加味小柴胡汤调控AKT/Bcl-xL/Bax/Caspase-3信号轴抑制癫痫小鼠海马神经元凋亡的机制研究Δ

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摘　要　目的　探讨加味小柴胡汤抑制急性癫痫模型小鼠海马神经元凋亡的作用机制。**方法**　将36只雄性KM小鼠随机分为正常对照组（生理盐水）、癫痫模型组（生理盐水）、加味小柴胡汤组[7 g/（kg·d）]、卡马西平组[阳性对照，30 mg/（kg·d）]，每组9只。除正常对照组外，其余各组小鼠均构建急性癫痫模型。造模成功后，各组小鼠连续灌胃相应药物/生理盐水2周，每天1次。给药结束后，观察小鼠海马CA1区超微结构及海马组织病理形态学变化，检测海马组织中TUNEL阳性细胞数以及蛋白激酶B（AKT）、胱天蛋白酶3（Caspase-3）、B细胞淋巴瘤-xL（Bcl-xL）、Bcl-2相关X蛋白（Bax）的表达水平和磷酸化AKT（p-AKT）/AKT比值。**结果**　与正常对照组比较，癫痫模型组小鼠海马CA1区超微结构及病理损伤严重；海马组织中TUNEL阳性细胞数显著增加（$P<0.05$），p-AKT、Bcl-xL表达均显著下调（$P<0.05$），Bax、Caspase-3表达均显著上调（$P<0.05$），p-AKT/AKT比值显著降低（$P<0.05$）。与癫痫模型组比较，加味小柴胡汤组小鼠海马组织超微结构、病理损伤及上述各指标均显著改善（$P<0.05$）。**结论**　加味小柴胡汤可抑制急性癫痫小鼠海马神经元凋亡；其机制可能与增强AKT磷酸化激活，提高p-AKT/AKT比值，上调Bcl-xL表达，下调Bax、Caspase-3表达有关。

关键词　加味小柴胡汤；癫痫；AKT/Bcl-xL/Bax/Caspase-3信号轴；神经元凋亡

Study on the mechanism of Jiawei xiaochaihu decoction inhibiting hippocampal neuronal apoptosis in epileptic mice via regulating AKT/Bcl-xL/Bax/Caspase-3 signaling axis

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ABSTRACT　OBJECTIVE To explore the mechanism of Jiawei xiaochaihu decoction against hippocampal neuronal apoptosis in acute epileptic model mice. **METHODS** Thirty-six male KM mice were randomly divided into four groups with 9 mice in each group: normal control group (normal saline), epilepsy model group (normal saline), Jiawei xiaochaihu decoction group [7 g/(kg·d)] and carbamazepine group [positive control, 30 mg/(kg·d)]. Except for the normal control group, the acute epilepsy model was established in the other groups. After successful modeling, mice in each group were given corresponding drugs or normal saline by intragastric administration once a day for 2 consecutive weeks. After drug intervention, the ultrastructure and pathological morphology of hippocampal CA1 region were observed. The number of TUNEL-positive cells in hippocampus was detected, and the expression levels of protein kinase B (AKT), Caspase-3, B-cell lymphoma-extra large (Bcl-xL), Bcl-2-associated X protein (Bax), as well as the ratio of phosphorylated AKT (p-AKT) to AKT were determined. **RESULTS** Compared with the normal control group, severe ultrastructural and pathological damages were observed in the hippocampal CA1 region of epilepsy model group; the number of TUNEL-positive cells was significantly increased ($P<0.05$). The expression levels of p-AKT and Bcl-xL were significantly down-regulated ($P<0.05$), while the Bax and Caspase-3 were significantly up-regulated ($P<0.05$), accompanied by a remarkable decrease of p-AKT/AKT ratio ($P<0.05$). Compared with the epilepsy model group, hippocampal tissue ultrastructure, pathological damage, and the aforementioned indicators were significantly improved in Jiawei xiaochaihu decoction group ($P<0.05$). **CONCLUSIONS** Jiawei xiaochaihu decoction can inhibit hippocampal neuronal apoptosis in acute epileptic mice, and its mechanism may be related to activating AKT phosphorylation, increasing p-AKT/AKT ratio, up-regulating Bcl-xL expression and down-regulating the expression of Bax and Caspase-3.

KEYWORDS　Jiawei xiaochaihu decoction; epilepsy; AKT/Bcl-xL/Bax/Caspase-3 signaling axis; neuronal apoptosis

癫痫是一种由大脑神经元高度同步化异常放电所导致的神经系统疾病，具有反复发作、自发性等特点，全球范围内有数千万患者深受其困扰[1]。尽管目前的抗癫

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