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Research progress of serum uric acid in mood disorders

Mengyao Sun[1], Hongli Sun[2], Minghui Chen[2], Jiamiao Wang[3] and Aiping Xu[2,*]
[1] School of Clinical Medicine, Shandong Second Medical University, Weifang, Shandong, 261053, China
[2] Weifang Mental Health Center, Weifang, Shandong, 261000, China
[3] Shandong Mental Health Center, Jinan, Shandong, 250014, China

Corresponding authors: (e-mail: Paofu014@163.com).

Abstract Oxidative stress (OS) has been implicated as a pivotal contributor to the pathogenesis and progression of mood disorders. Uric acid (UA), the predominant non-enzymatic antioxidant in systemic circulation, exhibits robust antioxidative capacity to mitigate OS-induced damage while conferring neuroprotective effects on the central nervous system. Accumulating clinical evidence demonstrates statistically significant disparities in serum uric acid (SUA) levels among patients with major depressive disorder (MDD), bipolar disorder (BD), and healthy controls. These variations are hypothesized to stem from disease-specific dysregulation of oxidative stress intensity and adenosine homeostasis within the purinergic system. Critically, SUA level shows potential as a biomarker for distinguishing BD from MDD, particularly during early disease stages, thereby offering a novel strategy to address diagnostic challenges in psychiatric practice. This review systematically summarizes recent advances in SUA research within mood disorders, which provides important thinking for the differential diagnosis of MDD and BD in clinical practice.

Index Terms uric acid, major depressive disorder, bipolar disorder, oxidative stress, purinergic system, biomarker , differential diagnosis

I. The role of serum uric acid in oxidative stress defense and neuroprotection in mood disorders

Mood disorders are mainly divided into two categories: bipolar disorder (BD) and major depressive disorder (MDD). The clinical manifestations of BD are mainly characterized by mania, hypomania, depression or mixed episodes [1]. In recent years, the differential diagnosis and early identification of BD and MDD have been hot topics in both clinical and basic research. Currently, the clinical differentiation between the two mainly relies on the presence or absence of manic episodes of BD (BD-M) or hypomanic episodes [2]. However, most BD patients often present with depressive episodes of BD (BD-D) as their first symptom, so they are often misdiagnosed as MDD in the early stage, or it is difficult to detect mental abnormalities during hypomanic episodes. Data from investigations show that BD is often correctly diagnosed after a disease course of 7 to 10 years [3]. Recent studies have found that the levels of serum uric acid (SUA) differ among MDD, BD, and healthy individuals [4]-[6], and this difference seems to be of great significance in solving this medical problem. This article attempts to start from the role of uric acid (UA) in mood disorders, review the differences in SUA levels between MDD and BD patients and the possible mechanisms, in order to understand the possible causes of such differences and provide a certain theoretical basis for the differential diagnosis of MDD and BD in clinical practice, as well as the early identification of BD and the prediction of phase transitions in depressive episodes.

The purine metabolic pathway is the catabolic pathway of purine nucleotides in the body, involving a series of enzymatic reactions. Uric acid (UA) is generated as the final product in the purine metabolic pathway, and UA and intermediate products such as hypoxanthine nucleotide and guanine nucleotide can inhibit the generation of purine nucleotides, thereby maintaining the dynamic balance of UA production in the body [7]. Since the uricase in the human body does not have functional activity, UA generated in human cells cannot be metabolized but is excreted through the kidneys, intestines, and bile. This process involves various factors that regulate the excretion of this compound. In clinical practice, more attention is paid to the harmfulness of UA. For example, excessive UA in the blood can cause adverse consequences such as excessive inflammatory cytokines and cell damage, and even lead to hyperuricemia (HUA) and its related clinical complications, such as gout and kidney stones. Therefore, in clinical practice, it is emphasized to prevent HUA through lifestyle adjustments and to use drugs to lower serum uric acid (SUA) for the treatment of diseases such as gout [8].

In addition to its harmfulness, more than forty years ago, Ames et al. [9] first proposed the hypothesis that UA has antioxidant defense benefits. In the following decades, biochemical and related studies have confirmed that a

mild increase in UA concentration in the plasma can protect the human body, being able to remove free radicals in the blood and exert antioxidant effects [10]. Normally, the human brain consumes about 20% of the body's basal oxygen to support neuronal activity. The high oxygen consumption of neurons leads to the production of more reactive oxygen species (ROS) in the central nervous system (CNS) [11]. Compared with other organs, the antioxidant capacity of the brain is also relatively low, and the lipid structure of the neuronal cell membrane containing unsaturated fatty acids is highly sensitive to ROS [12]. Under oxidative stress (OS) conditions, the body's various systems respond strongly to produce excessive ROS, making the brain more susceptible to OS. ROS have potential neurotoxicity, causing damage to biomolecules and even cell death. Therefore, to maintain homeostasis, the body needs to mobilize a large number of antioxidants to participate in regulation. UA is one of the main non-enzymatic antioxidants in the human body, accounting for about 70% of the total antioxidant capacity (TAC) of the plasma [13], and the level of SUA can roughly serve as a marker of the body's antioxidant capacity.

Low SUA levels in the CNS may lead to a low defense ability against OS in brain cells. The level of SUA in the CNS is related to the UA level in peripheral blood, so UA may be an effective biomarker of the purinergic system. UA has a chemical structure similar to the psychoactive stimulant caffeine and can act as a factor in the intercellular space of the brain to stimulate the cerebral cortex and exert neuroprotective effects [14]. In recent years, studies have found that the purinergic system plays an important role in the occurrence and development of mental disorders, especially in relation to major depressive disorder (MDD), bipolar disorder (BD), schizophrenia, autism, anxiety disorders, and attention deficit hyperactivity disorder (ADHD) and other mental disorders. Purinergic receptors are divided into P1 and P2-R. P1-R is called the adenosine (Ado) receptor due to its selectivity for Ado, and the Ado receptors include A1, A2 (A2A, A2B), and A3 receptors. In mood disorders, the purinergic system mainly exerts its effects by regulating neurotransmitter release and neural plasticity, and the main receptors involved are A1 and A2A receptors [15]. On the one hand, UA, as an important molecule or receptor modulator in purinergic signaling, can affect the activity of various neurotransmitters, such as dopamine, γ-aminobutyric acid, norepinephrine, and serotonin, which play significant roles in the pathophysiology of MDD and BD [16]. On the other hand, low levels of UA in the CNS may lead to the excitation of A2A receptors, causing abnormal activation of the hypothalamic-pituitary-adrenal axis (HPA) and excessive secretion of glucocorticoids, resulting in neuroplasticity changes and memory impairment, thereby triggering depressive effects [15]-[17]. Studies have found that caffeine, which has a similar structure to UA, can also antagonize Ado receptors at moderate doses and exert antidepressant effects [18].

In summary, high levels of UA in peripheral blood have obvious multi-system hazards, but low levels of UA can cause a decline in the OS defense ability of brain cells. Moderately elevated UA can act as a protective factor during the OS process. From a molecular biology perspective, UA may be an effective biomarker of the purinergic system, mainly exerting mood-altering effects by participating in the regulation of Ado levels in the CNS and periphery. Currently, the specific mechanism of UA's role as a regulatory or signaling factor in the purinergic system remains unclear, and more prospective experiments can be conducted in the future to further study its role.

II. Serum uric acid in major depressive disorder

II. A.SUA levels in patients with MDD

The field of medical science has increasingly acknowledged the critical role of oxidative stress (OS) in major depressive disorder (MDD). Consequently, a growing number of researchers are focusing on investigating the connection between MDD and serum uric acid (SUA) levels. Existing studies indicate that individuals with MDD tend to exhibit significantly lower SUA levels compared to healthy controls. Large-scale cross-sectional studies conducted by MENG et al. [4] and BLACK et al. [19] both demonstrated that MDD patients had markedly reduced SUA levels, which were negatively correlated with the severity of depressive symptoms. Recent findings suggest that decreased SUA levels may serve as a state marker for MDD rather than a trait marker. Moreover, the severity of depressive symptoms, along with the duration of untreated or inadequately treated conditions, correlates with even lower SUA levels [16]. This implies that SUA levels fluctuate depending on the varying disease states of MDD and the progression of pharmacological treatment. Utilizing data from approximately 3,000 participants in the Netherlands Study of Depression and Anxiety (NESDA), BLACK et al. [19] revealed that depressive symptoms in MDD patients, whether accompanied by anxiety or not, were inversely associated with symptom severity and disease duration. Numerous domestic and international studies have identified a correlation between the severity of depressive symptoms and SUA levels. However, further longitudinal and experimental research is necessary to confirm whether SUA can function as a state marker for MDD. Additionally, an in-depth stratified analysis of drug treatment timing and type could be beneficial.

In contrast to the aforementioned conclusions regarding the general MDD population, several studies focusing on middle-aged and elderly women with MDD, as well as adolescent MDD patients, have reported higher SUA

levels compared to healthy individuals. By examining the relationship between SUA levels and depressive symptoms in approximately 10,000 middle-aged and elderly individuals across four provinces in China, it was observed that women with elevated SUA levels exhibited a significantly higher prevalence of depressive symptoms compared to men [20]. Subsequently, a large cross-sectional study categorized depressive states based on menopausal status and found that high SUA levels were linked to depressive symptoms or MDD in postmenopausal women, whereas no such association existed in premenopausal women [21]. These differences might be attributed to hormonal fluctuations during the perimenopausal and postmenopausal stages, which also contribute to increased UA levels and the onset of mental health issues. Among adolescents, numerous studies have indicated that SUA levels in adolescent or young MDD patients are higher than those in healthy individuals. A domestic study explored potential biomarkers of MDD in children and adolescents through plasma metabolic analysis. No significant differences were noted in gender, age, or BMI values between the two groups. The results showed that SUA levels were significantly higher in the MDD group compared to the healthy control group [22]. Conversely, some studies have reported opposite findings, with adolescent MDD patients exhibiting lower-than-normal SUA levels, particularly among those with suicidal attempts [23]. This inconsistency with prior research outcomes may stem from two factors: first, the more pronounced dysfunction in the antioxidant system among patients with attempted suicide, and second, the significantly higher proportion of female MDD patients in the observation group compared to the control group. High estrogen levels in women can reduce SUA levels by decreasing UA production and enhancing its excretion.

II. B.Mechanism of SUA level changes in patients with depressive disorder

A large domestic meta-analysis of in vivo OS markers for MDD showed that: The levels of TAC, paraoxonase and antioxidants including UA are low in MDD patients, and the levels of serum free radicals and oxidative damage products are higher than those in the healthy control group. After antidepressant treatment, TAC, SUA, etc., increase, and the levels of oxidative damage products decrease [24]. This suggests that the OS response in MDD patients, especially during acute exacerbation, is strong, resulting in low antioxidant levels. Because of its strong natural antioxidant properties, UA has been considered as a compensatory mechanism to counteract OS in MDD, which indicates that purine metabolism is accelerated during the onset of MDD. Studies have shown that there are abnormalities in the intermediate links of purine metabolism pathways in MDD patients. One of the above clinical trials, which was studied by metabolic analysis of plasma samples, found that the concentrations of adenosine, inosine, and inoxanthine were significantly decreased in MDD patients compared with healthy controls [22]. Therefore, the lower SUA levels in MDD patients may be related to the excessive consumption of antioxidants in vivo in response to a strong OS response.

Studies have shown that mild chronic inflammation is a key factor in the pathogenesis of MDD. As an anti-inflammatory agent, UA prevents the production of inflammatory cytokines, thereby alleviating the inflammation associated with MDD [25]; In addition, UA is involved in the regulation of vascular endothelial function and brain blood flow, both of which are abnormal in MDD patients. By improving endothelial function and promoting cerebral blood flow, UA can reduce the risk of depressive symptoms [10]. Finally, UA will interact in biological systems involved in emotion regulation and stress response, such as the renin-angiotensin system and the purinergic system [26]. In summary, UA is negatively associated with the risk of depressive symptoms overall through a variety of mechanisms, including antioxidant activity, neuroprotection, neurotransmitter modulation, anti-inflammatory effects, and modulation of endothelial function and cerebral blood flow.

III. Serum uric acid in bipolar disorder

III. A. SUA levels in patients with BD

Unlike MDD, existing studies have shown that BD patients have significantly higher SUA levels than MDD and healthy people, and BD is still significantly associated with higher UA levels after adjusting for the confounding effects of mood stabilizers and antipsychotics use [6]. In subsequent studies, it was further confirmed that SUA levels were significantly different between BD and MDD, and it was found that SUA levels may also be different in each subtype of BD, among which BD-M patients had the highest SUA levels. After excluding publication bias, a large meta-analysis of 28 studies in China involving 4482 BD, 1568 MDD and 2876 control healthy subjects showed that the SUA level of BD patients was significantly higher than that of MDD group and healthy control group, which showed high heterogeneity. Further analysis found that, The SUA level among different seizure state subgroups of BD was the main source of high heterogeneity, which was higher in the BD-D group, but lower in the BD-M group and the mixed seizure group. After comparison between subgroups, the SUA level of the BD-M group was significantly higher than that of the BD-D group [5]. In addition, many studies have found that the SUA level of BD-D patients is not statistically different from that of MDD [27]. LIU et al. [28] believed that the SUA level of BD-D patients was significantly higher than that of MDD patients. Through the analysis of confounding factors, the

proportion and age of newly diagnosed patients in MDD group were significantly higher than those in BD-D group, which may affect the accuracy of the research results and suggest that confounding factors should be more strictly controlled in the future. It is worth to note that KONG et al. stratified the hospitalized patients with first-episode MDD and BD-D according to different seasons and found that the SUA level of BD-D patients was significantly higher than that of MDD in summer and autumn, but there was no significant difference between spring and winter, indicating that SUA seems to have the potential to be a seasonal marker for the differential diagnosis of unipolar and bipolar depression [29]. In addition, SUA levels may also have predictive value for the risk of manic episodes in newly diagnosed MDD patients. OLIVEIRA et al. [30] conducted a prospective study. After 10 years of follow-up of MDD, they found that the SUA level of MDD patients in the transition group was significantly higher than that in the non-transition group regardless of gender, suggesting that the SUA level showed high accuracy in predicting the transition of MDD patients.

Most studies have found that SUA levels will decrease after treatment, and this conclusion is still most significant in the BD-M group, suggesting that SUA levels may also be a state biomarker for BD. A prospective study divided adult BD patients into BD-M group and BD-D group, and included patients with long-term drug treatment history. It was found that the decrease of SUA level was significantly positively correlated with the severity of the disease in BD-M patients, and was low to moderate positively correlated with the severity of the disease in BD-D patients [16]. Other studies have different conclusions and believe that SUA levels increase after drug treatment, which may be due to renal function damage caused by lithium salt, resulting in renal resistance to vasopressin, which may be related to different drug choices in treatment [6].

III. B. Mechanism of SUA level changes in patients with BD

The structure of UA is similar to that of caffeine. An appropriate amount of caffeine can exert antidepressant and anti-anxiety effects, and also has inhibitory effects on suicidal ideation and behavior, while excessive amounts of caffeine can cause anxiety, excitement or manic-like symptoms [15]. In the state of high SUA level, OS reacts strongly, and the chain oxidation reaction occurring in CNS cell membrane destroys its stability and permeability, and promotes the occurrence and development of BD [14]. Some evidence from genetic studies also highlights the key role of the purinergic system in manic episodes, and elevated SUA may be a specific phenomenon caused by metabolic abnormalities during manic episodes [31], which is consistent with the conclusion of the clinical study in the previous section that "BD patients have higher SUA levels, especially in manic episodes or mixed episodes". Therefore, the level of SUA is closely related to impulsivity, irritability, mood elevation, and psychomotor excitability. In the future, the direct effect of UA on emotional state in the field of neuropsychiatry can be further studied.

IV. Discussion

In summary, UA is one of the major non-enzymatic antioxidants in the circulation, which has the function of OS defense in the human body, and also has a neuroprotective effect on the CNS, and can regulate the signal transduction of a variety of neurotransmitters. The pathogenesis of MDD and BD may be related to the change of Ado receptor function or gene expression level, which is the core of purinergic system, resulting in the difference of SUA level in mood disorders. Among them, the decrease of SUA level in MDD may be caused by the decrease of Ado transformation and the increase of ADO activity, while BD is opposite. The study showed that the SUA level of MDD patients was significantly lower than that of BD patients, and this result was most significant between MDD and BD-M. Although it was not obvious between MDD and BD-D, there may be seasonal differences. SUA levels also have predictive value for the risk of a manic episode in patients with a current depressive episode. This suggests that SUA level has potential clinical significance for the differential diagnosis of the two diseases, and it is likely to be an effective biomarker to distinguish MDD from BD, which can be used as an auxiliary diagnostic item in clinical practice. In the future, more prospective studies are needed to clarify the clinical feasibility of SUA in the differential diagnosis of the two diseases, and it is more challenging to define the specific cut-off value of SUA in the two diseases. It is necessary to control multiple confounding factors, adopt large sample research design, and design observational trials for different races. Studies on BD in the past two years have found that the UA-related ratio, that is, the ratio of UA to albumin, creatinine, high-density lipoprotein and lymphocytes, seems to have better potential disease diagnosis ability than SUA level alone [32]. This suggests that in the future, we can also combine other laboratory tests with UA, starting from UA correlation ratio, to carry out more in-depth research on the differential diagnosis and early identification of BD and MDD.

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