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Purine metabolism is dysregulated in patients with major depressive disorder

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ABSTRACT

Introduction: The purine cycle and altered purinergic signaling have been suggested to play a role in major depressive disorder (MDD). Nevertheless, data on this topic are scarce. Based on previous studies, we hypothesized that compared with non-depressed controls, MDD patients have distinct purine metabolite profiles.

Methods: The samples comprised 99 MDD patients and 253 non-depressed controls, aged 20–71 years. Background data were collected with questionnaires. Fasting serum samples were analyzed using ultra-performance liquid chromatography coupled to mass spectrometry (UPLC–MS) to determine seven purine cycle metabolites belonging to the purine cycle. We investigated the levels of these metabolites in three settings: (1) MDD patients vs. non-depressed controls and (2) remitted vs. non-remitted MDD patients, and also (3) within-group changes in metabolite levels during the follow-up period.

Results: In logistic regression adjusted for age, gender, smoking, alcohol use, physical exercise, glycosylated hemoglobin, and high-density lipoprotein cholesterol, lower levels of inosine (OR 0.89, 95% CI 0.82–0.97) and guanosine (OR 0.32, 95% CI 0.17–0.59), and higher levels of xanthine (OR 2.21, 95% CI 1.30–3.75) were associated with MDD vs. the non-depressed group. Levels of several metabolites changed significantly during the follow-up period in the MDD group, but there were no differences between remitted and non-remitted groups.

Conclusions: We observed altered purine metabolism in MDD patients compared with non-depressed controls. Furthermore, our observations suggest that circulating xanthine may accumulate in MDD patients.

1. Introduction

Dysregulation of the purine cycle may be of relevance in major depressive disorder (MDD), a condition that is a major public health concern. In addition, altered metabolic activity of the purine cycle has been linked with several MDD-related systemic responses such as increased pro-inflammatory and oxidative processes (Kaddurah-Daouk et al., 2013, 2011). In the purine cycle, the purine nucleotides adenosine monophosphate (AMP), inosine 5-monophosphate (IMP), xanthine monophosphate (XMP), and guanosine monophosphate (GMP) are converted to uric acid, a potent antioxidant (Davies et al., 1986) (Fig. 1). Lowered plasma and serum levels of uric acid have been observed in MDD (Chaudhari et al., 2010; Kesebir et al., 2014; Wen et al., 2012). Moreover, lower cerebro-spinal fluid (CSF) levels of hypoxanthine and xanthine, the two metabolites preceding uric acid, have previously been linked with depression (Agren et al., 1983). Additionally, some studies have indicated a correlation between CSF levels of purine metabolites and monoamine metabolites such as homovanillic acid and 5-hydroxyindoleacetic acid, suggesting the parallel metabolism of purines and monoamines in the brain (Kaddurah-Daouk et al.,

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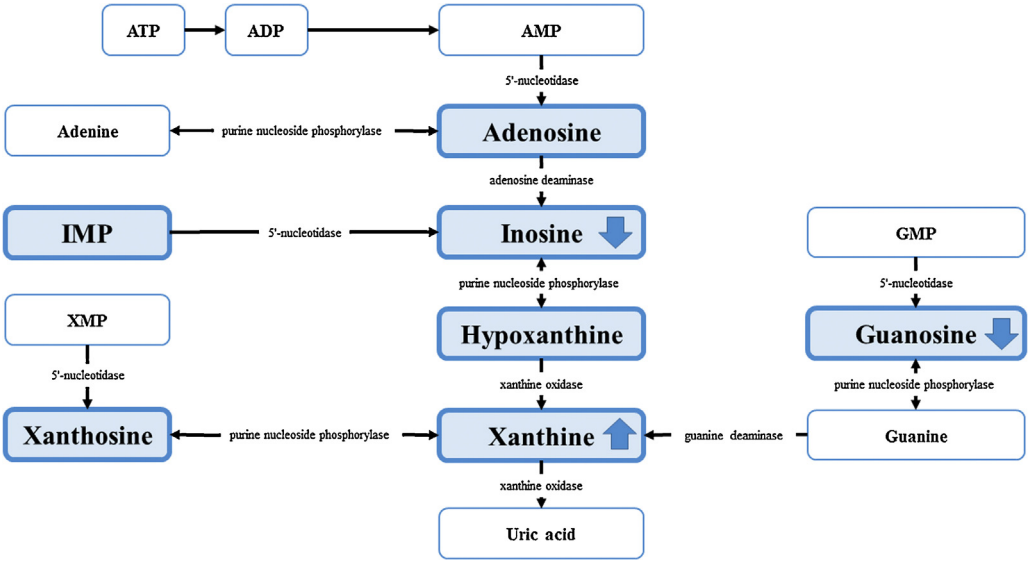

Fig. 1. Analyzed metabolites are marked with a darker shade. Arrows represent the levels of the metabolites in the MDD group compared to the non-depressed control group.

2012; Niklasson et al., 1983). Nevertheless, some other studies have failed to support the possible role of the purine cycle in MDD. (Steffens and Jiang, 2010) found no differences in the plasma levels of purine metabolites between depressed and non-depressed patients with heart failure. Similarly, no differences in CSF levels of purine metabolites were detected between individuals with current MDD, remitted MDD, and no MDD (Kaddurah-Daouk et al., 2012).

One of the purine cycle nucleosides, adenosine (the dephosphorylation product of AMP), has widespread neuromodulatory effects in the central nervous system (CNS). In conditions of increased energy need, activation of adenosine A1 receptors leads to inhibition of the neural release of glutamate, dopamine, serotonin, and acetylcholine (Abbracchio et al., 1995; Boison, 2008, 2007; Cunha, 2005). In addition to the CNS, adenosine receptors are systemically expressed, and their activation in the immune system suppresses the secretion of pro-inflammatory cytokines (Haskó et al., 2008), which have been implicated in the pathophysiology of depression (Woo et al., 2015).

Other nucleosides of the purine cycle, inosine and guanosine, also have systemic effects. For example, inosine and guanosine exert an anti-depressive effect by modulating NMDA receptors (Kaster et al., 2013, 2012). Moreover, both of these metabolites have systemic anti-inflammatory effects (Haapakoski et al., 2011; Jiang et al., 2007; Liaudet et al., 2001). Hypoxanthine, xanthine, and uric acid are the three final metabolites of the purine cycle. The conversion of hypoxanthine to xanthine, and xanthine to uric acid, is catabolized by the enzyme xanthine oxidase (XO). Interestingly, MDD patients have displayed elevated levels of XO and adenosine deaminase (ADA), another important enzyme of the purine cycle (Herken et al., 2007). To our best knowledge, no direct information on the blood–brain barrier (BBB) permeability of these purine metabolites is available. However, it is probable that serum levels of measured purine metabolites are correlated with CSF levels, as inosine and uric acid have been demonstrated to the permeate the BBB (Bowman et al., 2010; Levine and Morley, 1982). All intermediates of the purine cycle are closely related to either uric acid or inosine in their molecular structure. Moreover, caffeine, which closely resembles adenosine and binds to the same receptors, also permeates the BBB (McCall et al., 1982).

In order to further clarify the role of purine metabolism in MDD, the aim of the present study was to compare the serum levels of 7 metabolites relevant to purine metabolism (i.e., inosine, xanthine, guanosine, hypoxanthine, xanthosine, adenosine, and IMP) (1) between an MDD group and a non-depressed group, (2) with regards to the remission status of the MDD group, and (3) longitudinally within the remitted and non-remitted groups. We hypothesized that we would observe findings suggesting (1) increased activity of the purine cycle (i.e. decreased levels of adenosine, hypoxanthine, and xanthine; increased levels of inosine) during depression and (2) normalized activity of the purine cycle in the remitted (i.e. similar levels of the measured purine metabolites to the non-depressed control group), but not in the non-remitted group.

2. Methods

2.1. Study samples

The present study utilized two sample sets: (1) a naturalistic follow-up study sample of patients with MDD (i.e., the NeuroDep Study) and (2) a general population-based sample of non-depressed individuals (i.e., the Lapinlahti Study). The age distribution of all the participants was 20–71 years. Both studies were approved by the Ethics Committee of Kuopio University Hospital. All participants gave written informed consent before entering the study. Both of the used study samples represent the same population, and Kuopio University Hospital serves the municipality area of Lapinlahti.

2.1.1. Patient sample set (the NeuroDep Study)

The study sample set consisted of 99 outpatients with MDD recruited from the Department of Psychiatry at Kuopio University Hospital. At baseline, the diagnosis of MDD was confirmed by using the structured clinical interview for DSM-IV (SCID) (DSM-IV; American Psychiatric Association, 1994). Of the initial 99 patients, 78 participated in the follow-up study (mean follow-up time 8 months; range 5–13 months). We observed no differences in age ($p = 0.152$), sex ($p = 0.663$), marital status ($p = 0.575$), alcohol use ($p = 0.324$), smoking ($p = 0.964$), regular exercise ($p = 0.964$), or BDI scores ($p = 0.493$) between the individuals who continued to participate in the study and those who did not.

All participants gave venous blood samples at baseline and on follow-up. The initial exclusion criteria consisted of epilepsy,