antianginal agent, in the conscious dog. *J Cardiovasc Pharmacol* 1985; 7 : 709
2 Pieper GM, Gross GJ. Salutary action of nicorandil, a new antianginal drug, on myocardial metabolism during ischemia and on postischemic function in a canine preparation of brief, repetitive coronary artery occlusions: comparison with isosorbide dinitrate. *Circulation* 1987; 76 : 916
3 Gross GJ, Warltier DC, Hardman HF, Lamping KA. Enhanced subendocardial perfusion distal to a flow-limiting coronary artery stenosis in dogs: comparative effects of nicorandil, a potential new antianginal agent, and nitroglycerin. *J Cardiovasc Pharmacol* 1985; 7 : 977
4 Chen SL, Zang YM, Zhu MZ, Pan Z. Effects of stenosis on blood flow in the coronary artery of dogs. *Acta Physiol Sin* 1989; 41 : 96
5 Chen SL, Zang YM, Pan Z, Zhu MZ. The effects of coronary artery stenosis on cardiac function. *Chin J Pathophysiol* 1988; 4 : 276
6 Chen SL, Zang YM, Zhu MZ, Luo BQ, Liu DM, Liang H. The relationship between coronary artery stenosis and myocardial metabolism of oxygen demand in dogs. *Acta Physiol Sin* 1989; 41 : 272
7 Sakamoto S, Yokoyama M, Kashiki M, Fukuzaki H. Comparative effects of intracoronary vasodilators on restoring coronary perfusion during flow-reducing coronary stenosis in the dog. *J Am Coll Cardiol* 1987; 9 : 119
8 Vinter-Johansen J, Johnston WE, Crystal GJ, Mills SA, Santamore WP, Cordell AR. Validation of local venous sampling within the at rist left anterior descending artery vascular bed in the canine left ventricle. *Cardiovasc Res* 1987; 21 : 646
9 Miyazaki BY, Ogawa K, Satake T, Sugiyama S, Dzawa T. Vasodilative effect of nicorandil on coronary artery. *Arzneim Forsch* 1985; 35 : 504

中国药理学报 *Acta Pharmacologica Sinica* 1990 May; 11 (3) : 253-257

苦参碱的抗心律失常作用

张宝恒、王年生、李学军、孔祥军[1]、蔡予立[1]
(北京医科大学基础医学院药理教研室, 北京 100083, 中国)

Anti-arrhythmic effects of matrine

ZHANG Bao-Heng, WANG Nian-Sheng, LI Xue-Jun, KONG Xiang-Jun, CAI Yu-Li
(*Department of Pharmacology, College of Basic Medicine, Beijing Medical University, Beijing 100083, China*)

ABSTRACT Matrine (MT) is an alkaloid isolated from *Sophra alopecuroids* L. The LD_{50} of MT iv to mice was 72.1 mg / kg (95% CL 68.2-76.5 mg / kg). MT had significant effects on different experimental models of arrhythmias induced by aconitine, barium chloride or coronary ligation. The ECG of anesthetized rats was significantly changed after iv of MT. The HR was retarded and the PR and QT_c intervals were prolonged.

MT decreased the normal spontaneous beating in isolated rat atria and decreased the automaticity induced by norepinephrine in isolated rat ventricle. MT decreased the speed-up effect of isoproterenol on spontaneous beating rate in rat isolated atria. MT had no effect on the contraction of rabbit aorta strips induced by norepinephrine and rat taenia coli depolarized by high K^+. MT had negative chronotropic, negative automaticity and negative conduction effects. These actions may be the pharmacological basis for its anti-arrhythmic effects.

KEY WORDS matrine; arrhythmia; aconitine; barium chloride; heart atrium; heart ventricle; thoracic aorta

提要 大鼠 iv 苦参碱 (MT) 能显著对抗乌头碱、氯化钡和结扎冠脉所致的心律失常. iv MT 18.75 mg / kg, 心率明显减慢, P-R 和 Q-T_c 间期明显延长. MT 200 μmol / L 显著减慢离体大鼠右心房自发频率, 拮抗 Iso 诱发的心率加快, 量-效曲线非平行右移, 并明显拮抗离体大鼠左心室由 NE 诱发的心率加

Received 1988 Feb 16 Accepted 1989 Nov 30
[1] Now in *National Institutes of Pharmaceutical Research and Development, Beijing 102206, China*

快. MT 没有钙拮抗作用.

关键词 苦参碱; 心律失常; 乌头碱; 氯化钡; 心房; 心室; 胸主动脉

苦参碱(matrine, MT)是从豆科槐属植物苦豆子(*Sophora alopecuroides* L)中提得的生物碱[1]. 它有对抗氯仿诱发小鼠心室纤颤[2]、增加豚鼠乳头状肌[3]及右心房[4]的收缩力、提高哇巴因诱发豚鼠右心房心律失常的阈浓度[4]、抗炎症[5]等作用. 本文报道 MT 抗实验性心律失常的作用.

MATERIALS

苦参碱(MT)由盐池药厂提供, 纯度为 98.5%; 乌头碱系德国 E Merck 厂产品; 奎尼丁系意大利米兰药厂产品; 异丙肾上腺素(isoprenaline, Iso)、普萘洛尔和去甲肾上腺素(norepinephrine, NE) 为北京制药厂产品; 吲哚洛尔 (pindolol) 和 *N*-乙基哌克昔林 (*N*-ethyl perhexiline, NEP) 由北京大学化学系提供.

METHODS AND RESULTS

MT 按概率单位分析法求得 iv LD_{50} 为 72.1 mg/kg, 其 95% 可信限为 68.2–76.5 mg/kg.

MT 对实验性心律失常的影响

1 对乌头碱诱发大鼠心律失常的影响 大鼠 40 只, ♂, 体重 220 ± SD 16 g,分为 4 组, ip 乌拉坦 1.2 g/kg 麻醉, 用心电示波器连续观察并记录 II 导 ECG. 分别 iv MT 10 和 18.5 mg/kg, 5 min 后恒速舌 iv 乌头碱 0.8 μg/min, 观察室性早搏 (VP), 室速 (VT) 和室颤 (VF) 出现时乌头碱的用量 (Tab 1).

由 Tab 1 可以看出, MT 显著增加乌头碱诱发大鼠 VP, VT 和 VF 的用量, 说明 MT 能对抗乌头碱诱发的心律失常, 而且有剂量依赖性关系.

Tab 1. Effect of matrine (MT) on aconitine induced arrhythmias in rats. $n=10$, $\bar{x}$ ± SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$.

MT (mg/kg)	Dose of aconitine inducing arrhythmias (μg/kg)		
	VP	VT	VF
0	33±3	41±4	51±8
10	33±2*	47±10*	62±11**
0	33±3	41±5	49±6
18.75	36±4*	50±5**	69±13***

VP: ventricular premature systole; VT: ventricular tachycardia; VF: ventricular fibrillation.

2 对 $BaCl_2$ 诱发大鼠心律失常的影响 大鼠 32 只, ♀, 体重 201 ± 12 g, 分为 4 组, ip 水合氯醛 0.3 g/kg 麻醉, 分别于舌 iv MT 或 NS 3 min 后快速舌 iv (3 s 注完) $BaCl_2$ 5 mg/kg, 对照组可立即出现双相性心律失常、室速、室性二联律、偶发性室性早搏, 而渐恢复窦性心律(Tab2).

结果表明 MT 与已知钙通道阻滞剂 NEP[6] 相似, 都能显著缩短 $BaCl_2$ 诱发心律失常的时程.

Tab 2. Effect of MT on $BaCl_2$ (5 mg/kg) induced arrhythmias in rats. $\bar{x}$ ± SD. $^{**}P<0.05$, $^{***}P<0.01$ *vs* NS. † $P>0.05$ *vs* *N*-ethyl perhexiline (NEP).

Drug	(mg/kg)	*n*	Duration of arrhythmias (min)
NS	—	8	26±11
NEP	2.0	7	11±8**
MT	7.5	8	14±11** †
MT	10.0	8	6±5** †

3 对结扎大鼠左冠状动脉前降支诱发早期缺血性心律失常的影响 ♂性大鼠 37 只, 体重 368 ± 28 g, ip 戊巴比妥钠 60 mg/kg 麻醉, 于左心房下缘 1 mm 处结扎左冠状动脉前降支, 结扎前 2 min, 对照组 iv NS, 另 3 组分别 iv MT 和苯妥英钠. 统计结扎后 30 min 内心律失常开始出现的时间、室性心律数和 VT 持续的时间(Tab 3).结果表明, MT 与苯

Tab 3. Effect of MT on arrhythmias induced by coronary occlusion in rats. $\bar{x} \pm$ SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* NS. $^{\dagger}P>0.05$, $^{\dagger\dagger}P<0.05$ *vs* phenytoin (Phe).

Drug	(mg / kg)	n	Onset of VP (s)	VP (beats in 30 min)	Duration of VT (s)
NS		13	245 ± 30	1664 ± 876	109 ± 62
Phe	20	7	336 ± 48***	788 ± 354***	43 ± 26**
MT	10	9	312 ± 48*** †	1455 ± 676* ††	75 ± 50* †
MT	18.75	13	228 ± 54* ††	887 ± 459** †	47 ± 44** †

妥英钠相似，能明显减弱大鼠冠脉结扎后诱发的早期缺血性心律失常.

MT 对大鼠 ECG 的影响 大鼠 12 只，♀♂各半，乌拉坦 1.2 g / kg 麻醉，记录正常 ECG 3 次 (10 min 内)，以 HR，P–R，Q–T_c 之均数作为给药前的对照值，然后立即 iv MT 18.75 mg / kg，记录给药后 1, 5, 10, 20, 30, 40, 50 和 60 min 的 ECG. 结果发现各指标在给药后 1 min 时即出现明显变化：HR 减慢，P–R 延长，Q–T_c 延长，作用持续达 40 min. 其峰值分别为：HR 由给药前的 412 ± 54 降到 344 ± 78 bpm ($P<0.05$)，P–R 间期由 57 ± 3 延长到 65 ± 8 ms ($P<0.05$)，Q–T_c 由 146 ± 7 延长到 159 ± 13 ms ($P<0.01$).

MT 对大鼠离体心脏、结肠和主动脉条的影响

1 对大鼠离体右心房自发频率的影响 大鼠 37 只，♀♂皆有，体重 375 ± 21 g，击后脑处死，将心房摘出，置于 20 ml，32 ± 1℃，通 95% O_2 + 5% CO_2 的 L–R 液浴管中，一端系于 L 形玻璃管上，另一端连接在张力换能器和平衡记录仪上，平衡 1 h，记录对照组与给 MT 及吲哚洛尔后心房自发频率的变化(Tab 4).

Tab 4. Effects of MT on spontaneous beats of right atria in rats. $\bar{x} \pm$ SD. $^{*}P>0.05$, $^{***}P<0.01$ *vs* NS. $^{\dagger}P>0.05$, $^{\dagger\dagger}P<0.05$ *vs* pindolol.

Drug (μmol / L)	n	Before	After	Change (bpm)
NS	12	69 ± 9	68 ± 8	−0.5 ± 1.5
Pindolol 0.23	6	78 ± 11	60 ± 4***	−17.7 ± 10.2***
MT 50	7	77 ± 13	73 ± 12* ††	−4.6 ± 2.3* ††
MT 220	12	67 ± 11	60 ± 10*** †	−8.0 ± 5.6*** †

2 MT 对 Iso 加速大鼠离体右心房自发频率的影响 同前法，测定 Iso 对右心房自发频率的累积量–效关系曲线，另取标本分别加入 MT 或吲哚洛尔，10 min 后再测定 Iso 的量–效关系曲线 (Fig 1).

从 Fig 1 可见，MT 拮抗 Iso 加速右心房自发频率的作用，量–效曲线右移，并抑制 Iso 的最大效应. 吲哚洛尔也拮抗 Iso 加速离体右心房自发频率作用，但量–效曲线呈平行右移.

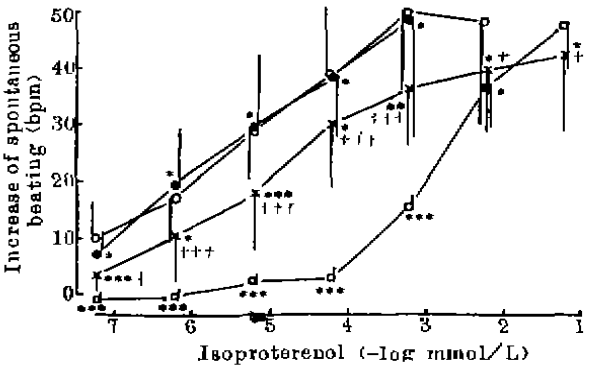

Fig 1. Effects of matrine on the speed-up effect of isoproterenol on spontaneous beating rate in rat isolated atria. (○)NS($n=12$), (●)Matrine 50 μmol / L ($n=7$), (×) Matrine 220 μmol / L ($n=12$), (□) Pindolol 0.23 μmol / L ($n=6$) $\bar{x} \pm$ SD. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* NS. $^{\dagger}P>0.05$, $^{\dagger\dagger\dagger}P<0.01$ *vs* pindolol.

3 对高 K^+ 去极化后累加 $CaCl_2$ 诱发离体大鼠结肠收缩的影响 在同上条件下，用大鼠 24 只制备结肠标本，调整前负荷为 2 g，置于无 Ca^{2+} 的 L–R 液中稳定 1 h 然后改用 40 mmol / L 的高 K^+ L–R 液，15 min 后，按累积法加入 $CaCl_2$，以对照组最大收缩张力为

100%，作出量-效曲线。给 MT 后结肠段的收缩曲线与对照组相似，而已知的钙拮抗剂 NEP 使结肠段收缩显著减弱，量-效曲线右移 (Fig 2).

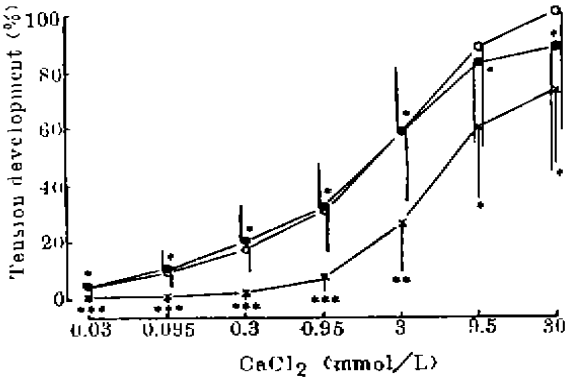

Fig 2. Effects of matrine on contraction of K^+-depolarized in isolated rat taenia coli induced by $CaCl_2$. (O)NS ($n=8$), (●) Matrine 220 μmol/L ($n=9$), (×) NEP 0.7 μmol/L ($n=7$), $\bar{x}\pm$ SD. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* NS.

4 对 NE 诱发兔胸主动脉条收缩的影响 兔 12 只，体重 2.3 ± 0.4 kg，击头处死，取胸主动脉，剪成 3 × 20 mm 螺旋条，在同上条件下，将主动脉条置于 L-R 液浴管中平衡 1 h，加入 NE 5 μmol/L，记录收缩张力变化，冲洗恢复后，再分别加入 MT 220 μmol/L，或等容量的 NS，10 min 后，再给同样浓度的 NE 记录张力变化。给 MT 后主动脉条对 NE 引起的收缩张力变化与 NS 对照组无明显差异.

5 对 NE 诱发离体大鼠左心室收缩频率加快的影响[7] 大鼠 20 只，♀♂兼用，体重 220 ± 18 g. 击头处死，取左心室，前负荷 2 g，放置于 K-H 液中平衡 2 h，待自发收缩完全停止后，加入 NE 5.8 μmol/L，约 3 min 后出现节律性收缩，10 min 频率稳定后给 MT，则心率显著减慢(Tab 5).

由 Tab 5 可以看出 MT 能显著减慢由 NE 诱发左心室收缩频率，但作用较奎尼丁弱.

Tab 5. Effects of MT on beating rate of ventricles induced by norepinephrine in rats. $\bar{x}\pm$ SD. $^*P>0.05$, $^{***}P<0.01$ *vs* NS. $^{\dagger}P>0.05$, $^{\dagger\dagger\dagger}P<0.01$ *vs* quinidine (Qu).

Drug (μmol/L)		*n*	Before	After (in 3 min)	Change (bpm)
NS		6	27±10	27±9	0.2±0.8
Qu	50	4	15±3	0***	−15.0±3.1***
MT	70	5	30±11	28±10*†	−2.0±1.6* †††
MT	220	5	27±8	21±6*** †††	−5.6±2.1*** †††

DISCUSSION

MT 能拮抗乌头碱、氯化钡、结扎冠脉诱发的心律失常，这种作用随剂量的增加而加强. 说明其抗心律失常机理的多样性. 从 MT 对多种心律失常的对抗作用，说明其能明显减低异位节律性，对离体右心房的自律性也能明显对抗. 在对大鼠 ECG 的作用中，发现 MT 能使 P-R 间期延长，也能使 Q-T_c 间期延长，这种负性传导作用能阻断折返的传导. 负性自律性、负性传导、负性频率的作用可能是 MT 抗心律失常作用的药理基础.

MT 能减慢 Iso 诱发大鼠离体右心房自发频率的加快，并能对抗大鼠离体左室由 NE 诱发的自动频率，说明 MT 有抗 β 肾上腺素受体的作用，但与吲哚洛尔不同，可能是机能性对抗.

MT 对 NE 诱发兔主动脉条收缩张力无明显影响，对离体大鼠结肠由高钾去极化诱发的收缩也无明显影响. 说明 MT 对平滑肌电位依赖性钙通道和受体控制性钙通道无明显影响.

REFERENCES

1 Zhao BG. Studies on the alkaloids of *Sophora alopecuroides* L. *Acta Pharm Sin* 1980; **15**: 182

2 张宝恒、戚世祥、齐 治、马 丽、肖菊英、严宝霞. 抗心律失常中草药的筛选. 中草药 1984; **15**: 139

3 Li RS, Chen SY. Effects of seven alkaloids of *Sophora alopecuroides* on contractility of papillary muscles of guinea pigs. *Acta Pharmacol Sin* 1986; 7: 219

4 Xin HB, Liu SF. Effects of matrine on myocardial contraction and arrhythmia in isolated heart atria. *Ibid* 1987; **8**: 501

5 Tan HR, Zhang BH. An experimental study of matrine's anti-inflammatory effect. *Chin J Integ Trad West Med* 1985; **5** : 108
6 Meng HP. Zhang BH. Calcium antagonistic action of N-ethyl perhexiline maleate. *Acta Pharmacol Sin* 1986; **7** : 239
7 Zhang JX, Dong YL, Cheng WZ. Effect of changrolin on arrhythmia in rat. *Acta Univ Med Second Shanghai* 1988; **8** : 140
8 Zhang BH, Zhang SC. The pharmacology and clinical application of calcium antagonists. *Acta Pharm Sin* 1980; **15** : 118

中国药理学报 *Acta Pharmacologica Sinica* 1990 May; **11** (3) : 257-260

雷尼替丁与西咪替丁对豚鼠离体心肌自律性的影响

罗晓星、谭月华 (第四军医大学药理教研室, 西安 710032, 中国)

Effects of ranitidine and cimetidine on automaticity in isolated myocardium of guinea pig

LUO Xiao-Xing, TAN Yue-Hua (*Department of Pharmacology, Fourth Military Medical University, Xi-an 710032, China*)

ABSTRACT At 0.1 - 30 μmol / L, neither ranitidine (Ran) nor cimetidine (Cim) inhibited the rate of spontaneous contraction in isolated right atria of guinea pig. When the concentration was higher than 100 μmol / L, both Ran and Cim exhibited weak negative chronotropic effects with IC_{50} of 109 ± 3 and 436.5 ± 1.9 μmol / L, respectively. However, the positive chronotropic effects of histamine (H) were markedly antagonized by Ran and Cim with IC_{50} of 0.40 ± 0.29 and 1.8 ± 0.6 μmol / L respectively. Ran (0.1 μmol / L) and Cim (1 μmol / L) competitively antagonized the concentration- dependent response of positive chronotropic effect mediated by H and had no influence on that induced by isoproterenol in right atria of guinea pig. Ran (10 μmol / L) and Cim (50 μmol / L) prevented the abnormal automaticity elicited by H and H (0.12 ± 0.09 μmol / L) + Oua (0.04 ± 0.02 μmol / L) which acted synergically. The abnormal autamaticity induced by Oua (1.5 ± 2.3 μmol / L) was antagonized by Ran (10 μmol / L) and not by Cim (50 μmol / L). Our results suggest that these effects of Ran and Cim are mainly attributed to cardiac H_2 receptor blockade.

KEY WORDS histamine H_2 receptor blockaders; histamine; ranitidine; cimetidine; isoproterenol; ouabain; myocardium

提要 雷尼替丁(Ran)与西咪替丁 (Cim) 可有效地拮抗组胺 (H) 诱发豚鼠离体右心房正性变时效应, 其 IC_{50} 分别为 0.40 ± 0.19, 1.8 ± 0.6 μmol / L, 并可竞争性拮抗 H 正性变时量-效反应. Ran, Cim 可预防 H 诱发、以及 H+哇巴因 (Oua) 协同诱发的自律性, 对 Oua 诱发的自律性, Ran 可抗之, Cim 则否. 以上提示, Ran 和 Cim 的上述作用主要系竞争性拮抗 H_2 受体.

关键词 组胺 H_2 受体阻滞剂; 组胺; 雷尼替丁; 西咪替丁; 异丙肾上腺素; 哇巴因; 心肌

急性心肌缺血、心性变态反应、心脏外科手术及使用某些药物, 均可致组胺(histamine, H)释放, 诱发各种心律失常[1]. H_2 受体拮抗剂雷尼替丁 (ranitidine, Ran)与西咪替丁 (cimetidine, Cim)抗早期缺血性心律失常作用, 已在整体动物实验中得到证实[2,3]. 本文采用豚鼠离体心肌标本, 分析其作用机理, 比较其作用强度及异同.

MATERIALS

Ran 系浅黄色粉末结晶, 西南制药二厂产品; Cim 为江苏武进制药厂产品; H 由上海生化研究所药厂生产; 哇巴因(ouabain, Oua)为德国 Merck 厂产品; 普萘洛尔(propranolol, Pro), 异丙肾上腺素(isoproterenol, Iso) 系北

Received 1989 Jul 17 Accepted 1989 Dec 6