Central levels of tryptophan metabolites in subjects with bipolar disorder

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Abstract
The kynurenine pathway of tryptophan degradation produces several neuroactive metabolites such as kynurenic acid (KYNA), quinolinic acid (QUIN), and picolinic acid (PIC) thought to be involved in the pathophysiology of psychosis, major depression, and suicidal behavior. Here, we analyzed cerebrospinal fluid (CSF) concentrations of tryptophan, kynurenine, KYNA, QUIN, and PIC utilizing ultra-performance liquid chromatography - tandem mass spectrometry system (UPLC-MS/MS) in persons with bipolar disorder (n = 101) and healthy controls (n = 80) to investigate if the metabolites correlated with depressive symptoms or to the history of suicidal behavior. Furthermore, we analyzed if genetic variants of the enzyme amino-β-carboxymuconate-semialdehyde-decarboxylase (ACMSD) were associated with the CSF concentrations of PIC and QUIN. We found that CSF KYNA and PIC concentrations, as well as the kynurenine/tryptophan ratio were increased in bipolar disorder compared with controls. CSF PIC concentrations were lower in subjects with a history of suicidal behavior than those without, supporting the hypothesis that low CSF PIC is a marker of vulnerability for suicidality. Bipolar subjects taking antidepressants had higher CSF concentrations of kynurenine and KYNA than subjects not given

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1. Introduction

Bipolar disorder is a severe psychiatric disorder typically presenting with recurrent manic and depressive episodes. Affective episodes are separated by states of euthymia when the mood is neutral and manic or depressive symptoms are absent. The disease is almost always chronic, and the typical age of onset is 15–25 years of age (Merikangas et al., 2011). A cross-sectional study, including 11 countries, suggests that the lifetime prevalence is around 2.4% (Merikangas et al., 2011). The lifespan of subjects with bipolar disorder is reduced by 9–17 years (Chang et al., 2011; Laursen et al., 2013) due to somatic comorbidities (Kessing et al., 2015; Vancampfort et al., 2015; Correll et al., 2017), lack of physical activity (Vancampfort et al., 2017) as well as an increased suicide rate (Dome et al., 2019). Among all suicide cases, it is estimated that bipolar disorder-associated cases account for approximately 3–14% (Schaffer et al., 2015) and that among subjects with bipolar disorder, 20–60% attempt suicide at least once in their lifetime and that 4–19% of all patients end their life by committing suicide (Rihmer et al., 2017; Dome et al., 2019).

The kynurenine pathway of tryptophan degradation (see Fig. 1) produces several neuroactive metabolites such as, quinolinic acid (QUIN), an agonist of glutamatergic N-methyl-D-aspartate (NMDA)-receptors (Stone, 1993; Schwarz et al., 2012), picolinic acid (PIC), a small molecule suggested to have neuroprotective properties (Grant et al., 2009) and kynurenic acid (KYNA), an endogenous antagonist at NMDA- and α7-nicotinic acetylcholine (α7nACh) receptors. While the antagonistic properties of KYNA at NMDA receptors are well established, contrasting results are available for its action as an antagonist of α7nACh receptors (Stone 2020). Previous post-mortem and cerebrospinal fluid (CSF) studies showed increased central levels of KYNA and its precursor kynurenine in patients with bipolar disorder with a history of psychosis (Miller et al., 2004; Olsson et al., 2010; Lavebratt et al., 2014, Sellegren et al., 2016; Sellegren et al., 2019).

In contrast, some studies have reported decreased peripheral levels of KYNA in bipolar disorder (Birner et al., 2017; Liu et al., 2018; Poletti et al., 2018; van den Ameene et al., 2020). In a recent study, we investigated the intra- and inter-relationships between peripheral and central KYNA levels in a large cohort of well-characterized euthymic patients with bipolar disorder type I/II and matched healthy controls (Sellegren et al., 2019). In line with previous studies from our group, we found that high CSF KYNA correlated with a history of psychotic episodes (Olsson et al., 2012; Lavebratt et al., 2014; Sellegren et al., 2016), and that ongoing depressive symptoms, on the other hand, tended to associate with decreased plasma KYNA concentrations. Low plasma concentrations of KYNA have previously been found in patients with treatment-resistant depression (Myint et al., 2007; Maes et al., 2011; Schwieler et al., 2016; Kadriu et al., 2019). CSF KYNA concentrations have also been shown to inversely correlate to depressive symptoms in patients with major depressive disorders with a history of suicidal behavior (Bay-Richter et al., 2015).

QUIN and PIC, metabolites produced in the other branch of the kynurenine pathway, have also been suggested to be involved in the pathophysiology of suicidal behavior. We have found that CSF QUIN levels are increased in suicide attempters in close proximity of the attempt, and the levels associate with the degree of suicidal intent (Erhardt et al., 2013). In line with this, Steiner and colleagues have found increased QUIN-immunoreactivity in microglia in the anterior cingulate gyrus in the post-mortem brain of suicide victims suffering from either severe depression or schizophrenia (Steiner et al., 2011). With regard to the periphery, both normal and low plasma QUIN concentrations have been observed in depression (Savitz et al., 2015; Schwieler et al., 2016; Liu et al., 2018; Ryan et al., 2020). Correspondingly, both plasma and CSF PIC concentrations are found to be decreased in suicide attempters at the time of the suicide attempt, and the reduction in CSF was observed up to two years after the attempt (Brundin et al., 2016). Low CSF PIC is therefore suggested to indicate vulnerability for suicidal behavior (Brundin et al., 2016). In line with this, deficient activity of the enzyme amino-α-carboxymuconate-semialdehyde-decarboxylase (ACMSD) has been suggested to be associated with suicidal behavior (Brundin et al., 2016). ACMSD produces PIC from the same precursor, 2-amino-3-carboxymuconate-6-semialdehyde (ACMS), which non-enzymatically degrades to QUIN. Decreased ACMS activity can thus lead to excess QUIN concentrations at the expense of PIC production. Low PIC/QUIN may thus also be indicative of suicide risk (Brundin et al., 2016).

In subjects with bipolar disorder, plasma QUIN has only been analyzed in two studies, one showing concentrations on par with controls (van den Ameene et al., 2020) and the other showing lower concentrations (Liu et al., 2018) compared to healthy controls. Plasma PIC levels have been shown to be lower in patients with bipolar depression compared with healthy controls (Aarsland et al., 2019; Ryan et al., 2020). However, these studies did not separate patients with suicidal behavior from the patient popu-
Fig. 1 Kynurenine pathway of tryptophan degradation.

In summary, although several studies have analyzed KYNA in both plasma and CSF of patients with bipolar disorder, a limited number of studies have analyzed PIC and QUIN, and to our knowledge, no one has analyzed central levels of these metabolites in bipolar patients. In the present study, we will analyze CSF concentrations of tryptophan, kynurenine, KYNA, QUIN and PIC in subjects with bipolar disorder and healthy controls. We will further investigate if any of these metabolites correlate with depressive symptoms or with a history of suicidal behavior in the patient group and investigate if ACMDS gene variants affect the CSF concentrations of PIC, QUIN, or the PIC/QUIN ratio in subjects with bipolar disorder with or without suicidal behavior.

2. Experimental procedure

2.1. Subjects

Patients were enrolled in the St. Göran bipolar project (SBP), which provides assessment, treatment, and follow-up of patients with bipolar disorder. All patients met the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for being diagnosed with Bipolar Disorder type I or II but at the time of CSF sampling, all patients were euthymic (see also Supplemental Material). Patients were recruited from the bipolar unit at the Northern Stockholm Psychiatric Clinic, Stockholm, Sweden. Population-based controls were selected randomly by Statistics Sweden (SCB; www.scb.se). KYNA has previously been analyzed with HPLC in a subset of the healthy controls (Sellgren et al., 2016, 2019). For exclusion criteria and clinical assessments see Supplemental Materials. This study has been approved by the Regional Ethics Committee in Stockholm (2005/554-31/3) and all participating subjects granted oral and written informed consent after complete description of the study. CSF sampling was performed between 9:00 am to 10:00 am after a night of fasting. 12 mL of CSF was collected, aliquoted, and stored in −80°C pending analysis. CSF was analyzed using UPLC-MS/MS. Genotyping was performed at the Genomics Core Facility at University of Gothenburg, Sweden. See Supplemental Materials for full description of methods.

2.2. Analysis of kynurenine pathway metabolites in human cerebrospinal fluid material

Tryptophan, L-kynurenine, pyridine-2,3-dicarboxylic acid (QUIN), KYNA, and PIC were all purchased from Sigma-Aldrich (MO, USA). The Internal standards (IS): Tryptophan-d3, Kynurenine-d4, QUIN-d3 were obtained from Toronto Research Chemicals, Canada. KYNA-d5 and PIC-d5 were obtained from C/D/N Isotopes Inc. (Quebec, Canada). Solutions for the mobile phases: water, methanol and formic acid 99% were all UPLC-MS grade (Chromasolve, Honeywell, VWR International AB, Stockholm, Sweden).

2.3. Ultra performance liquid chromatography - tandem mass spectrometry (UPLC-MS/MS)

Tryptophan, kynurenine, KYNA, QUIN and PIC in CSF were quantified by UPLC-MS/MS system using a Xevo TQ-XS triple-quadrupole
mass spectrometer (Waters, Manchester, UK) equipped with a Z-spray electrospray interface and a Waters Acquity UPLC I-Class FTN system (Waters, MA, USA). The MS was operated in electrospray-positive multiple reaction monitoring (MRM) mode. The system was operated using a source temperature of 150 °C, capillary voltage of +3.0 kV, desolvation temperature 650 °C, desolvation gas flow rate 1000 l/h and detector gain 1 was used. The column was Acquity HSS T3 2.1 × 150 mm, 1.8 μm (Waters, Product Number [PN]: 186,003,540) and set to a temperature of 50 °C. The two mobile phases were composed of A: 0.6% formic acid in water and B: 0.6% formic acid in methanol (UPLC grade). An isolator column (Waters, 2.1 × 50 mm column, PN: 186,004,476) was installed to retain contaminants from the mobile phase. The flow rate was set at 0.3 ml/min and the run time for each sample was 13.0 min. The m/z for the MRM transitions of each individual analyte were: Tryptophan, 205 > 118; Kynurenine, 209 > 94; KYNA, 190 > 116; QUIN, 168 > 78; PIC, 124 > 78 and for the internal standards (IS): Tryptophan-d4, 208 > 119; Kynurenine-d4, 213 > 94; QUIN-d3, 171 > 81; KYNA-d5, 195 > 121; PIC-d4, 128 > 82. For full details and method validation see Schwieler et al., 2020.

2.4. Sample preparation

Human CSF (30 μl), calibrator sample and quality control (QC) sample was mixed with 30 μl of IS working solution (1 μM of Tryptophan-d4, Kynurenine-d4, QUIN-d3, KYNA-d5 and PIC-d4 in 1% formic acid) during 15 s in LC-MS Certified Clear Glass 12 × 32 mm vials (Waters, PN: 186005662CV) before transfer to an autosampler (set to 4 °C) that injected 3 μl into the UPLC MS/MS system. Standards of each analyte were used to establish a linear calibration curve (0.1 nM-10 μM (TRP 10-100 μM)). The standard curve was calculated by 1/X-weighted least squares linear regression of standard curve calibration concentrations and the peak area ratios of analyte to IS. An S/N ratio of three and S/N ratio of ten was used for estimating lowest level of detection (LOD) and lowest level of quantification (LOQ), respectively (Tryptophan 10 μM/10 μM; L-kynurenine 0.1 nM/0.25 nM; QUIN 2.5 nM/5 nM; KYNA 0.1 nM-0.5 nM; PIC 1 nM/5 nM). Spiked CSF with all metabolites in two different concentrations was used as QC in order to test the accuracy and precision between plates. In accordance with the guidelines of bioanalytical method validation from EMA and the US FDA we accepted QC variations less than 15% and all values presented are within LOQ. For details of the method, see Schwieler et al., 2020.

2.5. Statistical analysis

All statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS) 25 for Mac and GraphPad Prism 8 for Mac. To evaluate the normal distribution, we used DAgostino and Pearson tests. Reported correlation coefficients are Spearman’s, two-tailed. Group analyzes were performed using Mann-Whitney U-tests, Chi-square tests, logistic regression analyzes or linear mixed model. Bonferroni correction was used to adjust for multiple comparisons (twelve tag SNPs) when analyzing the genetic data. Based on previous literature, we hypothesize that CSF KYNA is increased in subjects with bipolar disorder (Olsson et al., 2012; Lavebret et al., 2014; Sellgren et al., 2016; Sellgren et al., 2019) and that PIC is lower in patients with a history of suicide ideation (Bay-Richter et al., 2015; Schwieler et al., 2020). Therefore, we did not correct for multiple testing regarding kynurenine pathway metabolites.

All reported p-values, except for CSF PIC levels, are two-tailed. Data are expressed as Median ± InterQuartile Range (IQR). A statistical significance was considered when p<0.05.

3. Results

3.1. CSF levels of tryptophan metabolites

CSF tryptophan, kynurenine, KYNA, QUIN, and PIC were measured in 181 subjects; 101 patients with bipolar disorder (40 males, 61 females) and 80 healthy controls (39 males, 41 females). CSF concentrations of kynurenine, KYNA, PIC as well as the ratios kynurenine/tryptophan and PIC/QUIN were found to be significantly higher in subjects with bipolar disorder compared to healthy controls. A linear mixed-effects model was performed with log (metabolite concentration/ration) entered as dependent variable; diagnosis (healthy control or patient), age, and BMI entered as fixed-effects and nicotine as random-effect. Demographic and clinical characteristics are summarized in Table 1.

3.2. Association between pharmacological treatment and CSF tryptophan metabolites

3.2.1. Antidepressant drugs

Subjects with bipolar disorder treated with antidepressant drugs showed significantly higher CSF levels of kynurenine and KYNA, as well as higher kynurenine / tryptophan ratio compared to patients with bipolar disorder not using antidepressants (Kynurenine: logistic regression with dependent variable antidepressant use or not use, covariates age and BMI, β = 0.3, p = 0.02; KYNA: logistic regression with dependent variable antidepressant use or not use, covariate age, β = 0.92, p = 0.001; kynurenine/tryptophan: logistic regression with dependent variable antidepressant use or not use, covariate age, β = 0.06, p = 0.02). No differences were found for any other metabolite measured (tryptophan: Mann Whitney U test, p = 0.53; QUIN: logistic regression with dependent variable antidepressant use or not use, covariate age, β = 0.02, p = 0.45; PIC: Mann Whitney U test, p = 0.64; ratio PIC/QUIN: logistic regression with dependent variable antidepressant use or not use, covariate age β = 0.33, p = 0.39) (see Fig. 2).

3.2.2. Antipsychotic drugs

No differences in CSF tryptophan metabolites were found between subjects with bipolar disorder using, or not using, antipsychotic drugs (tryptophan: Mann Whitney U test, p = 0.59; kynurenine: logistic regression with dependent variable antidepressant use or not use, covariates age and BMI, β = -0.009, p = 0.45; KYNA: logistic regression with dependent variable antidepressant use or not use, covariate age, β = 0.001, p = 1.0; QUIN: logistic regression with dependent variable antidepressant use or not use, covariate age, β = 0.32, p = 0.20; PIC: Mann Whitney U test, p = 0.29; ratio kynurenine/ tryptophan: logistic regression with dependent variable antidepressant use or not use, covariate age, β = 0.008, p = 0.71; ratio PIC/QUIN: logistic regression with dependent variable antidepressant use or not use, covariate age, β = -0.43, p = 0.32).

3.2.3. Lithium

No differences in CSF tryptophan metabolites were found between subjects with bipolar disorder using, or not using, lithium (tryptophan: Mann Whitney U test, p = 0.15; kynure-
Table 1  Demographic and clinical characteristics of the study population.

| Characteristics   | Median (IQR) Healthy Controls (n = 80) | Bipolar disorder patients (n = 101) | P-value |
|-------------------|----------------------------------------|-------------------------------------|---------|
| Age (years)       | 33 (27.3–43.8)                         | 43 (35.5–54)                        | <0.0001 |
| Sex (male/female) | 39 / 41                                | 40 / 61                             | 0.22    |
| BMI (kg/m²)       | 23.48 (21.6–25.7)                      | 25.33 (22.4–38.8)                   | 0.003   |
| Nicotine (yes/no) | 17 / 63                                | 39 / 59                             | 0.008   |
| Bipolar I disorder|                                        | n = 45                              |         |
| Bipolar II disorder|                                      | n = 43                              |         |
| Bipolar disorder NOS |                                      | n = 5                               |         |
| Other diagnosis   |                                        | n = 7                               |         |
| Lithium           |                                        | 53%                                 |         |
| Topiramate        |                                        | 2%                                  |         |
| Clonazepam        |                                        | 2%                                  |         |
| Lamotrigine       |                                        | 14%                                 |         |
| Valproate         |                                        | 9%                                  |         |
| Stimulant medication |                                      | 17%                                |         |
| Antidepressant medication |                                | 42%                                |         |
| Anxiolytic medication |                                      | 18%                                |         |
| Antipsychotic medication |                                 | 33%                                |         |
| Sedative medication |                                      | 39%                                |         |
| Suicidal behavior (yes/no) |                              | 19 / 79                             |         |
| MADRS             | 0 (0–2) (80)                           | 2.5 (0–5.75) (98)                   | <0.0001 |
| YMRS              | 0 (0–0) (80)                           | 0 (0–1.75) (100)                    | <0.0001 |
| CSF Tryptophan (µM)| 1.5 (1.3–1.6) (80)                    | 1.4 (1.2–1.7) (99)                  | 0.73    |
| CSF Kynurenine (nM)| 32.9 (26.6–40.1) (80)                | 44.6 (32.5–62.1) (100)              | 0.06    |
| CSF KYNA (nM)     | 1.3 (0.9–1.7) (71)                     | 1.7 (1.2–2.4) (99)                  | 0.007   |
| CSF PIC (nM)      | 10.2 (6.6–14.0) (78)                   | 13.3 (8.3–19.8) (101)               | 0.001   |
| CSF QUIN (nM)     | 18.2 (13.4–23.2) (80)                  | 21.2 (15.4–29.1) (100)              | 0.48    |
| CSF kynurenine / tryptophan | 22.2 (18.6–26.8) (80) | 31.86 (23.0–39.8) (99)              | 0.04    |
| CSF PIC / QUIN    | 0.5 (0.3–0.9) (78)                     | 0.5 (0.4–1.0) (100)                 | 0.02    |

a Mann-Whitney test  
b Chi-square test  
c Linear Mixed Model.  
d Body mass index.  
e Information missing for 1 subject.  
f Information missing for 3 subjects.  
g Bipolar disorder not otherwise specified.  
h Suicide attempt or self-harm.  
i Montgomery-Åsberg Depression Rating Scale.  
j Young Mania Rating Scale.  
k Information missing for 2 subjects.  
l Information missing for 9 subjects.

Table 2  Distribution of mood episode history and duration of illness.

| Age of patients with BD | Number of mood episodes (median, IQR) | Duration of illness in years (median, IQR) |
|-------------------------|---------------------------------------|------------------------------------------|
|                         | Depressive  | Hypomanic | Manic   | Mixed  |                          |                          |
| <35 (n = 26)            | 8 (3–12.5) | 2 (0.5–5) | 1 (1–3.5) | 0 (0–0) | 17 (13.5–19) |                         |
| 36–50 (n = 41)          | 6 (3–17)  | 6 (2–29)  | 1 (1–4.25) | 0 (0–1) | 22 (19–25)  |                          |
| 51– (n = 34)            | 7 (3–14)  | 2.5 (0.25–8.75) | 1 (0–4) | 0 (0–0) | 35.5 (24.25–45.25) |                          |

nine: logistic regression with dependent variable antidepressant use or not use, covariate age and BMI, $\beta = 0.02$, $p = 0.16$; KYNA: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = 0.17$, $p = 0.38$; QUIN: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = 0.01$, $p = 0.54$; PIC: Mann Whitney U test, $p = 0.17$; ratio kynurenine/tryptophan: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = 0.02$, $p = 0.25$; ratio PIC/QUIN: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = -0.74$, $p = 0.07$.)
3.2.4. Lamotrigine

Lamotrigine was the only metabolite that was increased in the CSF of patients with bipolar disorder patients using lamotrigine, compared to those not using the drug (logistic regression with dependent variable antidepressant use or not use, covariates age and BMI, $\beta = 0.04, p = 0.03$). No differences in CSF tryptophan, KYNA, QUIN, PIC, ratio kynurenine/tryptophan and ratio PIC/QUIN were found between subjects with bipolar disorder using, or not using, lithium (tryptophan: Mann Whitney U test, $p = 0.07$; KYNA: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = 0.40, p = 0.13$; QUIN: covariate age, $\beta = -0.02, p = 0.64$; PIC: Mann Whitney U test, $p = 0.08$; ratio kynurenine/tryptophan: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = 0.03, p = 0.21$; ratio PIC/QUIN: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = 0.84, p = 0.09$).

3.2.5. Valproate

No differences in CSF tryptophan metabolites were found between subjects with bipolar disorder using, or not using lithium, (tryptophan: Mann Whitney U test, $p = 0.2$; kynurenine: logistic regression with dependent variable antidepressant use or not use, covariates age and BMI, $\beta = -0.006, p = 0.81$; KYNA: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = -0.08, p = 0.87$; QUIN: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = -0.18, p = 0.09$; PIC: Mann Whitney U test, $p = 0.32$; ratio kynurenine/tryptophan: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = -0.12, p = 0.82$; ratio PIC/QUIN: logistic regression with dependent variable antidepressant use or not use, covariate age, $\beta = 0.91, p = 0.13$).

3.3. Association between symptoms and CSF tryptophan metabolites

No correlations between MADRS score and any of the analyzed metabolites were found in subjects with bipolar disorder (tryptophan $r = -0.06, p = 0.57$; kynurenine $r = -0.12, p = 0.26$; KYNA $r = -0.07, p = 0.55$; QUIN $r = -0.19, p = 0.06$; PIC $r = -0.16, p = 0.12$; kynurenine/tryptophan $r = -0.14 p = 0.16$; PIC/QUIN $r = -0.08, p = 0.44$).

No correlations between YMRS score and any of the analyzed metabolites were found in subjects with bipolar disorder (tryptophan $r = 0.10, p = 0.35$; kynurenine $r = -0.002, p = 0.99$; KYNA $r = -0.12, p = 0.25$; QUIN $r = -0.02, p = 0.82$; PIC $r = 0.02, p = 0.87$; kynurenine/tryptophan $r = -0.01, p = 0.93$; PIC/QUIN $r = 0.02, p = 0.87$).

Number of depressed, manic, hypomanic and mixed episodes did not show any correlation with any of the kynurenine metabolites. Number of manic episodes showed a tendency towards negative correlation with the CSF levels of kynurenine, tryptophan, KYNA and QUIN, with no significant results.
of KYNA ($r = -0.21, p = 0.06$), but did not reach statistical significance.

### 3.4. Tryptophan metabolites in bipolar disorder patients with or without suicidal behavior

CSF levels of tryptophan were found to be higher (Mann Whitney U test, $p = 0.03$) while CSF PIC levels (Mann Whitney U test, $p = 0.048$) and the CSF kynurenine / tryptophan ratio (logistic regression with dependent variable patients with BD with or without suicide, covariates age and antidepressant use $\beta = -0.08, p = 0.04$) were found to be lower in bipolar disorder subjects with a history of suicidal behavior compared to subjects without any history of suicidal behavior. CSF levels of kynurenine ($\beta = -0.005, p = 0.72$), KYNA ($\beta = -0.48, p = 0.19$), QUIN ($\beta = -0.03, p = 0.42$), or the PIC/QUIN ratio ($\beta = -0.71, p = 0.88$) did not differ (logistic regression with dependent variable patients with BD with or without suicide, covariates age, BMI and antidepressant use) between subjects with and without a history of suicidal behavior (see Fig. 3).

### 3.5. Common genetic variation in ACMSD and suicidal behavior

We investigated the effects of common variants in ACMSD (twelve tag SNPs) on CSF PIC, CSF QUIN and the ratio PIC/QUIN in genotyped patients and controls ($n = 172$; 99 subjects with bipolar disorder and 73 healthy controls). Two SNPs (rs10928521 and rs6722883, minor allele frequency in Europe 0.2 and 0.1, respectively) associated to CSF PIC/QUIN ratio ($\beta = -1.6; p = 0.024$ and $\beta = -1.7; p = 0.0012$, Bonferroni corrected) and remained significant after adjustment for age and sex ($\beta = -1.7; p = 0.012; \beta = -1.6; p = 0.024$, Bonferroni corrected).

In bipolar disorder subjects with suicidal behavior ($n = 19$), linear regression analysis showed that one out of twelve SNPs (rs6722883) negatively associated with the CSF PIC/QUIN ratio (dependent variables: suicidal/no suicidal behavior; independent variable SNPs associated to the ratio PIC/QUIN, after adjustment for age, sex and Bonferroni correction: ($\beta = -1.77; p = 0.001$).

### 4. Discussion

In the present study, we analyzed five metabolites of the kynurenine pathway of tryptophan degradation (tryptophan, kynurenine, KYNA, QUIN, and PIC) in CSF from subjects with bipolar disorder and healthy controls. In line with our previous studies (Olsson et al., 2012; Sellgren et al., 2016; Sellgren et al., 2019), we found that CSF KYNA is increased in bipolar disorder subjects compared with controls. Consistently, patients also showed an increased CSF kynurenine/tryptophan ratio. CSF concentra-
tions of tryptophan did not differ between bipolar subjects and healthy controls, indicating that the induction of the pathway is not substrate-driven. Rather, present results support previous studies showing that the first and rate-limiting step in the pathway is induced and/or that the conversion of kynurenine towards 3-hydroxykynurenine in subjects with bipolar disorder is compromised. Thus, increased expression of the enzyme tryptophan-dioxygenase 2 (TDO2) (Miller et al., 2004) and reduced expression of kynurenine 3-monoxygenase (KMO) (Lavebatt et al., 2014) have previously been suggested to occur in subjects with bipolar disorder.

Furthermore, we found an increase in the CSF concentration of PIC, as well as in the ratio PiC/QUIN, in subjects with bipolar disorder. We have previously shown that brain immune markers, such as interleukin (IL)−1β and IL-8, are elevated in these patients (Söderlund et al., 2011; Isgren et al., 2015, 2017). Given that interferon-γ (IFN-γ) and IL-1β are potent inducers of IDO and TDO2, we hypothesize that the activation of the pathway is associated with immune activation of the brain. Yet another possible explanation may be related to a dysfunctional Hypothalamic-Pituitary-Adrenal (HPA) axis (Belvederi Murri et al., 2016) as glucocorticoids are essential regulators of TDO2 (Nakamura et al., 1987).

A second aim of the present study was to investigate if the kynurenine pathway metabolites correlated with depressive symptoms or the history of suicidal behavior. Previous studies from our group show that CSF QUIN levels are increased in suicide attempters at the time of a suicide attempt (Erhardt et al., 2013), whereas CSF PIC levels are reduced both at the time of attempt as well as several years after, indicating that low CSF PIC may constitute a marker of vulnerability for suicidal behavior (Brundin et al., 2016; Schwieler et al., 2020). Although CSF PIC levels were generally higher in patients with bipolar than healthy controls, we found that the PIC levels were significantly lower in bipolar disorder patients with previous suicidal behavior compared to those without. Compared to healthy controls, though, CSF PIC levels were not lower in bipolar disorder patients with previous suicidal behavior. CSF QUIN levels did not differ between bipolar disorder subjects with a history of suicidal ideation and those without. Importantly, the lumbar puncture of these patients was not performed in close proximity to a suicide attempt, as it was in our previous studies showing increased CSF QUIN in suicide attempters (Erhardt et al., 2013; Schwieler et al., 2020). Rather, in our current study, at least one year, but in some cases up to seven years, had passed since the last suicide attempt.

Suicide behavior was assessed by asking about any previous performed action of self-harm and/or suicide attempt. The answers were no / yes, and in case of patients responding yes, they were asked how many times. Thus, these results are in line with our longitudinal observations that a long-term reduction in PIC levels could be present in patients prone to suicidal behavior, and that high QUIN precedes acute suicidal behavior (Bay-Richter et al., 2015).

With regard to depressive symptoms, no correlations were found with any of the kynurenine metabolites. This could potentially be due to the fact that the bipolar subjects in our study were chiefly euthymic and took different medications to counteract their current symptoms.

An essential finding of the present study is the association between antidepressant treatment and increased CSF levels of kynurenine and KYNA, as well as lamotrigine use and increased CSF kynurenine levels. This is in line with rodent studies showing decreased KMO gene expression, increased astrocytic gene expression of both kynurenine aminotransferase (KAT) 1 and KAT 2, and reduced levels of brain QUIN in animals treated with antidepressants selectively blocking the reuptake of serotonin. Shifting the activity of the kynurenine pathway towards the production of the NMDA receptor antagonist KYNA at the expense of QUIN may indeed be part of the therapeutic effectiveness of antidepressants (Kocker et al., 2012; Eskelund et al., 2017).

In line with our recent publication (Brundin et al., 2016), tag SNP data was used to test the hypothesis that SNPs in the ACSMD gene region contributed to PIC and/or QUIN production. In the present study, we found a negative association between the ratio PIC/QUIN and the tag SNPs rs6722883 and rs10928521, supporting our previous results showing that certain polymorphisms of the ACSMD gene could be associated with excessive formation of QUIN, at the expense of PIC. In addition, chromium picolinate, which is a mix of the mineral chromium and PIC, has been shown to have positive effects on subjects with major depression, more specifically atypical depression (Davidson et al., 2003; Docherty et al., 2005). Although the purpose of those studies was not to increase PIC concentrations per se, the consecutive increase of the metabolite might partly explain the improvement of symptoms of the subjects.

In the present study, positive correlations between age and levels of CSF kynurenine, CSF KYNA, CSF PIC, and CSF QUIN were found. These data are in line with previous studies (Erhardt et al., 2001; Coggan et al., 2009; Erhardt et al., 2013; de Bie et al., 2016; Sorgdrager et al., 2019) showing that the activity of the kynurenine pathway increases with age, a phenomenon suggested being mechanistically linked to increased inflammatory signaling (de Bie et al., 2016). Furthermore, sex was also found to be associated with CSF concentration of kynurenines. Thus, the concentrations of CSF kynurenine and CSF PIC were higher in males than in females. This may be explained by the fact that females, on average, are shorter than males and that metabolites in the CSF generally display a rostrocaudal concentration gradient (Sjöström et al., 1975; Bertilsson et al., 1982; Tarnaris et al., 2011). In a previous study, we have found that CSF KYNA levels negatively correlated with back length (Nilsson et al., 2007). Present results, taken together with previous studies, imply that both age and sex are relevant confounding factors that must be taken into account when evaluating CSF kynurenine metabolites.

In conclusion, the results of the present paper confirm activation of the brain kynurenine pathway, reflected by increased CSF KYNA and CSF PIC as well as increased ratios of kynurenine/tryptophan and PIC/QUIN in patients with bipolar disorder. Furthermore, in support of the hypothesis that low PIC levels may indicate vulnerability to suicidal ideation, we found that CSF PIC was lower in bipolar disorder patients with a history of suicidal behavior compared to patients without. We also confirm that genetic variance in the enzyme ACSMD associates with the ratio PIC/QUIN. Thus, targeting the ACSMD enzyme or give supplement containing PIC and thus substituting for the low PIC levels might...
constitute potential therapeutic approaches in suicidal behavior.

Declaration of Competing Interest
C.M.S. is a scientific adviser for Outermost Therapeutics (of no relevance to this work). S.E. discloses grant support from AstraZeneca and Jansen Pharmaceuticals as principal investigator and has been a speaker for Roche Pharmaceuticals, AstraZeneca, Eli Lilly, Orion Corporation Orion Pharma and Bristol Myers Squibb (none of these are relevant to this work). The remaining authors declare that they have no conflict of interest.

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Contributors
ML and SE designed the study. LS, EP, CS, NK and AT performed the experiments and collected the data. SE, LS, LB and AT interpreted the data and wrote the article. All authors contributed with critical review of the manuscript and approved the final version.

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Supplementary materials
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