

小胶质细胞的神经递质受体在 阿尔茨海默病中的作用

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摘要 阿尔茨海默病(Alzheimer's disease, AD)是一种因蛋白错误折叠、聚积影响神经细胞功能,从而导致认知功能下降、行为异常的神经退行性疾病。小胶质细胞是中枢神经系统(central nervous system, CNS)中重要的免疫细胞之一,在AD病理过程中,根据其激活状态的不同小胶质细胞发挥神经保护或神经毒性作用。小胶质细胞上表达各类神经递质受体,这些受体参与介导小胶质细胞与神经细胞的双向沟通,在AD的病理进程中起到了不同的作用。该文重点介绍了小胶质细胞表面的 γ -氨基丁酸(GABA)能、谷氨酸能、大麻素、胆碱能和肾上腺素能受体,以及它们与AD之间的关系,即小胶质细胞上的神经递质受体可以介导或影响小胶质细胞产生的神经保护或毒性作用,从而影响AD病理。阐明小胶质细胞上的神经递质受体在AD中的作用机制将会为探索合适的AD治疗靶点提供重要思路。

关键词 小胶质细胞; 神经递质受体; 阿尔茨海默病

The Role of Neurotransmitter Receptors on Microglia in Alzheimer's Disease

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Abstract AD (Alzheimer's disease) is a neurodegenerative disease caused by accumulation of misfolded proteins in neurons, which affects the normal functions of neurons and finally leads to cognitive decline in the aged people. Microglia is a major kind of immune cells and plays neuroprotective or neurotoxic roles according to its different states in CNS. Various neurotransmitter receptors express in microglia and mediate the bidirectional communication between microglia and neurons, and dysregulation of these receptors also play different roles in the pathogenesis of AD. This article reviewed the GABA (γ -aminobutyric acid) receptors, glutamatergic receptors, cannabinoid receptors, cholinergic receptors, and adrenergic receptors on microglia cells and the roles they played by influencing the signal transmission between microglia and neurons in AD. Elucidating the mechanism of neurotransmitter receptors on microglia in AD will provide important insights for exploring appropriate therapeutic targets for AD.

Keywords microglia; neurotransmitter receptor; Alzheimer's disease

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阿尔茨海默病(Alzheimer's disease, AD)是一种多因素诱发的神经退行性疾病。作为一种全球性的健康疾病,目前全世界约有4 400万人患有痴呆症。预计到2050年,AD患者将增加三倍以上^[1]。从AD被发现至今,人们一直在努力寻找能有效改善或治愈AD的治疗方法。

AD主要的病理学特征是脑内淀粉样蛋白(β -amyloid, A β)沉积形成的老年斑和神经原纤维缠结(neurofibrillary tangle, NFT),最终导致突触损伤和神经元凋亡^[2]。近年来,由小胶质细胞过度激活或增生引发的炎症反应在AD病理过程中的作用也越来越受到人们的重视。

小胶质细胞作为一种中枢神经系统(central nervous system, CNS)内免疫细胞,它参与了脑内神经保护和修复过程,在脑内免疫系统中起着不可替代的作用^[3]。但对AD病人脑组织的解剖研究中发现,其中炎症及趋化因子与正常样本相比明显升高,小胶质细胞的激活程度与状态和CNS的损伤程度相关^[3]。

1 小胶质细胞神经递质受体与AD

当研究发现小胶质细胞的状态可以影响神经细胞和脑内稳态后,小胶质细胞接收的外界信号是否会改变其状态的问题也逐渐被科学界所关注。过去认为,脑内神经细胞只是被动单向地接收小胶质细胞发出的信号。但后续的研究表明,小胶质细胞-神经细胞的关系是一种双向的信号沟通,且神经系统损伤会激活邻近的小胶质细胞^[4]。有理论认为,神经元会将其细胞状态传递给相关的小胶质细胞^[5]。其证据之一就是小胶质细胞表面表达谷氨酸受体等一系列神经递质受体,这些受体与整个神经系统的稳态息息相关^[6]。小胶质细胞通过这些受体感应神经递质的刺激,并分泌包括活性氧(reactive oxygen species, ROS)、白细胞介素(interleukins, ILs)和肿瘤坏死因子 α (tumor necrosis factor α , TNF α)在内的趋化因子和细胞因子,这些物质的释放失调都与AD病理相关^[7]。所以,小胶质细胞及其神经递质受体与AD病理也有密切关系。

小胶质细胞本身缺乏突触结构,神经递质是如何作用在小胶质细胞上的呢?科学界曾经提出过一种模型来解释小胶质细胞被激活的机制,也就是AGNATI和FUXE提出的“容积传递”(volume transmission)的模型^[5]。容积传递是指神经递质或神经肽

在远离细胞或突触释放部位的位置上产生神经信号作用。在该模型中,神经活性物质不仅存在于突触间隙中,而且还可以扩散到细胞外部的空间,并激活突触外受体。由于递质在胞外空间的扩散,小胶质细胞的神经递质受体也会被激活。

在下文中,本综述将介绍小胶质细胞中的几类较常见的神经递质受体,并对它们与AD之间的联系进行一定的探讨。

1.1 GABA能受体

γ -氨基丁酸(γ -aminobutyric acid, GABA)是哺乳动物CNS中的主要抑制性神经递质,在调节整个大脑的神经元信号传递中起着关键作用^[8]。GABA受体功能障碍在AD病理中的作用也一直是AD的研究重点之一^[8]。GABA在CNS中的主要受体有两种:GABA_A受体和GABA_B受体(GABA_AR和GABA_BR),GABA_AR是充当配体门控离子通道的离子型受体,而GABA_BR是代谢型G蛋白偶联受体^[9]。目前认为,GABA_AR主要表达于神经元表面,而是否在小胶质细胞上表达尚且缺乏明确证据^[10]。有报道在体外培养的人小胶质细胞中发现GABA_AR表达^[11]。因此,研究者推测GABA_AR很可能在特定的条件下才能在小胶质细胞表达^[10]。代谢型受体GABA_BR已被明确证明在小胶质细胞上表达,因此目前检测到的小胶质细胞表面的GABA受体主要是GABA_BR^[12]。

目前已发现,GABA能受体可以调节小胶质细胞的炎症反应,GABA能受体激动剂在小胶质细胞中抑制IL-6的释放^[12],而IL-6促进神经元内谷氨酸的释放^[13],所以GABA能受体能够通过抑制IL-6从而抑制谷氨酸所引发的神经兴奋性毒性^[14]。

但目前AD病理中,小胶质细胞上的GABA能受体的变化尚未完全明确。GABA_BR 1亚基被观察到在AD病人脑部伴随着tau病理特征的加重而快速上调,在疾病晚期时有一定下降^[15]。对AD病人的GABA_AR的研究发现,在脑海马CA区GABA_AR α 1和 α 5亚基水平降低,而 β 1、 β 2、 β 3、 γ 亚基不受影响^[16]。但是以上都是对脑组织的检测,在AD过程中小胶质细胞表面的GABA能受体变化目前未见报道,所以小胶质细胞GABA能受体是否对神经细胞具有保护作用还需要进一步的研究。

1.2 谷氨酸能受体

谷氨酸是CNS中主要的兴奋性神经递质之一^[17],谷氨酸能信号的过度刺激容易导致兴奋性毒

性,影响神经细胞存活^[18]。谷氨酸受体可以分为离子型或代谢型受体^[19]。离子型谷氨酸受体根据其药理结合特性可分为 α -氨基-3-羟基-5-甲基-4-异恶唑丙酸(α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, AMPA)受体、海人藻酸(kainic acid, KA)受体和 *N*-甲基-*D*-天门冬氨酸(*N*-methyl-*D*-aspartate, NMDA)受体,目前已知小胶质细胞上表达AMPA与NMDA受体^[20-21]。代谢型谷氨酸受体可根据受体蛋白的结构、药理学作用以及基因相似性分为三组: I、II和III类,这三组又可细分为八个亚型(mGlu1-8)。I类代谢型谷氨酸受体包括mGlu1和mGlu5, II类包括mGlu2和mGlu3,而mGlu4、mGlu6、mGlu7和mGlu8属于III类,所有的三组代谢型受体均在小胶质细胞中表达^[22-24]。

AD中的兴奋性毒性主要表现在过量的谷氨酸能使神经元NMDA受体功能激活,引发细胞内钙超载^[6],而小胶质细胞上的NMDA受体激活后,可促进NO、TNF α 、IL-1等因子的释放^[20]。研究表明,在不引发炎症的刺激条件下激活AD小鼠脑内AMPA受体,可引起小胶质细胞的IL-6含量上升并增强其吞噬能力^[25]。另外研究发现,AMPA受体的激活会影响肌动蛋白的聚合反应,进一步影响小胶质细胞的运动与迁移^[21]。因此推测可能在AD早期,离子型谷氨酸受体的轻度激活会促进小胶质细胞释放炎症因子并增强其吞噬脑内A β 能力,起到一定神经保护作用。随着AD病理的恶化,谷氨酸受体过度激活导致小胶质细胞炎症因子释放过量,进一步加重神经炎症。

多数代谢型谷氨酸受体在小胶质细胞中均有表达。其中I类mGlu5a受体激活后可导致小胶质细胞中TNF α 分泌的减少^[26],并且mGlu5很可能与A β 的形成有关: mGlu5受体的激活能帮助APP通过 α 分泌酶裂解为对AD病理相对无害的sAPP α 和p3肽,而不是通过 β 分泌酶(beta-secretase 1, BACE1)裂解出有神经毒性的A β ^[27]。小胶质细胞还表达II类mGlu2和mGlu3受体,其中II类受体的激活被认为有神经毒性作用^[28], II类mGlu受体可被AD中的A β 和嗜铬粒蛋白A间接激活,引发小胶质细胞谷氨酸的释放,继而在反馈通路中结合小胶质细胞中的II类mGlu受体,并增强其毒性,形成恶性循环。因此, II类受体的激动剂能诱发小胶质细胞的神经毒性作用,而II类受体的拮抗剂已被证明能在AD中抑制这种毒性作用,发

挥对神经细胞的保护作用^[29]。

与II类受体相反, III类受体具有神经保护作用。已发现小胶质细胞主要表达III类受体中的mGlu4、mGlu6和mGlu8^[30]。III类mGlu受体的激活可诱导小胶质细胞的轻度激活,但这种激活不会产生神经毒性。有研究发现,激活第III类mGlu受体的激活可防止小胶质细胞释放谷氨酸,降低其对脂多糖和A β 的反应,并且降低小胶质细胞对神经元的毒性^[31]。因此,选择性调节小胶质细胞III类受体可能是针对AD等神经退行性疾病的治疗方法之一^[31]。

1.3 大麻素受体

内源性大麻素系统(endogenous cannabinoid system, ECBS)由内源性化合物、化合物的合成和代谢酶以及特异性受体组成,主要参与神经传导、突触可塑性、情绪调节和应激反应等生理活动^[32]。

现已发现的内源性大麻素受体有两种: 大麻素受体1(Cannabinoid receptor 1, CB1)受体和大麻素受体2(CB2)。在人脑中, CB1主要表达于神经元,在小胶质细胞上也有表达。有报道称,激活CB1可以抑制神经毒性,提高AD小鼠的认知能力,而CB1敲除加剧了AD小鼠的病理症状^[33-34]。但也有报道CB1激活会导致乙酰胆碱信号转导减少等副作用,从而导致认知障碍^[35]。小胶质细胞上的CB1在此过程中的具体作用仍需进一步阐明。

CB2在CNS中主要表达在小胶质细胞与免疫细胞上,其主要作用是调节炎症因子的释放^[35-36]。研究发现, AD中小胶质细胞CB2受体的表达量显著升高^[36]。CB2的激活可以在一定程度上抑制小胶质细胞促炎因子的释放并且刺激其迁移^[37],这可能有助于在AD病理初期将小胶质细胞募集到神经元损伤的部位。另外,在AD患者的大脑组织样本中还发现位于A β 斑块附近的小胶质细胞中CB2表达量上升,并且CB2的表达会刺激小胶质细胞对A β 的吞噬^[38]。在动物模型中,用A β 预处理的C6星形胶质瘤细胞和大鼠中也观察到CB2表达的增加^[39]。

基于这些特点,靶向小胶质细胞CB2的药物在AD治疗中表现出一定潜力^[40]。例如, CB1/CB2激动剂WIN55,212-2可以降低A β 介导的神经毒性^[41]。CB2激动剂JWH-015通过干扰JAK激酶/信号转导和转录激活因子1(Janus kinase/signal transducer and activator of transcription 1, JAK/STAT1)途径,增强了小胶质细胞对A β 的吞噬作用^[42]。胆碱酯酶抑制剂

与CB2激动剂的双效药物在AD小鼠中也表现出对认知障碍的改善效应^[43]。上述研究表明, CB2是AD病理潜在的药物靶点之一。

1.4 胆碱能受体

乙酰胆碱是第一个被发现的神递质, 是中枢胆碱能系统的重要递质, 对人的学习、记忆能力有重要作用^[44]。研究表明, AD晚期时胆碱能信号传递异常, 胆碱能神经元变性和丢失^[45]。乙酰胆碱受体分为毒蕈碱型受体(muscarinic acetylcholine receptors, mAChRs)和烟碱型受体(nicotinic acetylcholine receptors, nAChRs)两种, 这两类受体在小胶质细胞上都有表达^[46-47]。

mAChRs属于G蛋白偶联受体超家族, 可分为5种亚型和两种亚类, 分别为M1、M3、M5(第一亚类)和M2、M4(第二亚类)^[48]。mAChRs在AD领域相关研究主要集中在神经元上^[49]。第一亚类的mAChRs激活导致神经元去极化从而增加神经兴奋性, 第二亚类的mAChRs可以使神经元产生突触前、突触后抑制^[50]。小胶质细胞上已经发现表达M3受体, 使用干扰素观察到小胶质细胞可引发其M3受体表达上调, 说明M3受体参与小胶质细胞的免疫功能^[51]。在mAChRs激动剂卡巴胆碱作用后, 小胶质细胞的吞噬能力随着激动剂浓度的增加而降低^[51]。推测小胶质细胞可能通过mAChRs调节其吞噬A β 能力来影响AD病理。

nAChRs是由五聚体亚基构成的配体门控型的离子通道蛋白, 在CNS中主要由 α 亚基($\alpha 2 \sim \alpha 10$)和 β 亚基($\beta 2 \sim \beta 4$)组合成不同的受体亚型^[52]。其中研究较多的是 $\alpha 7$ 亚型的nAChRs, 是脑内最丰富的nAChRs之一, 其在小胶质细胞上表达^[53], 对Ca²⁺高度通透, 其激活后通过IP₃途径增加细胞内Ca²⁺浓度调节神经元电信号, 影响脑内神经传递^[54]。

研究发现, $\alpha 7$ nAChR表达量在AD小鼠脑内上调^[55], 并且 $\alpha 7$ nAChRs会与A β 相互作用, 产生 $\alpha 7$ nAChRs-A β 复合物, 但这种相互作用产生的生理意义尚未明确, 一些研究认为这种结合具有神经保护作用, 另一些研究则声称其在神经元中产生神经毒性^[54]。小胶质细胞上 $\alpha 7$ nAChRs的激活被认为与炎症有关, 胆碱能信号可以通过激活 $\alpha 7$ nAChRs抑制活化小胶质细胞促炎因子的释放, 并通过促进神经营养因子分泌产生神经保护作用^[56]。在补充胆碱能饮食的AD小鼠中发现, $\alpha 7$ nAChRs表达量显著上升,

同时小胶质细胞的炎症缓解^[57]。 $\alpha 7$ nAChRs还可以调节小胶质细胞的吞噬作用, 研究表明, AD大鼠脑中小胶质细胞 $\alpha 7$ nAChRs激活后, 会增强小胶质细胞的吞噬作用^[58]。同样 $\alpha 7$ nAChRs特异性激动剂在AD小鼠中也可促进小胶质细胞对A β 的吞噬作用, 改善小鼠的认知障碍^[59]。因此, 已有利用 $\alpha 7$ nAChRs激动剂对AD进行治疗的药物研究^[58,60]。

综上, 小胶质细胞中胆碱能受体对AD的影响可能有以下两方面: 一方面通过激活或抑制调节小胶质细胞的吞噬作用, 从而促进对A β 的吞噬, 产生一定神经保护效应; 另一方面, 抑制过度活化的小胶质细胞中炎症因子的分泌并减弱其吞噬能力, 从而减轻其CNS的神经毒性。

1.5 肾上腺素能受体

肾上腺素能受体是介导儿茶酚胺作用的一类受体, 肾上腺素能受体分布广泛, 在许多组织器官上都有表达^[61]。肾上腺素能受体主要根据其激活后的生理作用分为 α -肾上腺素能受体(α -adrenergic receptor, α -AR)和 β -肾上腺素能受体(β -adrenergic receptor, β -AR)两种亚类, α -AR包含 $\alpha 1$ 和 $\alpha 2$ 亚型, β -AR则可分为 $\beta 1$ 、 $\beta 2$ 和 $\beta 3$ 三种亚型^[62]。目前小胶质细胞中已发现有 $\alpha 1$ -AR、 $\alpha 2$ -AR、 $\beta 1$ -AR和 $\beta 2$ -AR的mRNA表达^[63]。其中 α -AR在AD领域研究较少, 但有报道称, $\alpha 2$ -AR能通过依赖G蛋白的信号传导破坏A重复序列的排序相关受体(sorting-related receptor with A repeat, SorLA)和成熟APP之间的共定位和相互作用, 促进A β 生成, 影响AD病理^[64]。

β -AR也参与AD病理^[65]。研究表明, β -AR介导的去甲肾上腺素能传递与记忆有关, β -AR激活可强化大脑海马区的LTP, 并诱导LTP相关蛋白的合成^[65]。有报道称, $\beta 1$ -AR激动剂可减轻AD小鼠的认知缺陷^[66]。另外有研究发现, A β 会与 $\beta 2$ -AR相互作用, 导致神经元中 $\beta 2$ -AR的降解, 从而导致AD脑内肾上腺素能受损^[67]。小胶质细胞中的 β -AR主要与炎症有关。研究发现, $\beta 1/\beta 2$ -AR激动剂可以减轻小鼠因注射A β 引起的小胶质细胞激活; 并且服用 β -AR拮抗剂和敲除 $\beta 1$ -AR和 $\beta 2$ -AR基因的小鼠损失了因环境富集作用带来的小胶质细胞的抗炎保护作用^[68]。 $\beta 2$ -AR激动剂还抑制小胶质细胞中促炎因子(如IL-6和TNF α)的产生^[69], 并且 β -AR激动剂还能抑制LPS介导的小胶质细胞活化^[70]。还有研究发现, 小胶质细胞中肾上腺素能递质的耗尽, 会使得小胶质细胞的吞噬作用受

到阻碍,影响小胶质细胞对A β 等物质的吞噬能力^[71]。根据以上研究可以推测,肾上腺素能受体的激活促进小胶质细胞对A β 的吞噬,并缓解过量促炎因子导致的神经炎症,而小胶质细胞上肾上腺素能受体功能的受损可能导致了AD病理的进一步发展。

2 结语与展望

综上所述,小胶质细胞通过细胞表面的神经递质受体实现与神经元的双向交流和调控,从而更好地调控其吞噬清除和分泌炎症因子的作用,维持CNS稳态^[72]。在此过程中,其表面的神经递质受体通过接受不同的递质信号,发挥不同的调节作用;而这些神经递质受体表达或功能异常也会通过神经炎症等方式与AD的发生、发展密切相关。但由于AD病理的复杂性,且目前对这些受体的研究仍主要集中在神经元上,我们实际上对小胶质细胞上的神经递质受体及其在AD中的具体机制知之甚少。另外,本综述未涉及一些其他类型的小胶质细胞神经递质受体,包括腺苷能受体^[73]、嘌呤能受体^[74]、阿片类药物受体^[75]等。相信随着对该领域研究的深入,更多小胶质细胞神经递质受体在AD病理中参与的机制会被发现,为寻找有效的AD干预靶点提供重要思路。

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