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甲基莲心碱对麻醉猫心脏电-机械活动的影响

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Effects of neferine on heart electro-mechanical activity in anaesthetized cats

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ABSTRACT Neferine, an alkaloid extracted from the green seed embryo of *Nelumbo nucifera* Gaertn, has been shown to have anti-arrhythmic action. Neferine 1-10 mg/kg iv dose-dependently decreased the monophasic action potential amplitude (MAPA), prolonged the monophasic action potential duration (MAPD). It also decreased LVP, dP/dt , prolonged SCL, and reduced arterial blood pressure in a dose-dependent manner. These effects were similar to those of quinidine, and different from tetrandrine. The latter had an inhibitory effect on LVP and dP/dt , but had no influence on MAPA and MAPD. The results indicate that neferine and quinidine have similar effects on heart electro-mechanical activity.

KEY WORDS neferine; heart; electrophysiology; quinidine; tetrandrine; action potentials

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摘要 甲基莲心碱(Nef) 1-10 mg/kg iv 剂量依赖性抑制麻醉猫单相动作电位幅度(MAPA), 延长单相动作电位时程(MAPD), 同时使LVP和 dP/dt 降低, 也可使BP降低, SCL延长, 其作用与奎尼丁相似, 不同于粉防己碱。结果表明Nef在影响在位猫心脏电活动的同时, 使心脏的收缩性也受到抑制。

关键词 甲基莲心碱; 心脏; 电生理学; 奎尼丁; 粉防己碱; 动作电位

甲基莲心碱(neferine, Nef)具有较广泛的抗实验性心律失常作用^(1,2), 这可能与降低心肌自律性、兴奋性及延长不应期有关⁽³⁾; 离体心肌电生理研究证明, 其作用可能与非特异性抑制心肌 Na^+ , K^+ , Ca^{2+} 的跨膜转运有关⁽⁴⁾。为给临床试用提供充分的理论依据, 本文在麻醉猫观察Nef对在体心脏电-机械活动的影响, 并与粉防己碱(tetrandrine, Tet)、奎尼丁(quinidine, Qui)进行对比性研究。

METHODS

猫17只, 体重 $2.5 \pm SD 0.6$ kg, ♀♂不拘, 乌拉坦·氯醛糖250·60 mg/kg ip 麻醉, 分离一侧颈动脉和颈浅静脉, 按在人体长程记录单相动作电位方法⁽⁵⁾, 将自制的Ag-AgCl

单极导管接触电极(直径约 1.5 mm)经颈浅静脉插入右心室, 参考电极置于颈部皮下, 引导右心室内膜单相动作电位(MAP), 另将连在压力换能器上的一直径约 1 mm 的塑料空心管(内充肝素·盐水), 由颈总动脉插入左心室, 引导左心室压力(LVP), 连于另一换能器的塑料管插入一侧股动脉记动脉血压(BP), 以上各信号输至日本产 RM-6000 型八道生理记录仪, 记录 LVP, MAP 和左室压力变化最大速

率 dP/dt 和 BP, MAP 作为心脏电活动指标, LVP 和 dP/dt 作为心脏机械收缩活动的影响, 同时观察血压变化. Nef, Qui 和 Tet 0.5 mg/(kg·min) 分别恒速股 iv, 观察不同剂量药物对猫心脏电-机械活动和 BP 的影响.

RESULTS

Nef 对麻醉猫在体心脏电-机械活动的影响 如 Fig 1 所示, Nef 剂量依赖性地使在体

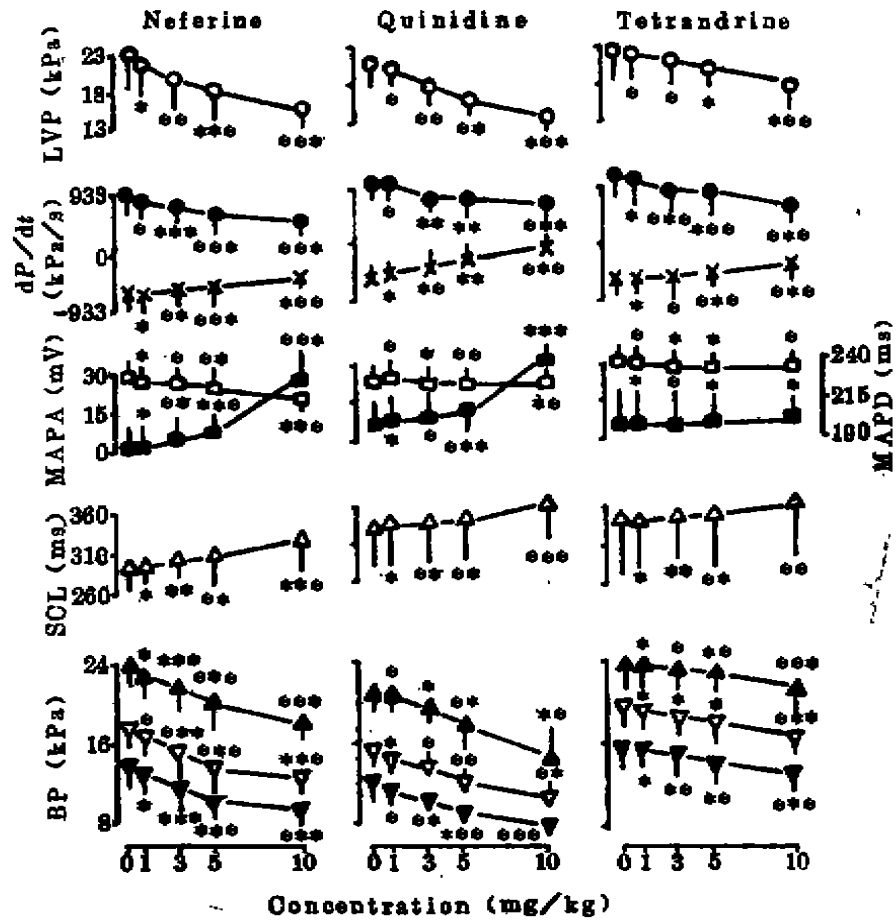


Fig 1. Effects of neferine, quinidine and tetrandrine on heart electro-mechanical activity and arterial blood pressure in anaesthetized cats. Monophasic action potential amplitude (MAPA, □), Monophasic action potential duration (MAPD, ■), n = 5-7 cats, $\bar{x} \pm SD$. *P > 0.05, **P < 0.05, ***P < 0.01 vs control (0 mg/kg).

猫($n=7$)心脏 MAPD 延长, 也可使 MAP 降低, 同时心室性周期(SCL)延长, 剂量达 10 mg/kg 时, MAPD 及 SCL 从给药前的 177 ± 24 和 286 ± 27 ms 延长到 236 ± 21 和 317 ± 45 ms, MAPD 延长与 SCL 延长无关; MAPA 从给药前的 27 ± 5 mV 降低到 23 ± 3 mV。在心脏电活动受到影响的同时, 心脏的收缩性也受到抑制, LVP 和 dP/dt 也依剂量降低, 给药达 10 mg/kg, LVP 从给药前的 24 ± 7 kPa 降低到 18 ± 4 kPa, $\pm dP/dt$ 从 917 ± 232 和 $-(613 \pm 168)$ kPa 降到 549 ± 177 和 $-(407 \pm 126)$ kPa。

Nef 在影响心脏电-机械活动同时, 也依剂量降低麻醉猫的 BP, 10 mg/kg 时使收缩压(SP)、舒张压(DP)和平均压(MP)分别从给药前的 23 ± 2 , 14 ± 2 和 17 ± 2 kPa 降低到 17 ± 4 , 9 ± 2 和 12 ± 3 kPa。

Qui 对麻醉猫在体心脏电-机械活动的影响 如 Fig 1 所示, Qui 对在体猫($n=5$)心脏电-机械活动的影响与 Nef 相似, 剂量依赖性地延长 MAPD 和 SCL, 10 mg/kg 时, MAPD 及 SCL 从给药前的 193 ± 32 和 329 ± 60 ms 延长到 240 ± 33 和 356 ± 62 ms, MAPA 受到抑制, 从 26 ± 3 mV 降低到 22 ± 5 mV; 在影响心脏电活动同时, 心脏收缩性也受到抑制, 10 mg/kg 时, Qui 使 LVP 从给药前的 21 ± 2 kPa 降低到 14 ± 1 kPa, $\pm dP/dt$ 从 933 ± 170 和 $-(573 \pm 89)$ kPa 降低到 574 ± 76 和 $-(267 \pm 47)$ kPa。

Qui 对麻醉猫 BP 也有依剂量降低作用, 10 mg/kg 时, SP, DP 和 MP 分别从给药前的 20 ± 3 , 12 ± 2 和 15 ± 2 kPa 降低到 14 ± 2 , 7 ± 1 和 9 ± 1 kPa。

Tet 对麻醉猫在体心脏电-机械活动的影响 如 Fig 1 所示, Tet 对在体猫($n=5$)心脏 MAPD 和 MAPA 无显著影响, 这与 Nef 和 Qui 的作用不同, 但对 SCL 有依剂量延长作用, 10 mg/kg 时, SCL 从给药前的 336 ± 64 ms 延长到 360 ± 70 ms。Tet 剂量依赖性地抑制心肌收缩性, 最先抑制心脏 dP/dt , 对 LVP 较大剂

量时才抑制明显。剂量达 10 mg/kg 时, LVP 从给药前的 22 ± 4 kPa 降低到 18 ± 2 kPa, dP/dt 从给药前的 893 ± 415 和 $-(653 \pm 197)$ kPa 降低到 533 ± 236 和 $-(493 \pm 186)$ kPa。

对 BP 的影响, Tet 在 5 mg/kg 时有明显的降低作用; 10 mg/kg 时, 使 SP, DP 及 MP 从给药前的 21 ± 3 , 15 ± 2 和 19 ± 3 kPa 降低到 19 ± 3 , 13 ± 1 和 16 ± 2 kPa。

DISCUSSION

Nef 剂量依赖性地使 MAPA 降低, MAPD 延长, 这表明 Nef 可使心脏除极速率降低, 复极延长, 与此同时 Nef 使心肌机械收缩活动减弱, 表现在 LVP 和 dP/dt 的降低, 这与在离体豚鼠乳头状肌的研究⁽⁴⁾一致: 跨膜电位 APA, \dot{V}_{max} 降低, 延长 APD 和 ERP 的同时, 抑制心肌收缩性。这种作用与 Qui 对猫在体心脏电-机械活动的影响基本相似, 而不同于 Tet, Tet 是一钙拮抗剂, 在抑制心肌机械收缩活动时, 对 MAP 无明显影响, 也基本不影响跨膜电位⁽⁹⁾。Nef, Qui 和 Tet 都使 SCL 依剂量延长, 说明三者对猫窦房结自律性都有抑制作用, 此外, 三者对麻醉猫 BP 依剂量地降低可能与它们扩张外周血管的作用有关。

Nef 对麻醉猫在体心脏电-机械活动的作用, 表现与 Qui 相似, 不同于 Tet, 提示其抗心律失常作用机理可能与 Qui 相似, 即 Nef 对心肌 Na^+ , K^+ , Ca^{2+} 跨膜转运可能具有非特异性抑制作用, 后者有待证实。

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麦冬总皂甙抗心律失常作用及其电生理特性

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Anti-arrhythmic effects and electrophysiological properties of *Ophiopogon* total saponins

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ABSTRACT The arrhythmias induced by chloroform-epinephrine, BaCl₂, and aconitine were prevented and antagonized by *Ophiopogon* total saponins (OTS) which were extracted from the root of *Ophiopogon japonicus* (Thunb) Ker-Gawl. The incidence of ventricular arrhythmia produced by ligation of the left anterior descending coronary artery was effectively decreased without any changes in the hemodynamic indices of dogs. The electrophysiological effects of OTS *in vivo* and *in vitro* were studied by means of contact electrode and intracellular microelectrode techniques. The results showed that OTS shortened APD₁₀, APD₅₀, APD₉₀; decreased APA and V_{max} of both monophasic and transmembrane action

potentials. OTS also increased the ERP/APD ratio and prevented or abolished the arrhythmias provoked by ouabain and aconitine. The anti-arrhythmic properties of OTS lead us to draw an inference that the anti-arrhythmic mechanism may be related to the blocking of sodium and calcium channels.

KEY WORDS *Ophiopogon japonicus*: saponins; arrhythmia; coronary circulation; action potentials; aconitine; calcium channel blockers

摘要 麦冬总皂甙(OTS) 10 mg/kg iv 可有效地预防或对抗由 CHCl₃-Adr, BaCl₂, Aco 所诱发的心律失常, 并使结扎犬冠状动脉 24 h 后的室性心律失常发生率由 87±8 降至 57±7%。电生理实验表明 OTS 15 mg/kg 可明显降低兔单相动作电位的 V_{max}, 缩短其 APD₁₀, APD₅₀; OTS 50 μg/ml 也使豚鼠乳头状肌细胞跨膜动作电位的 APA, V_{max} 明显降低, APD₁₀, APD₅₀ 明显缩短, 同时 ERP/APD 显著增大。

关键词 麦冬; 皂甙类; 心律失常; 冠状动脉循环; 动作电位; 乌头碱; 钙通道阻滞剂

麦冬 [*Ophiopogon japonicus* (Thunb) Ker-Gawl] 有滋阴生津等作用, 是古验方生脉散的主要成份之一。药理实验表明麦冬有改善心肌缺血缺氧状态的作用^(1,2), 临床曾用于冠心病的治疗⁽³⁾。有报道麦冬的水或乙醇提取液对 BaCl₂, 乌头碱(aconitine, Aco)等诱发的心律

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