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摘要 从阿拉伯艾蒿提取到两种苯并二氮杂䓬受体的配基，毛地黄黄酮和玄参黄酮. 两种化合物在体外可抑制[^{3}H]地西泮和大鼠皮层细胞膜的结合，IC_{50}值分别为1.3 μmol·L^{-1}和23 μmol·L^{-1}. 两种化合物GABA比分别为1.1和1.2，都可少量增加[^{35}S]TBPS的结合，提示这种化合物是苯并二氮杂䓬受体的拮抗剂或部分激动剂.

关键词 阿拉伯艾蒿；黄酮类；毛地黄黄酮；玄参黄酮；γ-氨基丁酸-A受体；脑；细胞膜

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Effects of 3'-angeloyloxy-4'-acetoxy-3', 4'-dihydroseselin on myocardial dysfunction after a brief ischemia in anesthetized dogs

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ABSTRACT The effect of a 30-min infusion of 3'-angeloyloxy-4'-acetoxy-3', 4'-dihydroseselin (Pd-Ia), a coumarin isolated from *Peucedanum praeruptorum* Dunn 0.15 mg·kg^{-1}·min^{-1} on regional myocardial dysfunction was examined in 16 anesthetized open-chest dogs subjected to a 15-min occlusion of the left anterior descending coronary artery followed by a 3-h reperfusion. Segment lengths of left ventricular wall were measured with an ultrasonic micrometer. The control caused a decrease in the % of segment shortening (SS %) throughout the reperfusion period (n=8), while Pd-Ia ameliorated segment function immediately after reperfusion and restored the SS % to 41±51 % of the baseline value (n=8, P<0.05 *vs* control) 5 min after reperfusion without any significant changes in cardiohemodynamics. The improvement of myocardial function induced by Pd-Ia was maintained at least 3 h after reperfusion. These findings revealed that Pd-Ia had a cardioprotective action in stunned myocardium.

KEY WORDS coumarins; myocardial reperfusion injury; hemodynamics; ultrasonography

Our previous studies showed that the crude extract of the root of a Chinese traditional herb bai-hua qian-hu (*Peucedanum praeruptorum* Dunn, BQ) increased the coronary blood flow in isolated rabbit hearts and anesthetized cats[1]. The racemate of 3'-angeloyloxy-4'-acetoxy-3', 4'-dihydroseselin[2]

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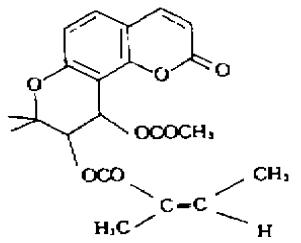
(Pd-Ia), an effective component of BQ displayed a Ca^{2+} channel blocking action[3]. But there is no information on the effect of Pd-Ia on regional myocardial dysfuction after a brief (<20 min) ischemia, ie, "stunned myocardium"[4] (SM), which is a critical phenomenon during spontaneous reperfusion after coronary spasm or thrombosis, and in interventional recanalization with angioplasty or thrombolysis[5]. In the present study, the effects of Pd-Ia on SM of anesthetized dogs were examined.



3'-angeloyloxy-4'-acetoxy-3',4'-dihydroseselin

MATERIALS AND METHODS

Drugs Pd-Ia was extracted at the Department of Pharmacognosy and Phytochemistry, Meiji College of Pharmacy, Japan[6], and dissolved freshly in 50 % polyethylene glycol (PEG) 200 solution before each experiment.

Dog and preparation Healthy mongrel dogs of either sex weighing 13.6 ± 2.6 kg (n = 16) after overnight fasting were anesthetized with thiopental sodium 20 mg·kg^{-1} iv and ventilated by inhalation of a mixture of O_2 and N_2O (1:2 vol/vol) to which 0.8—1.5 % enflurane was added. The cardiohemodynamic parameters were measured as described previously[7]. The left anterior descending coronary artery (LAD) was dissected free distal to its first major diagonal branch. An occluder was looped around the LAD so that it might ligate or release the vessel. Segment lengths of left ventricular wall were measured with an *ultrasonic dimension system* (UDM-5C, MECC, Japan). Two pairs of piezoelectric crystals (5 MHz) were implanted into the ischemic subendocardial layer perfused by LAD and the normal one by left circumflex artery (LCX) respectively. Each pair of crystals was implanted 6—14 mm apart and 7—9 mm deep. End-diastolic (EDL) and end-systolic length (ESL) were defined as the length just before the onset of +LV dp/dt_{max} and the one 20 ms before the −LV dp/dt_{max}[8], respectively. The % of segment shortening (SS%) was calculated by the equation: SS % = [(EDL − ESL)/EDL] × 100. All parameters were monitored simultaneously on a multichannel recorder (RM-6000, Kohden, Japan).

Experimental protocol Sixteen dogs (8 in each group) were infused with 4.5 ml of either Pd-Ia (0.15 mg·kg^{-1}·min^{-1}) or its solvent PEG through the right jugular veins for 30 min at a rate of 0.15 ml·min^{-1} with a pump (Model 975C, Harvard Apparatus, USA). Fifteen minutes after the start of infusion, LAD was occluded for 15 min followed by a 3-h reperfusion. The ligation was released slowly (over 1 min) to avoid occurrence of arrhythmia after reperfusion.

Statistical analysis All data were expressed as $\bar{x} \pm s$. Each parameter within a group was compared with its own baseline value before infusion of PEG or Pd-Ia using paired t test. Unpaired t test was used between groups.

RESULTS

Iv infusion of Pd-Ia at a rate of 0.15 mg·kg^{-1}·min^{-1} or PEG (control) for 30 min showed no significant changes in HR, MAP, rate pressure product [RPP, = SAP × HR, an indirect index of myocardial O_2 consumption (MOC)], LVEDP and +LV dp/dt_{max} throughout the experiment. Both EDL and ESL in myocardium perfused by LAD before occlusion showed no significant differences between the control and the Pd-Ia groups. The segment function of LAD region showed dyskinesis or akinesis during occlusion in both groups. Both EDL and ESL in non-ischemic region perfused by LCX showed no significant differences between the 2 groups during occlusion or after reperfusion, and they were normalized to the preocclusion level (Fig 1).

There were no significant differences in SS % of LAD region between the Pd-Ia group (−51 ± 48 %) and the control group (−83 ± 28 %) during occlusion. In the control

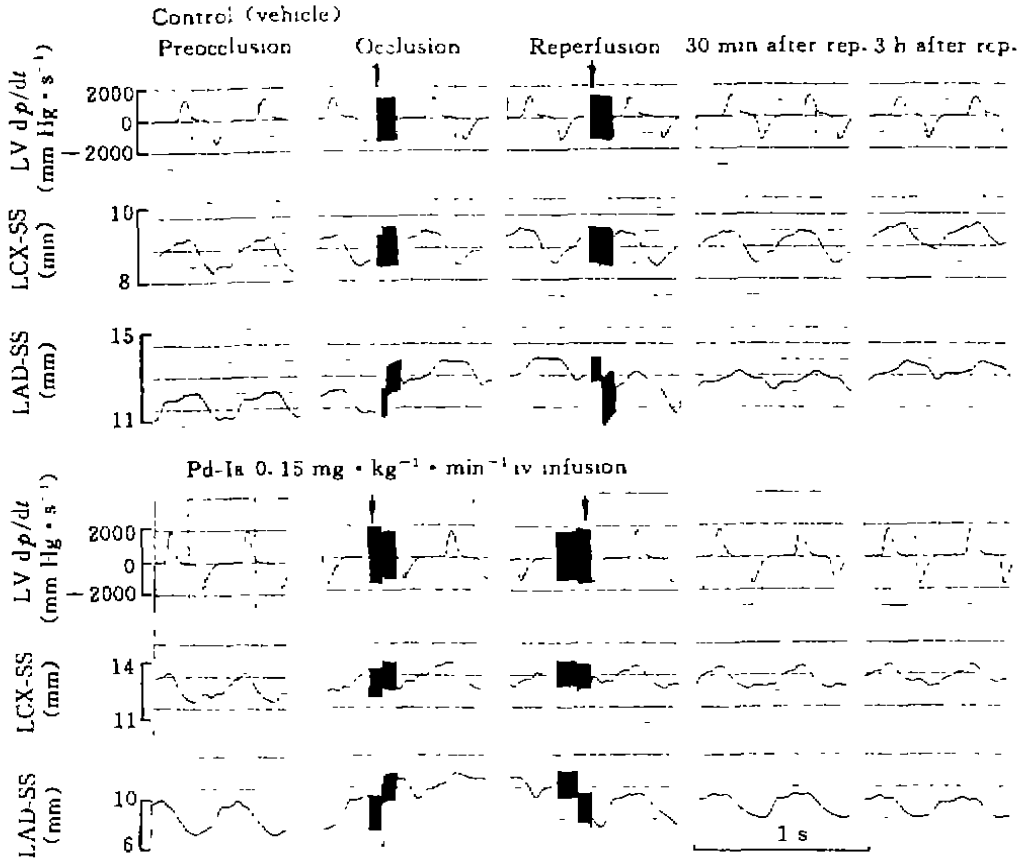


Fig 1. Cardiohemodynamic tracings before and during a 15-min occlusion of left anterior descending coronary artery (LAD) followed by a 3-h reperfusion in a vehicle treated dog and a Pd-Ia treated dog. LCX-SS: segment shortening in the region perfused by the left circumflex coronary artery; LAD-SS: SS in the region by LAD.

group, contractile dysfunction in ischemic region persisted throughout the remainder of the reperfusion and the SS % remained depressed at -26 ± 18 % of the baseline value 3 h after reperfusion. In contrast, Pd-Ia ameliorated the segment function immediately after reperfusion, and restored the SS % to 41 ± 51 % of the baseline value ($P<0.05$ *vs* control) 5 min after reperfusion. The improvement of myocardial function induced by Pd-Ia was maintained at least 3 h after reperfusion (Fig 2).

DISCUSSION

The major findings of the present study were that Pd-Ia significantly ameliorated the regional contractile dysfunction in SM at the dose which did not affect the cardiohemodynamics.

The cardioprotective mechanisms of Pd-Ia in SM may be related to an improvement of the distribution of myocardial blood flow between the ischemic and nonischemic regions, a decrease in MOC, and an inhibition of Ca^{2+} influx into ischemic myocardial cells. In this study, Pd-Ia did not reduce afterload indicated by MAP, preload by LVEDP and MOC by RPP during the experiments. Accordingly, we can not explain the beneficial effects of it due to cardiohemodynamic modifications. It is well known that cytosolic Ca^{2+} overload was

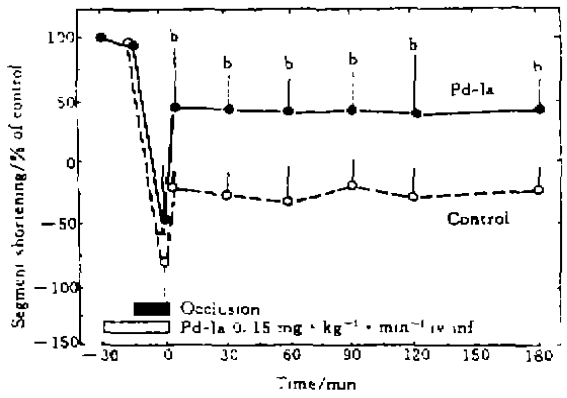


Fig 2. Effects of Pd-Ia on % of segment shortening of ischemic myocardial region. A 30-min infusion of Pd-Ia was started 15 min before a 15-min occlusion of coronary artery followed by a 3-h reperfusion. $n=8$. $\bar{x}\pm s$. $^aP>0.05$, $^bP<0.05$ *vs* control.

involved in the genesis of myocardial dysfunction after reperfusion[9]. Indeed, a Ca^{2+} antagonist has been shown to improve the recovery of dysfunction of SM in intact animals[10]. Since Pd-Ia possessed a Ca^{2+} channel blocking activity, it would attenuate postischemic myocardial dysfunction, but so far, we have no evidence to confirm them.

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3'-当归酰氧基-4'-乙酰氧基-3',4'-双氢邪蒿内酯对麻醉犬短时缺血后心肌功能不良的影响

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摘要 静脉输入3'-当归酰氧基-4'-乙酰氧基-3',4'-双氢邪蒿内酯(0.15 mg·kg^{-1}·min^{-1}) 30 min 对15 min 闭塞犬左前降枝伴3 h 再灌注后心肌收缩功能的影响被研究. 用超声微测距法测定心肌节段收缩(SS)长度表明：该药迅速改善心肌收缩功能不良，再灌后 5 min 即使SS%恢复到用药前的41±51 % ($P<0.05$, $n=8$)，对血流动力学无明显影响.

关键词 香豆素类；心肌再灌注损伤；血液动力学；超声波描记术