) and assayed, undiluted, according to manufacturer's instructions (Coccaro et al., 2014). All samples, for all assays, were run together to avoid problems with assay drift and inter-assay variability.

2.5. Statistical analysis

Comparisons between groups were performed by t-test, analysis of variance and covariance, and by X^2 tests. Correlational analyses were conducted by multiple regression analyses. Alpha = 0.05 denoted statistical significance. While plasma levels of AEA, KA and QA were normally distributed, this was not true for IL-6, 2-AG, KYN, and PIC, thus, each were log-transformed before analysis. Finally, because some of the variables (e.g., IL-6) are likely to covary with demographic (age, sex, ethnicity, socioeconomic status), physical (Body Mass Index: BMI), and state depression (Beck Depression Inventory (Beck and Brown, 1996)) variables, each analysis included each of these variables as a covariate.

3. Results

3.1. Demographic / behavioral characteristics of subjects

Healthy (HSP) and psychiatric (PSP) study participants differed modestly, but significantly, in age only. No group differences were observed for sex, ethnicity, socioeconomic status, or BMI. As expected, HSP and PSP groups differed in GAF scores, in BDI state depression scores, and in EPQ-N and EPQ-P but not EPQ-E, and in TPQ-HA but not in TPQ-NS or TPQ-RD scores. Patient demographics are reported in Table 2.

3.2. Plasma levels of IL-6, ECs and KP metabolites as a function of study group

Table 3 shows the mean raw values for the analytes measured in this study. Kynurenine levels were significantly higher in the HSP vs. PSP cohort ($p = 0.031$). A statistical trend was observed for increased tryptophan levels in the HSP cohort ($p = 0.067$).

3.3. Relationship between plasma IL-6, ECs, and KP metabolite levels

Multiple regression analysis with IL-6 level as dependent variable and each of the KP metabolites as independent variables (with relevant covariates, see methods) revealed a significant relationship between IL-6 and PIC levels only (Standardized $\beta = -0.338$, $p < 0.001$; Fig. 1A). A similar analysis revealed a significant relationship between IL-6 level and 2-AG level only (Standardized $\beta = 0.251$, $p = 0.001$; Fig. 1B). Placing PIC and 2-AG levels in the same model with IL-6 level revealed that the relationship between PIC and 2-AG levels ($\beta = -0.255$, $p = 0.002$; Fig. 1C) and between PIC and IL-6 levels ($\beta = -0.321$, $p < 0.001$) were both, unique and statistically significant.

3.4. Relationship between IL-6, PIC, and 2-AG levels with EPQ personality traits

Multiple regression analysis with IL-6 level as dependent variable and EPQ-N, EPQ-P and EPQ-E as independent variables (with relevant covariates) revealed a statistical trend with EPQ-P only (Standardized $\beta = -0.14$, $p = 0.066$). Similar analyses revealed a significant relationship between PIC and EPQ-N (Standardized $\beta = 0.255$, $p = 0.007$; Fig. 2) but no significant relationship between 2-AG and any of the EPQ variables.

3.5. Relationship between IL-6, PIC, and 2-AG levels with TPQ personality traits

Multiple regression analysis with IL-6 level as dependent variable and TPQ-HA, TPQ-NS, and TPQ-RD as independent variables (with relevant covariates) revealed a significant relationship for IL-6 and TPQ-NS (Standardized $\beta = 0.222$, $p = 0.016$; Fig. 3). Similar analysis showed a statistical trend for PIC and TQP-NS (Standardized $\beta = -0.177$, $p = 0.078$) and for PIC and TPQ-RD (Standardized $\beta = -0.185$, $p = 0.065$) but no significant relationship between 2-AG and any of the

Table 2
Patient Demographics.

	Healthy Study Participants (HSP: N = 56)	Psychiatric Study Participants (PSP: N = 96)	P-Value	Group Differences
Demographics				
Age	31.3 ± 8.6	35.8 ± 7.5	(p = 0.001)[1]	HSP < PSP
Sex (% Male)	48	43	(p = 0.612)[1]	HSP = PSP
Ethnicity (% White/% AA/% Other)	63/25/12	74/21/5	(p = 0.190)[2]	HSP = PSP
Body Mass Index (BMI)	27.3 ± 4.1	27.0 ± 5.3	(p = 0.675)[3]	HSP = PSP
SES Score	44.0 ± 12.6	45.0 ± 11.8	(p = 0.592)[1]	HSP = PSP
BDI State Depression Score	2.6 ± 9.1	11.6 ± 11.4	(p < 0.001)[3]	HSP < PSP
Psychosocial Function (GAF)	83.0 ± 4.5	61.2 ± 11.0	(p < 0.001)[1]	HSP > PSP
Personality Traits				
Neuroticism (EPQ-N)	10.4 ± 2.3	12.6 ± 2.4	(p < 0.001)[3]	HSP < PSP
Psychoticism (EPQ-P)	9.9 ± 1.6	10.8 ± 2.0	(p < 0.001)[3]	HSP < PSP
Extraversion (EPQ-E)	10.7 ± 1.9	11.2 ± 2.4	(p = 0.185)[3]	HSP = PSP
Novelty Seeking (TPQ-NS)	20.3 ± 5.0	18.4 ± 6.6	(p = 0.228)[3]	HSP = PSP
Harm Avoidance (TPQ-HA)	10.2 ± 5.5	15.4 ± 7.3	(p < 0.001)[3]	HSP < PSP
Reward Dependence (TPQ-RD)	15.8 ± 4.0	15.2 ± 4.2	(p = 0.185)[3]	HSP = PSP

Unless noted, all values are reported as the mean ± SD.
[1] ANOVA; [2]Chi-Square, [3]ANCOVA (with age, sex, race, SES as covariates).

Table 3
Mean Levels of IL-6, ECs and KP Metabolites.

	Healthy Study Participants (HSP: N = 56)	Psychiatric Study Participants (PSP: N = 96)	P-Value	Group Differences
IL-6 (pg/mL)	1.42 ± 1.41	1.15 ± 1.60	p = 0.658[1]	HSP = PSP
2-AG (nmol/L)	43.96 ± 28.09	38.65 ± 25.70	p = 0.802[1]	HSP = PSP
AEA (nmol/L)	1.09 ± 0.48	1.12 ± 0.54	p = 0.668[2]	HSP = PSP
TRP (umol/L)	81.70 ± 10.71	41.90 ± 24.35	p = 0.067[1]	HSP = PSP
KYN (umol/L)	1.98 ± 0.80	1.60 ± 1.14	p = 0.031[1]	HSP > PSP
KYNA (nmol/L)	39.53 ± 17.92	39.67 ± 18.04	p = 0.281[2]	HSP = PSP
QUIN (nmol/L)	203.56 ± 97.46	181.32 ± 87.99	p = 0.158[2]	HSP = PSP
PIC (nmol/L)	90.24 ± 73.33	114.81 ± 86.62	p = 0.662[1]	HSP = PSP

All values are reported as the mean ± SD.
[1] ANCOVA on log transformed values; [2]ANCOVA on non-transformed values (with age, sex, race, SES as covariates).

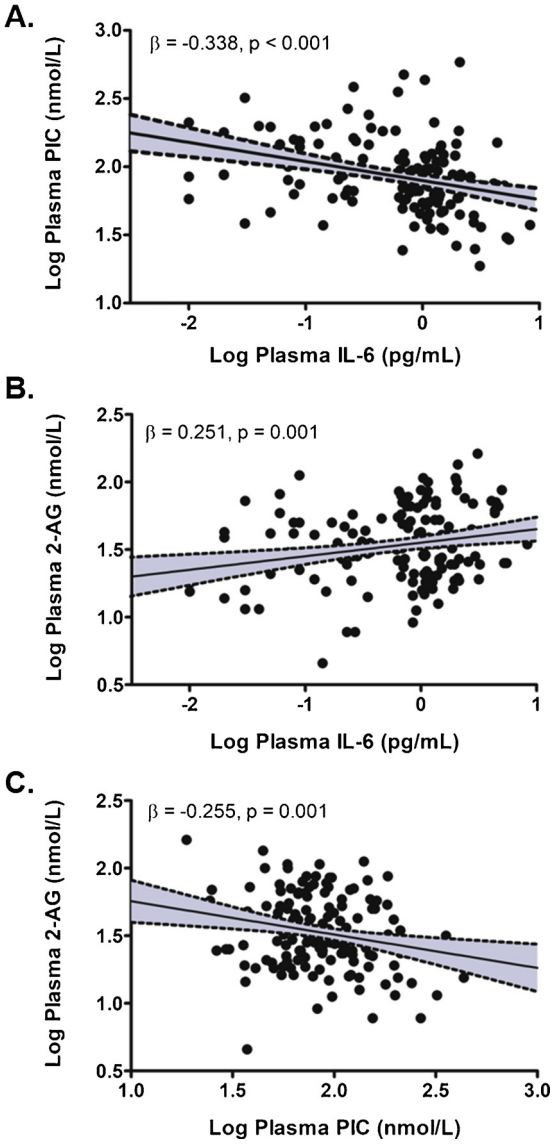

Fig. 1. Partial plots for the relationship between (A) Log Plasma IL-6 and Log Plasma PIC, (B) Log Plasma IL-6 and Log Plasma 2-AG, and (C) Log Plasma PIC and Log Plasma 2-AG in all subjects (n = 152). Demographics, BMI, and BDI Depression score variables were included in each statistical model, as detailed in the methods. Shaded regions represent confidence intervals (CI = 95%).

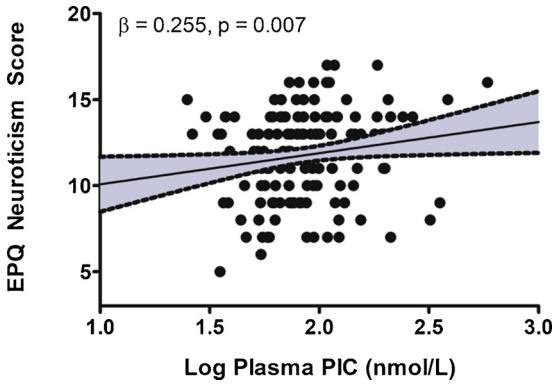

Fig. 2. Partial plots for the relationship between Log Plasma PIC and EPQ-N in all subjects (n = 145). Demographics, BMI, and BDI Depression score variables were included in each statistical model, as detailed in the methods. Shaded regions represent confidence intervals (CI = 95%).

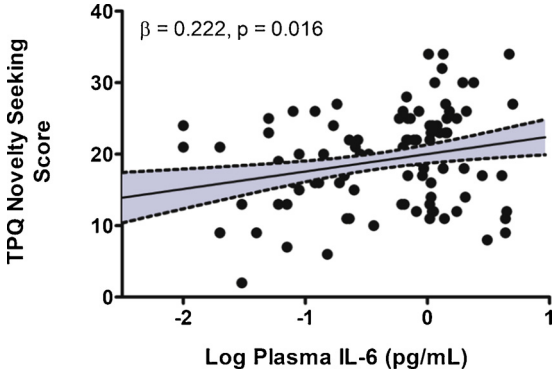

Fig. 3. Partial plots for the relationship between Log Plasma IL-6 and TPQ-NS in all subjects (n = 115). Demographics, BMI, and BDI Depression score variables were included in each statistical model, as detailed in the methods. Shaded regions represent confidence intervals (CI = 95%).

TPQ variables.

4. Discussion

This is the first study to examine circulating ECs in a sizable group of study participants with and without history of psychiatric disorder in order to examine the relationship between circulating ECs, KP metabolites and dimensions of affect and affect regulation. The primary finding in this study is that the KP metabolite, picolinic acid, has a positive relationship with assessments of affect regulation (affective intensity and affective lability), while circulating ECs display no relationship to these assessments.

Second, we found that levels of 2-AG are positively correlated with levels of the pro-inflammatory cytokine, IL-6 (Fig. 1B). A previous study

has found that suicide victims, whom often show increased IL-6 levels in their blood and brain tissue (Dowlati et al., 2010; Janelidze et al., 2011; Lindqvist et al., 2009; O'Donovan et al., 2013), exhibit increased 2-AG levels in the brain, as well as upregulation of cannabinoid receptor 1 (CB1)-mediated signaling in the prefrontal cortex (Hungund et al., 2004; Vinod et al., 2005); these studies, however, did not assess the relationship between ECs and inflammation in their patient cohort. Furthermore, studies have shown that increased endocannabinoid system activity appears to exert an antidepressant-like effect in animal models of depression, while a reduction in the endocannabinoid system activity is present in animals with chronic mild stress (Micale et al., 2015; Serra and Fratta, 2007; Zhong et al., 2014). Interestingly, acute stress, vulnerability to which has been linked to the occurrence of depression and suicidality, promotes the elevation of 2-AG in the midbrain region (Hohmann et al., 2005). Increases in 2-AG have been observed in several neuropathological conditions with an inflammatory component, including Alzheimer's disease, Parkinson's disease and multiple sclerosis (Alhouayek et al., 2014). Additionally, administration of 2-AG or inhibition of its degradation causes an anti-inflammatory and neuroprotective effect in animal models of multiple sclerosis, Parkinson's disease and head trauma (Baker et al., 2000; Di Marzo et al. 2005, Panikashvili et al., 2006). Interestingly, down-regulation of the endocannabinoid system occurs in Huntington's disease (HD; Pazos et al., 2008), and a recent study has demonstrated that elevation of 2-AG restores synaptic plasticity of cortical neurons in an animal model of HD (Sepers et al., 2018). Overall, evidence from previous animal and clinical studies suggests that 2-AG exerts neuroprotective, anti-inflammatory as well as anti-depressant properties. On the basis of these studies, it is possible that in our patient cohort the 2-AG levels are increased in response to elevated IL-6 concentrations as a natural defense mechanism against inflammation.

Third, we identified a negative association between levels of PIC and IL-6 (Fig. 1A). This is in agreement with a previous study where we demonstrated that IL-6 levels are increased in suicidal individuals with low circulating and CSF levels of PIC (Brundin et al., 2016). While little is known about the biological role of PIC, some studies point towards a protective role (Grant, Coggan, & Smythe, 2009). PIC is produced by the amino-β-carboxymuconate-semialdehyde-decarboxylase (ACMSD) enzyme of the kynurenine pathway from 2-amino-3-carboxymuconic acid-6-semialdehyde, the same metabolite that is also non-enzymatically converted into QUIN. The spontaneous conversion to QUIN increases under conditions when the activity of ACMSD is reduced, such as when the enzyme is saturated, inactive or absent (Bryleva and Brundin, 2017). Increased levels of QUIN could potentially increase levels of inflammation, as previous cell culture and animal studies have shown that QUIN is able to stimulate the production of MCP-1 and cytokines, such as IL-6 in glial cell populations (Block and Schwarz, 1994; Guillemin et al., 2003; Schiefer et al., 1998). We have previously proposed that ACMSD may serve as a "break", limiting the formation of QUIN and the resulting inflammation (Thirtamara-Rajamani et al. 2017). Thus, when ACMSD activity is decreased (resulting in decreased PIC concentrations), the level of IL-6, potentially produced in response to QUIN, would be higher, consistent with the results of the present study (Fig. 1A). This study suggests that the relationship between inflammation and picolinic acid needs to be further investigated.

Fourth, we found an inverse association between levels of PIC and 2-AG independent of levels of IL-6 (Fig. 1C). The interactions between the kynurenine pathway and endocannabinoid system has been poorly explored. To our knowledge, this is the first study to report the association between endocannabinoids and kynurenine pathway metabolites. The endocannabinoid system is involved in the regulation of the stress response, as evidenced in multiple human and animal studies (Lutz et al., 2015). For example, pharmacological blockade or genetic deletion of cannabinoid CB1 receptor increases stress-induced hypothalamic-pituitary-adrenal axis (HPA axis) activation and secretion of glucocorticoids (Patel et al., 2004; Steiner et al., 2008; Urigüen et al., 2004). Glucocorticoids activate TDO in mice (Knox, 1951; Voigt and Sekeris, 1980), which (like IDO1) is the first enzyme of the kynurenine pathway, potentially stimulating the production of the downstream metabolite PIC. Thus, it is possible that the decrease in 2-AG would raise the levels of PIC through increased stimulation of the kynurenine pathway by glucocorticoids in our patient cohort, however it is unknown if HPA axis-mediated activation of the kynurenine pathway occurs in humans. Supporting this notion, recent animal studies have shown that CB1-receptor mediated signaling can mitigate the excitotoxic effects of QUIN, by reducing the availability of the NR1 subunit of NMDA receptors (Aguilera-Portillo et al., 2019; Rangel-Lopez et al., 2015). It would follow then that as QUIN levels decrease and PIC levels rise, endocannabinoid levels would fall to rebalance levels of glutamate neurotransmission. Clearly, further studies investigating the interactions between kynurenine pathway metabolism and ECS are needed.

Finally, after we determined that the KP metabolite PIC and the endocannabinoid 2-AG were associated with levels of IL-6, we explored whether PIC and 2-AG levels account for significant variance in emotionality as assessed by EPQ and TPQ personality traits. We found a significant, positive, association between IL-6 levels and TPQ-NS scores, and a significant, positive, association between PIC levels and EPQ-N scores. Despite this, we found no association between ECs and EPQ or TPQ scores in our patient cohort.

The finding that levels of IL-6 correlate with TQP-NS scores was unexpected. Novelty-Seeking (NS) is a personality trait associated with exploratory activity in response to novel stimuli and is associated with impulsive decision making. Numerous animal and clinical studies have demonstrated that infection and inflammation reduce novelty-seeking behaviors (Haba et al., 2012; Harrison et al., 2015; Kusnecov et al., 2018). For example, humans with toxoplasmosis, an infectious disease caused by the parasite *Toxoplasma Gondii*, display a marked decrease in NS (Flegr et al., 2003; Skallová et al., 2005). These patients also exhibit increased plasma levels of pro-inflammatory cytokines, including IL-6 (Beaman et al., 1994; Hamdani et al., 2015; Saeij et al., 2005). It is unclear what would account for the positive association between IL-6 and TPQ-NS in our study, however it is possible that the peripheral markers of inflammation measured here do not explain the inflammatory state of the central nervous system. Indeed, we have previously shown that IL-6 levels in the plasma and CSF do not correlate in some psychiatric patients (Coccaro et al., 2015; Lindqvist et al., 2009). Future studies on the role of inflammation in emotionality will be required to validate these findings and may be aided by examining inflammatory markers in cerebrospinal fluid.

We also observed a positive association between plasma PIC levels and EPQ-N scores. To our knowledge, this is the first study to examine the relationship between KP metabolites and these personality traits. Aside from its well-studied metal chelating properties, little is known about the biological role for PIC. *in vitro* studies have demonstrated that PIC can counteract the neurotoxic effects of QUIN (Beninger et al., 1994; Jhamandas et al., 1998), suggesting a potential neuroprotective role. On the other hand, neuroticism is often associated elevated levels of inflammatory markers, depression (Luchetti et al., 2014; Pawlowski et al., 2014; Schmidt et al., 2018), and high levels of stress (Abbasi, 2016). Thus, the observed association may be in part due to activation of the kynurenine pathway in response to stress.

Our study has several strengths and limitations. The study included a well characterized patient cohort, and a standardized approach to minimize the effect of extraneous factors on inflammatory marker levels and on levels of KP metabolites and ECs. Additionally, all patients in this study were free of all medications for at least four weeks, thereby reducing the effect these medications may have on plasma biomarkers. Limitations include: 1) the cross-sectional nature of this study design, 2) this study was correlative, and cannot establish causality and 3) as previously stated, plasma levels of the measured cytokines, kynurenine pathway metabolites and endocannabinoids may not accurately reflect

levels of these compounds in the central nervous system.

5. Conclusion

First, circulating levels of IL-6, 2-AG, and PIC were significantly inter-correlated across all subjects. Second, a positive association between circulating IL-6 and TPQ-NS scores, and between circulating PIC and EPQ-N scores, was also found. Finally, PIC levels were significantly associated with 2-AG levels but independent of IL-6 levels. These data suggest a novel relationship between the kynurenine pathway and the endocannabinoid system, impacting personality traits that may influence mental disorders.

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Dr. Coccaro reports being on the Scientific Advisory Board of Azevan Pharmaceuticals and is a consultant to Avanir Pharmaceuticals, Inc.; Dr. Hill reports having received consulting fees from Pfizer International and receiving consulting fees and unrestricted operating funds from GW Pharmaceuticals; Neither Drs. Brundin, Coussons-Read, or Heilman report any conflicts of interest.

Declaration of Competing Interest

Dr. Coccaro reports being on the Scientific Advisory Board of Azevan Pharmaceuticals and is a consultant to Avanir Pharmaceuticals, Inc.; Dr. Hill reports having received consulting fees from Pfizer International and receiving consulting fees and unrestricted operating funds from GW Pharmaceuticals; Neither Drs. Brundin, Coussons-Read, or Heilman report any conflicts of interest.

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