

纳洛酮通过加强压力反射抑制缺血性心律失常

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Naloxone suppresses ischemic arrhythmias via potentiating baroreflex

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AIM: To study the relationship between the anti-arrhythmia action of naloxone (Nal) and its effect on baroreflex sensitivity (BRS).

METHODS: Acute myocardial infarction was produced by ligating coronary artery in Sprague-Dawley rats. Ventricular extrasystole (VE), tachycardia (VT), and fibrillation (VF) were recorded on ECG. The slopes of linear regression (b) from systolic blood pressure and cardiac cycle after intravenous injection (iv) of phenylephrine $2 \mu\text{g}$ was taken as the BRS. The area of infarct was estimated after TTC staining. **RESULTS:** Nal 0.5 mg iv, intracisternal injection (ic) of Nal 0.1 mg , and ic β -endorphin (β -End) antiserum $10 \mu\text{L}$ suppressed the ischemic arrhythmias, arrhythmia score was 1.8 ± 1.1 (Nal iv) vs 3.8 ± 2.1 (Saline iv); 1.7 ± 1.5 (Nal ic) vs 4.0 ± 2.6 (Artificial CSF ic) and 1.7 ± 1.6 (β -End antiserum ic) vs 4.1 ± 2.0 (Serum ic) ($P < 0.05$) and potentiated the BRS, BRS was 4.2 ± 1.8 (Nal iv) vs 2.9 ± 0.8 (saline iv); 4.5 ± 1.7 (Nal ic) vs 2.8 ± 0.7 (Artificial CSF ic) and 4.4 ± 1.1 (β -End antiserum ic) vs 3.0 ± 0.9 (Serum ic) ($P < 0.05$). BRS showed

negative relations to the arrhythmia scores with r of -0.69 for iv Nal, -0.72 for ic Nal, and -0.67 for ic β -End antiserum ($P < 0.05$). **CONCLUSION:** Nal suppressed ischemic arrhythmias via antagonization of beta-endorphin and potentiation of BRS.

KEY WORDS naloxone; pressoreceptors; myocardial infarction; beta-endorphin; arrhythmia

目的 研究纳洛酮 (Nal) 抗心律失常作用与其对压力反射敏感性 (BRS) 影响的关系。 **方法:** 以冠状动脉结扎法制备 Sprague-Dawley 大鼠急性心肌梗塞模型, 心电图记录室性早搏 (VE), 室性心动过速 (VT) 和心室颤动 (VF); 静脉注射苯肾上腺素后同步记录的收缩压与心动周期变化的回归直线斜率 (b) 为 BRS; TTC 染色法评价梗死范围。 **结果:** Nal 0.5 mg iv, 小脑延髓池注射 (ic) Nal 0.1 mg 和 ic β -内啡肽 (β -End) 抗血清 $10 \mu\text{L}$ 可抑制缺血性心律失常, 心律失常积分为 1.8 ± 1.1 (Nal iv) vs 3.8 ± 2.1 (生理盐水 iv); 1.7 ± 1.5 (Nal ic) vs 4.0 ± 2.6 (人工脑脊液 ic) 和 1.7 ± 1.6 (β -End 抗血清 ic) vs 4.1 ± 2.0 (血清 ic) ($P < 0.05$); 并可加强 BRS, BRS 为 4.2 ± 1.8 (Nal iv) vs 2.9 ± 0.8 (生理盐水 iv); 4.5 ± 1.7 (Nal ic) vs 2.8 ± 0.7 (人工脑脊液 ic) 和 4.4 ± 1.1 (β -End 抗血清 ic) vs 3.0 ± 0.9 (血清 ic) ($P < 0.05$)。 BRS 与心律失常积分呈负相关, r 值分别为 -0.69 (Nal, iv); -0.72 (Nal, ic) 及 -0.67 (β -End 抗血清, ic)。 P 值均 < 0.05 。 **结论:** Nal 通过拮抗中枢 β -End 及加强 BRS 起抗心律失常作用。

关键词 纳洛酮; 压力感受器; 心肌梗死; β -内啡肽; 心律失常

纳洛酮 (naloxone, Nal) 有抗缺血性心律失常作用^[1], 离体实验表明 Nal 拮抗心脏局部的内源性阿片肽 (EOP) 的 κ 受体^[2]. 中枢神经系统在缺血性心律失常中起作用, 过低的压力反射敏感性 (BRS) (迷走反射功能 \downarrow) 是急性心肌梗死 (AMI) 早期发生室颤的独立预报因子^[3,4,5], EOP 可抑制 BRS, 而 Nal 可拮抗 EOP 而增强 BRS^[6,7], 为探讨 Nal 的抗心律失常作用是否与加强 BRS 有关及其可能的作用部位, 本实验比较了静脉 (iv) 及小脑延髓池 (ic) 分别注射 Nal 对 BRS 及缺血性心律失常的影响.

MATERIALS AND METHODS

药品 纳洛酮 (Sigma), 苯肾上腺素 (上海天丰制药厂, 批号 880501), β -内啡肽抗血清 (第二军医大学神经生物学教研室制备^[8]) 效价 1:30000 与其它 EOP 的交叉反应 < 1 %.

急性心肌梗死模型制备 Sprague-Dawley 大鼠, ♂, 体重 280 \pm 42 g (由上海中英合资西普尔-必凯动物中心提供), 以 20 % 乌拉坦 1.3 g \cdot kg⁻¹ ip 麻醉, 右股动静脉分别插管以记录血压和给药, 四肢皮下插入电极记录心电图, 气管插管行人工呼吸, 经左侧第四肋间开胸, 以肺动脉圆锥与左心耳交界处的左冠状静脉为标志, (此处冠状动脉与之伴行) 以 3/8 Cr 3 \times 6 不锈钢小园针 5-0 丝线穿过左心耳下缘 2 mm 浅层心肌, 穿线后稳定 15 min (如此时出现心律失常和收缩压低于 9.3 kPa 持续 5 min 以上则废除该鼠). 冠脉结扎后, 连续记录 30 min 的 ECG 及血压变化. 于 AMI 后 4 h 处死, 取心脏行 TTC 染色以评价梗死范围.

BRS 测定 苯福林 2 μ g iv 同步记录收缩压 (SBP) 和心动周期, 取 5 个点的 SBP 与心动周期求出其回归直线斜率 b 值代表 BRS, 单位 ms \cdot kPa⁻¹.

心律失常的评价 心律失常的严重程度以冠状动脉结扎后 30 min 内出现的室性早搏 (VE) 个数, 室性心动过速和室颤 (VT+VF) 的持续时间 (s) 及其对数

值 lg VE, lg (VT+VF); VE, VT, VF 的发生率, 心律失常积分 (arrhythmia score) (Tab 1) 等来表示.

Tab 1. Score for ischemic arrhythmias between 0-30 min after coronary artery ligation.

- 0=0-49 VE
- 1=50-499 VE
- 2 =>500 VE and / or 1 episode of spontaneously reverted VT or VF
- 3 =>1 episode of VT or VF, total duration < 60 s
- 4=VT or VF, total duration 60-119 s
- 5=VT or VF, total duration > 120 s
- 6=Lethal VF occurs after 15 min of occlusion
- 7=Lethal VF occurs between 4 and 14 min 59 s
- 8=Lethal VF occurs between 1 and 3 min 59 s
- 9=Lethal VF occurs within 1 min

梗死范围的评价 见参考文献[9].

小脑延髓池给药法 麻醉大鼠, 尽量屈曲其头部, 在枕骨大孔下缘上方持针成 30 度斜面向尾部方向进针, 至有落空感并回抽有脑脊液时, 表示针尖已到位, 缓慢推注药品, 5 min 内推完.

实验设计与统计 大鼠随机分为给药组及对照组, iv Nal 以等容量生理盐水为对照, ic Nal 及 ic β -EP 抗血清则分别以等容量人工脑脊液 (ACSF) 及正常兔血清为对照, 在插管后 10 min 测定 BRS 作为基础值, iv, ic Nal 后 10 min, ic β -EP 抗血清后 15 min 再测定一次 BRS, 作为给药后 BRS 值, 稳定 5 min 后结扎冠脉. 各组给药后冠状动脉结扎前的 BRS 值均作为梗死前 BRS 与梗死后的心律失常积分进行直线相关回归分析, 并进行相关系数的显著性检验, 各组均与各自的对照组进行 t 检验, 心律失常积分以 t 检验, 心律失常发生率以 χ^2 检验处理, 各组间梗死面积以方差分析处理.

RESULTS

各组给药前 HR 和 BP 无显著差异, 在 iv, ic Nal 10 min, ic β -EP 抗血清 15 min 时各组 HR 和 BP 均无明显差别.

各组给药前 BRS 无明显差别. 而 iv, ic Nal, ic β -EP 抗血清较对照组 BRS 明显提高. 心律失常严重程度和心律失常积分明显降低. 但心律失常的发生率并未明显降低 (Tab 2).

以给药后梗死前的 BRS 与梗死后的心律失常积分间进行直线回归, 发现无论 iv, ic 纳洛酮组, ic β -EP 抗血清组, BRS 均与心律失常积分之间呈现负相关, r 值分别为 -0.69 (iv, Nal 组), -0.72 (ic, Nal 组) 和 -0.67 (ic, β -EP 抗血清组), $P < 0.05$. (Fig 1)

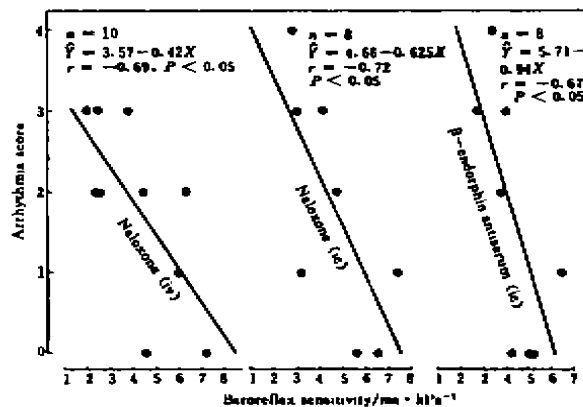


Fig 1. Relation between baroreflex sensitivity and arrhythmia score after coronary ligation in intravenous (iv) or intracisternal (ic) naloxone and β -endorphin antiserum in Sprague-Dawley rats.

各组以 TTC 染色评估的梗死面积无显著

差异. (Tab 2)

DISCUSSION

本实验首次发现静脉 (外周) 及小脑延髓池 (中枢) 给予 Nal 的抗心律失常作用均与其加强 BRS 有关, 说明提高 BRS 具有抗心律失常作用, 同时本实验还首次发现中枢给予 β -EP 抗血清也具有与 Nal 相似的加强 BRS 及抗心律失常作用, 提示内源性阿片肽拮抗剂 Nal 的抗心律失常机制在于拮抗中枢 β -EP 对 BRS 的抑制作用从而加强 BRS.

外周 Nal iv 有抗心律失常作用, 但因其可透过血脑屏障, 难以区分其作用是外周或中枢机制, 结合 ic Nal 与 β -EP 抗血清的结果, 说明其作用机制为中枢性, 这一结论与文献⁽²⁾所发现的 Nal 通过拮抗心脏局部 κ 受体起抗心律失常作用不同, 以往文献^(1, 2)未同时比较中枢与静脉给药的抗心律失常效果. 同时未观察 Nal 对 BRS 的影响及其与抗心律失常作用的关系, 且为离体实验的结果, 可能是这一差别的原因.

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Tab 2. Effects of naloxone and β -endorphin antiserum given intravenously (iv) and intracisternally (ic) on baroreflex sensitivity and arrhythmia 0-30 min after coronary ligation. $\bar{x} \pm s$, ^b $P < 0.05$, vs control group.

	n	Dose	BRS	Incidence (%)			lg VE	lg duration (VT+VF)	Arrhythmia score	Infarct size (%)
				VE	VT	VF				
Naloxone, iv	10	0.5 mg	4.2 ± 1.8 ^b	80	30	10	2.2 ± 0.9	1.2 ± 0.36 ^b	1.8 ± 1.1 ^b	25 ± 8
Saline, iv	8	0.1 mL	2.9 ± 0.8	87	63	37	2.7 ± 0.7	1.9 ± 0.6	3.8 ± 2.1	30 ± 6.5
Naloxone, ic	8	0.1 mg	4.5 ± 1.7 ^b	75	37	25	2.0 ± 0.7	1.2 ± 0.4 ^b	1.7 ± 1.5 ^b	27 ± 8
Artificial CSF, ic	8	10 μ L	2.8 ± 0.7	87	63	50	2.7 ± 0.8	2.0 ± 0.9	4.0 ± 2.6	29 ± 8
β -Endorphin antiserum, ic	8	10 μ L	4.4 ± 1.1 ^b	75	50	25	1.9 ± 0.9	1.3 ± 0.4 ^b	1.7 ± 1.6 ^b	25 ± 7
Serum, ic	6	10 μ L	3.0 ± 0.9	100	83	67	2.9 ± 0.4	2.1 ± 0.6	4.1 ± 2.0	26 ± 7

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东亚钳蝎蝎毒二、三级提取物对快反应心肌细胞动作电位的影响

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Influence of the 2nd and 3rd grade abstracts from scorpion venom of *Buthus martensii* Karsch on action potentials of fast response myocardiocytes

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AIM: To screen the active components of sodium channel blockade action from *Buthus martensii* Karsch (BMK) scorpion venom. **METHODS:** Myocardiocytes of mice were

cultured. Action potentials of fast response myocardiocytes were recorded. The effects of 22 contents of BMK scorpion venom in a concentration of 3 mg · L⁻¹ were tested and compared with that of TTX 2.5 mg · L⁻¹, nimodipine (Nim) 3 mg · L⁻¹ and BaCl₂ 24.4 mg · L⁻¹. **RESULTS:** BMK-1 and other 19 contents significantly decreased depolarization parameters V_{max}, APA, OS, and MDP, which was similar to that of TTX and different from that of Nim and BaCl₂. **CONCLUSION:** The variations in the action potentials of fast response myocardiocytes indicated that 20 contents of BMK scorpion venom had sodium channel blockade action.

KEY WORDS cultured cells; myocardium; action potentials; scorpion venoms

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