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综 述

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抑制性离子通道甘氨酸受体的研究进展

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摘 要：抑制性离子通道甘氨酸受体(glycine receptors, GlyRs)属于配体门控离子通道受体超家族的一员，在中枢神经系统中广泛分布。GlyRs对维持视觉、听觉、感觉和运动功能至关重要，其结构或功能异常会导致各种严重的神经系统疾病。本文旨在对GlyRs的结构、功能及调控机制进行深入的综述和分析，并探讨其在各种中枢神经系统疾病中的作用，为开发特异性靶向GlyRs的新型药物提供理论参考。

关键词：抑制性离子通道；甘氨酸受体；神经系统疾病

Advances in inhibitory ion channel glycine receptors

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Abstract: Glycine receptors (GlyRs) belong to the ligand-gated ion channel receptor superfamily and are widely distributed throughout the central nervous system. GlyRs are essential for maintaining visual, auditory, sensory and motor functions, and abnormalities in its structure and function can lead to various neurological disorders. This review aims to provide an extensive analysis of the structure, function and regulatory mechanisms of GlyRs, and evaluate its role in various central nervous system

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diseases. Ultimately, this review will provide theoretical support for the development of novel drugs specifically targeting GlyRs.

Key words: inhibitory ion channel; glycine receptor; nervous system diseases

甘氨酸是分子量最小、结构最简单的氨基酸，是中枢神经系统中的一种抑制性神经递质，主要分布于大脑、脊髓和脑干[1, 2]。甘氨酸在突触传递过程中扮演非常重要的角色，甘氨酸的作用靶点主要有3个，包括抑制性离子通道甘氨酸受体(glycine receptors, GlyRs)、*N*-甲基-*D*-天冬氨酸受体(*N*-methyl-*D*-aspartic acid receptor, NMDAR)的GluN1亚基和GluN3A亚基[3]。

GlyRs是中枢神经系统中重要的细胞膜蛋白。GlyRs主要存在于脊髓、脑干和大脑皮层等部位，通过参与神经传导，对身体运动控制、痛觉感知以及情绪认知等功能进行精准调控[4–7]。作为重要的抑制性离子通道受体，GlyRs的功能障碍会导致严重的神经系统疾病，如过度惊骇病、慢性炎症疼痛、酒精中毒和僵人综合征等[8–11]。因此，GlyRs结构和功能的研究已经成为神经科学领域的热点之一。

20世纪80年代，科学家已经纯化GlyRs并对其生理功能展开了研究[12, 13]。然而，由于GlyRs结构和功能的复杂性以及研究技术的局限性，大多数研究仅集中在体外水平，主要研究GlyRs的神经药理学机制，关于其在神经系统中分布和功能的研究十分缺乏，极大限制了我们对GlyRs调控脑功能机制的理解。本篇综述首先系统总结了GlyRs的结构、功能和分布，阐述了GlyRs功能缺陷相关的神经系统疾病，并对GlyRs各个亚基作为特定脑疾病干预靶点的潜力进行了概述。

1 GlyRs结构、组织分布和功能

1.1 GlyRs的结构和组织分布

抑制性GlyRs属于五聚体配体门控离子通道受体(pentameric ligand-gated ion channel receptors, pLGICs) Cys-loop家族中的成员，在其结构中央能够形成一个选择性透过氯离子的跨膜通道[14]。在人类的神经系统中，GlyRs由α1~4 (48 kDa)和β亚基(58 kDa)共同组成同源五聚体或者异源五聚体。5个亚基围绕中心离子传导孔对称排列成环形，每个亚基包含一个细胞外结构域(extracellular domain, ECD)和四个跨膜结构域(transmembrane domain，TMD，即TM1、TM2、TM3和TM4)以及TM3和TM4之间的大细胞内环(intracellular loop domain, IL)，其为配体结合区、离子通道孔和细胞内调节位点提供结构基础。当甘氨酸与GlyRs结合时，每个ECD相对于TMD旋转，导致TMD结构域顶部向外倾斜，从而打开通道孔，GlyRs实现从闭合到开放的转变[15, 16](见图1、2)。

在脊椎动物中，功能性GlyRs通常包括由α亚基组成的同源五聚体或者α和β亚基组成的异源五聚体。1982年Betz等从大鼠脊髓中纯化出GlyRs，之后于1988年通过运用凝胶电泳法、免疫印迹等方法发现天然异聚体GlyRs的结构为五聚体跨膜结构，同时发现α亚基与β亚基的构成比为4∶1或者3∶2，但由于当时实验技术的局限性，Betz等认为3∶2的模型较为符合当时实验结论[13, 17]。随着实验技术的发展，2012年Dent等利用单分子成像和逐步光漂白技术确定非洲爪蟾卵母细胞GlyRs的亚基化学计量比为3∶2 [18]，而同年Lynch等利用原子力显微镜对单个结合的α1β受体成像，从而推断GlyRs的化学计量比为2∶3 [19]。到目前为止，GlyRs异构体的亚单位化学计量比还没有形成一致的结果，限制了GlyRs的进一步研究。但在2021年Gouaux等和Wang等都利用高分辨冷冻电子显微镜的技术证实天然异聚体GlyRs是由4个α亚基和1个β亚基组成[20, 21]，这与先前化学计量比2∶3或者3∶2的预测不同，Gouaux等和Wang等利用较为严谨的实验技术确定GlyRs的计量比，推翻了传统的预测，他们的研究表明异聚体GlyRs在突触后膜中的排列方式为受体提供了重要的结构和功能基础，为GlyRs研究靶点提供结构支撑。

GlyRs的各个亚基在发育过程中有不同的变化。在出生前，α1亚基的转录量很少，但在出生后开始明显增加。α1亚基的mRNA在脑干和脊髓中表达最高，同时也在丘脑和下丘脑区域中有少量表达。随着神经系统的发育，α2亚基的水平呈现出明显的变化。出生前，α2亚基在中枢神经系统皮层中广泛表达，出生后大约20天左右，α2亚基的表达急剧下降，只有在视网膜、听觉脑干核和一些高级脑区才能观察到一些转录。在此过程中，α2亚基逐渐被α1亚基所取代。α3亚基的转录

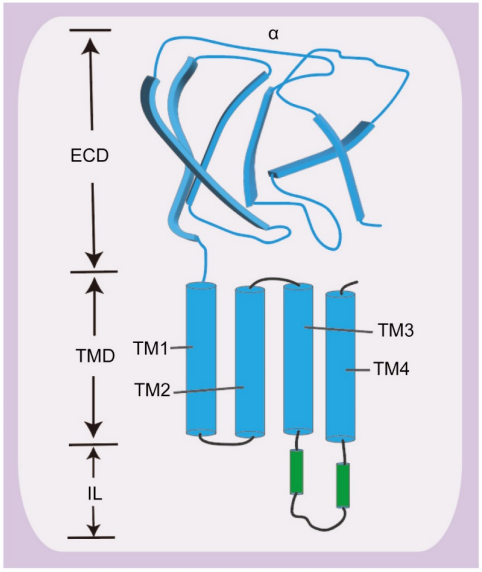

图 1. 甘氨酸受体(GlyR)单体结构示意图

Fig. 1. Schematic diagram of monomeric structure of glycine receptor (GlyR). The intracellular loop domain (IL) between TM3 and TM4 is indicated by simple line segments. ECD, extracellular domain; TMD, transmembrane domain.

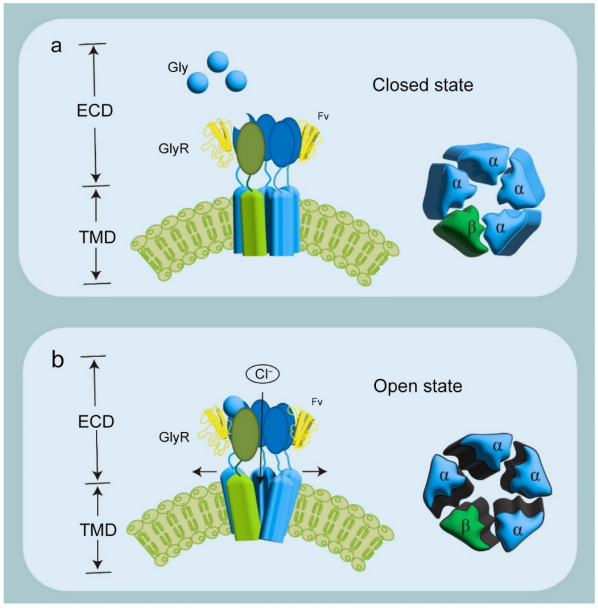

图 2. 甘氨酸受体(GlyRs)与甘氨酸结合前后的变化简图

Fig. 2. Schematic diagram of changes in glycine receptors (GlyRs) before and after binding with glycine. *a*: Closed state of GlyR. *b*: Open state of of GlyR. ECD, extracellular domain; TMD, transmembrane domain; Fv, fragment variable.

在分布和发育过程中的变化与α1亚基基本相似，都是在出生后开始增加，但在整个发育阶段，α3亚基的表达较弱。在成熟的中枢神经系统中，α4亚基的表达水平非常低[22, 23]。在中枢神经系统发育过程中，β亚基主要在脊髓、大脑皮层、海马和小脑中表达，这是与α亚基的区域特异性表达的差别之一[24]。β亚基首先需要与突触后支架蛋白结合，才能进行突触锚定，并与α亚基结合后形成有功能的GlyRs [25]。

1.2 GlyRs的功能

1.2.1 参与神经元发育和神经元兴奋

研究显示，α2亚基在神经系统的发育过程中表达水平较高，但随着神经系统的逐渐成熟，其表达水平逐渐下降[23]，提示α2亚基可能在早期大脑发育中发挥着重要的作用。此外，在大脑发育的早期阶段，细胞质内氯离子的浓度高于细胞外，激活GlyRs会导致氯离子的外排，从而引起细胞去极化。这个效应会使细胞膜上的电压门控钙离子通道和NMDARs通道打开，导致细胞内钙离子浓度升高，该过程对神经元的发育至关重要[26, 27]。

尽管GlyRs在脊髓、脑干及大脑皮层等部位广泛分布[28]，但是研究表明，GlyRs在海马体也有较多分布[29]。海马体中的GlyRs主要位于神经元突触外，缓慢调控海马神经元的兴奋性[30]。已有证据表明，外源性给予甘氨酸可以抑制大鼠齿状回的神经元高度兴奋性[31]。除外源性甘氨酸外，海马体中还存在GlyRs内源性配体，包括丙氨酸和牛磺酸。牛磺酸可以通过去除镁离子从而显著抑制癫痫发作[32, 33]，提示GlyRs在海马体中的功能可能与癫痫发作相关。

1.2.2 参与突触传递

在以往大部分的研究中，GlyRs的激活会导致神经元的兴奋性而不是抑制性，但最近研究发现GlyRs也存在于突触前末梢，该部位受体的激活可以改变膜电位、钙水平和递质的释放[34]，从而参与中枢神经系统兴奋性的传递。当GlyRs被激活时，氯离子通道开放，神经元的静息电位升高，细胞膜的阻抗降低，神经元去极化程度增强。因此，对于同一突触，GlyRs激活会导致突触后电位降低，最终实现抑制性突触的传递。这种现象可以用欧姆定律ΔV = IR (V代表电压，I代表电流，R代表电阻)来解释，被称为“分流”效应[28]。此外，先前的研究已经发现甘氨酸和γ-氨基丁酸(γ-aminobutyric acid, GABA)共定位在海马中间神经元，进一步的研究显示GlyRs和γ-氨基丁酸A型受体(γ-aminobutyric acid type A receptors, $GABA_ARs$)之间存在交叉抑

制[33, 35]，即两者之间存在相互依赖性的状态，提示二者可能协同调控突触的传递功能。

2 GlyRs激动剂

GlyRs可被各种内源性配体激活，其包括完全激动剂甘氨酸和部分激动剂，部分激动剂有牛磺酸、β-丙氨酸和GABA等，GlyRs与激动剂结合导致氯离子内流，调节平衡电位，诱导细胞膜超极化，进而抑制神经元的活动[14, 36]。甘氨酸是GlyRs的完全激动剂，可以有效地激活GlyRs，而部分激动剂的作用介于完全激动剂和拮抗剂之间，牛磺酸等部分激动剂的作用与自身浓度、受体的结构和细胞类型等多种因素相关，在低浓度时其能抑制GlyRs的反应，而高浓度时则相反，促进GlyRs的抑制作用，部分激动剂相对于完全激动剂通道开放效率较低[37]。近年来，关于激动剂结合GlyRs过程的研究已经较为成熟，由于GlyRs属于传统的pLGICs结构，pLGICs功能涉及到三种状态的之间的转换，即静息状态、开放状态和脱敏状态，当激动剂与GlyRs结合时，通道从静息状态改变为开放和脱敏状态[16, 38]。目前的研究也开发了其他的激动剂，伊维菌素是一种GlyRs的特殊激动剂，其与甘氨酸没有结构相关性，但仍能特异而有效地激活GlyRs [39]。伊维菌素是与细胞膜附近的特定部位结合，而不是甘氨酸结合的经典位置，因此竞争拮抗剂士的宁不会抑制伊维菌素的激活，而伊维菌素却会减轻小鼠体内士的宁的毒性[40]。

现如今学者们对GlyRs激动剂的研究不仅局限于内源性配体，而且对于外源性激动剂也有发现，常见的外源性物质如麻醉剂和酒精也可以对GlyRs进行调节[41]，同时也有学者称这两种为正向变构调节剂(positive allosteric modulators, PAMs)，在甘氨酸存在的情况下对GlyRs的作用效果更明显[42]。在近几年的疾病研究中，学者发现由于大多数与GlyRs功能障碍相关的病理涉及到GlyRs活性降低，因此PAMs在大多数情况下是可取的，也是值得去深入研究其机理和作用的分子位点。

3 GlyRs与过度惊骇病

过度惊骇病是一种罕见的遗传性非癫痫性疾病。动物研究显示，编码α亚基的基因发生突变会导致小鼠在出生后大约14天左右出现异常的声音惊吓反射。当受到强声或者噪声刺激时，小鼠会表现出僵直、震颤和伸直反射受损的症状[23]。人体中GlyRs α1亚基的基因错义点突变会破坏GlyRs的功能，导致听觉和触觉过度刺激，产生过度的惊吓反应，严重时还可能出现肌肉僵硬的情况[43]。在与过度惊骇病相关的数十种基因错义点突变中，最常见的突变是α1亚基的R271Q或R271L突变[44, 45]。编码β亚基的*GLRB*基因突变也会引发类似的病理反应[46]。正常的抑制性甘氨酸能的突触需要α1和β亚基正确编码的蛋白质。如果蛋白质编码出现问题，就会引发一系列的疾病。细胞表面α1和β亚基蛋白表达的缺失与过度惊骇病有关，显性突变通常会导致这些亚基在细胞膜上过表达，从而降低通道的开放概率、单通道电导或甘氨酸敏感性，损害通道功能[8, 46]，进而导致不可逆的身体损伤。

目前研究显示，大麻中的某些成分可以缓解慢性疼痛、癫痫发作、抑郁和肌肉痉挛，并且在临床上可以用作抗癫痫药物的选择[47]。大麻的主要有效成分为四氢大麻酚(tetrahydrocannabinol, THC)和大麻二酚(cannabidiol, CBD)，其中CBD在治疗癫痫发作方面更有效和安全。GlyRs是大麻素在中枢神经系统中的重要靶点。去羟基大麻二酚(dehydrocannabidiol, DH-CBD)是一种非精神活性的合成大麻素，可以增强脑干突触前α1亚基功能，进而缓解过度惊骇症状[48]。虽然有证据表明DH-CBD对慢性疼痛、癫痫等临床疾病具有很好的治疗作用[49, 50]，但其进一步的临床应用仍需进一步探讨。

4 GlyRs与慢性炎症性疼痛

慢性疼痛是一种普遍存在的病理状态，影响着全世界约20%的人群[51, 52]。慢性炎症性疼痛具有多种表现形式和病理机制，其中脊髓背角的甘氨酸能系统在疼痛中的作用已经被广泛研究[52–54]。研究表明，脊髓背角甘氨酸能神经元能够直接控制疼痛和瘙痒感觉[55]。将疼痛相关介质(如prostaglandin E2，PGE2)外源性应用于脊髓组织也会导致甘氨酸能传递的短期改变[56, 57]。PGE2的受体磷酸化与特定α3亚基的功能抑制有关[55]。PGE2有选择性地抑制GlyRs的功能，这为治疗慢性炎症性疼痛提供了新的理论支持。疼痛感觉的传递通路会通过脊髓背角、脊髓丘脑束和脊髓旁束传递到更高级的中枢神经系统[58]，在脊髓背角中，α1和α3亚基高度表达[59, 60]，这促进了众多学者对脊髓背角α1和α3亚基功能的研究。

甘氨酸在中枢神经系统中的广泛分布使人们对其在疼痛传导中的作用产生了兴趣，使用GlyRs相关的镇痛药治疗神经性疼痛也成为关注焦点[61]。已有研究证明甘氨酸转运蛋白1型和2型(glycine transporter 1/2, GlyT1/2)抑制剂可以调节突触和非突触附近的甘氨酸浓度，从而用于镇痛[62, 63]。尽管GlyRs可以作为治疗慢性炎症性疼痛的新靶点，但目前还没有相关PAMs获得批准[64]。慢性疼痛治疗仍然主要采用传统药物治疗，如阿片类药物、抗抑郁药、抗惊厥药物和非甾体抗炎药。然而，最近的研究明确指出，非精神活性大麻素——DH-CBD可以缓解动物的慢性炎症性疼痛和急性疼痛，为慢性疼痛的治疗提供了新的方法[49]。

5 GlyRs与酒精依赖

酒精被认为是全球疾病负担的重要因素之一，据全球数据报道，酒精使用障碍患者的预期寿命缩短了大约20年[65]。从最初的饮酒到对酒精的依赖是一个长期而复杂的过程，随着饮酒频率的增加，生命因酒精相关原因而终结的风险呈指数级增长[66]。近年来的研究显示，Cys-loop离子通道中的受体与酒精中毒密切相关，包括GlyRs、$GABA_A$受体和其他离子通道受体[67, 68]。Mascia等学者在1988年首次证实了酒精增加鸡脊髓神经元中甘氨酸敏感性的现象[69]。此外，GlyRs还参与乙醇对多巴胺系统的激活作用，可以调节乙醇的摄入[60, 70]。后续研究显示，乙醇反过来也可以调节α1亚基的功能[71]，并证实乙醇的调节功能对α1亚基的第二和第三跨膜结构域的残基起着至关重要的作用[69, 72]。

尽管大多数的研究集中在跨膜结构域上，但GlyRs细胞内结构域也可能作为乙醇在GlyRs中作用的靶点或中介。α1亚基的内细胞环结构域受G蛋白βγ (G protein βγ, Gβγ)异源二聚体调节，GlyRs与Gβγ之间的功能互作对乙醇调控GlyRs的功能至关重要[73]。干扰Gβγ结合的多肽可以阻断乙醇对GlyRs的调控作用，进一步表明乙醇对GlyRs的调控作用需要G蛋白的参与[74]。目前对酒精的药理学研究主要集中在$GABA_A$和GlyRs上，部分原因是这些受体与人类酒精依赖有遗传关联，另一原因是这些离子型受体已经有了较为详细的结构信息[68]。

6 GlyRs与僵人综合征

僵人综合征是一种罕见的疾病，其特征是下肢轴端和近端肌肉的波动性僵硬，肌电图上伴有叠加的疼痛痉挛和持续的运动单位电位[75]。GABA和甘氨酸介导的抑制性突触传递对调节脑干和脊髓运动神经元的兴奋性至关重要，其中甘氨酸能神经传递的损伤可能导致复杂的运动和行为障碍。僵人综合征与GlyRs自身抗体有关，僵人综合征的自身抗原包括细胞内突触囊泡蛋白、gephyrin和GlyR α1亚基[76–78]。目前关于僵人综合征的研究较少，大多数只是个案研究，尽管GlyRs抗体在患有僵人综合征的患者中异常高表达，但GlyRs抗体对僵人综合征的作用机制还未明确[79]。

7 总结与展望

GlyRs与各种神经生理功能如呼吸节律、肌肉张力和运动协调等密切相关[80, 81]。研究已经证实，α1

表1. 神经系统疾病中GlyRs亚基及其他靶点

Table 1. GlyRs subunits and other targets in neurological diseases

Disease	Involved subunits	Effects	Symptoms	Additional targets	References
Hyperekplexia	α1, β	Variants in *GLRA1* and *SLC6A5*	Neonatal hypertonia and an exaggerated startle reflex	GlyT2	[44, 45, 83]
Alcohol use disorders	α1, α2	Increase in circulating pro-inflammatory cytokines (TNF-α and IL-1β)	Craving and addiction	$GABA_B$ receptor	[73, 84–86]
Stiff person syndrome	α1	GAD ↑	Progressive rigidity and muscle spasms	GABA	[87–89]
Chronic inflammatory pain	α3	Interleukin-induced rapid potentiation of GABAergic neurons	Neuropathic and centralized pain/central sensitization	JAK/STAT pathway	[60, 90, 91]

Glutamate decarboxylase (GAD) is the rate-limiting step in the decarboxylation of *L*-glutamate to γ-aminobutyric acid (GABA). TNF-α, tumor necrosis factor; IL-1β, interleukin 1β; *GLRA1*, gene encoding glucagon-like peptide 1 receptor; *SLC6A5*, gene encoding solute carrier family 6; GlyT2, glycine transporter 2.

和β亚基与临床惊厥症密切相关，α1、α2亚基与酒精使用障碍相关，α3亚基与慢性炎症疼痛密切相关(见表1)。这为研发特异性靶向GlyRs各亚基的特异性药物提供了新的方向[82]。尽管GlyRs可能成为多种神经系统疾病的潜在治疗靶点(图3)，但目前的研究多集中在GlyRs调控慢性炎症性疼痛领域，对于其它神经系统疾病的研究较少。值得关注的是，大量研究已经确定增强α3亚基的药物可缓解慢性疼痛，因此开发靶向Gα3亚基镇痛药意义重大。当前，针对GlyRs激动剂、拮抗剂以及双相调节剂的研究呈现增长趋势，这些研究对于理解GlyRs的激活和抑制机制具有重要意义。调节剂的研究也为基于GlyRs亚基的药物和试剂开发提供了创新和特异性的科学基础。

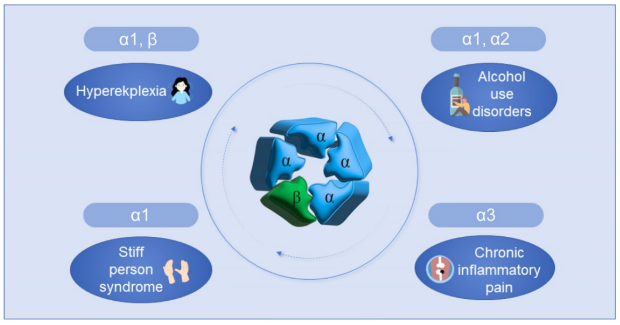

图 3. 甘氨酸受体(GlyRs)各亚基在神经系统相关疾病中的作用

Fig. 3. The role of glycine receptor subunits in neurological disorders. Various subunits of the glycine receptor are implicated in psychiatric disorders. GlyRs α1 subunit has a great influence on various diseases. GlyRs α1, α2 and β subunits are related to hyperekplexia and alcohol use disorder, while GlyRs α3 subunit is related to chronic inflammatory pain.

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