NMDA受体在焦虑症发生发展中的作用

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摘要 随着社会生活压力的增大, 焦虑症逐渐成为当代最常见的精神类疾病之一。焦虑症的发病机制涉及多个系统功能的调节紊乱, 并且人类的多个脑区参与焦虑的发生。NMDA受体是由7种不同的亚基组成的多聚体复合物, 介导着中枢神经系统的兴奋性神经传递, 并且其不同亚基在焦虑症的发病机制中均发挥着重要作用。此外, 焦虑症动物模型的相关研究已经表明, NMDA受体通过影响恐惧条件反射以及恐惧消退来参与焦虑的产生。该文旨在介绍焦虑症中NMDA受体不同亚基表达水平及其下游信号通路发生的变化, 以及氯胺酮、美金刚和*D*-环丝氨酸等NMDA受体相关药物在治疗焦虑症方面的研究进展。

关键词 NMDA受体; 亚基; 焦虑症; 恐惧条件反射; 恐惧消退

The Role of NMDA Receptor in the Occurrence and Development of Anxiety Disorder

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Abstract With the increasing pressure of social life, anxiety has gradually become one of the most common mental diseases. The pathogenesis of anxiety disorder involves the regulation disorder of many system functions, and many brain areas of human participate in the occurrence of anxiety. NMDA receptor is a polymeric complex composed of seven different subunits that mediate excitatory neurotransmission in the central nervous system, and its different subunits play an important role in the pathogenesis of anxiety disorders. In addition, studies in animal models of anxiety disorders have shown that NMDA receptors are involved in the generation of anxiety by influencing fear conditioning and fear extinction. This article aims to review the expression levels of different NMDA receptor subunits and their downstream signaling pathways in anxiety disorders, as well as the research progress of NMDA receptor related drugs in the treatment of anxiety disorders, such as ketamine, memantine and *D*-cycloserine.

Keywords NMDA receptors; subunits; anxiety disorder; fear conditioning; fear extinction

焦虑症可分为广泛性焦虑症(general anxiety disorder, GAD)、社交恐惧症(social anxiety disorder, SAD)、惊恐障碍(panic disorder, PD)和特异性恐慌症(specific phobia, SP)等, 已成为当今社会常见的精神类疾病[1]。据统计, 焦虑症在非洲的患病率为5.3%, 亚洲为2.8%, 欧洲为10.4%, 全球达到7.3%[2-3]。焦虑症主要表现为过度和持久的恐惧、焦虑以及回避在外部(例如社交场合)和内部环境(例如身体感觉)中

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感知到的威胁。目前, 心理和药物治疗是焦虑症的主要治疗方法。例如, 心理治疗主要包括认知行为疗法(cognitive-behavioral therapy, CBT)、人际关系疗法和支持疗法。而药物治疗主要是针对γ-氨基丁酸能、5-羟色胺(5-hydroxytryptamine, 5-HT)能、去甲肾上腺素能系统以及组胺受体的药物, 如苯二氮卓类药物、选择性5-羟色胺再摄取抑制剂(selective serotonin reuptake inhibitors, SSRIs)、α和β-肾上腺素能、抗组胺等药物。虽然这些药物治疗的疗效优于其他疗法, 但是其伴随不良副作用包括认知功能障碍、体重增加、性功能障碍、镇静、依赖和戒断等。因此, 焦虑症药物治疗的研究重点已经转移到其他神经递质和途径, 比如谷氨酸(glutamic acid, Glu)和神经肽等[4-7]。

N-甲基-*D*-天冬氨酸受体(*N*-methyl-*D*-asparte receptor, NMDAR)是Glu的配体门控离子通道, 而Glu是中枢神经系统(central nervous system, CNS)中主要的兴奋性神经递质。它们广泛分布于大脑发育的各个阶段, 并且与神经元发育和突触可塑性等正常的大脑功能密切相关[8]。NMDAR激动剂或者拮抗剂能够影响人类各个方面的情绪, 包括恐惧、焦虑、抑郁以及损害学习和记忆功能。例如, 美金刚作为一种NMDAR拮抗剂, 可通过阻断NMDAR用于Glu能系统, 治疗GAD[9]; *D*-环丝氨酸(*D*-cycloserine, DCS)是一种NMDAR甘氨酸(Glycine, Gly)位点激动剂, 向小鼠体内长期注射DCS可以导致小鼠产生抗忧郁和抗焦虑行为[10]; 强迫症患者海马内Glu含量增高, 应用不同浓度NMDAR拮抗剂NVP-AAM077和Ro25-6891均能降低其海马Glu浓度, 并且对焦虑样行为和强迫行为均有明显抑制作用[11]。上述结果表明, NMDA受体与焦虑症存在密切联系。

1 焦虑症的发病机制

焦虑症作为一个与压力密切相关的疾病, 其发病机制涉及多系统功能的调节紊乱。脑内神经递质的改变常参与焦虑的发生。GABA作为CNS中主要的抑制性神经递质, 其中间神经元组成的抑制神经回路, 在调节正常和病理状态下的焦虑反应中起着关键作用[12]。临床上, 苯二氮卓类药物作为GABA-A受体的正变构调节剂, 可通过增强GABA能活性来改善患者的焦虑症状[13]。另外, CNS中的5-HT广泛参与调节情绪、认知、焦虑、学习、记忆、奖赏和睡眠等功能。临床上, SSRIs通过阻断5-HT再摄取, 并限制5-HT与其他神经递质系统的反应, 从而发挥治疗焦虑症作用[14]。神经肽Y(neuropeptide Y, NPY)是CNS中大量表达的内源性神经肽, 涉及多种神经精神疾病, 包括癫痫、抑郁症和焦虑症等。有研究表明, 伏隔核(nucleus accumbens, NAc)中NPY神经元消融可以显著增加大鼠的焦虑样行为, 与之相反, NPY神经元的化学激活可以减少大鼠的焦虑样行为[15]。去甲肾上腺素(norepinephrine, NE)在CNS中过度激活可以导致焦虑症状, 并有文献表明, 在压力条件下, 促肾上腺皮质激素释放因子可以通过激活蓝斑–颞侧海马中的NE信号通路, 从而释放NE并引起焦虑症状。而动物模型研究发现, 拮抗CNS内的β-肾上腺素受体可以减轻可卡因导致的焦虑症状[16]。另外, 神经内分泌功能紊乱也参与焦虑症的发生。有文献表明, 在焦虑症患者的体内可以发现下丘脑–垂体–肾上腺(the hypothalamic-pituitary-adrenal, HPA)轴过度活跃, 引起糖皮质激素分泌紊乱, 进而导致焦虑症状产生[17], 并且临床上不同类型的抗焦虑药物, 包括苯二氮卓类、SSRIs等可以通过调节HPA轴发挥治疗焦虑症的作用[18]。此外, 下丘脑–垂体–甲状腺轴[19]和下丘脑–垂体–性腺轴[20]功能紊乱均参与焦虑症的发生。

另外, 人体大脑中的某些脑区[包括杏仁核、海马和内侧前额叶皮层(medial prefrontal cortex, mPFC)、下丘脑、中脑和脑干等]也参与了焦虑的调节以及人体对危险的反应能力。它们的主要作用是评估环境对个人的危险程度, 并选择适当的应对措施, 从而形成防御模式。例如, 海马体在处理与周围环境相关的信号以及做出相应的焦虑反应中发挥重要作用; 中脑导水管周围灰质, 除了对内源性疼痛产生抑制作用外, 还是调节恐惧和焦虑的神经系统的尾端; 杏仁复合体及其传出的神经元投射参与条件性恐惧的获得、巩固和表达, 并可能在焦虑症的发病机制中发挥作用[7,21-23]。

2 NMDA受体与焦虑症

2.1 NMDA受体简介

CNS兴奋性神经递质绝大部分都是通过Glu的囊泡释放的, 它同时激活突触前和突触后的代谢型谷氨酸受体(metabotropic glutamate, mGluR)和离子型谷氨酸受体(ionotropic glutamate receptor, iGluR)。

iGluR可分成三种结构不同的功能类型：NMDA、AMPA(α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid)与红藻氨酸型。与其他类型受体相比，NMDAR有几个独特的特性，包括细胞外Mg^{2+}的电压依赖性阻断、Ca^{2+}的高通透性以及需要两种通道激动剂Glu和Gly(或*D*-丝氨酸)[24]。

NMDAR是由7种不同亚基(NR1、NR2A-D和NR3A-B)组装成的多聚体复合物，其中NR1是基本的功能单位，NR2作为调节亚单位，而NR3主要起抑制作用。在CNS中，绝大部分NMDAR由两个Gly结合NR1亚基和两个Glu结合NR2亚基构成[8]，而NR3亚基通过与Gly结合从而发挥作用[25]。

2.2 NR1亚基在焦虑症中的作用

在成年大鼠脑中，NR1几乎表达于大脑发育的各个阶段。NR1在大鼠幼儿期时就已经在大脑皮质各层的神经细胞中表达，并且在大鼠出生后第二周达到最高水平，然后平稳下降[26-27]。与啮齿类动物相似，NR1在人类胎儿的妊娠中期就已经在大脑皮层中表达，并随着胎儿年龄的增长而表达增加[28]。

NR1表达水平与正常大鼠的学习和记忆相关，几乎所有的海马神经元都需要正常水平的NR1来维持正常大鼠的学习和记忆能力。NR1作为NMDAR基本的功能单位，其基因*Grin1*的敲除对于小鼠而言是致命的，而*Grin1*基因敲低的小鼠会导致NR1的部分功能丧失或亚型突变[29]。*Grin1*基因敲低小鼠作为精神分裂症代表性模型，与野生型小鼠相比，其在高架零迷宫的开臂区域和旷场实验的中央区域时间更长，这可能反映了小鼠焦虑相关行为的减少，并且NMDAR缺陷小鼠的低焦虑相关行为也可能表明慢性NMDAR缺陷导致的行为抑制减少[30]。KALEV[31]等研究发现，在急性癫痫模型中，*Grin1*敲除可以防止癫痫发作，但是*Grin1*的过度表达则促进了恐惧记忆的形成。LI等[32]研究表明，坐骨神经慢性压迫损伤(chronic constriction injury, CCI)大鼠会导致抑郁和焦虑行为，其大鼠海马NR1亚单位磷酸化水平下降，而慢性电针治疗能有效地逆转p-NR1的下降，并且完全消除CCI大鼠的焦虑样行为，提示电针对CCI大鼠的抗焦虑作用，这可能与恢复海马NR1磷酸化有关。另有文献报道，产前应激诱导的成年子代焦虑样行为可能与降低海马中NR1的表达相联系[33]。另外进一步研究表明，NMDAR偶联细胞外受体激酶(extracellular receptor kinase, ERK)信号在海马和前额叶皮质(prefrontal cortex, PFC)中参与焦虑样行为[34]。与之相反，有文献报道，海马齿状回*Grin1*基因敲除的小鼠表现焦虑行为减少，这可能是由于腹侧海马损伤与抗焦虑作用密切相关[35-36]。啮齿类动物的海马不同区域发挥不同的功能，例如背侧海马的损伤会影响空间记忆能力，但对焦虑没有影响，而腹侧海马的损伤会降低焦虑，但对空间记忆能力没有影响，这可能解释了上述两种相反的结果[37]。上述结果提示NR1表达水平变化及其下游相关信号通路与焦虑的发生密切联系。

不同的NMDAR活性药物也会通过NR1来发挥抗焦虑作用。例如，环亮氨酸作为NR1亚基的变构Gly位点拮抗剂，将其注射入NAc内可以显著缓解大鼠的焦虑情绪[38]；美金刚作为一种NMDAR拮抗剂，可以通过抑制mPFC和NAc外壳的NR1-钙调节蛋白激酶II(calmodulin kinase II, CaMKII)-ERK这一通路的活性来减轻酒精戒断所导致的焦虑样行为[39]。

2.3 NR2亚基在焦虑症中的作用

NR2亚基在大脑多个区域的发育过程中均有表达，并且受到差异性调节。在啮齿类动物中，NR2B和NR2D在胚胎发育过程中广泛表达。而在成人中，NR2A和NR2B主要表达于前脑中，NR2C主要分布在小脑和嗅球，NR2D主要在中脑结构中表达，包括间脑和中脑。在哺乳动物胚胎期，含有NR2B的NMDAR占主导地位，是胚胎发育过程中表达的主要调节亚基。NR2A的表达在出生时开始逐渐增加，并且在整个CNS变得丰富，而NR2B的表达保持稳定且较低的水平。因此，在哺乳动物发育过程中，皮层和海马等大脑区域的NMDAR从主要含NR2B转变为含NR2A。这种发育转换与啮齿类动物相似，并且有研究表明，在大鼠海马中NR2A的表达得到进一步的增加。而NR2C在出生后的一周内，逐渐取代NR2B成为成人小脑中主要的NR2亚单位。NR2D主要在幼年发育过程中表达，而在成人大脑中通常下降到低水平。除了在大脑中的区域表达模式外，在不同神经元群体也发现含NR2的不同亚型。其中，NR2C与NR2D在皮层和海马的中间神经元和胶质细胞特异表达；NR2D也存在于小脑高尔基体细胞中。此外，不同的NR2亚基在亚细胞水平上的定位也不同。在成人前脑中，NR2A受体主要定位于突触，而NR2B受体定位于突触周围或者突触外部位[40-43]。

以往研究发现胚胎氯胺酮治疗在成年后代中

产生焦虑样行为, 并且PFC上NR2A与NR2B的表达减少。在用NR2B-shRNA慢病毒敲除3~4周龄大鼠海马CA1区的NR2B, 可显著减少PFC中NR2A的表达量, 并明显降低8周龄成年后代大鼠的焦虑行为。这提示胚胎氯胺酮治疗对成年后代产生焦虑样行为, 可能是由于成年大鼠PFC中NR2A相关的NMDAR表达和功能降低所致[44]。另有文献表明, 产前应激诱导成年子代产生焦虑样行为可能与降低海马、PFC和纹状体NR2A的表达相联系[33]。最新有文献报道, 卡里奥高条件冷冻(Carioca high-conditioned freezing)大鼠与对照组相比, 表现出焦虑样行为。同时其腹侧海马区的突触后致密蛋白95(postsynaptic density protein 95, PSD-95)、NR1的表达增加, NR2A的表达量减少[45]。上述结果表明, NR2A的表达水平变化与焦虑的发生密切相关。此外, NR2A也可能通过某些相关通路与焦虑相联系。JI等[46]研究表明, Sigma-1受体激活可以通过NR2A-环磷腺苷效应元件结合蛋白(cAMP-response element binding protein, CREB)-脑源性神经营养因子(brain-derived neurotrophic factor, BDNF)信号通路来改善单次延长应激大鼠模型中的焦虑样行为。另外最新的研究发现, 维生素D3改善尼古丁戒断期间的焦虑样行为, 下调了海马区NR2A的表达, 这可能与NMDAR/一氧化氮合酶(nitric oxide synthase, NOS)通路的抑制相关[47-48]。

SUN等[49]研究表明, 长时间自发性癫痫发作可致成年雄性Wistar大鼠空间学习记忆缺陷伴有焦虑样行为, 同时使海马NR2B/PSD-95表达下调。另外, DELAWARY等[50]研究发现, 在小鼠杏仁核降低NR2B的Tyr-1472位点磷酸化水平会导致小鼠焦虑样行为增加。另有文献表明, 杂合的*Grin2b*$^{+/C456Y}$基因突变的小鼠, NR2B蛋白表达水平显著降低, 并表现出焦虑样行为[51]。上述文献表明, NR2B的表达与焦虑的发生密切联系。

HILLMAN等[52]研究发现, *GRIN2C*基因敲除小鼠与野生型小鼠相比, 前者条件性恐惧和工作记忆的获得存在缺陷, 而条件性恐惧的获得与焦虑的形成密切相关。SILVA等[53]研究发现, 在幼年小鼠中, NR2B替换NR2C亚基增加了焦虑和恐惧相关的行为, 并可能与额叶皮层的5-HT和导水管周围灰质的乙酰胆碱水平变化相关。上述研究表明, NR2C可能通过影响神经递质的水平变化, 从而导致焦虑样行为的发生。SALIMANDO等[54]利用行为学测试和电生理技术, 发现*GRIN2D*基因敲除的小鼠表现出焦虑和抑郁样行为, 并伴随终纹床核(bed nucleus of stria terminalis, BNST)突触增强的中断。因此在BNST神经元上进行进一步的研究, 在BNST中条件性敲除*GRIN2D*基因, 结果发现产生更多的焦虑和抑郁样行为。上述研究表明, *GRIN2D*基因敲除可能导致BNST上兴奋性突触功能的中断, 从而产生焦虑和抑郁样行为。

不同的NMDA受体活性药物也会通过NR2来发挥抗焦虑作用。例如, NMDAR拮抗剂NVP-AAM077和Ro25-6921分别能够显著降低NR2A和NR2B的表达, 从而对大鼠焦虑样行为有明显的抑制作用, 以及不同剂量DCS作为NMDAR部分激动剂通过抑制NR2A和NR2B的表达, 从而发挥抗焦虑作用[11]。

2.4 NR3亚基在焦虑症中的作用

NR3A广泛存在于脊髓、脑干、下丘脑、杏仁核、海马的CA1区、丘脑以及大脑皮层中, 而NR3B广泛分布于脊髓、脑干、小脑、纹状体和海马、尾壳核、NAc和大脑皮层等区域。在哺乳类动物中, NR3A在胚胎中的表达水平很低, 但在发育早期大量表达, 随着年龄的增长而下降, 并在成年大脑中达到低水平。与NR3A相反, NR3B在出生后水平较低, 并随着年龄增长而逐渐增加。而在啮齿类动物中, NR3A在产后早期以及新生幼崽中表达水平很高, 从出生后的第七周开始表达下降, 直到成年期仍然很低。NR3B在发育早期表达很低, 并随着大脑的发育而开始表达增加, 并且在成年啮齿类动物中保持高水平。NR3A和NR3B在不同类型的神经细胞(包括中间神经元、椎体细胞、运动神经元、三叉神经细胞、视网膜神经节和无长突细胞等)中均有表达, 。而在超微结构上, NR3A存在于兴奋性突触的突触后膜[55-58]。

文献表明, NR3A对运动、痛觉、神经保护和认知功能具有重要的影响。*GRIN3A*基因敲除的小鼠在社交互动测试中, 表现为社交互动和社交方式的减少, 其代表小鼠社交行为受损[59]。NR3B在头颅和脊髓的躯体神经元中大量表达, 对运动功能有重要作用[60]。NIEMANN等[61]对*GRIN3B*基因敲除的小鼠模型进行行为分析, 发现小鼠的学习、运动以及协调能力均有所降低, 并且在新环境中社交互动减少以及焦虑样行为增加。另外, EHSANIFAR等[62]

在密闭室内将孕鼠暴露于柴油机废气颗粒物, 用莫里斯水迷宫和高架十字迷宫测试8~9周雄性仔鼠的焦虑和学习记忆能力, 发现其仔鼠出现焦虑和学习能力缺陷, 并且小鼠海马NR2A和NR3B表达水平减少。上述文献均表明, NR3B表达水平变化与焦虑的发生存在联系。

3 NMDA受体与焦虑症的发生发展

NMDAR由于其Ca^{2+}高通透性和长时程, 在兴奋性突触后电流过程中介导大量的Ca^{2+}内流, 从而触发突触后神经元的多个下游信号事件, 比如突触可塑性, 突触效能长时程增强(long-term potentiation, LTP)等[63]。因此, 突触NMDAR激活的频率和持续时间可以导致突触效能的增强或者抑制, 而这与焦虑症中恐惧记忆的形成相联系。NMDAR还可以通过激活许多亚细胞信号来参与焦虑的形成, 例如, NMDAR通过抑制神经型一氧化氮合酶(neuronal nitric oxide synthase, nNOS)的活性, 从而减少脑内NO的产生来实现抗焦虑作用[64]; NMDAR还可以通过激活CaMKII-ERK通路导致酒精戒断后的焦虑样行为[65]。

条件性恐惧模型作为一种研究焦虑症的动物模型受到了极大的关注。有研究报道, 影响恐惧条件反射的药物可能具有治疗焦虑症的潜在效用[66-67]。而NMDAR参与杏仁核和海马中恐惧条件反射的获得和表达, 并且恐惧条件反射所需的记忆储存和潜在的突触可塑性过程可能取决于NR2B的功能[68]。例如, 在恐惧条件化训练后5 min到10 min, 海马CA1区细胞膜上NR2B随着NR1的增加而发生瞬时增加, 但是后者的增加可以被NR2B的抑制剂所阻断[41]。另有文献表明, 基底外侧杏仁核(basolateral amygdala, BLA)内Glu能突触的NMDAR主要以NR1/NR2A/NR2B的异源三聚体的形式存在, 其受体动力学和药理学受NR2A性质所支配, 并且NR2B可以激活这些突触上CaMKII依赖的LTP[69]。

恐惧消退对恐惧条件反射起抑制作用, 并且涉及杏仁核新的学习和突触变化, 包含第二信使的磷酸化状态和*BLA*基因表达模式的下游变化[68,70]。大脑皮质mPFC的NMDAR依赖的突触可塑性参与编码恐惧记忆消退, 而记忆消退的巩固涉及NMDAR依赖的突触可塑性, 并且NMDAR介导的BLA神经可塑性参与大鼠条件性恐惧的获得和表达。与此一致的是, 有文献表明, 竞争性和非竞争性的阻断NMDAR可以破坏恐惧消退, 同时通过甘氨酸-β共激动剂位点与部分激动剂双环丝氨酸增强受体活性从而促进恐惧消退[71]。另外, 前脑中NR2B过表达的转基因小鼠表现出更快的恐惧消退[72]。

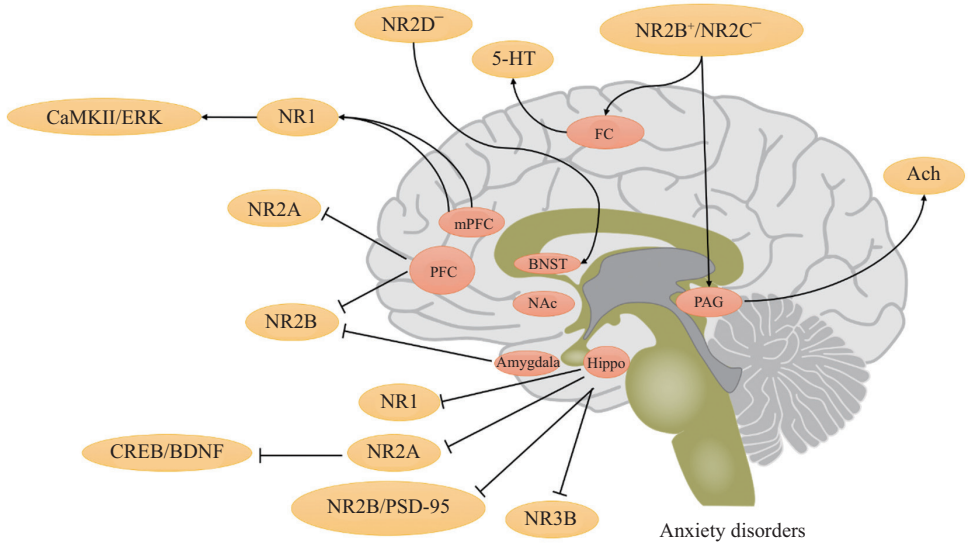
此外, NMDAR由于亚细胞定位不同, 其对神经元信号传导、突触可塑性和学习产生完全相反的影响。例如, 位于突触中NR1/2A异构体可以激活ERK信号, 从而消除恐惧条件反射, 而突触和突触外NMDAR的共同激活可以关闭这些通路, 并诱导抑制恐惧消退[73]。故NMDAR参与焦虑症的发生发展(图1)。

4 NMDA受体治疗焦虑症的相关研究

NMDAR相关药物可以通过影响NMDAR与离子载体复合物结合, 从而发挥治疗焦虑症的作用。治疗药物包括对NMDAR位点本身的竞争性抑制: AP-5、AP-7; 非竞争性抑制离子通道: 氯胺酮、美金刚及MK801等; 甘氨酸位点激动剂: *D*-环丝氨酸[74]。

NMDAR竞争性拮抗剂在不同的动物模型中发挥抗焦虑作用已经得到证实。AP-5可以通过注射海马CA3[75]、杏仁核[76]以及BNST[77]等脑区发挥抗焦虑作用。然而也有研究表明, 将AP-5注射到背侧海马未发挥抗焦虑作用, 而注射到腹侧海马可以发挥抗焦虑作用, 这可能是由于腹侧和背侧海马之间存在功能性分离[78-80]。同时, AP-7注射到大鼠的mPFC和BNST, 在高架十字迷宫及旷场实验中也表现出类似的抗焦虑作用[81-83]。NMDA竞争性拮抗剂CGP37849[84]也可能具有抗焦虑的作用。

非竞争性的NMDAR拮抗剂在治疗焦虑症方面也得到了广泛的研究。氯胺酮最初作为麻醉剂进行研究开发, 并在多项临床和临床前研究中显示出快速持久的抗抑郁作用[85], 但是关于氯胺酮对焦虑的影响, 临床前研究存在不一致。ENGIN等[86]发现大鼠在给予氯胺酮后, 在高架十字迷宫等行为学实验中表现出抗焦虑状态, 而WALKER等[87]发现氯胺酮对大鼠焦虑行为不会产生影响。有文献表明, 氯胺酮对于焦虑相关行为的不同影响可能取决于焦虑范式、给药方式及测试物种差异等因素[88]。最近临床发现, 对于GAD和SAD患者每周给予氯胺酮治疗, 可以有效地缓解患者的焦虑症状以及改善个人生活质量[89]。美金刚是一种NMDAR拮抗剂, 用于治疗阿尔



+: 过表达; − : 敲除; →: 激活; ⊣: 抑制。FC: 额叶皮层; PFC: 前额叶皮层; mPFC: 内侧前额叶皮层; BNST: 终纹床核; NAc: 伏隔核; PAG: 导水管周围灰质; Amygdala: 杏仁核; Hippo: 海马体; CaMKII: 钙调蛋白激酶II; ERK: 细胞外受体激酶; CREB: 环磷酸腺苷效应元件结合蛋白; BDNF: 脑源性神经营养因子; PSD-95: 突触后致命蛋白95; 5-HT: 5-羟色胺; Ach: 乙酰胆碱。

+: overexpression; − : knock out; →: activation; ⊣: inhibition. FC: frontal cortex; PFC: prefrontal cortex; mPFC: medial prefrontal cortex; BNST: bed nucleus of stria terminalis; NAc: nucleus accumbens; PAG: periaqueductal grey; Amygdala: amygdala; Hippo: Hippocampus; CaMKII: calmodulin kinase II; ERK: extracellular receptor kinase; CREB: cAMP-response element binding protein; BDNF: brain-derived neurotrophic factor; PSD-95: postsynaptic density protein 95; 5-HT: 5-hydroxytryptamine; Ach: acetylcholine.

图1 NMDA受体在焦虑症发病中的作用

Fig.1 The role of NMDA receptor in the pathogenesis of anxiety disorders

茨海默病患者。SCHWARTZ等[90]临床研究发现, 美金刚可能是作为焦虑症的一种强化治疗。其他的非竞争性NMDAR拮抗剂MK801、PCP及其部分衍生物在高架和旷场实验中均表现出抗焦虑作用[91-92]。

DCS作为NMDAR甘氨酸位点激动剂, 是目前研究治疗焦虑症最为广泛的药物之一[93]。迄今为止的研究主要集中在心理治疗或者恐惧学习背景下DCS对焦虑的影响。在动物模型上的研究已经表明, DCS可以消除条件性恐惧的形成[94], 并且临床上, DCS已被研究用于增强PD、SAD和特定恐惧症的心理治疗[95]。

最后, N_2O作为一种常用的牙科吸入性麻醉剂, 也是一种NMDAR拮抗剂。有研究表明, N_2O可以有效减少由阿片类药物所导致的焦虑样作用[96]。

5 结语与展望

焦虑症作为一种常见的精神类疾病, 给家庭和社会带来巨大的经济负担, 以往焦虑症治疗药物主要是γ-氨基丁酸、5-羟色胺能系统药物, 其所带来的副作用很大。越来越多的证据表明, NMDAR参与焦虑症的发病机制, 并且调节恐惧条件反射的获得和消退。尽管NMDAR不同亚基在焦虑症中的作用得到了广泛的研究, 但是不同亚基在焦虑症中的确切作用机制尚不明确。此外, 临床试验已经表明, NMDAR相关药物在治疗焦虑症方面存在一定的疗效。因此, 在未来研究中更加深入地阐明NMDA受体在焦虑症中的确切作用机制, 有助于探索焦虑症潜在的治疗靶点。

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