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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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NEURODEGENERATION AND NMDA

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Abstract.

The N-methyl D-aspartate receptor is one of the key receptors in the human brain. As a result of radioligand analysis, it was found that the highest density of this receptor is located in the hippocampus, striatum, cortex, and amygdala. Associative memory, learning, and synaptic density are all directly related to the effective functioning of the NMDA receptor. Recent studies have shown that the number of NMDA receptors and their morphological structure decreases with age, in particular, some subunits change their shape, as well as the use of antidepressants, such as selective serotonin reuptake inhibitors, cause a delayed side effect, which manifests itself in the form of a quantitative decrease in NMDA in the brain. The antagonist of this receptor – memantine, inhibiting it can reduce the clinical picture of Alzheimer's disease, reducing tremor and papillary reflex. Another NMDA antagonist, ketamine, was used for anesthesia, but due to strong hallucinations during the period of recovery from anesthesia, it became less and less used. These substances also contribute to the work of the NMDA receptor in the future, and also affect synaptic density. Therefore, it is important to know the composition of the receptor, its downstream signaling pathways, and age-related changes in order to effectively prevent neurodegenerative diseases of the brain.

Key words. Alzheimer's disease, NMDA, CREB, glutamate, Mg^{Mg2+}, GluN2, ion channels, neurodegeneration, excitoxicity, synaptic density.

Introduction.

Currently, age-related changes in cognitive processes occurring at the molecular level are poorly understood. Studies in rodents show that with age, there is a decrease in the number of N-methyl-D-aspartate receptors (NMDARs) in synapses, which consist of GluN2B subunits. There is a correlation between a decrease in these subunits and a deterioration in cognitive function.

Excitatory glutamatergic neurotransmission via the N-methyl-d-aspartate receptor (NMDAR) is crucial for synaptic plasticity and neuronal survival. However, excessive NMDAR activity causes excitoxicity and promotes cell death, which is at the heart of a potential mechanism of neurodegeneration that occurs in Alzheimer's disease (AD). Studies show that different outcomes of NMDAR-mediated reactions are induced by regionalized receptor activity followed by different downstream signaling pathways. Activation of synaptic NMDARs initiates plasticity and stimulates cell survival. In contrast, activation of extrasynaptic NMDARs promotes cell death and thus contributes to the etiology of AD, which can be blocked by the drug AD-memantine, an NMDAR antagonist that selectively blocks the function of extrasynaptic NMDARs. In this regard, it is possible to use new methods for the prevention of senile brain diseases. In particular, increasing the stimulation of NMDARs, as well as preventing neurodegenerative diseases from a young age, to preserve NMDARs receptors and prevent their loss with age.

The aim of the study was to study the NMDA receptor and its effect on both the pathogenesis of Alzheimer's Disease and its physiological features. The aim of the study was to study the effects of synaptic density and various secondary messengers on the biochemical cascade after activation of this type of receptor.

Materials and methods.

Foreign articles devoted to the study of various NMDA stimulation were analyzed NMDA. The analysis included the results of preclinical studies conducted for the period from 2015 to 2020.

Alzheimer's disease.

There is increasing evidence that a decrease in the number of synapses and a deterioration in their receptor composition correlates with a decrease in cognitive function, as well as with age in rodents and primates [1,2]. AD progression was associated with gradual damage to the function and structure of the hippocampus and neocortex, vulnerable brain regions used for memory and cognition. Synapse loss can be caused by the inability of living neurons to maintain functional axons and dendrites, or by neuronal death. Synaptic dysfunction may be caused by excessive synaptic$^{Ca2+uptake}$ in response to excessive activation of glutamate receptors, namely NMDARs. Glutamate is the main excitatory neurotransmitter in the brain, acting on ionotropic and metabotropic glutamate receptors. Ionotropic glutamate receptors (iGluRs), responsible for rapid neuronal communication at excitatory synapses, consist of three subfamilies: a-amino-3-hydroxy-5-methyl-4-isoxazolpropionic acid (AMPA), kainate receptors, and NMDAR. However, over-stimulation of glutamatergic signaling leads to excitotoxicity [3].

NMDAR activity has recently been linked to the theory of AD as a synaptic dysfunction. Abnormal$^{Ca2+signaling}$ leads to a gradual loss of synaptic function and eventual death of neuronal cells, which is clinically correlated with a progressive decline in cognitive functions and memory and the development of pathological foci in the brain. This, in turn, confirms the reasonableness of clinical trials of Memantine, an NMDAR antagonist, as a symptomatic and neuroprotective treatment for AD. Memantine, an uncompetitive NMDA receptor antagonist, is approved for use in moderate to severe AD. It has been widely prescribed to relieve symptoms and improve quality of life in AD, even if it did not improve over-arousal and hippocampal or general brain atrophy.

It is also important to take into account the fact that the areas affected by AD are mainly composed of NMDARs receptors NMDARs consisting of GluN2A and GluN2B subunits [3].

According to the World Health Organization, Alzheimer's disease is the leading cause of dementia, accounting for 60-70% of cases. The symptom of this chronic neurodegenerative disease worsens over time-from early forgetfulness to gradual deterioration of speech, orientation and behavior, and late severe loss of memory and some body functions until final death.

The etiology of AD is complex and multifactorial. The early onset of familial asthma is caused by a genetic mutation(s) in the genes of presenilins (PS1, PSPS1, PS2) and amyloid-like precursor protein (APP), which affect a single pathogenetic mechanism in APP synthesis and proteolysis and cause excessive production of amyloid β (Aß) [4]. However, the reason for the late occurrence of sporadic AD remains poorly understood. It is believed that the main risk factor is genetics involving multiple genes. Other risk factors include aging, apolipoprotein (Apo) E4 genotype, head injury, and vascular disease. The main deterministic and risky AD genes are listed in Table 1.

NMDAR for BA

The defining features of AD are marked changes in both brain histology and human behavior. AD of the brain is characterized microscopically by extracellular amyloid plaques and intraneuronal NFTs. Accumulated data have shown that the soluble forms of Aß and tau work together, regardless of their accumulation in plaques and tangles, to bring healthy neurons to a diseased state, and that such distinctive toxic properties of Aß require the presence of tau [5]. Cognitive impairments in AD are closely related to synaptic plasticity, in which NMDAR plays a crucial role [6]. Excitatory glutamatergic neurotransmission via NMDAR is crucial for synaptic plasticity and neuronal survival. However, excessive NMDAR activity causes excitotoxicity and promotes cell death, which underlies the potential mechanism of neurodegeneration that occurs in AD [7]. The main factors influencing NMDAR signaling in AD are glutamate availability and modulation of NMDAR channel functions [7].

Beta Amyloid and NMDAR

In Alzheimer's Disease (AD), the "cascade hypothesis" of amyloid beta (Aß) postulates an initiating event of amyloidosis with subsequent accumulation of tau protein preceding subsequent brain atrophy and cognitive suppression [8]. From studies using methods such as amyloid-PET and florbetapir-PET, it was known that beta-amyloid deposition occurs selectively first in the cerebral cortex, starting from the temporo-basal and fronto-medial regions and sequentially affecting the primary sensorimotor regions and the medial temporal lobe. It was followed by the hippocampal regions, then the striatum, basal forebrain, thalamus, and finally the brainstem and cerebellar nuclei [9-11]. Beta-amyloid deposition in the medial parietal cortex appears to be the first stage of AD development, although Tau protein aggregates in the medial temporal lobe precede beta-amyloid deposition in cognitively healthy elderly people [12]. Beta-amyloid is produced by endoproteolysis of the amyloid precursor protein (APP), which is achieved by sequential cleavage of APP by groups of enzymes called b-and g-secretases [13]. Aß is formed as a monomer but is easily aggregated to form multimeric complexes.

The initial amyloid hypothesis postulated that the accumulation of beta-amyloid in the brain is the main factor determining the pathogenesis of AD. Cell studies and animal experiments have confirmed that oligomeric, soluble Aßs, rather than insoluble amyloid plaques, have a toxic effect [14,15]. Thus, according to the modified hypothesis of the amyloid cascade, soluble oligomeric forms of A-b induce a neurodegenerative triad [4].

The Aß peptide was first identified as a component of extracellular amyloid plaques in the mid-1980s. Currently, a large number of studies have proved the presence of intracellular beta-amyloid in neurons [13]. Studies also show that beta-amyloid is produced intracellularly in the compartments of the endosome [16-21], ER (endoplasmic reticulum) [22,23], and the trans-pole of K. Golgi - in neurons [18]. Secreted beta-amyloid, which forms the extracellular pool of beta-amyloid, can be absorbed by cells and internalized into intracellular pools. Aß binds to the nicotinic acetylcholine receptor with high affinity, which leads to internalization of the receptor and accumulation of beta-amyloid intracellularly [7,19]. In addition to nicotinic receptors, internalization of beta-amyloid has been reported via LRP (Low-density lipoprotein receptor related protein) [20], RAGE (scavenger receptor for advanced glycation end products) [21], and NMDAR [24]. The uptake of beta-amyloid was completely blocked by NMDAR antagonists, which indicates the involvement of this receptor in the re-uptake of the peptide [25].

Cognitive function ultimately depends on synaptic plasticity, where LTP is associated with synapse growth and LTD is associated with synapse loss. Aß is associated with inhibition of LTP (increased synaptic transmission between two neurons that persists for a long time – the main component of synaptic plasticity) [26] and activation of LTD (decreased efficiency of neuronal synapses – their depression) [27,28]. During LTP induction, a strong and prolonged release of glutamate from the presynaptic terminal activates AMPA receptors, and subsequent depolarization removes the blockade of the Mg channel of NMDAR and provides an influx of Ca. This strong activation of NMDARs triggers Ca/calmodulin-dependent protein kinase II (CaMKII), an indirect signaling cascade that ultimately leads to increased synaptic strength.

In contrast, moderate activation of NMDARs causes a moderate increase in postsynaptic Ca and triggers phosphatase-mediated

Table 1. *The main deterministic and risky AD genes.*

Genes	Locus	Function normal	Involvement in AD
Presenilin -1 (PS-1)	Xp. 14	Processing of amyloid precursor protein and Aß formation	Cause of early onset of AD
Presenilin-2 (PS-2)	Xp. 1	Processing of amyloid precursor protein and Aß formation	Cause of early onset of AD
APP (amyloid precursor)	Xp. 21	Regulates synaptic function	Cause of early AD
onset Apolipoprotein E4	Xp. 19	Transport CS	is a risk factor for AD

LTD [29]. Activation of synaptic NMDARs and a significant increase in [Ca] are required for LTP, whereas internalization of synaptic NMDARs, activation of perisynaptic NMDARs, and a decrease in [Ca] increase is required for LTD. LTP induction promotes the selection of AMPA receptors and the growth of dendritic spines, while LTD induces spines depression and synaptic loss [30]. Pathologically elevated Aß can indirectly cause partial blocking of NMDAR and shift the activation of NMDAR-dependent signaling cascades towards pathways involved in LTD induction and synaptic loss [31.15]. This model is consistent with the fact that Aß worsens LTP [26,32] and stimulates LTD [33,34,27]. Although the mechanisms underlying Aß -induced LTD are not yet fully elucidated, they may involve desensitization of receptors [35] or internalization and subsequent destruction of dendritic spines [36,37].

Beta-amyloid modulates NMDARs-related responses; pre - exposure to Aß reduced the NMDA-induced increase in [Ca] and pre - exposure to NMDA reduced the Aß response. In addition, simultaneous exposure to Aß plus NMDA synergistically increased [Ca] levels, an effect mediated by GluN2B-containing NMDARs [38]. Accumulated data indicate that glutamate receptors are dysregulated by Aß oligomers, which leads to a violation of glutamatergic synaptic transmission, which corresponds to an early cognitive deficit. Theoretically, there are several potential roles of the NMDA receptor in Aß -related mechanisms [39] first, the function of the NMDA receptor may be an important downstream target of Ab; second, NMDA receptors may be necessary for the action of Aß on synaptic transmission and plasticity.

Tau protein and NMDAR

Tau is one of the main components of NFT, which is a pathological sign of AD. In a healthy brain, tau protein (tau) is an exclusively axonal protein involved in the assembly and stabilization of microtubules. In contrast, in the brain of AD, tau is hyperphosphorylated and forms fibrils that appear as neuropil filaments in dendrites and as NFTs in the somatodendritic compartment and axons. Strong evidence has been provided that the deposition of cerebral amyloid precedes cerebral tau pathology in familial autosomal dominant AD, while the appearance of NFT precedes Aß pathology in the vast majority of affected regions in sporadic AD [40,41]. For the first time, the possibility that tau reduction altered A-b levels or aggregation and disconnected the brain was excluded. Aß depends on top-down pathogenic mechanisms [42].

Tau not only contributes to axonal structure by maintaining microtubule stability, but also plays an important role in regulating synaptic function. Tau is required for Fyn-mediated NMDAR activation in PSD [42], and tau has been shown to be important for the induction of LTD [43], as well as BDNF-dependent morphological plasticity [44]. Fyn, a member of the Src tyrosine kinase family [45], can phosphorylate tau in its tyrosine 18 residue to produce pY18-tau [46] and can bind to tau via one or moreproline-rich (PxxP) motifs in tau [46-48]. Fyn phosphorylates the NMDAR subunit GluN2B in y1472 [49], which enhances the interaction between NMDARs and PSD-95 in PSD [50] and enhances the activity of GluN2B-containing NMDARs [51]. Some experiments have shown that tau is usually highly enriched in axons relative to dendrites [52], but in response to Aß, tau is extensively redistributed into the somato-dendritic compartment [53,54]. Excess Fyn accompanies excess tau in dendrites in AD and increases the activity of NMDA receptors there, flooding the dendrites with harmful calcium levels. This calcium-induced excitotoxicity can damage postsynaptic sites and cause neuronal death. Some results have confirmed that glutamate-induced excitotoxicityis inhibited by a decrease in tau [41,42] and worsened by an overexpression of tau [55,56]. In turn, glutamate-induced excitotoxicity increases экспрессию tau expression [57,58] and its phosphorylation [57]. It has recently been reported that activation of extrasynaptic NMDA receptors induces Tau overexpression with simultaneous neuron degeneration and reduced neuronal survival [59].

Some atypical types of NMDAR reception in AD

Presynaptic NMDARs:

Traditionally, NMDARs are thought to be located on the postsynaptic membrane, while recent anatomical and physiological data suggest that they may also exist on presynaptic terminals. Presynaptic NMDARs (preNMDARs) can regulate presynaptic glutamate release, as well as alter synaptic transmission and plasticity [60-63]. Thus, the composition of the preNMDAR subunit is crucial for modulating where and how preNMDARs affect glutamate release. The subunit composition of preNMDARs shows strong variability; depending on the brain region, all four subunits of GluN2 (Glu2A-D) and GluN3A can be included [64]

The presynaptic GluN2B subunit has been found in many brain regions, such as the hippocampus [65-67], cerebellum [68], entorhinal cortex [69], somatosensory [70], and visual cortex [71]. Although it appears and peaks later in development [72,73], the GluN2A subunit can also be included in preNMDAR sites [74]. In cerebellar parallel fiber-Purkinje cell synapses, preNMDARs are predominantly diheteromeric GluN1/GluN2A [75]. In addition, the GluN2B and GluN3A subunits, probably combining to form the trigeteromeric GluN1/GluN2B/GluN3A, are essential preNMDARs in the developing visual cortex L2 / 3 [76,77].

preNMDARs have been reported to regulate both spontaneous and evoked release. Although the two forms of release were initially thought to use the same mechanism, emerging evidence suggests that preNMDARs control evoked and spontaneous release by different mechanisms. preNMDARs can control spontaneous release independently of Mg and Ca while regulation of evoked release depends on frequency, relying on the more traditional Mg-dependent pathway [78-81] showed that preNMDARs in L5 pyramidal cells regulate evoked and spontaneous release via the RIM1ab and jnk2-dependent pathways, respectively.

In addition, activation of preNMDARs is necessary for the induction of LTD [82,79], but it is noteworthy that the roles of preNMDARs change during development. Induction of LTD in the pyramidal visual cortex cells of young mice (up to postnatal 20 days) requires presynaptic activation, whereas in older mice, LTD induction requires postsynaptic activation of NMDARs [60]. In contrast to these results, [83] shows that in

the somatosensory cortex of 2 - to 3-week-old rats and mice, it is postsynaptic rather than preNMDARs processes that are necessary for the induction of LTD. This contradictory result may be caused by different observed brain regions. Not only being essential for LTD induction, preNMDARs are also involved in LTP induction [84,85] reported that preNMDARs play a key role in LTP induction in mouse corticostriatal synapses. Activation of preNMDARs induces BDNF secretion through amplification of Ca signals in axonal terminals, which indicates that preNMDARs are just as important as postsynaptic NMDARs in LTP induction [85].

Bell et al. (2007) [86] found that subjects with moderate cognitive impairment show a paradoxical increase in glutamatergic presynaptic density, which then depletes and decreases with disease progression. These results showed that neurite degeneration and reduced presynaptic terminal density окончаний negatively affect neurotransmission and cognitive function in the later stages of AD. While some progress has already been made, much remains to be done to clarify the exact functions and molecular mechanisms of preNMDARs.

Glial NMDARs:

While neuronal NMDARs are widely studied, they are also expressed in many non-neuronal cells, including astrocytes. Astrocytic NMDA receptors are poorly understood compared to neuronal receptors. Emerging dataindicate that astrocytic NMDARs have pronounced structural and functional properties, including weak susceptibility to Mg blockade and lower Ca permeability [87]. NMDAR expression and function in astrocytes was demonstrated in cultured astrocytes in the mouse neocortex [88-91]. All seven identified NMDAR subunits (GluN1, GluN2A-D, and GluN3AB) were detected in primary human astrocytes. Increasing data indicate that astrocytes express NMDARs with a three-heteromeric configuration combining GluN1, GluN2C, or D and the GluN3 subunit [92,93]. Glutamate and QUIN can activate astrocytic NMDARs, which in turn increases Ca influx and induces a signaling cascade [46]. It has been established that astrocytic functional NMDARS are able to respond to neuronal glutamatergic input, which is accompanied by dynamic intracellular Ca elevation, triggering gliotransmitter-mediated regulation of synapse function [94-96]. Astrocytic NMDARs may also be involved in neuroinflammatory processes, as well as contribute to morphological transformations characteristic of reactive astrogliosis, and mediate the release of proinflammatory cytokines [97-99]. In particular, astrocytic NMDARs may contribute to AD due to their role in promoting glutamate excitotoxicity [46]. Our studies have shown that A-b-induced early synaptotoxicity can be enhanced after treatment with blockade of astrocytic GluN2A and GluN2B, and nerve growth factor (BDNF) can act as a mediator in synaptoprotection of astrocytic GluN2 activation [91]. In the co-culture system, it was found that pretreatment of astrocytes with 1 mM or 10 mM NMDA to activate GluN2A or GluN2B before exposure to Aß 1-40-40 prevented the introduction of Aß PSD-95 and a decrease in synaptophysin. Whereas blockade of astrocytic GluN2A with TCN-201 or GluN2B with ifenprodil: respectively, both exacerbated the synaptotoxic effects of Aß.

In addition, NMDARS are also expressed by oligodendrocyte line cells as mediators of intracellular Ca accumulation, which leads to reduced oligodendrocyte survival and white matter damage [100-102]. The dominant force underlying NMDA-induced currents in mature oligodendrocytes is actually increased extracellular K^+ released when neuronal or astrocytic NMDARs are activated. An increased level of oligodendrocytic Ca will be gated by the transient receptor potential of the cationic channel (TRP) a1 [103]. NMDAR of oligodendrocyte progenitor cells (OSCs) can also contribute to myelination. Activation of NMDARs in OPC cultures increased migration [60], core protein expression [104], and differentiation [60].

Rather surprisingly, a recent study showed that NMDARs are present in primary cultures of microglia from the cerebral cortex and hippocampus of mice [105], and exposure to NMDAR co-agonists resulted in induced internal currents and an intracellular increase in Ca sensitive to inhibition by the non-competitive NMDAR channel blocker MK801 [106,107]. Activation of NMDAR in microglia leads to significant phosphorylation of ERK1 / 2. Phosphorylation of ERKs, namely nmdar, interacts with mitogen-activated protein kinase, and signaling via MAPK depends on CaM and NCS1 in neurons, whereas signaling via NMDAR in microglia depends only on CaM. NMDAR function was potentiated in microglia from transgenic APPSw;Ind mice, indicating that the NCS1–NMDAR interaction is relevant to receptor function in the microglia of a mouse model with AD [105].

Metabotropic NMDARs:

Считалось, что NMDAR-dependent synaptic plasticity was thought to be completely controlled by Ca influx, and elevated cytoplasmic [Ca] acts as a second messenger in the postsynaptic neuron. More recent data suggest that when glutamate binds, NMDARs can cause long-term changes in synaptic function in the absence of calcium conduction [107-110]. In other words, NMDAR can act as a metabotropic receptor and signal metabotropically, without the need for Ca influx through the channel. [107-110].

Conventional wisdom suggests that NMDARs trigger LTP through a high level of Ca influx, while the metabotropic receptor arises from synaptic depression induced by low-frequency stimulation (LFS), which is called NMDAR-dependent LTD [111,112]. Recent results have shown that glutamate binding alone is sufficient to induce conformational changes in NMDARs that trigger p38MAPK signaling cascades, and, in turn, to induce LTD [107-109]. It is noteworthy that an increase in Ca can induce LTD; however, maintaining the initial level of intracellular Ca is necessary for metabotropic activation of NMDAR, which leads to synaptic depression [107].

Consistent with this metabotropic signaling, some researchers have found that pre-NMDARs can control spontaneous release without the need for Mg and Ca, while evoked release was sensitive to Mg [78,80]. Pre-NMDARs promote transmitter release in part through protein kinase c signaling [78]. These data suggest that pre- NMDARs can" signal " metabotropically, and further support the assumption that evoked and spontaneous release occurs through various mechanisms [113,114]. Although some conclusions support an ion flux-independent mechanism

for NMDAR-dependent LTD [110,83], it has been challenged by some recent discoveries [115-117].

In addition, some studies have shown that astrocytic cells can also act through metabotropic NMDAR signaling pathways [118,119], which may involve phospholipase C-o mediated Ca elevation in the endoplasmic reticulum and activation of Cd protein kinase [118], but much remains to be done to clarify this complex mechanism [87].

Early synaptic dysfunction in AD is associated with an increase in the level of A-b oligomers, which causes rapid NMDAR-dependent synaptic depression and loss of dendritic spines [76,63]. While some studies have shown that Aß -induced NMDAR-dependent synaptic depression does not require ion flow through the receptor [108] and is blocked by AP-5, but not by MK-801, it is suggested that the metabotropic effect of NMDARs contributes to Aß -induced synaptic dysfunction. This may be a common mechanism between metabotropic NMDAR-dependent LTD and Aß -induced synaptic depression [120].

Discussion.

Currently, there is reliable evidence ($p<0.05$) that synaptic dysfunction in Alzheimer's disease is due to excessive synaptic Ca2+ input in response to excessive NMDARs activation. Since other iGluRs are associated with triggering LTP and increasing the efficiency of neuroplasticity processes (AMPAR in particular). It is also important to take into account the fact that areas affected by Alzheimer's disease have mainly NMDARs receptors consisting of GluN2A and GluN2B subunits.

Excessive NMDAR activity causes excitotoxicity and promotes cell death, which underlies a potential mechanism of neurodegeneration that occurs in AD. It is known that deposits of beta-amyloid (Aß) and tau protein (tau) also play a role in the pathogenesis of early hereditary Alzheimer's disease.

Accumulated data indicate that glutamate receptors are dysregulated by Aß oligomers, which leads to a violation of glutamatergic synaptic transmission, which corresponds to an early cognitive deficit. Beta-amyloid, as a product of perverted synthesis, can also use NMDAR as a downstream target or even a receptor. In addition, NMDAR-induced calcium excitotoxicity may contribute to Aß accumulation.

Previously, activation of extrasynaptic NMDA receptors was also found to induce overexpression of tau protein with simultaneous neuron degeneration and reduced neuronal survival.

Various forms of NMDAR have been found to contribute to the development of Alzheimer's disease. In particular, astrocytic NMDARs may contribute to AD due to their role in promoting glutamate excitotoxicity. The NCS1–NMDAR interaction is relevant to receptor function in the microglia of a mouse model with Alzheimer's disease.

Typically, activation of preNMDARs induces BDNF secretion through amplification of Ca signals at axonal terminals, indicating that preNMDARs are just as important as postsynaptic NMDARs in LTP induction. However, in individuals with moderate cognitive impairment, glutamatergic presynaptic transmission processes were subsequently enhanced, which contributed to the activation of LTD and further neurodegeneration.

The metabotropic receptor arises from synaptic depression induced by low-frequency stimulation (LFS), which is called NMDAR-dependent LTD. This reaction is especially sharply caused by low-frequency stimulation of the extrasynaptic forms of NMDAR, which are dominated GluNby the GluN2B subunit. Their expression and incorporation into the receptors increases with age.

Thus, it is assumed that there are indeed two different forms of NMDAR-dependent LTD: one requires an ion flux, and the other does not. There are certain interactions between the Aß/tau protein oligomers and NMDAR, and it is possible that the relationship may be mutual.

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