Effect of Prenatal Inflammation on Hippocampal Glutamate Receptor 1 Level in the Middle-Aged Mice and the Correlation with Learning and Memory

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Abstract: *Objective:* Prenatal inflammation can affect the development of the offspring's physiological system, resulting in many neuropsychiatric conditions, such as neurodevelopmental disorders. Synaptic plasticity is the basis of learning and memory in the central nervous system. Alpha-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid receptors (AMPAR) is an ionic glutamate receptor in the mammalian central nervous system, mediating the delivery of excitatory neurotransmitters, which plays a crucial role in long-term potentiation considered as molecular associations of learning and memory. Studies have suggested that inflammatory cytokines reduce the phosphorylation of AMPAR subunit GluR1 and the surface expression of GluR1, affecting the process of memory consolidation. Therefore, this study aimed to investigate the effect of prenatal inflammation on hippocampal AMPAR subunit GluR-1 in the middle-aged mice and the correlation with learning and memory.

Methods: Maternal mice were intraperitoneally injected with LPS (50 μg/kg) or normal saline at days 15-17 of pregnancy, and their offspring were named as LPS group and control group respectively. The spatial ability of learning and memory was examined with Morris water maze at the ages of 3 months and 15 months at each group. The level of GluR-1 was measured using Western blotting.

Results: The 15-month control group (compared to the 3-month control group) and the 15-month LPS group (compared to the 15-month control group) had significantly longer learning swimming distance (P = 0.014 and 0.011), and lower memory percentage of swimming distance in the target quadrant (P = 0.021 and 0.014) in the Morris water maze, and significantly lower levels of hippocampal GluR-1 (Ps< 0.001). Correlation analysis showed that only the hippocamppal level of GluR-1 in the 15-month mice negatively correlated with swimming distance and positively correlated with the percentage of swimming distance in target quadrant.

Conclusion: Our results suggested that the middle-aged CD-1 mice had decreased GluR-1 content in hippocampus, which correlated with impaired ability of spatial learning and memory, and maternal exposure to inflammation in the late pregnancy accelerated this change.

Keywords: Aging, Glutamate receptor, Learning and memory, Lipopolysaccharide, Hippocampus.

1. INTRODUCTION

With the continuous extension of the average life expectancy of human beings, the aging trend of the world population structure has become increasingly prominent, and the aging problem has been paid more and more attention. Aging is a complex natural phenomena. There are degenerative changes in physiological and pathological process, including the molecules, cells, and organ function with ages [1]. In particular, one of the significant feature is the decline in cognitive function, especially the hippocampus-dependent spatial learning and memory [1-2]. Age-related cognitive decline is the most main risk factor for dementia, and Alzheimer's disease is one of the most common types of dementia at old age [3]. After normal growth, development and maturation, there is a significant decline in memory and intelligence activity in the middle-old age [4]. So far, the etiology of Alzheimer's disease has not been clarified. Therefore, one of the major scientific medical challenges now and in the future will be to examine aging processing, etiologies and anti-aging.

In the central nervous system, the changes in synaptic plasticity may be involved in age-related cognitive function decline [5]. Synapses are the structural basis of information transmission, which are the specific connections and information transmission sites between neurons and neurons or between neurons and effectors in the central nervous system. Synaptic plasticity means that the morphology and function of synapses will be as the change of neural activity, which is the basic neural mechanisms of learning and memory, mainly including long-term potentiation and long-term depression [6]. Alpha-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid

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receptors (AMPARs) are ionic glutamate receptors regulated fast excitatory neurotransmission and synaptic plasticity in the mammalian brain. AMPARs are tetramers comprised of four glutamate receptor subunits (GluR-1–GluR-4), respectively coded by Gria 1, Gria 2, Gria 3 and Gria 4 genes, enrichment in dendritic spines on postsynaptic membrane and play a critical role in long-term potentiation, which is considered to be molecular mechanism underlying learning and memory [7-9]. Previous studies have shown that increased subunit GluR-1 expression of AMPARs in the hippocampal CA1 and CA2 subregions can improve hippocampus-dependent spatial learning and memory in rats [10-11].

It is well known that strict high nutritional requirements, hormones and immune changes during pregnancy make pregnant women more vulnerable to various infections [12,13]. The offspring whose mothers are infected during pregnancy have a higher risk of neurodevelopmental or neuropsychological disorders [14]. Interestingly, a study showed that the injection of lipopolysaccharide (LPS) during at gestation day (gd) 15 elevated pro-inflammatory cytokine levels in maternal serum, amniotic fluid, and fetal brain at 4 h, and levels decreased but remained elevated at 24 h as well as resulted in 3285 genes up-regulation in the brain of the offspring, which contributes to the extensive down-regulation of key nerve development genes [15]. Therefore, maternal bacterial infections, the most common adverse exposures during pregnancy, can cause systemic inflammation, which is considered to be an important risk factor affecting the development of fetal physiological system in the critical period of fetal development [16-18].

LPS is a kind of water-soluble glycosylated lipid complex, which is the main cell wall component of Gram-negative bacteria, composed of a conserved biphosphorylated lipid A, a central core, and a polysaccharide O antigen [19-20]. LPS administration has been widely used in experimental animals because it can be employed to simulate maternal gestational or other regional infections, which is the most effective natural inflammation factor. LPS exposure can activate the maternal immune system, interfere with the balance between pro-inflammatory factors and anti-inflammatory factors, and have adverse effects on fetal nerve development in animals [20, 21]. Previous experimental animal studies have proved that maternal exposure to LPS in late pregnancy can accelerate the changes of aging-related behaviors, especially accelerated age-associated learning and memory impairment (AAMI) and alter the expression of hippocampal synaptic proteins (such as synaptotagimin, syntaxin-1), and acetylation of H4K8 and H3K9 in offspring [22], and also accelerate the mother-self AAMI [23].

It is therefore of a great interest to investigate the effect of prenatal inflammation on hippocampal AMPARs subunit GluR-1 during aging and the correlation with learning and memory. In the present study, the models of normal aging in mice and accelerated aging of maternal inflammatory exposure during pregnancy in mice were used to explore whether aging is accompanied by the change of hippocampal GluR-1 content and whether prenatal inflammatory exposure aggravate this change. Finally, we evaluated whether change of hippocampal GluR-1 is related to the change ability of spatial learning and memory.

2. MATERIALS AND METHODS

2.1. Animals and Treatments

CD-1 mice (2 months, females 25-27 g, males 28-30 g) were purchased from Hunan Slac Jingda Laboratory Animal Co. Ltd. The colony was raised in our laboratory animal room. Water and food was available *ad libitum*, maintained temperature (22 ± 1) ℃, humidity (50 ± 5) % with a 12-h light/dark cycle (light on: 7:00 a.m.). After 2 weeks' acclimation to the colony room, male mice were paired with females (1 : 2) and the presence of a vaginal plug was designated as gestational day (gd) 0. All pregnant mice were housed in single cage and randomly received intraperitoneal injections of LPS or the same volume of normal saline at gds 15-17, and their offspring was respectively named as LPS group or control group. On the post-natal day 21, pups (24, male) were separated from their mothers, and were housed in plastic cages (25.5 cm × 15 cm × 14 cm, with wood-shaving bedding). Twelve male mice in control group were randomly divided into 3-month control group and 15-month control group. And the same is true for the LPS group. The animals were treated in compliance with the guidelines for humane treatment set by the Association of Laboratory Animal Sciences and the Center for Laboratory Animal Sciences at Anhui Medical University.

2.2. Morris Water Maze

Morris water maze (MWM) task was used to detect the spatial ability of learning and memory in the animals [24]. The experimental device is a circular

black tank with a diameter of 150 cm, and high 30 cm filled with water (22±2 ℃), contained a black cylindrical platform (10 cm in diameter, 24 cm in heigh). The tank was surrounded by white cloth curtain with three black clues (circular, triangular, square) [25]. The camera system was installed above to collect the movement track of mice in the water maze, and then the image was analyzed by Any-maze software （American stoelting company). The experimental process is divided into two stages: the place navigation trial (the learning phase) and the probe trial (the memory phase). In the place navigation trial, the platform which is 1 cm below the surface of the water is fixed to the target quadrant (defined as the fourth quadrant as the target quadrant). The experiment lasted for 7 days. Before the first test, the mice were put on the platform for 30 s. Then the mouse was released into the water from different starting positions, facing to the wall. The mouse was allowed a maximum of 60 s to find the platform. Then the mouse was maintained the platform for 30 s. If the platform was not found within the 60 s, the mouse was guided to the platform and kept there for 30 s. In the probe trial, the mouse was put into water from the quadrant at opposition to the target quadrant, and completed the probe trial for 60 s without the platform 120 min after the last place navigation trial [25]. In this experiment, the average swimming distance during the place navigation trial was considered as index of learning ability and the percentage of the target quadrant swimming distance to the total distance in the probe trial was thought as a index of memory ability.

2.3. Tissue Preparation

At the 15 days after the behavior experiment was completed, the mice were anesthetized by 3% halothane inhalation and the neck was dislocated and the animal was killed. The hippocampus was quickly isolated from the brain on ice and frozen in the −86℃ cryopreservation refrigerator.

2.4. Western Blotting

The western-blot experiment was carried out according to a previously described method [26]. Protein tissue was extracted by protein neutral lysis buffer (RIPA), and the SDS-PAGE protein loading buffer was heated in a boiling water bath for 10 min to fully denaturate the protein. After the sample was cooled to room temperature, the proteins were loaded into the SDS-PAGE gel for electrophoresis (80 v/30 min, 120v/1h). Then, the protein components were transferred to polyvinylidene difluoride (PVDF) membranes for 110 min. The membranes were saturated and blocked with 5 % fat-free milk at room temperature for 2 h and incubated overnight at 4 ℃ with primary antibody (rabbit anti-GluR-1 1 : 1000, abcam). Subsequently, the membranes were washed three times / 10 min in PBST at room temperature and incubated for 2 h with the horseradish peroxidase-labelled secondary antibody (1 : 20000, zs-bio). The membranes were washed three times / 10 min in PBST. The immunolabeled protein bands were detected using the ECL Western blot detection kit. Graphs of blots were obtained in the linear range of detection and were quantified for the level of specific induction by scanning laser densitometry. The densitometric analysis of immunoreactivity was conducted using the Image J software and calculates the relative expression of GluR-1.

2.5. Statistical Analysis

All data met the normal distribution and the results were represented by mean ± square standard deviation. The results of the GluR-1 content and the memory performance in the MWM were analyzed using independent-samples *t* test. The data from the learning phase in the MWM was analyzed using repeated measures analysis of variance (rm-ANOVAs). Then, Pearson's correlation test was used to analyze the correlations between the relative levels of hippocampal GluR-1 proteins and MWM performance. All data were analyzed by SPSS16.0 statistical software, and $P<0.05$ was of statistical significance. The Origin 8.0 software is used for drawing.

3. RESULTS

3.1. Performance in the MWM

The learning phase

The rm-ANOVAs showed (Figure **1A**) that the swimming distances progressively decreased with the increase of days for all the mice [$F_{(6,120)} = 71.367$, $Ps < 0.01$], and the swimming distances between the four groups had significant difference [$F_{(3,22)} = 14.996$, $Ps < 0.01$]. The 15-month control group had significantly longer swimming distance than the 3-month control group [$F_{(1,10)} = 8.870$, $P = 0.014$]. The 15-month LPS group had significantly longer swimming distance compared to the same age control group [$F_{(1,10)} = 9.706$, $P = 0.011$]. However, at 3 months of age, there was no significant difference between LPS group and control group [$F_{(1,10)} = 2.090$, $P = 0.218$].

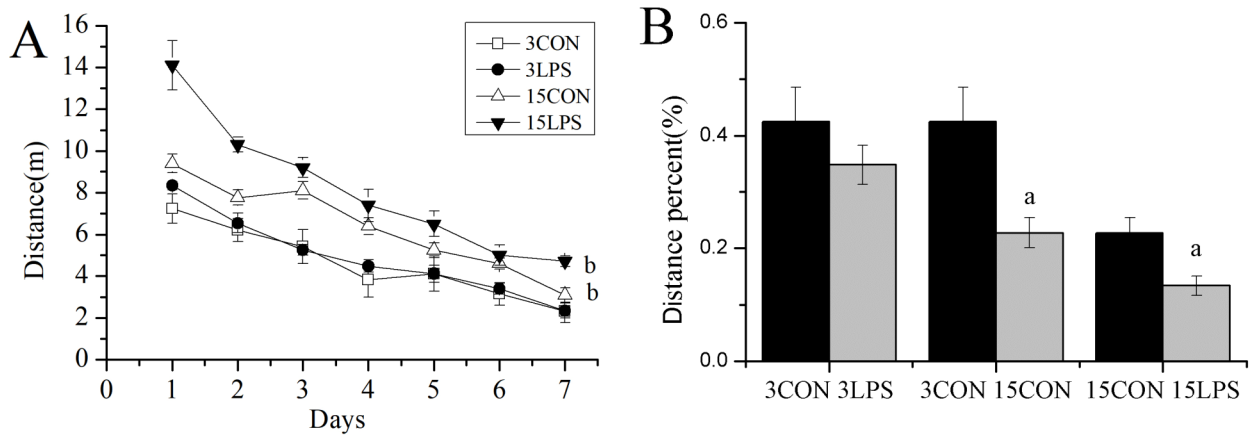

Figure 1: The performance of mice in the Morris water maze. **A** and **B** respectively represent the swimming distance in the learning phase and the percentage of swimming distance in the target quadrant in the memory phase in each group. [a]*P*<0.05 indicates significant difference effects in the 15-month control group (compared to the 3-month control group) or the 15-month LPS group (compared to the 15-month control group), with six mice in each group. 3CON: 3-month-old control group; 3LPS: 3-month-old LPS group; 15CON: 15-month-old control group;15LPS: 15-month-old LPS group.

The memory phase

Compared to the 3-month control group, the 15-month control group exhibited significantly lower swimming distance percentage in the target quadrant (*t* = 2.971, *P* = 0.021; Figure **1B**). The 15-month LPS group exhibited significantly lower swimming distance percentage in the target quadrant in comparison to the same-age control group (*t* = 2.962, *P* = 0.014), but there was no significant difference between the 3-month groups (*t* = 1.094, *P* = 0.300).

3.2. Level of GluR-1 Content

As shown in Figure **2**, the 15-month control group showed significantly decreased GluR-1 content than the 3-month control group (*t* = 14.029, *P*< 0.001). So did the 15-month LPS group compared to the same-age control group (*t* = 14.636, *P*< 0.01). But there was no significant difference between 3-month LPS group and control group (*t* = 0.039, *P* < 0.970).

3.3. Correlations between the MWM Performance and GluR-1 Content in the Hippocampus

Pearson's correlation test showed that the level of GluR-1 in hippocampus of the 15-month control and LPS groups was negatively correlated with swimming distance (*r* = −0.853, *P* = 0.03; *r* = −0.919, *P* = 0.01, respectively), and positively correlated with the percentage of swimming distance in target quadrant (*r* = 0.968, *P* = 0.002; *r* = 0.906, *P* = 0.013, respectively), but there was no significant correlation between GluR-1 level and the swimming distance and swimming

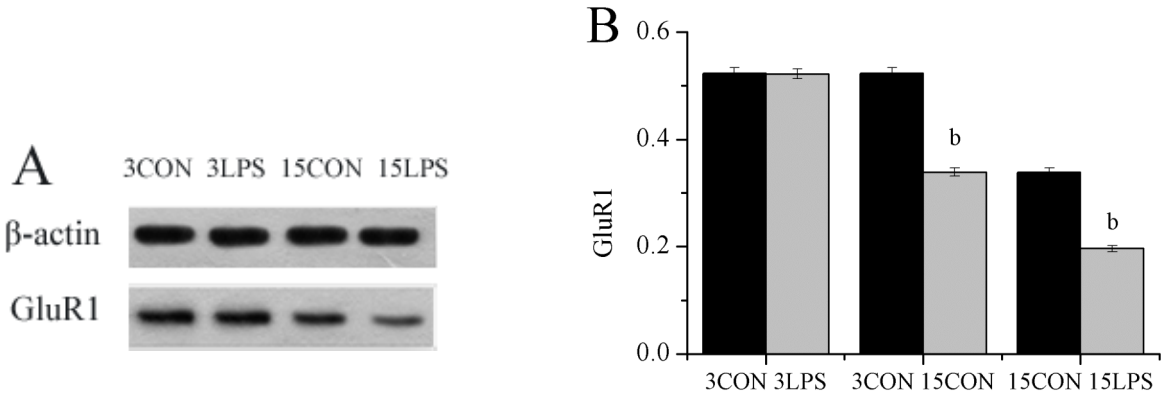

Figure 2: Western blotting detection of GluR-1 in hippocampus of the mice. [b]*P*<0.01 indicates significant difference effects in the 15-month control group (compared to the 3-month control group) or the 15-month LPS group (compared to the 15-month control group), with six mice in each group. 3CON: 3-month-old control group; 3LPS: 3-month-old LPS group; 15CON: 15-month-old control group;15LPS: 15-month-old LPS group.

Table 1: The Correlations between Hippocampal GluR-1 Level and the Performances in Morris Water Maze

Ages	Groups	Performances	GluR1 *r* (*P*)
3 months	Control	Learning swimming distance	− 0.439 (0.384)
		% of swimming distance in the target quadrant	0.300 (0.564)
	LPS	Learning swimming distance	− 0.081 (0.878)
		% of swimming distance in the target quadrant	0.150 (0.777)
15 months	Control	Learning swimming distance	− 0.853 (0.03[a])
		% of swimming distance in the target quadrant	0.968 (0.002[b])
	LPS	Learning swimming distance	− 0.919 (0.01[a])
		% of swimming distance in the target quadrant	0.906 (0.013[a])

[a] $P<0.05$ [b] $P<0.01$

distance percentage in the target quadrant ($P > 0.05$) in the 3-month control group and LPS group, as shown in Table **1**.

4. DISCUSSION

In the current study, we report that the middle-aged (15-month-old) CD-1 mice had significantly longer swimming distance in the learning phase, significantly lower swimming distance percentage in the target quadrant in the memory phase compared to the young (3-month-old) mice in the MWM. Similarly, the 15-month LPS group (compared to the same-age control group) had significantly longer learning swimming distance and significantly lower memory percentage of swimming distance in the target quadrant in the MWM. These results indicated that spatial impairment of learning and memory indeed occur in the middle-aged CD-1 mice due to aging and prenatal inflammatory insults can accelerate this damage. Our findings was consistent with the earlier studies, which suggested that aging could lead to hippocampal-related cognition (spatial learning and memory) impairment [22, 30, 32], and embryonic inflammatory exposure (possible due to maternal infections in the late pregnancy) could result in the decrease of hippocampal-related spatial learning and memory in MWM at early middle-age (400-day-old) in CD-1 mice [31]. So, it has been widely agreed that the physiological functions are degenerated as the increase of age in human and animals such as rodent, and the hippocampus is especially vulnerable to aging [27].

The structural and functional integrity of hippocampus is very important for normal learning, memory consolidation and synaptic plasticity [28-29]. In mammalian brain, the hippocampus, composed of CA1, CA3 and DG subregions, plays an essential role in spatial learning and memory [33]. Glutamate is a major excitatory neurotransmitter, which mediates rapid excitatory synaptic transmission and plays an important role in regulating neuron activity involved in many physiological functions in the central nervous system [34]. Glutamate mediates on neighboring neurons by binding to glutamate receptors, which are composed of ionized glutamate receptors, including the AMPARs, N-methyl-D-aspartate receptors (NMDARs) and kainate receptors, and metabolic glutamate receptors (mGluRs), respectively [35]. The changes in quantity and the unit composition of AMPARs, that is glutamate-gated iron channel receptor, affect glutamate signal transmission in the central nervous system, as well as, regulate the expression of synaptic plasticity. These AMPARs are critical to almost all aspects of brain functions, including learning, memory and other cognitive domains, as they mediate the vast majority of rapid excitatory neurotransmission in the central nervous system. GluR-1 is highly expressed in the hippocampus, the central amygdala and the cerebellum. GluR-1 is particularly important for structural and functional plasticity because it can induce structural stabilization and increase synaptic intensity. Meanwhile, GluR-1 is the main molecular determinant of long-term potentiation which represents electrophysiological synaptic plasticity, so it is thought to underline learning and memory [36]. In the hippocampus, 90 % of the AMPARs complexes were composed of GluR-1/2 or GluR-2/3 heterotetramer receptors, and nearly 80 % of the synaptic AMPARs in CA1 pyramidal neurons composed of GluR-1/2 heterotetramer receptors [37-38]. Postsynaptic AMPAR endocytosis induced by maternal sleep deprivation

leaded to long-term potentiation damage and long-term depression increase as well as hippocampal synaptic plasticity damage, in turn the emotional and cognitive functions were impaired in offspring. AMPAR endocytosis inhibitor could antagonize AMPAR endocytosis induced by maternal sleep deprivation, to restore normal synaptic plasticity and reduce behavioral impairment and improve cognitive function in offspring [39]. AMPA receptor containing GluR-1 plays an crucial role in synaptic plasticity of the hippocampus and learning and memory [11]. Previous studies demonstrated that IL-1β decreased the phosphorylation and surface expression of AMPAR subunit GluR-1, which affected the process of memory reconsolidation [40]. In current studies, the level of hippocampal GluR-1 in the middle-aged (15 months old) CD-1 mice was significantly lower compared to the young (3 month old) mice, indicating that aging could lead to the decline of GluR-1 in hippocampus.

According to the hypothesis of fetal origin of adult diseases, early exposure to adverse factors in life, especially in embryonic stage, will cause permanent "programmed changes" in fetal tissues and organs, reduce the resistance of individuals to external adverse factors (such as stress, inflammation, aging and so on), and increase individual susceptibility to many chronic diseases such as Alzheimer disease, diabetes mellitus, hypertension and so on [41]. Infective inflammation is one of the most common adverse factors during pregnancy. The stimulation of inflammation to the immune system in adulthood, even at a low level, can lead to learning and memory impairment [42-43]. Antenatal inflammatory exposure damages synaptic plasticity and has long-term effects on brain development and function [44]. LPS is a classical inflammatory stimulator in experimental animal models. Exposure to LPS in pregnant female mice can simulate early inflammatory stimulation in mice [45], then activate immune cells, leading to higher expression of pro-inflammatory cytokines such as interleukin-1β and tumor necrosis factors-α [42]. The pro-inflammatory cytokines can enter brains of offspring mice passing through placental barrier and blood brain barrier, resulting in programmed change of expression in synaptic-plasticity related genes in midlife onwards. Our previous study also found that maternal exposure to low-dose LPS could lead to early learning and memory impairment in offspring, although did not lead to death or developmental abnormalities [32]. However, does the maternal exposure to low-dose LPS during pregnancy aggravate the age-related decline of hippocampal GluR-1? The current study showed that the hippocampal level of GluR-1 significantly decreased in the 15-month-old LPS group in comparison with the 15-month control group, answering to the question.

Then, is the hippocampal level of GluR1 linked to the changes of spatial learning and memory? In the current study the Pearson's correlation analysis showed that the levels of GluR-1 in the hippocampus in both the 15-month control group and the LPS group negatively correlated with the swimming distance in the learning phase of MWM, and positively correlated with the percentage of swimming distance in the target quadrant in the memory phase of MWM. These results suggested that the decreased hippocampal level of GluR-1, via resulting in dysfunction of synaptic transmission and synaptic plasticity in the hippocampus [46-47], may be associated with the impairment of spatial learning and memory which is hippocampus-dependent. Our results is supporting the previous work that AMPARs containing GluR-1 plays an important role in hippocampal synaptic plasticity involved in learning and memory [11].

5. CONCLUSION

In general, our experiment revealed that aging could lead to a decrease in hippocampal GluR-1 content and spatial learning memory impairment. And the prenatal exposure to inflammation can accelerate the decrease of the GluR-1 content in the hippocampus and the impaired extent of the spatial learning and memory in the midlife. As hypothesized, the decreased hippocampal level of GluR-1 may be connected with the damage of the spatial learning and memory. The study lend good support to the notion that spatial learning and memory is affected by GluR-1 content whether it is in the normal-aging midlife or in the midlife with prenatal inflammatory insult. But in this experiment, only the Western blotting is used, which is single, and not specific to each sub region of the hippocampus. More work needed on animal studies before a confirmation is established.

CONFLICT OF INTEREST

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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