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Amino acids and acylcarnitines as potential metabolomic markers of schizophrenia: new approaches to diagnostics and therapy

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ABSTRACT

Background. Schizophrenia is a socially significant mental illness with insufficiently studied etiology and pathogenesis. A number of hypotheses of schizophrenia pathogenesis (dopamine, glutamate, kinurenin and serotonin hypotheses) bring together the fact that amino acids are precursors or intermediate metabolic products of these metabolites. Amino acids and their metabolites play an important role as significant substrates and regulators in many metabolic pathways.

The aim of this review is to analyze the literature data on the studies of amino acids and acylcarnitines in patients with schizophrenia.

Methods. A literature search was conducted using PubMed databases for articles published in English and covering the period from the first articles on this topic, dated 1977 to April 2019. Combinations of the following keywords were used to search for “schizophrenia”, “antipsychotics” and “amino acids”, “acylcarnitines”, “metabolomics”.

Results. The review summarizes the data on the content of amino acids and acylcarnitines in the peripheral blood of schizophrenia patients and their dynamics in the course of pharmacotherapy with antipsychotic drugs. The potential of determining amino acids as biomarkers of therapeutic response and side effects, as well as their use in the treatment of patients with schizophrenia, are considered.

Conclusion. Further investigation of the spectrum of amino acids and their metabolites with the using of mass spectrometric methods of metabolic analysis can lead to the discovery of new therapeutic targets and strategies, assess their role in the pathophysiology of schizophrenia, identify mechanisms that ensure the development of antipsychotic antipsychotics, and drug-induced side effects antipsychotics, in particular, **metabolic syndrome.**

Key words: amino acids, acylcarnitines, schizophrenia, antipsychotics, metabolomics, potential marker.

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Аминокислоты и ацилкарнитины как потенциальные метаболомные маркеры шизофрении: новые подходы к диагностике и терапии

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РЕЗЮМЕ

Введение. Шизофрения относится к социально значимым психическим заболеваниям с недостаточно изученной этиологией и патогенезом. Целый ряд гипотез патогенеза шизофрении (дофаминовую, глутаматную, кинуреновую и серотониновую) объединяет то, что предшественниками или промежуточными продуктами обмена этих метаболитов являются аминокислоты. Аминокислоты и их метаболиты играют важную роль в качестве основных субстратов и регуляторов во многих метаболических путях.

Цель – анализ литературных данных об исследованиях аминокислот и ацилкарнитинов у больных шизофренией.

Методы. Литературный поиск был проведен с использованием базы данных PubMed для статей, опубликованных на английском языке по данной тематике в период с 1977 по апрель 2019 г. Были применены комбинации следующих ключевых слов для поиска: «шизофрения», «антипсихотики» и «аминокислоты», «ацилкарнитины», «метаболомика».

Результаты. В обзоре обобщены данные о содержании аминокислот и ацилкарнитинов в периферической крови больных шизофренией и их динамика в процессе фармакотерапии антипсихотическими препаратами. Рассмотрены потенциальные возможности определения аминокислот в качестве биомаркеров терапевтического ответа и побочных эффектов, а также их применение в комплексной терапии больных шизофренией.

Заключение. Дальнейшее исследование спектра аминокислот и их метаболитов с помощью современных масс-спектрометрических методов метаболомного анализа может привести к открытию новых терапевтических мишеней и стратегий; позволит оценить их роль в патофизиологии шизофрении, выявить механизмы, обеспечивающие как развитие антипсихотического эффекта нейролептиков, так и лекарственно-индуцированных побочных эффектов антипсихотиков, в частности метаболического синдрома.

Ключевые слова: аминокислоты, ацилкарнитины, шизофрения, метаболомика, потенциальный маркер, антипсихотическая терапия.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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INTRODUCTION

According to modern foreign lines of research, the use of omic's technologies in psychiatry and neurology will allow a breakthrough in understanding the neurobiology of mental and neurodegenerative disorders. These technologies have great potential for promoting an understanding of the biochemical and molecular foundations of these disorders and can, in turn, develop and improve diagnostic and therapeutic technologies [1–4].

Schizophrenia is considered a socially significant mental illness with insufficiently studied etiology and pathogenesis [5]. A number of hypotheses of the pathogenesis of schizophrenia (dopamine, glutamate, kynurenic and serotonin) are united by the fact that amino acids are the precursors or intermediate products of metabolism of these metabolites. Amino acids and their metabolites play an important role as the main substrates and regulators in many metabolic pathways [6]. The first studies of the level of individual amino acids in peripheral blood and cerebrospinal fluid in schizophrenia date back to the 1980s, are intensively ongoing at present and have received new development with the widespread introduction of modern mass spectrometric metabolic methods [7–10].

The purpose of this review is to analyze the literature on studies of amino acids and acylcarnitines in patients with schizophrenia.

A literature search was conducted using the PubMed database for articles published in English or other languages, but with an abstract in English. The depth of the search covers the period from the first articles on this topic dated 1977 to April 2019. Such a search allows us to evaluate the interest in the role of amino acids in the pathogenesis of schizophrenia as in historical aspect, and relevance, and scientific novelty at the present stage of development of medical science. The following keywords and their combinations were used to search: "schizophrenia", "antipsychotics" and "amino acids", "acylcarnitines", "metabolomics".

STUDY OF THE ROLE OF AMINO ACIDS AND ACYLCARNITINES IN THE PATHOGENESIS OF SCHIZOPHRENIA

The most studied amino acid and its role in the pathogenesis of schizophrenia is glutamate, which is associated with the development of the glutamatergic hypothesis of schizophrenia. Glutamate is the predominant excitatory neurotransmitter of the central nervous system, acting on different types of receptors, among which N-methyl-D-aspartate (NMDA) glutamate receptors, kainate-glutamate receptors and metabotropic glutamate receptors are distinguished. Glutamate plays a critical role in synaptic maintenance and plasticity, and is also involved in learning and memory formation [11]. A number of independent studies have shown an increase in the level of serum glutamate in patients with schizophrenia [8, 9, 12–16] and its correlation with the duration of the disease [17, 18]. One recent study showed that glutamate levels were elevated both in patients with the first episode of schizophrenia and in healthy individuals at high risk for schizophrenia [9]. In a study by M. Orešič et al. (2011) it was shown that the content of glutamate in serum in various psychoses (schizophrenia, bipolar affective disorder and non-affective psychosis) is increased in all cases of psychoses compared with healthy volunteers, which allowed the authors to suggest a common metabolic abnormality associated with glutamate in psychotic disorders [13]. In connection with the latest trends in foreign literature, the search for peripheral disease markers raises the question of a possible correlation of the concentration of metabolites in the brain and on the periphery. According to some researchers, the dependence of glutamate concentrations between the brain and blood is weak due to the limited and strictly controlled passage of glutamate through the blood-brain barrier [19]; the level of serum glutamate does not correlate with the level of glutamate in the brain, measured using nuclear magnetic resonance spectroscopy [20]. At the same time, a change in serum glutamate level may have neurological significance, since it is closely related to the metabolism of γ-aminobutyric acid, the main inhibitory neurotransmitter, in addition, it may indicate an insufficient energy supply to the brain during schizophrenia, since glutamate is mobilized as an alternative fuel glucose with insufficient intake of the latter in the brain [14]. Earlier studies demonstrated a correlation between the following amino acids in the plasma and cerebrospinal fluid of healthy volunteers: glutamate, glutamine, threonine, serine, glycine, methionine, leucine, tyrosine, phenylalanine, ornithine, lysine, histidine, arginine [21]. Studies by G. Alfredsson confirm a positive correlation between glutamate levels in cerebrospinal fluid and serum [22]. Data on the content of other amino acids in the blood serum of patients with schizophrenia are contradictory. In the work of L. Bjerkenstedt et al. (1985) noted significantly higher plasma concentrations of taurine, methionine, valine, isoleucine, leucine, phenylalanine and lysine in patients with schizophrenia compared with

the control group of the subjects. The resulting data was interpreted as a change in the affinity of the L-transport system for neutral amino acids or a decrease in its overall transport ability in schizophrenia. Elevated plasma levels of competing amino acids can limit brain absorption by tyrosine, which leads to a compensatory increase in the sensitivity of dopamine receptors [23]. T. Fukushima et al. (2014) explain the change in the metabolic composition of the serum of patients with schizophrenia with oxidative stress, which may be involved in the pathogenesis of this disease. The authors found that the levels of γ-glutamylcysteine, linoleic acid, arachidonic acid, D-serine, 3-hydroxybutyrate, glutathione, 5-hydroxytryptamine, threonine and tyrosine were significantly lower, while the levels of D-lactate, tryptophan, kynurenine and glutamate were significantly higher in patients with schizophrenia compared with healthy individuals [17]. When studying the level of L-arginine in patients with the first episode of schizophrenia, there were no statistically significant differences in this metabolite between the group of patients and healthy people [24]. A study of glycine, serine, and glycine/serine ratios in patients with schizophrenia who did not receive antipsychotic therapy revealed that glycine and glycine/serine ratios were reduced in patients with schizophrenia compared with the control group. Serine levels were increased in patients with schizophrenia, while no differences were found with antipsychotics [25]. Plasma levels of D-serine and the ratio of D-serine to total serine were significantly lower in individuals with schizophrenia compared with healthy donors, with D-serine levels negatively correlating with negative symptoms of schizophrenia [26]. In earlier studies, it was shown that in addition to lowering the level of D-serine and the ratio of D-serine to total serine, there is an increase in total (D- and L-) serine and L-serine in patients with schizophrenia [27]. When analyzing correlations with positive and negative symptoms of schizophrenia, negative correlations of serine levels and negative schizophrenia symptoms were confirmed, and correlations were also found between glycine levels and negative and positive symptoms on the PANSS scale [28]. Based on the reduction of schizophrenia symptoms after administration of D-serine, I. Bendikov et al. (2007) suggested a decrease in the level of endogenous D-serine due to a decrease in its synthesis or an increase in degradation in the brain. They showed a decrease in the level of D-serine and the ratio of D-serine to L-serine in the cerebrospinal fluid of patients with schizophrenia [29]. Other studies have confirmed a decrease in the level of D-serine in cerebrospinal fluid in men with the first episode of schizophrenia [30]. In addition, significantly higher levels of alanine, glycine, leucine and phenylalanine are found in the cerebrospinal fluid of patients with schizophrenia compared with healthy people [31]. The position that the impaired metabolism of D-serine may be a predictor of schizophrenia has been confirmed in recent articles [32, 33]. S. Saleem al. (2017) reports an increased concentration of glycine, serine, glutamate, homocysteine and arginine in the blood of patients with schizophrenia [34]. In a study of the activity of phosphoserine phosphatase (PSP), an enzyme that limits the rate of L-serine synthesis in peripheral mononuclear blood cells of patients with schizophrenia, it was shown that the concentration of L-serine in blood plasma was statistically significantly higher only in male patients [35]. In a study by Y. He (2012), four amino acids — arginine, glutamine, histidine, and ornithine — were proposed as candidates for schizophrenia biomarkers [36]. In 2013, a large-scale study was conducted involving more than 100 patients with schizophrenia and healthy volunteers to search for potential biological markers of this disease and develop a diagnostic test system [14]. With the help of metabolic profiling of blood serum, an increase in the content of glutamate, aspartate, hydroxyproline, serine, phenylalanine, glyceric, tetradecanoic, hexadecanoic, oleic, octadecanoic, β-hydroxybutyric, pyruvic, linolenic, and eicosenoic acids in the blood was shown to decrease. A metabolic analysis of urine revealed statistically significant increases in cystine, valine, isoleucine, glutamate, suberic, 3-hydroxysebaric, 3-hydroxyadipic, 2-ethyl 3-hydroxypropionic, 4-pentenoic and threonine, β-hydroxybutyric acids, as well as a decrease in 2, 3-hydroxybutanoic, glycolic acids. Within the identified metabolites, a diagnostic panel for the prognosis of schizophrenia was proposed, including five metabolites (glyceric, eicosenoic, β-hydroxybutyric, and pyruvic acids, and cystine) [14].

B. Cao (2018) showed an increase in the concentrations of serum cysteine, γ-aminobutyric acid, glutamine and sarcosine and a decrease in arginine, L-ornithine, threonine, taurine, tryptophan, methylcysteine and kynurenine in the group of schizophrenia patients, adjusted for gender, age and index body weight compared to healthy individuals. In addition, in patients with the first episode of schizophrenia, in contrast to patients with recurrent schizophrenia, a decrease in the level of aspartate and an increase in the level of glutamine in the blood serum were recorded [37]. Recent studies on

the association of increased tryptophan degradation with changes in the integrity of the white matter of the brain and the level of glutamate in the white matter of the brain in patients with schizophrenia are of interest. A decrease in tryptophan levels and an increase in the ratio of kynurenine / tryptophan in patients compared with the control were revealed. In patients with schizophrenia, a decrease in plasma tryptophan levels corresponded to a lower structural integrity of the white matter of the brain. In both patients and healthy people, the kynurenine/tryptophan ratio inversely correlated with the level of glutamate in the white matter of the brain [38].

In recent years, few studies have appeared in which acylcarnitines, intermediate products of the oxidation of fatty and organic acids, are also proposed as biomarkers of complex diseases [39]. Acylcarnitine is involved in energy production through □-oxidation of fatty acids and detoxification of metabolites through the formation and excretion of acylcarnitine esters. A connection was found between the increase in the concentration of branched amino acids and acylcarnitines containing an odd number of carbon atoms [39]. In the work of M.L. Liu et al. (2015) it was shown that in schizophrenia changes in metabolites are mainly associated with acylcarnitine metabolism, lipid metabolism and tryptophan metabolism, which leads to a combination of biomarkers, including C10:1 acylcarnitine and tryptophan [40]. Analysis of the spectrum of 29 acylcarnitines in the blood plasma of 225 patients with schizophrenia and 175 healthy people, comparable by age and sex, showed significantly higher levels of C4–OH (C3–DC) and C16:1, against the background of low concentrations of C3, C8, C10, C10:1, C10:2, C12, C14:1–OH, C14: 2, and C14:2–OH in patients with schizophrenia compared with healthy individuals [41].

An analysis of the literature data allows us to conclude that in most studies, higher concentrations of glycine, serine, glutamate, homocysteine and arginine in blood samples of patients with schizophrenia are detected. Regarding the level of other amino acids in the literature, conflicting results are presented.

AMINO ACIDS AS THERAPEUTIC RESPONSE MARKERS ON ANTIPSYCHOTIC THERAPY AND DRUG-INDUCED SIDE EFFECTS

The next area of research is the study of the effect of antipsychotic therapy on the amino acid spectrum and the possibility of using these indicators to predict the response to therapy. In the study by T.Y. He et al. (2012), five amino acids were identified (arginine, glutamine, histidine, ornithine and methionine), significantly different in patients with schizophrenia compared with healthy individuals, and their content was analyzed depending on the use of antipsychotic therapy. As a result, data were obtained on a higher content of ornithine and a reduced content of arginine, glutamine and histidine in patients with schizophrenia who are not receiving antipsychotic therapy compared with a group of healthy individuals [36]. Asparagine, citrulline, phenylalanine and cysteine were higher, while tyrosine and tryptophan were significantly lower in patients not receiving antipsychotic therapy than in healthy people. Patients taking antipsychotics showed an increased level of asparagine compared with patients without therapy, an increase in phenylalanine and a decrease in tryptophan, in contrast to the control group of volunteers [42]. There was a decrease in tyrosine content in patients with the schizophrenia onset before age 20 and not receiving therapy, and a lower tyrosine/phenylalanine ratio compared to patients with the late onset of schizophrenia (after 20 years) [43]. A study of the effect of the atypical antipsychotic clozapine on serum amino acids revealed significantly higher levels of serum aspartate, glutamate, isoleucine, histidine and tyrosine and significantly lower concentrations of serum asparagine, tryptophan and serine in patients with schizophrenia who are resistant to clozapine treatment compared to control. Clozapine treatment for 12 weeks significantly reduced serum glutamate level, but did not approach the level of healthy volunteers and did not affect the concentration of other amino acids [44]. However, A.E. Evins et al. found that treatment with clozapine increases serum aspartate levels, with clinical improvement negatively correlating with baseline glycine concentrations [45]. A change in the content of peripheral amino acids during treatment with clozapine in patients with schizophrenia resistant to therapy has been shown in other studies. Thus, a decrease in plasma D-serine and the ratio of D-serine/L-serine was found, and this ratio, as well as the level of glycine and the ratio of glycine/L-serine, increased significantly after clozapine therapy. The results obtained led to the conclusion that these amino acids and their ratios can be markers of therapeutic efficacy in patients with a therapeutically resistant form of schizophrenia [46]. When examining the content of glycine, serine, alanine, and homocysteine in patients receiving different antipsychotic

therapy (typical antipsychotics, clozapine, risperidone/olanzapine), it was found that patients had a lower plasma serine level compared to the control, correlating with the number of negative symptoms of schizophrenia. The serine/glycine ratio was also reduced in patients, while plasma homocysteine level, on the contrary, was significantly increased. Despite the fact that no differences in the absolute level of amino acids were found depending on the type of antipsychotic taken by patients, the serine/glycine ratio was significantly increased in patients treated with clozapine and was practically comparable with the level in healthy individuals [47]. Monotherapy with an atypical antipsychotic risperidone led to an increase in tryptophan levels after 8 weeks of treatment and serum phenylalanine, but it further reduced the levels of aspartate and glycine lowered before the start of therapy [48]. The content of a number of amino acids can be used to assess the prognosis of response to therapy (responders and non-responders). Patients without response to therapy showed lower baseline methionine values compared with patients with good clinical response and healthy volunteers; the ratio of tryptophan to other large neutral amino acids in patients not responding to antipsychotic therapy decreased during treatment compared with patients with a good clinical response [15]. Of the wide range of metabolic biomarkers studied by B. Cao (2018), six – oleoylcarnitine, linolylcarnitine, L-acetylcarnitine, LysoPC, D-glutamic acid and L-arginine – were identified as the most stable and predictably changed during 8 weeks of treatment with antipsychotic drugs [49].

Changes in homocysteine levels were associated with gender and basic metabolic parameters (body mass index, glucose, triglycerides and other indicators) in schizophrenia patients with the first episode receiving monotherapy with atypical antipsychotics (olanzapine or rispiridone) [50].

A study by L. Leppik (2018) demonstrated changes in the content of the spectrum of amino acids and biogenic amines, associated simultaneously with the dynamics of some indicators of the metabolic syndrome, in particular with body mass index (BMI), after antipsychotic therapy after 7 months in patients with the first episode schizophrenia. A positive association of BMI with changes in proline, aspartate, histidine, α-aminoadipic acid, alanine, and kynurenine under the influence of antipsychotic therapy was demonstrated. In contrast, the content of taurine and spermine was negatively associated with an increase in BMI during pharmacotherapy [51].

Thus, there is practically no study of the role of amino acids in the development of undesirable severe side effects of antipsychotic therapy, with the exception of studies of glutamate, for which it is proven that it participates in the mechanisms of development of tardive dyskinesia [52]. At the same time, in recent years, there has been a need to search for potential biomarkers for the development of undesirable effects for predicting their occurrence, especially the metabolic syndrome, which comes to the fore in the frequency of its occurrence and the burden of medical, economic and social consequences against the background of the widespread use of atypical antipsychotics [49, 53].

PROSPECTS FOR APPLICATION OF AMINO ACIDS, ACYLCARNITINES AND DRUGS INFLUENCING THEIR EXCHANGE IN COMPLEX THERAPY OF PATIENTS WITH SCHIZOPHRENIA

Identified changes in the amino acid spectrum create the prerequisites for the development of promising new therapeutic strategies in terms of the use in the treatment of mental disorders of amino acids or drugs that affect their metabolism [54–60].

The first experimental use of glycine in preclinical models of schizophrenia was carried out before the role of NMDA receptors in mediating the psychomimetic effects of phenylcyclidine and glycine was demonstrated. In the early to mid-1980s, Tothand Lajtha, firstly, demonstrated that non-essential amino acids cross the blood-brain barrier when administered in high doses, and secondly, of a number of amino acids, only glycine reduces the behavioral effects caused by phenylcyclidine. The first randomized, double-blind, clinical trial showing a significant reduction in the negative symptoms of schizophrenia in response to glycine was published in 1994 [55]. This was later confirmed in a number of independent studies [54, 56, and 57]. When comparing the effects of glycine and cycloserine on the negative symptoms of schizophrenia, it was found that glycine consumption gives a more pronounced clinical response. This suggests that complete agonists such as glycine and D-serine may be more effective than partial agonists such as D-cycloserine [56], while other placebo-controlled studies have not shown the benefit of glycine therapy for compared with placebo for the negative symptoms of schizophrenia [61].

Based on the positive clinical results with glycine, a series of studies was conducted with an al-

ternative glycine site agonist, D-serine [62]. The initial clinical trial included 29 patients treated for 6 weeks with either D-serine or placebo. A significant reduction in the negative symptoms of schizophrenia has been shown in patients receiving D-serine [63]. These results were subsequently reproduced in other works [64–66]. However, when studying the effect of low doses of D-serine, there was no significant difference between taking the drug and placebo [67]. Similar results were also obtained in a study using D-alanine, an agonist with a lower affinity for the glycine site of the NMDA receptor [68].

Nevertheless, large doses of amino acids necessary for clinical improvement make them inappropriate for wide therapeutic use, which requires alternative approaches.

Blockade of the type 1 glycine transporter to inhibit glycine reuptake and increase synaptic glycine concentration is an effective strategy to increase N-methyl-D-aspartate receptor transmission. For this purpose, a study was conducted on the drug bitopertin, a glycine reuptake inhibitor, in patients with schizophrenia with predominant negative symptoms who are resistant to antipsychotic therapy. As a result, treatment with bitopertin for 8 weeks was associated with a significant reduction in the negative symptoms of schizophrenia. Thus, bitopertin-mediated inhibition of glycine reuptake may represent a new treatment option for schizophrenia with the possibility of eliminating negative symptoms [69].

Inhibition of D-amino acid oxidase, an enzyme that catabolizes D-amino acids, such as D-serine and D-alanine, can increase the availability of NMDA receptor glycine site agonists [70]. Sodium benzoate is a natural D-amino acid oxidase inhibitor approved by the FDA as a safe food preservative. In a small, randomized, double-blind, placebo-controlled study, sodium benzoate significantly improved the positive, negative, and cognitive symptoms in schizophrenic patients taking additional antipsychotics. Although larger studies are needed to confirm these results, it opens up prospects for the development of new drugs based on inhibition of D-amino acid oxidase [70].

A 12-week open, uncontrolled study was conducted aimed at studying the effectiveness of acetyl-L-carnitine on clinical symptoms and cognitive functioning in 15 patients with schizophrenia while taking clozapine. However, the analysis of the data of nine patients who completed the study completely did not show significant differences between different treatment methods, which can be associated with an extremely small sample size [71].

A meta-analysis of 10 studies on the effect of biologically active fatty acid supplements on standard antipsychotic therapy for patients with schizophrenia showed positive results in terms of improving psychotic symptoms and (or) reducing extrapyramidal side effects from antipsychotic drugs [72].

CONCLUSION

Thus, we can state the fact that in recent years the number of works has been steadily growing, in which modern proteomic and metabolic methods of analysis attempt to identify biomarkers of mental and neurodegenerative disorders in the serum or plasma of patients [73–75]. Most of the literature data was obtained on small cohorts of patients. The ambiguity and inconsistency of a number of studies are due to the varying duration of the disease, the therapy used, the leading symptoms and other factors.

As a rule, small molecules and metabolic products are involved in various pathways of molecular transformations, which makes it difficult to use individual substances as potential biomarkers. In this connection, it is promising to solve this problem by simultaneously determining the metabolic spectrum of a number of molecules, the combined changes of which can already serve as potential biomarkers.

Based on the analysis of the literature, it seems to us that the most promising potential biomarkers are amino acid and acylcarnitine profiles in the aggregate, further study of which may lead to the discovery of new therapeutic targets and strategies, and will also help to better understand the pathophysiology of schizophrenia along with a deeper knowledge of the mechanisms that provide for the development of therapeutic effect, and drug-induced side effects of antipsychotics, in particular metabolic syndrome.

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