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Research Article

Psychic trauma causes increased impulsivity in a model of gambling addiction by altering dopamine and serotonin metabolism in the prefrontal cortex

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ABSTRACT

BACKGROUND: Gambling addiction (gambling) involves frequently repeated episodes of gambling that are detrimental to social, professional, material, and family values. Gambling addiction is often combined with posttraumatic stress disorder.

AIM: This study aimed to examine the effect of predator presentation stress on the manifestations of gambling addiction in an animal model in a test of probability and magnitude of reinforcement in the Iowa gambling task and monoamine metabolism in the prefrontal cortex of rats.

MATERIALS AND METHODS: Rats were trained in a test of probability and magnitude of reinforcement in the Iowa gambling task in a 3-beam maze. Each run in arm 1 of the maze was reinforced with one sunflower seed, each second run in arm 2 with two seeds, and each third run in arm 3 with three seeds. Correspondingly, half of the runs in arm 2 and 2/3 of the runs in arm 3 were left unreinforced. After training, the animals were placed in a terrarium with a tiger python, one of which was victimized for its food requirements. On day 14 after predator presentation, dopamine and serotonin metabolism in the prefrontal cortex was determined using high-performance liquid chromatography with electrochemical detection.

RESULTS: The levels of the dopamine metabolite dioxyphenylacetic acid and the ratio of dioxyphenylacetic acid to dopamine in the prefrontal cortex decreased. The levels of serotonin, its metabolite 5-hydroxyindoleacetic acid, and the ratio of 5-hydroxyindoleacetic acid to serotonin in the prefrontal cortex were also decreased in rats after exposure to a predator. Moreover, predator presentation induced significant behavioral changes in rats, increasing impulsivity in making choices in a test of probability and magnitude of reinforcement in the Iowa gambling task. The acute vital stress of predator presentation increased the number of escapes to arm 3 of the maze, suggesting that the animals exhibited more risky behavior when choosing reinforcements of different strengths and probability.

CONCLUSIONS: The animal model showed that the depletion of the dopaminergic and serotoninergic systems of the prefrontal cortex underlies pathological gambling addiction and inadequate decision-making caused by posttraumatic stress disorder.

Keywords: stress; posttraumatic stress disorder (PTSD); gambling addiction; dopamine; serotonin.

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Научная статья

Психическая травма вызывает повышение импульсивности в модели игровой зависимости, изменяя обмен дофамина и серотонина в префронтальной коре

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АННОТАЦИЯ

Актуальность. Игровая зависимость (gambling) включает частые повторные эпизоды азартной игры, которые доминируют в ущерб социальным, профессиональным, материальным и семейным ценностям. Игровая зависимость часто сочетается с посттравматическим стрессовым расстройством.

Цель — изучение влияние стресса предъявления хищника на проявления игровой зависимости на животной модели в тесте вероятности и величины подкрепления в IOWA Gambling task и обмен моноаминов в префронтальной коре головного мозга у крыс.

Материалы и методы. Крыс обучали в тесте вероятности и величины подкрепления IOWA Gambling task в 3-лучевом лабиринте. Каждая побежка в рукаве 1 лабиринта подкреплялась 1 семенем подсолнуха, каждая вторая побежка в рукаве 2 — 2 семенами, каждая третья побежка в рукаве 3 — 3 семенами. Соответственно, половина заходов в рукав 2 и 2/3 заходов в рукав 3 оставались без поощрения. После обучения животных помещали в террариум к тигровому питону, где одно из них становилось жертвой его пищевых потребностей. На 14-й день после предъявления хищника определяли обмен дофамина и серотонина в префронтальной коре головного мозга с помощью высокоэффективной жидкостной хроматографии с электрохимической детекцией.

Результаты. Показано снижение содержания метаболита дофамина диоксифенилуксусной кислоты и отношения содержания диоксифенилуксусной кислоты к содержанию дофамина в префронтальной коре. Обнаружено также снижение содержания серотонина, его метаболита 5-гидроксииндолуксусной кислоты и отношения содержания 5-гидроксииндолуксусной кислоты к содержанию серотонина в префронтальной коре у крыс после контакта с хищником. При этом предъявление хищника вызывало у крыс значительные изменения в поведении, повышая импульсивность в принятии выбора в тесте вероятности и величины подкрепления в IOWA Gambling task. Острый витальный стресс предъявления хищника повышал число побежек в третий рукав лабиринта, что говорит о проявлении у животных более рискованного поведения, наблюдающегося в ситуации выбора подкрепления разной силы и вероятности.

Заключение. На модели у животных показано, что в основе патологической зависимости от азартных игр и неадекватного принятия решений, вызванных посттравматическим стрессовым расстройством, лежит истощение дофаминергической и серотонинергической систем префронтальной коры головного мозга.

Ключевые слова: стресс; посттравматическое стрессовое расстройство (ПТСР); игровая зависимость; дофамин; серотонин.

Как цитировать
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ЭКО•ВЕКТОР

BACKGROUND

Gambling addiction, or simply gambling, involves frequent and repeated episodes of gambling that can negatively affect social, professional, material, and family values [1]. Gambling is often associated with posttraumatic stress disorder (PTSD) [2]. These conditions may share a common cause or arise in response to similar environmental factors. Gambling can provide psychological relief and help avoid PTSD associated symptoms [3]. Gambling can be a form of avoidance experience to cope with PTSD symptoms, such as compulsive and impulsive behavior disorders [4]. It may be a way to avoid negative emotions and tension caused by traumatic experiences. However, excessive gaming can lead to poor mental and physical health, which can worsen PTSD symptoms.

PTSD is a mental and behavioral disorder that can develop after exposure to a highly traumatic event, such as combat, man-made disasters, traffic accidents, sexual assault, child abuse, domestic violence, or other life-threatening situations (National Institute of Mental Health, 2017). The incidence of PTSD ranges from 1% to 12% in the general population and can reach up to 30% in populations affected by emergencies [5].

Military personnel are particularly susceptible to gambling because of the increased risk of PTSD associated with exposure to extreme stressors. Compared with other mental health disorders, gambling in individuals with combat experience is understudied [6]. Studies have shown that military personnel are more likely to develop gambling problems than the general population [7], and military status may be a significant risk factor [8].

A previous study demonstrated a relationship between stressor reactivity and brain dopaminergic, noradrenergic, and serotoninergic activity [9].

Various animal models have been developed to investigate the pathophysiology of PTSD, each mimicking a specific manifestation of the disorder [10]. For this study, the predator presentation exposure model, which is more natural for our model organisms (rats), was used. The model produces behavioral, molecular, and physiological changes that mimic the changes observed in patients with PTSD [11].

In a study of gambling, the authors proposed dividing the complex structure of human gambling into the following subtypes: impulsive, compulsive, and addictive. To investigate the impulsive component of gambling in humans, researchers currently use the IOWA gambling task test. The test design includes unpredictable consequences of choices and the need to apply behavioral skills to maximize long-term gains. Recently, researchers have developed animal models for the IOWA gambling task test, which are mostly complementary but have some features [12].

The ventromedial prefrontal cortex in humans has traditionally been linked to risky decision making. Neuroimaging data suggest that individuals with a smaller volume of the ventromedial prefrontal cortex are more likely to engage in high-risk gambling and have a desire to win [13, 14].

Thus, this study aimed to investigate the effect of predator presentation stress on gambling manifestations in the IOWA gambling task probability and reinforcement value test, as well as monoamine metabolism in the prefrontal cortex of rats.

MATERIALS AND METHODS

This study used 40 male Wistar rats obtained from the Rappolovo Laboratory Animal Nursery located in the Leningrad region.

Modeling the stress of predator presentation

The animals were placed in a terrarium with a tiger python, and one of them became a victim of the predator's nutritional needs. The surviving animals were then kept in the terrarium behind a transparent partition for 30–40 min. Pronounced fear reactions were recorded in rats during psychic trauma and manifested as behavioral acts such as freezing, pile-ups, vertical stands, and prolonged and altered grooming. The animals exhibited agitated and uncontrolled movements within the terrarium. No control group of rats (n = 10) was exposed to any stressors.

IOWA gambling task: probability and reinforcement value test

Before predator presentation, the rats underwent training in a probability and reinforcement value test. The setup comprised two parts: a starting chamber measuring 35 × 50 × 35 cm and three arms measuring 50 × 15 × 35 cm each. An automatic feeder was placed at the end of each arm of the maze. Food reinforcement was present in each arm before the rat was launched into the maze. The next feeding was given when the rat left the arm and returned to the starting chamber. Each day, the animal was placed in the starting chamber and tested by jogging for 10 min without any light or sound cues. The rats were housed in standard plastic cages and fed a special diet. They had access to water at all times; however, their access to food was limited to 4 h per day. Before each test, the rats were deprived of food for 20 h. For 3 weeks, the rats were trained to run in a three-beam maze using the training mode of delivery. During the training period, the rats received one sunflower seed at each choice of arm 1, two seeds were placed in arm 2, and three seeds in arm 3. The training lasted for 5 days. The animals were not tested for the following 2 days. On day 1, the animals had unrestricted

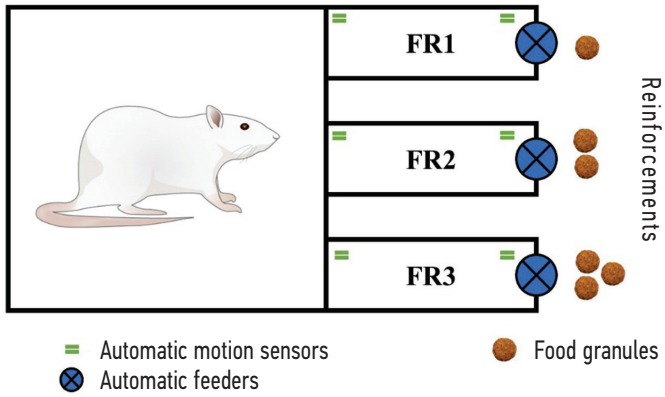

Fig. 1. Schematic of setting the probability test and reinforcement value
Рис. 1. Схема установки теста вероятности и величины подкрепления

Fig. 2. Rat brain and study area
Рис. 2. Головной мозг крысы и область исследования

access to food, whereas on day 2, they were subjected to a 20-h food-deprivation period with free access to water [15, 16].

During the subsequent training stage, the reinforcement feeding method used in the main experiment was implemented, and the reinforcement mode was altered. Feeder 1 dispensed one sunflower seed in the FR1-1 mode (i. e., each run in arm 1 of the maze was reinforced with food), feeder 2 dispensed two seeds in the FR2-2 mode (i.e., every second run in arm 2 was reinforced with food), and feeder 3 dispensed three seeds in the FR3-3 mode (i.e., every third run in arm 3 was reinforced with food) [17]. Predator experiments were started the day after the maze training (Fig. 1).

High-performance liquid chromatography with electrochemical detection (HPLC/ED) method

On day 14 after predator presentation and the day immediately following behavioral impulsivity testing, the animals were euthanized by decapitation. A study found that changes in monoamine metabolism developed gradually after predator presentation, and a decrease in activity was observed in brain structures on day 14. This reflects the development of depression-like states and PTSD [18]. The prefrontal cortex was isolated from coronal brain slices on ice. Rat brain samples were frozen and stored at –80°C until chromatographic analysis. The brain samples were homogenized in 0.1-N HCl and then centrifuged at 14,000 g for 15 min [19]. The levels of dopamine (DA) and its metabolites, dioxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and the levels of 5-hydroxytryptamine (serotonin, 5-HT) and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) were determined using HPLC/ED on a Beckman Coulter chromatographic system with an LC4C amperometric detector (BAS). The levels of monoamines and their metabolites in brain structures were expressed in ng/mg of tissue (Fig. 2) [20].

Statistical processing was performed using GraphPad Prism 8 (GraphPad Software, Inc., USA). Differences in monoamine metabolism in brain structures were evaluated through one-factor analysis of variance with the post hoc Bonferroni criterion used to compare the significance of differences between groups. The sample was pretested for normal distribution using the Kolmogorov–Smirnov criterion. The proportion of arm visits in the probability and reinforcement value tests was evaluated using Student's *t*-test. Differences were considered significant at $p < 0.05$. Data are presented as the arithmetic mean ± standard error of the mean.

RESULTS

In this study, the effects of predator presentation stress on impulsivity were investigated using a probability and reinforcement value test.

The experimental group exhibited a statistically significant ($p < 0.001$) decrease in visits to arm 1 of the maze compared with the control group (Fig. 3, *a*). Visiting arm 1 resulted in a reward with a high probability (100%) but with the lowest food reinforcement (one sunflower seed). Animals that had experienced a psychotraumatic event showed a statistically significant increase ($p < 0.05$) in the number of visits to arm 3 compared with the control group (Fig. 3*b*). An animal's visit to this arm ensured a reward with a low probability of 33% but with the highest food reinforcement of three sunflower seeds. In addition, the total number of visits to all three arms by the experimental rats was twofold ($p < 0.001$) lower than that by the control rats (Fig. 3, *b*).

In the prefrontal cortex of rats, the DOPAC content decreased significantly from 1.54 ± 0.31 to 0.52 ± 0.18 ng/mg tissue after exposure to a predator ($p < 0.05$) compared with that in intact rats. Similarly, the DOPAC/DA ratio decreased significantly from 3.73 ± 1.21 to 1.10 ± 0.33 after predator presentation compared with the control group ($p < 0.05$) (Fig. 4).

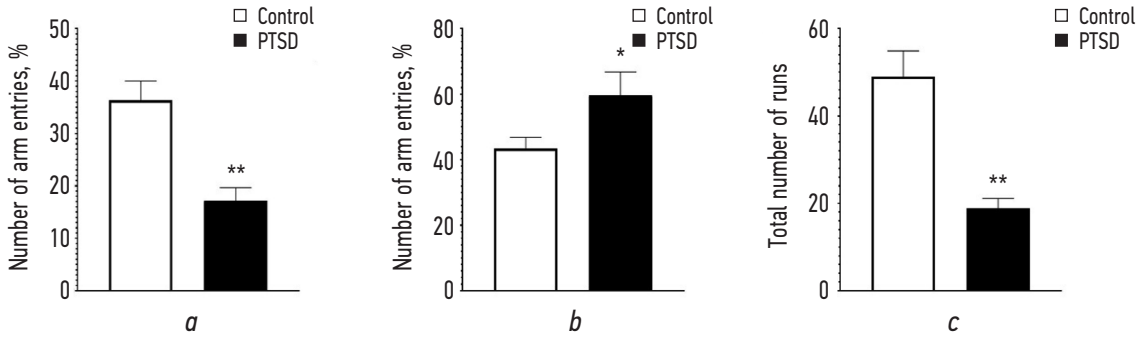

Fig. 3. Effect of predator presentation stress on the behavior of rats when choosing the probability and strength of food reinforcement in a three-arm maze: *a*, specific weight of visits to arm 1 of the maze; *b*, specific weight of visits to arm 3 of the maze; *c*, total number (*n*) of runs in the arms. PTSD, post-traumatic stress disorder. * $p < 0.05$; ** $p < 0.001$

Рис. 3. Влияние стресса предъявления хищника на поведение крыс в ситуации выбора вероятности и силы пищевого подкрепления в трехлучевом лабиринте: *a* — удельный вес посещений первого рукава лабиринта; *b* — удельный вес посещений третьего рукава лабиринта; *c* — суммарное количество (*n*) пробежек в рукава. * $p < 0,05$; ** $p < 0,001$

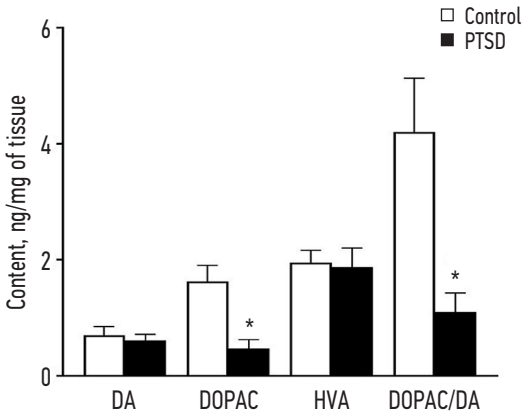

Fig. 4. Levels of dopamine and its metabolite DOPUK in the prefrontal cortex of intact control and animals that survived predator presentation. * $p < 0.05$, significant differences compared with the control group. DA, dopamine; DOPAC, dioxyphenylacetic acid; HVA, homovanillic acid

Рис. 4. Содержание дофамина и его метаболита ДОФУК в префронтальной коре мозга у интактного контроля и животных, переживших предъявление хищника. * $p < 0,05$ — достоверные отличия по сравнению с контрольной группой. DA — дофамин, DOPAC — диоксифенилуксусная кислота, HVA — гомованилиновая кислота

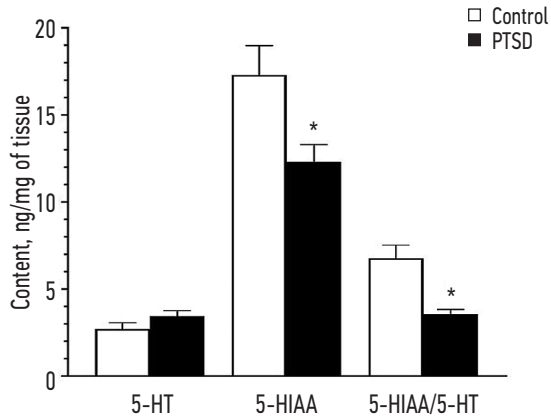

Fig. 5. Levels of serotonin and its metabolite 5-HIUC in the prefrontal cortex of intact control animals and animals that survived predator presentation. * $p < 0.05$, significant differences compared with controls. 5-HT, 5-hydroxytryptamine, serotonin; 5-HIAA, 5-hydroxyindoleacetic acid

Рис. 5. Содержание серотонина и его метаболита 5-ГИУК в префронтальной коре мозга у интактных контрольных животных и у животных, переживших предъявление хищника. * $p < 0,05$ — достоверные отличия по сравнению с контрольной группой. 5-HT — 5-гидрокситриптамин, серотонин, 5-HIAA — 5-гидроксииндолуксусная кислота

In the prefrontal cortex of rats, 5-HIAA levels decreased significantly from 17.29 ± 1.68 to 12.70 ± 1.08 ng/mg tissue ($p < 0.05$) compared with intact rats. In addition, the 5-HIAA/5-HT index was significantly decreased after exposure to a predator compared with the control group (intact animals) from 6.75 ± 0.77 to 3.70 ± 0.28 ($p < 0.05$; Fig. 5).

DISCUSSION

The results of this study indicate that a single application of the animal model of PTSD caused significant changes in animal behavior. Specifically, it increased impulsivity in decision making during the probability and reinforcement value test and altered the exchange of monoamines in the prefrontal cortex of rats. Exposure to a superstrong stressor can lead to cognitive and mood disorders in humans and animals [21, 22]. A study revealed that rats exposed to vital stress experience changes in their cognitive abilities, including increased anxiety and compulsiveness, and a decrease in communicative behavior and vertical motor activity [23].

However, no study has examined the relationship between stress exposure and the development of gambling. One of the defining characteristics of gambling

is the presence of uncertainty. The unpredictability and uncertainty of rewards are believed to increase the sensitivity of reinforcement systems [24]. An animal model study suggested that uncertainty in probability and reinforcement value testing can increase the activation of reward-related stimulus salience. Changing the mode of reinforcement significantly increases attention and attraction directed toward the reward signal, making uncertain cues more appealing [25]. The effect of uncertainty on the overvaluation of rewards is also evident in humans. A study reported that problem gamblers exhibit increased attention to uncertain gambling-related cues compared with control individuals, indicating that these stimuli acquire greater significance in players and may possess motivational properties [15].

Direct evidence shows that the dopaminergic system in animals becomes more sensitive to conditions similar to gambling. This is demonstrated by their increased responsiveness to a single dose of amphetamine [23]. Rats with maximum reinforcement uncertainty exhibited the greatest locomotor response after amphetamine administration. This finding is consistent with the observation of a more pronounced locomotor response in rats trained to press a lever for a reward with varying reinforcement schedules following amphetamine administration. Repeated exposure to reinforcement uncertainty results in increased self-administration of amphetamine [23]. In the IOWA gambling task, the administration of the indirect adrenomimetic phenamine at a dose of 0.5 mg/kg led to an increase in the number of entries into the high reinforcement arm with a low probability of reward [12].

Poststress cognitive disorders are associated with changes in the volume of the prefrontal cortex, amygdala, and hippocampus. These areas are important for studying the effects of stress because of their high levels of corticosteroid receptors, which may underlie their influence on the excitation of midbrain dopaminergic neurons in response to aversive stimuli.

The study's results suggest that exposure to reward uncertainty and gambling may sensitize the brain's dopamine system, which could facilitate the transition from casual gambling to gambling addiction. A previous study showed that changes in monoamine metabolism in the prefrontal cortex develop gradually by day 14 after predator presentation, reflecting the development of depression-like states and PTSD [3]. The study did not find statistically significant changes in dopamine levels in the prefrontal cortex of animals on day 14 after exposure to a predator, which is consistent with the findings of a previous study [26]. However, a significant decrease in the concentration of dopamine metabolites, specifically the DOPAC content, was observed on day 14 after predator presentation compared with the values in intact rats. On day 14 after predator presentation, the DOPAC/DA index decreased compared with the control group.

Furthermore, the levels of 5-HT and its metabolite 5-HIAA reduced in the prefrontal cortex of rats following exposure to a predator. On day 14 after predator presentation, the 5-HIAA/5-HT index was lower than that in the control (intact) group. Neurons that contain 5-HT are situated in the brainstem and project to various forebrain regions, including the amygdala, bed nuclei of the terminal striatum, hippocampus, hypothalamus, and prefrontal cortex. In a previous study, the anxiogenic effects were mediated by serotonin neurons located in the dorsal suture nucleus through 5HT2 receptors. These neurons project to the amygdala and hippocampus [27].

Human data indicate a correlation between 5-HT levels and impulsivity, which may affect decision making. In addition, some gene variants related to the functioning of the serotoninergic system are associated with deficits in decision making during gambling, which is consistent with the results of our experiments. Patients with depression who exhibited increased selection of unfavorable choices in gambling and made mistakes were found to carry a specific form of the serotonin transporter gene (5-HTTLPRs).

The study data indicate that the prefrontal cortex's serotonin system is involved in the increase in impulsivity caused by predator presentation stress. These findings suggest that serotoninergic synaptic transmission may negatively affect decision making during play tests.

CONCLUSIONS

The results of this study suggest a depletion of the dopaminergic and serotoninergic brain systems in rats 14 days after exposure to a predator. Specifically, a decrease in the content of the dopamine metabolite DOPAC and the DOPAC/DA ratio in the prefrontal cortex and a decrease in the content of 5-HT, its metabolite 5-HIAA, and the 5-HIAA/5-HT ratio in the same brain region were observed. The predator presentation caused significant behavioral changes in rats, leading to increased impulsivity in decision making during the probability and reinforcement value test in the IOWA gambling task. The experiments demonstrated that acute stress induced by predator presentation resulted in more escapes into arm 3 of the maze, indicating that the animals exhibited riskier behavior when choosing between reinforcements of varying strength and probability. This study demonstrates that the depletion of the dopaminergic and serotoninergic systems in the prefrontal cortex underlies pathological gambling and inadequate decision making caused by PTSD in an animal model.

ADDITIONAL INFORMATION

Authors' contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis,

interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study. Personal contribution of each author: S.S. Pyurveev, A.A. Lebedev, S.G. Tsikunov — planning and conducting the experiment, writing and editing the article; I.V. Karpova — data collection, writing and editing the article; E.R. Bychkov — data processing, writing and editing the article; P.D. Shabanov — development of the general concept.

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Conflict of interest. The authors declare the absence of obvious and potential conflicts of interest related to the publication of this article.

Ethics approval. The present study protocol was approved by the local Ethics Committee of the Institute of Experimental Medicine (protocol No. 6, 2022 June 14).

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