补肾安志方对肾不藏志不寐大鼠焦虑失眠的改善机制研究Δ

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摘　要　目的　探讨补肾安志方（BSAZD）对肾不藏志不寐模型大鼠的改善机制。**方法**　将36只SD大鼠随机分为正常组（生理盐水）、模型组（生理盐水）、右佐匹克隆组（阳性对照组，0.27 mg/kg）和BSAZD低、中、高剂量组（5.85、11.70、23.40 g/kg），每组6只。除正常组外，其余各组均采用D-半乳糖联合DL-4-氯苯丙氨酸的方法制备肾不藏志不寐大鼠模型。造模结束后，灌胃相应药液/生理盐水，每天1次，连续14 d。末次给药后，观察大鼠行为学及海马组织病理形态学变化；采用非靶向代谢组学技术分析各组大鼠的血清差异代谢物及其富集的相关通路。**结果**　与模型组比较，BSAZD高剂量组大鼠开放臂进入次数、开放臂停留时间、睡眠时间均显著增加/延长（$P<0.05$），闭合臂进入次数、闭合臂停留时间、入睡潜伏期均显著减少/缩短（$P<0.05$）；海马组织神经元排列基本整齐，细胞核大小、形态及位置基本正常。非靶向代谢组学分析结果显示，BSAZD高剂量组对比模型组大鼠的血清差异代谢物包括氧化型谷胱甘肽、谷氨酸等，差异代谢物主要富集于γ-氨基丁酸能突触、谷氨酸能突触、环磷酸腺苷信号通路、2-氧代羧酸代谢等。**结论**　BSAZD可改善肾不藏志不寐大鼠睡眠质量，缓解焦虑样行为；其作用机制可能与调控γ-氨基丁酸能突触、谷氨酸能突触通路，恢复神经递质平衡，进而减轻氧化应激损伤，以及调节环磷酸腺苷信号通路促进神经修复和2-氧代羧酸代谢通路改善能量供应等相关。

关键词　补肾安志方；肾不藏志不寐；失眠症；非靶向代谢组学；差异代谢物

Study on the improvement mechanism of Bushen anzhi decoction on anxiety and insomnia in rats with kidney failing to store spirit

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ABSTRACT　OBJECTIVE To explore the intervention mechanism of Bushen anzhi decoction (BSAZD) in rats with insomnia induced by kidney failing to store spirit. **METHODS** A total of 36 SD rats were randomly divided into normal group (normal saline), model group (normal saline), eszopiclone group (positive control group, 0.27 mg/kg), and low-, medium- and high-dose BSAZD groups (5.85, 11.70, 23.40 g/kg), with 6 rats in each group. Except for the normal group, rats in the remaining groups were subjected to combined administration of D-galactose and DL-4-chlorophenylalanine to establish the rat model of insomnia due to kidney failing to store spirit. After successful modeling, corresponding liquid medicine or normal saline was intragastrically administered once daily for 14 consecutive days. After the last administration, behavioral indicators and hippocampal histopathological morphology of rats were detected. Untargeted metabolomics was adopted to screen serum differential metabolites and enrich relevant signaling pathways. **RESULTS** Compared with the model group, the high-dose BSAZD group exhibited significantly increased open arm entries , open arm time and sleep time ($P<0.05$), accompanied by markedly decreased closed arm entries, closed arm time and sleep latency ($P<0.05$). Hippocampal neurons in the high-dose BSAZD group were arranged regularly, and the size, morphology and location of cell nuclei were nearly normal. Untargeted metabolomics analysis identified oxidized glutathione, glutamate and other differential metabolites in serum of rats in the high-dose BSAZD group; these differential metabolites were mainly enriched in GABAergic synapse, glutamatergic synapse, cAMP signaling pathway and 2-oxocarboxylic acid metabolism pathway. **CONCLUSIONS** BSAZD can improve sleep quality, relieve anxiety-like behaviors in rats with insomnia due to kidney failing to store spirit. Its therapeutic mechanism may be associated with regulating GABAergic and glutamatergic synaptic pathways to restore neurotransmitter balance and further alleviate oxidative stress injury, modulating the cAMP signaling pathway to

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