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Tryptophan *via* serotonin/kynurenine pathways abnormalities in a large cohort of aggressive inmates: markers for aggression

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ABSTRACT

Aggressive behavior is one of the most challenging symptoms in psychiatry, and biological markers for aggression lack of large sample validations. Serotonin (5-HT) and other neuroactive compounds deriving from Tryptophan (Trp), including kynurenine (Kyn), have not yet been investigated in large cohorts of aggressive individuals to validate their potential as biomarkers of aggression.

In 361 male inmates we measured serum levels of Trp, 5-hydroxytryptophan, 5-HT, Kyn, the ratios 5-HT/Trp * 1000 and Kyn/Trp * 1000, and performed Structured Clinical Interview for DSM-IV Axis-I and -II Disorders (SCID-I and -II), global assessment of functioning (GAF), and scales for aggressive behavior, impulsivity, adult attention-deficit/hyperactivity disorder (ADHD), and intelligent quotient (IQ).

Aggressive compared to non-aggressive inmates exhibited lower Trp and Kyn serum levels but higher levels of 5-HT and 5-HT/Trp * 1000, higher levels of impulsivity and ADHD indices, lower IQ and GAF, higher prevalence of mood disorders, drug abuse/dependence, and borderline, conduct and antisocial behaviors. Interestingly, Kyn/Trp * 1000 was positively correlated to the number of severe aggressive acts ($r = 0.593$, $P < 0.001$). After adjusting for confounding factors, logistic regression analysis indicated that 5-HT/Trp * 1000, antisocial behavior, and GAF were predictors of aggressive behavior. The model combining these three predictors had an area under the ROC curve of 0.851 (95% CI 0.806–0.895).

This study indicates that while circulating Trp is reduced in aggressive individuals, the combination of biological (5-HT/Trp ratio) and psychopathological (antisocial behavior and GAF) markers discriminates between aggressive and non-aggressive behavior suggesting the potential of a multi-marker approach in psychiatry given the heterogenic nature of mental diseases.

1. Introduction

According to the World Health Organization, injuries and violence are a threat to health in every country of the world (Krug et al., 2002). Aggressive behavior is therefore a major concern in social and criminal justice settings and in mental health (Cornaggia et al., 2011). Until now, while the psychopathological risk factors for aggression have been largely investigated (Comai et al., 2012a; Siever, 2008), the biological factors are still matter of debate. Most importantly, the relationship between neurobiological and psychosocial factors at the basis of aggressive behavior is not yet elucidated by basic and clinical research (Comai et al., 2012a) due to a lack of large cohort studies and interdisciplinary approaches. The essential amino acid tryptophan (Trp) is not only the precursor of serotonin (5-HT) but is also degraded to other

Abbreviations: Trp, Tryptophan; 5-HTP, 5-hydroxytryptophan; 5-HT, serotonin; Kyn, kynurenine; BBB, blood–brain barrier; TDO, tryptophan 2,3-dioxygenase; IDO, indoleamine 2,3-dioxygenase; MacCVI, MacArthur Community Violence Instrument; LSARS, Lethality of Suicide Attempt Rating Scale; SCID-I, Structured Clinical Interview for DSM-IV Axis-I Disorders; SCID-II, Structured Clinical Interview for DSM-IV Axis-II Disorders; GAF, global assessment of functioning; ASPD, antisocial personality disorder; BIS, Barratt Impulsiveness Scale; CAARS, Conners' Adult ADHD Rating Scale; IQ, Intelligence quotient.

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neuroactive compounds, including the neurotoxic quinolinic acid and the neuroprotective kynurenic acid, along the enzymatic cascade known as kynurenine (Kyn) pathway (Schwarcz et al., 2012) (Fig. 1). The first step of this pathway is regulated by the tryptophan 2,3-dioxygenase (TDO) and indoleamine 2,3-dioxygenase (IDO) enzymes (Schwarcz et al., 2012). The ratio Kyn/Trp is currently used as a good estimate of IDO enzymatic activity (Comai et al., 2011; Myint and Kim, 2014; Schwarcz et al., 2012). While 5-HT is not able to cross the blood–brain barrier (BBB) and therefore total 5-HT serum levels could not be used as indices of central 5-HT activity, its precursor Trp crosses the BBB *via* the large neutral amino acid transporter (Fernstrom and Wurtman, 1971). However, this issue needs to be clarified since it has been demonstrated that in case of augmented brain 5-HT levels, 5-HT can cross the BBB from the brain to the circulating blood through the 5-HT transporter (Nakatani et al., 2008). In any case, peripheral levels of 5-HT although not linked to brain 5-HT can be interesting markers of disease and/or response to treatment (Comai et al., 2010; Fontana et al., 2008; Freedman et al., 1981; Irwin et al., 1981). Research has shown that total peripheral Trp concentrations accurately reflect the rate of influx of Trp and thus 5-HT levels into the brain (Comai et al., 2011; Fernstrom and Wurtman, 1971), and that fluctuations in the blood levels of both Trp and Kyn, which also crosses the BBB, directly affect the metabolism of the Kyn pathway in the brain (Fukui et al., 1991). Dysregulation of both 5-HT and Kyn pathways, resulting in hyper- or hypo-function of active metabolites, has been associated to several psychiatric and neurodegenerative disorders (Brown et al., 1982; Comai et al., 2012a; Hanley et al., 1977; Schwarcz et al., 2012). 5-HT is the most studied neurotransmitter related to the pathophysiology of aggression (Brown et al., 1982, 1979; Coccaro, 1992; Linnoila and Virkkunen, 1992) and one of the targets of anti-aggressive medications (Comai et al., 2012b). In general, the dogmatic view of a low 5-HT activity linked to aggression (Brown et al., 1979; Coccaro, 1992; Linnoila and Virkkunen, 1992) appears true only for certain type of aggressive behavior such as impulsive aggression, defined as a disproportionate reaction to any provocation, real or perceived (Coccaro, 1992). Indeed, functional aggression, a natural form of social behavior aimed at the establishment of a territory, social dominance and defense of resources, seems positively associated to 5-HT function (de Boer and Koolhaas, 2005). Similarly, the question of whether the precursor of 5-HT, Trp, is altered in aggressive or suicidal individuals is still controversial. Several studies have indicated that a Trp depletion may lead to increased aggression (Cleare and Bond, 1995; LeMarquand et al., 1999; LeMarquand et al., 1998), but other research examining the plasmatic levels of Trp found elevated levels of the amino acid associated with the presence of antisocial (Tiihonen et al., 2001; Virkkunen and Narvanen, 1987) and conduct (Virkkunen et al., 2003) violent behaviors.

Therefore, the complex neurobiology of aggression, 5-HT and Trp needs clarifications and especially lacks of large cohort human studies. The role of Kyn in mood disorders and neurodegenerative diseases has been already investigated (Schwarcz et al., 2012), but no studies have yet examined its possible involvement in aggression. Here, we studied for the first time both Trp metabolic pathways in aggression, in particular severe aggression meant as the intent to seriously harm or kill others or themselves, because by sharing the same precursor, impairments in the 5-HT pathway may be the cause or the consequence of impairments in the Kyn pathway and *viceversa*. In this study, we thus filled this gap in knowledge by showing in a large cohort of severe aggressive and non-aggressive inmates that peripheral levels of Trp and its metabolites *via* 5-HT and Kyn were different comparing severe aggressive *versus* non-aggressive individuals and most importantly, that 1) they correlated to psychopathological features previously associated to aggression and 2) combined with psychopathological features they became markers of aggressive behavior.

2. Materials and methods

2.1. Participants

Participants were recruited in a federal penitentiary in Montreal, Quebec, Canada, between October 2007 and November 2011. Venous blood samples were withdrawn between 8:00 and 10:00 a.m. after an overnight fasting, allowed to clot at room temperature and centrifuged at 3000 *g* for 10 min. The obtained serum was stored at −80°C. The study was approved by the Ethical Review Boards of the Institut Philippe-Pinel de Montréal, McGill University and Université du Québec à Trois-Rivières, and by Correctional Service Canada, and followed the principles of the Helsinki Declaration. All participants, after adequate information, gave their written consent.

2.2. Biological assessment

2.2.1. Serum levels of Trp, 5-hydroxytryptophan (5-HTP), 5-HT and Kyn

Compounds were quantified following the method of Comai et al. (2011) Trp, 5-HTP and 5-HT were analyzed using a high performance liquid chromatography (HPLC) system equipped with a Shimadzu RF-10 AXL fluorometric detector set at excitation and emission wavelengths of 285 and 345 nm, respectively, and an analytical Platinum EPS-C18 100 A column (5 μm; 250 mm × 4.6 mm; Alltech, Deerfield, IL). Kyn was determined using a HPLC equipped with a Shimadzu SPD-10 A UV–Vis detector set at 360 nm and an analytical Grace Smart RP-18 column (5 μm; 250 mm × 4.6 mm; Alltech). The chromatographic separation was conducted using an isocratic gradient of acetonitrile-phosphate buffer 0.004 M, pH 3.5.

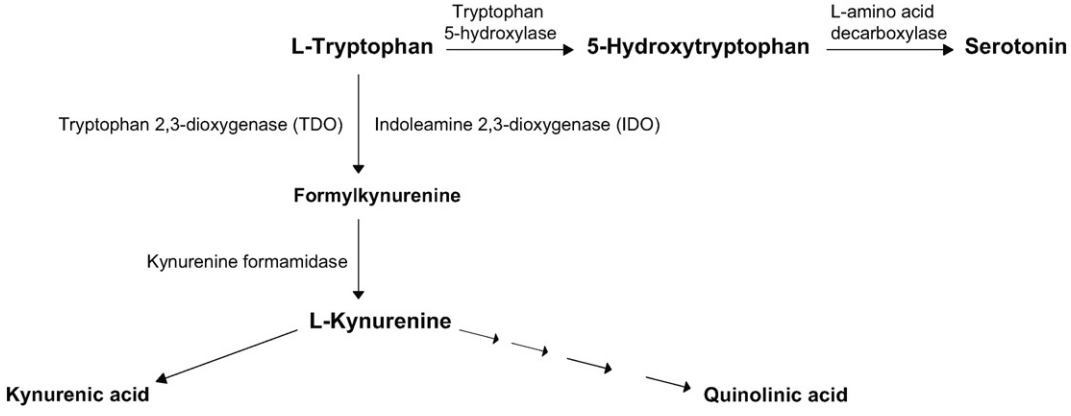

Fig. 1. Schematic diagram of the tryptophan metabolism *via* serotonin and kynurenine.