doi:10.3969/j.issn.2095-4344.2013.11.009 [http://www.crter.org]
Han HY, Zhang YC, Ji SQ, Liang QM, Zhu SQ, Xue Z. Integrin beta 1 inhibits long-term potentiation induced by amyloid beta-protein. Zhongguo Zuzhi Gongcheng Yanjiu. 2013;17(11): 1959-1964.

Integrin beta 1 inhibits long-term potentiation induced by amyloid beta-protein*★

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Abstract

BACKGROUND: Inhibition of integrin activity in the hippocampal slices of mice cannot influence the induction of long-term potentiation, but bring rapid long-term potentiation attenuation, proving integrin plays a key role in maintaining and stabilizing the long-term potentiation after induction.

OBJECTIVE: To explain the influence of integrin beta-1 subunit during the inhibition of long-term potentiation induced by amyloid beta-protein in rat hippocampus CA1 *in vivo* using electrophysiological technology.

METHODS: Fifteen Sprague-Dawley rats were equally randomized into control group treated with normal saline, amyloid beta-protein group treated with amyloid beta-protein, and integrin beta-1 subunit inhibitor group treated with selective antagonist for integrin beta-1 subunit. Excitatory postsynaptic potentials were recorded from 10 minutes before amyloid beta-protein administration till 3 hours after high-frequency tetanic stimulation.

RESULTS AND CONCLUSION: In the control group, excitatory postsynaptic potentials were enhanced significantly with an increment of 30%. In the amyloid beta-protein group, excitatory postsynaptic potentials were obviously restraint within 3 hours after high-frequency tetanic stimulation and had no remarkable increase. It can be speculated by the results that integrin beta-1 subunit may be important to the long-term potentiation inhibited by amyloid beta-protein in the rat hippocampal CA1 region *in vivo*. The special inhibitor or antibody of integrin beta-1 subunit has the ability to stop the mediation.

Key Words: tissue construction; tissue construction and bioactive factors; Alzheimer's disease; neurotoxicity; amyloid beta-protein; long-term potentiation; integrin beta-1 subunit; hippocampal CA1 region; high-frequency stimulation; excitatory postsynaptic potential; the National Natural Science Foundation of China; tissue construction photographs-containing paper

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Supported by: the National Natural Science Foundation of China, No. 30700244*

Received: 2012-06-06
Accepted: 2012-07-24
(Y20120319016/YJ • W)

INTRODUCTION

Alzheimer's disease is the most prevalent neurodegenerative disease and the most common cause of elderly dementia. Three major pathology features of Alzheimer's disease are as follows, the extracellular abnormal deposition of amyloid beta-protein and the senile plaque formed by glial cell activation, the neurofibrillar tangles formed by intracellular tau-protein's abnormal phosphorylation, dysfunction of synapses and neuron progressive death[1].

Amyloid beta-protein is the major component of senile plaque, which is one of the key pathologic mechanisms of Alzheimer's disease. It is reported that in Alzheimer's disease, cognitive dysfunction presents earlier than the senile plaque forming. Thus it is also believed that Alzheimer's disease is a "synaptive disorder"[2]. Recent research has proved that accumulation of amyloid beta-protein is a key to mediating cognitive deficits in Alzheimer's disease as amyloid beta-protein promotes synaptic dysfunction and triggers neuronal death[3-4]. The abnormalities of

synaptic structure and function are the pathology of cognitive dysfunction in the early stage of Alzheimer's disease[5], while senile plaques are the results in the late period[6]. Long-term potentiation is a universally accepted electrophysiology parameter which reflects synapse plasticity[7-8]. Lately, it is reported that the induction of long-term potentiation can be inhibited by exogenous amyloid beta-protein[9-10]. This inhibition is recognized as the foundation of synaptic silence in the early stage of Alzheimer's disease[11-12].

Integrin family is a class of cellular adhesive molecules with adhesive and signal-transduction function, mediating the interaction between cell-cell and cell-extracellular matrix[13]. Integrin is a heterodimer with α and β subunits through non-covalent binding. Subunit α has 16 subunits, while β has nine subunits. Their combination forms 24 heteromeric bodies. The subunits which have close relationship with neurosynaptic function includes α1, α3, α5, β1 and β3[14-15]. One amino acid sequence of amyloid beta-protein, arginine-histidine-aspartate, is structurally similar with a recognition sequence of integrin, arginine-glycine-aspartate, which is possibly the binding site between amyloid beta-protein and integrin, and works as a structural basis of their combination[16]. Existing evidence has shown that inhibition of integrin activation in mouse hippocampal slices cannot impair the induction of long-term potentiation, but can bring about its rapid decrease, which indicate integrin is critical to the maintainability and stability of long-term potentiation after induction[17]. Another research observed that during the maturation of synapse there was reduction of glutamate releasing and transduction of N-methyl-D-aspartic acid receptor subunits, all of which could be blocked by integrin inhibitor and specific antibody of β3 receptor, thus indicating that integrin mediates the transformation of the synapse from immature to maturation[18]. Moreover, recent studies have implicated integrins in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor trafficking and glycine receptor lateral diffusion, highlighting their multifaceted functions at the synapse[19]. All of the above show that integrin participates in the regulation of neuron synapse activation, and is important to transmitters transferring, induction of long-term potentiation and maturation transduction of synapses[20]. The present study was to assess the influence of integrin beta-1 subunit during the inhibition of long-term potentiation induced by amyloid beta-protein in the rat hippocampal CA1 field *in vivo* through electrophysiological technology.

MATERIALS AND METHODS

Design

A case-control animal experiment

Time and setting

This study was conducted at the Department of Physiology, School of Basic Medical Sciences, Huazhong University of Science and Technology, China from January 2008 to January 2010.

Materials

Fifteen healthy clean grade male Sprague-Dawley rats, weighing 250–300 g, were used in this study. All experimental animals were provided by the Animal Center, Tongji Medical College and Tongji Hospital, Huazhong University of Science and Technology, China. All protocols of this study complied with the *Guidance Suggestions for the Care and Use of Laboratory Animals* issued by the Ministry of Science and Technology of China[21].

The main reagents and apparatus are introduced as follows:

Reagent and instrument	Source
Amyloid beta-protein (1–42)	Sigma
Syringes, ophthalmic forceps, surgical scissors, absorbent cotton, bone wax, electronic scales, stereotaxic apparatus	Narishige
Micro adding sample appliance (10 μL), BL-420F bio-functional experiment system, temperature controlling board, tungsten microelectrode, polyurethane, physiological saline, rat anti-human integrin beta-1 monoclonal antibody (JB1A)	Millipore

Methods

Experimental animals grouping

Fifteen rats were averagely randomized into three groups: control group, amyloid beta-protein group, and integrin inhibitor group.

Alzheimer's disease sample preparation

All rats were intraperitoneally anaesthetized by 20% urethane solution (1.0–1.5 g/kg). Body temperature was controlled at about 37.0 ℃. The rats were fixed on the stereotaxic apparatus. Stereo location was according to the position of bregma: stimulating electrode located 4.2 mm post-bregma and 3.8 mm right of midline, recording electrode located 3.4 mm post-bragma and 2.5 mm right of midline, the hole for intracerebroventricular injection located 1.0 mm post-bregma and 0.9 mm right of midline[22]. Alzheimer's disease models were prepared with amyloid beta-protein by the method of intracerebroventricular injection. We have looked through the reference to determine the final dose was 5 μL with a concentration of 10 μmol/L[22]. Rats in control group were injected with 5 μL normal saline.

Integrin beta-1 subunit intervention

We injected integrin beta-1 subunit selective inhibitor (JB1A) 30 minutes before injecting amyloid beta-protein. The hole for JB1A intracerebroventricular injection located in 1.0 mm post-bregma and 0.9 mm right of midline[22]. The dose was also 5 μL with a concentration of 10 μmol/L[22].

Electrode recording

After injecting with normal saline, amyloid beta-protein, and specific inhibitor of integrin beta-1 subunit separately, excitatory postsynaptic potential would be recorded in the right hippocampal hemisphere, stratum radiatum in the CA1 field in response to the stimulation of the ipsilateral Schaffer collateral-commissural pathway, persistently from 10 minutes before vehicle applying to 3 hours after high-frequency stimulation. More detailed method is: gain stable excitatory postsynaptic potential by regulating the depth of electrodes; record excitatory postsynaptic potential baseline for 10 minutes as test stimulation (0.033 Hz, intensity adjusted to get a 50% excitatory postsynaptic potential maximum). Saline or JB1A were then applied (10 μL in 5 minutes, intracerebroventricular injection) and excitatory postsynaptic potential baseline was recorded for 30 minutes as the same test stimulate. Then saline or amyloid beta-protein was applied (5 μL in 5 minutes, intracerebroventricular injection) and the baseline was recorded for another 10 minutes. High-frequency stimulation was 200 Hz, with intensity adjusted to get a 75% excitatory postsynaptic potential maximum, containing 10 trains of 20 stimuli, inter-stimulus interval 5 ms, inter-train interval 2 seconds. Then the parameters were recovered to test stimulate, and excitatory postsynaptic potentials were recorded for 180 minutes. In the self-comparison, 20 excitatory postsynaptic potential values were also selected for each at post-high-frequency stimulation 1, 2, 3 hours, which were compared with the baseline.

Main outcome measures

Long-term potentiation and excitatory postsynaptic potential in the rat right hippocampus.

Statistical analysis

The experimental values were mean±SEM. SPSS 16.0 was used. Two-tailed paired *t*-test and non-paired *t*-test were used for statistical comparison. A value of $P < 0.05$ was considered significant.

RESULTS

Quantitative analysis of experimental animals

Experiment data were obtained in all of the 15 rats for result analysis. No rats were off.

Post-high-frequency stimulation long-term potentiation change in the CA1 field of rat right hippocampus

In the control group, long-term potentiation was successfully induced, mean (144.0±16.0)% (n=5), maximum 172.3%, appeared at about 2.0–2.5 hours after high-frequency stimulation; for the amyloid beta-protein treated rats, long-term potentiation was significantly inhibited, mean (99.5±4.7)% (n=5, $P < 0.001$); in the integrin beta-1 subunit inhibitor group, long-term potentiation presented obviously recovery, which was close to the control, mean (141.9±7.4)% (n=5, $P > 0.05$), maximum 159.2%, appeared at 2–2.9 hours post-high-frequency stimulation (Figure 1).

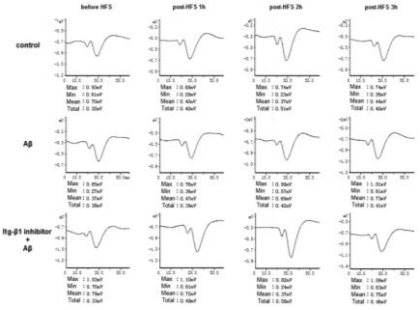


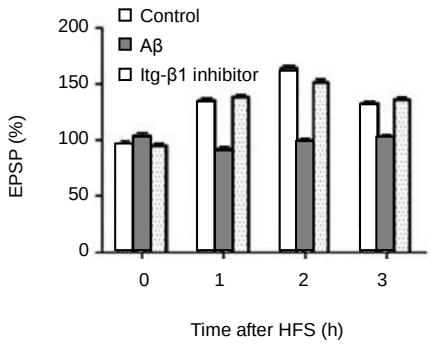
Figure 1 Comparison of long-term potentiation (LTP) in different periods between different groups. Representative graphs of excitatory postsynaptic potentials in the control group, integrin beta-1 (Itg-β1) inhibitor group and Itg-β1+amyloid beta-protein (Aβ) inhibitor group. The ordinate stands for the LTP. The abscissa stands for time post high-frequency stimulation (HFS)

Post-high-frequency stimulation excitatory postsynaptic potential change in the CA1 field of rat right hippocampus (Table 1)

Table 1 The comparison between mean excitatory postsynaptic potentials percentage at different time after high-frequency stimulation (mean±SEM, %)

Group	Time after high-frequency stimulation (h)		
	1	2	3
Control	135.6±2.9	163.9±2.8	132.7±2.4
Amyloid beta-protein	92.1±1.4	99.6±2.0	102.8±2.5
Integrin beta-1 subunit inhibitor	138.6±2.7	151.5±4.9	136.2±3.0

It was found that the peak in the control group occurred after 2 hours ($P < 0.01$); for the amyloid beta-protein treated rats, long-term potentiation was consistently flat after high-frequency stimulation without any remarkable potentiation ($P > 0.05$); in the integrin beta-1 subunit inhibitor group, the peak was also at 2 hours post-high-frequency stimulation ($P < 0.01$; Figure 2).



Integrin beta 1-subunit inhibitor (Itg-β1) inhibitor (JB1A) relieved amyloid beta-protein (Aβ)-induced long-term potentiation (LTP) inhibition. Twenty EPSP values were selected for each group at post-HFS 1, 2, 3 h, which were compared with baseline (post-HFS 0 h). $^aP < 0.01$, *vs.* 0 h

Figure 2 The comparison between mean excitatory postsynaptic potentials (EPSP) percentage in different time after high-frequency stimulation (HFS)

DISCUSSION

We put forward the hypothesis according to the change of synapse activation in early pathology in Alzheimer's disease. For the treatment limitation in the late period of Alzheimer's disease, we hope to study the early mechanism of the change of synapse function, to clarify the mechanism of Alzheimer's disease, to explore the early clinical interview, to delay or even reverse the disease progression, and finally to improve the patients' prognosis and living quality.

The advanced studies have shown that amyloid beta-protein has synapse toxicity before formation of senile plaques. We also have found that because amyloid beta-protein will adhere to the cell membrane in the early period, the shape of cells will change. According to that, we confer that the combination of amyloid beta-protein and integrin will start up the downstream signal pathways and lead to synapse silence. It may be the important factors of the early mechanism of Alzheimer's disease.

Several studies have observed that administration of exogenous amyloid beta-protein *via* intracerebroventricular injection could actually prominently inhibit long-term potentiation in the CA1 area of rat hippocampus, confirming amyloid beta-protein is a neurotoxin in Alzheimer's disease[23]. Other prior studies have shown that the neurotoxicity induced by amyloid beta-protein in the rat hippocampus could be decreased by specific inhibitors to both integrin-α1 and αV[24]. In the present experiment, pre-treatment by specific inhibitors to integrin beta-1 subunit (JB1A) was also partly effective to prevent this long-term potentiation inhibition induced by amyloid beta-protein, remarkably increasing mean and maximum of excitatory postsynaptic potential after high-frequency stimulation. Compared with the control, however, long-term potentiation was not totally recovered after pre-treatment by JB1A, which was possibly caused by the complicated mechanism of long-term potentiation inhibition. Excitatory postsynaptic potential baseline was influenced by neither amyloid beta-protein nor JB1A, both of which were only active during induction and maintaining of long-term potentiation. It may suggest that the neurotoxicity from interaction of amyloid beta-protein and integrin took place in strengthening mechanism of memory. The efficiency of integrin beta-1 subunit specific inhibitor in preventing long-term potentiation inhibition encouraged the confidence of researching more other possibly efficacy integrin inhibitors to be used as protectors of synapses in patients with Alzheimer's disease.

During the present research, long-term potentiation was gradually increased after high-frequency stimulation, coming to the maximum in 2 hours, and then gradually decreased, but still much higher than the baseline. Our results are not quite the same with that reported in the foreign literature because of the experiment condition, such as the change of weather, the damage of electrode, the interrupt of the environment, the difference of animal

species, and the animal health status. However, we have done our best to improve it. Something that we could not avoid was the electrophysiological activation influenced by extrusion, damage, excitation and intracranial pressure change through lateral ventricle injection. We have done slowly during the injection, kept the pinhead stay several minutes after the injection, covered the puncture hole with bone wax, provided intervention agents to extend excitatory postsynaptic potential recording time, making it go back in balance completely. All we have done can reduce the impact of the experiment condition as far as possible.

Taken together, we have found integrin beta-1 subunit is an important mediate-factor in neuro-dysfunction caused by amyloid beta-protein, considering prior studies about its importance in neurodegeneration. It is suggested that agents targeting integrin beta-1 subunit may be a potential therapy to early Alzheimer's disease. The specific mechanism needs further research. And in the future, further researches would be necessary to find what way integrin inhibitor acts in the neurotoxic progression of senile plaque forming.

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β1 整合素抑制 β 淀粉样蛋白对记忆长时程增强的作用*★

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文章亮点：

1 阿尔茨海默病病理过程中，远在 β 淀粉样蛋白沉积形成老年斑之前，β 淀粉样蛋白即可通过和整合素亚基干扰神经元突触电生理活动，影响正常递质的释放，是阿尔茨海默病早期临床症状解释的假说。文章应用在体电生理检测阐明了整合素 β1 亚基对活体大鼠海马 CA1 区中长时程增强的作用。

2 β1 整合素介导活体大鼠海马 CA1 区 β 淀粉样蛋白，抑制长时程增强作用，而应用其特异性的拮抗剂或抗体可以阻断这种介导作用。

关键词：

组织构建；组织构建与生物活性因子；阿尔茨海默病；神经毒性；β 淀粉样蛋白；长时程增强；β1 整合素亚基；海马 CA1 区；高频刺激；兴奋性突触后电位；国家自然科学基金；组织构建图片文章

摘要

背景：抑制小鼠海马脑片整合素活动后，虽然不会影响长时程增强的诱导，但却带来快速的长时程增强衰减，证明整合素对于诱导后长时程增强的维持和稳定起到关键的作用。

目的：通过在体电生理技术阐明整合素的 β1 亚基在活体大鼠的海马 CA1 区中 β 淀粉样蛋白抑制长时程增强的过程中所起到的作用。

方法：将 15 只 SD 大鼠等分为对照组、β 淀粉样蛋白组和 β1 整合素拮抗剂组，分别给予生理盐水，β 淀粉样蛋白和 β1 整合素的选择性拮抗剂，记录自给予 β 淀粉样蛋白前 10 min 至高频强直刺激后 3 h 时的兴奋性突触后电位。

结果与结论：给予对照组大鼠高频强刺激后兴奋性突触后电位明显增强，增幅在 30%以上。β 淀粉样蛋白组大鼠给予高频强刺激后兴奋性突触后电位在 3 h 中被显著抑制，没有出现明显的变化。而 β1 整合素拮抗剂组大鼠给予高频强刺激后兴奋性突触后电位又出现明显的增强。推测 β1 整合素在活体大鼠的海马 CA1 区中 β 淀粉样蛋白抑制长时程增强的过程中可能起着重要的介导作用，而其特异性的拮抗剂或抗体可以阻断这种介导作用。

基金资助：课题由国家自然科学基金(30700244)资助。

作者贡献：薛峥进行实验设计，对文章负责；朱遂强审校，实验实施为张逸驰、韩海燕、季淑琼和梁奇明，实验评估为梁奇明，资料收集为季淑琼，张逸驰与韩海燕成文。韩海燕与张逸驰对文章的贡献相同，故并列为第一作者。

利益冲突：课题未涉及任何厂家及相关雇主或其他经济组织直接或间接的经济或利益的赞助。

伦理要求：实验经过华中科技大学同济医学院动物伦理委员会批准。实验过程中对动物的处置符合 2009 年《 Ethical issues in animal experimentation》相关动物伦理学标准的条例。

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中图分类号: R318　文献标识码: B

文章编号: 2095-4344(2013)11-01959-06

韩海燕，张逸驰，季淑琼，梁奇明，朱遂强，薛峥. β1 整合素抑制 β 淀粉样蛋白对记忆长时程增强的作用[J].中国组织工程研究，2013，17(11):1959-1964.

(Edited by Wang L)