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# KALSIY GOMEOSTAZI VA GLUTAMATERGIK SIGNALIZATSIYANING ALSGEYMER KASALLIGIDAGI SINAPTIK DISFUNKSIYADAGI ROLI: POLIFENOLLARNING NEYROPROTEKTOR POTENTSIALI

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***Annotatsiya:*** *Alsgeymer kasalligi (AK) amiloid-β (Aβ) to‘ planishi va patologik Tau o‘ zgarishlari bilan bir qatorda, erta sinaptik disfunksiya, glutamatergik neyrotransmissiya va kalsiy ($Ca^{2+}$) signalizatsiyasining buzilishi, mitoxondrial disfunksiya, oksidativ stress va neyroyallig‘ lanish bilan kechuvchi ko‘ p omilli neyrodegenerativ jarayondir. Ushbu obzorning maqsadi AK bilan bog‘ liq sinaptik disfunksiyada glutamatergik signalizatsiya va neyronal $Ca^{2+}$ gomeostazining fiziologik ahamiyatini tizimlashtirish hamda polifenollarning ushbu jarayonlarni modulyatsiya qilish potentsialini baholashdan iborat. Fiziologik sharoitda AMPA va NMDA retseptorlari orqali nazoratlangan ion oqimlari, endoplazmatik retikulum va mitoxondriya bilan $Ca^{2+}$ almashinuvi sinaptik plastiklik va neyron bioenergetikasini ta’ minlaydi. AK modellarida Aβ/Tau bilan bog‘ liq o‘ zgarishlar retseptor funksiyasi, organellalar o‘ rtasidagi $Ca^{2+}$ almashinuvi va mitoxondrial metabolizmni izdan chiqarishi mumkin. Kalamush bosh miyasi sinaptosomalarida olingan mahalliy eksperimental ma’ lumotlar ayrim polifenollar L-glutamatga bog‘ liq $Ca^{2+}$ javoblarini va NMDA/VGCC bilan bog‘ liq funksional jarayonlarni modulyatsiya qilishini ko‘ rsatadi. Biroq funksional $Ca^{2+}$ o‘ zgarishlarini to‘ g‘ ridan-to‘ g‘ ri retseptor bog‘ lanishi yoki insonda terapevtik samara bilan tenglashtirish mumkin emas. $Ca^{2+}$ disgomeostazi Aβ yoki Tau gipotezasining o‘ rnini bosuvchi emas, balki sinaptik, mitoxondrial va oksidativ mexanizmlarni o‘ zaro bog‘ lovchi muhim fiziologik-patofiziologik komponent sifatida qaralishi maqsadga muvofiq.*

***Kalit so‘ zlar:*** *Alsgeymer kasalligi; sinaptik disfunksiya; glutamat; NMDA-retseptor; AMPA-retseptor; kalsiy gomeostazi; mitoxondriya; polifenollar; sinaptosoma.*

# РОЛЬ КАЛЬЦИЕВОГО ГОМЕОСТАЗА И ГЛУТАМАТЕРГИЧЕСКОЙ СИГНАЛИЗАЦИИ В СИНАПТИЧЕСКОЙ ДИСФУНКЦИИ ПРИ БОЛЕЗНИ АЛЬЦГЕЙМЕРА: НЕЙРОПРОТЕКТОРНЫЙ ПОТЕНЦИАЛ ПОЛИФЕНОЛОВ

***Аннотация:*** *Болезнь Альцгеймера (БА) представляет собой многофакторный нейродегенеративный процесс, протекающий наряду с накоплением амилоида-β (Aβ) и патологическими изменениями Tau, с ранней синаптической дисфункцией, нарушением глутаматергической нейротрансмиссии и кальциевой ($Ca^{2+}$) сигнализации, митохондриальной дисфункцией, оксидативным стрессом и нейровоспалением. Цель настоящего обзора — систематизировать физиологическое значение глутаматергической сигнализации и нейронального $Ca^{2+}$ гомеостаза в синаптической дисфункции при БА, а также оценить потенциал полифенолов в модуляции данных процессов. В физиологических условиях контролируемые ионные потоки через AMPA- и NMDA-рецепторы, а также обмен $Ca^{2+}$ с эндоплазматическим ретикулумом и митохондриями обеспечивают синаптическую пластичность и биоэнергетику нейрона. При моделях БА изменения, связанные с Aβ/Tau, могут нарушать функцию рецепторов, межорганелльный обмен $Ca^{2+}$ и митохондриальный метаболизм. Локальные экспериментальные данные, полученные на синаптосомах головного мозга крыс, показывают, что отдельные полифенолы модулируют $Ca^{2+}$-ответы, связанные с L-глутаматом, и функциональные процессы, связанные с NMDA/VGCC. Однако функциональные изменения $Ca^{2+}$ нельзя напрямую отождествлять со связыванием рецептора или терапевтическим эффектом у человека. Дисгомеостаз $Ca^{2+}$ следует рассматривать не как замену амилоидной или Tau-гипотезы, а как важный физиолого-патофизиологический компонент, связывающий синаптические, митохондриальные и оксидативные механизмы.*

***Ключевые слова:*** *болезнь Альцгеймера; синаптическая дисфункция; глутамат; NMDA-рецептор; AMPA-рецептор; кальциевый гомеостаз; митохондрия; полифенолы; синаптосома.*

**CALCIUM HOMEOSTASIS AND GLUTAMATERGIC SIGNALING IN SYNAPTIC DYSFUNCTION IN ALZHEIMER'S DISEASE: NEUROPROTECTIVE POTENTIAL OF POLYPHENOLS**

***Annotation:*** *Alzheimer's disease (AD) is a multifactorial neurodegenerative process characterized, alongside amyloid-β (Aβ) accumulation and pathological Tau changes, by early synaptic dysfunction, disrupted glutamatergic neurotransmission and calcium ($Ca^{2+}$) signaling, mitochondrial dysfunction, oxidative stress, and neuroinflammation. This review aims to systematize the physiological relevance of glutamatergic signaling and neuronal $Ca^{2+}$ homeostasis in AD-related synaptic dysfunction, and to evaluate the potential of polyphenols to modulate these processes. Under physiological conditions, controlled ion flux through AMPA and NMDA receptors, together with $Ca^{2+}$ exchange with the endoplasmic reticulum and mitochondria, sustains synaptic plasticity and neuronal bioenergetics. In AD models, Aβ/Tau-related changes may disrupt receptor function, inter-organelle $Ca^{2+}$ exchange, and mitochondrial metabolism. Local experimental data obtained on rat brain synaptosomes indicate that certain polyphenols modulate L-glutamate-dependent $Ca^{2+}$ responses and NMDA/VGCC-related functional processes. However, functional $Ca^{2+}$ changes cannot be directly equated with receptor binding or therapeutic efficacy in humans. $Ca^{2+}$ dyshomeostasis should not be regarded as a substitute for the amyloid or Tau hypotheses, but as an important physiological–pathophysiological component linking synaptic, mitochondrial, and oxidative mechanisms.*

***Key words:*** *Alzheimer's disease; synaptic dysfunction; glutamate; NMDA receptor; AMPA receptor; calcium homeostasis; mitochondria; polyphenols; synaptosome.*

**Kirish**

Alsgeymer kasalligi neyrodegenerativ kasalliklar orasida sinaptik funksiya va kognitiv jarayonlarning progressiv buzilishi bilan tavsiflanadi. Aβ va patologik Tau uning asosiy morfomolekulyar belgilari bo‘ lsa-da, zamonaviy qarashlar kasallikni bir yo‘ nalishli amiloid kaskad sifatida emas, balki sinaptik signalizatsiya, ion gomeostazi, organellalar funksiyasi, oksidativ stress va yallig‘ lanish o‘ zaro ta’ sir qiladigan tarmoq sifatida baholaydi [1–5].

Fiziolog nuqtai nazaridan sinaps AK patogenezini tushunish uchun qulay funksional darajadir. Neyromediator ajralishi, postsinaptik retseptorlar faolligi, membrana potensiali va $Ca^{2+}$ signalining amplitudasi hamda davomiyligi sinaptik plastiklikni belgilaydi. Shu sabab glutamatergik signalizatsiya va $Ca^{2+}$ gomeostazining buzilishi morfologik o‘ zgarishlar bilan funksional neyronal etishmovchilik o‘ rtasidagi muhim bog‘ lanishlardan biri hisoblanadi [6–10].

Ushbu obzor klinik davolash natijalarini emas, birinchi navbatda eksperimental neyrofiziologiyani markazga qo‘ yadi. Inson to‘ qimalari va klinik tadqiqotlardan olingan ma’ lumotlar eksperimental mexanizmlarni inson patofiziologiyasi bilan solishtirish va translyatsion chegaralarni belgilash uchun qo‘ llaniladi.

**Tadqiqot metodologiyasi (adabiyotlarni tanlash tamoyillari)**

Ushbu obzorda Alsgeymer kasalligida sinaptik disfunksiya, glutamatergik signalizatsiya va $Ca^{2+}$ gomeostazining fiziologik mexanizmlarini yorituvchi ilmiy ishlarga ustuvorlik berildi. Asosiy e’ tibor eksperimental neyrofiziologik tadqiqotlar, jumladan sinaptosomalar, neyronal modellar, $Ca^{2+}$ dinamikasini baholash va elektrofiziologik yondashuvlarga qaratildi. So‘ nggi yillardagi tadqiqotlar bilan bir qatorda AMPA/NMDA-retseptorlar, sinaptik plastiklik va $Ca^{2+}$ signalizatsiyasi fiziologiyasini asoslovchi fundamental ishlar ham tahlil qilindi. Inson to‘ qimalariga oid tadqiqotlar eksperimental natijalarni inson patofiziologiyasi bilan qiyoslash maqsadida qo‘ llanildi.

Adabiyotlar tahlili

**1. Aβ va Tau patologiyasi: sinaptik fiziologiya bilan bog‘ lanishi**

Amyloid precursor protein (APP) membrana oqsili bo‘ lib, β- va γ-sekretazalar ishtirokida amiloidogen yo‘ l bilan parchalanganda Aβ peptidlari hosil bo‘ ladi. Aβ42 agregatlanishga moyilroq; ayniqsa eruvchan Aβ oligomerlari sinaptik funksiyaga ta’ sir qiluvchi biologik faol shakllar sifatida qaraladi [11–14].

Tau normal sharoitda mikrotrubochkalarni barqarorlashtirish va aksonal transportni ta’ minlashda ishtirok etadi. Patologik fosforlanish va konformatsion o‘ zgarishlar Tauning mikrotrubochkalardan ajralishi, agregatlanishi va neyron ichi transport jarayonlarining buzilishi bilan bog‘ liq [15–17]. Aβ va Tauni bir-biriga qat’ iy ketma-ket sabab sifatida emas, sinaptik va hujayraviy signal yo‘ llarida o‘ zaro ta’ sir qiluvchi patologiyalar sifatida talqin qilish maqsadga muvofiq.

Aβ oligomerlari retseptor traffigi, membrana xususiyatlari va $Ca^{2+}$ signalizatsiyasiga ta’ sir qilishi mumkin. Eksperimental modellarda Aβ ta’ siri NMDA va AMPA retseptorlari bilan bog‘ liq $Ca^{2+}$ kirishi, sinaptik tarmoq holati va membrana mexanikasiga bog‘ liq ekani ko‘ rsatilgan [18–20]. Bu ma’ lumotlar Aβ →NMDA giperaktivatsiyasi kabi soddalashtirilgan modeldan ko‘ ra ko‘ p komponentli fiziologik yondashuvni qo‘ llab-quvvatlaydi.

**2. Sinaptik disfunksiya va glutamatergik signalizatsiya**

Glutamat markaziy asab tizimining asosiy qo‘ zg‘ atuvchi neyromediatori bo‘ lib, ionotrop AMPA, NMDA va kainate retseptorlari hamda metabotrop glutamat retseptorlari orqali ta’ sir qiladi. Tez qo‘ zg‘ atuvchi postsinaptik tokning katta qismi AMPA-retseptorlar bilan bog‘ liq. AMPA orqali $Na^+$ kirishi postsinaptik membranani depolyarizatsiya qilib, NMDA-retseptor kanalidagi potentsialga bog‘ liq $Mg^{2+}$ blokini yengillashtiradi (1-jadval) [21–24].

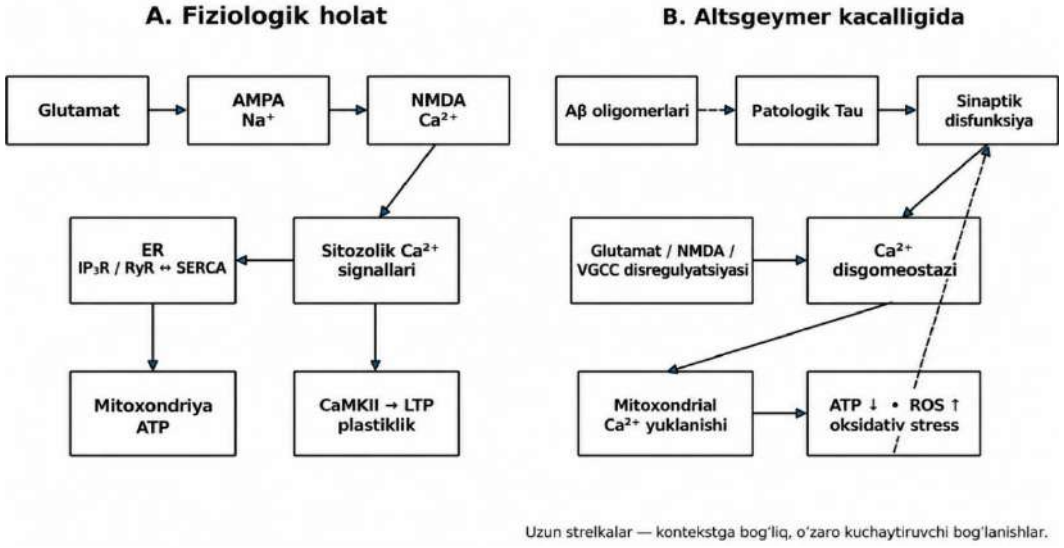
NMDA-retseptor faollashishi uchun glutamat bilan bir qatorda glitsin yoki D-serin ko-agonisti va etarli depolyarizatsiya talab etiladi. Kanal ochilganda $Na^+$ va $Ca^{2+}$ kirishi, $K^+$ chiqishi yuz beradi. Fiziologik $Ca^{2+}$ signali CaMKII va boshqa signal kaskadlari orqali sinaptik plastiklik, LTP va xotira mexanizmlarida ishtirok etadi [25–28]. Shu sabab NMDA-retseptorni o‘ z-o‘ zidan “toksik retseptor” sifatida ta’ riflash noto‘ g‘ ri.

Patologik sharoitda signalning joyi, davomiyligi va retseptor subtipi ahamiyat kasb etadi. Sinaptik va ekstrasinaptik NMDAR signallari turlicha hujayraviy natijalar bilan bog‘ lanishi mumkin [29–31]. Inson AD miyasi bo‘ yicha sistematik obzor va meta-tahlil glutamatergik tizimda bir xil giperfunktsiya emas, balki miya hududiga bog‘ liq geterogen o‘ zgarishlar, jumladan ayrim hududlarda glutamat, qayta qamrab olish, GluA2/3 va GluN2B ko‘ rsatkichlarining pasayishini ko‘ rsatgan [32].

**Jadval 1**

**Glutamat retseptorlarining fiziologik roli va AK konteksti**

| Retseptor | Asosiy ion/signal | Fiziologik vazifa | AKdagi ahamiyati |
|---|---|---|---|
| AMPA | $Na^+/K^+$; GluA2 bo‘ lmasa $Ca^{2+}$ ham | Tez EPSC, depolyarizatsiya, LTPda retseptor traffiki | Retseptor traffiki va subbirlik tarkibi o‘ zgarishi mumkin |
| NMDA | $Ca^{2+}$, $Na^+/K^+$; $Mg^{2+}$ blok | Coincidence detection, LTP/LTD, $Ca^{2+}$ signal | Sinaptik/ekstrasinaptik balans va subbirlikka bog‘ liq disregulyatsiya |
| Kainate | $Na^+/K^+$ | Pre- va postsinaptik modulyatsiya | Kamroq o‘ rganilgan, tarmoq qo‘ zg‘ aluvchanligiga ta’ sir |
| mGluR | G-protein/ikkinchi messenjerlar | Neyromediator ajralishi va plastiklik modulyatsiyasi | Aβ va sinaptik signal yo‘ llari bilan o‘ zaro ta’ sir |




**1-rasm.** Fiziologik sinaptik $Ca^{2+}$ signalizatsiyasi va Alsgeymer kasalligida $Ca^{2+}$ disgomeostazining integrativ modeli.

### 3. Neyronal $Ca^{2+}$ gomeostazi

$Ca^{2+}$ neyronda universal ikkinchi messenjer bo‘ lib, neyromediator ajralishi, gen ekspressiyasi, fermentlar faolligi, plastiklik va metabolizmni boshqaradi. Funksional natija faqat umumiy $Ca^{2+}$ miqdoriga emas, signalning amplitudasi, davomiyligi va subhujayraviy lokalizatsiyasiga bog‘ liq [33–35].

Plazmatik membrana orqali $Ca^{2+}$ NMDAR va potentsialga bog‘ liq $Ca^{2+}$ kanallari (VGCC) orqali kirishi mumkin. ERdan $Ca^{2+}$ $IP_3R$ va RyR orqali ajraladi, SERCA esa uni ER lyumeniga qayta yig‘ adi. PMCA va NCX sitozolik $Ca^{2+}$ni hujayradan chiqarishda ishtirok etadi. Mitoxondriya $Ca^{2+}$ni MCU kompleksi orqali qabul qilib, fiziologik sharoitda metabolik talab bilan ATP ishlab chiqarishni muvofiqlashtirishga yordam beradi (2-jadval) [36–40].

AKda “$Ca^{2+}$ doimo yuqori” degan ta’ rif etarli emas. Asosiy masala $Ca^{2+}$ signalining fazoviy-vaqtiy nazorati va organellalar o‘ rtasidagi taqsimlanishining buzilishidir. ER–mitoxondriya kontaktlari orqali ortiqcha $Ca^{2+}$ uzatilishi mitoxondrial yuklanish, bioenergetik disfunksiya va ROS hosil bo‘ lishi bilan bog‘ lanishi mumkin (1-rasm) [41–44].

*Jadval 2*

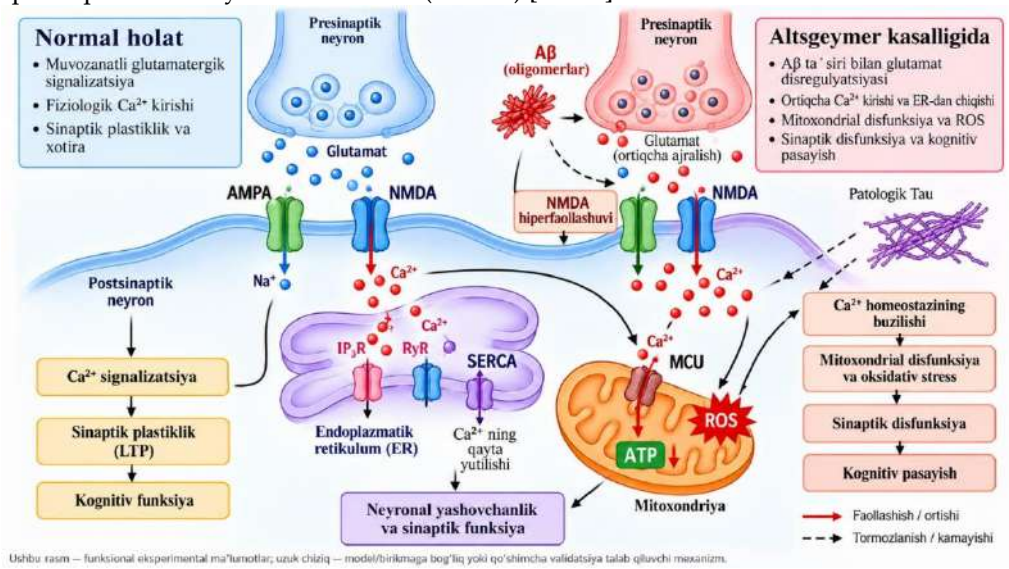
Neyronal $Ca^{2+}$ transportining asosiy tizimlari

| Tizim | Lokalizatsiya | Funksiya | Disregulyatsiyada ehtimoliy natija |
|---|---|---|---|
| NMDAR | Postsinaptik membrana | Ligand va potentsialga bog‘ liq $Ca^{2+}$ kirishi | Ortiqcha/noto‘ g‘ ri lokal signal |
| VGCC | Plazmatik membrana | Depolyarizatsiyaga bog‘ liq $Ca^{2+}$ kirishi | Qo‘ zg‘ aluvchanlik va $Ca^{2+}$ yuklamasi o‘ zgarishi |
| $IP_3R$ / RyR | ER | ERdan $Ca^{2+}$ ajralishi | Tsitozolik va mitoxondrial signalning kuchayishi |
| SERCA | ER | $Ca^{2+}$ni ERga qaytarish | ER zaxirasi va sitozolik signal o‘ zgarishi |
| PMCA / NCX | Plazmatik membrana | $Ca^{2+}$ni hujayradan chiqarish | $Ca^{2+}$ klirensining sekinlashishi |
| MCU kompleksi | Mitoxondriya ichki membranasi | Mitoxondrial $Ca^{2+}$ qabul qilinishi | Ortiqcha yuklanish, ROS va ATP disfunktsiyasi |

**4. Aβ/Tau–$Ca^{2+}$ va mitoxondriya–ROS o‘ qi**

Aβ va Tau bilan bog‘ liq patologik jarayonlar $Ca^{2+}$ signalizatsiyasi bilan ikki tomonlama o‘ zaro ta’ sir qiladi. Aβ oligomerlari membrana retseptorlari, ER $Ca^{2+}$ chiqishi va mitoxondrial funksiyaga ta’ sir qilishi mumkin; o‘ z navbatida $Ca^{2+}$-bog‘ liq kinazalar, fosfatazalar va proteazalar Tau fosforlanishi, sitoskelet va sinaptik funksiyaga ta’ sir ko‘ rsatadi [45–47]. Bu munosabatni qat’ iy bir yo‘ nalishli kaskad emas, o‘ zaro kuchaytiruvchi tarmoq sifatida ko‘ rish to‘ g‘ riroq.

Mitoxondriyaga fiziologik $Ca^{2+}$ kirishi degidrogenazalar va ATP sintezini metabolik talabga moslashtirishi mumkin. Ortiqcha yoki uzoq davom etuvchi $Ca^{2+}$ yuklanishi esa elektron-transport zanjiri disfunksiyasi, membrana potensiali o‘ zgarishi va ROS hosil bo‘ lishi bilan bog‘ liq. ROS esa lipidlar, oqsillar va $Ca^{2+}$ transport tizimlarini shikastlab, qaytar aloqa halqasini kuchaytirishi mumkin (3-rasm) [41–44].




**3-rasm.** Alsgeymer kasalligida sinaptik glutamatergik signalizatsiya, $Ca^{2+}$ gomeostazi, ER–mitoxondriya aloqasi va Aβ/Tau patologiyasining integrativ mexanizmi.

Natijalar va ularning tahlili

**1. Polifenollar va $Ca^{2+}$ signalizatsiyasi: fiziologik yondashuv**

Polifenollar an’ anaviy ravishda antioksidant xususiyatlari bilan muhokama qilingan bo‘ lsa-da, zamonaviy ma’ lumotlar ularning membrana oqsillari, kinazalar, yallig‘ lanish signallari, mitoxondriya va ion gomeostaziga ham ta’ sir qilishi mumkinligini ko‘ rsatadi [48–50]. Shu sabab ularni faqat ROSni neytrallovchi birikmalar sifatida emas, ko‘ p nishonli funktsional modulyatorlar sifatida o‘ rganish maqsadga muvofiq (2-rasm).

Kalamush bosh miyasi sinaptosomalarida Khoshimov va hammualliflar tomonidan o‘ tkazilgan ishlar polifenollar–glutamat–$Ca^{2+}$ o‘ qini eksperimental o‘ rganishga qaratilgan. Euphorbin, PC-6, PC-7 va keyingi birikmalar ishtirokidagi

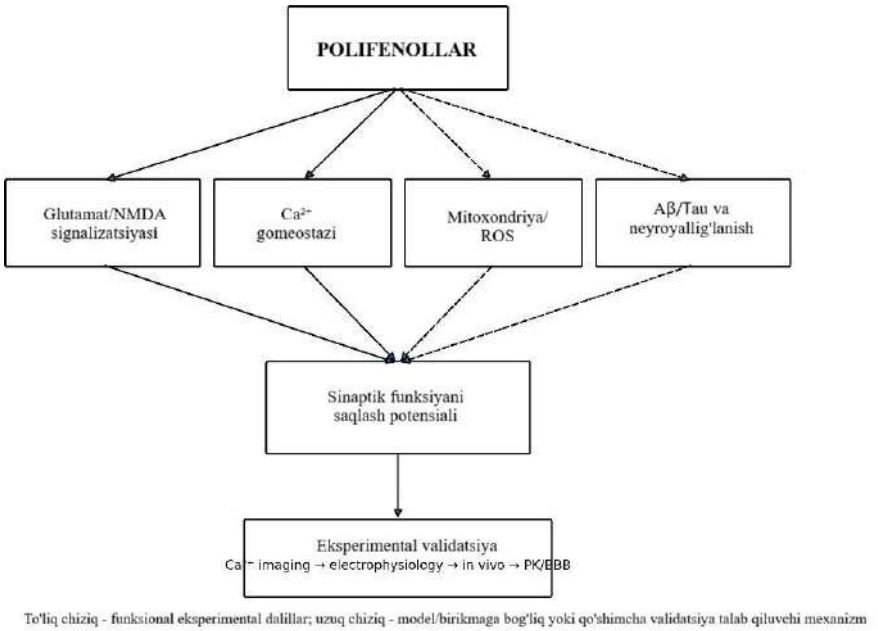
tajribalarda L-glutamatga bog‘ liq $Ca^{2+}$ javoblari, farmakologik blokatorlar va fluoresent indikatorlar orqali funksional o‘ zgarishlar baholangan [51–56]. 2023 yilgi PC-6/PC-7 ishida mualliflar NMDA-retseptor ion kanali ochilishini regulyatsiya qilish sohasida polifenollar va glutamat o‘ rtasida “possible competition” mavjudligini taklif qilgan; obzorda bu to‘ g‘ ridan-to‘ g‘ ri molekulyar bog‘ lanish isboti emas, funksional farmakologik talqin sifatida qabul qilindi [55].

2024 yilgi modellangan AK sharoitida PC-7 bilan o‘ tkazilgan in vivo ishda xulq-atvor ko‘ rsatkichlari va keyin ajratilgan sinaptosomalarda $Ca^{2+}$ dinamikasi birgalikda baholangan [57]. Bu ex vivo sinaptosomal natijalarni organizm darajasidagi funktsional fenotip bilan bog‘ lashga qaratilgan muhim bosqichdir. Biroq $Ca^{2+}$ ko‘ rsatkichlaridagi o‘ zgarish kognitiv natijaning bevosita sababi ekanini aniqlash uchun elektrofiziologik va molekulyar validatsiya zarur (3-jadval).

**Jadval 3**

**Khoshimov va hammualliflarning $Ca^{2+}$/glutamat yo‘ nalishidagi eksperimental ishlari**

| Yil/birikma | Model | Baholangan jarayon | Natijaning ehtiyotkor talqini | Obzordagi o‘ rni |
|---|---|---|---|---|
| 2017 Cytisinum | Kalamush miyasi sinaptosomalari | Glutamatergik mediatorlar va $Ca^{2+}$ | $Ca^{2+}$ kanal/glutamat tizimiga funktsional ta’ sir | Metodologik boshlanish |
| 2018 Euphorbin | Sinaptosomalar | L-glutamat va $Ca^{2+}$ javobi | Glutamatga bog‘ liq $Ca^{2+}$ modulyatsiyasi | Polifenol yo‘ nalishining boshlanishi |
| 2021 PC-7 | Sinaptosomalar | Sitozolik $Ca^{2+}$ dinamikasi | VGCC/NMDA bilan bog‘ liq mexanizm taklif qilingan | Funktsional $Ca^{2+}$ farmakologiyasi |
| 2022 PC-6/PC-7 | Sinaptosomalar | NMDA bilan bog‘ liq $Ca^{2+}$ transporti | Glutamat bilan funktsional raqobat ehtimoli | Mexanizmni aniqlashtirish |
| 2023 PC-6/PC-7 | Sinaptosomalar | L-glutamat, $Mg^{2+}$ va blokatorlar | NMDA kanal ochilishini regulyatsiya qilishga ta’ sir | Asosiy lokal eksperimental dalil |
| 2024 PC-7 | In vivo AK modeli + sinaptosoma | Xulq-atvor + $Ca^{2+}$ | Organizm va sinaptik darajani bog‘ lash | *Ex vivo →in vivo* ko‘ prik |




***2-rasm.*** Polifenollarning sinaptik $Ca^{2+}$ signalizatsiyasiga ehtimoliy ko‘ p nishonli ta’ sir nuqtalari.

**2. Mavjud dalillar, hal etilmagan masalalar va istiqbolli yo‘ nalishlar**

Sinaptosoma sinaptik terminalning ko‘ p funksional komponentlarini saqlab qolgani uchun neyromediator transporti, membrana retseptorlari va $Ca^{2+}$ dinamikasini nisbatan izolyatsiyalangan sharoitda o‘ rganishda qimmatli modeldir. Biroq u butun neyron tarmog‘ i, gliya, qon–miya to‘ sig‘ i va sistemali farmakokinetikani to‘ liq aks ettirmaydi.

Shu sabab sinaptosomal natijalarni to‘ g‘ ridan-to‘ g‘ ri inson AKga ko‘ chirish emas, keyingi bosqichda validatsiya qilish kerak.

Fluoresent $Ca^{2+}$ o‘ lchovlari birikmaning funksional ta’ sirini ko‘ rsatadi, ammo molekulaning qaysi retseptor subbirligi yoki bog‘ lanish sayti bilan to‘ g‘ ridan-to‘ g‘ ri o‘ zaro ta’ sir qilganini avtomatik ravishda isbotlamaydi. Shuning uchun istiqbolli polifenollar uchun $Ca^{2+}$ imaging natijalarini patch-clamp elektrofiziologiyasi, retseptor subtipiga selektiv farmakologiya, bog‘ lanish/struktura-funktsional tahlil va mutatsiya eksperimentlari bilan birlashtirish maqsadga muvofiq.

Keyingi translyatsion zanjir ADga mos neyron kulturalari yoki iPSC-modellar, in vivo hayvon modellari, miya to‘ qimasida kontsentratsiyani aniqlash, farmakokinetika va qon–miya to‘ sig‘ idan o‘ tishni baholashni qamrab olishi kerak. Shunda “polifenol →retseptor/kanal →$Ca^{2+}$ →sinaptik funksiya →kognitiv fenotip” zanjirining qaysi bo‘ g‘ inlari haqiqatan sababiy ekani aniqlanadi.

Xulosalar

Altsgeymer kasalligida sinaptik disfunksiya Aβ va Tau patologiyasi, glutamatergik signalizatsiya, $Ca^{2+}$ gomeostazi, ER–mitoxondriya aloqasi va oksidativ stress o‘ zaro ta’ sir qiladigan ko‘ p darajali jarayon sifatida qaralishi kerak. Fiziologik NMDAR–$Ca^{2+}$ signalizatsiyasi sinaptik plastiklik uchun zarur; patologik holatda esa signalning lokalizatsiyasi, davomiyligi va organellalar o‘ rtasida taqsimlanishining buzilishi funktsional etishmovchilikka hissa qo‘ shishi mumkin.

$Ca^{2+}$ disgomeostazi amiloid yoki Tau gipotezasining o‘ rnini bosuvchi emas, balki ularni membrana, sinaps va mitoxondrial mexanizmlar bilan bog‘ lovchi muhim fiziologik-patofiziologik komponentdir. Polifenollar, ayniqsa sinaptosomal modellarda o‘ rganilgan PC-6, PC-7, Euphorbin va boshqa birikmalar, glutamatga bog‘ liq $Ca^{2+}$ javoblarini modulyatsiya qilish potentsialini ko‘ rsatadi. Ularning aniq molekulyar nishonlari va translyatsion ahamiyatini elektrofiziologik, struktura-funktsional va farmakokinetik usullar bilan tasdiqlash kelgusi tadqiqotlarning mantiqiy davomidir.

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