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二[二甲氨基]-二苯甲烷对豚鼠心乳头状肌动作电位的影响[1]

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Effects of bis(dimethyl amino)-diphenyl methane (BDDM) on action potentials in guinea pig papillary muscle

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ABSTRACT The effects of BDDM on action potentials and slow respone action potentials in guinea pig papillary muscle were investigated by microelectrode technique. BDDM prolonged action potentials duration at 30, 50, 90, and 100% repolarization (APD_{30}, APD_{50}, APD_{90}, APD_{100}) and prolonged the effective refractory period (ERP), so ERP/APD value became greater. BDDM (51.6 μmol/L) decreased the APA, V_{max} and prolonged APD_{50}, APD_{90}. In barium-induced ventricular autorhythmicity, BDDM suppressed the maximal diastolic potential (MDP), APA and reduced the rate of spontaneous rhythm. These results suggest that BDDM may unspecifically inhibit the currents of Ca^{2+}, K^+, and Na^+.

KEY WORDS bis(dimethyl amino)-diphenyl methane (BDDM); papillary muscles; action potentials; barium

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提要 二[二甲氨基]-二苯甲烷(BDDM)能延长豚鼠心乳头状肌细胞 APD、ERP，使 ERP/APD 比值增大；较高浓度时可降低 APA 和 0 相除极最大速率(V_{max})；降低慢反应动作电位 APA 和 V_{max}，并延长 APD_{90}；抑制 Ba^{2+} 诱发的乳头状肌自发电活动，降低 APA 和 MDP。结果提示 BDDM 对心肌细胞 Ca^{2+}，K^+，Na^+ 的跨膜转运有抑制作用。

关键词 二[二甲氨基]-二苯甲烷；乳头状肌；动作电位；钡

4，4′-二[二甲氨基]-二苯甲烷(4，4′-*bis*(dimethyl amino)-diphenyl methane，BDDM)有抗实验性心律失常作用[1]，心室乳头状肌生理特性影响的实验提示[2]，此作用可能与其抑制钙内流有关。本文在离体豚鼠右心室乳头状肌上，用玻璃微电极技术，进一步观察 BDDM 对心室肌动作电位参数及不同慢反应电活动的影响，为 BDDM 的抗心律失常作用提供电生理学依据。

MATERIALS AND METHODS

豚鼠 34 只，♀♂不拘，体重 328±SD 45 g，击头致昏，速取心脏，放入经 95%O_2+5%CO_2 饱和的 Tyrode 液中，制备右心室乳头状肌标本，并将其以水平方向固定于 2 ml 的浴槽内，用 36±0.5℃，pH 7.2-7.4 的 Tyrode 液循环灌流，速度 5.5 ml/min。以 1 Hz，3 ms，1.5 倍阈电压的刺激驱动标本。

记录电极为充以 KCl 3 mol/L 的玻璃微电极，电阻 10-40 MΩ，微电极由 Ag-AgCl 丝与微电极放大器相连，输出信号分两路；一路输入双线示波器的上线进行观察，并输入光线示波器记录，另一路经电子微分器微分后输入双线示波器下线进行观察和光线示波器记录。标本稳定 1 h 开始实验，一个标本只用一种药物，用南京无线电厂研制的博士-851 型微电子计算机联机分析、处理图形，并打印结果。

BDDM 白色粉末，兰州大学化学系陈淑英教授合成提供，实验前，先加少量稀盐酸溶解，再用蒸馏水稀释成 1%的溶液，贮于 4℃冰箱备用。盐酸利多卡因 (*lidocaine*, *Lid*)天津人民制药厂。

RESULTS

BDDM 对豚鼠心室乳头状肌快反应动作电位参数的影响 BDDM 12.9 μmol/L 作用于豚鼠心室乳头状肌标本 20 min 后，动作电位时程(APD)缩短；BDDM 25.8，51.6 μmol/L 使 APD_{100}，APD_{90}，APD_{50}，APD_{30} 延长；BDDM 51.6 μmol/L 还能使动作电位幅度(APA)及 0 相最大除极速率(V_{max})下降，膜电位(RP)负值减小(Tab 1)。

Tab 1. **Effects of bis(dimethyl amino)-diphenyl methane (BDDM) on action potential parameters and effective refractory period (ERP) in guinea pig papillary muscles.** n=6，$\bar{x}$±SD. *P>0.05，**P<0.05，***P<0.01.

		BDDM (μmol/L)		
Parpmeter	Control	12.9	25.8	51.6
APA(mV)	125±5	125±5*	123±6*	120±7***
RP(mV)	89±2	88±1*	88±2*	86±2**
V_{max}(V/s)	271±41	270±37*	251±31*	234±43**
APD_{30}(ms)	101±11	98±9**	109±7**	107±11**
APD_{50}(ms)	148±11	144±13**	162±11***	167±11***
APD_{90}(ms)	202±18	194±19***	217±19**	229±17***
APD_{100}(ms)	224±17	217±19***	243±20***	254±18***
ERP(ms)	160±23	163±19*	183±26***	205±34***
ERP/APD	0.7±0.1	0.8±0.1***	0.8±0.1***	0.8±0.1***

BDDM 对有效不应期(ERP)的影响 在基本刺激节律为 1 Hz 的基础上，每 8 次刺激插入 1 次期前收缩，逐步缩短期前刺激和基本节律刺激之间的间隔，以期前刺激能引起动作电位产生的最短时间间隔为 ERP，以上方法由电子计算机控制输出。BDDM 12.9 μmol/L，可使豚鼠心乳头状肌 ERP 缩短，但 ERP/APD 比值增大；BDDM 25.8，51.6 μmol/L 使 ERP/APD 比值增大(Tab 1)。

BDDM 对高 K^+ 除极慢反应动作电位的影响 提高灌流液中 K^+ 浓度为 18 mmol/L，NaCl 相应降低，以保持溶液渗透压不变。以刺激强度大于正常阈值 4 倍，波宽 8 ms 的电刺激也不能使豚鼠心室乳头状肌产生动作电位，证实此时快钠通道基本失活[3]，给异丙肾上腺素 1 μmol/L，改用 0.25 Hz，5 ms，2 倍阈电压刺激，又出现动作电位。其 V_{max} 为 10.0±1.9 V/s(n=7)，呈慢反应型[4]。BDDM 25.8，103.2 μmol/L 可使慢反应动作电位之 APA 及 V_{max} 降低，APD_{90} 延长(Tab 2)。

Tab 2. **Effect of BDDM on slow response action potentials pretreated with KCl 18 mmol/L in guinea pig papillary muscles. n=7, $\bar{x}$±SD. *P>0.05, **P<0.05, ***P<0.01.**

Parameter	Control	BDDM (μmol/L) 25.8	51.6
APA(mV)	72±7	68±6**	63±9***
V_{max}(V/s)	10±2	9±2***	8±2***
APD_{50}(ms)	69±8	72±9*	78±13***
APD_{90}(ms)	123±15	132±17**	141±23***

BDDM 对 Ba^{2+} 诱发异常自律性的影响 在灌流液中加入 $BaCl_2$ 3 mmol/L 时，APA 降低，约 20 min 后出现自发活动，舒张电位从 −80 mV 上移到 −50 mV 左右。BDDM 25.8 μmol/L 作用于豚鼠乳头状肌标本(n=5)20 min 后，APA 从 72±4 降低到 66±4 mV ($P<0.01$)；自动发放频率由 105±9，降低到 93±9 bpm($P<0.01$)；BDDM 51.6 μmol/L 使 APA 由 72±4 降到 60±5 mV ($P<0.01$)；MDP 从对照的 55±4 降到 46±9 mV($P<0.01$)，频率从 105±9 降到 86±8 bpm ($P<0.01$)。Lid 55.4，110.8 μmol/L 使自发频率从 98±4，分别降到 85±6，77±5 bpm(P 均<0.01)。

DISCUSSION

药物对心肌细胞的电生理影响，是抗心律失常药的作用基础[5]。BDDM可使 APD，ERP 延长，ERP/APD 比值增大，这些作用能使单向传导阻滞变为双向传导阻滞，有利于中止折返冲动[6]。V_{max} 减低能阻滞冲动在未完全复极的心肌纤维内传导，发挥其抗心律失常作用。较高浓度的 BDDM 能降低心肌细胞的 APA 和 V_{max}，说明 BDDM 对 I_{Na} 有抑制作用。

内向整流电流(I_K)的减少，与慢内向电流(I_{si})的增加，是形成心室肌动作电位坪台期的主要原因[7]。维拉帕米等慢通道阻滞剂，可使动作电位时程延长，其原因是复极化时，K^+ 外流可由于细胞内 Ca^{2+} 减少而减少[8]；Hoffman 等也证明，当细胞外 Ca^{2+} 减少时，动作电位时程延长[9]。BDDM 小剂量使动作电位时程缩短，与阻滞心肌细胞的钙内流有关；BDDM 25.8，51.6 μmol/L 也使动作电位时程延长；在高 K^+ 除极后慢反应动作电位中，BDDM 能降低 APA 和 V_{max}，延长动作电位时程。提示 BDDM 不但能阻滞心肌细胞的 Ca^{2+} 内流，而且能降低心肌细胞的 K^+ 外流。

Ba^{2+} 诱发的自发性电活动主要是通过降低钾电导，增加跨膜净 I_{si} 内流所致[10]。BDDM 和 Lid 均能使 Ba^{2+} 诱发的慢反应型自发电活动的频率减慢；BDDM 还能使其 APA 及 MDP 降低，也提示 BDDM 具有 Ca^{2+} 通道阻滞作用。以上实验结果表明：BDDM 对心肌细胞的 Ca^{2+}，K^+，Na^+ 跨膜转运均表现抑制作用。

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达唑氧苯对麻醉兔脑血管阻力的作用[1]

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Effect of dazoxiben on cerebrovascular resistance in rabbits

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ABSTRACT The effects of dazoxiben, a TXA_2 synthetase inhibitor, and indomethacin were compared on cerebrovascular resistance (CVR) and levels of serum TXB_2, 6-keto-$PGF_{1\alpha}$ (the stable metabolites of TXA_2 and PGI_2, respectively) and on protection from acute brain ischaemia caused by ia arachidonic acid (AA) in rabbits. The flow represented the cerebral blood flow (CBF) in two internal jugular arteries were measured with electromagnetic flow meter after occlusion of bilateral vertebral arteries and external jugular arteries. CVR was represented as blood pressure/(CBF·100 g brain). Serum TXB_2 and 6-keto-$PGF_{1\alpha}$ levels were determined by radioimmunoassay. The results showed that CVR and BP, EEG, ECG were not affected by treatment with iv dazoxiben 2 or 10 mg/kg. The CVR was enhanced by 35.5 and 49.8% at 30 and 40 min, respectively after iv indomethacin 10 mg/kg. The serum TXB_2 level (872 ± 85) was inhibited to 511 ± 169 pg/ml ($n=5$, $P<0.05$) and 6-keto-$PGF_{1\alpha}$ increased from 668 ± 309 to 890 ± 357 pg/ml ($n=5$, $P<0.05$) at 30 min after iv 2 mg/kg dazoxiben. However, both TXB_2 and 6-keto-$PGF_{1\alpha}$ decreassed by 26.4 and 32.7%, respectively at 40 min after iv indomethacin 10 mg/kg. In a model of cerebral ischaemia caused by ia AA in rabbits, the EEG change and enhancement of CVR were antagonized by iv dazoxiben 10 mg/kg completely, but only partly antagonized by indomethacin 10 mg/kg. The

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