chronic unpredicted mild stress (CUMS) model were used to evaluate the potential antidepressant effects of SOMCL-668. Western blotting assay was adopted to detect BDNF- GSK3β (glycogen synthase kinase 3β) pathway in the CUMS model. Immunostaining, immunoprecipitation, BDNF (brain-derived neurotrophic factor) secretion and neurite outgrowth were adopted to reveal the allosteric function of SOMCL-668 on sigma-1 receptor. **RESULTS** A single administration of SOMCL-668 decreased the immobility time in TST and FST, which were abolished by pretreatment of sigma-1 receptor antagonist BD1047. In the CUMS model, chronic application of SOMCL-668 rapidly ameliorated anhedonia-like behavior (within a week), accompanying with the enhanced expression of BDNF and phosphorylation of GSK3β (Ser-9) in the hippocampus. SOMCL-668 also rapidly promoted the phosphorylation of GSK3β (Ser-9) in an allosteric manner *in vitro*. In the cultured primary neurons, SOMCL-668 enhanced the sigma-1 receptor agonist-induced neurite outgrowth and the secretion of BDNF. **CONCLUSION** SOMCL-668, a novel allosteric modulator of sigma-1 receptors, elicits a potent and rapid acting antidepressant effect. The present data provides the first evidence that allosteric modulation of sigma-1 receptors may represent a new approach for antidepressant drug discovery.

Key words: allosteric modulation; antidepressant; sigma-1 receptors; brain-derived neurotrophic factor; glycogen synthase kinase 3β

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T1-6

PDE4抑制剂FCPR03抗抑郁及改善神经炎症作用的研究

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摘要:目的 研究化合物FCPR03对LPS诱导的神经炎症和小鼠抑郁症行为改善作用。**方法** 利用1 mg·L^{-1} LPS诱导BV-2小胶质细胞活化的方法来模拟体外神经炎症模型,评价FCPR03的体外抗神经炎症作用;采用对小鼠腹腔注射1.2 mg·kg^{-1} LPS 24 h后产生抑郁样行为的模型,来评价FCPR03的体内抗抑郁及改善神经炎症作用。**结果** ①1 mg·L^{-1} LPS刺激BV-2细胞24 h后,能显著地增加促炎性细胞因子(TNF-α,COX-2和iNOS)蛋白水平的产生,而经过FCPR03预处理后能浓度依赖性的降低细胞因子水平,提示FCPR03具有很好的抗神经炎症作用。②腹腔注射1.2 mg·kg^{-1} LPS 24 h后,旷场实验结果显示,各组间水平得分和垂直得分均没有统计学差异。而在悬尾和强迫游泳实验中,和正常组相比,模型组不动时间显著升高,给药后能够剂量依赖性的降低小鼠的不动时间,表现出很好的抗抑郁作用。**结论** PDE4抑制剂FCPR03能够改善LPS诱导的神经炎症,降低促炎性细胞因子的水平,同时还能够降低小鼠在悬尾和强迫游泳中不动时间,表明FCPR03同时具有抗抑郁和改善神经炎症的双重作用。

关键词:抑郁症; FCPR03; 细胞因子; 小胶质细胞; 神经炎症
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T1-7

Effects of chronic mild stress on behavioral and neurobiological parameters-role of glucocorticoid

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Abstract: Major depression is thought to originate from maladaptation to adverse events, particularly when impairments occur in mood-related brain regions. Hypothalamus-pituitary-adrenal (HPA) axis is one of the major systems involved in physiological stress response. HPA axis dysfunction and high glucocorticoid concentrations play an important role in the pathogenesis of depression. In addition, astrocytic disability and dysfunction of neurotrophin brain-derived neurotrophin factor (BDNF) greatly influence the development of depression and anxiety disorders. Therefore, we investigated whether depression-like and anxiety-like behaviors manifest in the absence of glucocorticoid production and circulation in adrenalectomized (ADX) rats after chronic mild stress (CMS) exposure and its potential molecular mechanisms. The results demonstrate that glucocorticoid-controlled rats showed anxiety-like behaviors but not depression-like behaviors after CMS. Molecular and cellular changes included the decreased BDNF in the hippocampus, astrocytic dysfunction with connexin43 (cx43) decreasing and abnormality in gap junction in prefrontal cortex (PFC). Interestingly, we did not find any changes in glucocorticoid receptor (GR) or its chaperone protein FK506 binding protein 51 (FKBP5) expression in the hippocampus or PFC in ADX rats subjected to CMS. In conclusion, the production and circulation of glucocorticoids are one of the contributing factors in the development of depression-like behaviors in response to CMS. In contrast, the effects of CMS on anxiety-like behaviors are independent of the presence of circulating glucocorticoids. Meanwhile, stress decreased GR expression and enhanced FKBP5 expression via higher glucocorticoid exposure. Gap junction dysfunction and changes in BDNF may be associated with anxiety-like behaviors.