YOPIQ BOSH MIYA JAROHATLAR BILAN KASALLANGAN BEMORLARDA IKKILAMCHI NEYROPROTEKSIYANING PATOGENETIK TAMOYILLARI.

(Sharh maqolasi)

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Annotatsiya: yopiq bosh miya jarohati butun dunyo bo‘ylab o‘lim va og‘ir nogironlikning asosiy sababidir. Qurbonlarini davolash va reabilitatsiya qilish turli mamlakatlar byudjetlariga katta ziyon yetkazadi. Psixologik va jismoniy yuk, hayot sifatining pasayishi va sezilarli xarajatlar faqat ushbu bemorlarni boshqarishning qo‘shimcha, yanada murakkab va samarali variantlari zarurligini ta'kidlashi mumkin. Neyroproteksiya kontseptsiyasi ishemiya tomonidan qo‘zg‘atilgan murakkab patofiziologik o‘zgarishlardan foydalangan holda yaxshiroq natijaga erishish vositasi bo‘lib, ko‘plab terapevtik va jarrohlik strategiyalarining markazida bo‘lib kelgan va shunday bo‘lib qoladi. Eksitotoksiklik, apoptoz va oksidlovchi stressdan yallig‘lanishgacha bo‘lgan YBMJning turli mexanizmlarini keltirib chiqaradigan bir necha turdagi asoratlar o‘rganildi va ularning aksariyati klinik bosqichda umidsizlikka olib keldi va zararning har bir bosqichida zararning u yoki bu yo‘lini oldini olish yoki oqibatlarni minimallashtirish uchun himoya - neyroproteksiya qilish kerak. Bu esa neyroproteksiyaning muhim davolash taktikasi bo‘lib qolayotganini ko‘rsatadi. Ushbu sharhda klinik jihatdan o‘rganilgan neyroproteksiya usullari, ularning mexanizmlari, natijalari neyroproteksiyaning potentsial maqsadlari va maqsadli davolash usullari haqida qisqacha ma'lumot berilgan.

Kalit so‘zlar: neyroproteksiya, yopiq bosh miya jarohati, apoptoz, yallig‘lanish, eksitotoksiklik, oksidlovchi stress, kallidinogenaza.

ПАТОГЕНЕТИЧЕСКИЕ ОСНОВЫ ВТОРИЧНОЙ НЕЙРОПРОТЕКЦИИ У БОЛЬНЫХ С ЗАКРЫТЫМИ ЧЕРЕПНО-МОЗГОВЫМИ ТРАВМАМИ.

(Комментарий к статье)

Аннотация: Закрытая черепно-мозговая травма является основной причиной смерти и тяжелой инвалидности во всем мире. Лечение и реабилитация жертв ложатся огромным бременем на бюджеты разных стран. Психологическая и физическая нагрузка, снижение качества жизни и значительные расходы могут только подчеркнуть необходимость дополнительных, более сложных и эффективных вариантов лечения этих пациентов. Концепция нейропротекции как средства достижения лучших результатов путем использования сложных патофизиологических изменений, вызванных ишемией, была и остается основой многих терапевтических и хирургических стратегий. Изучено несколько типов осложнений, вызывающих различные механизмы НМЗП, от эксайтотоксичности, апоптоза и окислительного стресса до воспаления, и большинство из них привели к разочарованию на клинической стадии, а на каждой стадии повреждения необходима защита — нейропротекция — для предотвращения того или иного пути повреждения или минимизации последствий. Это свидетельствует о том, что нейропротекция остается важной тактикой лечения. В этом обзоре представлен краткий обзор клинически изученных методов нейропротекции, их механизмов, результатов, потенциальных целей нейропротекции и таргетной терапии.

Ключевые слова: нейропротекция, закрытая черепно-мозговая травма, апоптоз, воспаление, эксайтотоксичность, окислительный стресс, каллидиногеназа.

PATHOGENETIC PRINCIPLES OF SECONDARY NEUROPROTECTION IN PATIENTS WITH CLOSED HEAD INJURIES.

(Review article)

Abstract: closed head injuries are the leading cause of death and severe disability worldwide. Treatment and rehabilitation of their victims cause significant damage to the budgets of different countries. Psychological and physical burden, reduced quality of life and significant costs can only emphasize the need for additional, more complex and effective options for managing these patients. The concept of neuroprotection, as a means of achieving better outcomes by exploiting the complex pathophysiological changes induced by ischemia, has been and remains at the heart of many therapeutic and surgical strategies. Several types of complications have been studied, which cause different mechanisms of TBI, from excitotoxicity, apoptosis and oxidative stress to inflammation, and most of them have led to clinical disappointment, and at each stage of damage, protection - neuroprotection - is necessary to prevent one or another path of damage or minimize the consequences. This indicates that neuroprotection remains an important treatment tactic. This review provides a brief overview of clinically studied neuroprotection methods, their mechanisms, results, potential targets of neuroprotection and targeted therapies.

Keywords: neuroprotection, closed brain injury, apoptosis, inflammation, excitotoxicity, oxidative stress, kallidinogenase.

KIRISH

Yopiq bosh miya jarohati (YBMJ) butun dunyo bo‘ylab o‘lim va og‘ir nogironlikning asosiy sababidir. YBMJ qurbonlarini davolash va reabilitatsiya qilish turli mamlakatlar byudjetlariga katta zarar olib keladi [1, 5]. Miya shikastlanishi intensiv terapiya taktikasida miya shishi doimo mutaxassislarning diqqat markazida bo‘lib kelgan. Shikastlanish natijasida jarohat hududlarida ba'zi hujayralarni mexanik ravishda yo‘q qilish kuzatiladi. Xuddi shu narsa, ammo diffuz tarzda, penumbrada sezilarli gipoksiya va arterial gipotenziya bilan sodir bo‘ladi. Hujayralarning bir qismi nobud bo‘lganda ("shikastlangan neyronlar hovuzi"), kaltsiy, kaliy va biologik faol moddalarning yuqori konsentratsiyasi bo‘lgan giperosmolyar suyuqlik hujayra ichi va hujayralararo bo‘shliqqa kirib, membranalarning shikastlanishiga va qo‘shni hujayralarning o‘limiga olib keladi, ularning hujayra ichidagi tarkibi "shafqatsiz doira" tamoyiliga muvofiq sitotoksik ta'sir ko‘rsatadi [3, 4, 6].

Miya ishemiyasi - qon ta'minoti buzilishi tufayli miya hujayralarining to‘satdan nobud bo‘lishi. Bu energiya almashinuvining buzilishi, membrana depolarizatsiyasi, oqsil sintezining ingibitsiyasi, Ca2+ oqimi, glutamatning haddan tashqari stimulyatsiyasilanib chiqarilishi, sitoskeletal va membrananing shikastlanishi, mikroglial faollashtirilgan yallig‘lanish va hujayra membranalarining lizosomal o‘limi bilan boshlanadigan halokatli patofiziologik hodisalar kaskadi bo‘lib xizmat qiladi. Ushbu hodisalar birlashganda, sinergik tarzda harakat qiladi va ular o‘z-o‘zidan ko‘ra kuchliroq ta'sir ko‘rsatadi [4-7]. BMJ tarqalishi ko‘pincha mehnatga layoqatli yoshdagi aholida kuzatilgan bo‘lsada, hozirda tasdiqlangan yagona davolash to‘qima plazminogen faollashtiruvchisi bo‘lib, u o‘zining cheklovlari tufayli (kichik vaqt oralig‘i va qon ketish xavfi) ko‘p bemorlar uchun har doim ham mos kelmaydi [8-10]. Miya shikastlanishini davolashning yangi yondashuvlari keng qamrovli o‘rganildi va ularning ba'zilari shikastlanish natijasida kelib chiqqan yoki undan keyin bir necha soniya yoki daqiqalar ichida sodir bo‘lgan patofiziologik o‘zgarishlarga bevosita murojaat qiladi.

ASOSIY QISM

Neyroproteksiya 1980-yildan beri o‘rganilib kelinmoqda, birinchi klinik sinovlar o‘tkazilgan va bu turli darajadagi muvaffaqiyatlarga erishgan [11, 12]. Neyroproteksiya odatda hujayra ichidagi kaltsiyning ko‘payishini ingibitsiya qilish yoki erkin radikal reaktsiyalarining faollashishini va hujayra o‘limini bostirish orqali miya to‘qimalarining infarkti hajmini cheklash yoki kamaytirishga hamda atrofdagi zaif hujayralarni saqlashga qaratilgan jarayon sifatida ta'riflanadi [13]. Yakuniy maqsad neyronlarning yo‘qolishini to‘xtatish yoki hech bo‘lmaganda sekinlashtirish orqali kasallikning rivojlanishini va ikkilamchi zararni oldini olish yoki sekinlashtirishdir. Neyroprotektiv terapiyaning asosiy maqsadlari oksidlovchi stress, mitoxondrial disfunktsiya, apoptoz, autofagiya, eksitotoksiklik va yallig‘lanish o‘zgarishlarini bartaraf etishdir [8]. Ba'zan ishemik deb ataladigan bu patofiziologik o‘zgarishlar miya yarim ishemiyasi sindromining natijasidir va ko‘pchilik ishemik neyronlarning o‘limiga sabab bo‘ladigan kaskad [14]. Yuqoridagi o‘zgarishlarga to‘g‘ridan-to‘g‘ri yoki bilvosita ta'sir ko‘rsatadigan bir nechta potentsial farmakologik vositalar ularning neyroprotektiv salohiyati uchun o‘rganilgan va kelajakda antiishemik vositalar sifatida foydalanish umidida bir nechta klinik sinovlardan o‘tgan. Ushbu sharhning maqsadi neyroproteksiyaga qiziqishning patofiziologik mexanizmlarini o‘rganish va natijalardan qat'iy nazar, klinik sinovdan o‘tgan neyroprotektiv muolajalar haqida umumiy ma'lumot berishdir.

Neyroproteksiyaga qaratilgan ishemiyaning patafiziologik mexanizmlari

1.1 Eksitotoksiklik - bu glutamat kabi ko‘p miqdorda toksik neyrotransmitterlarning hujayradan tashqari bo‘shliqqa chiqishi tufayli asab hujayralarining haddan tashqari qo‘zg‘alishi bilan tavsiflangan jarayon bo‘lib, natijada hujayra o‘limiga ya'ni apoptozni jadallashtiradi [15-18]. Glutamatning giperproduksiyasi glutamat ionotrop retseptorlari - N-metil D-aspartat (NMDA) retseptorlari, a-amino-3-gidroksi-5-metil-4-izoksazolpropion kislotasi (AMPA) retseptorlarini qo`zg`atib, Ca+ning hujayra ichiga siljishiga va depolarizatsiyasiga olib keladi [19-21]. Hujayra ichidagi Ca+ning yuqori darajasi asab hujayralariga toksik ta'sir qiladi. Ko`p miqdordagi kaltsiy fosfolipazlar, proteazlar va kalpain kabi bir qancha fermentlarning faollashtiruvchisi bo‘lib, hujayra tuzilishiga va dezoksiribonuklein kislotasiga (DNK) halokatli ta'sir ko‘rsatadi [22]. Sitozolda kaltsiy yuqori darajasi bilvosita yana bir tezkor ta'sirini ya`ni mitoxondrial o‘tish membranalarining blokirovkasi bo‘lib, ular bo‘shliq vazifasini bajaradi, shu bilan o‘tkazuvchanlikni oshiradi, shish paydo bo‘lishiga va reaktiv kislorod turlarining chiqishiga olib keladi [21]. Bundan tashqari, bularning barchasi adenozin trifosfat (ATF) ishlab chiqarilishiga ta'sir qiladi [24], bu ion gradientlarining yo‘qolishiga va glutamatning so‘rilishini to‘xtatilishiga va keyinchalik to‘planishi tufayli glutamat retseptorlarining faollashuvining buzilishiga olib keladi [24]. Shunday qilib, glutamatning eksitotoksikligi miya ishemiyasi sindromi patologiyasining muhim jihati va uning nekroz, apoptoz va autofagiya boshlanishi uchun asosdir. Eksitotoksiklik jarayoniga to‘g‘ridan-to‘g‘ri ta'sir qilish orqali natijani yaxshilash maqsadida bir nechta usullar tekshirildi. Umumiy g‘oya glutamat chiqarilishini ingibitsiya qilish yoki miyadagi glutamat retseptorlari ta'sirini blokirovka qilishdir. Turli xil dori-darmonlar qoniqarsiz natijalar bilan klinik sinovlardan o‘tkazildi.

1.2 Kaltsiy kanal blokatori. Ushbu kichik guruhga nimodipin kabi dorilar kiradi, dastlab gipertenziyani davolash uchun ishlab chiqilgan digidropiridinli kaltsiy kanallari blokatori. Hozirgi vaqtda u asosan miyadagi vazospazmini va unga bog‘liq ishemiyani oldini olish uchun ishlatiladi. Shuningdek, Ca+ kanallarni bloklash orqali ishemk hududda qisqaruvchanlikni kamaytiradi va O_2ga bo`lgan ehtiyojni kamaytiradi. U kuchlanishga bog‘liq kaltsiy kanallariga ta'siri tufayli

neyroprotektor sifatida taklif qilingan. Dastlab istiqbolli bo‘lsada, uning TBI bemorlariga ta'sirini baholagan 28 ga yaqin sinovlar nazorat guruhiga nisbatan nimodipin bilan davolangan bemorlarda o‘lim darajasida farq yo‘qligini aniq ko`rsatdi [25].

1.3 NMDA antagonistlari. Asosan NMDA retseptorlari (NMDAR) ta'siriga ingibitiv yoki antagonist qiluvchi ta'sir ko‘rsatadigan anestetiklardan tashkil topgan NMDA antagonistlari NMDAR ionotropiyasi tufayli eksitotoksiklikni davolash uchun tekshirilgan. Ular ikkita toifaga bo‘linadi: raqobatbardosh (glutamatni bog‘lash joyini blokirovka qilish) va raqobatdosh bo‘lmagan (NMDARni allosterik bog‘lash orqali ingibitsiya qilish) antagonistlari bizning e'tiborimiz mavzusidir. NMDA antagonistlari orasida magniy, raqobatdosh bo‘lmagan antagonist va kuchlanish bilan bog‘langan kaltsiy kanallarining blokeridir [26]. Magniy potentsial antieksitotoksik vosita sifatida o‘rganilgan va ayniqsa kalamush insult modelida o‘rta miya arteriyasi (O`MA) oklyuziyasidan so‘ng darhol qo‘llanilganda umid beruvchi natijalarni ko‘rsatdi [27]. Magniyning samaradorligini baholash bo‘yicha ikkita yirik (intravenoz magniy insult tadqiqoti) tadqiqot o‘tkazildi.

YBMJ boshlanganidan keyin 12 soat ichida yuqori dozali magniyning ko‘p markazli randomizatsiyalangan nazorat ostida sinovi [28] va ko‘p markazli, randomizatsiyalangan, ikki marta platsebo-nazorat ostidagi tadqiqot [29], unda III-bosqich tadqiqoti boshlanganidan keyin 2 soat ichida magniy boshqariladi [30]. Afsuski, ikkala tadqiqot ham nazorat guruhi bilan solishtirganda, o‘lim yoki nogironlik bo‘ladimi, natijalarda sezilarli yaxshilanishni ko‘rsata olmadi [28, 30]. Yana bir raqobatbardosh antagonist Selfotel eksperimental tadqiqotlarda O`MA oklyuziyasidan keyin 5 minut ichida yuborilganda infarkt hajmini sezilarli darajada kamaytirishi ko‘rsatilgan [31-33]. U odamlarda o‘zining samaradorligi va xavfsizligini II-bosqich tadqiqotida va 90-kundagi Barthel indeksini mustaqil baholash orqali baholangan natijalarning sezilarli yaxshilanishini nazorat qilish bilan solishtirganda isbotladi [34]. Biroq, insult boshlanganidan keyin 6 soat ichida 567 bemorni o‘z ichiga olgan ikkita ko‘rko‘rona, randomizatsiyalangan, platsebo-nazoratli, parallel dizayndagi ikkita sinov 3-bosqichi sinovlari yuqori o‘lim darajasi va asosiy natijaga terapevtik ta'sir ko‘rsatmasligi sababli to‘xtatildi [35].

1.4 AMPA antagonistlari. Raqobatbardosh AMPA retseptorlari (AMPAR) antagonisti YM872, zonampanel nomi bilan tanilgan, kinoksalindionga asoslangan dori, uning neyroprotektiv xususiyatlari uchun ham tekshirilgan [36]. YM872 infarkt hajmini kamaytirishi va kalamush embolik insult modelida simptomlarni yaxshilashi mumkinligi ko‘rsatilgan [37]. Ushbu mexanizm kortikal to‘qimalarning yo‘qolishi va miya shishishining kamayishi bilan bog‘liq deb ishoniladi [38]. Biroq, gallyutsinatsiyalar, katatoniya va qo`zg`atuvchanlik kabi jiddiy nojo‘ya ta'sirlar tufayli klinik sinovlar erta tugatildi [39].

2. Apoptoz. Uzoq vaqt davomida YBMJdan keyin hujayra o‘limi faqat plazma membranasining buzilishi va hujayra ichidagi tarkibning chiqishi bilan yakunlangan zarar yetkazuvchi hodisalar bilan tavsiflangan nekrozning natijasi deb hisoblangan [40]. Bu hodisa ishemik penumbrada sodir bo‘ladi [41]. Biroq, qo‘shimcha dalillar shuni ko‘rsatdiki, apoptoz-dasturlashtirilgan hujayra o‘limining bir shakli, hayvonlar modellarida ishemik miya shikastlanishidan keyin muhim rol o‘ynaydi [42, 43]. Bu hodisa asosan apoptotik kaskadlar bilan belgilanadi va ular ko‘plab o‘zgarishlarni o‘z ichiga oladi. Jumladan: hujayra ichidagi Ca+ning ko‘payishi, mitoxondrial disfunktsiyani rag‘batlantiradigan va antiapoptotik jarayonni to‘xtatadigan prostata apoptozi javobi 4 kabi oqsillarning ko‘payishi, mitoxondrial membrananing depolarizatsiyasi, yakuniy natija sifatida kaspazalarning sitoxrom C faollashuvi va yadro DNKining chiqarilishi [44]. So‘nggi paytlarda apoptoz ta'siriga qarshi turish orqali

neyroproteksiyaga erishish maqsadi ko‘pchilikning e'tiborini tortdi [45]. Bir nechta antiapoptotik birikmalar eksperimental modellarda muvaffaqiyatli sinovdan o‘tkazildi, ular zarar maydonini sezilarli darajada qisqartirish, kaspazani ingibitsiya qilish, proapoptotik gen ekspressiyasini blokirovka qilish va antiapoptotik gen ekspressiyasini rag‘batlantirish. Biroq, eksperimental natijalar har doim ham klinik natijalarga to‘g‘ri kelavermaydi. Klinik jihatdan baholangan formulalar orasida eritropoetin (EPO) va serebrolizin YBMJni davolashda foydalanish mumkinligi uchun sinovdan o‘tkazildi.

2.1 Eritropoetin (EPO). Eritropoezni rag‘batlantirish orqali qizil qon hujayralarini ishlab chiqarish funktsiyasidan tashqari, qarama-qarshi tadqiqotlar EPO bir qator harakatlarga ega ekanligini ko‘rsatdi, shu jumladan angiogenezni rag‘batlantirish, EPO retseptorlarini faollashtirish orqali hujayra omon qolishini rag‘batlantirish, buning natijasida to‘qimalarga antiapoptotik ta'sir ko‘rsatadi [46, 47]. Rekombinant inson eritropoetini (rhEPO) bilan oldindan inkubatsiya qilingan kortikal hujayralarda ko‘rsatilgan XIAP va c-IAP2 apoptoz ingibitori genlarining ko‘payishi orqali apoptotik va antiapoptotik gen ekspressiyasiga ta'sir qiladi deb ishoniladi [48]. Bundan tashqari, rhEPOdan so‘ng, gipokampusning CA1 ishemik hududida B-hujayrali limfoma extralarini (bcl-xL) ko‘payishi ko‘rsatilgan [49]. Pilot tadqiqotida BMJ bilan og‘rigan bemorlarda EPO ning xavfsizligi va foydasini ko‘rsatgan bo‘lsada, bu natijalar kengroq tadqiqotda tasdiqlanmagan [50, 51]. Bundan tashqari, YBMJ boshlanganidan keyin 9 soat ichida granulotsit-koloniyani stimulyatsiya qiluvchi omil (G-CSF) yoki platsebo olgan miya ishemiyasi sindromi bo‘lgan 328 bemorda o‘tkazilgan kengroq tadqiqot (AXIS-2) 90-kuni birlamchi yakuniy nuqta yoki klinik natijada hech qanday farqni aniqlamadi [9].

2.2 Serebrolizin. Serebrolizin - past molekulyar og‘irlikdagi neyropeptidlarning tozalangan peptidlari va cho‘chqa miyasidan olingan erkin aminokislotalarning aralashmasi, shu jumladan: (lekin ular bilan cheklanmasdan) miyadan olingan neyrotrofik omil, glial hujayradan olingan neyrotrofik omil, asab o‘sish omili [52, 53]. Erkin radikal hosil bo‘lishini, mikroglial faollashuvni, neyroyallig`lanishni, kalpain faolligini/apoptozni bostirish orqali neyroprotektiv xususiyatlar va eksitotoksiklikga qarshi samaradorlikni ko‘rsatdi, shuningdek, neyrotrofik faollikni namoyish etdi [54-57]. Oldingi tadqiqotlar serebrolizinning funktsional natijani sezilarli darajada yaxshilashi degan xulosaga keldi, ammo infarkt hajmini kamaytirmadi [58]. Bu neyroblastlarning ko‘payishi, ko‘chishi va omon qolishi bilan bog‘liq deb ishoniladi [59]. Bundan tashqari, ushbu tadqiqotlardan birida 30, 60 va 90-kunlarda o‘ng o‘rta miya arteriyasining pulsatsiyalanish indeksining (PI) pasayishi kuzatildi [60]. Ushbu ma'lumotlarning barchasi miya ishemiyasi sindromida Serebrolizinning klinik qo‘llanilishini ko‘rsatadi, ammo qo‘shimcha tadqiqotlar talab etiladi.

3. Yallig‘lanish. Markaziy asab tizimining yallig‘lanishi haqidagi birinchi xabarlar 1900-yillarga to‘g‘ri keladi va keyingi kashfiyotlar neyrogenezni modulyatsiya qilishda yallig‘lanish vositachilariga ta'sir qiladi. Miya shikastlanishining har qanday shakli, u gipoksiya, ishemiya yoki infektsiya bo‘lsin, jiddiy oqibatlarga olib keladi va xarakterli yallig‘lanish reaktsiyalarini keltirib chiqaradi. Miya yallig‘lanishi BMJdan keyin shikastlanishning ikkilamchi mexanizmi sifatida qaraladi va reaktiv kislorod turlari yoki nekrotik hujayralar kabi bir qancha omillarning natijasidir [61, 62]. Asosiy ishtirokchilar va vositachilar mikrogliya, astrositlar va periferik makrofaglardir. Bu omillar mikrogliyaning faollashishiga olib keladi, bu esa sitokin ishlab chiqarishni ko‘paytirishga va miya qon tomirlarida adgezion molekulalarining induksiyasiga olib keladi [63, 64]. Adgezion molekulalari o‘z navbatida, aylanib yuruvchi leykotsitlarning yopishishini keltirib chiqaradi, bu esa mikrotomirlarning tiqilib qolishiga va miya parenximasiga immun

hujayralarining infiltratsiyasiga olib keladi. Faollashgan yallig‘lanish hujayralari ikki tomonlama ta'sirga ega bo‘lgan bir qator yallig‘lanishga qarshi va yallig‘lanishga qarshi sitokinlar va kimyokinlar kabi turli xil sitotoksik molekulalarni ishlab chiqaradi. Bir tomondan, u miyaning immun himoyasini ta'minlaydi, boshqa tomondan, u qon-miya to‘sig‘ini buzilishiga va neyronlarning o‘limiga olib keladigan yallig‘lanishning regenerativ halqasini qo‘zg‘atadi [65, 66]. Yillar davomida va muvaffaqiyatli eksperimental tadqiqotlardan so‘ng, ma'lum yallig‘lanishga qarshi strategiyalarning qiymatini baholash uchun bir nechta klinik sinovlar o‘tkazildi. Ushbu sinovlarning ba'zilari kutilmagan yon ta'sirlar yoki samarasizligi tufayli muvaffaqiyatsizlikka uchragan bo‘lsada, bir nechtasi hali ham neyroyallig‘lanishga ijobiy tasir qiladi deb ishontirmoqda.

3.1 Kranioserebral gipotermiya (KSG). KSG ishemiya yoki BMJdan keyin davr tana haroratini ma'lum vaqt davomida boshqarish orqali natijalarni yaxshilashga qaratilgan [67]. Gipotermiya metabolizmni sekinlashtirib, miyaning kislorodga bo‘lgan talabini kamaytirish orqali neyroprotektiv vosita sifatida ishlaydi [68-71]. Bir qancha keyingi tadqiqotlar shuni ko‘rsatdiki, gipotermiya metabolik yo‘llarga ushbu chegaralardan tashqari ta'sir qiladi. Aniqlanishicha, gipotermiyaning neyroprotektiv ta'siri ostida yotgan mexanizmlar quyidagilardan iborat: miya metabolizmi, mitoxondriyal shikastlanish va disfunktsiya, reperfuziya shikastlanishi, ion pompasi disfunktsiyasi va hujayra ichiga kaltsiy oqimi, neyroeksitotoksiklikni bloklash, sitotoksik shish paydo bo‘lishi, hujayra ichidagi atsidoz, erkin radikal ishlab chiqarish, apoptoz, kalpain-proteolizi, DNK shikastlanishi, tomir o‘tkazuvchanligi, qon-miya to‘sig‘ining o‘tkazuvchanligi, qon ivishining faollashuvi, mikrotrombning shakllanishi va immunitetning oshishi [72].

Biroq, gipotermiyaning neyroprotektiv ta'sirini tushuntirish uchun bitta omildan foydalanish juda qiyin, chunki gipotermiya ishemik kaskadning eksitotoksiklik, apoptoz, yallig‘lanish, erkin radikal ishlab chiqarish, qon oqimi va intrakranial bosimgacha bo‘lgan ko‘plab yo‘llariga ta'sir qiladi [73, 74]. Immunologik nuqtai nazardan, gipotermiyaning asosiy ta'siri nafaqat mikrogliyaning faollashishi va ishemik hududlarda neytrofillar sonining kamaytiradi [75]. Shuningdek, reaktiv kislorod turlari (ROS) [76], adgezion molekulalari, makrofag yallig‘lanish oqsili-3 a, yallig`lanish oldi sitokinlar, o‘simta nekrozi omili alfa (TNF-a), interleykin 6 (IL-6), interleykin 1 (IL-1) va reaktivlar sonini faollashtirilgan B hujayralarining kappa yengil zanjirini kuchaytiruvchi omil (NF-kB) kamaytiradi. Bundan tashqari, u yallig‘lanishda muhim ferment tizimi bo‘lgan mitogen bilan faollashtirilgan protein kinazaga ta'sir qilishi ko‘rsatilgan [78]. Birgalikda bu dalillar TBIdan keyingi terapiyada maqsadli haroratni boshqarish muhim rol o‘ynashini ko‘rsatadi.

3.2 Minosiklin. Minosiklin - keng spektrli bakteriostatik antibiotik, tetratsiklinlar oilasiga mansub yallig‘lanishga qarshi, antiapoptoz, gemato-enseffalik barierni (GEB) himoya qilish, mikroglial faollashuvni kamaytirish, matritsa metalloproteinaza (MMP)-9ni kamaytirishdan azot oksidi (NO) hosil bo‘lishigacha bo‘lgan bir qancha neyroprotektiv xususiyatlarga ega. [79-82]. Minosiklinning yallig‘lanishga qarshi funktsiyalari kaspaza-3, kaspaza-1, siklooksigenaza-2, induksiyalangan azot oksidi sintaza, p38 mitogen bilan faollashtirilgan protein, NF-a.B, NF-blok, NF-blok kabi bir nechta hujayra maqsadlarini blok qilishni o‘z ichiga oladi [83-85. Uning GEB yaxlitligini himoya qilish NADga bog‘liq deatsetilaz sirtuin-3 (SIRT-3)/prolil gidroksilaza domenini o‘z ichiga olgan protein 2 (PHD-2) orqali gipoksiyani qo‘zg‘atuvchi omil 1-alfa yo`li (HIF-1a) hujayra reaktsiyalarini bloklash orqali sodir bo‘ladi [86]. Biroq, BMJga qarshi mumkin bo‘lgan terapevtik foydalanish uchun qo‘shimcha klinik tadqiqotlar hali ham talab qilinadi.

4. Oksidlanish stress. YBMJdagi oksidlovchi stress reaktiv kislorod turlari va boshqa erkin radikallar ishlab chiqarishning ko‘payishi sifatida ifodalanadi. Bu jarayonda asosiy rolni fosfolipaza A2 va araxidon kislotasi bajaradi. Ishemiya paytida glutamatning chiqarilishi va hujayra ichidagi Ca2+ning ko‘payishi sitozoldagi Ca2+ga bog‘liq PLA2ni faollashtiradi, bu fosfolipid gidroliziga va erkin yog‘kislotalarining ajralishiga olib keladi [87, 88]. Boshqa tomondan, erkin araxidon kislotasining hujayra ichidagi to‘planishi oksidlovchi zararni kuchaytiradigan reaktiv kislorod turlarining shakllanishiga yordam beradi [88]. Yakuniy natija to‘g‘ridan-to‘g‘ri neyron hujayralarining o‘limi yoki mitoxondriyal disfunktsiyasi kuzatilib, glial hujayra faollashuvi, oqsilning noto‘g‘ri qatlamlanishi, gen ekspressiyasi, hujayra signalizatsiyasi va proteasomal anomaliyalar kabi boshqa hodisalardir oqibatida bo`ladi va ushbu mexanizmlarning ba'zilari apoptozga boshlaydi [89-92]. Oksidlanish stressdagi moddalar eksitotoksisiklik, hujayra nafasini blok qilish va yallig‘lanishning qo‘shimcha mahsuloti ekanligi ko‘rsatilgan [93]. Oksidlanish stressini neytrallash ishemiyanini davolash uchun qiziqarli potentsial terapevtik variant bo‘lsada, hayotiy birikmalarni topish juda qiyin bo‘lib chiqdi.

4.1 Sitikolin. Sitikolin - sitidin difosfat xolin sifatida ham tanilgan, ikki molekula, sitidin va xolindan tashkil topgan birikma bo‘lib, xolindan fosfatidilxolin hosil bo‘lishida vositachi hisoblanadi. Eksperimental tadqiqotlarda u ko‘p maqsadli va markaziy asab tizimining bir nechta kasalliklariga qarshi samarali ekanligi ko‘rsatilgan [94-96]. Ikkala molekula ham qon-miya to‘sig‘idan o‘ta oladi [97]. Qon tomirlarida sitikolin ko‘p bosqichli ta'sirga ega bo‘lgan uzoqroq vaqt oynasiga ega ekanligi ko‘rsatilgan [98, 99]. Klinik tadqiqotlarda shunga o‘xshash natijalar funktsional natijalarning aniq yaxshilanishi bilan olingan. Sitikolinning antioksidant ta'siri fosfolipaza faollashishini oldini olish yoki susaytirish orqali amalga oshiriladi.

4.2. Edaravon. Edaravon - past molekulyar og‘irlikdagi antioksidant bo‘lib, reaktiv kislorod turlarining ko‘p turlari orasida peroksil radikallarini aniq maqsad qilib oladi. Amfifilligi tufayli u lipidda ham, suvda ham eriydigan peroksil radikallarini o‘zlashtiradi va elektronni radikalga o‘tkazadi. Shunday qilib, zanjirli kimyoviy reaktsiyalarni boshlaydigan suvda eriydigan peroksil radikallarini, shuningdek zanjirni saqlaydigan yog‘da eriydigan peroksil radikallarini tozalash orqali lipid oksidlanishini ingibitsiya qiladi. Ishemik miya infarktining o‘tkir bosqichida preparat himoya ta'sirini ko‘rsatadi, miya shishi, nevrologik simptomlar va neyronlarning sekin o‘limi kabi ishemik serebrovaskulyar kasalliklarning paydo bo‘lishi va rivojlanishini bostiradi [103].

5. Bir nechta maqsadli variantlar. Qon tomirlarini davolashning yangi terapevtik variantlarini izlashda ko‘plab birikmalar ishemiya bilan qo‘zg‘atilgan patofiziolojik o‘zgarishlarga ko‘p maqsadli va ko‘p qirrali ta'sir ko‘rsatdi; Ular orasida ikkita birikma, N-butilftalid (NBP) va inson siydik tizimidan kallidinogenaz allaqachon tasdiqlangan va Xitoyda klinik foydalanish uchun kiritilgan.

5.1 N-Butilftalid (NBP). Selderey yog‘ining tarkibiy qismlaridan biri ajoyib ko‘p yo‘nalishli neyroprotektiv xususiyatlarni namoyish etdi. U trombotsitlar agregatsiyasi ta`siri sababli antitrombotik ta'sirni ko‘rsatdi, bu trombotsitlar siklik adenozin monofosfat (cAMF) darajasini oshirish va serotoninning chiqarilishini blok qilish orqali yuzaga keladi [102]. Keng ko‘lamli tadqiqotlar, shuningdek, NBP Bcl-2 va HIF-1a darajalarini oshirish va kaspaza-3 ifodasini kamaytirish orqali antiapoptotik ta'sirga ega degan xulosaga keldi [103]. Bundan tashqari, u mitoxondriyadagi Na+/K+-ATFaz va Ca2+-ATFazni yaxshilash va sitoxrom c chiqarilishini kamaytirish orqali mitoxondriyal shikastlanishga qarshi himoya xususiyatlarini ko‘rsatdi [104]. Bundan tashqari, eksperimental modellarda NBP uzoq muddatli

administratsiyadan keyin antioksidant ta'sir ko‘rsatdi. Asosiy mexanizm malondialdegid (MDA) darajasining oshishi [105] va vodorod peroksid (H_2O_2) ga bog‘liq radikallarni to‘planishining pasayishi [106]. Bularning barchasi iskemiyaga qarshi samarali ekanligini ko‘rsatdi. Keng klinik sinovlardan so‘ng, NBP allaqachon tasdiqlangan va qoniqarli natijalar bilan 12 yil davomida Xitoyda ishlatilgan.

5.2 Inson siydigi kallidinogenazasi. Kallidinogenaza - kallikrein/kinin tizimining (KKS) tarkibiy qismi bo‘lgan kallikrein to‘qimalarining ishemiyaga qarshi himoya ta'siri klinik va eksperimental tadqiqotlarda ko‘rsatilgan. KKS regulyatori va kallikrein ishlab chiqaruvchisi bo‘lgan inson siydik kallidinogenazasi yallig‘lanishga qarshi, apoptotik, angiogen va neyrogenez faolligini namoyish etadi va Xitoyda insultni davolash uchun tasdiqlangan [107]. Bir qator tadqiqotlar shuni ko‘rsatdiki, kallidinogenazasi funktsional kamchiliklarni yaxshilaydi [108, 109], angiogenezni rag‘batlantiradi va miya qon oqimini yaxshilaydi [110]. Asosiy mexanizm qon tomir endotelial o‘sish omili va apelin/APJ yo‘lining ko‘tarilishi va bradikinin B1 va B2 retseptorlari faollashuvidir [111, 112]. Bundan tashqari, kallidinogenazasi kognitiv samaradorlikni yaxshilashi va plazmada Ab1-40 va Ab1-42 darajalarini kamaytirishi ko‘rsatilgan [113]. Bundan tashqari, to‘qimalarni kallikreinni oldindan davolash neyronal azot oksidi sintaza faolligini ingibitsiya qilish va hujayradan tashqari signal bilan boshqariladigan kinaz 1 (ERK1) va NF-kB faollashuvi orqali glutamatdan kelib chiqqan oksidlovchi stressni kamaytirishi ko‘rsatilgan, natijada miyadan kelib chiqqan neyrotrofik omilning mRNK va antiapoptotik gen Bcl-2 oqsilining ko‘payishiga olib keladi [114].

XULOSA

YBMJni davolashning yangi terapevtik usullarini izlash har doim qiziqarli bo‘lib kelgan. Biroq patologiyaning murakkabligi tufayli yangi neyroprotektiv preparatlarni ishlab chiqish yanada qiyin vazifa ekanligini isbotladi. Bir tomondan, muvaffaqiyatsiz klinik izlanishlar sonining tobora ortib borayotgani YBMJning murakkabligini va yaxshiroq nazorat qilinadigan sinovlarga ehtiyoj borligini ta'kidlaydi. Boshqa tomondan, YBMJdan keyingi ko‘plab patofiziologik faoliyatlarning ikki tomonlama ta'siri konsentratsiyasi, vaqti, joyi va yuzaga kelgan sharoitlariga qarab foydali yoki zararli bo‘lishi mumkin. Biroq, klinik foydalanishga muvaffaqiyatli kiritilgan bir nechta birikmalar bilan ijobiy natijalar ko‘rsatdiki, yangi samarali neyroprotektiv variantlarni kashf qilish jarayoni uzoq va iqtisodiy qimmat bo`lsa ham, neyroproteksiya hali ham hayotiy va kelajak uchun eng yaxshi davolash usullaridan biri hisoblanadi.

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