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甲基黄酮醇胺盐酸盐对离体豚鼠乳头状肌动作电位的影响

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Effects of methylflavonolamine hydrochloride on action potentials of isolated guinea pig papillary muscles

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ABSTRACT Methylflavonolamine hydrochloride (4′-methyl-7-(2-hydroxy-3-isopropylamino-propoxy)-flavone hydrochloride, MFA) is a new compound synthesized by Shanghai Institute of Pharmaceutical Industry in China. Its effects on the fast and evoked slow response action potentials of isolated guinea pig papillary muscles have been studied by intracellular microelectrode techniques. The data were automatically analysed by a microcomputer system. At concentrations of 5–75 μmol/L, MFA caused a significant decrease in the duration required for 30, 50, 90% repolarization and a shift in the plateau to more negative transmembrane potentials. MFA 5 μmol/L had no effect on the maximal upstroke velocity during phase 0 (V_{max}) but decreased it at 75 μmol/L. MFA had no significant effects on other AP parameters. It significantly inhibited the slow AP induced by isoprenaline or histamine (1 μmol/L) after myocardial cells were depolarized in high K^+ (25 mmol/L) solution. The results suggest that MFA inhibits the inward Ca^{2+} current and at high concentration inhibits also the Na^+ current.

KEY WORDS flavones; methylflavonolamine; papillary muscles; action potentials; neurologic refractory period

提要 甲基黄酮醇胺盐酸盐(MFA)5–75μmol/L 显著缩短离体豚鼠乳头状肌正常快反应 AP 的 APD, 坪台电位降低, RP, ERP 及 3 相复极时程(DP_3)无显著影响, ERP/APD_{90} 增大. MFA 5 μmol/L 对 APA 及 V_{max} 无影响, 高浓度时(75 μmol/L)使 V_{max} 降低; 明显抑制 Iso 和 His 引起的慢反应 AP. 提示 MFA 对 Ca^{2+}及高浓度时对 Na^+的跨膜转运均有抑制作用.

关键词 黄酮类; 甲基黄酮醇胺; 乳头状肌; 动作电位; 神经性不应期

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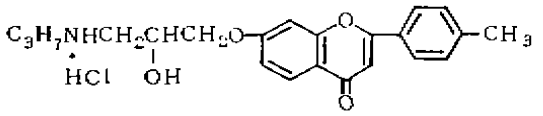
甲基黄酮醇胺盐酸盐 (methylflavonolamine hydrochloride, MFA)化学名为 4′-甲基-7-(2-羟基-3-异丙胺基-丙氧基)-黄酮盐酸盐,是上海医药工业研究院合成的新化合物, 其具有抗多种实验性心律失常[1]、抗心肌缺血[2]及抗血小板聚集[3]的作用, 该药还有弱 β 受体阻断作用[4]和钙拮抗作用[5]. 本文用电生理学的方法, 观察 MFA 对离体豚鼠右心室乳头状肌快和慢反应动作电位的影响, 来探讨其抗心律失常作用的机理.



Methylflavonolamine hydrochloride (MFA)

MATERIALS AND METHODS

MFA 为上海医工院提供的纯品, 使用时用蒸馏水配制, 经预热后直接加入浴槽内.

豚鼠, ♀♂不拘, 体重 318 ± SD 42 g, 击头致昏. 取右心室乳头状肌, 水平固定于 5 ml 的浴槽内, 改良台氏液[6]以 20 ml/min 灌流, 通入 100 % O_2,灌流液温度 34 ± 0.5℃, pH 7.4 ± 0.5.

取内充 KCl 3 mol/L 的玻璃微电极(电阻 20–40 MΩ), 用固定电极法引出动作电位(AP), 用 Ag-AgCl 电极引导至微电极放大器(MEZ-8201, Nihon Kohden), 后者双路输出 AP, 一路输入到示波器摄影, 另一路输入到 DOCTOR-851 型智能仪(南京医学院生理教研室, 南京电生理仪器厂)进行动态观察及记录, 由刺激器经隔离器输出 1 Hz, 2 ms, 150%

阈强度的方波驱动标本. 标本至少稳定 1 h. 整个实验都在微机程序控制下自动实时分析和测量 AP 的各项参数.

有效不应期(ERP)测定: 刺激强度提高到 5 倍阈强度, 由微机自动控制在每 8 个驱动脉冲后插入一个期前刺激, 逐渐改变驱动刺激与期前刺激间的间隔, 自动测出 ERP.

引导慢反应 AP 时, 先以 KCl 3 mmol / L 台氏液灌流 1 h, 然后换以高 K^+(25 mmol / L) 台氏液(其中 Na^+浓度随 K^+浓度增加而等 mmol / L 地减少, 以保持灌流液渗透压不变) 使心肌细胞除极, 快 Na^+通道失活, 快反应 AP 消失[7]. 加入异丙肾上腺素(Iso)或组织胺(His) 1 μmol / L, 同时将刺激改为 0.25 Hz, 3 ms, 4 倍阈强度(以引起快反应 AP 时的阈强度为准), 即可引出慢反应 AP. 慢反应 AP 稳定 30 min 后开始实验.

3 相时程(duration of phase 3, DP_3) 测量: $DP_3 = APD_{90} - APD_{50}$

取在同一细胞内完成实验的数据, 用方差分析检验.

RESULTS

MFA 对快反应 AP 的影响 MFA 对快反应 AP 的作用主要表现在 5–75 μmol / L 范围内逐渐使坪台电位降低, 斜率变大, 时程缩短, 甚至几乎消失, 以至使 AP 发生畸变, 3 相斜率变化不明显, Fig 1 为一原始记录. MFA 使动作电位复极化到 30, 50, 90%的时程(APD_{30}, APD_{50}, APD_{90})浓度依赖性地平行

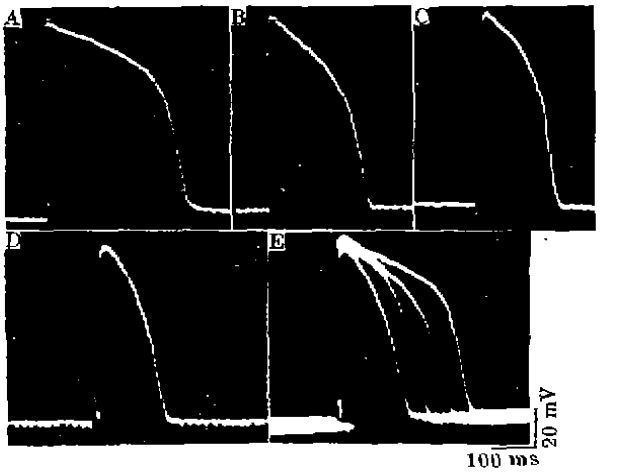


Fig 1. Effects of methylflavonolamine hydrochloride (MFA) on fast response action potentials of guinea pig papillary muscles. A) Control; B, C, D) 30 min after MFA 5, 25, 75 μmol / L, respectively; E) Superimposed photographs of A–D, for comparison. Driving rate : 1 Hz.

Tab 1. Effects of MFA on fast response action potentials of guinea pig papillary muscles. $n = 7$, $\bar{x} \pm SD$. $^*P > 0.05$, $^{**}P < 0.05$, $^{***}P < 0.01$ *vs* **control.**

	Control	30 min after MFA (μmol / L) 5	25	75
APA (mV)	106 ± 6	106 ± 7*	103 ± 5*	103 ± 7*
V_{max} (V/s)	182 ± 28	166 ± 39*	156 ± 36*	131 ± 26**
APD_{30} (ms)	148 ± 26	118 ± 23**	104 ± 20***	84 ± 30***
APD_{50} (ms)	193 ± 34	157 ± 29**	140 ± 30***	118 ± 39***
APD_{90} (ms)	233 ± 37	198 ± 30*	184 ± 36**	162 ± 37***
DP_3 (ms)	40 ± 5	41 ± 6*	41 ± 3*	41 ± 6*
RP (mV)	−80 ± 5	−82 ± 8*	−80 ± 5**	−79 ± 7*
EPR (ms)	213 ± 36	230 ± 26*	229 ± 24*	230 ± 26*
EPR / APD_{90}	0.91 ± 0.25	1.17 ± 0.19*	1.29 ± 0.27*	1.49 ± 0.38***

APA: action potential amplitude; V_{max}: maximal upstroke velocity; APD_{30}, APD_{50} and APD_{90}: action potential duration at 30, 50 ,90 % level of repolarization, respectively; DP_3: duration of phase 3; RP; resting potential; ERP: effective refractory period.

缩短，RP, DP_3, ERP 无显著变化，但因 APD_{90} 缩短，ERP／APD_{90} 相对增大，MFA 5 μmol／L 时不影响 APA 及 V_{max}，75 μmol／L 使 V_{max} 显著减小(Tab 1).

MFA 对慢反应 AP 的影响 以慢反应 AP 轨迹下所围面积(area circumscribed by slow action potential trace, ACSAPT)及其 V_{max} 为观察指标. MFA 5, 25 μmol／L 明显抑制 Iso 或 His 诱发的慢反应 AP. 其 ACSAPT 均缩小，V_{max} 均有所降低 (Fig 2, Tab 2).

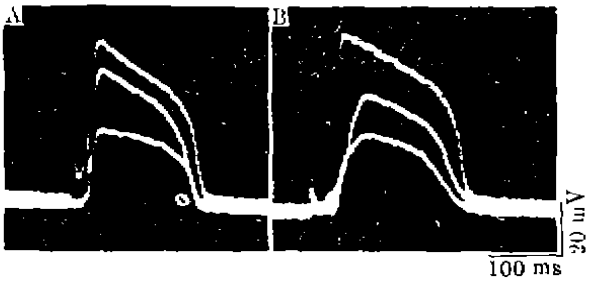


Fig 2. Effects of MFA on slow AP of depolarized guinea pig papillary muscles in high K^+(25 mmol／L) Tyrode's solution, induced by isoprenaline 1 μmol／L (A) and histamine 1 μmol／L (B). Upper tracing: Control; Middle and lower tracing: 30 min after MFA 5 and 25 μmol／L, respectively. Driving rate: 0.25 Hz.

Tab 2. Effects of MFA on slow action potentials of guinea pig papillary muscles induced by isoprenaline (Iso) or histamine (His). $\bar{x}$ ± SD. $^*P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* control.

		n	Control	30 min after MFA (μmol／L) 5	25
ACSAPT	Iso	7	12.0±2.5	10.9±2.2*	9.6±1.9**
(V·ms)	His	6	13.7±1.9	11.5±2.1*	10.9±1.8**
V_{max}	Iso	7	14.8±8.8	6.7±2.8**	5.9±2.8**
(V/s)	His	6	12.0±3.2	8.0±2.5*	5.8±1.5***

ACSAPT: area circumsribed by slow action potential trace; V_{max}: maximal upstroke velocity of the slow action potentials.

DISCUSSION

在心室肌细胞，AP 的坪台期和复极相的产生与维持，主要因素是缓慢的 Ca^{2+}／Na^+跨膜内流形成的 I_{si} 电流[8]. MFA 使坪台消失，APD 缩短，这可能是该药通过某种途径对 I_{si} 产生了阻滞作用，因为本文观察了 3 相时程的变化在 APD 变化中所起的作用，MFA 不影响 DP_3 及 ERP，推测该药可能不影响 K^+通道，APD 的缩短可能主要因代表坪台期的 APD_{30}, APD_{50} 缩短所致. MFA 5 μmol／L 不影响 V_{max}，75 μmol／L 使该参数显著减少，这可能是高浓度时阻滞 Na^+通道的结果，这与钙拮抗剂在高浓度时也抑制 Na^+内流的观点[9]相一致，如维拉帕米和 bepridil 对豚鼠乳头状肌和浦氏纤维 AP 的快 Na^+通道也有抑制作用[10].

慢反应 AP 的 ACSAPT 可大致反映 Ca^{2+}内流的总量，其 V_{max} 则反映 Ca^{2+}内流的强度[11]. MFA 使慢反应 AP 中上述两个指标减小，表明该药具有 Ca^{2+}拮抗作用，且这种作用不是 β 受体阻断的结果，因为 MFA 对 His 及 Iso 诱发的慢反应 AP 均有抑制作用，已知 His 是通过激活 H_2 受体诱发慢反应 AP 的，β 受体阻断剂对此 AP 没有抑制作用[11]. 本文研究初步认为 MFA 为一种新的 Ca^{2+}阻滞剂，具有Ⅳ类抗心律失常药的电生理特性.

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前胡丙素对离体豚鼠心房及人体心肌顺应性的影响

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Effects of praeruptorin C on isolated guinea pig atrium and myocardial compliance in patients

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ABSTRACT Praeruptorin C (Pra-C, 2-methyl-, 10-(acetyloxy)-9,10-dihydro-8,8-dimethyl-2-oxo-2*H*, 8*H*-benzo[1,2-*b*:3,4-*b'*] dipyran-9-ol ester of 2-butenoic acid) was first isolated by Chinese researcher. Pra-C 10 μmol / L reduced automatic rhythm and positive chronotropic effects of $CaCl_2$ in right atrium. Its antagonistic effects on isoproterenol-mediated increase in beat rate were non-competitive with a pD'_2 of 4.8. Pra-C 5-50 μmol / L shortened functional refractory period with little effects on the excitability and epinephrine-induced ectopic automaticity. Modification of myocardial compliance during 2 wk oral Pra-C therapy in patients with hypertrophic cardiomyopathy was also investigated.

KEY WORDS coumarins; heart atrium; heart rate; myocardial contraction; neurologic refractory period

提要 前胡丙素(Pra-C)明显抑制离体豚鼠心房的自律性及 $CaCl_2$ 的正性频率作用; 抑制左房收缩力的 IC_{50} 值为 49 μmol / L; 缩短功能性不应期; 对左房兴奋性、肾上腺素诱发的异位自律性无影响. Pra-C 对异丙肾上腺素的正性频率作用,表现为非竞争性拮抗, $pD'_2 = 4.8$. 临床研究显示 Pra-C 治疗 2 wk 后, 肥厚性心肌病患者心肌顺应性有一定改善.

关键词 香豆素; 心房; 心率; 心肌收缩; 神经性不应期

前胡丙素(praeruptorin C, Pra-C)的化学名是 10-乙酰氧基-9,10-二羟基-8,8-二甲基-2-氧代 2*H*, 8*H*-苯并[1,2-*b*: 3,4-*b'*]二吡喃-9-醇-2-甲基-2-丁烯酸酯, 是我国首次从伞行科白花前胡中提取的有效成分[1]. 它明显抑制 KCl、$CaCl_2$ 引起的兔主动脉条收缩, 对离体血管和心肌收缩力的抑制作用均与拮抗细胞外钙内流有关. 本文进一步研究它对离体豚

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