·综 述·

人参皂苷Rg1通过调控细胞膜受体改善记忆研究进展

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[摘要]细胞膜受体-G蛋白偶联受体30(G protein-coupled receptor 30,GPR30)、烟碱乙酰胆碱受体(acetylcholine receptor,nAChR)、酪氨酸激酶受体(receptor tyrosine kinases,RTKs),γ-氨基丁酸受体(γ-aminobutyric acid receptor,GABAR)和甘氨酸受体(glycine receptor,Glycine R)在学习记忆中扮演重要角色。这些细胞膜受体可能是人参皂苷Rg1改善记忆的潜在靶点。人参皂苷Rg1通过激活上游的细胞膜受体、级联神经细胞钙调蛋白激酶Ⅱ、磷脂酰肌醇3-激酶信号通路、细胞外调节蛋白激酶、雷帕霉素靶蛋白等信号通路调节海马突触可塑性或促进突触再生,从而发挥改善学习记忆的功能。这些上游细胞膜受体均是人参皂苷Rg1的作用靶点。

[关键词]老龄化;学习记忆;人参皂苷Rg1;作用靶点

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人口老龄化正成为中国的主要社会问题之一。2050年约1/3人口年龄将超过60岁[1]。认知下降广泛存在于老年人群中,也是目前寿命延长后一个急需解决的重大难题。尽管与年龄相关的记忆下降并不等同于阿尔茨海默病(Alzheimer's disease,AD)中出现的破坏性的记忆力损害,但是衰老是引起AD等神经退行性疾病的首要原因。中医学认为衰老与激素的调节有关。《黄帝内经》中记载:"女子七岁,肾气盛,齿更发长。二七而天癸至……七七,任脉虚,太冲脉衰少,天癸竭,地道不通,故形坏而无子也。"记载中表明"天癸"在人体衰老过程发挥重要的作用,而古书中记载的"天癸"即是现代生物医学中的性激素。动物实验也证实,雌激素补充疗法能抗衰老或调节衰老引发的海马神经细胞损伤[2-3]。

中医学认为,肾藏精,精生髓,脑为髓海,"在下为肾,在上为脑,虚则皆虚"(《医碥·卷四》)。也就是说,肾精充盛则脑髓充盈,肾精亏虚则髓海不足。脑髓盈满,则耳目聪明,精力充沛;脑髓空虚,可出现记忆减退。补肾填精益髓为缓解记忆减退的重要方法。人参为五加科植物人参的根。《本草纲目》中记载:"人参,味甘微寒。主补五脏,安精神,定魂魄,止惊悸,除邪气,明目,开心益智。久服,轻身延年。"中国是药用人参的发源地,人参作为珍贵中药材应用历史悠久。人参皂苷类是人参中的主要有效成分,由人参的茎叶或根部提取精制而成,含有18种以上的人参单体皂苷。其中主要单体包含人参皂苷Rb1、Rb2、Rc、Rd、Rg1等。人参皂苷Rg1是人参主要活性成分之一,具有促进海马神经再生、提高神经突触可塑性、增强学习记忆力、抗衰老、抗疲劳、提高免疫力、辅助抗肿瘤、修复性功能等药理学作用。药物代谢动力学研究结果显示,人参皂苷Rg1可以通过血脑屏障,并分布在整个脑区[4]。

细胞膜受体主要由跨膜结构域及效应结构域组成。参与学习记忆的发生的细胞膜受体主要包括G蛋白偶联受体30(G protein-coupled receptor 30,GPR30)、烟碱乙酰胆碱受体(nicotinic acetylcholine receptors,nAChR)、酪氨酸激酶受体(receptor tyrosine kinases,RTKs)、γ-氨基丁酸受体(γ-aminobutyric acid receptor,GABAR)和甘氨酸受体(glycine receptor,Glycine R)等。笔者对人参皂苷Rg1保护老年小鼠学习记忆的下降及其机制进行了探索,结果表明人参皂苷Rg1连续腹腔注射30 d,能明显增强中老年小鼠海马突触可塑性,促进海马内脑源性神经营养因子(brain derived neurotrophic factor,BDNF)的表达、树突脊再生,从而改善小鼠学习记忆[5]。然而人参皂苷Rg1作用后,可能参与的细胞膜受体还不清楚。因此,现就人参皂苷Rg1改善学习记忆可能性的细胞膜受体进行综述。

1 GPR30

GPR30为一类由375个氨基酸组成的7次跨膜的G蛋白偶联受体。GPR30与配体结合时具有高亲和力、高特异性、可置换性等膜受体的特性。同时,免疫细胞化学结果也提示GPR30主要定位于细胞膜[6]。GPR30与其配体结合后通过第二信使系

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统发挥间接的转录调控作用,该过程更容易调控,而且更符合学习记忆及突触可塑性的调控机制。在神经系统,GPR30和多种老年性疾病的发生相关,通过激活GPR30能改善帕金森病、脑血管病[7-9]。GPR30介导多种神经功能的发挥,主要包括调节神经递质的释放和神经保护的功能[10]。超微结构进一步显示GPR30定位于海马的树突脊和轴突末端[6],而且报道直接指出,GPR30能介导雌二醇调节海马结构可塑性的功能[11]。人参皂苷Rg1具有类雌激素特性,激活雌激素受体而发挥神经保护或增强记忆的功能[12-14]。LI等[15]研究指出,中药通络救脑方(由栀子和三七组成)及其活性成分人参皂苷Rg1通过非经典雌激素受体发挥对AD的保护,而此处的非经典雌激素受体和GPR30有重要关联。CHEN等[13]研究指出人参皂苷Rg1对Aβ25-35诱导的PC12死亡是通过胰岛素样生长因子1(insulin-like growth factor 1,IGF-1)受体和雌激素受体关联作用的,这与GPR30的作用极为相似。

2 乙酰胆碱受体(acetylcholine receptors,AChR)

乙酰胆碱(acetylcholine,ACh)是脑内非常经典的神经递质之一,其在学习记忆中起着重要的作用。ACh主要通过与突触后膜上的两大受体结合发挥作用,AChR可分为毒蕈碱型乙酰胆碱受体(muscarinic acetylcholine receptors,mAChR)和nAChR,mAChR为G蛋白偶联受体家族,而nAChR属于配体门控离子通道超家族。nAChR有神经保护作用,特异性烟碱受体激动剂使α7和α4β2 nAChR亚型激动,可发挥神经保护作用[16]。α7和α4β2在改善认知能力方面也有重要作用[17-18]。人参皂苷Rg1已被证实可以改善慢性氧化性损伤,可能的机制和提高啮齿动物脑中胆碱乙酰转移酶(choline acetyltransferase,ChAT)的水平有关[19]。而ChAT是Ach合成的关键酶,说明人参皂苷Rg1可促进脑内Ach的合成。JIN等[20]报道指出人参皂苷Rg1能改善脂多糖诱导的认识损伤,而作用的主要靶点即为α7 nAChR。CHOI等[21]指出nAChR是人参皂苷类化合物作用神经细胞的重要靶点,也间接指出nAChR作为人参皂苷Rg1对学习记忆的保护的靶点之一。

3 RTKs

酪氨酸激酶受体B(tyrosine kinase receptor B,TrkB)广泛存在于中枢神经系统,是BDNF的功能性受体。TrkB可与BDNF特异性结合,参与神经细胞的生存、生长、分化过程。BDNF-TrkB通路是学习记忆保护重要的靶点[22-23]。在AD轻度认知障碍患者的海马和皮质中,BDNF mRNA水平和蛋白质含量均降低[24]。人参皂苷Rg1可以通过上调突触可塑性相关蛋白p-TrkB和BDNF,恢复长时程增强(long-time potentiation, LTP),改善AD小鼠的记忆[25]。WAN等[26]研究指出,人参皂苷通过促进BDNF-TrkB改善慢性脑缺血引起的记忆下降。KEZHU等[27]报道了人参皂苷Rg1对慢性束缚应激诱导的记忆损伤是由BDNF-TrkB部分介导的。笔者前期研究也发现,人参皂苷Rg1上调突触可塑性相关蛋白p-TrkB和BDNF的表达,恢复弱θ节律波(theta-burst stimulation, TBS)诱导的LTP,改善衰老小鼠的学习记忆[5]。因此,包含TrkB在内的RTKs很可能是Rg1改善衰老记忆减退的重要靶点。

4 GABAR

GABAα是配体门控离子通道超家族成员之一,由8个不同的亚基(α,β,γ,δ,θ,ε,ρ和π)组成。GABA能神经传递在学习和记忆过程中发挥重要作用[28-30]。GABAα受体可被用作治疗认知障碍药物的作用靶点。星形胶质细胞可产生和释放GABA以影响神经细胞信号[31]。人参皂苷Rg1通过降低星形胶质细胞替代基因1(astrocyte elevated gene-1,Aeg-1)的表达水平来降低星形胶质细胞的活化,从而提高认知功能[32]。星形胶质细胞活化的减少可能使得GABA的产生和释放减少,从而改善学习记忆。BAE等[33]指出人参皂苷的代谢物化合物K能促进GABA自主的释放,激活GABAR参与学习记忆的调控。

5 Glycine R

甘氨酸(Glycine)和GABAα同属于配体门控离子通道超家族成员。Glycine被认为是除了GABA以外的最重要的抑制性神经递质。Glycine广泛分布在中枢神经系统中,在神经信号的传递过程中起着重要的基础作用,还参与各种生理和病理反应[34]。Glycine作为神经递质有着双重作用[35]:低浓度时,它是N-甲基-D-天冬氨酸受体(N-methyl-D-aspartate receptor,NMDAR)的共激动剂,结合NMDAR上的甘氨酸共激活位点,发挥兴奋性作用,产生LTP;高浓度时,它是中枢系统主要的抑制性神经递质,激活Glycine R,产生长时程抑制。人参皂苷Rg1可以显著改善吗啡损伤的空间学习能力,并恢复吗啡抑制的LTP,这种作用依赖于NMDAR[36]。LEE等[37]指出人参皂苷能抑制NMDAR,而这个调节作用和Glycine R密切相关[38]。

6 总结

为还原传统中药人参延缓衰老、促进认知的作用本质，本研究在前期研究的基础上，结合国内外研究现状，对人参皂苷 Rg1 改善记忆的作用靶点进行了展望。尽管其他的信号通路(钙调蛋白激酶Ⅱ、磷脂酰肌醇 3-激酶信号通路、细胞外调节蛋白激酶、雷帕霉素靶蛋白等)也介导了人参皂苷 Rg1 的保护作用[39-41]，笔者认为人参皂苷 Rg1 的作用还是通过上游的细胞膜受体发挥级联下游的信号通路。因此，上游靶点的揭示将更加有助于阐述人参皂苷的作用机制。

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