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牡丹皮及奎尼丁对体外培养乳鼠心肌细胞动作电位的影响

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内容提要 实验采用细胞内微电极记录的方法，记录了体外培养心肌细胞的动作电位。并初步观察了奎尼丁及牡丹皮提取液对培养心肌细胞动作电位的影响。奎尼丁 4mg/L 对培养心肌细胞呈典型的奎尼丁电生理效应，证明实验方法可靠。牡丹皮提取液对动作电位 幅度、时程及Vmax均有抑制作用。

体外培养心肌细胞是进行心肌细胞药理学研究的较好工具，其电生理研究的进展为药理学研究提供了一个新领域。目前，国内多用在位心或离体心肌片进行电生理研究，利用体外培养心肌细胞进行电生理研究及药理研究尚未见报道。本研究在这方面进行了一些探索，并初步观察了奎尼丁及中药牡丹皮的电生理作用，现报告如下。

材料和方法

一、标本与药物：全部实验均用培养 5～12天的 Wistar 种乳鼠心肌细胞团。培养方法详见有关文献[1]。细胞团选择生长状态良好，自律性搏动规律有力者。奎尼丁(意大利产)、牡丹皮（为毛茛科植物牡丹*Paeonia Suffruticosa* Andr的根皮）制成水煮酒沉提取液，浓度为生药 1g/ml，pH6.8，离子浓度为：K^+0.8mE*q*，无 Na^+及Ca^{++}。实验时以灌流液稀释至所需浓度。

二、灌流系统：细胞溶槽置于倒置显微镜载物台上，以恒温的Eagle培养基持续灌流标本。温度维持在32±1°C。灌流液内充以 $CO_2$5%和 $O_2$95%的混合气体，pH保持在7.4。

三、电位记录：电信号用玻璃微电极引导，电极尖端阻抗为 10～30mΩ，充灌 3M KCl。电极插入心肌细胞，电信号经微电极放大器，再经前置放大器显示在示波器上，用示波器照相机拍照动作电位图形。给药前，首先记录正常电位 1 分钟，然后给药，给药后 1 分钟记录，进行自身前后对比。测量参数为：动作电位幅度(AP)；静息电位(RP)；超射(OS)；动作电位时程(DT)；O相最大上升速率(Vmax)。

结 果

一、正常电位记录：共记录21个细胞，电极在细胞内维持时间最长可达 1 小时以上。动作电位图形呈三角形状，无明显平台期，见图 1 。多数细胞具有明显的舒张期自动去极化电位，动作电位幅度在54～87 mV之间，静息电位在40～67mV之间，将本结果与有关文献报导的数据进行了比较，详见表 1 。

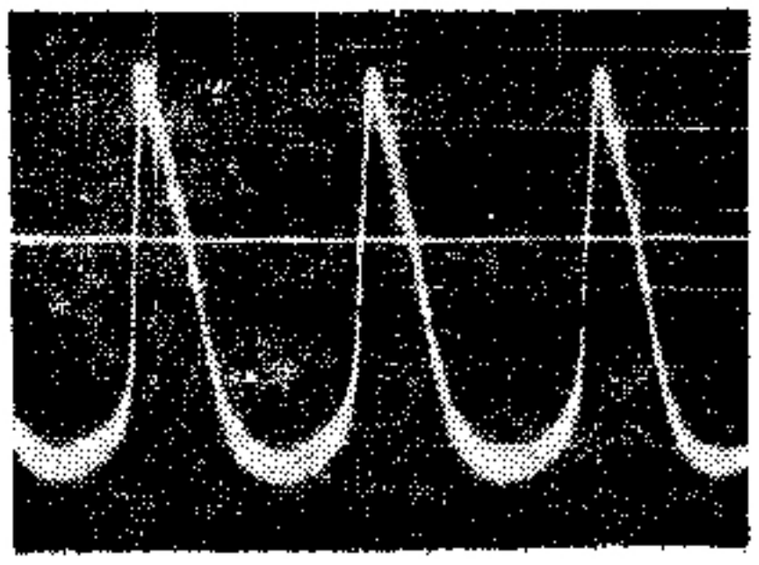

图 1 外体培养乳鼠心肌细胞自律性动作电位，每格 12.5mV、100ms(下同)横线为零位线

表 1 体外培养心肌细胞膜电位各参数的比较

	AP mV	RP mV	OS mV	DT ms	V_{max} V/S
本 文	65.5 ±2.1	−52.3 ±1.9	17.0 ±2.6	218.2 ±22.7	3.1±0.2
Schanne[2]	87.4 ±1.0	−44.8 ±0.6	22.4 ±0.8	—	8.6±0.4
Athias[3]	40−110	−60.4 ±4.3	21.8 ±1.8	145±13	89±13
		−40−80	0−30	92−205	5−300

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二、奎尼丁及牡丹皮对体外培养心肌细胞动作电位的影响，实验分六组进行，奎尼丁组、牡丹皮四种浓度组，对照组。结果见表2。

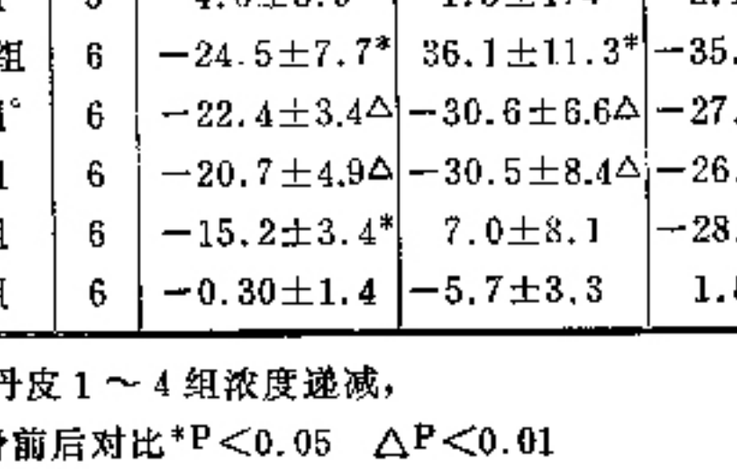
表2　各组细胞给药前后膜电位的变化率

	实验次数	M±SE		
		AP	DT	Vmax
对照组	5	4.6±3.9	1.5±1.4	−2.1±1.3
奎尼丁组	6	−24.5±7.7*	36.1±11.3*	−35.4±8.5*
丹—1组°	6	−22.4±3.4△	−30.6±6.6△	−27.5±5.6△
丹—2组	6	−20.7±4.9△	−30.5±8.4△	−26.2±10.4
丹—3组	6	−15.2±3.4*	7.0±8.1	−28.1±5.6△
丹—4组	6	−0.30±1.4	−5.7±3.3	1.8±1.7

°牡丹皮1～4组浓度递减，

自身前后对比*$P<0.05$　△$P<0.01$

奎尼丁组，灌流液中药物浓度为4mg/L，实验重复六次。给药前后细胞动作电位有明显的变化，细胞搏动频率减慢，动作电位幅度降低，Vmax减慢，动作电位时程延长，见图2。



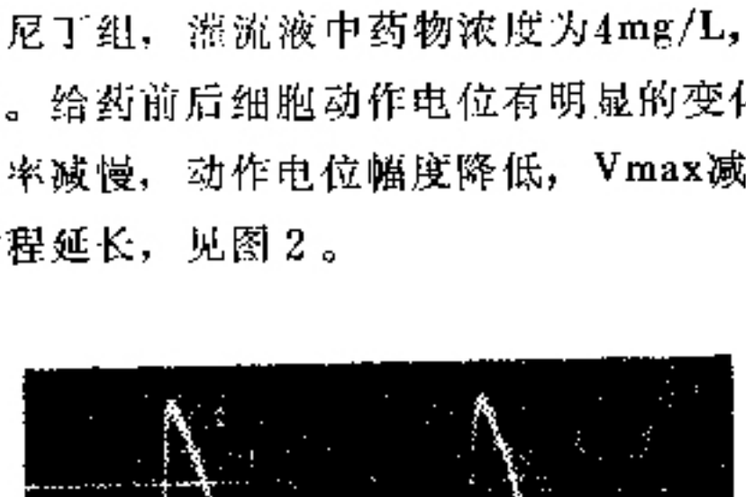
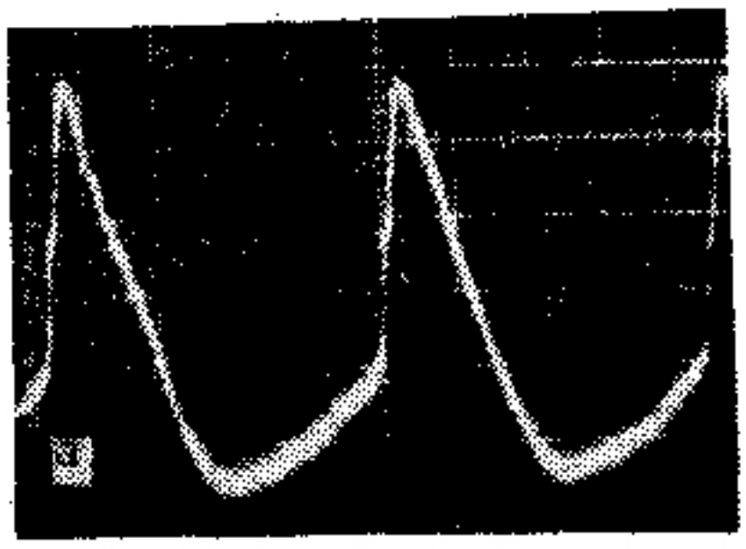


图2　奎尼丁(4mg/L)对体外培养乳鼠心肌细胞动作电位的影响a为给药前，b为给药后

牡丹皮四种浓度分别为1mg/ml、0.5mg/ml、0.25mg/ml、0.125mg/ml。每组重复六次实验。结果表明，牡丹皮对心肌细胞动作电位幅度，时程及Vmax均有抑制作用，随药物浓度升高作用加强，见图3。

对照组给予不含任何药物的灌流液，实验重复五次。结果动作电位无明显变化，证明实验系统及给药过程没有明显的人为干扰。



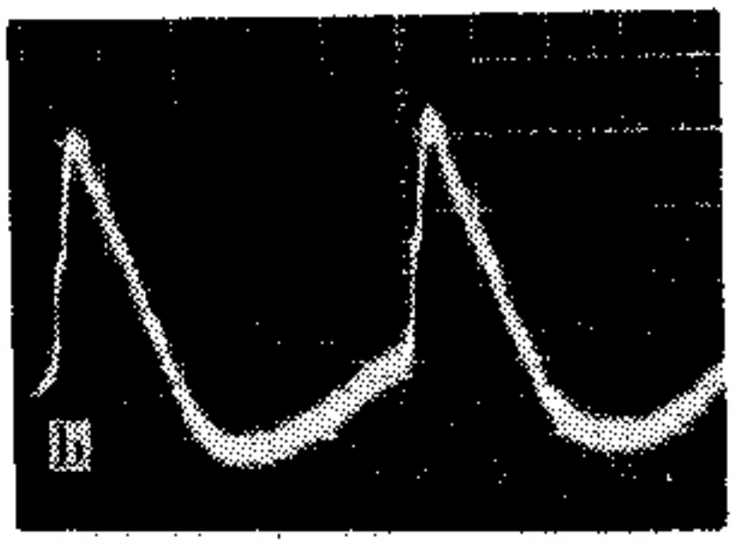


图3　牡丹皮(0.5mg/ml)对体外培养乳鼠心肌细胞动作电位的影响，a为给药前，b为给药后

讨　论

本研究记录的体外培养心肌细胞动作电位的各项参数与Athias及Schanne等人报告的结果基本相同。给奎尼丁后呈典型的奎尼丁电生理效应[2,3]，与在位心及心肌片实验结果相同。对照组给予不含任何药物的灌流液后，细胞动作电位无明显变化。表明实验方法可靠。牡丹皮降低动作电位幅度、减少Vmax，可能是作用于Na^+通道的结果，值得深入研究。实验中还观察到牡丹皮给药后细胞收缩力减弱，从而使细胞能量消耗减轻，与整体动物实验牡丹皮降低心肌耗氧量，保护缺血心肌的作用相符[4]。

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Experimental Study of Heat Purgating Mixture

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Purgation method had been found very useful in treating acute infections, such as pneumonia, dysentery, acute pancreatitis and biliary infections, etc. Further experimental study was carried out in order to explore its mechanism. A Heat Purgating Mixture (HPM contains *Rheum palmatum*, Mirabilite, *Scrophularia ninpoensis* and *Glycyrrhiza uralensis*) as representative prescription was used. The result showed that this mixture could lower the body temperature in animal models of acute infections, and its efficacy was better than that resulting from magnesium sulfate solution and water, $P<0.05$ and <0.01. It was observed that the ratio of PMN in blood and its phagocytic function, total serum complement activity could be raised by HPM, $P<0.01$ and <0.05. In vitro, the bacteriocidal effect of the serum obtained after administration of this mixture was stronger than the control. In rabbits given endotoxin intravenously, the normalization of endotoxemia was much easier when HPM was given. All these data indicated that the HPM is helpful in reducing the elevated body temperature, enhancing the host defence and counteracting endotoxemia.

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Effects of Quinidin and *Paeonia Suffruticosa* on Action Potential of Cultured Myocardial Cells

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The action potential of cultured myocardial cells of newborn rats was recorded by intracellular microelectrodes. Using quinidin 4 mg/L, the amplitude of the action potential was decreased by 24.5%, while its duration was prolonged for 36.1%, and the maximum rate of depolarization during upstroke (Vmax) was decreased by 35.4%, which showed typical electrophysiological efficacy of quinidin. Using the extract of *Paeonia suffruticosa* 0.5 mg/ml, the amplitude, duration and Vmax of action potential were decreased 22.4%, 30.1% and 27.5% respectively. These actions were progressively reduced as the concentration of *Paeonia suffruticosa* extract was lowered. The dosage and reaction was in positive correlation. In electrophysiological study, applying cultured myocardial cells was more advantageous than using the heart in situ or the myocardium in vitro. This report provided our results of preliminary study, and further research will be done on the pharmacology in cultured myocardial cells, on paeonol and paeonicorin, which were the active principles of *Paeonia suffruticosa*.

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The Effect of *Rheum Palmatum* in Different Doses on Blood Rheology in Rabbits

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In the present paper, the results of a study on the hemorheological effect of *Rheum palmatum* L., a Chinese drug, in different doses on rabbits are reported. Hemorheology tests were carried out before and after administration of the drug to check changes in hematocrit, whole blood viscosity, plasma viscosity, electrophoretic time of erythrocytes in their own plasma and plasma osmotic pressure. The rabbits used in the experiments were divided into two testing groups. In group A, it was observed that 4 hours after administration in dose of 3 g, there appeared a diphase effect of the drug on viscosity and hematocrit accompanied by an uniform increase in plasma osmotic pressure. In group B of rabbits, to which the drugs in dose of 6 g were administrated, the testing data showed that a change with time took place. Blood viscosity, hematocrit, electrophoretic time and plasma osmotic pressure were found lower than normal at first (within 2 hours), and then went up to higher level. It seems that the diphase changes in the two cases are caused by the increase of plasma osmotic pressure through adjusting the balance between diuresis and anti-diuresis.

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