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左旋四氢巴马汀及其同类药加强兔电针镇痛

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Potentiation of electroacupuncture analgesia by *l*-tetrahydropalmatine and its analogues in rabbits

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ABSTRACT *l*-Tetrahydropalmatine (*l*-THP), tetrahydroberberine (THB) and *l*-stepholidine (*l*-SPD) are the homologues of tetrahydroprotoberberines and have a common antagonistic effect to central dopamine receptors. In the present experiment, the potassium iontophoretic dolorimetry was used to determine the pain threshold of rabbits. Unilateral "Hegu" point (the dorsum of the front paw, between 1st and 2nd metacarpals) and "Waiguan" point (the dorsum of the foreleg, between radius and ulna, 2 cm above the wrist joint) of each rabbit were electrically needled. The effects of iv *l*-THP 8 mg/kg, THB 16 mg/kg or *l*-SPD 4 mg/kg on electroacupuncture analgesia were investigated. The experimental results indicated that these 3 agents enhanced the potency of electroacupuncture analgesia and prolonged the duration as well. This investigation gives the evidence that the drug possessing antagonistic effect to central dopamine receptors could be used as a synergist of acupuncture analgesia.

KEY WORDS *l*-tetrahydropalmatine; tetrahydroberberine; *l*-stepholidine; acupuncture; analgesia; berberines

摘要 在兔 K^+ 透入测痛模型上, iv *l*-THP 8 mg/kg 及其同类药 THB 16 mg/kg 和 *l*-SPD 4 mg/kg 加大电针单侧“合谷”和“外关”穴引起的痛阈升高幅度, 并延长痛阈升高的持续时间, 表明 *l*-THP、THB 和 *l*-SPD 具有加强电针镇痛强度和延长电针镇痛后效应的作

关键词 *l*-四氢巴马汀; 四氢小檗碱; *l*-千金藤定; 针刺; 镇痛; 小檗因类

左旋四氢巴马汀 (*l*-tetrahydropalmatine, *l*-THP) 具有镇痛、镇静、肌松和抗心律失常等多种药理功能, 副作用小, 呼吸抑制轻微, 为临床广泛应用的一种非麻醉性镇痛药⁽¹⁻⁴⁾。四氢小檗碱 (tetrahydroberberine, THB)^(2,5) 和左旋千金藤定 (*l*-stepholidine, *l*-SPD)⁽⁶⁾ 具有与 *l*-THP 相似的化学结构和药理功能, 为已在临床应用的两个 *l*-THP 同类药。现已证实 *l*-THP, THB 和 *l*-SPD 可阻断中枢多巴胺受体, 是脑内新类型多巴胺受体阻滞剂⁽⁷⁻⁹⁾。一些中枢多巴胺受体阻滞剂具有加强针刺镇痛的作用⁽¹⁰⁻¹²⁾。为进一步了解中枢多巴胺系统与针刺镇痛的关系, 并寻找合理的针刺镇痛的增效剂以提高针刺麻醉的疗效, 本文采用兔实验, 试将 *l*-THP 与电针联合应用, 观察 *l*-THP 对电针镇痛的影响, 比较其同类药 THB 和 *l*-SPD 对电针镇痛的作用。

MATERIALS AND METHODS

l-THP 注射液 (广东湛江制药厂)。THB 和 *l*-SPD 由中国科学院上海药物研究所提供。

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THB 用前先'用 H_2SO_4 0.1 mol/L 溶解, 再用 $NaOH$ 0.5 mol/L 中和, 使 pH 达 4.4. l -SPD 溶液制备方法相同, pH 为 4.6.3 药由耳缘静脉 iv.

兔 51 只, 体重 $2.4 \pm SD$ 0.3 kg, ♀♂ 兼用, 由本校实验动物部提供. 采用 K^+ 透入法测痛. 用直流电将 K^+ 透入兔耳尖皮肤作痛刺激, 以头及前肢的防御性动作为痛反应, 记录痛反应时 mA 为痛阈. 用 G-6805 型治疗仪电针兔一侧前肢的“合谷”(前爪伸面, 第 1 和第 2 掌骨之间)和“外关”(前肢伸面桡骨和尺骨之间, 腕关节上 2 cm)穴, 频率 2-3 Hz, 强度以引起爪微动为度, 电针持续 30 min.

实验设 4 组: (1) 单纯给药组, (2) 电针加药组, (3) 电针对照组(电针+生理盐水)和 (4) 空白对照组(生理盐水). 实验中(1)组与(4)组兔; (2)组与(3)组兔交替一次, 间隔一周.

RESULTS

l -THP 对电针镇痛的加强作用 Fig 1-A 显示了 l -THP 镇痛和加强电针镇痛的作用. iv l -THP 8 mg/kg 5 min 痛阈升高, 作用持续 20 min, 痛阈提高最大值达 0.94 ± 0.90 mA, 显示该剂量 l -THP iv 可产生明显的镇痛作用. 与 l -THP 的镇痛作用相比, 电针的镇痛作用出现较慢, 10 min 时痛阈升高, 作用持续时间较长, 至停针后 10 min, 痛阈提高最大值为 0.79 ± 0.49 mA. 在电针 10 min 时加用 l -THP 8 mg/kg, 可见痛阈进一步升高, 痛阈提高的最大值达 2.78 ± 1.57 mA. 另外, 电针与 l -THP 合用后, 痛阈升高的持续时间显著延长, 实验中看到电针停止后 60 min 时, 镇痛作用仍存在, 此时痛阈为 0.81 ± 0.43 mA 高于处理前痛阈水平 0.38 ± 0.24 mA ($P < 0.05$) (数据未在 Fig 1-A 中显示). 结果表明 l -THP 可加强电针的镇痛强度和延长电针镇痛的后效应. 实验中另外观察了 6 只电针无镇痛作用的兔加用 l -THP (8 mg/kg) 后的痛阈变化情况, 结果显

示电针与 l -THP 合用引起的痛阈提高值仅为 0.72 ± 0.21 mA, 与单用 l -THP 的镇痛效果相近 ($P > 0.05$), 提示 l -THP 不能改善电针无效兔的针效. 我们在实验中还观察了 l -THP 4 和 16 mg/kg iv 对痛阈和电针镇痛作用的影响, 结果显示 4 mg/kg 无镇痛作用, 也不加强电针镇痛, 而 16 mg/kg 镇痛作用显著, 亦有加强电针镇痛的作用, 且作用强于 8 mg/kg 剂量组, 提示 l -THP 的镇痛和加强针刺镇痛作

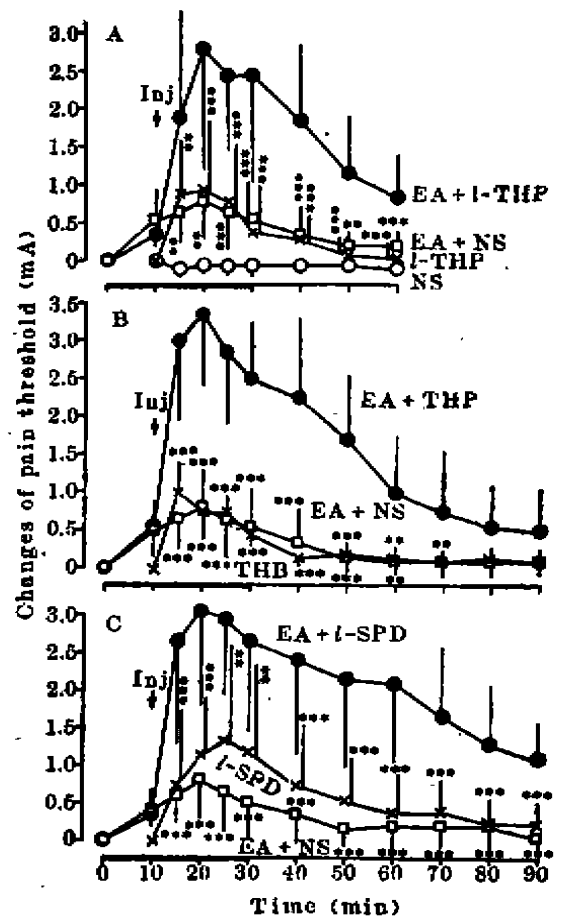


Fig 1. Effects of A) l -THP (8 mg/kg iv, $n=8-10$), B) THB (16 mg/kg iv, $n=8$) and C) l -SPD (4 mg/kg iv, $n=8$) on electroacupuncture (EA) analgesia in rabbits. The K^+ iontophoretic dolorimetry was used to determine the pain threshold. Unilateral "Hegu" and "Waiguan" points of each rabbit were electrically needled. Black bar represents EA. $\bar{x} \pm SD$. ** $P < 0.05$, *** $P < 0.01$ vs EA + l -THP group in A); vs EA + THB group in B); vs EA + l -SPD group in C).

用与剂量有关。

THB 和 *l*-SPD 对电针镇痛的加强作用

Fig 1-B, C 分别显示 THB 和 *l*-SPD 镇痛和加强电针镇痛的作用。从 Fig 1-B 可见 iv THB 16 mg/kg 后痛阈升高, 最大值可达 1.01 ± 0.41 mA, 作用持续 20 min。电针加用该剂量的 THB, 痛阈提高的最大值达 3.34 ± 0.96 mA, 且电针与 THB 合用引起痛阈升高的持续时间也明显延长, 达 80 min, 示 THB 亦具有加强电针镇痛强度和延长其镇痛后效应的作用。较小剂量的 *l*-SPD (4 mg/kg) iv 引起较强的镇痛作用 (Fig 1-C), 给药后痛阈提高的最大值为 1.33 ± 1.27 mA, 作用持续时间约 40 min。电针与该剂量的 *l*-SPD 合用, 两者的镇痛作用出现了明显的协同 (Fig 1-C), 合用后痛阈提高值可达 3.03 ± 1.25 mA, 且痛阈升高持续时间明显延长, 电针停止后 90 min 时痛阈仍高于处理前的水平, 提高值为 0.78 ± 0.58 mA ($P < 0.01$), 表明此时其镇痛作用仍然存在 (数据未在 Fig 1-C 中显示)。另外, 我们在 6 只兔上观察了 pH 对照液对电针镇痛的影响, 对照液为同容量的稀 H_2SO_4 , 结果 iv 该对照液不影响电针的镇痛作用。

DISCUSSION

已知 *l*-THP, THB 和 *l*-SPD 具有相似的化学结构⁽⁷⁾, 均有阻断中枢多巴胺受体的功能⁽⁷⁻⁹⁾。本实验也表明 3 药都加强了电针镇痛的强度, 并延长了电针镇痛的后效应。3 药的镇痛强度大致为: *l*-SPD > *l*-THP > THB, 其中 *l*-THP 和 THB 的强度对比以往已有报道⁽⁸⁾, 与此相符。THB 加强电针镇痛的幅度大于其它两药, 而 *l*-SPD 延长电针镇痛后效应的作用最为显著。现已知 3 药对多巴胺受体的亲和力不同^(8,9), 上述差别是否与此有关需研究。

3 药被认为是一新类型中枢多巴胺受体阻滞剂⁽⁷⁻⁹⁾, 主要作用于 D_1 受体^(6,14)。本实验显示在对针刺镇痛的影响上, 该类药与一些经典的多巴胺受体阻滞剂⁽¹⁰⁻¹²⁾相类似, 均呈加

强作用。这进一步证实中枢多巴胺受体的阻断有利于针刺镇痛。至于多巴胺受体亚型与该类药和针刺镇痛的关系的研究正在进行。

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Anti-lipid peroxidation and protection of ginsenosides against cerebral ischemia-reperfusion injuries in rats

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ABSTRACT The correlation between protective effect of ginsenosides $R_b + R_o$ and brain endogenously-derived prostacyclin synthesis, thromboxane A_2 formation and lipid peroxidation were estimated in rats. Ginsenosides $R_b + R_o$ 100 mg/kg iv 30 min before 4-vessel occlusion elevated 6-keto-PGF_{1 α} level, declined thromboxane B_2 and brain edema formation, reduced the rise of lipid peroxides and suppressed the reduction in both creatine phosphokinase (CK) and superoxide dismutase (SOD) activities in brain tissue after 40-min ischemia followed by 1-h reperfusion. Furthermore, these improvements were partially abolished by pretreating with iv indomethacin. It is concluded that ginsenosides possess protective effect on cerebral ischemia-reperfusion injury of rats and ginsenosides $R_b + R_o$ are the active principles. The underlying mechanism of protection is ascribed partially or mainly to the facilitated synthesis and release of prostacyclin, reduced formation of thromboxane A_2 and inhibited generation of free radicals and subsequent lipid peroxidation.

KEY WORDS transient cerebral ischemia; reperfusion injury; prostaglandins X; thromboxane A_2 ; free radicals; lipid peroxides; brain edema; ginseng; saponins; indomethacin

Ginsenosides and their components $R_b + R_o$ have protective effects on myocardial ischemia and reperfusion injury both *in vivo* and *in vitro*^(1,2) possibly via facilitating the synthesis and release of myocardial pro-

stacyclin, inhibiting formation of thromboxane A_2 and suppressing free radical generation and subsequent lipid peroxidation^(2,3). Ginsenosides decreased brain lactate content during anoxia, lowered the vertebral artery resistance in dog and protected against scopolamine-induced amnesia in rats. These results indicate that ginsenosides may dilate cerebral arteries and maintain cerebral function and metabolism. Recently, we found that ginsenosides protected against acute cerebral ischemia and reperfusion injuries in rats⁽⁴⁾ and manifestation of action agrees well with other investigations that *Panax notoginseng* protected against acute incomplete cerebral ischemia in rabbits⁽⁵⁾. However, the underlying mechanism of protection needs to be clarified. The aim of present investigation is to examine the possible beneficial action of ginsenosides $R_b + R_o$ on acute cerebral ischemia and reperfusion. In order to elucidate the mechanism of protection, correlation among the actions, prostacyclin synthesis and lipid peroxidation were also explored by means of interrupting the cyclooxygenase pathway of arachidonic acid metabolism with indomethacin.

MATERIALS

Ginsenosides components $R_b + R_o$ were extracted from the root of *Panax ginseng*

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