Psychoneuroendocrinology (2015) 52, 200—211

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/psyneuen

Neuroprotective kynurenine metabolite indices are abnormally reduced and positively associated with hippocampal and amygdalar volume in bipolar disorder

Jonathan Savitz[a,b,*], Robert Dantzer[c], Brent E. Wurfel[a], Teresa A. Victor[a], Bart N. Ford[a], Jerzy Bodurka[a,d], P.S.F. Bellgowan[a,b], T. Kent Teague[e,f,g], Wayne C. Drevets[h]

[a] *Laureate Institute for Brain Research, Tulsa, OK, USA*
[b] *Faculty of Community Medicine, University of Tulsa, Tulsa, OK, USA*
[c] *Division of Internal Medicine, Department of Symptom Research, MD Anderson Cancer Center, Houston, TX, USA*
[d] *College of Engineering, University of Oklahoma, Tulsa, OK, USA*
[e] *Departments of Surgery and Psychiatry, University of Oklahoma College of Medicine, Tulsa, OK, USA*
[f] *Department of Pharmaceutical Sciences, University of Oklahoma College of Pharmacy, Tulsa, OK, USA*
[g] *Department of Biochemistry and Microbiology, Oklahoma State University Center for Health Sciences, Tulsa, OK, USA*
[h] *Janssen Pharmaceuticals of Johnson & Johnson, Inc., Titusville, NJ, USA*

Received 17 September 2014; received in revised form 30 October 2014; accepted 17 November 2014

KEYWORDS
Bipolar disorder;
Inflammation;
Kynurenine;
Quinolinic acid;
Magnetic resonance imaging;
Hippocampus

Abstract Inflammation-related changes in the concentrations of kynurenine-pathway metabolites occur in depression secondary to medical conditions but have not been well characterized in primary bipolar disorder (BD), with contradictory results potentially attributable to the presence or absence of psychosis and/or medication effects. In contrast, reductions in hippocampal and amygdalar volume that theoretically reflect dendritic atrophy occurring in the context of a neurotoxic process are commonly reported in unmedicated BD patients. Here we tested whether the concentrations of putatively neuroprotective (kynurenic acid, KynA) and neurotoxic (3-hydroxy-kynurenine, 3HK and quinolinic acid, QA) kynurenine-pathway metabolites were altered in primary BD and whether these metabolites were associated with hippocampal and amygdalar volume. Twenty-five moderately-to-severely depressed unmedicated subjects and 38 moderately-to-severely depressed medicated subjects who met DSM-IV-TR criteria for BD, as well as 48 healthy controls (HCs) completed a structural MRI scan and provided a blood sample

* Corresponding author at: Laureate Institute for Brain Research, 6655 S. Yale Ave, Tulsa, OK 74136, USA. Tel.: +1 918 502 5104; fax: +1 918 502 5135.
E-mail address: jsavitz@laureateinstitute.org (J. Savitz).

http://dx.doi.org/10.1016/j.psyneuen.2014.11.015

for kynurenine metabolite analysis, performed using high performance liquid chromatography with tandem mass spectrometry. Gray matter volumes were measured with the automated segmentation software, FreeSurfer. A putative neuroprotective index, KynA/QA, was significantly lower in the BD subjects relative to the HCs, a finding that was unrelated to current treatment with medication or a prior history of psychosis. Further, another putative neuroprotective index, KynA/3HK was positively associated with hippocampal volume in the BD group after controlling for age, sex, body mass index (BMI), and intracranial volume (ICV). Kyn/3HK was significantly associated with total amygdalar volume in the BD group, but after controlling for age, sex, BMI, but not ICV, this association was reduced to a trend. In addition, Kyn/3HK was positively associated with amygdalar volume in the HCs although the association was no longer significant after accounting for the effects of age, sex, and BMI. The results raise the possibility that BD-associated abnormalities in kynurenine metabolism may impact the structure of the hippocampus and amygdala, highlighting a pathway through which inflammation may exert neuropathological effects in the context of depression.

1. Introduction

The phenomenological overlap between the behavioral changes observed in humans and animals suffering from infection (e.g. anhedonia, fatigue, sleep disturbances, and the desire for social isolation, a.k.a. sickness behavior) and certain symptoms of idiopathic major depression led to the hypothesis that the peripheral immune system communicates with the central nervous system (CNS) to modulate emotions and behavior, and that immunological dysregulation may be an important component of primary mood disorders (Dantzer et al., 2008). Immune mediators may affect neuronal functions directly or indirectly via alterations in the balance between potentially neuroprotective and neurotoxic kynurenine metabolites as a result of the activation of the kynurenine metabolism pathway (Fig. S1) (Dantzer et al., 2011; Miller et al., 2009; Schwarcz et al., 2012).

One of these kynurenine metabolites, quinolinic acid (QA), is a known neurotoxin that is produced in the brain by microglia and infiltrating macrophages QA activates *N*-methyl-D-aspartate (NMDA) receptors and additionally exerts neurotoxic effects via lipid peroxidation, and disruption of the blood-brain barrier (Schwarcz et al., 2012; Stone et al., 2012). Further, QA has the ability to initiate an inflammatory response or augment existing disease-associated inflammation by enhancing the production of pro-inflammatory proteins (Stone et al., 2013). Elevated concentrations of QA have been reported in both the serum and the cerebrospinal fluid (CSF) of patients with neurodegenerative and inflammatory disorders such as Alzheimer's disease and (AD) and systemic lupus erythematosus patients with neuropsychiatric symptoms (Ting et al., 2009; Vogelgesang et al., 1996).

Another kynurenine metabolite produced by macrophages and microglia that may have neurotoxic properties is 3HK, a free radical generator. In vitro work has demonstrated that the administration of pharmacological doses of 3-hydroxy-kynurenine (3HK) may kill hippocampal neurons (Okuda et al., 1996) and cortical neurons (Chiarugi et al., 2001), perhaps explaining why levels of 3HK have been reported to be elevated in the serum of AD patients (Schwarz et al., 2013) and in the brains of Parkinson's disease (PD) (Ogawa et al., 1992) patients *postmortem*.

In contrast, kynurenic acid (KynA) is a pleiotropic astrocyte-derived metabolite that at least in vitro, acts as an endogenous competitive *antagonist* of all ionotrophic excitatory amino acid receptors including the NMDA receptor (Birch et al., 1988). In addition, KynA is an α7 nicotinic receptor *antagonist*, an orphan G-protein-coupled receptor (GPR35) *agonist*, an aryl hydrocarbon receptor (AHR) *agonist*, and an enhancer of nerve growth factor (NGF) expression, potentially regulating the inflammatory response together with glutamatergic, cholinergic, and dopaminergic neurotransmission (Stone et al., 2013). Inducing an elevation in peripheral KynA by blocking the enzyme, kynurenine 3-monooxygenase (*KMO*), in mouse models of AD and Huntington's disease (HD) suppresses microglial activation, limits neuronal and synaptic loss, improves memory, alleviates anxiety, and extends lifespan possibly by decreasing QA concentrations and/or glutamate-induced excitotoxicity (Zwilling et al., 2011). Similarly, pharmacological inhibition of *KMO* is neuroprotective in animal models of cerebral ischemia (Moroni et al., 2003), a genetic reduction in KynA production increases vulnerability to excitotoxic insults (Sapko et al., 2006), while in humans, reduced concentrations of KynA have been reported in the CSF of MS patients (Rejdak et al., 2002). These data have led to a heuristic model that regards 3HK and QA as potentially neurotoxic and KynA as potentially neuroprotective (Amaral et al., 2013; Stone et al., 2012).

Because the various kynurenine metabolites impact the brain differently, their concentrations may be better expressed as ratios of neuroprotective to neurotoxic metabolites or neurotoxic to neuroprotective metabolites rather than as absolute values. Our previous work provided some support for this model in the context of primary mood disorders. In a morphometric MRI study, we reported a positive correlation between the KynA/QA ratio, a putative neuroprotective index (Johansson et al., 2013; Kocki et al., 2012), and total gray matter (GM) volumes of the hippocampus and amygdala in unmedicated patients with MDD but not in healthy controls (Savitz et al., 2014). Histopathological studies of rodents and humans (Cobb et al., 2013; Duric et al., 2013) indicate that reductions in GM volume of brain