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氟西汀对慢性不可预见应激模型大鼠海马磷脂酰乙醇胺的影响*

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摘要 目的: 探讨氟西汀对慢性不可预见应激 (Chronic Unpredictable Mild Stress, CUS) 模型大鼠海马内磷脂酰乙醇胺 (phosphatidylethanolamine, PE) 组成的影响。**方法:** (1) 将 24 只 SD 大鼠随机分为对照组 (Sham)、模型组 (CUS) 和氟西汀组 (Flx)。CUS 组和 Flx 组均接受 CUS 造模, 并且在造模后接受生理盐水 (1 mL/kg) 或氟西汀 (10 mg/kg) 腹腔注射, 连续 14 天; Sham 不进行 CUS 造模, 但是每天接受腹腔注射生理盐水。随后处死大鼠, 取海马进行脂质组学分析, 比较各处理组海马总的 PE 和 PE 小分子相对丰度、不同碳链长度和含不同不饱和和键 PE 的相对丰度差异。**结果:** (1) 与 CUS 组相比, Sham 组 PE 相对丰度明显减低, 而 Flx 组明显增高 ($P<0.05$); (2) 与 Sham 组相比, CUS 组 9 个 PE 小分子相对丰度发生变化, PE (34:1e)、PE (36:1p)、PE (36:2)、PE (36:2p)、PE (36:4)、PE (38:2)、PE (38:4) 和 PE (40:7) 共 8 个上调 ($P<0.05$ 或 0.01), PE (34:0p) 下调 ($P<0.05$), CUS 组碳链长度为 36 的 PE 丰度上升 ($P<0.05$), 碳链长度为 38 的 PE 丰度下降 ($P<0.01$), CUS 组含 0 个不饱和键、4 个不饱和键的 PE 丰度下调 ($P<0.01$, $P<0.05$), 而 1 个不饱和键的 PE 丰度上升 ($P<0.05$); (3) 与 CUS 组相比, Flx 组 6 个 PE 分子相对丰度减少, 包括 PE (34:1e)、PE (36:2)、PE (36:4)、PE (38:1p)、PE (38:6e) 和 PE (40:5p) ($P<0.05$ 或 0.01), Flx 组碳链长度为 34 的 PE 丰度下降 ($P<0.05$), 碳链长度为 36 的 PE 水平升高 ($P<0.05$), Flx 组含 1 个不饱和键的 PE 丰度下调 ($P<0.05$), 差异具有统计学意义。**结论:** 氟西汀可以调节 CUS 模型大鼠海马的 PE 水平。

关键词: 磷脂酰乙醇胺; 慢性不可预见应激模型; 氟西汀

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Effect of Fluoxetine on Phosphatidylethanolamine in Hippocampus of Rats with Chronic Unpredictable Stress*

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ABSTRACT Objective: To investigate the impact of fluoxetine on the composition of phosphatidylethanolamine in hippocampus of rats with chronic unpredictable stress. **Methods:** 24 SD rats were randomly divided into control group (sham), model group (CUS) and fluoxetine group (FLX). Cus group and FLX group received CUS stimulus, and each group received intraperitoneal injection of normal saline (1 mL / kg) or fluoxetine (10 mg / kg) for 14 consecutive days; sham did not conduct CUS stimulus, but received intraperitoneal injection of normal saline every day. 24 h after the last stimulation, the rats were killed, and the hippocampus was taken for lipomics analysis. The relative concentrations of total PE and different molecules, different carbon chain length and unsaturated bonds of PE in the hippocampus of each group were compared. **Results:** (1) Compared to CUS group, the relative concentrations of PE in the Sham group was significantly reduced, while the Flx group was significantly increased ($P<0.05$); (2) Compared to Sham group, there was significant difference on the relative concentrations of 9 molecules of PE, PE (34: 1e), PE (36: 1p), PE (36: 2), PE (36: 2p), PE (36: 4), PE (38: 2), PE (38: 4) and PE (40: 7) was increased and PE (34: 0p) was decreased in CUS group ($P<0.05$ or 0.01), the concentrations of PE with a carbon chain length of 36 in the CUS group was increased ($P<0.05$), and the concentrations of PE with a carbon chain length of 38 were decreased ($P<0.01$), the concentrations of PE with 0 and 4 unsaturated bonds decreased ($P<0.01$, $P<0.05$), while the PE concentrations of 1 unsaturated bond increased in CUS group ($P<0.05$); (3) Compared to CUS group, there was significant difference in Flx group on the relative concentrations of PE composition by molecules, PE (34: 1e), PE (36: 2), PE (36: 4), PE (38: 1p), PE (38: 6e) and PE (40: 5p) were increased ($P<0.05$ or 0.01); the concentrations of PE with the carbon chain length of 34 were decreased in Flx group ($P<0.05$), and the carbon chain length of 36 were increased ($P<0.05$); the concentrations of PE with 1 unsaturated bond were decreased in Flx group ($P<0.05$). **Conclusions:** Fluoxetine can regulate the level of PE in hippocampus of CUS model rats.

Key words: Phosphatidylethanolamine; Chronic Unpredictable Mild Stress model; Fluoxetine

Chinese Library Classification (CLC): R-33; R749.4 **Document code:** A

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前言

抑郁症是一种以心境障碍为突出表现的常见常见的精神疾病,发病机制复杂,目前中枢神经系统单胺类神经递质异常是国际公认的抑郁症发病机制假说之一^[1]。基于此假说,上世纪80年代开始,多种抗抑郁药物如选择性5-羟色胺再摄取抑制剂(Selective serotonin reuptake inhibitors, SSRIs)被开发且在临床中被广泛应用^[2],但其治疗谱窄,副作用较多,这与其治疗机制尚不明确有关。脂质组学是新型的代谢组学的一个重要分支,可以进一步反应内源性代谢产物的变化,对疾病发病机制的研究更为敏感和准确^[3]。一项来自荷兰的研究也证实,血浆鞘磷脂与抑郁焦虑症状之间存在相关关系,且与磷脂酰胆碱的趋势呈负相关,推测脂质代谢异常可能是抑郁症发病的潜在机制之一^[4]。

磷脂酰乙醇胺(phosphatidylethanolamine, PE)是甘油磷脂的重要成分之一,参与神经细胞代谢、突触间信号传递等作用^[5]。新近的研究发现,慢性不可预见应激(Chronic Unpredictable Mild Stress, CUS)可以导致大鼠大脑PE水平降低^[6]。然而,抑郁模型PE的组成特点以及抗抑郁药物对PE的调节作用尚不清楚。

本研究以慢性不可预见应激(CUS)抑郁大鼠为模型,观察氟西汀对该模型大鼠海马PE组成的变化,为进一步阐明氟西汀的抗抑郁作用提供新思路。

1 材料与方法

1.1 材料

1.1.1 动物 实验动物选择清洁级雄性8周龄左右的SD大鼠,体质量(200±20 g),由空军军医大学动物实验中心提供。实验已经被空军军医大学动物研究伦理委员会批准。

1.1.2 仪器和试剂 Q-Exactive Plus 质谱仪(Thermo Scientific);UHPLC Nexera LC-30A 超高效液相色谱仪(SHIMADZU);低温高速离心机(Eppendorf 5430R);色谱柱(Waters);乙腈(Thermo Fisher);异丙醇(Thermo Fisher);甲醇(Thermo Fisher);甲酸铵(Sigma, 70221)。

1.2 方法

1.2.1 实验分组及步骤 大鼠适应性饲养7天:饲养环境为恒温恒湿,室温(23±1)℃,湿度50%-55%,自由摄食和饮水,12h/12h(8:00-20:00)明暗控制。随后,大鼠随机分为对照组(Sham),模型组(CUS),氟西汀组(Flx)。Sham不进行CUS造模,CUS组和Flx组接受CUS造模。Sham组和CUS组每天接受腹腔注射生理盐水(1 mL/kg),FLX组接受腹腔注射氟西汀(10 mg/kg),连续14天。各处理腹腔注射生理盐水或者氟西汀的时间均为上午9:00至10:00。随后处死大鼠,通过脂质组学分析,观察大鼠海马内PE水平变化。

1.2.2 CUS模型构建 采用以下不同的应激处理方法对CUS组和Flx组大鼠进行构建CUS模型。(1)昼夜节律颠倒和光照性质改变(闪光刺激、昼夜颠倒、间断光照);(2)食物和饮水供应的改变(禁食、禁水);(3)居住环境的改变(单笼饲养、鼠笼倾斜、潮湿垫料);(4)短时间内足底电击;(5)强迫游泳;(6)束缚应激;(7)高温环境;(8)噪音干扰;(9)陌生气味;(10)陌生异常

物品(塑料杯、木勺、碎布片等)。CUS持续14天,大鼠每天接受2种刺激,刺激方式按照随机数字表法选取,使实验动物不能预测应激刺激的发生。

1.2.3 色谱-质谱分析 (1)样本制备:取各组大鼠脑组织样本,分别称取30±3 mg,加入200 μL纯水,MP匀浆,加入240 μL预冷甲醇,涡旋混合,加入800 μL MTBE,涡旋混合,室温放置20 min,8000×g 10℃离心15 min,取上层有机相,氮气吹干,质谱分析时加入400 μL异丙醇溶液复溶,涡旋,14000×g 10℃离心15 min,取上清进样分析。质控样本(QC)的制备:等量取各组样本混合为QC。QC样本用于测定进样前仪器状态及平衡色谱-质谱系统,并用于评价整个实验过程中系统稳定性。

(2)色谱条件:样品采用UHPLC Nexera LC-30A超高效液相色谱系统进行分离。柱温45℃;流速300 μL/min;进样量2 μL。流动相组成A:10 mM 甲酸铵乙腈水溶液(乙腈:水=6:4, v/v),B:10 mM 甲酸铵乙腈异丙醇溶液(乙腈:异丙醇=1:9, v/v)。梯度洗脱程序如下:0-7 min, B维持在30%;7-25 min, B从30%线性变化至100%;25.1-30分钟, B维持在30%。整个分析过程中样品置于10℃自动进样器中。为避免仪器检测信号波动而造成的影响,采用随机顺序,进行样本的连续分析。样本队列中每隔8个实验样本设置1个QC样品,用于监测和评价系统的稳定性及实验数据的可靠性。

(3)质谱条件:分别采用电喷雾电离(ESI)正离子和负离子模式进行检测。样品经UHPLC分离后采用Q Exactive plus 质谱仪进行质谱分析。ESI源条件如下:Positive: Heater Temp 300℃, Sheath Gas Flow rate 45 arb, Aux Gas Flow Rate 15 arb, Sweep Gas Flow Rate 1arb, spray voltage 3.0KV, Capillary Temp 350℃, S-Lens RF Level 50%. MS1 scan ranges: 200-1800. Negative: Heater Temp 300℃, Sheath Gas Flow rate 45arb, Aux Gas Flow Rate 15arb, Sweep Gas Flow Rate 1arb, spray voltage 2.5KV, Capillary Temp 350℃, S-Lens RF Level 60%. MS1 scan ranges: 250-1800。脂质分子和脂质碎片的质量电荷比,按照下列方法采集:每次全扫描(full scan)后采集10个碎片图谱(MS2 scan, HCD)。MS1在M/Z 200时分辨率为70,000, MS2在M/Z 200时分辨率为17,500。

(4)数据处理:采用LipidSearch software version 4.1进行峰识别、脂质鉴定(二级鉴定)、峰提取、峰对齐,定量等处理。主要参数为:precursor tolerance: 5 ppm, product tolerance: 5 ppm, product ion threshold: 5%。提取得到的数据,删除RSD>30%的脂质分子。对LipidSearch提取得到的数据,删除组内缺失值>50%的脂质分子,对数据进行总峰面积归一化。应用软件SIMCA-P 14.1(Umetrics, Umea, Sweden)进行模式识别,数据经Pareto-scaling预处理后,进行多维统计分析。

1.3 统计学分析

采用SPSS21.0进行数据统计分析,数据资料用表示。各组之间的比较用单因素方差分析,两两数据比较前进行方差齐性检验,满足方差齐性则采用Tukey检验,方差不齐则采用Dunnett T3检验。设P<0.05时有统计学意义。

2 结果

2.1 各组大鼠海马总PE相对丰度比较

与 CUS 组相比, Sham 组 PE 相对丰度明显减低, 而 Flx 组明显增高, 差异具有统计学意义 ($P < 0.05$)。见图 1。

2.2 Sham 组与 CUS 组大鼠海马内 PE 小分子丰度、不同碳链长度和不饱和键 PE 丰度比较

与 Sham 组相比, CUS 组 9 个 PE 小分子相对丰度发生变化, PE(34:1e)、PE(36:1p)、PE(36:2)、PE(36:2p)、PE(36:4)、PE(38:2)、PE(38:4)和 PE(40:7)共 8 个脂质分子相对丰度上调, PE(34:0p)下调, 差异具有统计学意义 ($P < 0.05$, $P < 0.01$)。与

Sham 组相比, CUS 组碳链长度为 36 的 PE 丰度上升, 碳链长度为 38 的 PE 丰度下降, 差异具有统计学意义, 差异具有统计学意义 ($P < 0.05$, $P < 0.01$)。与 Sham 组相比, CUS 组含 0 个不饱和键、4 个不饱和键的 PE 丰度下调, 而 1 个不饱和键的 PE 丰度上升, 差异具有统计学意义 ($P < 0.05$, $P < 0.01$)。见图 2、图 3。

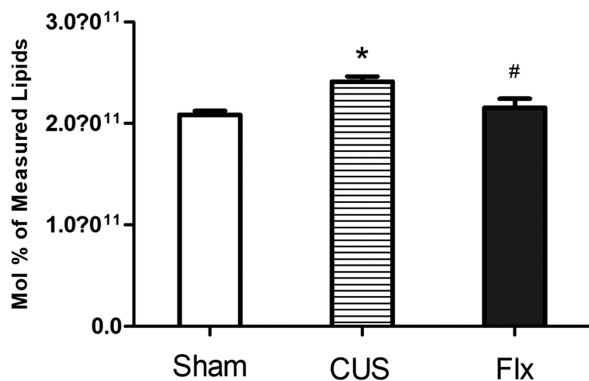


图 1 各组大鼠总 PE 相对丰度的比较 ($\bar{x} \pm s$)

Fig. 1 Comparison of PE in each group ($\bar{x} \pm s$)

Note: * $P < 0.05$.

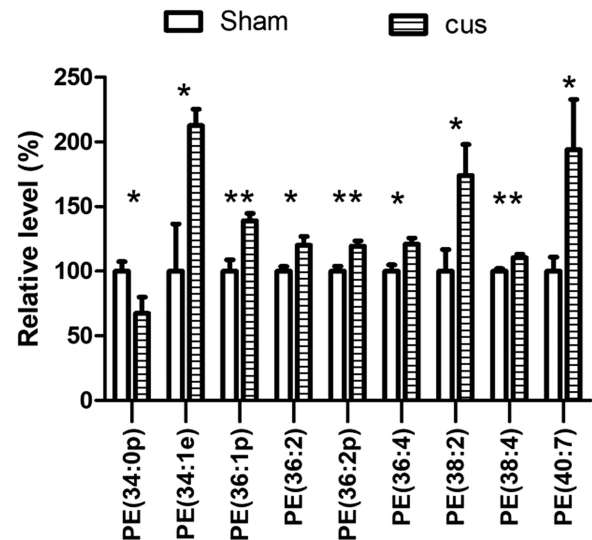


图 2 Sham 组与 CUS 组大鼠海马内 PE 小分子丰度差异情况

Fig. 2 Comparison of different molecules of PE in Sham and CUS

Note: * $P < 0.05$, ** $P < 0.01$.

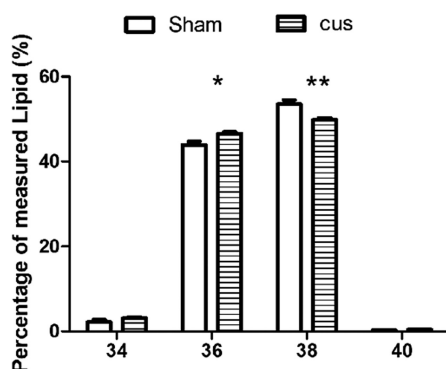


图 3 Sham 组与 CUS 组大鼠海马内不同碳链长度和不饱和键 PE 水平的差异情况

Fig. 3 Comparison of different degree of saturation and carbon chain lengths of PE in Sham and CUS

Note: * $P < 0.05$, ** $P < 0.01$.

2.3 CUS 组与 Flx 组大鼠海马内 PE 小分子丰度、不同碳链长度和不饱和键 PE 丰度比较

与 CUS 组相比, Flx 组 6 个 PE 分子相对丰度减少, 包括 PE(34:1e)、PE(36:2)、PE(36:4)、PE(38:1p)、PE(38:6e)和 PE(40:5p), 差异具有统计学意义 ($P < 0.05$, $P < 0.01$)。Flx 组碳链长度为 34 的 PE 丰度下降, 碳链长度为 36 的 PE 水平升高, 差异具有统计学意义 ($P < 0.05$)。Flx 组含 1 个不饱和键的 PE 丰度下调, 差异具有统计学意义。 ($P < 0.05$) 见图 4、图 5。

3 讨论

抑郁症患者或抑郁动物模型存在脂质代谢异常^[7]。临床研究发现, 内源性抑郁症患者的甘油三酯、胆固醇均低于正常人群^[8], 抑郁症患者 LDL、VLDL 和不饱和脂肪酸表达增高, 脂质

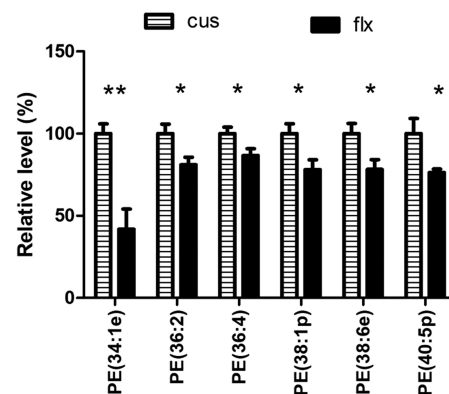


图 4 CUS 组与 Flx 组大鼠海马内 PE 小分子丰度水平的差异情况

Fig. 4 Comparison of different molecules of PE in CUS and Flx

Note: * $P < 0.05$, ** $P < 0.01$.

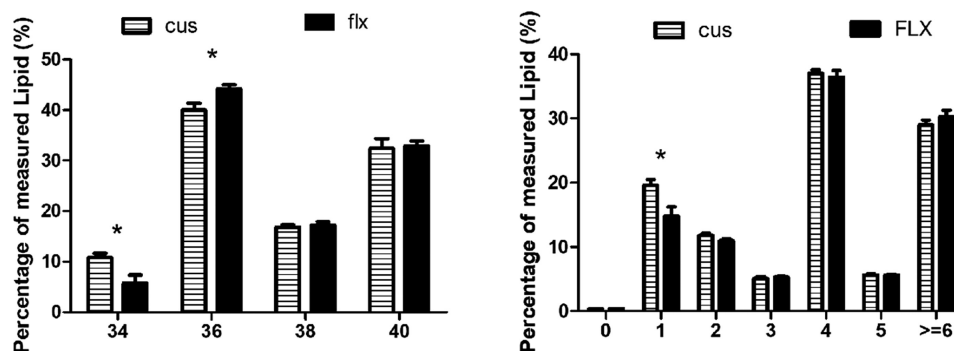


图 5 CUS 组与 Flx 组大鼠海马内不同碳链长度和不饱和键 PE 水平的差异情况

Fig.5 Comparison of different degree of saturation and carbon chain lengths of PE in CUS and Flx

Note: * $P < 0.05$, ** $P < 0.01$.

相关代谢产物, 醋酸盐和肌醇水平减低^[9]。基础研究也发现, 抑郁模型大鼠体内胆汁酸和色氨酸均显著增加, 胆固醇代谢发生显著变化^[10]。新近的脂质组学研究则进一步发现, 慢性不可预见应激 (Chronic Unpredictable Mild Stress, CUS) 模型可以导致大鼠海马和前额叶皮质多种脂质分子水平发生变化^[11]。上述结果提示脂质代谢异常很可能在抑郁症发病机制中具有重要作用。

海马是抗抑郁药物情绪调节和药效作用的主要靶点脑区^[12,13]。既往研究显示, CUS 模型大鼠海马和皮层内多种脂质浓度均发生改变^[9]。氟西汀是临床常用的抗抑郁药物之一, 已被证实氟西汀可以有效改善 CUS 模型大鼠的抑郁样行为^[14], 并且对海马的结构和功能均有调节作用^[15,16]。然而, 氟西汀对海马脂质组学的影响还有待进一步阐明。PE 是磷脂酰胆碱的重要前体和修饰后底物, 主要参与细胞器的融合, 氧化磷酸化或线粒体生物合成等生理过程, 在阿尔兹海默病、帕金森病的发病机制中均发挥重要作用^[17,18]。此外, PE 和磷脂酰胆碱等均是甘油磷脂重要成分之一, 参与构建细胞膜, 并在细胞信号调解方面发挥重要作用^[19,20]。研究表明, PE 会影响肝脏、循环系统中甘油三酯、低密度脂蛋白等多种脂质水平, 而且 PE 在极低密度脂蛋白的组装和分泌中起到重要作用^[18]。另一方面, PE 也是内源性大麻素系统中花生四烯酸乙醇胺形成的重要中间代谢物^[21]。研究显示, 内源性大麻素物质可以作用于突触前 CB1 受体, 调节 5-羟色胺和去甲肾上腺素等神经递质释放, 与抑郁症发生高度相关^[22]。另外, 儿童青少年抑郁症患者磷脂酰胆碱等脂质代谢物存在差异, 给予抗抑郁药物后, 包括 PE 在内的 10 种代谢差异物均参与脂质代谢通路^[23]。

本研究采用脂质组学技术, 观察了氟西汀对 CUS 模型大鼠海马 PE 组成及相对丰度的影响。结果发现, CUS 组 PE 水平显著高于对照组, 而氟西汀可以逆转这一变化。Xinyu Liu 等对于抑郁症患者血浆代谢组学分析显示, 抑郁症患者 PE 水平增高, 并且与抑郁症状严重程度呈正相关关系^[24], 此外, 饱和 PE 的稳定性改变与碳链长度和压力有关, 小极性头基 PE 分子和水分子相互作用, 也可形成高相变温度脂质膜而更加稳定^[25], 因此, 不同碳链长度和不饱和键数量均可影响 PE 的功能, 进而影响膜流动性, 导致整体功能改变。本研究进一步显示, CUS 造

模后, 海马存在多种 PE 小分子相对丰度的改变, 而且含不同数量不饱和键和碳链的 PE 水平低于对照组, 氟西汀可以部分逆转此效果。因此, 我们推测 PE 在抑郁症的发生和转归中发挥重要作用, 氟西汀的抗抑郁作用可能与其调节 PE 的组成和功能有关。

综上所述, 本研究发现 CUS 模型大鼠海马 PE 的组成和相对丰度发生改变, 而氟西汀则对此有调节作用, 为抗抑郁药物作用机制提供了新的思路 and 理论依据。但本研究具有一定的局限性, 本研究并未观察氟西汀对其他脂质代谢物和功能的影响, PE 变化所致深层次分子级联反应亦有待进一步研究。

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