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应激性抑郁样行为发生中海马 5-羟色胺 1A 受体的作用及其对 NMDA 受体和 AMPA 受体的调节*

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摘 要 为探讨慢性不可预见性温和应激(chronic unpredictable mild stress, CUMS)诱发抑郁样行为发生中海马 5-羟色胺 1A 受体(5-hydroxytryptamine receptor 1A, 5-HT1AR)表达与作用, 及其对谷氨酸 N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid, NMDA)受体和 α-氨基羟甲基异恶唑丙酸(α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, AMPA)受体的影响。通过建立 CUMS 动物模型, 给应激抑郁模型大鼠海马微量注射 5-HT1A 受体激动剂、给正常大鼠海马微量注射 5-HT1A 受体拮抗剂, 测量大鼠体重变化率, 并采用糖水偏爱测试、旷场实验和悬尾实验等方法对大鼠进行行为学检测, 运用 Western blot 和 ELISA 方法检测大鼠海马组织中 5-HT1AR 和 NMDAR 和 AMPAR 的关键亚基的表达以及磷酸化水平。结果显示, 与对照组相比, CUMS 组大鼠表现出抑郁样行为, 海马 5-HT1AR、AMPA 受体的 GluR2/3 亚基表达及磷酸化明显降低, NMDA 受体的 NR1 和 NR2B 亚基表达及磷酸化显著增加; 正常大鼠海马微量注射 5-HT1A 受体拮抗剂 WAY100635, 动物行为学表现及 AMPA 受体、NMDA 受体表达及磷酸化水平均与 CUMS 组相同; 注射 5-HT1A 受体激动剂 8-OH-DPAT 能逆转应激诱导的上述改变。以上结果表明, CUMS 诱发抑郁样行为与海马 5-HT1AR 表达下降, AMPAR 表达量及磷酸化水平降低, NMDAR 表达量及磷酸化水平升高有关。5-HT 通过 5-HT1AR 产生抗抑郁作用。5-HT1AR 激动剂抗抑郁作用与降低 NMDAR 表达量及磷酸化水平, 提高 AMPAR 表达量及磷酸化水平密切相关。

关键词 慢性不可预见性温和应激; 抑郁症; 海马; 5-HT1A 受体; NMDA 受体; AMPA 受体

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随着抑郁症发病率的上升, 有关抑郁发生机制与预防策略的研究越来越受到重视。研究认为, 应激事件是诱发抑郁症的重要原因, 而对其发生机制先后提出了单胺类递质失调假说(Stockmeier, 1997), 神经可塑性变化学说等(Anisman & Matheson, 2005)。近些年来, 谷氨酸及其受体与抑郁发生的关系的研究也比较广泛(Berman et al., 2000)。已有的研究显示, 单胺类递质失调可能是抑郁发生的基本问题, 而谷氨酸及其受体失调可能是一个重要原因。因此, 研究应激性抑郁发生中单胺类递质与谷氨酸递质之间的关系, 对于揭示抑郁发生机制具有重要意义。

目前, 国内外研究抑郁症发病机制和抗抑郁药物药理学主要采用慢性不可预见性温和应激(chronic unpredictable mild stress, CUMS)抑郁模型。CUMS 模型因能模拟出与人类抑郁症患者相似的行为学变化而成为有效的啮齿目动物抑郁模型 (Willner, Towell, Sampson, Sophokleous, & Muscat, 1987)。海马是抑郁症研究中涉及最多的脑区, 海马内谷氨酸能神经元分布多, 并接受 5-羟色胺(5-hydroxytryptamine, 5-HT)能神经纤维投射。海马发出的神经纤维可投射到额叶皮质、杏仁核等与情感有关的脑区。它不仅是应激反应的重要调节中枢, 更是受应激累及的最敏感区域, 与应激性抑郁症的发生密切相关(Sapolsky, 1996)。

5-羟色胺能神经功能低下是构成抑郁症的病理生理基础之一, 临床许多抗抑郁药物也是基于改

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善 5-HT 水平而研发和使用。5-羟色胺受体(5-hydroxytryptamine receptor, 5-HTR)在抑郁症的病因和抗抑郁药的药理机制中也有着重要作用。人类至少存在 7 种 5-HTR, 即: 5-HT1R、5-HT2R、5-HT3R、5-HT4R、5-HT5R、5-HT6R、5-HT7R, 且大部分已被克隆, 7 种类型又可分为若干亚型(刘效巍, 许晶, 2002)。目前, 普遍认为 5-羟色胺 1A 受体(5-hydroxytryptamine receptor 1A, 5-HT1AR)是与抑郁症关系最密切的受体之一, 在抑郁发生中海马中 5-HT1A 受体的表达变化还有争议(康汇婷, 王朝伟, 2010; López-Figueroa et al., 2004; 俞瑾 等, 2005)。此外, 单胺类递质失调假说不能完全解释抑郁症的发病机理(Budziszewska, Jaworska-Feil, Kajta, & Lasoń, 2000; 张凌, 毛玉婷, 2005; 张华, 2005), 而近几年的研究发现, 应激性抑郁发生与海马谷氨酸水平升高, N-甲基-D-天冬氨酸(N-methyl-D-aspartic acid, NMDA)受体过度激活有着密切的关系。NMDA 受体拮抗剂具有显著的抗抑郁效应(Berman et al., 2000)。也有研究发现 NMDA 受体和 α-氨基羟甲基异恶唑丙酸(α- amino-3-hydroxy-5-methylisoxazole-4-propionic acid, AMPA)受体均参与了应激性抑郁的发生, 二者相互作用, 且作用可能不同(Berman et al., 2000; Legutko, Li, & Skolnick, 2001)。由此可见, 应激性抑郁发生与 5-HT 及 5-HT1A 受体和谷氨酸及其 NMDA 和 AMPA 受体变化有着一定的关系, 但在应激性抑郁发生中海马 5-HT1A 受体和谷氨酸及其 NMDA 和 AMPA 受体之间是否有关及其具体作用与关系目前还不清楚。因此, 本实验在建立慢性不可预见性应激抑郁大鼠模型的基础上, 通过海马分别微量注射 5-HT1A 受体激动剂 8-OH-DPAT、拮抗剂 WAY100635 后, 测量体重变化率并采用糖水偏爱测试、敞箱实验及悬尾等方法观察动物行为变化, 运用 western blot 和 ELISA 方法检测海马 CA1 区内 5-HT1AR 表达、NMDA 受体和 AMPA 受体的表达及磷酸化, 探讨 5-HT1AR 对 NMDA 受体和 AMPA 受体的影响。

1　材料和方法

1.1　实验动物及分组

健康雄性 Sprague-Dawley 大鼠 40 只(250~300 g), 由陕西省中医研究院实验动物中心提供。实验前饲养一周以适应环境, 自由进食饮水。按照应激和药物处置因素将动物随机分为 4 组, 每组 10 只：对照/生理盐水组(CON/SAL 组); 慢性不可预见性温和应激/生理盐水组(CUMS/SAL 组); 慢性不可预见性温和应激/5-HT1AR 激动剂组(CUMS/8-OH- DPAT 组);对照/5-HT1AR 拮抗剂组(CON/ WAY100635 组)。

1.2　实验材料

Anti-5-HT1A, Anti-NMDA (NR1), Anti-NMDA (NR2B), Anti-AMPA (Glu2/3)均购于美国密理博公司, 内参 GAPDH 购于北京中衫金桥生物技术有限公司。NMDA 和 AMPA 受体磷酸化 ELISA 试剂盒购于美国 R&D 公司。5-HT1A 受体激动剂 8-OH-DPAT 为美国 sigma-Aldrich 公司产品, 拮抗剂 WAY100635 也为 Sigma 公司产品。脑立体定位仪(51600)为美国 Stoelting 公司产品。微量注射器(1 μL)为上海安亭微量进样器厂产品。

1.3　方法

1.3.1　脑立体定位及海马微量注射　大鼠实验前自由饮水, 禁食 18~24 h 后手术。以 2%戊巴比妥纳 40mg/kg 腹腔注射麻醉, 将大鼠固定于立体定位仪, 参照大鼠脑立体定位图谱(Paxins & Watson, 1998), 向大鼠单侧海马处(AP 4.8 mm, RL 2.4 mm, H 1.2 mm)植入一直径 0.9 mm, 长度 1.4cm 带有内芯的不锈钢套管, 用牙科磷酸水门汀固定。术后动物自由进食饮水, 且前 3 天每天腹腔给予青霉素 2 万单位, 一周后进行相关实验。CON/SAL 组: 正常饲养, 每周海马微量注射生理盐水 1 μL; CUMS/SAL 组: 在 CUMS 处理的同时每周海马微量注射生理盐水 1μL; CUMS/8-OH-DPAT 组: CUMS 处理, 且每周海马微量注射 8-OH-DPAT (10nmol) 1μL (Joca, Padovan, & Guimarães, 2003); CON/WAY100635 组: 正常饲养, 每周海马微量注射 WAY100635 (30nmol) 1μL (Joca et al., 2003)。在实验的第 1、7、14、21 天海马微量注射药物(董素平, 徐畅, 原婷婷, 安书成, 2011), 药品均用生理盐水配置, 采用微量注射器(1 μL)匀速给药, 1 min 内注完, 停针 1 min 防止药物外溢。然后, 将套管内芯插入套管内。4 组均进行行为学测试, 并且用 western blot 方法检测海马内 5-HT1AR、NMDA 受体和 AMPA 受体的表达, 用 ELISA 方法检测 NMDA 受体和 AMPA 受体的磷酸化。

1.3.2　CUMS 模型的建立　模型建立方法参见董素平等(2011)。大鼠单笼饲养, 采用鼠笼倾斜 24 h、明暗颠倒 24 h、4℃冰水游泳 5 min、45℃热水游泳 5 min、禁水 24 h、禁食 24 h、夹尾 1 min、水平摇晃 5 min、潮湿垫料 24 h 共九种刺激方法, 随机安排到 21 日内, 每日一种, 每种刺激至少出现 2 次, 同种刺激不能连续出现, 使动物不能预料刺激的发

生。CON/SAL 组、CON/WAY100635 组不予任何刺激, 正常进食饮水。各组分别在第 1、7、14、21 天称量动物体重, 应激建模 21 天后, 第 22 天进行糖水测试和旷场实验, 第 23 天进行悬尾实验进行行为学观察。

1.4 体重测量

分别在实验的第 1、7、14 和 21 天微量注射药物及应激前称量动物的体重。动物体重变化率 = (第 1、7、14、21 天的体重 − 第 1 天的体重) / 第 1 天的体重 × 100%。

1.5 行为学观察

1.5.1 糖水偏好测试 实验前在隔噪音、安静的房间内训练动物适应含糖饮水, 每笼同时放置 2 个水瓶, 第一个 24 h, 两瓶均装有 1%蔗糖水, 随后的 24h, 一瓶装有 1%蔗糖水, 一瓶装纯净水, 24 h 的禁食禁水后, 进行动物的糖水消耗实验, 同时给予每只大鼠预先定量好的一瓶 1%蔗糖水, 一瓶纯净水, 24 h 后测量糖水消耗量, 并计算动物的糖水偏爱率[糖水偏爱率= 糖水消耗 / 总液体消耗 × 100%] (董素平 等, 2011)。

1.5.2 旷场实验 实验装置为 100 cm × 100 cm × 40cm, 四周底面全部涂黑的无盖木制方箱。将方箱置于 Video Mot2 黑白多目标动物行为监测分析系统的摄像头下, 镜头对准箱底中央, 用系统将方箱地面内侧面积均分为 25 个方格。安静环境下, 将动物小心放在箱底中心, 观察 5 min 内活动情况。观察指标(1)水平穿行方格数：身体重心进入邻格; (2)竖直站立次数：前肢离开水平地面 1 cm 以上的次数; (3)修饰次数：理毛或者洗脸的次数, 分别计算水平运动得分、垂直运动得分和修饰得分。每次做完实验后清理箱内残留物, 清除上一只大鼠的气味, 以免影响下一只大鼠的行为(董素平 等, 2011)。

1.5.3 悬尾实验 在 Video Mot2 黑白多目标动物行为监测分析系统下进行悬尾实验(tail suspension test, TST)。实验装置由悬尾箱和 TST 软件分析系统组成。实验在安静环境下进行, 将大鼠头部向下, 尾根部 1/3 处固定在大鼠悬尾架上 5 min, 采用 Tail suspension monitor (德国 TSE 公司)记录其不动时间。做完每一只后将箱内残留物及气味清理干净, 以免影响下一只大鼠的行为。

1.6 Western blot 实验

各组大鼠于行为测试实验结束后 24 h 内断头处死, 取双侧海马组织并将其纵切分为二份, 一份用于制备细胞总蛋白, 另一份于−80℃冰箱备用。按 BCA 法测定的各组蛋白总量确定上样量, 样品经 10% SDS-PAGE 胶分离后, 经 4 ℃、18 V 恒压 1h 20min 转移至 PVDF 膜上; 5%脱脂奶粉室温封闭 1 h; 在一抗溶液中 4 ℃孵育过夜, 漂洗后在 HRP 标记的羊抗兔二抗溶液中室温孵育 1 h, β-actin 作内参。ECL 检测显带, X 光胶片曝光、冲洗, 采用英国 Syngene 公司的 G:BOX 凝胶成像系统测定其感光密度。设正常对照组受测蛋白条带与内参的光密度比值为 100%, 换算同一膜上其它组受测蛋白条带与内参的光密度比值进行比较。

1.7 ELISA 检测

将备用的另一份组织称重, 制成 10%脑组织匀浆, 离心, 取上清, 置−80℃冰箱备用。按 ELISA 试剂盒说明书进行操作, 最后在 450nm 波长测定吸光度(OD 值), 计算样品浓度。

1.8 数据处理

采用 SPSS 16.0 软件处理数据, 数据以平均值 ± 标准误(Mean ± SEM)表示, 组间差异采用单因素方差分析(one-way ANOVA), 组间多重比较行 LSD 检验; 体重变化率的比较采用重复测量方差分析检验; $p<0.05$ 表示在统计学上有显著性差异, $p<0.01$ 表示有极显著性差异, $p>0.05$ 表示无显著性差异。

2 结果

2.1 体重测量结果

各组大鼠体重增长率总体比较有显著差异, $F(3,23) = 25.715$, $p<0.01$。在 21 天内, CON/SAL 组(n=6)大鼠体重呈明显的上升趋势; CUMS/SAL 组(n=6)大鼠体重虽也有所增长, 但增长趋势相对 CON/SAL 组缓慢, 差异极其显著($p<0.01$); 与 CUMS/SAL 组相比, CUMS/8-OH-DPAT 组(n=6)体重增长率均极明显升高($p<0.01$); 与 CON/SAL 组相比, CON/WAY100635 组(n=6)体重增长率低且差异极其显著($p<0.01$)。如图 1。

2.2 行为学测试结果

2.2.1 糖水偏好实验 各组大鼠对糖水的偏爱程度在第 1 天实验前并无统计学差异。经历 21 天给药和应激后, 各组大鼠对糖水偏爱程度有显著性差异, $F(3,29) = 16.472$, $p<0.01$。与 CON/SAL 组相比, CUMS/SAL 组大鼠对糖水的偏爱率极显著降低($p<0.01$); 与 CUMS/SAL 组相比, CUMS/8-OH-DPAT 组糖水偏好率极显著提高($p<0.01$); 与 CON/SAL 组相比, CON/WAY100635 组糖水偏好率极显著降低($p<0.01$)。如图 2。

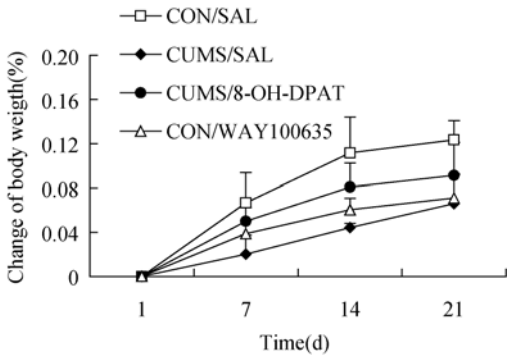

图 1　各组大鼠体重变化

Fig. 1.　Effects of different treatments on body weight change. Rats were weighed on the 1st, 7th, 14th, and 21st days of the experiment. The body weight change was calculated as changes in body weight(%) = (body weight on day1, 7, day 14, or day 21- body weight on day 1) /body weight on day 1. Mean ± SEM, *n*=6.

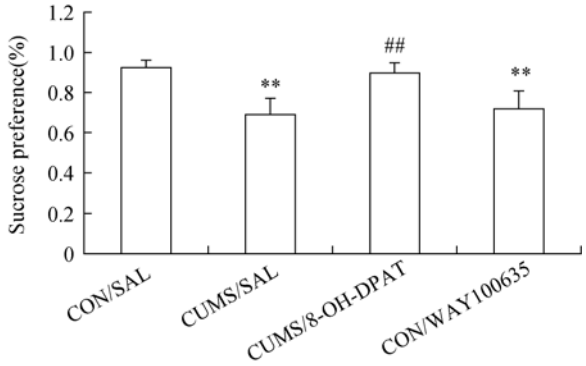

图 2　各组大鼠糖水偏好率

Fig. 2.　Effects of different treatments on sucrose preference. Mean ± SEM, *n*=7~8. **p*<0.05, ***p*<0.01 vs CON/SAL; ##*p*< 0.01 vs CUMS/SAL.

2.2.2　旷场实验　各组大鼠在旷场实验中的行为表现总体比较呈显著性差异(水平运动得分：$F(3,29)=5.411$, $p<0.01$; 垂直运动得分：$F(3,29)=20.511$, $p<0.01$; 自我修饰得分：$F(3,29)=8.119$, $p<0.01$)。经历了 21 天慢性不可预见性温和应激和/或微注射给药后, 与 CON/SAL 组相比, CUMS/SAL 组大鼠在旷场实验中各项运动得分均极显著降低($p<0.01$); 与 CUMS/SAL 组相比, CUMS/8-OH-DPAT 组大鼠水平运动得分有显著性提高($p<0.05$), 垂直运动和自我修饰运动有极显著提高($p<0.01$); 与 CON/SAL 组相比, CON/WAY100635 组在水平运动中得分有显著性降低($p<0.05$), 垂直运动和自我修饰运动中得分极显著降低($p<0.01$)。如图 3。

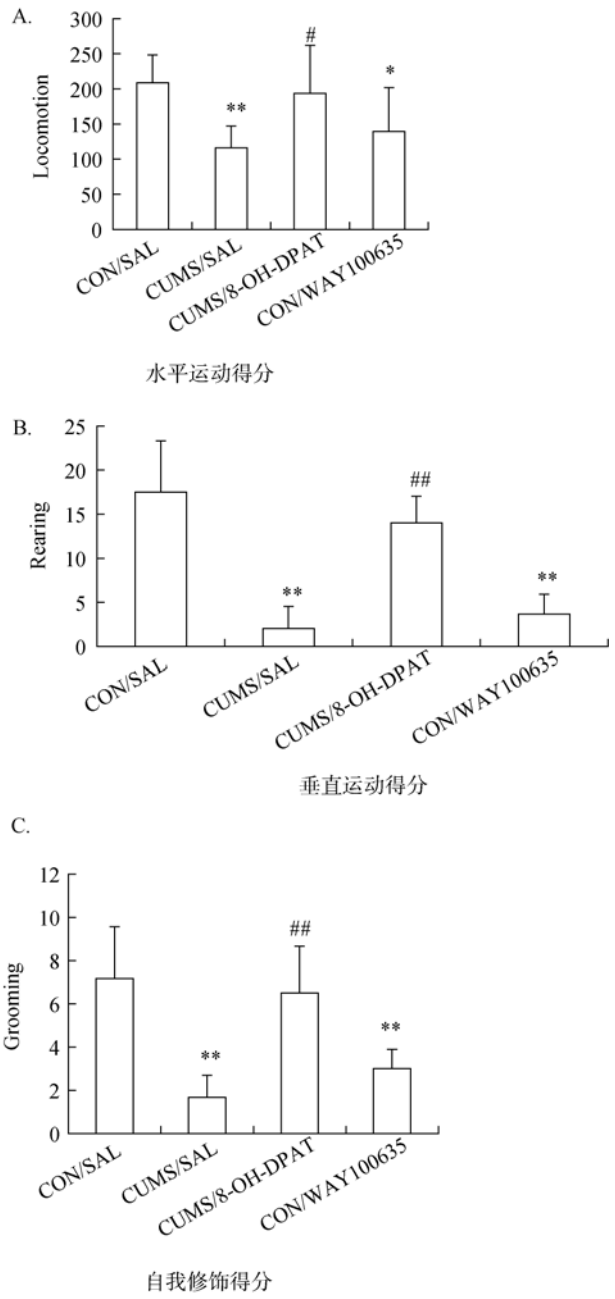

图 3　各组大鼠在旷场实验中的行为表现

Fig. 3.　Effects of different treatments on locomotion (A), rearing (B) and grooming (C) in the open field. Mean ± SEM, *n*=7~8. **p*<0.05,***p*<0.01vs CON/SAL; # *p*<0.05, ## *p*<0.01 vs CUMS/SAL.

2.2.3　悬尾实验　各组大鼠悬尾不动时间总体比较有显著性差异, $F(3,29)=7.317$, $p<0.01$。与 CON/SAL 组相比, CUMS/SAL 组大鼠悬尾不动的时间极显著增加($p<0.01$); 与 CUMS/SAL 组相比, CUMS/8-OH-DPAT 组悬尾不动时间极显著缩短($p<0.01$); 与 CON/SAL 组相比, CON/WAY100635 组大鼠悬尾不动时间极显著增加($p<0.01$)。如图 4。

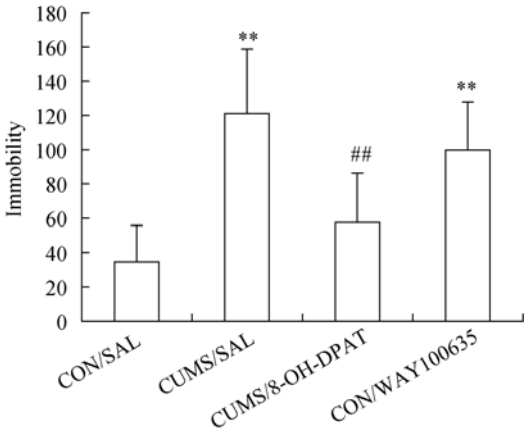

图 4 各组大鼠在悬尾实验中悬尾不动时间

Fig. 4. Effects of different treatments on immobility time in the tail suspension test. Mean±SEM. CON/SAL: *n*=7; CUMS/SAL: *n*=8; CUMS/8-OH-DPAT: *n*=7; CON/WAY100635: *n*=8. * $p<0.05$, ** $p<0.01$vs CON/SAL; ## $p<0.01$ vs CUMS/SAL.

2.2.4 Western blot 实验结果 CON/SAL 和 CUMS/SAL 组大鼠海马 5-HT1AR 表达量差异显著, $F(1,11)=7.285$。与 CON/SAL 相比, CUMS/SAL 组大鼠海马 5-HT1AR 表达量极显著下降($p<0.01$) (图 5)。CON/SAL 组、CUMS/SAL 组、CUMS/8-OH-DPAT 组和 CON/WAY100635 组大鼠海马 AMPA 受体 GluR2/3 亚基表达量差异显著, ($F(3,26)= 12.283$, $p<0.01$)。与 CON/SAL 组相比, CUMS/SAL 组大鼠海马 AMPA 受体 GluR2/3 表达量显著下降($p<0.05$); CON/WAY100635 组极显著下降 ($p<0.01$); 与 CUMS/SAL 组相比, CUMS/8-OH- DPAT 组大鼠海马 AMPA 受体 GluR2/3 表达量显著升高($p< 0.05$) (图 6)。各组大鼠海马 NMDA 受体 NR1 和 NR2B 表达量差异明显(NR1: $F(3,24)= 5.595$, $p < 0.01$; NR2B: $F(3,25)= 7.291$, $p < 0.01$)。与 CON/ SAL 组相比, CUMS/SAL 组大鼠海马 NMDA 受体 NR1 表达量显著升高($p<0.05$), NR2B 表达量极显著升高($p< 0.01$); CON/WAY100635 组大鼠海马 NMDA 受体 NR1 表达量较 CON/SAL 组显著升高 ($p<0.05$), NR2B 表达量 CON/SAL 组极显著升高($p< 0.01$); 与 CUMS/SAL 组相比, CUMS/8-OH-DPAT 组的大鼠海马 NMDA 受体 NR1 和 NR2B 表达量显著降低 ($p< 0.05$) (图 6)。

2.2.5 ELISA 实验结果 CON/SAL 组、CUMS/SAL 组、CUMS/8-OH-DPAT 组和 CON/WAY100635 组大鼠海马 AMPA 受体磷酸化水平差异显著, $F(3,31)= 48.286$, $p< 0.01$。与 CON/SAL 组相比, CUMS/SAL 组和 CON/WAY100635 组大鼠海马 AMPA 受体磷酸化水平极显著下降($p<0.01$); 与 CUMS/SAL 组相比, CUMS/8-OH-DPAT 组的大鼠海马 AMPA 受体磷酸化水平极显著升高($p < 0.01$) (图 7)。各组大鼠海马 NMDA 受体磷酸化水平差异极明显, $F(3,31)= 57.899$, $p< 0.01$。与 CON/SAL 组相比, CUMS/SAL 组和 CON/WAY100635 组大鼠海马 NMDA 受体磷酸化水平极显著升高($p<0.01$); 与 CUMS/SAL 组相比, CUMS/8-OH-DPAT 组的大鼠海马 NMDA 受体磷酸化水平极显著降低($p< 0.01$) (图 7)。

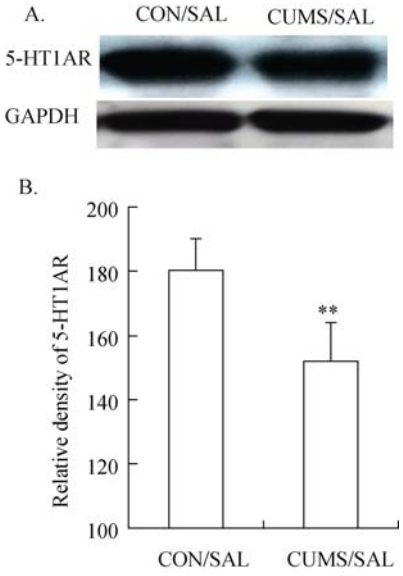

图 5 CON/SAL 组和 CUMS/SAL 大鼠海马 5-HT1A 受体的表达

Fig. 5. 5-HT1A R expressions in hippocampus in rats of CON/SAL and CUMS/SAL groups detected by Western blot. A: Bands of 5-HT1A R proteins in hippocampus. B: Comparison of the levels of 5-HT1AR expressions in hippocampus among different groups. Means ± SEM. *n*=6. * $p<0.05$,** $p<0.01$vs CON/SAL; # $p<0.05$, ## $p< 0.01$vs CUMS/SAL.

3 讨论

CUMS 动物模型因能模拟出与人类抑郁相似的核心症状(Matthews, Forbes, & Reid, 1995)而倍受青睐, 被广泛的用于抑郁发生机制及抗抑郁药物研究。

海马是调节情绪的重要脑区, 也是应激损伤的主要易感部位。应激导致海马 5-HT、Glu 等多种神经递质及受体失调(Drevets et al., 2007; Luo, An, &Zhang, 2008; 董素平 等, 2011), 慢性应激也可引

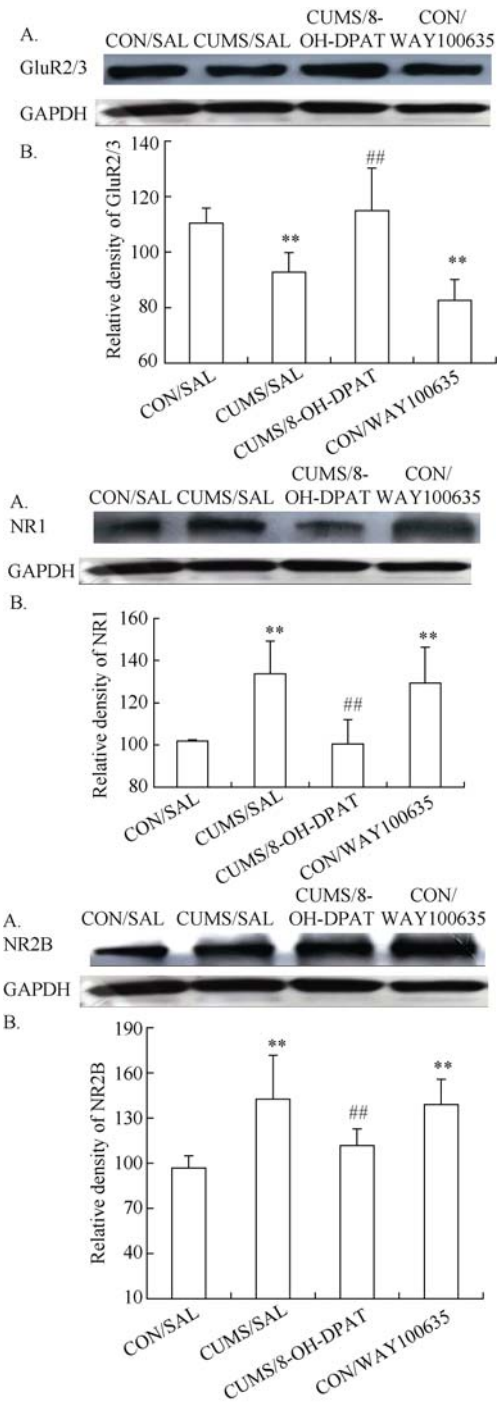

图 6　各组大鼠海马 AMPA 受体 GluR2/3 亚基及 NMDA 受体 NR1 和 NR2B 亚基的表达

Fig. 6.　AMPAR (GluR2/3) and NMDAR (NR1 and NR2B) expressions in hippocampus in rats of CON/SAL、CUMS/SAL、CUMS/8-OH-DPAT and CON/WAY100635 groups detected by Western blot. A: Bands of AMPAR (GluR2/3) and NMDAR (NR1 and NR2B) proteins in hippocampus. B: Comparison of the levels of AMPAR (GluR2/3) and NMDAR (NR1 and NR2B) expressions in hippocampus among different groups. Means ± SEM. n=6~7. *p<0.05,**p<0.01vs CON/SAL; # p<0.05, ## p<0.01 vs CUMS/SAL.

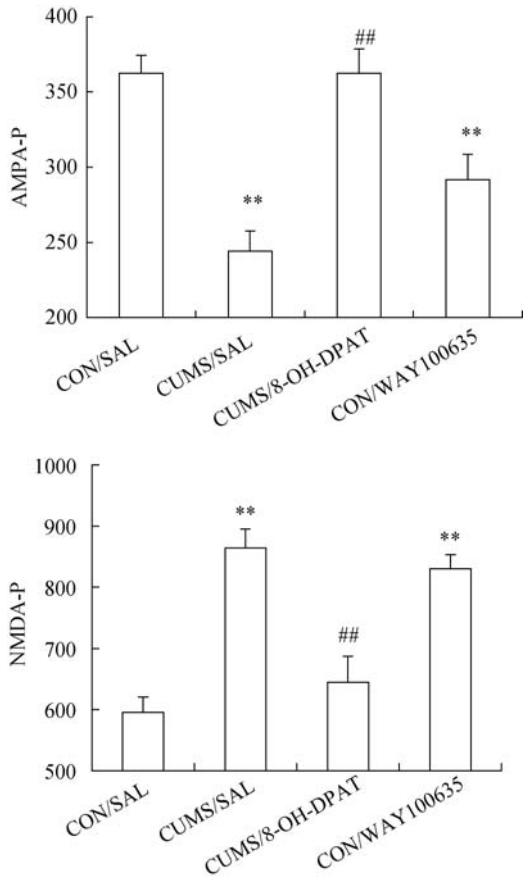

图 7　各组大鼠海马 AMPA 受体磷酸化及 NMDA 受体磷酸化水平

Fig. 7.　AMPAR P levels and NMDAR P levels in hippocampus in rats of CON/SAL、CUMS/SAL、CUMS/8-OH-DPAT and CON/WAY100635 groups detected by ELISA. Means ± SEM. n=7~9. *p<0.05,**p<0.01vs CON/SAL; # p<0.05, ## p<0.01 vs CUMS/SAL.

起海马损伤, 使其结构和功能变化(Nacher, Pham, Gil-Fernandez, & McEwen, 2004; Jayatissa, Bisgaard, West, & Wiborg, 2008)。有研究表明, 慢性应激可导致海马 CA3 区锥体细胞顶树突分支及树突棘数量减少, 抑制海马齿状回颗粒细胞再生(Duman, Malberg, & Thome, 1999; Carozzi et al., 2009; McLaughlin, Gomez, Baran, & Conrad, 2007)。抑郁症患者海马神经元损伤、萎缩、体积减小(McEwen, 1999)。总之, 应激引起海马结构与功能变化是抑郁发生的重要原因。

5-羟色胺作为一种重要的神经递质,与多种情绪行为表现有关。如, 酒精依赖、自杀、攻击性、焦虑症、情绪障碍等(Bleich et al., 2007)。有关 5-HT 与抑郁症发生的研究比较多, 体内色氨酸耗竭的实验表明血浆色氨酸减少导致脑内 5-HT 合成减少

(Leyton et al., 2006), 脑内 5-HT 神经传递减弱(Benkelfat, Ellenbogen, Dean, Palmour, & Young, 1994), 从而导致抑郁。躁郁大鼠海马 5-HT 含量显著降低, 5-HT3B 受体蛋白表达和 mRNA 表达水平显著升高, 通过药物下调海马过高的 5-HT3B 受体表达和 mRNA 水平, 上调 5-HT 含量可达到治疗的目的(李红华, 薛玲, 2011)。慢性应激会引起海马 5-HT 水平下降, 5-HT1A 受体下调等, 造成 5-HT 系统功能低下(Drevets et al., 2007)。海马注射 5-HT 可以抗慢性应激引起的抑郁样行为(Luo et al., 2008)。抑郁患者死后尸检也发现 5-HT 神经元、神经末梢缺失, 5-HT 浓度降低。抗抑郁药能增加突触内 5-HT 水平, 并影响 5-HT 受体密度。5-HT 受体种类较多, 然而目前普遍认为 5-HT1A 受体是与抑郁症关系最密切的受体之一。5-HT1A 受体属 G 蛋白偶联受体, 主要分布于额叶皮层、海马、外侧隔、中缝背核等部位(Lesch & Gutknecht, 2004; Sharp, Boothman, Raley, & Quérée, 2007)。5-HT1A 受体在脑内除作为突触后受体广泛分布于海马、皮层、连接皮层与海马的中间神经元、杏仁核和下丘脑外(Celada, Puig, Amargós-Bosch, Adell, & Artigas, 2004; Sharp et al., 2007), 也是中缝核神经元最重要的胞体自身受体(Verge et al., 1985)。5-HT1A 受体信号转导是通过第二信使环腺苷酸单磷酸酯(cAMP)的生成, 激活 K^+通道, 形成抑制性突触后电位而启动细胞效应(Müller, Carey, & De Souza Silva, 2007)。尽管有关抑郁发生中 5-HT1A 受体变化的报道不完全一致, 但多数学者的研究则显示抑郁患者 5-HT 水平及 5-HT1A 受体表达下降, 仅有俞瑾等(2005)的研究观察到抑郁症患者中海马 5-HT1A 受体的 mRNA 表达却显著增加。已有的研究发现, 在抑郁症患者中海马 5-HT1A 受体的结合力下降(康汇婷, 王朝伟, 2010), 5-HT1A 受体的 mRNA 表达显著减少(López- Figueroa et al., 2004)。电生理学研究表明抗抑郁药可增加海马 5-HT 1AR 的敏感化从而增进 5-HT 信号传递而达到一定的抗抑郁效应(Corradetti, Le Poul, Laaris, Hamon, & Lanfumey, 1996; Fornal et al., 1996)。5-HT1A 受体激动剂能显著降低慢性应激所致的大鼠抑郁程度, 该作用能够被 5-HT1A 受体拮抗剂阻断(Muñoz & Papp, 1999; 周建松 等, 2008)。锂、丙戊酸钠、选择性血清素再摄取抑制剂(SSRIs)、三环抗抑郁药(TCAs)及其它如电休克治疗(ECT)等, 均是通过直接或间接方式增加突触后 5-HT1A 受体信号调节途径发挥抗抑郁作用(Savitz, Lucki, & Drevets, 2009)。本实验结果发现 CUMS 组大鼠在表现抑郁样行为的同时, 海马 5-HT1A 受体的表达下降。海马微量注射 5-HT1A 受体拮抗剂 WAY100635 均可引起大鼠的抑郁样行为, 而在 CUMS 的同时微量给予 5-HT1A 受体激动剂 8-OH-DPAT 则可以明显改善应激引发的抑郁样行为。这一实验结果也充分说明应激引起抑郁发生与海马 5-HT 1A 受体减少密切相关。

谷氨酸及其受体失调是抑郁发生的一个重要原因。NMDA 受体在抑郁症的主要病理生理及抗抑郁药治疗中具有重要作用。应激能引起海马 Glu 水平升高, 通过 NMDA 受体过度激活而导致抑郁(董素平 等, 2011)。慢性应激能引发抑郁样行为表现, 而在应激的同时微量给予 NMDA 受体拮抗剂 MK-801, 可明显的缓解应激诱发的抑郁行为(李庆娇, 安书成, 2009)。脑出血后抑郁大鼠海马 NR1 和 NR2B 的表达量也显著升高(赵瑞珍, 唐启盛, 徐向青, 侯秀娟, 解华, 2008)。NR1 亚基是 NMDA 受体组成的必不可少的亚基(Wang, Da′Vila-Garcia, Yarl, & Gondre-Lewis, 2011)。NR1 缺陷小鼠表现出严重的情感淡漠(Fang et al., 2011), 其表达量变化会影响到 NMDA 受体的整体功能。但 NR1 与 NR2A 共同存在时才能被酪氨酸激酶磷酸化而提高其活性(Fang et al., 2011)。应激性抑郁发生与抗抑郁治疗通过调节谷氨酸受体亚基而影响树突棘(Ampuero et al., 2010)。因此, 抑郁症与 NMDA 受体关系密切, NMDA 受体数量、结构和磷酸化水平的改变均会影响中枢神经系统的功能。

AMPA 受体激动剂能减少啮齿类动物强迫游泳实验中的不动时间, 表现出和丙米嗪相同的抗抑郁效果, 且能增加脑源性神经营养因子(brain-derived neurotrophic factor, BDNF) mRNA 的表达(Legutko et al., 2001)。AMPA 受体拮抗剂 NBQX 可以有效阻止氯胺酮(ketamine)的抗抑郁效果, 推测 AMPA 受体的激活可能在氯胺酮引发的抗抑郁样行为中起重要的作用(Koike, Iijima, & Chaki, 2011)。且有研究表明, 长期的抗抑郁药治疗可增加 AMPA 受体在大鼠海马的表达, 如长期给予氟西汀, 可增加大脑皮质、海马和纹状体 AMPA 受体的丝氨酸 831-GluR1 和丝氨酸 845-GluR1 的磷酸化(Svenningsson et al., 2002), 进而起到促进其突触传递功能的作用。GluR2/3 是 AMPA 受体的重要亚基, 在 AMPA 受体介导的信号传递及其该受体的生物

物理特性中具有重要的作用(Wang et al., 2011)。我们的实验结果显示, CUMS 组大鼠在表现抑郁样行为的同时, 海马 NMDA 受体的 NR1 和 NR2B 亚基表达及 NMDA 受体磷酸化水平升高, AMPA 受体的 GluR2/3 亚基的表达及 AMPA 受体磷酸化水平降低。以上结果表明, 应激能引起海马 NMDA 受体和 AMPA 受体结构与功能变化与抑郁发生是相关的。

单胺类递质、受体与谷氨酸及受体在情绪行为调节中有着密切的关系(Hashimoto, 2011)。5-HT1AR 的拮抗剂 WAY100635 能减弱 NMDA 受体拮抗剂 MK801 的效应(Wedzony et al., 2000)。NMDA 受体的 NR1 亚基参与 5-HT1AR 激活对沙鼠海马的缺血性细胞损伤的神经保护作用(Salazar-Colocho, Del Río, & Frechilla, 2008)。NMDA 受体拮抗剂 MK-801 增加鼠脑中 5-HT1AR 的数量(Wedzony, Maćkowiak, Czyrak, Fijał, & Michalska, 1997)。刺激 5-HT1AR 选择性地抑制大鼠视皮层 NMDA 受体介导的突触兴奋(Edagawa, Saito, & Abe, 1999)。5-HT1AR 的拮抗剂 WAY100635 防止阻断海马 NMDA 受体引起的空间学习障碍(Carli, Silva, Balducci, & Samanin, 1999)。学习增加海马 AMPA 受体 GluR1, GluR2/3 的表达和 GluR1 的磷酸化水平, 训练前阻断 AMPA 受体没有这样的结果, 5-HT1AR 拮抗剂可抵消 AMPA 受体阻断剂 NBQX 的效应(Schiapparelli, Simón, Del Río, & Frechilla, 2006)。可见, 5-HT1AR 与谷氨酸受体之间存在一定关系。为了证明慢性应激性抑郁发生中 5-HT1AR 的变化及作用, 以及是否对谷氨酸受体调节, 实验通过 CUMS 建立应激性抑郁模型, 海马微量注射 5-HT1AR 激动剂 8-OH-DPAT, 结果发现, CUMS 可引起 5-HT1A 受体表达下降; 8-OH-DPAT 可以反转 CUMS 诱发的抑郁样行为学表现, 并显著抑制大鼠海马 NR1 和 NR2B 亚基表达及 NMDA 受体磷酸化的升高, 以及 GluR2/3 亚基表达及 AMPA 受体磷酸化的下调。而海马微量注射 5-HT1AR 拮抗剂 WAY100635 引起 NR1 和 NR2B 亚基表达及 NMDA 受体磷酸化的升高, GluR2/3 亚基表达及 AMPA 受体磷酸化的下调, 动物表现出与 CUMS 相似的抑郁样行为。说明在应激性抑郁发生中, 海马 5-HT1AR 调控了 NMDA 受体、AMPA 受体的表达及磷酸化水平。

综上所述, CUMS 导致 5-HT1A 受体表达下降。CUMS 和海马微量注射 WAY100635, 均能引起抑郁样行为表现。同时, CUMS 和海马微量注射 WAY100635 均能导致 NMDA 受体表达及磷酸化水平升高, AMPA 受体表达及磷酸化水平的下降。5-HT1A 受体的激动剂 8-OH-DPAT 引起海马 NR1 和 NR2B 亚基表达及 NMDA 受体磷酸化水平下降, GluR2/3 亚基表达及 AMPA 受体磷酸化水平升高, 并有效改善了慢性应激引起的抑郁样行为。说明慢性不可预见性温和应激, 使 5-HT1AR 表达下降。5-HT1AR 激活, 降低 NMDAR 表达量及磷酸化水平, 提高 AMPAR 表达量及磷酸化水平是其发挥抗抑郁作用的重要途径之一。

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Role of Hippocampal 5-HT1A Receptor and Its Modulation to NMDA Receptor and AMPA Receptor in Depression Induced by Chronic Unpredictable Mild Stress

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Abstract

Stressors markedly influence central neurochemical and hormonal processes and thus play a pivotal role in the occurrence of depressive illnesses. As the center for stress response and the potential target for stressful

provocation, the hippocampus is becoming a focus in depression research. Although a large number of behavioral paradigms have been proposed as animal models of depression, only a few are considered potentially useful research tools with sufficient validity. The most accepted one is the chronic unpredictable mild stress (CUMS) rodent model, in which rats are chronically and unpredictably subjected to a variety of stressors including immersion in cold water, tail pinch, day and night reversal, and so on. There are several theoretical mechanisms for depression, such as the monoamine neurotransmitter imbalance theory and the neural plasticity theory, but none of them can fully elucidate the formation of depression. Due to the weak and irregular anti-depressant effects of monoamines, glutamate (Glu) and its receptors, especially N-methyl-D-aspartic acid (NMDA) receptors and α-amino-3-hydroxy-5-methylisoxazole-4- propionic acid (AMPA) receptors, have gained more attention in recent years. As an important isoform of the 5-hydroxytryptamine (5-HT) receptor, the 1A receptor is highly expressed in the hippocampus. Numerous pharmacological and clinical studies show that the 1A receptor is correlated with the development and therapy of major depressive disorder, anxiety, and drug addiction. The present study investigates the expression and role of the 5-HT receptor 1A (5-HT1AR) and its relationship with NMDA and AMPA receptors in depression induced by CUMS.

The CUMS induced depression model was done using Sprague-Dawley rats that were given intra-hippocampal microinjections of drugs. The location of injections was determined by rat brain stereotaxic coordinates. The behavioral observations were conducted by measurement of weight changes, sucrose preference test, open-field test, and tail suspension test. The expression of 5-HT1AR was detected by Western blot, and the expression and phosphorylation of the NMDA and AMPA receptor's subunits were detected by Western blot and ELISA, respectively.

The results showed that CUMS rats had depressive-like behavior, lower expression of 5-HT1AR, lower expression and phosphorylation of AMPA receptor subunits (GluR2/3), and higher expression and phosphorylation of NMDA receptor subunits (NR1and NR2B) in the hippocampus in comparison with the CON/SAL group. Microinjection of WAY100635 (an antagonist of 5-HT1AR) into the hippocampus of CON/SAL animals resulted in similar animal depressive-like behaviors, as well as similar expression levels and phosphorylation of NMDA and AMPA receptor subunits observed in CUMS/SAL animals. Pretreatment with microinjection of 8-OH-DPAT (an agonist of 5-HT1AR) could rescue CUMS-induced depressive behavior, decrease expression of AMPA receptor subunits (GluR2/3), and increase expression of NMDA receptor subunits (NR1 and NR2B) in the hippocampus.

The results suggest that 5-HT may contribute to CUMS-induced depressive-like behaviors via 5-HT1AR, and the antidepressant effect of 5-HT1AR agonists may be mediated by NMDA and AMPA receptors.

Key words chronic unpredictable mild stress; depression; hippocampus; 5-HT1A receptor; NMDA receptor; AMPA receptor