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间尼索地平对麻醉大鼠动脉压力感受性反射敏感性的影响

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Effects of *m*-nisoldipine on arterial baroreflex sensitivity in anesthetized rats

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ABSTRACT Baroreflex sensitivity (BRS) in anesthetized rats was measured as the slope of the regression line of the concomitant maximal change in heart rate (ΔR-R) and blood pressure (ΔBP) induced by bolus iv phenylephrine or sodium nitroprusside. *m*-nisoldipine (*m*-Nis) iv 5, 10, 20 $\mu g \cdot kg^{-1}$ depressed the BRS (2.6±0.2, 2.4±0.3, 1.6±0.2, or 1.7±0.1, 1.6±0.2, and 1.4±0.2 $ms \cdot kPa^{-1}$, respectively) compared with before medication ($P < 0.01$). *m*-Nis may act directly on carotid sinus to depress the BRS, but not through cardiac β or M receptor nor through central nervous system.

KEY WORDS *m*-nisoldipine; heart rate; blood pressure; nitroprusside; phenylephrine; pressoreceptors

摘要 本文用苯福林或硝普钠 iv 于麻醉大鼠，引起 BP 最大变化(ΔBP)所致反射性 HR 最大变化(ΔR-R)的回归直线斜率为动脉压力感受性反射敏感性(BRS)的指标，测得 iv *m*-Nis 5，10，20 $\mu g \cdot kg^{-1}$均明显降低 BRS ($P<0.01$)，*m*-Nis 抑制 BRS 可能是直接作用于颈动脉窦压力感受器.

关键词 间-尼索地平；血压；心率；硝普盐；苯福林；压力感受器

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多种钙拮抗剂可增敏或抑制压力感受性反射的敏感性(BRS)[1-5]、新二氢吡啶类钙拮抗剂尼索地平(nisoldipine，Nis)可降低 BRS[6]，间尼索地平(*m*-nisoldipine，*m*-Nis)药理作用与 Nis 相似[7-9]，它对 BRS 的影响尚待研究. 本文研究目的为：(1) 观察有效降压剂量的 *m*-Nis 对 BRS 的影响，并与 Nis 比较，(2) 分析 *m*-Nis 影响 BRS 的可能部位.

MATERIALS

m-Nis 及 Nis：由我院药学系有机化学教研室合成并提供，按文献[7]配制其溶剂；苯福林注射液为上海天丰药厂产品；硝普钠为武汉第二制药厂生产；戊巴比妥钠为上海化学试剂厂产品. Sprague-Dawley 大鼠由河北省实验动物中心提供.

METHODS AND RESULTS

动脉 BRS 测定 大鼠 10 只、♂，体重 288±*s* 16 g. 戊巴比妥钠 45 $mg \cdot kg^{-1}$ ip 麻醉、股动脉插管，接压力换能器记录 BP 于 LMS-2A 型二道生理记录仪(成都仪器厂)、同时记录 II 导心电图. 股静脉插管以备给药. 待 BP 和 HR 稳定后，交替 iv 苯福林(0.5，1，2 $\mu g \cdot kg^{-1}$)及硝普钠(1，2，4 $\mu g \cdot kg^{-1}$)(避光条件下)，每次注射后以 0.2 ml 生理盐水冲洗，每两次注射间隔 5 min. 结果表明，iv 苯福林不同剂量后，BP 分别上升 2.1±0.7，2.9±1.1，4.0±1.1 kPa ($n=10$)；HR 相应减慢 24±8，30±11，41±13 bpm；iv 硝普钠不同剂量后，BP 分别下降 4.0±1.3，5.3±1.9，6.0±2.3 kPa ($n=10$)；HR 相应加快 32±7，49

±12，51±8 bpm. iv 两药后引起的心电图 R-R 间期最大变化值(△R-R)和 BP 最大变化值(△BP)均显著相关($\hat{Y}=0.88+4.1X$，$r=0.87$；$\hat{Y}=0.78+2.4X$，$r=0.91$，P 均 <0.01)，以二者直线回归斜率(△R-R·△ BP^{-1})代表 BRS. iv 苯福林升压后 BRS = 4.1 ms·kPa^{-1}，iv 硝普钠降压后 BRS = 2.4 ms·kPa^{-1}，2 h 内反复测定 BRS 均较稳定.

***m*-Nis 或 Nis 对动脉 BRS 的影响** 大鼠 50 只，♂，体重 268±15 g，随机分为 5 组，每组 10 只. 分别于 iv 溶剂、*m*-Nis 及 Nis (均避光)前后 iv 苯福林和硝普钠以测定动脉 BRS，结果表明，iv 等容量(1 ml·kg^{-1})溶剂前后 BP、HR 和动脉 BRS 无明显差别(配对 t 检验，$P>0.05$). iv *m*-Nis 5，10，20 μg·kg^{-1} 和 Nis 10 μg·kg^{-1}组 BP 分别下降 2.9±0.4，4.5±0.5，5.3±0.3 和 4.4±0.3 kPa，HR 相应加快 12±2，17±5，24±3 和 17±1 bpm. 在 BP、HR 恢复至原水平后(30 min 左右)，测得给药后动脉 BRS 均较给药前明显降低($P<0.01$，Tab 1).

延髓池内注射 *m*-Nis 对动脉 BRS 的影响 大鼠 20 只，♂，体重 288±9 g，随机分为 2 组，每组 10 只，戊巴比妥钠 45 mg·kg^{-1} ip 麻醉，给 *m*-Nis 组大鼠延髓池内缓慢(15 s)注入 *m*-Nis 5 μg·kg^{-1}(容量为 1.5 μl)，测得给药前后 BP、HR 和 iv 苯福林后动脉 BRS 均无明显差别(配对 t 检验，$P>0.05$). 以等量 *m*-Nis iv，BP 下降 3.3±0.3 kPa，HR 增加 12±3 bpm，待 BP、HR 恢复后测得动脉 BRS 较给药前明显降低($P<0.01$)；给对照组大鼠延髓池内注入溶剂 1.5 μl 未引起 BP、HR 及动脉 BRS 的变化(Tab 2).

Tab 2. Effect of intracisternal injection (ic) or iv *m*-Nis 5 μg·kg^{-1} on arterial baroreceptor reflex sensitivity (BRS) induced by iv phenylephrine (0.5, 1, 2 μg·kg^{-1}) in anesthetized rats. $n=10$, $\bar{x}\pm s$. $^aP>0.05$, $^cP<0.01$ *vs* before drug.

Drugs	BRS (ms·kPa^{-1}) to iv phenylephrine	
	Before	After
ic solvent	3.8±0.5	3.7±0.4
ic *m*-Nis	3.9±0.3	4.1±0.4[a]
iv *m*-Nis	3.9±0.3	2.6±0.3[c]

***m*-Nis 对心脏 β 或 M 受体的影响** 大鼠 20只，♂，体重277±12 g，随机分为2组. 每组10只，麻醉方法同上，第1组在1次 iv *m*-Nis 10 μg·kg^{-1}前后各 3 次 iv 异丙肾上腺素 0.2 μg·kg^{-1}致 BP 下降(4.0±0.7和3.7±0.5 kPa)和 HR 加快(16±2和15±1 bpm)，给药前后分别相比，均无明显差别($P>0.05$)；第2组1次 iv *m*-Nis 10 μg·kg^{-1}前后各3次电刺激(2 HZ，4 V，1 ms，持续5 s)右侧迷走神经外周端(手术切断右侧迷走神经)所致 HR 减慢(25±2和

Tab 1. Effect of iv *m*-Nis and Nis on arterial RBS response induced by iv phenylephrine (0.5, 1, 2 μg·kg^{-1}) and sodium nitroprusside (1, 2, 4 μg·kg^{-1}) in anesthetized rats. ($n=10$), $\bar{x}\pm s$. $^cP<0.01$ *vs* before drug.

Drugs	Dosage	Baroreceptor reflex sensitivity/ms·kPa			
		iv phenylephrine		iv sodium nitroprusside	
		Before	After	Before	After
Intravenous bolus					
Solvent	1 ml·kg^{-1}	4.0±0.5	4.1±0.4	2.4±0.2	2.3±0.2
m-Nis	5 μg·kg^{-1}	4.3±0.4	2.6±0.2[c]	2.2±0.3	1.7±0.1[c]
	10 μg·kg^{-1}	4.0±0.3	2.4±0.3[c]	2.3±0.1	1.6±0.2[c]
	20 μg·kg^{-1}	4.0±0.3	1.6±0.2[c]	2.4±0.2	1.4±0.2[c]
Nis	10 μg·kg^{-1}	3.6±0.3	2.6±0.4[c]	2.6±0.3	1.6±0.1[c]

24±4 bpm)无明显差别($P>0.05$).

***m*-Nis 对大鼠单侧颈动脉窦区隔离灌流的影响** 大鼠24只，♂，体重278±17 g，随机分为3组，每组 8只，第1组为 Krebs-Henseleit (K-H)液对照组，第2组为溶剂对照组，第3组为 *m*-Nis 组. 麻醉方法同上. 按文献[11]方法制成大鼠左侧颈动脉窦区隔离灌流模型. 手术操作完毕后，用37 ℃ O_2饱和的 K-H 液，蠕动泵隔离灌流左侧颈动脉窦区. 每隔10 min 改变蠕动泵转速以提高窦内压1次(每次持续20 s)，引起相应的 BP 下降. 同步记录窦内压(ISP)和 BP 于二道生理仪，以窦内压变化值(△ISP)和 BP 变化值(△BP)的回归直线斜率 BRS 表示压力感受器敏感性(kPa/kPa). 结果表明，当窦内压依次上升3.3，4.7和6.6 kPa 时，BP 相应下降4.7±0.5，6.0±0.9和8.6±0.7 kPa，窦内压在8.0－16.0 kPa 之间. 测得压力感受器敏感性 BRS＝1.2±0.1 (kPa/kPa)，2 h 内 BRS 无明显变化. 用溶剂(0.1 ml 加入 K-H 液中)灌流后，测得压力感受器的敏感性 BRS＝1.1±0.04 kPa/kPa，与 K-H 液相比无明显差别(两组 t 检验，$P>0.05$)；用 *m*-Nis (以等量溶剂溶解，加入 K-H 液中，终浓度为1 μmol·L^{-1})灌流后，测得压力感受器敏感性 BRS＝0.6±0.04 (kPa/kPa)，与溶剂隔离灌流时压力感受器敏感性 BRS＝1.1±0.04 kPa/kPa 相比，明显降低 ($P<0.01$) (Fig 1).

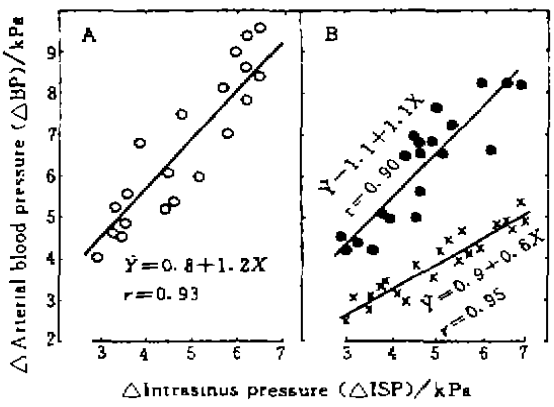

Fig 1. Arterial baroreflex sensitivities (kPa/kPa) of isolated carotid sinus in anesthetized rats perfused with (A) K-H solution, ○, (B) solvent ●, and *m*-Nis 1 μmol·L^{-1} ×. $n=8$, $\bar{x}\pm s$. $P<0.01$ *vs* solvent.

DISCUSSION

二氢吡啶类钙拮抗剂治疗高血压早期的主要不良反应为降压所致 HR 加快[12]，以致少数患者不能耐受. 本文结果证明，iv *m*-Nis 后麻醉大鼠 BRS 显著降低. 因此，有可能使该药在临床用于治疗高血压时，因降压所致 HR 加速的不良反应减弱. 故临床应用 *m*-Nis 治疗高血压时，可不合用或仅在用药早期合用β受体阻断药以克服 HR 加快的不良反应. 本文结果表明，*m*-Nis 不是通过心脏β或 M 受体而抑制动脉 BRS，延髓池内给予 *m*-Nis 不影响动脉 BRS，而静注等量 *m*-Nis 则使动脉 BRS 明显降低. 表明 *m*-Nis 的作用部位似在外周；大鼠单侧颈动脉窦区灌流实验表明，治疗浓度(1 μmol·L^{-1}) *m*-Nis 对动脉 BRS 有直接抑制作用.

REFERENCES

1 Mcleay RAB, Stallard TJ, Watson, RDS, Littler W A. The effect of nifedipine on arterial pressure and reflex cardiac control.
Circulation 1983; **67**: 1084－90.

2 Warltier DC, Zyvoloski MG, Gross GJ, Brooks HL. Comparative actions of dihydropyridine slow channel calcium blocking agents in conscious dogs: Alterations in baroreflex sensitivity.
J Pharmacol Exp Ther 1984; **230**: 376－82.

3 Zsotér TT, Nebitko RL, Chow R. The effect of verapamil, diltiazem and nifedipine on baroreceptor reflexes. Clin Invest Med 1988; **11**: 430－4.

4 Taylor DG, Kowalski TE. Comparison of calcium channel inhibitors on vagal heart rate response elicited by arterial baroreceptor reflexes in anesthetized dogs.
J Pharmacol Exp Ther 1984; **228**: 491－9.

5 Abdel-Rahman ARA, Ingenito AJ. Similarities and dif-

ferences in the effects of verapamil, diltiazem and nifedipine on arterial baroreflexes of anesthetized cats. Arch Int Pharmacodyn Ther 1985; 275: 33—46.

6 Nayler WG. Calcium antagonist. London, Academic Press, 1988; 227.

7 Fu SX, Li YS, Jin CJ, Ren LM. Effects of *m*-nisoldipine and nisoldipine on hemodynamics in anesthetized dogs. Acta Pharmacol Sin 1988; 9: 43—8.

8 Ren LM, Li YS, Fu SX, Jin CJ. Cardiovascular action of *m*-nisoldipine in anaesthetized rabbits and guinea pigs. Acta Pharmacol Sin 1988; 9: 426—30.

9 Li YL, Fu SX, Li YS. Prophylactic effects of *m*-nisoldipine and nisoldipine on reperfusion arrhythmia in hearts of rats. Acta Pharmacol Sin 1988; 9: 542—7.

10 Smyth HS, Sleight P, Pickering GW. Reflex regulation of arterial pressure during sleep in man. A quantitative method of assessing baroreflex sensitivity. Circ Res 1969; 24: 109—21.

11 Zhao G, He SY. The facilitating effect of atrial natriuretic factor on the carotid sinus baroreflex function. Acta Physiol Sin 1991; 43: 360—7.

12 Kageyama M, Nishimura K, Takada T, Miyawaki N, Yamauchi H. SD 3211, a novel benzothiazine calcium antagonist, alone and in combination with a beta-adrenoceptor antagonist, produces antihypertensive effects without affecting heart rate and atrioventricular conduction in conscious renal hypertensive dogs. J Cardiovasc Pharmacol 1991; 17: 102—7.

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二乙基二硫代氨基甲酸钠对沙土鼠脑缺血再灌注损伤的影响

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Effects of sodium diethyldithiocarbamate on ischemia-reperfusion-induced brain injury in Mongolian gerbil

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ABSTRACT Brain injury in Mongolian gerbil (*Merisones unguiculatus*) was induced by occluding bilateral common carotid arteries for 60 min followed by reperfusion for 5 or 30 min. Oxygen free radicals in brain tissue were measured by electron spin resonance (ESR) technique, malondialdehyde (MDA) was measured by fluorescence spectrometry, and superoxide dismutase (SOD) was measured by nitrite kit. Oxygen free radicals and MDA were not significantly increased, but activities of T-SOD and Mn-SOD were decreased after 60 min of cerebral ischemia. The free radicals were increased at 5-min reperfusion, and then reduced to the level of ischemia group after 30-min reperfusion. MDA was increased remarkably after reperfusion of 30 min, whereas the activity of SOD continued to decrease. Sodium diethyldithiocarbamate (DTC), iv 5—100 mg·kg^{-1} 15 min before occlusion, decreased the production of MDA and increased the activities of T-SOD and Mn-SOD. The formation of oxygen free radicals was depressed by iv DTC 50 mg·kg^{-1}. The result suggested that the protective effects of DTC on ischemia-reperfusion-induced brain injury might be induced by scavenging the oxygen free radicals, increasing the Mn-SOD activity and decreasing the production of MDA.

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