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组胺与麻醉猫缺血早期心律失常[1]

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Histamine and early ischemic arrhythmia in anesthetized cats[1]

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ABSTRACT Ligation of left anterior decending coronary artery caused various arrhythmias and reduced histamine content in ischemic myocardium in anesthetized cats. Intracoronary injection of compound 48-80 100 μg shortened the onset of VT and VF from 13 ± 5, 18 ± 5 min ($n=7$) in control to 7.2 ± 1.1 ($P<0.01$), 11 ± 5 min ($P<0.05$) ($n=6$) respectively, elevated the histamine concentration of plasma after acute coronary artery occlussion (15 ± 3, 26 ± 10 ng / ml, $P<0.05$, before and after ligation respectively). Iv chlorpheniramine (5, 10 mg / kg) or cimetidine (20, 40 mg / kg) dose-dependently reduced arrhythmia score, incidence of VF and mortality after myocardial ischemia, but with little influence on histamine content in ischemic myocardium and plasma. These results suggest that release of histamine from the ischemic myocardium is involved in the generation of early arrhythmias through H_1 and H_2 receptors in anesthetized cats subjected to acute coronary artery occlussion.

KEY WORDS histamine; myocardium; ischemia; arrhythmia; compound 48-80; chlorpheniramine; cimetidine

提要 结扎猫冠状动脉可致各种心律失常、左室缺血区心肌组胺(His)含量下降. 冠脉内注射化合物 48-80 100 μg 明显缩短 VT, VF 出现时间分别从对照组 13 ± 5, 18 ± 5 min ($n=7$) 提前到 7.2 ± 1.1 ($P<0.01$), 11 ± 5 min ($P<0.05$) ($n=6$), 且结扎后血浆 His 明显增加(结扎前后分别为 15 ± 3, 26 ± 10 ng / ml, $P<0.05$). Iv 氯苯吡胺(5, 10 mg / kg)或西咪替丁(20, 40 mg / kg)剂量依赖性减少心律失常得分、降低 VF 发生率, 而不影响心肌及血浆 His 含量, 提示麻醉猫缺血心脏释放 His, 通过 H_1 及 H_2 受体参与早期缺血性心律失常的产生.

关键词 组胺; 心肌; 缺血; 心律失常; 化合物 48-80; 氯苯吡胺; 西咪替丁

组胺(histamine, His)具高度致心律失常作用[1]. 急性心肌缺血后, 大鼠、豚鼠及兔左心室缺血区心肌 His 含量明显降低[2]; 犬急性心肌缺血早期心脏 His 释放量与早搏数目及室颤发生率相平行[1]; 组胺 H_2 受体拮抗剂减轻麻醉大鼠[3]、犬[4]心肌缺血早期心律失常. 但由于心脏 His 受体分布及其中介的反应存在明显的种属差异, His 在心肌缺血早期心律失常产生中的作用仍待证实. 结扎猫冠状动脉可致心律失常, 但尚未见其与心脏 His 释放或 His 受体关系的报道. 本文利用麻醉猫缺血性心律失常模型, 以观察心脏内源性 His 在缺血早期心律失常产生中的作用.

MATERIALS AND METHODS

药品与试剂 化合物 48-80(compound 48-80, CP 48-80)为 Sigma 产品; 西咪替丁(cimetidine, Cim)原料为西南制药厂生产, 将 Cim 用少量稀盐酸溶解后, 再用生理盐水配成母液备用; 氯苯吡胺(chlorpheniramine, Chl)注射液为北京制药厂生产. 以上各药均于临用前以生理盐水溶解或稀释. 二磷酸组胺为中国科学院上海生化研究所产品. His 测定中所用试剂均为 AR 级.

缺血性心律失常模型制备 猫 69 只, 体重 2.5 ± SD 0.3 kg, ♀♂不拘, im 氯胺酮 12.5 mg / kg 后, iv 氯醛糖 35 mg / kg 麻醉, 15 min 后行气管插管, 人工通气, 于左侧第 4 肋间开胸, 暴露心脏, 分离冠状动脉左前降支,

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在其发出第一分支后的主干下穿线，分离出一侧股动、静脉，插管后分别用于描记平均动脉血压及给药或输液.

手术完毕后记录血压及肢体Ⅱ导心电图，待血压稳定后，iv 药物或生理盐水，10 min 后结扎冠脉(假结冠组仅穿线而不结扎). Iv 后连续同步记录血压及心电图于四道生理记录仪(RM-6200，成都仪器厂)至结扎冠脉后 30 min 或猫室颤致死为止. 全过程用微量蠕动泵恒速输注生理盐水 0.2 ml / (kg · min).

实验分 3 部分：(1)结扎冠脉后心脏($n=5$)His 释放及心律失常发生情况，与假结冠组($n=5$)比较；(2)CP 48-80 冠状动脉内注射[5]后立即结扎冠脉($n=6$)对心脏 His 释放和心律失常的影响，与冠状动脉内注射生理盐水组($n=7$)比较；(3)His 受体拮抗剂 Chl，Cim 预处理对结扎冠脉后心脏 His 释放和心律失常的影响(分 5 组，每组 $n=7$)以及对 CP 48-80 作用的影响($n=11$).

心律失常记录 根据心电图变化将心律失常分为：早搏(ES)，包括房性、室性及结性早搏；室性心动过速(VT)，指连续 6 个或以上的室性早搏；心室纤颤(VF)；VT，VF 发生率及猫死亡率. 心律失常严重程度用心律失常得分[6]表示.

组胺测定 结扎冠脉 30 min 或猫 VF 致死后快速取心，用冰盐水洗净血液. 从冠脉左前降支支配的左室前壁及相对应的非左前降支支配的左室后壁分别取心肌各 0.2g，用高氯酸 0.5 mol / L 于 Potters 匀浆机(1400 rpm)制成匀浆. 取实验前后右心血制备血浆 0.5 ml，加高氯酸 0.5 mol / L 沉淀蛋白. 取上述心肌及血浆去蛋白后的上清液，依 HPLC 法[7]测定 His 含量.

RESULTS

缺血早期心律失常与心肌及血浆 His 含量变化 结扎猫冠脉可出现各种类型心律失常，包括单发或连发 ES，VT 及 VF. 在发生时间上存在两个时相：发生在 10 min 内(I_a 相)的心律失常主要为各型 ES，少见 VT，无死亡发生；10 min 后出现的(I_b 相)心律失常 ES 及 VT 频繁，尤以后者多见，猫主要在此时相死于 VF.

假结冠组左室前壁与后壁心肌 His 含量无差别；血浆 His 水平亦无变化，结冠组缺血区心肌 His 含量低于非缺血区，但 $P>0.05$，与假结冠组相比，缺血区心肌 His 含量显著下降($P<0.05$)，非缺血区心肌 His 含量亦减少，但 $P>0.05$；结扎冠脉前后血浆 His 含量变化不明显(Tab 1).

His 释放剂对缺血早期心律失常及 His 含量的影响 CP 48-80 组心律失常得分、VT 及 VF 发生率、猫死亡率与对照组无显著差别

Tab 1. Effects of left anterior decending coronary artery ligation (CAL) and intracoronary injection of compound 48-80 (CP 48-80) 100 μg + CAL on histamine content in myocardium and right ventricular plasma in anesthetized cats. $\bar{x} \pm SD$. $^{*}P>0.05$, $^{**}P<0.05$ *vs* **sham-ligation or saline;** $^{+}P>0.05$, $^{++}P<0.05$ *vs* **before.**

	In myocardium (ng / g)		In plasma (ng / ml)	
	Ischemic	Nonischemic	Before	After
Sham-ligation ($n=5$)	180 ± 55	176 ± 67	12 ± 4	12 ± 4^{+}
CAL ($n=5$)	114 ± 21**	150 ± 49*	9.6 ± 1.7	9.4 ± 1.6^{+}
Saline + CAL ($n=6$)	102 ± 18	130 ± 47	16 ± 4	16 ± 6^{+}
CP 48-80 + CAL ($n=6$)	109 ± 10*	142 ± 49*	15 ± 3	26 ± 10^{++}

Tab 2. Effects of intracoronary CP 48–80 100 μg or iv chlorpheniramine (Chl), cimetidine (Cim) on arrhythmia and mortality in anesthetized cats subjected to left anterior decending coronary artery ligation. $\bar{x} \pm SD$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* saline.

Drug (mg / kg)	*n*	Arrhythmia score	Log ES	Incidence (%) VT	Incidence (%) VF	Mortality (%)
Saline	7	7.7 ± 0.5	2.5 ± 0.4	100.0	100.0	71.4
CP 48–80	6	8.0 ± 0.0*	1.5 ± 0.4**	83.3*	100.0*	100.0*
CP 48–80+ Chl 10	6	3.7 ± 2.6**	2.2 ± 0.3*	16.7**	16.7**	0.0**
CP 48–80+ Cim 40	5	3.2 ± 1.9**	2.3 ± 0.5*	40.0*	0.0***	0.0**
Saline	7	7.7 ± 0.8	2.7 ± 0.4	85.7	85.7	85.7
Chlorpheniramine						
5	7	3.7 ± 2.4**	2.6 ± 0.4*	14 3**	14.3**	14.3**
10	7	2.6 ± 1.7**	2.2 ± 0.5*	28 6*	0.0***	0.0***
Cimetidine						
20	7	5.0 ± 1.4**	2.9 ± 0.3*	71.4*	14.3**	0.0**
40	7	2.7 ± 1.5**	2.2 ± 0.2**	28.6*	0.0***	0.0***

(Tab 2)，但 CP 48–80 使心律失常第二时相高峰明显前移，盐水对照组 VT，VF 出现时间分别为 13 ± 5，18 ± 5 min($n=7$)；CP 48–80 组 VT，VF 出现时间显著提前，分别为 7.2 ± 1.1($P<0.01$)及 11 ± 5 min($P<0.05$, $n=6$). CP 48–80 减少早搏数目(Tab 2)，而代之以提前出现的持续性 VT，其第二时相几乎全部以 VT 形式出现. 其中一只猫未发 ES 及 VT，而以突发 VF 致死.

CP 48–80 使结扎冠脉后血浆 His 水平较结扎前显著升高($P<0.05$)；左室缺血区心肌 His 含量略低于非缺血区($P>0.05$)(Tab 1).

His 受体拮抗剂对缺血早期心律失常及 His 含量的影响 H_1 受体拮抗剂 Chl 及 H_2 受体拮抗剂 Cim 均呈剂量依赖性减少心律失常得分($P<0.01$)、降低 VF 发生率及猫死亡率，Cim 40 mg / kg 还可减少 ES ($P<0.05$) (Tab 2). 此外，冠脉内注射 CP 48–80 前，予先 iv H_1 或 H_2 受体拮抗剂可对抗 CP 48–80 加重心律失常的效应，显著减少心律失常得分($P<0.01$)、降低 VF 发生率($P<0.05$, 0.01)及猫死亡率($P<0.05$) (Tab 2).

两种 His 受体拮抗剂对心肌及血浆 His 含量无显著影响.

平均动脉血压及心率的变化 麻醉猫用药前各组之间的 BP，HR 无显著差别. Iv Chl 5, 10 mg / kg 或 Cim 20, 40 mg / kg 呈剂量依赖性减慢 HR、降低 BP，这种变化在用药后的 2 min 内达高峰，然后逐渐恢复，于结扎冠脉前(除 Cim 40mg / kg 外)均可达用药前水平. 冠状动脉内注入 CP 48–80 100 μg 对 BP，HR 均无影响.

DISCUSSION

麻醉猫急性心肌缺血后出现各种类型心律失常，同时左室缺血区心肌组胺明显减少，与在啮齿动物观察到的结果[2]相符. 提示缺血可致心肌释放组胺. 本实验未观察到血浆组胺含量的增加(Tab 1)，这可能是组胺释放存在种属差异[2]，猫心肌组胺释放量偏低所致. 非缺血区组胺含量亦有所减少，提示组胺释放可能还有某种反射机理参与.

为避免化合物 48–80 的全身作用，本文采用冠脉内给药，化合物 48–80 可使结扎冠脉后血中组胺增加，同时心律失常加重，提示内源性组胺在缺血早期心律失常产生中占重要地位. 文献报道[8]用脱羧酶抑制剂选择性抑制组胺生成后，可减轻麻醉大鼠结扎冠脉早期心律失常的产生，与本文结果相符.

H_1 及 H_2 受体拮抗剂具显著抗缺血性心

律失常作用，且两种拮抗剂均可取消化合物48-80加重心律失常的效应，而对组胺含量无明显影响．提示内源性组胺的致心律失常作用由 H_1 及 H_2 两种受体中介．但目前对猫心脏组胺受体分布亚型了解较少，与大鼠心脏类似，猫心室肌组胺受体也甚稀少[9]，而 H_2 受体拮抗剂亦能对抗大鼠缺血性心律失常，提示在心肌缺血情况下心脏组胺受体可能在亲和力或数量上发生了某种变化，有待探讨．

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Effects of *m*-nisoldipine on anoxia-potentiated histamine and acetylcholine-induced contractions of the porcine isolated coronary artery

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ABSTRACT Anoxia (95% N_2 + 5% CO_2) potentiated the contractile response to KCl 20 mmol / L, histamine (His) 5 μmol / L and acetylcholine (ACh) 0.5 μmol / L in isolated porcine coronary arterial rings. Calcium antagonists *m*-nisoldipine (*m*-Nis) and nisoldipine (Nis) 0.4-250 nmol / L produced a concentration-dependent decrease in both KCl, His and anoxia-potentiated KCl, His or ACh-induced contractions. Chlorpheniramine 10 μmol / L but not cimetidine 10 μmol / L and atropine 10 μmol / L abolished contractions induced by His and ACh respectively. All 3 agents did not affect KCl response and the anoxia facilitation. Indomethacin 10 μmol / L markedly attenuated the further increase in tension by anoxia but failed to inhibit the response by these vasoconstrictors.

KEY WORDS *m*-nisoldipine; nisoldipine; indomethacin; histamine; acetylcholine; potassium chloride; coronary vessels; anoxia

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Anoxia augments contractile response to KCl[1], 5-HT[1,2] and $PGF_{2\alpha}$ [3] in isolated canine coronary artery. It has been suggested that the anoxic augmentation of the contraction is relative to coronary artery spasm[2]. The mechanism of the anoxia augmentation to the vasoconstrictors is