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蝙蝠葛碱和利多卡因单用和联合用药对犬心浦氏纤维电生理特性的影响

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提要 用标准微电极法证明, 蝙蝠葛碱(Dau) 1-30 μmol/L 浓度依赖性降低犬浦氏纤维 APA, V_{max} 和 MDP, 延长 APD_{50} ,APD_{90} 及 ERP, 并降低其自律性和兴奋性. 利多卡因(Lid) 100 μmol/L 明显缩短 APD_{50}, APD_{90} 和 ERP, APA 和 V_{max} 亦显著降低, 并可缩短由 Dau 延长的 APD_{50} 和 APD_{90}, ERP 亦呈缩短趋势.表明 Lid 可改变 Dau 部分电生理特征, 可能构成其增强 Dau 药效学, 对抗其心脏毒性的基础.

关键词 蝙蝠葛碱; 利多卡因; 浦氏纤维; 动作电位; 电生理学

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Rate-dependent depression of maximal rate of depolarization in guinea pig papillary muscle action potentials by changrolin

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ABSTRACT The rate-dependent block (RDB) of changrolin on the maximal rate of depolarization (V_{max}) of action potentials was studied in guinea pig right ventricular papillary muscles. The result was compared with that of class I A (quinidine), I B (mexiletine) and I C (lorcainide) drugs to approach the subclassification of changrolin, by using standard microelectrode techniques with computer. Mexiletin exhibited the fastest response in the onset rate of RDB. V_{max} reached 61% of its final value by the second beat during a train of stimuli. In response to a similar train of stimuli, quinidine, lorcainide and changrolin produced exponential falls of V_{max} with the constants of −0.143, −0.085 and −0.051 AP^{-1} (AP = action potentials), respectively. Time constants of re-

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covery for mexiletine, quinidine, lorcainide and changrolin were estimated as 1.58, 9.06, 13.37 and 55.16 s. These suggest that the kinetics of RDB of changrolin are similar to those of IC drugs.

KEY WORDS changrolin; quinazolines; quinidine; mexiletine; lorcainide; papillary muscles; action potentials; electrophysiology

Changrolin, 4–{3,5 –bis [(*N*–pyrrolidinyl) methyl]–4′–hydroxyanlilino}–quinazoline, is a novel type of anti–arrhythmic drug. Its significant efficacy has been reported in animal experiments and clinical trials, and it has also been classified as class I anti–arrhythmic drug[1–7]. It is now admittedly accepted that class I drugs may be subdivided into three groups (IA, IB and IC)[8,9]. They differ in their effects on cardiac electrical activities, especially in the kinetics of RDB. In this paper, we compared the effects of RDB of changrolin on V_{max} with those of class IA, IB and IC drugs, in order to approach the subclassification of changrolin.

MATERIALS AND METHODS

Guinea pigs of either sex weighing 392 ± SD 96 g were stunned. The right ventricular papillary muscle was cut and superfused with Tryrode's solution gassed with 95% O_2 + 5% CO_2 at 37 ± 0.2 ℃[10]. Preparations were allowed to equilibrate for 1 h before control recordings were taken, and were driven from bipolar platinum electrodes by rectangular stimuli of 2–ms duration and sufficient strength to produce a constant latency during trains of stimuli. Cumulative doses of drug were added to the superfusate, and at least 30 min was allowed at each concentration before taking further readings. During this time, the preparation remained quiescent. AP were recorded by glass microelectrodes filled with KCl 3 mol / L. The diameter of the tip of the microelectrodes was < 0.5 μm (resistances 10–30 MΩ). Signals were delivered to microelectrode amplifier, then to the oscilloscope, channel A of a DC amplifier and differentiator respectively. Differentiated signals were then fed into oscilloscope, and channel B of the DC amplifier. Amplified signals from channel A and channel B were delivered through a switch R to a microcomputer which automatically analyzed the action potentials and RDB. Sampling of the computer was triggered by the stimulator.

To study rate–dependent effects, the preparations were driven by trains of stimuli at varying rates and of sufficient duration to achieve a stable level of effect. Rest period sufficient to ensure full recovery from rate–depedent effects were interposed between trains of stimuli. The kinetics of the recovery were studied by applying single extrastimuli at varying intervals after the end of a train. Each experiment was performed on a single cell[11].

The changrolin was supplied by Prof CHEN Wei–Zhou, Shanghai Institute of Materia Medica, Chinese Academy of Sciences. Mexiletine was provided by Chang–Zhou Pharmaceutical Factory. Lorcainide was presented by Prof LIU Wei–Wan, Department of Pharmacology, Hubei Medical College.

RESULTS

Time–independent depression of V_{max}(resting block) Fig 1 showed that mexiletine produced some depression of the V_{max} of the first action potentials of a train of impulses, after a prolonged period of quiescence. This "resting block (RB)" was measured as a percentage decrease from the control value. Mexiletine 11.5, 23.2 and 46.4 μmol / L produced RB (%) 3.5 ± 2.2, 7.9 ± 2.7, 17.6 ± 3.8, respectively. Lorcainide 10 μmol / L also produced some RB while quinidine and changrolin did not.

RDB of V_{max} Fig 1 shows that repetitive stimulations produced a progressive fall of V_{max} to a new plateau level. The difference between this new plateau level and the V_{max} of

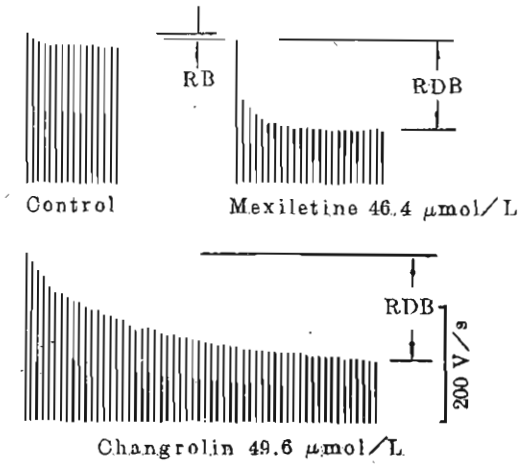

Fig 1. Rate-dependent block of mexiletine and changrolin

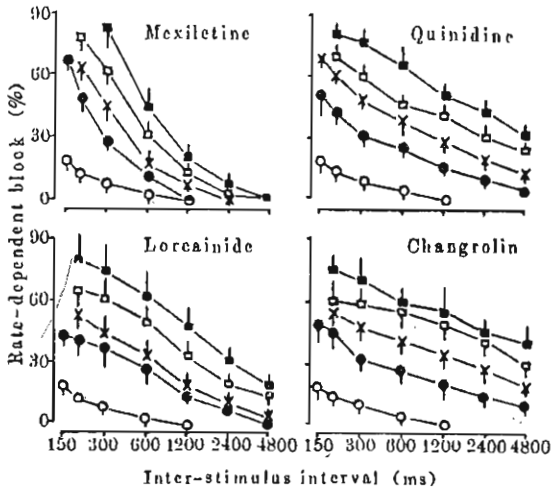

Fig 2. Relationships between rate, exprssed as the log of the interstimulus interval (ISI), and the percent rate-dependent reduction in V_{max} at various concentrations of drugs . (O) Control; Mexiletine (●) 11.5 μmol/L, (×) 23.2 μmol/L, (□) 46.4 μmol/L,(■) 92.8 μmol/L; Quinidine (●) 3.8 μmol/L, (×) 7.7 μmol/L, (□) 15.3 μmol/L, (■) 30.8 μmol/L; Lorcainide (●) 2.5 μmol/L, (×) 5.0 μmol/L, (□) 10.0 μmol/L, (■) 20.0 μmol/L; Changrolin (●) 12.4 μmol/L, (×) 24.8 μmol/L, (□) 49.6 μmol/L, (■) 99.2 μmol/L. $n=10$, $\bar{x}\pm SD$.

the first beat of the train was expressed as a percentage decrease, and was used as the measure of RDB. The amount of RDB that developed in the presence of mexiletine rose sharply with increasing stimulation frequency over a range of interstimulus interval (ISI) from 4800 to 200 ms (Fig 2). The RDBs produced by quinidine, lorcainide and changrolin were similar and varied much more gradually with changes in ISI than that produced by mexiletine.

Kinetics of onset of RDB Mexiletine 46.4, quinidine 15.3, lorcainide 10.0 and changrolin 49.6 μmol/L ultimately produced similar degrees of RDB, it could be seen that there were marked differences between them, in the speed at which V_{max} fell to the new plateau level. For quinidine, lorcainide and changrolin, the approach to this plateau was well fitted by a single exponential. This allowed an expression of the rate or onset of RDB in terms of the slope of that exponential[12]. For quinidine, this slope (at ISI of 300 ms) was estimated as -0.143 ± 0.008; -0.085 ± 0.011 AP^{-1} for lorcainide and -0.051 ± 0.005 AP^{-1} for changrolin (Fig 1).

In the case of mexiletine (Fig 1), however, the rate of onset of RDB was too rapid to be accurately estimated by this technique. During trains at ISI of 300 ms, mexiletine produced 61 ± 4% of its final rate-dependent fall in V_{max} by the second beat.

Recovery from RDB The rate at which V_{max} recovered at the end of a train towards its initial (resting) value was studied by adding single extrastimulus at varying intervals after a series of trains of stimuli at a constant frequency.

The time course of this process for all 4 drugs were found to be well fitted by single exponentials. The time constants (τ_{rc}) were 1.6 ± 0.7, 9.1 ± 0.4, 13.4 ± 1.8 and 55 ± 9 s for mexiletine, quinidine, lorcainide and changrolin, respectively.

DISCUSSION

This study shows that changrolin can de-

press V_{max} in a way of rate-dependence as other class I drugs do, its kinetics of RDB are closest to those of class IC drug.

The results are in consistent with the literature[12-14], in which the kinetics of onset of, and recovery from, RDB in a series of local anaesthetics and anti-arrhythmic drugs correlate very well with the molecular weights of the compounds. Mexiletine, quinidine, lorcainide and changrolin have molecular weight of 179, 324, 371 and 403 respectively. In terms of current concepts of the interaction of these drugs with the sodium channel, this can be explained by proposing that increasing molecular size somehow inhibits access to and egress from the receptor site.

Changrolin has the following characteristics: 1) markedly depressing V_{max}; 2) slowing conduction; and 3) remarkably slow onset rate of RDB. These are the prominent characteristics of class IC drugs. However, it was reported that changrolin could shorten APD and prolong ERP in guinea pig papillary muscles[5] and prolong both APD and ERP in dog Purkinje fibers[7]. Those are different from IC drugs. It was also reported that changrolin had some effects on K^+ and Ca^{2+} channels. More works are needed to classify definitely.

As the electrophysiological characteristics of changrolin, there may be some implications in its clinical uses. (1) Because of its very slow kinetics of RDB, it must be effective in a wider range of heart rate than other class I drugs. (2) Its potent effects on many kinds of arrhythmia could be explained by the combination of its slowest kinetics of RDB and its effect of increasing ERP/APD. It is conjectured and reported that changrolin may be effective in the arrhythmias which couldn't be controlled by other class I drugs. (3) It is expected that combining changrolin with other class I drugs may achieve much better therapeutic effects on the control of some kind of arrhythmias.

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常咯啉对豚鼠乳头状肌动作电位最大除极速率的频率依赖性抑制

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提要 用标准微电极技术, 研究了常咯啉对豚鼠右心室乳头状肌动作电位 V_{max} 的频率依赖性抑制作用(RDB), 并与 IA (奎尼丁), IB (美西律)和 IC (劳卡胺)类药物进行比较, 初步探讨其细分类, 美西律的 RDB 开始最快, 其第 2 个 V_{max} 所产生的抑制已占 RDB 的 61%; 奎尼丁、劳卡胺和常咯啉的 RDB 开始速率常数分别为 −0.143; −0.085 和 −0.051AP^{-1}(刺激间歇为 300 ms). 4 个药物 RDB 恢复的时间常数分别为 1.58, 9.06, 13.37 和 55.16s. 结果提示, 常咯啉的 RDB 动力学过程与 IC类药物最为相似.

关键词 常咯啉; 噻唑啉类; 奎尼丁; 美西律; 劳卡胺; 乳头状肌; 动作电位; 电生理学

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甲氧普胺对豚鼠乳头状肌动作电位 V_{max} 的影响

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Effects of metoclopramide on V_{max} of action potentials in guinea pig papillary muscles

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ABSTRACT The effects of metoclopramide (MCP) on V_{max} of action potentials of guinea pig papillary muscles were studied with intracellular microelectrodes. MCP 10-550 μmol / L abbreviated the action potential duration at 90 % repolarization (APD_{90}) and decreased the maximal rate of rise of action potential (V_{max}) dose-dependently. MCP caused rate-dependent and voltage-dependent reductions of V_{max} and retardation of the recovery of V_{max}. The results present the possible causes of depressant effect of MCP on Na channel.

KEY WORDS metoclopramide; papillary muscles; action potentials

提要 用细胞内固定微电极技术观察了甲氧普胺对豚鼠乳头状肌动作电位及其 V_{max} 特性的影响. 结果表明, 甲氧普胺使心室肌细胞的 APD_{90} 缩短, V_{max} 降低, 对动作电位的 V_{max} 的影响具有频率和电压依赖. 并使 V_{max} 值的恢复时间延长.

关键词 甲氧普胺; 乳头状肌; 动作电位

甲氧普胺(metoclopramide, MCP; 灭吐灵; 胃复安)一直作为止吐药用于临床[1]. MCP 的化学结构与普鲁卡因类似, 我们发现 MCP 也有抗心律失常作用[2], 本文观察 MCP 对豚鼠心室乳头状肌细胞动作电位的影响.

MATERIALS AND METHODS

MCP 由无锡县制药厂提供, 为白色粉末.

乳头状肌标本制备 豚鼠, ♀♂兼用, 击头致昏, 右心室乳头状肌置于 95% O_2+5% CO_2 饱和的 Tyrode 溶液 36 ± 0.5℃, pH 7.2-7.4. 灌流速度 10 ml / min.

取内充 KCl 3 mol / L 的玻璃微电极(电阻约 10-40 MΩ), 用固定电极法引出心肌细胞内动作电位, 通过 Ag-AgCl 丝经 FW-2 微

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