

关附甲素对豚鼠乳头状肌快反应动作电位的作用¹

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Effects of guan-fu base A on fast response action potentials of papillary muscles of guinea pigs

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ABSTRACT Guan-fu base A is a new alkaloid first isolated from the tuber of *Aconitum coreanum* in China. The electrophysiological effects of guan-fu base A were examined on the isolated papillary muscles of guinea pigs by glass-micro-electrode technique coupled with microcomputer real-time analysis. Guan-fu base A 50 $\mu\text{g/ml}$ had less effect on RP, but markedly decreased V_{max} and APA of the fast response action potentials. The action potential duration was shortened at all voltage levels and plateau height was lowered. ERP was prolonged relatively and activation voltage became more negative. The inhibition of guan-fu base A on V_{max} showed frequency dependent effects. The above results suggested that guan-fu base A could block the fast Na^+ channels and exhibited anti-arrhythmic action.

KEY WORDS guan-fu base A; anti-arrhythmia agents; papillary muscles; action potentials

Received 1988 May 24 Accepted 1989 Apr 1

¹ This paper was presented at the Third Chinese Cardiovascular Pharmacology Conference, Xi-an, 1986 Nov.

摘要 用玻璃微电极和微机实时分析技术观察关附甲素(GFA)对豚鼠乳头状肌快反应动作电位的作用。发现GFA 50 $\mu\text{g/ml}$ 使 V_{max} 和APA显著降低,对RP无明显影响,动作电位平台期缩短、电位压低,ERP相对延长,AV更负。对 V_{max} 的抑制具有明显的频率依赖性。上述结果提示GFA主要通过快Na通道阻滞而发挥抗心律失常作用。

关键词 关附甲素; 抗心律失常药; 乳头状肌; 动作电位

关附甲素(guan-fu base A, GFA)系关白附子[*Aconitum coreanum* (Levl.) Raipais]中的一种新生物碱,属 C_{20} 二萜生物碱七元环异叶乌头素(hetisine)类⁽¹⁾。动物实验证明,它能对抗乌头碱诱发大鼠心律失常,降低 CaCl_2 引起大鼠室颤发生率和死亡率,增加哇巴因诱发豚鼠室早、室颤的用量,提高猫、兔电刺激的致颤阈值^(2,3)。GFA使犬浦氏纤维的 V_{max} 和APA降低,ERP和 APD_{100} 延长⁽⁴⁾。本文采用玻璃微电极和微机实时分析技术,观察GFA对豚鼠乳头状肌快反应动作电位作用,进一步解释其抗心律失常机理。

MATERIALS AND METHODS

豚鼠,体重 $350 \pm \text{SD } 34 \text{ g}$,♀♂兼用,击昏后摘出心脏,选取直径 $<1 \text{ mm}$ 右心室乳头

状肌,置容量为2.5 ml的标本槽中,用95% O₂+5% CO₂饱和、pH 7.2-7.4、37±0.5℃的台氏液灌流。待标本稳定1.5 h后开始实验。

记录电极为充以KCl 3 mol/L玻璃微电极,电阻8-15 MΩ。从心肌细胞引出的AP信号经MEZ-7101微电极放大器后,分别输入示波器和微机实时分析系统⁽⁵⁾,后者每分钟打印各AP参数,并定时触发刺激器(SEN-7103),经隔离器(SS-302)输出1 Hz, 1 ms, 150%阈强度的方波驱动标本。待AP各参数稳定后才加药观察,并在同一细胞内完成实验。

有效不应期(ERP)及激活电位(AV)的测量:由微机系统自动测量。每隔7次基础刺激发出一次期外刺激,刺激强度为阈强度2倍,用逐次逼近法搜索最适点,以期外刺激能引起AP产生的最短刺激间隔为ERP,AP复极3相与该期外刺激所产生AP的0相交点的电位值为AV。

频率依赖性测定:由微机系统发出不同频率(0.1-10 Hz)的刺激脉冲,观察用药前后不同频率下稳态V_{max}值。

RESULTS

GFA对AP的影响 用含GFA 50 μg/ml的台氏液灌流标本,首先出现V_{max}降低,30 min后V_{max}, APA显著降低; RP无明显影响;动作电位时程APD₂₀, APD₅₀, APD₉₀均显著缩短,但APD₅₀与APD₉₀呈平行缩短,3相复极斜率无明显改变,主要表现平台期缩短、电位压低。用不含药物台氏液冲洗30 min后,AP各参数均有恢复(Tab 1, Fig 1)。

GFA对豚鼠乳头状肌纤维(n=5)的AP具有浓度依赖性作用。GFA 1 μg/ml, 30 min内AP各参数均无明显变化;浓度10 μg/ml, V_{max}已降低11%(P<0.01);浓度增至30 μg/ml时, V_{max}降低32%、同时APA降低、动作电位时程缩短。

GFA对ERP和AV影响 GFA 50 μg/ml

Tab 1. Effects of guan-fu base A(GFA) 50 μg/ml on fast response action potentials of guinea pig papillary muscles. n=8, $\bar{x} \pm SD$, *P>0.05, **P<0.05, ***P<0.01.

Parameters	Control	GFA (30 min)	Washout (30 min)
RP (mV)	-86±3	-85±3*	-85±3*
APA (mV)	122±6	115±6***	120±6**
V _{max} (V/s)	229±36	139±33***	185±31***
APD ₂₀ (ms)	77±23	62±23***	71±23**
APD ₅₀ (ms)	131±36	108±35***	121±35**
APD ₉₀ (ms)	153±37	129±37***	143±36**
ERP (ms)	160±45	144±42**	155±45*

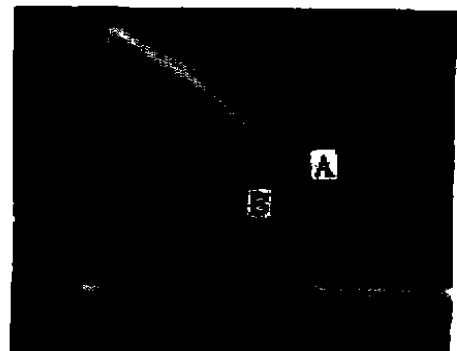


Fig 1. Effects of GFA on fast response action potentials of guinea pig papillary muscles. Microcomputer printout providing the measurements of the action potentials characteristics. A) Control, B) 30 min after GFA 50 μg/ml.

灌流30 min后, APD₉₀缩短, ERP也缩短(Tab 1)。但ERP/APD₉₀值从104±6%增至111±7%(P<0.05),表明ERP相对延长,而AV从-73±4 mV变为-76±5 mV(n=8)。

GFA对频率依赖性影响 分别以用药前和用药后30 min的最大稳态V_{max}值为100%,求出各频率时稳态V_{max}值的%。当GFA 50 μg/ml、频率0.1-10 Hz范围内时,频率愈快,稳态V_{max}值抑制愈明显,表现明显的频率依赖性效应(Fig 2)。无论对照或加药, RP均>-80 mV,改变每一频率后,一般20次刺激内V_{max}达到稳态。

DISCUSSION

由于电压钳制术测量I_N困难, V_{max}不失

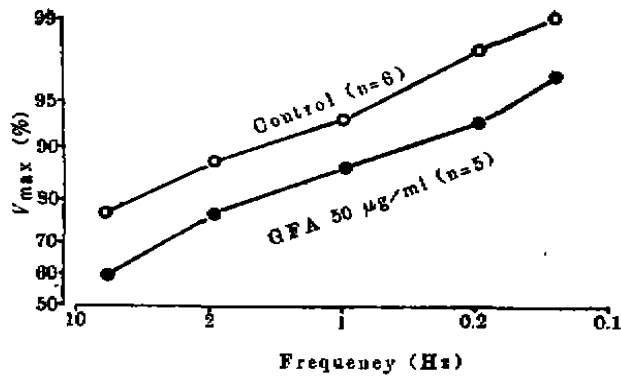


Fig 2. Effect of GFA 50 µg/ml on frequency-dependent decrease in V_{max} .

为衡量快通道 I_{Na} 的可靠指标⁽⁶⁾。GFA 显著降低 V_{max} 和 APA, 并呈浓度依赖性, 对 RP 无明显影响, 提示 GFA 抑制 I_{Na} 是通过阻滞特异性快 Na^+ 通道作用。GFA 抑制 V_{max} 具有明显频率依赖性, 可能与药物结合部位位于通道内侧和通道开放时亲和力较高有关⁽⁷⁾。GFA 降低 V_{max} , 减慢传导, 使单向传导阻滞变为双向传导阻滞, 有利于中止折返。而频率依赖性特性更有利于快速型心律失常治疗。

不应期主要反映 Na^+ 通道复活过程。GFA 缩短 ERP, 表明 GFA 尚能使 Na^+ 通道复活过程减慢。但 ERP/APD₅₀ 值增大, AV 变得更负, 提示可能引起的期外收缩的电位水平较负, 这样, 期外收缩的 V_{max} 较大, 传导较快, 不利于折返产生⁽⁸⁾。

值得指出, GFA 且能延长犬浦氏纤维动作电位时程⁽⁴⁾, 目前没有恰当解释, 可能与动物种类、细胞类型不同而组成动作电位的离子流性质不同有关。对豚鼠心室肌而言, I_{Na} 渐进性失活和缓慢外向电流 I_{x1} 的进行性激活是导

致平台期终止两个重要原因⁽⁹⁾, 鉴于 GFA 使平台期缩短、电位压低, 而主要由 I_{x1} 所致 3 相复极斜率无明显改变, 因而推测 GFA 缩短豚鼠乳头状肌动作电位时程更可能是通过对 I_{Na} 抑制所致, 有待证实。

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