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[二甲氨基]二苯骈碘杂六环枸橼酸盐对大鼠心肌缺血再灌注损伤的保护作用[1]

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Protective effects of 3, 6-dimethamidodibenzopyriodonium citrate on myocardial injury induced by ischemia and reperfusion in rats[1]

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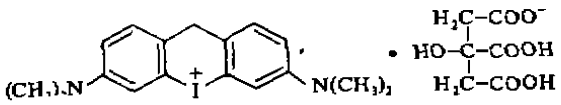
ABSTRACT 3, 6-Dimethamidodibenzopyriodonium citrate (I-65) 0.5 and 1 mg·kg^{-1} pretreatment reduced the size of myocardial infarct after ischemia for 40 min and reperfusion for 120 min. I-65 0.5 mg·kg^{-1} decreased myocardial creatine kinase, lactate dehydrogenase release, and Ca^{2+} accumulation after ischemia for 40 min and reperfusion for 120 min. The results show that I-65 prevents cardiac ischemia and reperfusion injury and the effect is considered to be related to inhibition of myocardial Ca^{2+} accumulation.

KEY WORDS iodonium compounds; myocardial infarction; myocardial reperfusion injury; creatine kinase; lactate dehydrogenase; calcium

摘要 3,6-[二甲氨基]-二苯骈碘杂六环枸橼酸盐(I-65) 0.25—1.0 mg·kg^{-1}呈剂量依赖性地缩小在体大鼠缺血再灌注心肌梗死范围，0.5 mg·kg^{-1}显著降低缺血再灌注大鼠心肌CK和LDH的释放，减少Ca^{2+}在心肌组织内聚积。说明I-65对大鼠心肌缺血再灌注损伤有保护作用。

关键词 碘鎓化合物；心肌梗死；心肌再灌注损伤；肌酸激酶；乳酸脱氢酶；钙

3,6-[二甲氨基]-二苯骈碘杂六环枸橼酸盐（3, 6-dimethamidodibenzopyriodonium citrate 0.5）是兰州大学化学系合成的化合物，编号为碘杂环-65（Iodium-heterocycle-65，I-65），具有降低血压，抑制心肌收缩力、抑制血小板聚集等作用[1,2]。未见文献报道关于该药对心肌缺血再灌注损伤的影响。本文用在体大鼠心肌缺血再灌注损伤模型，观察I-65的保护作用。



3,6-Dimethamidodibenzopyriodonium citrate (Iodonium-heterocycle-65, I-65)

MATERIALS AND METHODS

Sprague-Dawley大鼠，♂，体重264±*s* 32 g，由本校实验动物中心提供。I-65由兰州大学陈淑英和侯自杰合成馈赠，纯度95%以上，应用时用等渗葡萄糖液配成所需浓度。

SBR-1型二线示波器（汕头超声仪器厂），XDH-3型心电图机（上海医用电子仪器厂），180-80型原子吸收分光光度计（日立）。

大鼠40只，随机分为4组，ip戊巴比妥钠45 mg·kg^{-1}麻醉。进行大鼠左冠状动脉结扎术[3]。结扎40 min，再灌注120 min后，摘取心脏，除去心房，将心室横切成4片，置于pH 7.4的氯化硝基四氮唑蓝(NBT)溶液中，于37℃染色10 min。分离梗死与正常心肌，分别称重，计算梗死心肌占全心室肌湿重%[4]。

另30只大鼠，随机分为3组，结扎左冠状动脉40 min，再灌注20 min，取左心室前壁左半部分，精确称重后，制备成2.5%的匀浆。用肌酸显色法测定心肌肌酸激酶(creatine kinase，CK)活性[5]。用比色法测定心肌乳酸脱氢酶(lactate dehydrogenase，LDH)活性[5]。取左心室前壁右半部分，精确称重后，经硝酸、高氯酸等预处理，用原子吸收分光光度计测定心肌内

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钙含量.

整个实验过程中，连续监测标准 II 导联心电图. 结扎和再灌注前1 min，各 iv I-65一次，再灌组给等量等渗葡萄糖液.

所有结果均以 $\bar{x}\pm s$ 表示，用 t 检验测定组间差异的显著性.

RESULTS

I-65对大鼠缺血再灌注心肌梗死范围的影响 对照组大鼠心肌梗死范围占全心室肌湿重的37.0±5.2%，给予不同剂量的 I-65，大鼠缺血再灌注心肌梗死范围呈不同程度的缩小，并有剂量依赖关系. 说明 I-65能够缩小缺血再灌注心肌梗死范围(Tab 1).

Tab 1. Effects of I-65 on infarct size in rat hearts after ischemia for 40 min and reperfusion for 120 min. $n=10$, $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **reperfusion.**

I-65 mg·kg^{-1}	Weight of infarct myocardium/mg	Weight of ventricle/mg	Infarct size %
0	265±38	718±57	37.0±5.2
0.25	246±20*	683±64*	36.2±2.2*
0.5	185±32***	687±84*	26.8±3.2***
1.0	156±34***	730±84*	21.5±4.3***

I-65对缺血再灌注大鼠心肌 CK、LDH 活性及钙含量的影响 假手术组大鼠心肌 CK、LDH 活性分别为6.5±0.6及17.6±1.0 IU·g^{-1}，钙含量为24.7±3.1 μg·g^{-1}. 缺血再灌注后，心肌 CK、LDH 活性分别降低到5.9±0.6及15.7±1.6 IU·g^{-1}，而钙含量升高到27.4±2.3 μg·g^{-1}. 预先给予 I-65 0.5 mg·kg^{-1}，能使缺血再灌注心肌内 CK 和 LDH 活性回升，分别为6.5±0.5及17.7±1.2 IU·g^{-1}，并降低心肌内的钙含量(25.2±1.8 μg·g^{-1}). 表明该药能减轻心肌缺血再灌注损伤(Tab 2).

Tab 2. Effects of I-65 on creatine kinase (CK), lactate dehydrogenase (LDH) activity and Ca^{2+} content of myocardium in rat hearts after ischemia for 40 min and reperfusion for 20 min. $n=10$, $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **reperfusion;** $^{\dagger}P>0.05$, $^{\dagger\dagger}P<0.05$, $^{\dagger\dagger\dagger}P<0.01$ *vs* **sham operation.**

Group	CK/IU·g^{-1}	LDH/IU·g^{-1}	Ca^{2+}/μg·g^{-1}
Sham operation	6.5±0.6	17.6±1.0	24.7±3.1
Reperfusion	5.9±0.6††	15.7±1.6†††	27.4±2.3††
I-65 0.5 mg·kg^{-1}	6.5±0.5**†	17.7±1.2***†	25.2±1.8**†

DISCUSSION

本文结果表明，再灌注时心肌组织内 CK 和 LDH 活性明显降低，提示缺血再灌注能引起心肌细胞膜损伤，使细胞内 CK 和 LDH 大量释放，故损伤灶局部酶活性下降. I-65能明显减少心肌细胞内酶的释放，并呈剂量依赖性缩小大鼠缺血再灌注心肌梗死范围，说明 I-65对大鼠心肌缺血再灌注损伤有保护作用.

大量实验证明[1-8]，I-65为一新型钙通道阻滞剂，不仅阻滞钙内流，而且抑制肌浆网的钙转运. 本实验发现，再灌注时心肌组织内的钙含量明显增高，可能是缺血后再灌注导致细胞膜损伤，从而促使钙离子内流增加，致钙在心肌内聚积. I-65能抑制钙在心肌细胞内聚积，减轻缺血再灌注引起的心肌损伤，这与文献报道钙通道阻滞剂能抑制钙在心肌内聚积，减轻缺血再灌注对心肌的损伤相符[9]. 故认为 I-65的钙拮抗作用可能是其抗心肌缺血再灌注损伤的机制所在.

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369-372 (24)

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大鼠在胚泡着床前应用阿司匹林与醋氨酚对胚泡及胎仔发育的影响[1]

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Effects of preimplantation treatment with aspirin and acetaminophen on blastocyst and fetus in rats

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ABSTRACT Pregnant rats were treated with ig aspirin (Asp) and acetaminophen (Ace) on d 3 of pregnancy (positive vaginal smear = d 0). Blastocysts were collected on d 4 and evaluated for gross morphology, cell number, micronucleus, and mitotic index. Some rats were killed on d 20 and fetuses were examined for teratogenic effects. On d 4 a reduction of cell number per blastocyst was found in the rats treated with Asp 0.5, 1 $g \cdot kg^{-1}$, and Ace 1 $g \cdot kg^{-1}$, while the mitotic index, frequency of micronuclei, and frequency of blastocysts with morphological alterations were increased. The frequency of micronuclei was increased in rats exposed to Ace 0.25 and 0.5 $g \cdot kg^{-1}$. On d 20 major malformation and embryotoxicity were seen in Asp 0.5, 1, and Ace 1 $g \cdot kg^{-1}$ groups.

KEY WORDS aspirin; acetaminophen; blastocyst; micronucleus tests; teratogens; fetus

摘要 大鼠受孕 d 3时 ig 阿司匹林(Asp)或醋氨酚(Ace), d 4收集胚泡, 观察其形态, 细胞数, 微核及分裂相细胞. 结果Asp 0.5, 1 $g \cdot kg^{-1}$及Ace 1 $g \cdot kg^{-1}$使胚泡细胞数减少, 形态异常率, 微核率及分裂指数增高. Ace 0.25与0.5 $g \cdot kg^{-1}$呈胚泡微核诱导作用. 两药对着床后胚胎有胚胎毒与致畸作用.

关键词 阿司匹林; 醋氨酚; 胚泡; 微核试验; 致畸胎物; 胎儿

药物对着床前胚胎作用一般呈"全或无"模式[1], 但并不全然[2-4]. 阿司匹林(aspirin, Asp)在啮齿类动物器官形成期给药具致畸作

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