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Research paper

Uric acid in major depressive and anxiety disorders

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ABSTRACT

Background: Uric acid has neuroprotective effects, owing to its antioxidant properties. Lowered antioxidant capacity, causing increased oxidative stress, may be involved in affective disorders and might be altered by antidepressants. This study investigated the association of plasma uric acid, the greatest contributor to blood antioxidant capacity, with major depressive disorder (MDD) and anxiety disorders.

Methods: Data were from the Netherlands Study of Depression and Anxiety including patients with current (N = 1648), remitted (N = 609) MDD and/or anxiety disorders (of which N = 710 antidepressant users) and 618 controls. Diagnoses were established with the Composite International Diagnostic Interview. Symptom severity was assessed with the Inventory of Depressive Symptoms-Self Report, Beck Anxiety Inventory and Fear Questionnaire. Uric acid was measured in plasma. Analyses were adjusted for sociodemographic, health and lifestyle variables.

Results: Plasma uric acid adjusted mean levels were lower in current MDD and/or anxiety disorder(s) (289 μmol/l) compared to remitted disorders (298 μmol/l, $p < .001$) and controls (299 μmol/l, $p < .001$; Cohen's d .10). This finding was independent of antidepressant use. Depressive (β-.05, $p = .0012$), anxiety (β-.04, $p = .009$) and phobic (β-.03, $p = .036$) symptom severity, and symptom duration (β-.04, $p = .009$) were negatively associated with uric acid.

Limitations: Limitations include the lack of data on dietary intake which could be a potential confounding factor. From these cross-sectional findings, the association between uric acid and psychopathology cannot be inferred to be causal.

Conclusion: This large scale study finds plasma uric acid levels are lower in current, but not remitted, MDD and/or anxiety disorders, according to a dose-response gradient. This suggests the involvement of decreased antioxidant status in affective disorders, and points to their potential as an avenue for treatment.

1. Introduction

Uric acid is the end product of purine metabolism, which breaks down the nucleosides adenosine and guanosine. It is best known for its central role in the pathophysiology of gout, but higher uric acid has also been reported in metabolic syndrome (Yuan et al., 2015) and cardiovascular disease, and is associated with mortality risk (Zhao et al., 2013). However, uric acid's role in health and disease is multifaceted, and there are indications it also has health promoting qualities.

Higher uric acid has been associated with a reduced risk of developing neurological disorders, such as Parkinson's disease (Weisskopf et al., 2007). In multiple sclerosis uric acid is decreased and decreases further as the disease progresses (Moccia et al., 2015). In cognitive impairment (Irizarry et al., 2008) higher uric acid has been associated with a slower rate of decline.

These findings suggest uric acid has neuroprotective effects, owing to its potent antioxidant capacity. Uric acid contributes to over half of plasma antioxidant capacity (Ames et al., 1981) as a free-radical scavenger. It may be a particularly important central nervous system (CNS) antioxidant, due to its stabilizing effect on a second antioxidant, ascorbic acid, which is abundant in neurons (Bowman et al., 2010). Uric acid therefore could be especially significant in depression and anxiety disorders, which have been associated with increased oxidative stress (Black et al., 2015). Major depressive disorder (MDD) and anxiety disorders are the most prevalent psychiatric disorders (Kessler et al., 2005), and very often co-occur, with a comorbidity rate of around 60% (Lamers et al., 2011). Together they account for extensive morbidity worldwide (Whiteford et al., 2013). Their pathophysiology is still only partially understood. Oxidative stress has been suggested as a mechanism, and increased oxidative damage and lower levels of

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Table 1
Sample characteristics of controls, subjects with remitted MDD and/or anxiety disorder(s) and subjects with current MDD and/or anxiety disorder(s).

		Control subjects N 618 Mean (SD) Median (IQR) % "yes"	Subjects with remitted MDD and/or anxiety disorder (s) N 609 Mean (SD) Median (IQR) % "yes"	Subjects with current MDD and/or anxiety disorder (s) N 1648 Mean (SD) Median (IQR) % "yes"	p[a]
Demographics					
Age		41.1 (14.8)	44.4 (13.0)	41.2 (12.4)	< .001
Sex (female)		60.7%	69.6%	66.9%	.003
Years of education		12.8 (3.2)	12.5 (3.3)	11.8 (3.3)	< .001
Lifestyle					
Plasma cotinine ng/ml		.9 (.9–8.0)	1.0 (.9–89.0)	2.0 (.9–150.0)	< .001
Alcohol use	none/mild	23.0%	27.3%	36.9%	
	moderate	65.4%	61.1%	51.6%	
	heavy	11.7%	11.7%	11.5%	< .001
Supplement use		10.4%	11.7%	12.3%	.433
Physical activity (100 MET-min/wk)		28.5 (16.3–48.9)	28.5 (16.8–50.9)	27.9 (13.8–47.5)	.002
Body mass index (kg/m2)		25.0 (4.6)	25.9 (4.7)	25.7 (5.3)	.006
Metabolic syndrome (MetS)		19.1%	21.2%	22.0%	.329
Number of chronic diseases	0	64.1%	58.5%	55%	
	1	26.2%	86.7%	84.5%	
	≥ 2	.7%	13.3%	15.5%	< .001
Estimated GFR (ml/min/1.73 m^2)		104 (17)	101 (15)	105 (16)	< .001
Salicylate use		4.9%	5.9%	5.2%	.697
Cardiac medication use[b]		14.4%	16.1%	14.6%	.637
Antidepressants, symptom severity					
Antidepressant use	None	N.A.	86.5%	61.9%	
	SSRIs	N.A.	10.5%	25.4%	
	TCAs	N.A.	1.6%	4.1%	
	other AD	N.A.	1.3%	8.6%	< .001
Depressive symptoms (IDS)		8.4 (7.4)	14.3 (9.0)	29.2 (12.5)	< .001
Anxiety symptoms (BAI)		4.0 (4.8)	7.2 (6.5)	17.1 (10.8)	< .001
Phobic symptoms (FQ)		11.8 (12.1)	16.7 (13.0)	33.1 (20.7)	< .001
Duration of symptoms (% time with symptoms in the past 4 years)		N.A.	14.4 (23.3)	51.5 (36.2)	< .001
Plasma uric acid (μmol/l)		271 (71)	267 (71)	257 (71)	< .0001

[a] Reported values are p values for overall between group differences for Kruskal-Wallis tests and ANOVA.
[b] including antihypertensive drugs, diuretics, peripheral vasodilators, beta-blocking agents, calcium channel blockers and agents acting on the renin-angiotensin system. AD = antidepressants; BAI = Beck Anxiety Inventory; FQ = Fear Questionnaire; GFR = glomerular filtration rate; IDS = Inventory of Depressive Symptomatology; IQR = inter quartile range; N = number; MDD = major depressive disorder SD = standard deviation; SSRIs = selective serotonin re-uptake inhibitors; TCAs = tricyclic antidepressants; u/wk = units per week; yrs = years.

antioxidants (Black et al., 2015; Hovatta et al., 2010; Jiménez-Fernández et al., 2015; Liu et al., 2015) have been demonstrated in depression and anxiety disorders.

For many markers of oxidative stress measured peripherally it is unknown whether they are reflective of CNS levels. Plasma levels of uric acid however correlate highly with cerebrospinal fluid levels (r = .669, p = .001)(Bowman et al., 2010), making uric acid of particular interest in affective disorders.

Previous literature on uric acid in depression is limited in scope, findings are conflicting and only one previous study addresses uric acid in anxiety disorders (Lyngdoh et al., 2013). Two small meta-analyses (Jiménez-Fernández et al., 2015; Liu et al., 2015) (N = 306 and N = 762 cases) found lower uric acid in depression, but also reported very high heterogeneity (I^2 ± 90%), meaning the findings are highly inconsistent. Neither included a large study (N = 3716) that found no association between uric acid and affective disorders, with the exception of social phobia (Lyngdoh et al., 2013).

This study used a large sample with well-defined diagnoses to examine the relationship between plasma uric acid and MDD and/or anxiety. We hypothesized that uric acid would be lower in subjects with a disorder. To our knowledge this sample comprises a larger number of cases than all previous studies on this association combined and includes most major confounding factors. In addition, it addresses whether the association is independent of antidepressants, which may affect uric acid (Jiménez-Fernández et al., 2015). To gain insight into whether uric acid levels are a trait characteristic, or are associated are with the (severity and duration of the) state of a current episode, both current and remitted patients as well as severity and duration indicators were included.

2. Materials and methods

2.1. Population

Data were derived from the baseline measurement of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing longitudinal cohort study conducted among 2981 adults aged 18–65 years. Between 2004 and 2007 participants were recruited from the general population, primary care and mental health care organizations in the Netherlands. The NESDA sample includes participants with current or remitted major depressive disorder, dysthymia, and/or anxiety disorders (social phobia, generalized anxiety disorder, panic disorder, agoraphobia) as well as healthy control subjects. Persons with another primary psychiatric diagnosis of e.g. bipolar disorder, severe substance use disorder or a psychotic disorder were excluded. Diagnoses were ascertained using the lifetime version of the Composite International Diagnostic Interview (CIDI, version 2.1). At baseline, participants underwent a 4-h assessment, including blood sampling, written questionnaires, an interview and physical examination. A full description of the NESDA design has been published previously (Penninx et al., 2008). NESDA was approved by the Medical Ethics Committees of the participating institutes. All participants provided