论著

缬沙坦联合川芎嗪对血管性痴呆模型大鼠空间学习记忆能力的影响

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摘要　目的　比较缬沙坦和川芎嗪单独及联合应用对血管性痴呆（VD）模型大鼠空间学习记忆能力的影响，并探讨其可能的作用机制。方法　大鼠ip给予硝普钠2.5 mg·kg^{-1}后，夹闭双侧颈总动脉缺血10 min，再灌注10 min，重复2次，制备VD大鼠模型。VD模型制备后24 h，治疗组大鼠于每天上午9:00 ig给予缬沙坦8 mg·kg^{-1}，川芎嗪25 mg·kg^{-1}或缬沙坦＋川芎嗪（8＋25 mg·kg^{-1}），每天1次，连续15 d，同时设假手术和模型组。Morris水迷宫检测大鼠空间学习记忆能力；Morris水迷宫实验结束后第2天取海马，逆转录PCR检测海马组织白细胞介素1β（IL-1β）mRNA表达；免疫组织化学法检测海马肿瘤坏死因子α(TNF-α)，Bcl-2和Bax蛋白表达。结果　末次给药后连续5 d进行大鼠定位航行训练，训练的第3，4和第5天，模型组大鼠逃避潜伏期分别为43±19，22±10和（16±7）s，与假手术组32±15，16±8和（10±6）s比较明显延长（P<0.05）；第6天，模型组大鼠在平台象限停留时间为(35.3±10.0)s，跨越虚拟平台（3.4±1.7）次，平台象限游程百分比为(30±6)%，与假手术组（6.3±2.5）s，(51±11)次和（38±8）%比较明显降低（P<0.05）；模型组大鼠海马组织IL-1β mRNA和海马CA1区TNF-α，Bcl-2和Bax蛋白表达与假手术组比较明显增加（P<0.05）。与模型组比较，第4和第5天，缬沙坦、川芎嗪单用和联合应用组大鼠逃避潜伏期明显缩短，分别为18±9和（13±7）s，18±9和（14±7）s及17±8和（11±7）s（P<0.05，P<0.01）；联用组大鼠跨越平台的次数、在平台象限停留的时间及平台象限游程百分比均明显增加，分别为（5.6±1.9）次，（50±8）s和（37±6）%（P<0.05），缬沙坦和川芎嗪单用组上述指标改变不明显；二者联用组海马IL-1β mRNA，TNF-α和Bax蛋白表达均明显降低，Bcl-2蛋白表达明显增强（P<0.01）；缬沙坦和川芎嗪单用组海马CA1区Bcl-2蛋白表达增强，Bax蛋白表达降低（P<0.01），海马组织IL-1β mRNA表达无明显变化；缬沙坦组海马CA1区TNF-α蛋白表达减少（P<0.05）；川芎嗪组TNF-α蛋白表达无明显改变。结论　缬沙坦及川芎嗪可改善VD大鼠学习记忆功能，二者联用作用更加明显。该作用可能与其抑制炎症反应及抑制海马神经元凋亡有关。

关键词　　缬沙坦　川芎嗪　血管性痴呆　白细胞介素1β　肿瘤坏死因子α　Bcl-2　Bax

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Effects of coadministration of valsartan and ligustrazine on spatial learning and memory in vascular dementia model rats

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Abstract

OBJECTIVE To investigate the effect of coadministration of valsartan and ligustrazine on spatial learning and memory in vascular dementia (VD) rats and the possible mechanism. **METHODS** A VD model was established by ip giving rats sodium nitroprusside 2.5 mg·kg^{-1}, followed by ischemia 10 min/reperfusion 10 min via blocking the bilateral carotid artery. After 24 h, the rats were divided into sham, model, valsartan 8 mg·kg^{-1}, ligustrazine 25 mg·kg^{-1} and valsartan+ligustrazine (8+25 mg·kg^{-1}) groups. The drugs were ig given,once a day for 15 d. The spatial learning and memory ability of VD rats were measured with Morris water maze once daily for 5 d after the last drug administration. On the 6th day, the hippocampal tissue of rats was taken and the expression of interleukin 1β (IL-1β) mRNA was determined by RT-PCR. The expression of tumor necrosis factor-α (TNF-α), Bcl-2 and Bax proteins in the hippocampal tissue was detected by immunohistochemical method. **RESULTS** On the 3rd, 4th and 5th day after the last drug treatment, the escape latency of rats in VD model group was 43±19，22±10 and (16±7)s, which was obviously increased compared with 32±15, 16±8 and (10±6)s in the sham group (P<0.05). On the 6th day, the time of rats spent in the target quadrant was (35.1±10.0)s, the number of times of crossing the platform was 3.4±1.7, and the run percentage of the target quadrant was (30±6)% in model group, compared with (51±11)s , 6.3±2.5 and (38±8)% in the sham group (P<0.05) while IL-1β mRNA expression in hippocampal tissue, TNF-α, Bcl-2 and Bax proteins in CA1 area of hippocampus were increased. On the 4th and 5th day, compared with the VD model group, valsartan and ligustrazine given separately or combination could shorten the escape latency, which was 18±9 and (13±7)s, 18±9 and (14±7)s, and 17±8 and (11±7)s, respectively (P<0.05, P<0.01). Coadministration could increase the number of times rats cross the platform, the time spent in the target quadrant and the run percentage of the target quadrant of rats. They were 5.6±1.9, (50±8)s and (37±6)％, respectively (P<0.05). However, there was no obvious change in groups given valsartan and ligustrazine separately. The expression of IL-1β mRNA, TNF-α

and Bax proteins was obviously reduced and Bcl-2 protein was obviously enhanced in coadministration group ($P<0.01$). In the groups given valsartan and ligustrazine separately, the expression of Bax was reduced, and Bcl-2 was enhanced, but IL-1β mRNA expression showed no significant difference. TNF-α expression was decreased in valsartan group, but there was no significant difference in ligustrazine group. **CONCLUSION** Valsartan and ligustrazine can improve learning and memory abilities in VD model rats, especially in drug combination group. This action may be related to the inhibition of inflammatory reaction and hippocampal neurons apoptosis in rats.

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