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甘氨酸在心血管疾病中的保护作用 *

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摘要　甘氨酸是一种结构最简单的氨基酸，在动物体内广泛存在，为一碳、蛋白质、多肽、核苷酸类、卟啉类以及胆盐代谢中的关键物质．甘氨酸不仅是中枢神经系统的抑制性神经递质，而且还广泛参与代谢调控、抗氧化、抗凋亡等病理生理学过程．本文就甘氨酸在心肌缺血、高血压和高血糖等引起的心血管疾病中的作用进行综述．

关键词　甘氨酸，甘氨酸受体，高血压，心肌缺血，心血管疾病
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甘氨酸是一种最简单的天然氨基酸，又名氨基乙酸或乙氨酸，是唯一不具有旋光活性的人体非必需氨基酸，在机体内广泛存在，为一碳、蛋白质、多肽、核苷酸类、卟啉类以及胆盐代谢中的关键物质[1]．甘氨酸还是中枢神经系统中重要的抑制性神经递质[2-4]．在非神经组织，甘氨酸通常被认为具有中性的生物学意义，并在补充其他氨基酸的研究中用作氮量控制[5]．作为一种非必需氨基酸，甘氨酸虽能在人体内合成，但含量可能不能完全满足机体的代谢需要[6-7]．长期的甘氨酸缺乏可引起生长发育不良和免疫功能缺陷等健康问题[3, 8-10]．外周的甘氨酸还有抗氧化、抗炎、改善睡眠、细胞保护等作用[11]．而甘氨酸在心血管疾病中的作用则是近年来越来越受到重视的一个新领域．

1　甘氨酸的基本特性

甘氨酸含有一个氨基和一个羧基，在 20 个组成蛋白质的氨基酸中分子质量最小．动物细胞通过膳食蛋白质或者从头合成获得甘氨酸．人类每日大约合成 45 g 内源性甘氨酸，从饮食中吸收 3～5 g 甘氨酸．甘氨酸的合成途径主要包括：丝氨酸合成、胆碱合成、苏氨酸合成和羟脯氨酸合成(图 1)．其在体内的吸收通过一系列转运体，最经典吸收途径为与钠、氢、氯的协同转运．甘氨酸通过甘氨酸降解系统、丝氨酸羟甲基转移酶和由过氧化物酶体 D- 氨基酸氧化酶作用转化成乙醛酸这三个途径降解[2-4]．

在人体内甘氨酸不仅参与构成蛋白质，而且也是很多重要物质如甲硫氨酸、胆碱、一些重要的激素以及脱氧核糖核酸的基本结构．甘氨酸是内源性抗氧化剂还原性谷胱甘肽的组成氨基酸，当机体发生严重应激反应时常靠外源补充，因此有时也称为半必需氨基酸．大多数蛋白质只含有少量甘氨酸，但是在弹性蛋白和胶原蛋白这两种体内主要蛋白质中大约占 1/3．甘氨酸是中枢神经系统介导快速抑制性神经递质的主要元件之一，在脊髓和脑干结合并激活甘氨酸受体(glycine receptor，GlyR)可引起突触后膜超级化．甘氨酸也可以与谷氨酸共激活 N- 甲基 -D- 天冬氨酸型谷氨酸受体(N-methyl-D-

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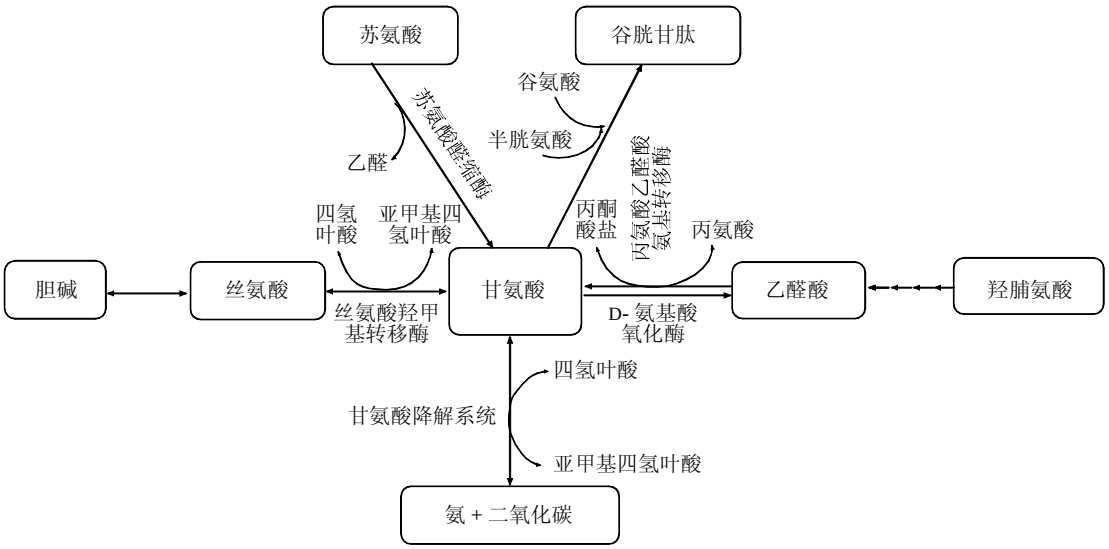

Fig. 1　Glycine synthesis and metabolism
图 1　甘氨酸的合成与代谢

aspartate type glutamate receptor，NMDAR)，成为整个中枢神经系统的兴奋性神经递质[12]．低浓度的甘氨酸优先与 NMDAR 结合发挥兴奋作用，但是高浓度的甘氨酸与 GlyR 结合呈现抑制效应[13]．2 种亚型的甘氨酸转运体(glycine transpoter，GlyT)可以调节突触部分的甘氨酸浓度，从而实现对 GlyR 及 NMDAR 活性的控制．GlyT1 亚型表达于星形胶质细胞的抑制性和兴奋性突触以及谷氨酸能神经元的子集上，GlyT2 的表达主要限于抑制性甘氨酸神经元的突触前末梢[14-15]．最近的研究表明，甘氨酸脱羧酶(glycine decarboxylase，GLDC)缺失，可以引起非酮性高甘氨酸血症(小鼠的血浆平均甘氨酸浓度达到 889 μmol/L，而正常小鼠血浆平均甘氨酸浓度仅为 239 μmol/L)，导致大脑中甘氨酸累积，造成严重的精神发育迟缓[16]．胶质瘤局部缺血区丝氨酸和甘氨酸代谢对肿瘤细胞的存活起关键作用，如果 GLDC 缺失、甘氨酸代谢异常，会生成有毒的氨基丙酮和甲基乙二醛，累积并杀死细胞[17]．研究者正利用 GLDC 依赖性细胞可被阻断 GLDC 活性的药物杀死的特点，寻找潜在的药物．

2　甘氨酸受体

甘氨酸的许多功能系通过激活细胞膜上的 GlyR 实现．GlyR 为一种门控氯离子通道，由不同的亚基(α1～α4 和 β 亚基)组成[18-20]．GlyR 主要分布于哺乳动物的脊髓和脑干[21]，精子、胰腺、肾脏和肝脏等组织细胞也表达 GlyR[19, 22-23]，我们发现大鼠心肌细胞中有 GlyRα2 的表达(未发表数据)．GlyR 既可以是 α 亚基构成的同源性受体，也可以是 α 和 β 亚基组成的异源性受体如 3β/2α 或 2β/3α．α 四种不同的亚型(α1～α4)和一个 β 亚基分别由不同的基因编码．在成熟脊髓和脑干表达的主要是 GlyRα1β 异聚体，而在胎儿 / 新生儿的神经系统同源 GlyRα2 亚基则占主导地位[24]．中枢 GlyR 可选择性通透氯离子，介导快速抑制性突触反应，在中枢神经系统的反射活动、随意运动调节和感觉信号处理中起重要作用．

我们课题组发现，当细胞 ATP 耗竭时，甘氨酸能明显增强细胞活性，拮抗 ATP 耗竭所引起的损伤反应．甘氨酸的这一细胞保护特性系通过细胞膜上的 GlyR 所介导，并且与 GlyR 的氯离子通道功能无关[22]．在此基础上还证明，GlyR 所介导的的细胞保护作用与激活 AKT 和 ERK1/2 信号通路以及抑制 P38 信号通路密切关联[25]．

3　甘氨酸对心血管功能的保护作用

3.1　拮抗心脑缺血性损伤

甘氨酸能够拮抗肝、肾、小肠和骨骼肌的缺血再灌注损伤，在临床上可用于冲洗供体器官，提高肝移植成功率[26]．在开展猪的心脏移植手术时，对

供体进行甘氨酸预处理能明显缓解移植过程长时间缺血引起的缺血性损伤，改善右心功能[27]. 在一项双盲、安慰剂对照的临床试验中，对 200 名急性缺血性中风患者连续 5 天舌下给甘氨酸 0.5、1.0 或 2.0 g/d，每天 1 g 和 2 g 甘氨酸治疗后中风病人临床症状显著改善，30 天死亡率呈下降趋势[28]. 通过大鼠心肌缺血再灌注损伤模型，我们证实甘氨酸通过抑制 p38MAPK 及 JNK/SAPK 磷酸化活性，下调 FasL 的表达从而抑制心肌细胞的凋亡，进而对心缺血再灌注损伤的心肌起到保护作用[29]. 我们还发现，甘氨酸通过抑制 JNK 磷酸化，抑制细胞凋亡，进而明显减轻小鼠脑缺血再灌注损伤，改善神经功能. 并通过离体实验进一步证实，甘氨酸的这一神经保护作用是通过甘氨酸受体途径介导的[30](图 2). 此外，甘氨酸的保护缺血心肌细胞的机制还与抑制线粒体通透性转换[31]、抑制心肌细胞内脂多糖(lipopolysaccharides，LPS)诱导的胞浆钙离子浓度增加和肿瘤坏死因子 α(tumor necrosis factors，TNFα)的合成密切相关[32]. 甘氨酸通过增加细胞内 ATP 和谷胱甘肽含量，改善心肌细胞能量代谢，对大鼠烧伤后的心肌收缩功能具有保护作用[33]. 甘氨酸的上述效应，可能是通过激活心肌细胞上的 GlyR 发挥的[34].

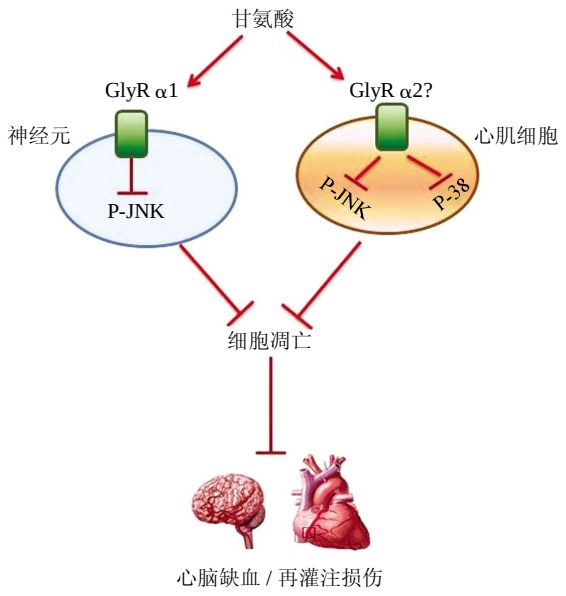

Fig. 2　Protective effect of glycine on cerebral and myocardial ischemia-reperfusion injury

图 2　甘氨酸对心脑缺血再灌注损伤的保护作用

3.2　降血压作用

研究表明，在大鼠迷走神经运动背核注入微量甘氨酸可剂量依赖性地诱导动脉压和心脏速率增加[35]. 动物试验结果提示，妊娠期膳食蛋白质不平衡引起的子代高血压和心血管发育畸形，可以通过出生后在饮食中补充甘氨酸而逆转[36-37]. 大鼠喂养蔗糖诱导糖尿病后，服用甘氨酸可以降低血浆游离脂肪酸和血压水平[38]，其降血压机制可能与抗氧化、增强一氧化氮活性、恢复血管组织谷胱甘肽有关[39]. 大鼠持续饮用含 1%甘氨酸的水 8 周，代谢综合征高血压、高甘油三酯可以缓解[40]. 但是也有研究结果报告，甘氨酸并不能降低慢性硝基左旋精氨酸甲酯(NG-nitro-L-arginine-methlester，L-NAME)诱导的或自发性高血压大鼠的高血压[41].

内皮细胞损伤引起的内皮功能紊乱也是高血压的主要发生机制. 甘氨酸能抑制人内皮细胞 NF-κB 通路活化，减少炎症因子白介素 6 生成，具有抗炎作用[42]. 血管内皮生长因子(vascular endothelial growth factor，VEGF)可迅速增加内皮细胞内钙离子浓度，这一作用能被甘氨酸所钝化，因此甘氨酸还具有抗血管生成的作用[43].

3.3　调节糖、脂代谢作用

在肥胖和胰岛素抵抗患者的血浆中，甘氨酸浓度明显低于正常对照人群[44-45]. 动物实验证实，在给糖尿病大鼠的饮食中补充甘氨酸后，可以明显减少血浆甘油三酯和游离脂肪酸浓度[38, 46]. 如果给严重的Ⅱ型糖尿病患者饮食中补充甘氨酸和半胱氨酸，可以阻止其谷胱甘肽合成的减少[47]. Nguyen 等[48]给老年艾滋病患者口服高剂量的甘氨酸和半胱氨酸，发现也可以通过增加谷胱甘肽合成而提高胰岛素敏感性，显著改善线粒体燃料氧化. 但是，全基因组关联分析数据并不支持甘氨酸代谢相关基因的变异与Ⅱ型糖尿病相关[49]. 在高脂饮食的大鼠，甘氨酸还能通过激活下丘脑外侧区的迷走神经背侧复合体的 NMDA 受体，降低肝源性极低密度脂蛋白分泌[50]. 口服甘氨酸能显著降低酒精性肝损伤大鼠的胆固醇、磷脂、游离脂肪酸和甘油三酯在循环血及肝脏中的蓄积[51]. 甘氨酸能够减轻并延缓Ⅰ型糖尿病大鼠的糖尿病并发症，其机制可能与降低血糖、抗氧化和抑制非酶糖基化过程有关[52-53]. 离体实验表明，甘氨酸与胰岛 α 细胞上的 GlyR 结合后，刺激胰高血糖素释放[54]. 最近的临床研究发现，甘氨酸和葡萄糖清除率成正相关，但是饮食

补甘氨酸是否能有效干预胰岛素抵抗仍待进一步研究[55-56].

4 临床应用的安全性

甘氨酸是一种毒性非常低的化合物，已在临床上用于改善认知功能障碍和痴呆，尤其是作为一种辅助常规抗精神病的药物，用于增强抗精神病药 物治疗精神分裂症等[57-60]. 在上述试验中，口服甘氨酸几天到数周，高剂量给药浓度可高达 0.8 g•kg•d^{-1}，服用者对此浓度耐受，未见不良反应[58]. 根据动物的行为、血浆和尿液的生理指数，Wang 等[1]提出适量补充甘氨酸(例如，对幼猪在饮食中给予高达 2%的甘氨酸补充剂量)是安全的. 然而，过多的甘氨酸摄入以及过高的甘氨酸浓度也可能引起氨基酸失衡和毒性反应. 典型的甘氨酸中毒表现为视力障碍、刺痛、面颈部烧灼感、动脉血压降低、心脏损害以及恶心和呕吐. 例如，静脉注入 1.5 g•kg^{-1}•d^{-1} 甘氨酸 90 min 后幼猪的颅内压和心肌损伤较给予甘露醇对照组明显增加[61]. 在成年大鼠，连续 2 周在饮食中补充甘氨酸 3.2 g•kg^{-1}•d^{-1}，能引起海马和小脑的胶质细胞形态异常改变[62]. 研究发现连续 3 个月给大鼠饮食补充甘氨酸 5 g•kg^{-1}•d^{-1} 后，体重明显减轻[63]. 因此，在膳食中补充甘氨酸仍需把握好剂量问题.

5 展 望

甘氨酸结构虽然简单，但在多个重要的生命过程中不可或缺，其通过抗氧化、抗炎、抗凋亡、增加对缺氧的耐受性等机制在心脑血管疾病的发生中起保护作用. 作为一种氨基酸，它易溶于水，吸收迅速并且不需要耗能运输. 甘氨酸对于细胞的作用与剂量关系密切，合理的剂量选择是甘氨酸对细胞保护作用的必要条件，过高浓度的甘氨酸对于细胞具有毒性作用. 总体而言，甘氨酸是一个温和且有效的细胞保护剂. 适当地补充甘氨酸可能有助于治疗肥胖、糖尿病和心血管疾病，尽管精确的作用和详尽的机制仍有待深入研究.

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Protective Effect of Glycine on Cardiovascular Disease*

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Abstract Glycine is the simplest amino acid in natural, widely exists in animal body, a key material for one carbon, proteins, peptides, nucleotides, porphyrins and bile salt metabolism. Glycine is not only an inhibitory neurotransmitter in the central nervous system, but also widely involved in the regulation of metabolism, antioxidation and anti-apoptosis intissues. The major objective of this article is to provide an overview of recent findings about the protective effects of glycine on cardiovascular disease caused by myocardial ischemia, hypertension and hyperglycemia.

Key words glycine, glycine receptor, hypertention, myocardial ischemia, cardiovascular disease
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