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Uric Acid and Central Nervous System Functioning (A Literature Review)

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Abstract—The high level of uric acid in blood distinguishes humans from other studied species of mammals. The reason behind this is the absence of the enzyme uricase, which is evolutionary determined. Today, hyperuricemia can be considered as a factor of "diseases of civilization." However, uric acid can also have positive effects, because it intensifies cognitive processes. The high level of uric acid in blood probably facilitated the emergence of intellectually advanced primates. Later, it enhanced the human's motivation for active work. In the present review, these points are substantiated using data by V.P. Efroimson on the role of hyperuricemia and gout in the development of genius, V.S. Rotenberg's Search Activity Concept, and the R. Johnson's hypothesis on the role of uric acid as a messenger when it is necessary to change the behavioral responses of animals upon transition to active feeding. The nonspecific activating role of hyperuricemia is the factor that links all three hypotheses together. In addition, the enhancement of cognitive functions and motivations in hyperuricemia has been confirmed in different population samples. The biochemical basis for such effects is the potential for uric acid synthesis in the central nervous system and the penetration of the blood-brain barrier by its precursors, the interrelations between the metabolism of uric acid in the central nervous system and the metabolism of catecholamines and dopamine, and the neuroprotective and antioxidative properties of uric acid.

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INTRODUCTION

The relationship between the characteristics of purine metabolism and the CNS activity has been actively studied since the 1950s. The highest realization of this relationship is the formation of genius against a background of hyperuricemia and gout, which is summarized in the monograph by V.P. Efroimson *Genetics of Genius* (2002). According to Efroimson, the frequency of gout among eminent personalities and recognized geniuses is at least 15–20%, whereas among men of older age groups is does not exceed 0.6–2%. These data are difficult to subject to conventional statistical processing, but the degree of confidence in them is high (Golubovskii, 1999). There is no doubt in "... the real existence of specific internal mechanisms of a mighty, mostly hereditary stimulus leading to an irrepressible creative activity, whatever it is expressed in..." (Efroimson, 2002, p. 353). The specificity of purine metabolism in humans plays an important role in these mechanisms. Today, this specificity is regarded primarily in the context of the role of hyperuricemia as a risk factor of "diseases of civilization," although in the living organism, an integrated changing system, none of the metabolites can be considered one-sided. Therefore, it is necessary to summarize the available data on the relationship between purine metabolism and CNS activity.

SPECIFIC FEATURES OF PURINE METABOLISM IN HUMANS

It is known that the specificity of purine metabolism in the majority of primates, including humans, is determined by the loss of the enzyme uricase, which converts uric acid to allantoin. Therefore, uricemia in humans is relatively high (0.14–0.42 mmol/L, while, for example, in rats it is 0.06–0.09 mmol/L). The role of the loss of uricase for the evolutionary process was first indicated by Orowan (1955), who considered this loss in the context of the combination of favorable mutations as a possible driving force in the development of intelligence in primates (which is more likely than occasional abrupt changes). According to Parmar (2009), the significance of the high level of uricemia in humans is associated with the fact that a system of urate reabsorption has been formed in kidneys in the course of evolution and still functions there, despite its high energy cost; as a result, more than 90% of the filtered uric acid is reabsorbed, which is very strange for an indifferent substance. V.N. Titov et al. (2011) considered the formation of the reabsorption system of uric acid from the standpoint of its antioxidant action, suppression of inflammation, and maintenance of blood pressure.

It was shown for Japanese and American population samples that uricemia depends on both genetic factors (polygenic inheritance theory) and lifestyle (Gulbrandsen et al., 1979). Twin studies confirm the importance of genetic factors in the context of polymorphism of enzymes involved in purine metabolism (Inouye et al., 1984; Ooki et al., 1990).

METABOLISM OF URIC ACID AND INTELLECTUAL ACTIVITY

Orowan (1955) was the first to emphasize the structural similarity of uric acid and the known psycho stimulants caffeine and theobromine. In gout, both the concentration of uric acid in the blood and its pool increase (Efroimson, 2002). Back in 1778, Cullen noted that wise persons suffer from gout more often than those who do not have much intellectual abilities (emphasis was shifted to the mental activity, although at that time gout was associated primarily with a high financial situation) (Katz and Weiner, 1972).

The relationship between hyperuricemia and intellectual activity, as well as the motivation to achieve and increase social status, was then identified in different population samples. However, while the attention of researchers in the 1960–1980s was focused on this relationship (Stetten and Hearon, 1959; Dunn et al., 1963; Brooks and Mueller, 1966; Kasl et al., 1966; Montoye et al., 1967; Anumonye et al., 1969; Kasl et al., 1970; Bloch and Brackenridge, 1972; Katz and Weiner, 1972; Fowler, 1973; Mertz, 1974; Burroni et al., 1981; Sofaer and Emery, 1981; Inouye et al., 1984; Sakamoto et al., 1986; Ooki et al., 1990), in recent studies (Bolgova et al., 2009; Hartung et al., 2010; Villegas et al., 2010) devoted to investigation of cardiovascular risk factors, this relationship usually was not taken into consideration (originally an open-minded approach adds value to the data.) Therefore, it is necessary to consider the results of the two groups of studies.

For example, the high social status of patients with gout was mentioned by British clinicians Popert and Hewitt (1962): a group of 95 patients with gout included 13 directors, 10 senior managers, 6 physicians and 11 skilled workers (the sample was formed in the 1960s in the countryside, where the number of highly qualified personnel could not be significant). A higher uricemia level was recorded in officials compared to masters (Dunn et al., 1963). The relationship between elevated levels of uric acid in the blood and affiliation to the higher social classes was confirmed by Dunn et al. (1963), in contrast to Acheson (1969). At the same time, the very concept of a social class cannot be defined clearly. Analysis is complicated by the multifactorial control of purine metabolism: in modern conditions, hyperuricemia becomes part of many vicious circles of pathogenesis and occurs as a complication of pharmacotherapy, which is reflected on its distribution. Therefore, the above relationship is more likely to be identified in more homogeneous samples.

A positive correlation between uricemia and intellectual development (according to tests) was shown in American conscripts (Stetten and Hearon, 1959). A similar correlation between uricemia and academic performance of students was found by Bloch and Brackenridge (1972). The association between the development of intelligence (according to IQ) and gout was found in individuals belonging to a partnership whose members had a high IQ value. The reference group included their closest relatives, which reduced the variability of hereditary and social factors (Sofaer and Emery, 1981), although this publication, entitled "Genes for Super-intelligence?," was perceived ambiguously. An example of another expressive name is "Gout Hazard as the Price for Development of Intelligence?" (Mertz, 1974).

According to tests of male students, Kennett and Cropley (1975) confirmed the importance of uric acid for human intellectual activity. They assumed that the effect of uric acid is most likely realized at the level of cortical stimulation and/or facilitation of learning processes. The correlation between uricemia and extracurricular activity, commitment to work, leadership, and responsibility was shown in a similar sample, whereas the correlation between uricemia and the level of intelligence was detected but was not significant (Dunn et al., 1963). A significant positive correlation between uricemia and IQ was shown (Inouye et al., 1984).

Studies in female volunteers are less numerous. It is more difficult to establish a correlation between the state of purine metabolism and CNS activities in them because of the influence of the hormonal background. Nevertheless, Sakamoto et al. (1986) showed a positive correlation between academic performance and uricemia in female students and a higher level of uric acid in persons who were exposed to more intense stressors.

It should be noted that the results of the majority of studies indicate the potential effect of hyperuricemia on the motivation for activities rather than the degree of intelligence development. The former in many respects is crucial for the realization of individual abilities (Efroimson, 2002). In this aspect—as a "stimulant" of activity—hyperuricemia draws our attention.

This can be confirmed by the data obtained by Kasl et al. (1966) of a higher level of uric acid in the blood of those male students who, despite their low performance in school, strived to continue their education in college; the level of uricemia in them correlated with the duration of learning. The correlation between the level of uric acid in the blood and IQ was nonsignificant, unlike the correlation between uricemia and school rating, as well as the desire to achieve—inconsistence between IQ and a high school rating (Kasl et al., 1970). In addition, the commitment to achieve was stronger in those volunteers who were the first children in the family, although the relationship of

purine metabolism with the birth order was not confirmed (Wallage et al., 1967).

In professors at the University of Michigan (a sample of 113 individuals), highly significant positive correlations between uricemia and intensity of activity, professional productivity, ability to cooperate, organizational skills, and demands on oneself, as well as a breadth and multifaceted nature of activities, were found. The levels of uric acid in the blood were somewhat greater in the holders of higher ranks (Brooks and Mueller, 1966). A similar correlation between uricemia and the level of professional position was registered in managers in Edinburgh (Anumonye et al., 1969). Moreover, the concentration of uric acid in the blood of the group surveyed was above the reference standards. Uricemia positively correlated with the number of types of activity and the vigor ("drive") of managers, but the correlation between professional responsibility and uricemia, unlike the aforementioned survey of professors, was negative, which is associated with socio-cultural differences. The correlation between the leadership in business and uricemia was established by Montoye et al. (1967), and the correlation between the vigor ("drive") and uricemia was shown by Lorenzia et al. (2010); this correlation was identified in a sample of men and in the total population sample (adjusted for the effect of diet). The correlation between uricemia, increased working capacity, and the level of claims was registered in the military, although the uric acid content was associated with the neurotic personality type (Dzhergeniia and Ushakov, 2010). The hereditary determinism of uricemia was demonstrated, as well as a correlation of the latter with indicators of the total activity (Ooki et al., 1990).

In our opinion, the correlation of hyperuricemia with a realized motivation to be active is indirectly confirmed by data of recent years. For example, a higher uricemia was registered in German chefs as compared to office staff. This could have been attributed to nutritional habits, but these groups did not differ by body mass index and dietary energy (although, judging by the level of plasma triglycerides and saturated fatty acids in erythrocyte membranes, chefs consumed more animal products). Along with the greater uricemia, chefs had a significantly higher commitment to work and its subjective importance, as well as professional perfectionism (Hartung et al., 2010).

In male middle-aged Chinese citizens, hyperuricemia to a certain extent can be associated with higher education and skilled, specialized work (only a decrease in the number of persons with hyperuricemia who had no education was statistically significant). The analysis is complicated by the prevalence of metabolic syndrome and the use of antihypertensive drugs among the surveyed subjects (Villegas et al., 2010). This situation reduces the possibility of establishing a correlation between purine metabolism and cognitive functions (although it increases the value of those correlations that can be revealed against the background of interference). However, neither Villegas et al. (2010) nor Hartung et al. (2010) discussed the aspects of interest to us: their attention was focused on the role of uric acid in the pathogenesis of "diseases of civilization." Upon the transition of asymptomatic hyperuricemia to clinically manifested gout, analysis is complicated by the negative impact of gout on the quality of life (Katz and Weiner, 1972).

A.E. Il'ina et al. (2008) and, to a certain extent, Katz and Weiner (1972) considered hyperuricemia as a possible consequence rather than the cause of high social status and material welfare of persons examined in the studies of 1950–1960s cited above. Katz and Weiner (1972) still indicate a possible role of increased activity of the surveyed persons with hyperuricemia in their achievements. Fowler (1973), who studies the relationship between uricemia and motivation for activity, showed a greater expression of this motivation among the subjects with hyperuricemia compared to the normouricemic subjects (although the same trend was observed for hypouricemia); however, this correlation disappeared in the total sample.

Given the enormous importance of childhood for further development of the personality, it is of particular interest to study the relationship between purine metabolism and intellectual functions in children. For example, back in 1981, Italian clinicians identified a significantly higher level of uricemia in children with a high degree of talent than in the children with delayed intellectual development. This pattern was detected in a heterogeneous sample of children aged from a few months to 16 years, from which children with epilepsy and behavior disorders, as well as specially gifted children, were not excluded (Burroni et al., 1981). A question arises as to whether the effect on the CNS of uric acid, the level of which in the prepubertal age is low, can be realized and what the consequences of its increase might be during the formation of the hormonal background in boys (Katz and Weiner, 1972), an issue that is little discussed in the literature. Under these conditions, hereditary factors, which to a large extent determine the pool of uric acid, should have an effect.

Rovda and Kazakova (2003) proved the necessity to replace the nosological form "neuro-arthritic diathesis" with "purinosis," based on the leading role of hyperuricemia in its development. In this case, the importance of hereditary factors is beyond doubt. Along with this, Russian clinicians have found that children with hyperuricemia often come from families with a high motivation for education and with better material and living conditions; their parents often are employees (Bolgova et al., 2009). The authors consider hyperuricemia as a "disease of excess" associated with a good financial situation, with which we can agree, but only partially. Of course, it is proved today that purine metabolism depends on lifestyle and that a change of a lifestyle leads to the distribution of hyperuricemia in modern populations. However, it is diffi-

cult enough to assume the identification of such dependence among children and adolescents, and the distinctions in lifestyle among the surveyed persons can hardly be regarded as principal. Indeed, despite the unequal financial position, they do not belong to the polar social groups; they live in the same region (the majority live in towns) and have similar living conditions, including diet. Under such circumstances, hyperuricemia in children and adolescents is more likely to be identified in the presence of hereditary factors. That is why, in our point of view, the data described in this paper not only do not refute the causal relationship between hyperuricemia and the motivation for mental activity, but also, to some extent, confirm it, because hyperuricemia could affect the members of the families surveyed who strived to receive education. In the children and adolescents themselves, the action of this biochemical factor will be complemented by the positive influence of the family and the opportunities for early development. Such a situation could take place in prominent dynasties, the representatives of which suffered from gout, as was discussed by V.P. Efroimson (2002). Bolgova et al. (2009) did not provide data on the anamnesis of purine metabolism disorders, which does not allow us to confirm our assumptions.

HYPERURICEMIA AS A POSSIBLE LINK BETWEEN THE CONCEPTS OF V.P. EFROIMSON, V.S. ROTENBERG, AND JOHNSON

As discussed above, numerous studies covering different population groups in different countries in the last 50 years have shown a certain correlation between hyperuricemia and realized motivation to be active. In this context, we should refer to the Search Activity Concept suggested by V.S. Rotenberg (2001) together with V.V. Arshavsky, which logically elucidates many global biological phenomena, including sleep and wakefulness, resistance to stress, the development of personality, and the direction of its activity. Assuming that hyperuricemia may serve as a "stimulant" of exploratory behavior (although this requires further biochemical substantiation, which is partly discussed below), the concept of search activity is in good agreement with the following findings of Efroimson (2002). Firstly, the stimulatory effect of hyperuricemia is not specific to the area of activity (in outstanding individuals suffering from gout, these areas are extremely diverse). Secondly, maintenance of search activity under a possible effect of hyperuricemia may, to some extent, counteract the adverse influence of the latter on the cardiovascular system and metabolism, which undoubtedly takes place in the modern world. According to Rotenberg (2001), maintenance of search activity is an important factor of physical health. These patterns probably allowed outstanding gout sufferers to work extremely actively and fruitfully for a long time, despite the factors of cardiovascular and other risks and an adverse lifestyle (Efroimson, 2002).

Rahe et al. (1974) used the individual data of several persons to show an increase in uricemia under the influence of emotional and/or physical stressors. In this case, the uricemia of all examined subjects, whose activity was confirmed not only by this article but also by the very fact of participation in such a long-term study, was classified as "high normal." Our attention was drawn not only by the increase in the uric acid blood level before the participation of two volunteers in sports competitions (a possible secondary response to the release of catecholamines) but also by patterns of biochemical changes in a stressful situation that depended on its perception (as established by the authors). For example, stress factors considered by the surveyed subjects in the context of positive changes were accompanied with a preliminary increase in the uricemia level, whereas factors that were perceived as negative and unsurmountable, sometimes leading to defeats, occurred against a background of an increasing concentration of cholesterol in the blood (before and after the action of the factor, the level of cortisol also increased). Naturally, there is an association with the Search Activity Concept of Rotenberg (2001). Furthermore, in one of the volunteers who participated in the study (Rahe et al., 1974), the correlation between cholesterolemia and uricemia was negative. This apparently casuistic case deserves attention due to the fact that other researchers observed a pronounced correlation between uricemia and school achievements and between uricemia and the results of tests for the expression of motivation in subgroups with a high uricemia and a relatively low cholesterolemia (Kasl et al., 1970). Nevertheless, there are opposite data: in United States Air Force cadets, uricemia and cholesterolemia increased under the influence of stressors; however, the increase in uricemia was associated with stress accompanied with fear and uncertainty, whereas the increase in cholesterolemia was associated with the leading to mobilization of physical and mental effort (Clark et al., 1975).

It was shown that high uricemia was associated with a decrease in the risk of dementia and better cognitive performance in adulthood (after adjustment for cardiovascular risk factors) (Euser et al., 2009).

In addition to the results of studies performed with volunteers, under the assumption of the role of hyperuricemia as a "stimulant" of exploratory behavior, it is necessary to consider the hypothesis of Johnson et al. (2009) on the possible activatory role of uric acid, when it is necessary to modify the behavioral responses of animals upon the transition to procuring food ("the foraging response"). It is known that uricemia increases in starvation. In the protein breakdown phase, which occurs after the exhaustion of lipid reserves and is accompanied with a rapid decrease in body weight, the content of uric acid in the blood greatly increases simultaneously with an increase in

locomotor activity and the cortisol level. Uricemia is negatively correlated with the lipid reserves and positively correlated with the cortisol level in the blood plasma of birds that performed migration over the Mediterranean Sea.

In Antarctic emperor male penguins, which starve for a long time when nesting on ice, a dramatic increase in uricemia is observed exactly when the protein breakdown phase begins and the bird leaves the nest in search for food (Robin et al., 1998; Jenni et al., 2000). In arctic ground squirrels and Syrian hamsters, the escape from hibernation with subsequent active food procuring is accompanied with a 3- to 4-fold increase in uricemia (in the case of functioning uricase, the relationship between uricemia and preservation of lipid reserves was not confirmed (Okamoto et al., 2006)). Johnson et al. (2010) consider the example of the thirteen-lined ground squirrel, which hibernates at 4°C. A periodic rise in its body temperature to ensure the functioning of uricase and the excretion of allantoin prevents the accumulation of uric acid, the activating role of which during long-term hibernation is inexpedient. These examples indicate that hyperuricemia is not only a marker of catabolic processes but also an activation factor in animals.

Similarly to other biologically active metabolites, uric acid has an optimum concentration range in blood. The relationship between uricemia and intellectual human activity is linear only within certain limits and can be expressed either by a wavy line or a curve line in the form of inverted letter U rather than by a straight line (Stevens et al., 1975). A striking example is the Lesch–Nyhan syndrome, when a significant hyperuricemia is combined with mental retardation (Murray et al., 1990). On the other hand, as noted by Kutzing and Firestein (2008), pharmacological correction aimed at reducing the level of uric acid in the blood should not increase the risk of pathological conditions associated with its low level.

OTHER ASPECTS OF THE EVOLUTIONARY SIGNIFICANCE OF URIC ACID

The positive role of uric acid in the course of evolution is also determined by its contribution to the maintenance of an adequate blood pressure level in the case of limited sodium intake by forming a hypersensitivity to it. Furthermore, in the case of high uricemia, the role of fructose in the creation of energy reserves increases, which facilitate the survival in the absence of food (Watanabe et al., 2002; Johnson et al., 2009, 2010; Titov et al., 2011). Of course, these metabolic features stopped being benefits and became risk factors in modern humans. This is elucidated in modern literature and is not the subject of this article. However, in this context, it is necessary to consider one more mutation that is fixed in human ancestors and, to some extent, interrelated with the loss of active uricase. It is the absence of *L*-gulonolactone oxidase and, respectively, the synthesis of ascorbic acid (the combination of these two mutations is even considered one of the key factors in human evolution (Johnson et al., 2009)). The loss of active *L*-gulonolactone oxidase occurs earlier than the loss of uricase. On the one hand, ascorbic acid counteracts the aforementioned changes in the metabolism of carbohydrates (including fructose), which are associated with a high uricemia. It has a uricosuric effect and inhibits the synthesis of uric acid (Vasdev et al., 2002; Gao et al., 2008). On the other hand, the benefits of increased uricemia may be associated with the antioxidant role of uric acid, which to some extent replaces the ascorbic acid. This once again confirms the relationship between the respective absences of the enzymes (Ames et al., 1981, Murray et al., 1990; Johnson et al., 2008, 2009). Thus, the concentration of uric acid in human blood plasma (0.14–0.42 mmol/L) is several times higher than the concentration of ascorbic acid (0.04–0.14 mmol/L). However, the level of the latter in the blood of animals that are able to synthesize it is 3–4 times higher, whereas uricemia usually does not exceed 0.10 mmol/L in the presence of active uricase. A sufficiently high concentration determines the significant contribution of uric acid to the total antioxidant activity of human blood plasma (Ames et al., 1981; Johnson et al., 2009).

EFFECTS OF URIC ACID ON FREE RADICAL PROCESSES

Ascorbic acid as an antioxidant, in contrast to uric acid, can be reduced (Sevanian et al., 1991). However, the irreversible interaction of uric acid with radicals is sometimes an advantage. For example, uric acid stabilizes ascorbic acid in biological media, especially in blood serum. This is associated with the formation of complexes between uric acid and iron ions, which are not involved in lipid peroxidation (Sevanian et al., 1991). The synergistic interaction between uric and ascorbic acids was confirmed under conditions of exhaustive physical loads in volunteers (Yanai and Morimoto, 2004).

Uric acid inactivates free radicals. In the physiological concentration range, it has a number of effects that may ensure a protective effect in vivo (which is valuable, as the studies in model systems, which are difficult to extrapolate to the entire organism, are numerous). Namely, it prevents the damage of hemoglobin by free radicals, protects erythrocyte membranes from peroxidation, is oxidized by singlet oxygen radicals and hydroxyl radicals easier than deoxynucleosides, and prevents the inactivation of superoxide dismutase by hydrogen peroxide (Ames et al., 1981; Sevanian et al., 1991; Becker, 1993; Johnson et al., 2008, 2009). The antioxidant effect of uric acid was confirmed in vivo in human lungs. It was shown in isolated organs that uric acid protects from injuries caused by reperfusion (Becker, 1993). In addition, uric acid at physiological concentrations inhibits

xanthine oxidase in human blood plasma by the feedback mechanism (Tan et al., 1993); decreased production of superoxide anion by xanthine oxidase facilitates the antioxidant effect.

At the same time, similarly to other antioxidants, uric acid can have a prooxidant effect. Free radicals can be generated during its interaction with peroxynitrite and as a result of the activation of NADPH oxidase. The antioxidant activity of uric acid is usually realized in biological media, whereas prooxidant mechanisms are often activated by uric acid when it enters the cell. The role of uric acid in the vascular wall remodeling has been elucidated in detail (Watanabe et al., 2002; Johnson et al., 2008). A damaging effect on the vascular wall is also exerted by xanthine oxidase, which is involved in the generation of free radicals. Basal expression of this enzyme in humans is low but increases in hypoxia, ischemia, the release of cytokines, surgery, chronic heart failure (CHF), and coronary artery changes. Xanthine oxidase is present in blood plasma; it can bind to glycosaminoglycans on the endothelial surface, which increases its stability and ability to generate free radicals. Endothelial damage is commonly associated with this form of the enzyme. In CHF, the amount of xanthine oxidase synthesized in the endothelium also increases (6 times in atherosclerotic lesion areas); as a result, the level of purine metabolites in the systemic circulation may not reflect local disturbances of purine metabolism (George and Struthers, 2009).

In view of the above, not all authors unconditionally agree with the classification of uric acid among the factors of risk and pathogenesis of the cardiovascular system. It is most likely that the negative role is played by xanthine oxidase. For example, Parmar (2009) supports the hypothesis that uric acid is more likely a marker rather than a cause of pathological processes. The inhibition of xanthine oxidase is more expedient as compared to other mechanisms of hypouricemic action because it additionally reduces oxidative stress. The beneficial effect of allopurinol was shown in clinical practice in patients with metabolic syndrome with endothelial dysfunction and diabetes mellitus type 2 with hypertension; its cardioprotective properties were shown in CHF, the mechanism of which was substantiated experimentally (Yiginer et al., 2008; George and Struthers, 2009).

Unfavorable activation of xanthine oxidase in the endothelium leads to the release of uric acid. Under these conditions, its antioxidant properties help to maintain the capability of endothelium for vasorelaxation in oxidative stress and prevent the inactivation of endothelial enzymes. The possibility of such effects in vivo (in human coronary vessel endothelium) was demonstrated (Becker, 1993). Intravenous administration of uric acid restored endothelial function (retaining the response to acetylcholine) in patients with diabetes mellitus type 1 and smokers (Waring et al., 2006). With allowance for the antioxidant properties of uric acid, it was even assumed that an increase in uricemia caused by thiazide diuretics may provide them with additional benefits (Reyes, 2005).

Unfortunately, under conditions of severe atherosclerosis, the effect of uric acid may no longer be beneficial, and it becomes a damaging factor for the endothelium, which is associated with the oxidation of lipoproteins in areas of atherosclerotic lesions. RNA and DNA, which are released as a result of necrosis and apoptosis of vascular cells, become an additional source of uric acid (Hayden and Tyagi, 2004).

URIC ACID AND ANTIOXIDANT DEFENSE IN THE CNS

The content of uric acid in the cerebrospinal fluid accounts for only 7–10% of its content in the blood plasma, which is also discussed below, whereas the level of ascorbic acid is even higher than in the blood plasma (Ames et al., 1981; Reiber et al., 1993; Becker et al., 2004). Synergism of the antioxidant action of uric acid and ascorbic acid can be considered on the whole-body level, but the features of antioxidant defense in different organs and tissues are different. For example, in Alzheimer's disease, a positive correlation between the levels of uric and ascorbic acids in the cerebrospinal fluid, but not blood plasma, was identified, which may indicate an important role of such synergy in the CNS (Bowman et al., 2010). The pathogenesis of Alzheimer's disease, multiple sclerosis, and optic neuritis is associated with hypouricemia (<0.120 mmol/L), in which the ability of uric acid to inactivate free radicals associated with inflammation may decrease (Kutzing and Firestein, 2008). However, the degree of deterioration of cognitive functions in Alzheimer's disease was not correlated with the concentration of uric acid in the cerebrospinal fluid and blood plasma (Bowman et al., 2010). The problem of whether hypouricemia is a factor in the pathogenesis of these diseases or a secondary phenomenon remains unsolved. For example, it was demonstrated that the content of uric acid in the striatal and nigral dopaminergic neurons in patients with Parkinson's disease is decreased and that this decrease is involved in the development of oxidative stress (Church and Ward, 1994). In epidemiological studies, cases of simultaneous detection of gout and multiple sclerosis have not been registered. In multiple sclerosis, a significant decrease in the content of uric acid in the blood and cerebrospinal fluid was detected; in most cases, the expression of such changes reflects the severity of the disease (Mattle et al., 2004; Amorini et al., 2009; Dujmovic et al., 2009). However, Becker et al. (2004) did not observe such a decrease. Reduced uricemia is associated with an increased consumption of antioxidants and weakening of antioxidant defense (Dujmovic et al., 2009). Amorini et al. (2009) consider this phenomenon in the context of primary loss of protection against free radicals formed with the involvement of

NO rather than as a consequence of inflammation and damage of CNS structures; in addition, they point to a possible protective effect of an early increase in uricemia. At the same time, the content of uric acid in the cerebrospinal fluid significantly depends on the state of the blood-brain barrier and purine metabolism in the CNS; for this reason, this parameter is not a reliable marker of the course of the disease (Mattle et al., 2004; Dujmovic et al., 2009).

In the model of allergic encephalomyelitis in mice (a model of multiple sclerosis), it was shown that uric acid can scavenge peroxynitrite, which is of particular importance in the pathogenesis of multiple sclerosis; it blocks its interaction with tyrosine and prevents apoptosis. Along with the inactivation of peroxynitrite, another mechanism of the protective action of uric acid is the maintenance of the protective function of the blood-brain barrier and the prevention of the penetration of inflammatory cells in the CNS (Hooper et al., 2000; Mattle et al., 2004). In vitro, by the expression of peroxynitrite inactivation, uric acid is not inferior to ascorbic and surpasses the latter in the presence of iron ions; however, ascorbic acid does not exhibit protective properties in vivo. In this model, the protective effect of inosine was shown, which itself cannot scavenge peroxynitrite but is the precursor of uric acid (Scott et al., 2002).

The protective activity of uric acid was also confirmed in the model of pneumococcal meningitis in rats: when uricemia increases to a level characteristic of a normal human, the severity of inflammation decreases depending on the concentration of uric acid (Kastenbauera et al., 2001). Hypouricemia due to renal losses of uric acid is often detected in patients with infectious processes in the CNS in cases of AIDS; in this context, it has a prognostic significance (Collazos et al., 2000).

Furthermore, the neuroprotective effect of uric acid was established in cerebral ischemia models. In clinical practice, it was found that a decrease in the uric acid blood level in the first week after stroke is correlated with an unfavourable prognosis (Brouns et al., 2010). The technical feasibility and safety of uric acid administration was shown in volunteers (Amaro et al., 2008). It was demonstrated that a combined therapy with plasminogen tissue activator and uric acid in stroke reduces lipid peroxidation and prevents a reduction in uricemia in the early period (but does not change the lethality and the CNS state in the late period of the disease). A multicenter clinical study of phase III to identify the benefits of such therapy was started (Amaro et al., 2008).

RELATIONSHIP BETWEEN THE TOTAL POOL OF URIC ACID AND ITS METABOLISM IN THE CNS AND THE TRANSPORT OF URIC ACID THROUGH THE BLOOD-BRAIN BARRIER

The presence of uric acid in the brain was confirmed by Toshihiko et al. (1984) and Mueller et al. (1985). In contrast to the data obtained by López Jiménez et al. (1989), the presence of xanthine oxidase in the brain was also proved (Bowman et al., 2010). Thus, the formation of uric acid in situ is possible. It was shown in vivo that uric acid is synthesized in the striatum of rat brain and that allopurinol administered intracranially or intraperitoneally reduces its amount (Mueller et al., 1985). After allopurinol infusion, the basal content of uric acid in the striatum is reduced by 26% (Nomikos et al., 1994). Since the striatum is related to the formation of complex motor acts and behavior aimed at procuring food, these patterns may be important in the context of the above behavioral responses that are sensitive to hyperuricemia.

Repeated intravenous administration of allopurinol to dogs leads to its accumulation at high concentrations in the cerebrospinal fluid and inhibition of xanthine oxidase in the subarachnoid space. The decrease in the level of uric acid in the cerebrospinal fluid is more pronounced than in the blood plasma; however, this decrease is not associated with the systemic inhibition of xanthine oxidase (Kim et al., 1987).

On the other hand, xanthine oxidase does not function in all CNS structures. Allopurinol does not affect the transport of hypoxanthine through the basolateral membrane of the choroid plexus of the sheep brain ventricles in situ, indicating the absence of synthesis of xanthine from hypoxanthine and uric acid from xanthine in these brain regions (Redzic et al., 2002).

Electroshock causes a twofold increase in uricemia and changes the concentration of uric acid in the rat striatum interstitium; however, the latter is caused by the disruption of functions of the blood-brain barrier. Accordingly, a single injection of allopurinol into the striatum has no effect on the increase in the level of uric acid in it, and a course systemic administration of allopurinol prevents it (Nomikos et al., 1994).

Normally, uric acid is not actively transported from the blood into the brain: the ratio of its concentrations in the blood serum and cerebrospinal fluid is 10 : 1 (Becker et al., 2004) or 14 : 1 (Ames et al., 1981). For 99% of examined subjects, the dependence $y = 0.1x \pm 0.010$ mm/L was shown, where x and y is uric acid in the blood and CSF, respectively (Reiber et al., 1993). A similar relationship was shown in individuals with Alzheimer's disease, which indicates that uric acid is synthesized outside the CNS and its access to the brain is limited (Bowman et al., 2010). Nevertheless, the factors that cause the high levels of uric acid in the

cerebrospinal fluid in meningitis include not only the blood-brain barrier dysfunction, changes in the liquor dynamics and neutrophilia in the CNS, but also an increase in the level of hypoxanthine and xanthine or the activity of xanthine oxidase in the CNS (Ueda et al., 1985).

A question arises as to the mechanisms of membrane transport of purines through the blood-brain barrier. It is known that nucleic acids and ATP are always formed from amphibolic intermediates but not from the purine bases coming with food. The brain, like some other tissues, is not able to synthesize purine nucleotides *de novo* because of the small amount of pyrophosphoribosyl pyrophosphate amidotransferase and depends on the entry of purine bases or nucleosides synthesized by the liver (Murray et al., 1993).

The transport of purine bases and nucleosides through the basolateral membrane is performed by different systems. Significant saturable transport of adenine, adenosine, guanosine, and inosine through the blood-brain barrier was shown. There are two independent transport systems. In one of these, cross-inhibition is performed by guanosine and inosine; in the other, it is performed by adenine, adenosine, and hypoxanthine. The latter was studied in the choroid plexus of the brain ventricles in situ; it was shown that hypoxanthine transport across the basolateral membrane does not depend on Na^+ ions and can proceed in both directions. The capacity of this transport system is great and comparable to those of some amino acids; simple diffusion is almost not observed. However, it is known that in vivo this system mainly provides the excretion of purines from the cerebrospinal fluid into the blood (Redzic et al., 2002).

The presence of xanthine oxidase in the brain capillaries is also worth mentioning, which largely determines the activation of free radical processes (e.g., in ischemia). For example, the activity of xanthine oxidase in rat brain capillaries is 3.7 times larger than in the cortex homogenates. When capillaries are incubated with xanthine, the latter is rapidly captured and the amount of xanthine and uric acid increases, which is prevented by allopurinol (Betz, 1985). The system that ensures the transport of hypoxanthine also transports adenine. In contrast to the studies by Redzic et al. (2002) of the perfused choroid plexus of brain ventricles, which showed that this system transported purines from the cerebrospinal fluid into the blood, Betz (1985) showed that hypoxanthine is transported from the blood to the brain after bolus injections of substances into the carotid artery.

Possible Targets of Uric Acid and the Involvement of Receptor Systems

Purinergic signalling is among the most ancient regulatory systems. In the 1970s, Burnstock demonstrated the existence of purinergic neurons. The characteristic features of purinergic neurotransmission are summarized in a fundamental review (Burnstock, 2007). Two subtypes of purine receptors were distinguished: P_1 receptors, the ligand of which is adenosine (four subtypes: A_1, A_{2A}, A_{2B}, and A_3) and P_2 receptors, the ligands of which are ATP and ADP. The antagonism of methylxanthines (including caffeine) with respect to adenosine receptors is well known. The stimulation of rats' locomotor activity by caffeine is mediated by A_1 receptors (Antoniou et al., 2005). However, unlike caffeine, uric acid has no effect on the binding of adenosine by A_1 receptors of the brain (Hunter et al., 1990). Analysis of these systems in detail is beyond the scope of this review. We shall only mention the study by Schmidt et al. (2009), who showed in several models the antinociceptive properties of allopurinol, which are realized through A_1 receptors when the level of adenosine and other purines in the cerebrospinal fluid increases.

When released into the extracellular space, ATP and GTP, guanosine, adenosine, hypoxanthine, and xanthine are involved in the intercellular interactions. In the CNS, they mediate both the immediate reactions and longer responses. After ischemia or injury, an active release of endogenous purines (especially guanosine and, to a lesser extent, adenosine) is observed, which ensure the trophic effects that are realized through the purinergic receptors on the cell membrane surface or after the entry of purines into the intracellular media. It was shown long ago (Essman, 1967) that the functions of the CNS (including memory) can be normalized by the administration of exogenous precursors of nucleic acids, as well as by uric acid. These data were confirmed by Chen et al. (2000), who showed that the memory of senescence-accelerated mice improved after the administration of a mixture of nucleotides and nucleosides. The efficacy of purine derivatives in restoring memory in Alzheimer's disease is currently studied in clinical practice (preclinical studies showed that they increase the level of neurotrophic factors). In this context, it is also possible to modulate other neurotransmitter systems, such as glutamate exchange (Rathbone et al., 1999).

Moreover, purines can control the ratio of activities of the sympathetic and parasympathetic systems by modulating the adrenergic and cholinergic transmission. Unlike methylscopolamine, which does not penetrate the blood-brain barrier, scopolamine increases the extracellular levels of uric acid in the striatum of mice, whereas pilocarpine has an opposite effect (Mueller, 1987).

The pharmacological effects of adrenergic agents can be partially realized through the purine receptors. The distribution of uric acid in the CNS structures corresponds to that of catecholamines; a release of catecholamines can stimulate the synthesis of uric acid (Rovda and Kazakova, 2003). Rovda et al. (1993) showed that blood sera with increased levels of uric acid stimulated the electrophysiological effects of snail neurons. The stimulation of the sympathetic fibers in the caudate nucleus of rats (which abounds in dopam-

inergic neurons) led to the activation of the synthesis of uric acid (Mueller et al., 1985), which was suppressed by α-adrenergic blockers (Puschel et al., 1987). On the other hand, it was shown that, in hyperuricemic guinea pigs, the level of uric acid in the striatum and substantia nigra increased (allopurinol had an opposite effect) and that the content of noradrenaline in the striatum also increased (Church and Rappolt, 1999). The influence of catecholamines on the activity of ATPases and monoamine oxidase and, therefore, on the excitability of neurons is associated with the inhibition of lipid peroxidation. Uric acid can have a similar inhibitory effect; its possible role in the implementation of CNS functions that are mediated by catecholamines was assumed (Toshihiko et al., 1984; Rovda and Kazakova, 2003). Catecholamines attract the attention of researchers in terms of a possible relationship between hyperuricemia and exploratory behavior, because Rotenberg (2001) considers catecholaminergic mechanisms as a basis of the latter.

There is evidence for the neurotransmitter or neuromodulatory role of purines with respect to benzodiazepine receptors. Inosine and hypoxanthine are considered to be endogenous ligands of the latter (Skolnick et al., 1980; Wagner and Katz, 1983). The affinity of these compounds is much lower than that of the classical ligands. However, the possibility of purinergic modulation in vivo is confirmed by the increase in the amount of purines during depolarization and a relatively small amount of receptors required for the realization of the effect of benzodiazepines (Skolnick et al., 1980). The anxiogenic effects of purines realized through benzodiazepine receptors, which can be involved in the mechanism of their action on behavior and motivation, were shown in vivo (Wagner and Katz, 1983). Inosine, 2-deoxyinosine, and 2-deoxyguanosine can completely eliminate the increase in exploratory responses caused by diazepam at doses that do not change the behavior of intact mice, whereas 7-methylinosine, which shows no affinity for benzodiazepine receptors in vitro, has no such effect (Crawley et al., 1981). Guanosine monophosphate has an anxiolytic effect on rats in the elevated plus maze and in the light/dark preference test in rats, similarly to diazepam. However, it does not change the results of the open-field test and the content of purines in the cerebrospinal fluid (Almeida et al., 2010).

The purinergic system is closely associated with the serotonergic system and the folic acid exchange. These systems are capable of mutual compensation when the functions of the CNS are disturbed (Brooks et al., 1978).

The purinergic system is regarded as a promising target of influence on the pathogenesis of bipolar disorder and depression. Persons with bipolar disorder who did not receive treatment until the survey had hyperuricemia. The efficacy of allopurinol in the complex therapy correlated with changes in uricemia (Machado-Vieira et al., 2011).

Purines modulate the effects of neurotransmitters that are important in the pathogenesis of depression, namely, dopamine, γ-aminobutyric acid, and serotonin (Machado-Vieira et al., 2011). In rat striatum, a correlation between the uric acid levels and the dopamine metabolite homovanillic acid was found. The extracellular uric acid levels in the substantia nigra changed after infusion of γ-aminobutyric acid and haloperidol, which was associated with changes in the dopamine exchange (Neill, 1990). Systemic administration of morphine increases the amount of uric acid (as well as dopamine, serotonin, and dopamine metabolites) in the rat striatum. Morphine enhances the oxidative metabolism of both dopamine and xanthine by the receptor mechanism (Enrico et al., 1998). Amphetamine, which causes dopamine release, changes the pool of uric acid: it dose-dependently increases its amount in the caudate nucleus and nucleus accumbens (a similar effect on the uric acid pool is exerted by pilocarpine, which was discussed above). The elimination of this effect by haloperidol indicates that changes in uric acid metabolism are associated with a dopamine exchange (Mueller, 1990).

The release of dopamine with the activation of appropriate receptors can occur simultaneously with changes in the uric acid level in the striatum. However, the relationship between the exchange of dopamine and uric acid in rat striatum is chronodependent (the correlation between the concentrations is detected in the daytime). At night, the level of dopamine metabolites increases, whereas the uric acid level is unchanged compared to the daytime period and varies during the shift from day to night and night to day (Neill, 1990). The last fact can also testify to the activatory role of uric acid.

In light of the involvement of purines in the realization of food behavior, it should be noted that the dopaminergic processes in the nucleus accumbens are regarded as a temporal modulator of this behavior. Rats receiving a food reward demonstrated an increased amount of uric acid and then an increased amount of the dopamine metabolite homovanillic acid in the caudate nucleus and nucleus accumbens. These changes were reproduced in certain animals for 3 months (Joseph and Hodges, 1990).

Thus, the results of research in many fields and at different organizational levels of living organisms confirm the possibility of the influence of uric acid on behavioral responses, cognitive functions, and the motivation to be active. Of course we are far from associating integrated phenomena, such as processes in the CNS, with a single substance. It would be also incorrect to consider hyperuricemia only in a positive aspect, without regard to its role in the pathogenesis of "diseases of civilization." However, the responsiveness of the CNS to uric acid, including the evolutionary aspect—the evolution of intellectually developed primates and their subsequent motivation to be active—should not cause principal objections. Further studies in this field are required.

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