DOI: 10.11844/cjcb.2025.02.0007
中国细胞生物学学报 Chinese Journal of Cell Biology 2025, 47(2): 221–228 CSTR: 32200.14.cjcb.2025.02.0007

木犀草素调节Nrf2/HO-1/NLRP3信号通路对抑郁症小鼠海马神经元凋亡的影响

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摘要 该研究主要探讨木犀草素(Luteolin)对抑郁症小鼠海马神经元凋亡及核因子E2相关因子2/血红素加氧酶1/Nod样受体蛋白3(Nrf2/HO-1/NLRP3)信号通路的影响。该研究先构建抑郁症小鼠模型, 将造模成功小鼠随机分为模型组(Model组), 木犀草素低、高剂量组(Luteolin-L、Luteolin-H组), 木犀草素高剂量+Nrf2抑制剂组(Luteolin-H+ML385组), 另取正常健康小鼠作为对照组(Control组); 然后对所有小鼠进行抑郁样行为检测; ELISA检测海马组织炎症及氧化应激水平; HE染色检测海马组织CA3区病理损伤情况; TUNEL染色检测神经元凋亡情况; Western blot检测Nrf2/HO-1/NLRP3信号通路及凋亡相关蛋白表达情况。结果表明, Model组较Control组海马组织结构受损, 神经元出现神经元性脓疱变性, 排列松散, 核固缩深染, 部分核碎片化, 核仁模糊甚至消失, 糖水偏好指数、SOD、GSH水平及Bcl-2、Nrf2、HO-1表达水平降低; 强迫游泳静止时间, TNF-α、IL-6、IL-β、MDA水平及神经元凋亡率、Bax、NLRP3表达水平升高(P<0.05); 木犀草素处理可改善海马组织病理损伤, 升高糖水偏好指数、SOD、GSH水平及Bcl-2、Nrf2、HO-1表达水平, 降低强迫游泳静止时间、TNF-α、IL-6、IL-β、MDA水平及神经元凋亡率、Bax、NLRP3表达水平(P<0.05); Nrf2抑制剂ML385处理可部分减弱木犀草素对抑郁症小鼠海马神经元凋亡的改善作用。总之, 木犀草素可抑制抑郁症小鼠海马神经元凋亡, 其作用机制与激活Nrf2/HO-1/NLRP3信号通路相关。

关键词 木犀草素; 核因子E2相关因子2/血红素加氧酶1/Nod样受体蛋白3信号通路; 抑郁症; 海马神经元; 凋亡

The Impacts of Iuteolin on Hippocampal Neuronal Apoptosis in Depressed Mice by Regulating the Nrf2/HO-1/NLRP3 Signaling Pathway

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Abstract The aim of this study was to investigate the impacts of Luteolin on hippocampal neuronal apoptosis and Nrf2/HO-1/NLRP3 (nuclear factor-erythroid 2-related factor 2/heme oxygenase 1/NOD-like receptor thermal protein domain associated protein 3) signaling pathway in mice with depression. In this study, a depression mouse model was constructed, and successfully modeled mice were randomly assigned into a model group, Luteolin-L and Luteolin-H groups, and Luteolin-H+ML385 group (Luteolin-high dose+Nrf2 inhibitor group). Normal healthy mice were also selected as the control group. Then all mice were tested for depression like behavior. ELISA was applied to detect inflammation and oxidative stress levels in hippocampal tissue. HE staining was applied to

收稿日期: 2024-12-06 接受日期: 2024-12-24
黑龙江省卫生计生委科研课题(批准号: 2018-159)资助的课题
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Received: December 6, 2024 Accepted: December 24, 2024
This work was supported by the Research Project of Heilongjiang Provincial Health and Family Planning Commission (Grant No.2018-159)
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detect pathological damage in CA3 region of hippocampal tissue. TUNEL staining was applied to detect neuronal apoptosis. Western blot was applied to detect the Nrf2/HO-1/NLRP3 signaling pathway and the expression of apoptosis related proteins. The results showed that compared with the control group, the hippocampal tissue structure in the model group was damaged, neuronal pustular degeneration of neurons appeared, with loose array, hyperchromia of nuclei, partial nucleus fragmentation, blurred or even disappeared nucleolus, and the sugar and water preference index, SOD and GSH levels and the expression of Bcl-2, Nrf2 and HO-1 were decreased. Static time, TNF-α, IL-6, IL-β, MDA levels, neuronal apoptosis rate, Bax, NLRP3 expression were increased (P<0.05). Luteolin treatment could improve the pathological injury of hippocampal tissue, increase the sugar water preference index, SOD, GSH levels and the expressions of Bcl-2, Nrf2 and HO-1, decrease the resting time of forced swimming, TNF-α, IL-6, IL-β, MDA levels, neuronal apoptosis rate, Bax and NLRP3 expression (P<0.05). Treatment with ML385, an Nrf2 inhibitor, partially attenuates the effect of luteolin on hippocampal neuron apoptosis in depressed mice. In conclusion, Luteolin can alleviate hippocampal neuronal apoptosis in mice with depression, and its mechanism of action is related to the activation of the Nrf2/HO-1/NLRP3 signaling pathway.

Keywords Luteolin; nuclear factor-erythroid 2-related factor 2/heme oxygenase 1/NOD-like receptor thermal protein domain associated protein 3 signaling pathway; depression; hippocampal neurons; apoptosis

抑郁症属于一种常见的精神障碍疾病, 主要表现为厌食、情绪低落、思维延缓、活动减少、易怒喜哭、快感缺失、嗜睡等, 具有持久性且易反复发作, 严重时会出现自杀倾向及行为, 严重影响患者正常生活甚至威胁患者生命健康, 是造成全球精神健康相关疾病负担的主要原因[1-2]。随着社会经济的高速发展, 人们生活工作压力的增大, 抑郁症的发病率及病死率逐年升高[3]。目前主要通过心理、药物及物理进行治疗, 药物治疗主要通过服用氟西汀、文拉法辛等抗抑郁类药物, 而物理治疗主要通过经颅磁刺激、改良电休克等进行, 这虽然可以显著降低患者自杀死亡率, 但对于难治性抑郁症效果甚微, 故探索新型安全有效的治疗药物与途径仍是目前的研究重点[4-5]。木犀草素是存在于多种水果及蔬菜中的一类黄酮类化合物, 具有抗炎、抗氧化、抗凋亡、神经保护等多种生物学活性, 其在神经相关疾病的治疗中发挥重要作用[6]。研究显示, 木犀草素可改善慢性不可预知温和刺激(chronic unpredictable mild stimulation, CUMS)诱导的迟发性抑郁症样行为[7]。核因子E2相关因子2/血红素加氧酶1/Nod样受体蛋白3(nuclear factor-erythroid 2-related factor 2/heme oxygenase 1/Nod-like receptor thermal protein domain associated protein 3, Nrf2/HO-1/NLRP3)信号通路是经典的抗氧化、抗炎通路, 在神经相关疾病的发展中发挥重要作用, 研究显示, 激活Nrf2/HO-1/NLRP3信号通路可促进小胶质细胞向M2型转化, 抑制炎症反应, 改善抑郁样行为, 从而减轻CUMS所致的抑郁[8]。本文主要探究木犀草素能否通过调控Nrf2/HO-1/NLRP3信号通路影响抑郁症小鼠神经元凋亡, 以期为抑郁症的治疗寻求新策略。

1 材料与方法

1.1 主要材料

SPF级BALB/c小鼠购自山东艾茂达康生命科学有限公司, 生产许可号为[SCXK(鲁) 2023 0010]; 木犀草素(≥98%, YLK-B0834D)购自优利科(上海)生命科学有限公司; ML385(纯度99%, M304758)购自上海阿拉丁生化科技股份有限公司; 肿瘤坏死因子-α(tumor necrosis factor-alpha, TNF-α)(CSB-E04741m)、白细胞介素-6(interleukin-6, IL-6)(CSB-E04639m-IS)、白细胞介素-β(interleukin-β, IL-β)(CSB-E08054m) ELISA试剂盒购自武汉华美生物工程有限公司; 丙二醛(malondialdehyde, MDA)(XK-E12031)、超氧化物歧化酶(superoxide dismutase, SOD)(XK-E12032)、谷胱甘肽(glutathione, GSH)(XK-E11749) ELISA试剂盒购自上海晅科生物科技有限公司; B淋巴细胞瘤-2基因相关X蛋白质(B lymphoblastoma-2 gene-associated X protein, Bax)(FNab00809)、B淋巴细胞瘤-2基因(B lymphoblastoma-2 gene, Bcl-2)(FNab00839)抗体购自武汉菲恩生物科技有限公司; Nrf2(PL0403301)、HO-1(251323)、NLRP3(PL0402307)抗体购自深圳市豪地华拓生物科技有限公司。

1.2 方法

1.2.1 抑郁症小鼠模型构建 所有实验小鼠适应性喂养1周, 然后对造模小鼠进行白噪声、拥挤环境、明暗颠倒、鼠笼倾斜、不筑巢、在塑料管内固定等刺激, 每天进行任意2种刺激方式, 且相同刺激方式不同时出现, 连续刺激4周, 若发现小鼠糖水消耗率降低, 强迫游泳静止时间延长等抑郁行为, 表明抑郁症小鼠造模成功[9]。本实验经哈尔滨市第一专科医院伦理审批通过([2023]伦审批科257号)。

1.2.2 分组与处理 将造模成功小鼠随机分为模型组(Model组), 木犀草素低、高剂量组(Luteolin-L、Luteolin-H组), 木犀草素高剂量+Nrf2抑制剂组(Luteolin-H+ML385组), 另取正常健康小鼠作为对照组(Control组); 木犀草素低、高剂量组[10]: 每天分别给予5、10 mg/kg木犀草素灌胃; 木犀草素高剂量+ML385组[11]: 每天给予10 mg/kg木犀草素灌胃及21 mg/kg ML385腹腔注射, 注射剂量根据大小鼠之间剂量换算而得; 连续给药8天。

1.2.3 糖水消耗实验 先将小鼠单笼放置, 然后放置2个含1%蔗糖水的水瓶, 第二天将其中一个蔗糖水瓶换成双蒸水, 然后将小鼠禁食禁水24 h后, 放置相同的一个1%蔗糖水瓶和一个双蒸水瓶, 1 h后取走水瓶, 计算糖水偏好指数。

1.2.4 强迫游泳实验 在实验前24 h对小鼠进行强迫游泳训练, 然后将小鼠置于水温(20±2) ℃, 水深35 cm玻璃缸中, 先适应2 min, 然后记录5 min内小鼠累计的静止不动时间, 即为强迫游泳静止时间。

1.2.5 炎症与氧化应激水平检测 抑郁样行为检测结束, 将各组小鼠断头处死取海马组织, 任选其中6个制成匀浆, 4 ℃、2 000 r/min离心10 min后取上清, ELISA试剂盒检测TNF-α、IL-6、IL-β水平及MDA、SOD、GSH水平。

1.2.6 海马组织病理观察 取各组剩余6个海马组织CA3区, 清洗干净后, 4%多聚甲醛4 ℃固定24 h, 梯度乙醇脱水后浸蜡包埋, 切片机切5 μm切片, 然后常规处理后, 依次进行苏木素室温染色8 min, 伊红室温染色45 s, 显微镜观察海马组织病理形态。

1.2.7 神经元凋亡检测 将1.2.6石蜡切片进行脱蜡至水、抗原修复, 然后与TUNEL染液避光孵育, 再加入DAB显色后, 用苏木素复染, 显微镜下观察神经元凋亡情况。

1.2.8 Nrf2/HO-1/NLRP3信号通路相关蛋白检测 取1.2.5海马组织匀浆与蛋白裂解液在冰上充分反应, 提取总蛋白定量, 而后进行蛋白变性、电泳、转膜、封闭, 然后与Nrf2(1:500)、HO-1(1:500)、NLRP3(1:500)一抗低温反应过夜, 再与HRP标记二抗(1:10 000)室温反应1 h, 再与ECL反应2 h, 采集图像并进行蛋白条带灰度分析。

1.3 统计学方法

采用SPSS 25.0进行统计分析, 计量资料符合正态分布以$\bar{x}\pm s$描述, 多组间比较采用单因素方差分析, 组间两两比较采用SNK-q检验。以$P<0.05$时表示差异有统计学意义。

2 结果

2.1 木犀草素对抑郁症小鼠抑郁样行为的影响

模型组较对照组糖水偏好指数降低, 强迫游泳静止时间延长($P<0.05$); 木犀草素低、高剂量组较模型组糖水偏好指数升高, 强迫游泳静止时间减短; 其中木犀草素低、高剂量组之间差异显著($P<0.05$), 木犀草素高剂量+ML385组较木犀草素高剂量组糖水偏好指数降低, 强迫游泳静止时间延长($P<0.05$)(表1)。

表1 各组小鼠抑郁样行为比较

Table 1 Comparison of depression-like behavior of mice in each group

组别 Groups	糖水偏好指数/% Sugar and water preference index /%	强迫游泳静止时间/s Force swimming stationary time /s
Control	72.56±7.53	102.45±11.25
Model	43.27±4.69[a]	224.18±23.79[a]
Luteolin-L	55.82±5.87[b]	176.49±18.91[b]
Luteolin-H	70.35±7.42[bc]	121.62±13.06[bc]
Luteolin-H+ML385	57.31±6.15[d]	173.57±18.26[d]

$\bar{x}\pm s$, n=12; [a]$P<0.05$, 与Control组比较; [b]$P<0.05$, 与Model组比较; [c]$P<0.05$, 与Luteolin-L组比较; [d]$P<0.05$, 与Luteolin-H组比较。

$\bar{x}\pm s$, n=12; [a]$P<0.05$ compared with Control group; [b]$P<0.05$ compared with Model group; [c]$P<0.05$ compared with Luteolin-L group; [d]$P<0.05$ compared with Luteolin-H group.

表2 各组小鼠炎症因子水平比较

Table 2 Comparison of levels of inflammatory factors in mice in each group

组别 Groups	TNF-α /pg·mg^{-1}	IL-6 /pg·mg^{-1}	IL-β /pg·mg^{-1}
Control	52.46±5.34	36.78±4.08	23.71±2.46
Model	147.83±15.08^{a}	95.22±9.93^{a}	79.64±8.02^{a}
Luteolin-L	106.57±11.27^{b}	68.51±7.25^{b}	55.43±5.67^{b}
Luteolin-H	60.28±6.12^{bc}	39.29±4.38^{bc}	28.19±2.93^{bc}
Luteolin-H+ML385	102.55±11.19^{d}	65.81±6.97^{d}	52.37±5.35^{d}

$\bar{x}\pm s$, n=6; ^{a}P<0.05, 与Control组比较; ^{b}P<0.05, 与Model组比较; ^{c}P<0.05, 与Luteolin-L组比较; ^{d}P<0.05, 与Luteolin-H组比较。

$\bar{x}\pm s$, n=6; ^{a}P<0.05 compared with Control group; ^{b}P<0.05 compared with Model group; ^{c}P<0.05 compared with Luteolin-L group; ^{d}P<0.05 compared with Luteolin-H group.

表3 各组小鼠氧化应激水平比较

Table 3 Comparison of oxidative stress levels of mice in each group

组别 Groups	MDA /nmol·g^{-1}	SOD /U·mg^{-1}	GSH /μmol·g^{-1}
Control	6.75±0.71	19.62±2.03	20.85±2.19
Model	16.33±1.74^{a}	9.15±1.04^{a}	7.52±0.82^{a}
Luteolin-L	12.58±1.38^{b}	13.06±1.47^{b}	12.37±1.34^{b}
Luteolin-H	7.21±0.82^{bc}	18.97±1.96^{bc}	19.26±2.05^{bc}
Luteolin-H+ML385	11.86±1.26^{d}	12.76±1.35^{d}	13.18±1.45^{d}

$\bar{x}\pm s$, n=6; ^{a}P<0.05, 与Control组比较; ^{b}P<0.05, 与Model组比较; ^{c}P<0.05, 与Luteolin-L组比较; ^{d}P<0.05, 与Luteolin-H组比较。

$\bar{x}\pm s$, n=6; ^{a}P<0.05 compared with Control group; ^{b}P<0.05 compared with Model group; ^{c}P<0.05 compared with Luteolin-L group; ^{d}P<0.05 compared with Luteolin-H group.

2.2 木犀草素对抑郁症小鼠炎症因子水平的影响

模型组较对照组TNF-α、IL-6、IL-β水平升高(P<0.05); 木犀草素低、高剂量组较模型组TNF-α、IL-6、IL-β水平降低(P<0.05); 其中木犀草素低、高剂量组之间差异显著(P<0.05); 木犀草素高剂量+ML385组较木犀草素高剂量组TNF-α、IL-6、IL-β水平升高(P<0.05)(表2)。

2.3 木犀草素对抑郁症小鼠氧化应激水平的影响

模型组较对照组MDA水平升高, SOD、GSH水平降低(P<0.05); 木犀草素低、高剂量组较模型组MDA水平降低, SOD、GSH水平升高(P<0.05); 其中木犀草素低、高剂量组之间差异显著(P<0.05); 木犀草素高剂量+ML385组较木犀草素高剂量组MDA水平升高, SOD、GSH水平降低(P<0.05)(表3)。

2.4 木犀草素对抑郁症小鼠海马组织病理形态的影响

对照组海马组织结构正常, 神经元排列紧密整齐, 细胞核清晰; 模型组海马组织结构受损, 神经元出现神经元性脓疱变性, 排列松散, 核固缩深染, 部分核碎片化, 核仁模糊甚至消失; 木犀草素低、高剂量组海马组织结构相对正常, 神经元较为完整, 排列相对整齐, 核固缩现象减轻, 其中木犀草素高剂量组改善最显著; 木犀草素高剂量+ML385组海马组织结构及神经元受损严重(图1)。

2.5 木犀草素对抑郁症小鼠神经元凋亡的影响

模型组较对照组神经元凋亡率、Bax表达水平升高, Bcl-2表达水平降低(P<0.05); 木犀草素低、高剂量组较模型组神经元凋亡率、Bax表达水平降低, Bcl-2表达水平升高(P<0.05); 其中木犀草素低、高剂量组之间差异显著(P<0.05); 木犀草素高剂量+ML385组较木犀草素高剂量组神经元凋亡率、Bax表达水平升高, Bcl-2表达水平降低(P<0.05)(图2~图4)。

2.6 木犀草素对Nrf2/HO-1/NLRP3信号通路的影响

模型组较对照组NLRP3表达水平升高, Nrf2、HO-1表达水平降低(P<0.05); 木犀草素低、高剂量组较模型组NLRP3表达水平降低, Nrf2、HO-1表达水平升高(P<0.05); 其中木犀草素低、高剂量组之间差异显著(P<0.05); 木犀草素高剂量+ML385组较木犀草素高剂量组NLRP3表达水平升高, Nrf2、HO-1表达水平降低(P<0.05)(图5和图6)。

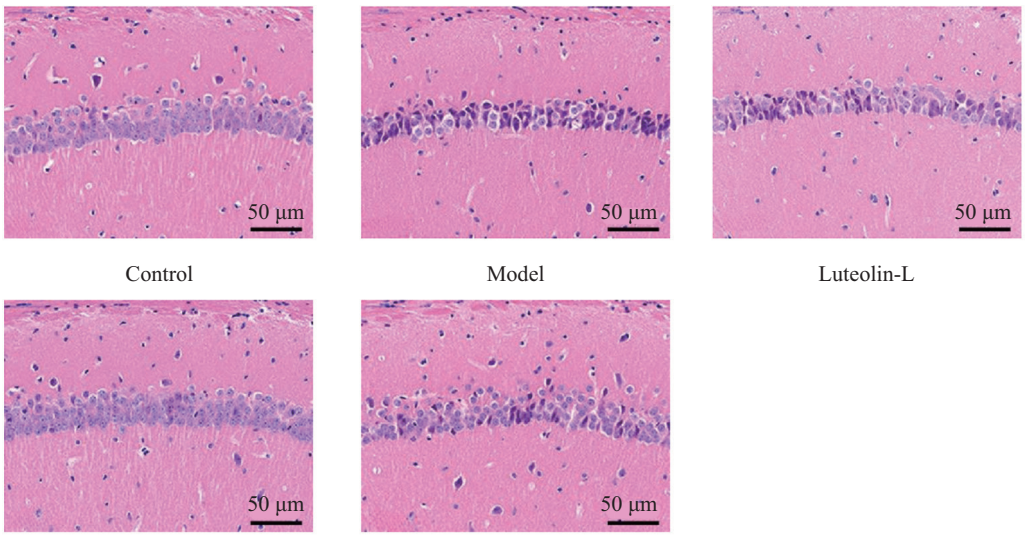


图1 HE染色观察海马组织病理形态

Fig.1 Hippocampal histological morphology was observed by HE staining

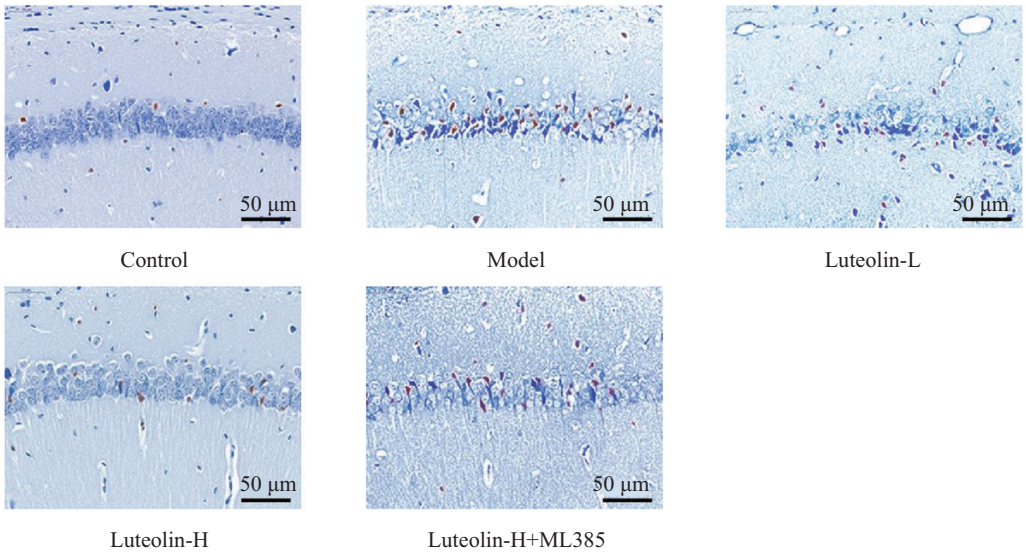


图2 TUNEL染色观察神经元细胞凋亡

Fig.2 Apoptosis of neuronal cells was observed by TUNEL staining

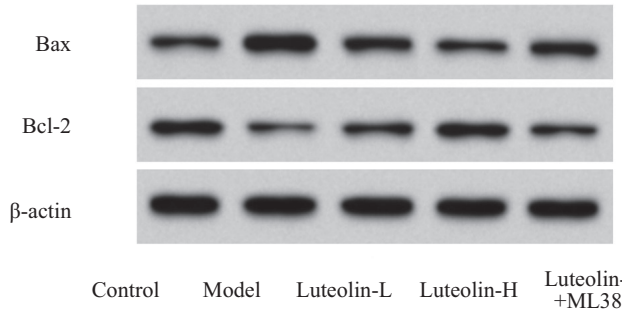
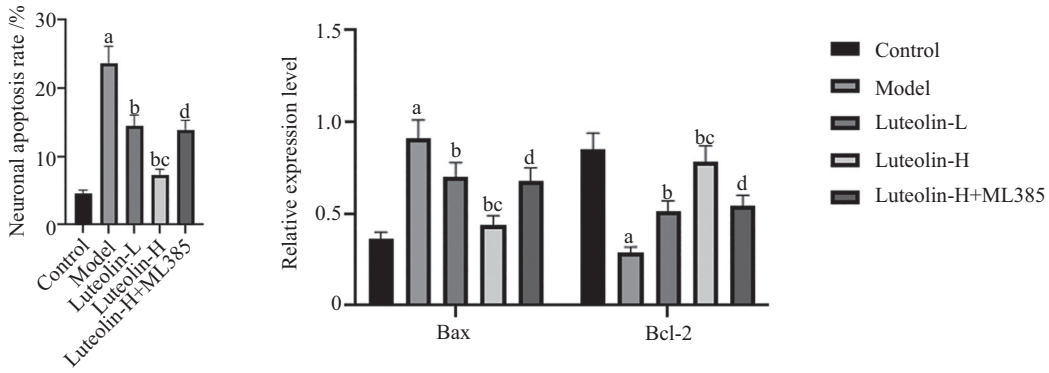


图3 Western blot检测Bax、Bcl-2表达情况

Fig.3 Western blot analysis of Bax and Bcl-2 expression



$\bar{x}\pm s$, n=6; [a]P<0.05, 与Control组比较; [b]P<0.05, 与Model组比较; [c]P<0.05, 与Luteolin-L组比较; [d]P<0.05, 与Luteolin-H组比较。

$\bar{x}\pm s$, n=6; [a]P<0.05 compared with Control group; [b]P<0.05 compared with Model group; [c]P<0.05 compared with Luteolin-L group; [d]P<0.05 compared with Luteolin-H group.

图4 各组小鼠神经元凋亡及凋亡相关蛋白表达比较

Fig.4 Comparison of neuronal apoptosis and apoptosis-related protein expression in each group

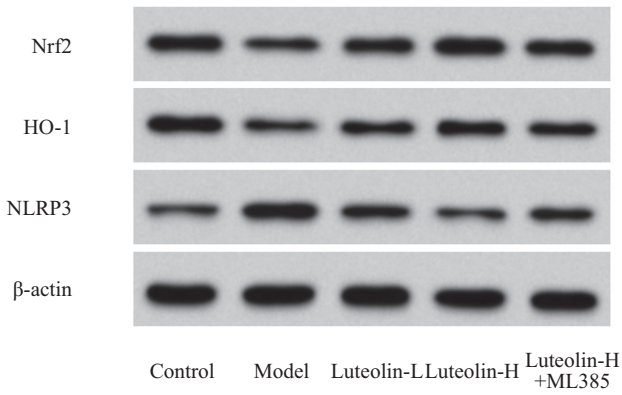
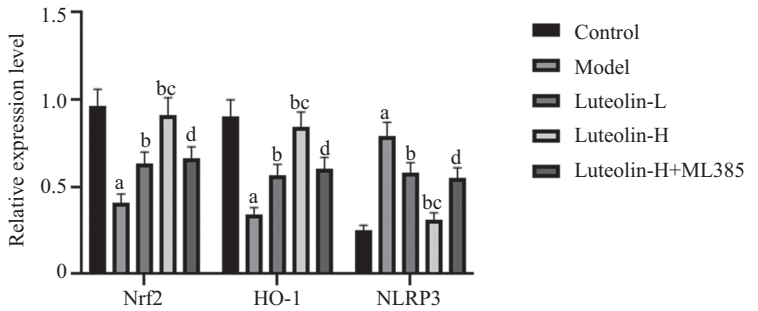


图5 Western blot检测Nrf2、HO-1、NLRP3表达

Fig.5 Western blot analysis of Nrf2, HO-1, NLRP3 expression



$\bar{x}\pm s$, n=6; [a]P<0.05, 与Control组比较; [b]P<0.05, 与Model组比较; [c]P<0.05, 与Luteolin-L组比较; [d]P<0.05, 与Luteolin-H组比较。

$\bar{x}\pm s$, n=6; [a]P<0.05 compared with Control group; [b]P<0.05 compared with Model group; [c]P<0.05 compared with Luteolin-L group; [d]P<0.05 compared with Luteolin-H group.

图6 各组小鼠Nrf2/HO-1/NLRP3信号通路相关蛋白表达比较

Fig.6 Comparison of Nrf2/HO-1/NLRP3 signaling pathway related proteins in each group

3 讨论

抑郁症是一种可受遗传、环境、性激素失调、肠道菌群失调、免疫系统异常、神经递质异常等多因素影响的慢性、易反复的异质性精神疾病, 常表现为食欲低下、探索欲与活动度低、绝望等症状, 严重时可威胁患者生命健康。对于抑郁症目前尚无特效治疗药物与方法, 寻求新型治疗方式与药物至关重要。而黄酮类化合物木犀草素在抗炎、抗氧

化、抗凋亡、抗癌、神经保护等多方面具有医用价值, 尤其在神经炎症性疾病及神经退行性疾病等研究中发挥重要作用[12-13]。研究显示, 木犀草素可抑制大脑中小胶质细胞的激活, 改善阿尔茨海默病小鼠的抑郁样行为[14]。木犀草素可通过抑制TNF-α、IL-6、IL-β、MDA水平及Bax、NLRP3表达, 抑制炎症、氧化应激及神经凋亡反应, 改善慢性疼痛诱导的焦虑和抑郁样症状[15]。本文研究结果显示, 木犀草素可升高糖水消耗率, 减短强迫游泳静止时间, 改善海马组织神经元损伤, 改善抑郁症小鼠抑郁样行为。

神经炎症与抑郁症发生密切相关, 大脑受到刺激, 可激活胶质细胞释放大量炎症因子, 引发神经炎症, 并且可降低神经营养因子水平, 破坏神经可塑性, 促使神经元损伤[16-17]。研究显示, 抑制促炎细胞因子TNF-α、IL-6和IL-β上调及LPS诱导的星形胶质细胞的活化, 可抑制炎症反应, 减弱抑郁样行为, 改善小鼠的焦虑样行为[18]。氧化应激同样与抑郁症发生密切相关, 大脑受到多种致病因素的刺激, 可导致脑内活性氧大量生成, 产生大量氧化脂质, 而后活性氧与抗氧化剂失衡, 引发脑内氧化应激, 触发促炎信号, 造成神经元DNA损伤, 最终诱导细胞凋亡[19]。研究显示, 降低MDA、TNF-α、IL-6和IL-β的水平, 升高SOD、GSH水平, 可抑制小胶质细胞和星形胶质细胞的活化, 抑制炎症及氧化应激反应, 减轻CUMS诱导的大鼠的抑郁样行为[20]。本文研究结果显示, 木犀草素可降低MDA、TNF-α、IL-6和IL-β的水平, 升高SOD、GSH水平, 说明木犀草素可抑制炎症及氧化应激反应, 减轻小鼠抑郁症。

神经元凋亡是抑郁症发病机制的关键介质, Bax、Bcl-2作为神经元凋亡关键蛋白, 两者相互拮抗共同调控神经元凋亡进程。研究显示, 抑制Bax表达, 促进Bcl-2表达可减弱CUMS诱导的抑郁样行为和海马神经元凋亡[21]。另外抑制TNF-α、IL-6和IL-β的水平及Bax表达, 促进Bcl-2表达可抑制炎症反应及神经元凋亡, 可有效改善CUMS诱导的体重减轻和抑郁样行为[22]。本文研究结果显示, 木犀草素可抑制Bax表达, 促进Bcl-2表达, 说明木犀草素可抑制神经元凋亡, 减轻小鼠抑郁症状。

Nrf2/HO-1信号通路是一个经典的抗氧化通路, 当机体受到氧化刺激, 可激活Nrf2使其与Keap1解离, 然后从细胞质转移至细胞核, 再与抗氧化反应原件结合, 激活HO-1, 提高机体SOD、GSH等抗氧化酶活性, 提高机体抗氧化能力[23]。而NLRP3作为炎症相关重要通路, 当机体受到刺激时, NLRP3可被激活, 然后通过ASC招募pro-Caspase-1, 形成NLRP3炎性小体, 促进IL-β等炎症因子的成熟与分泌, 进而加剧机体炎症反应[24]。另外, Nrf2可通过负调控NLRP3, 降低TNF-α、IL-6等炎症因子水平, 进而提高机体抗氧化、抗炎能力, 抑制神经元凋亡, 改善小鼠抑郁样行为。研究显示, 激活Nrf2/HO-1/NLRP3通路, 可减轻脂多糖诱导的大鼠神经炎症, 改善抑郁样行为[25]。激活Nrf2/HO-1通路可降低TNF-α、IL-6和IL-β的水平, 阻止海马炎症损伤, 改善小鼠的抑郁样行为[26]。另外, 激活Nrf2/HO-1通路可降低MDA、TNF-α、IL-6和IL-β的水平, 升高SOD活性, 抑制海马组织氧化应激和炎症损伤, 减少CUMS所致大鼠抑郁样行为[27]。本文研究结果显示, 木犀草素可上调Nrf2、HO-1表达, 下调NLRP3表达, 推测其可能通过激活Nrf2/HO-1/NLRP3信号通路抑制抑郁症小鼠海马神经元凋亡, 对木犀草素高剂量处理的抑郁症小鼠进行ML385处理, 发现其可部分逆转木犀草素对抑郁症小鼠神经元凋亡的改善作用, 说明木犀草素可通过激活Nrf2/HO-1/NLRP3信号通路抑制抑郁症小鼠海马神经元凋亡。

综上所述, 木犀草素可减轻抑郁症小鼠海马神经元凋亡, 其作用机制与激活Nrf2/HO-1/NLRP3信号通路相关。另外抑郁症的发病机制较复杂, 木犀草素也可能通过调控其他通路影响抑郁症的发生发展, 且本研究实验内容不全面, 仍需进一步探究论证。

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