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# 酮舍林对清醒高血压大鼠动脉压力感受性反射血压控制的影响[1]

孔宪波、程 勇、苏定冯[2] (第二军医大学药理教研室，上海 200433，中国)

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**Effect of ketanserin on arterial baroreflex-blood pressure control in conscious hypertensive rats**

KONG Xian-Bo, CHENG Yong, SU Ding-Feng
(*Department of pharmacology, Second Military Medical University, Shanghai 200433, China*)

**ABSTRACT** The effect of ketanserin on arterial baroreflex-blood pressure control (ABR-BP) were studied in conscious freely-moving spontaneously hypertensive rats (SHR) and renovascular hypertensive rats (RVHR). The ABR-BP was measured by using a new method comparing with the pressor responses (in area) to angiotensin II before and after blocking the baroreflex efferent pathway by guanethidine and methyl atropine. It was found that ketanserin enhanced markedly the ABR-BP in both groups of hypertensive rats (SHR: 51% to 74%; RVHR: 59% to 77%). This suggests that the enhancement of ABR-BP may be involved in the anti-hypertensive effects of ketanserin.

**KEY WORDS** ketanserin; pressoreceptors; blood pressure; hypertension; inbred SHR rats; renovascular hypertension

**提要** 在清醒自由活动的自发性高血压大鼠和肾血管性高血压大鼠研究了 Ket 对动脉压力感受性反射血压控制成分(ABR-BP)的影响. ABR-BP 的测定采用比较化学阻断反射弧的传出通路前、后血管紧张素 II 升压面积的方法. 结果表明 Ket 能非常显著地增强 2 种高血压大鼠的 ABR-BP (SHR 由 51%到 74%, RVHR 59%到 77%). Ket 的降压作用可能与其升高 ABR-BP 有关.

**关键词** 酮舍林; 压力感受器; 血压; 高血压; 近交 SHR 大鼠; 肾血管高血压 肾性高血压

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[2] To whom correspondence should be addressed.

酮舍林(ketanserin, Ket)是一种新型抗高血压药，可选择性地阻断 5-羟色胺 2 型($S_2$)受体、高浓度时尚有 $\alpha_1$-肾上腺素能受体阻断作用[1]. Ket 在高血压病人及大鼠的降压效果确切，但其作用机制尚不是很明确. Ket 对动脉压力感受性反射(arterial baroreflex, ABR)的影响可能是其抗高血压作用机制之一. Ket 可影响 ABR 的心率控制成分(ABR-heart rate or heart period control, ABR-HP)[2]，但是 Ket 对 ABR 的血压控制成分(ABR-blood pressure control, ABR-BP)的影响尚未见报告. 本文研究 Ket 对自发性高血压大鼠(SHR)和肾血管性高血压大鼠(RVHR)的 ABR-BP 的影响.

## MATERIALS AND METHODS

**药品** Ket 由比利时 Janssen 公司赠送. 血管紧张素 II (angiotensin II, Ang II)、胍乙啶和甲基阿托品皆系 Sigma 公司产品.

**高血压动物模型** SHR 由上海市高血压研究所提供, ♂, 4 月龄, 体重 257 ± *s* 30 g. RVHR 的制备系采用 Sprague-Dawley 大鼠, ♀, 3 月龄. 麻醉下开腹, 分离左肾动脉, 放置内径 0.2 mm 的银夹子, 制成两肾一夹(2K1C)型 RVHR. 术后 4 wk, 收缩压超过 19.95 kPa (150 mm Hg)的大鼠被选入本实验.

**清醒自由活动大鼠血压监测方法** 大鼠用安定和氯胺酮麻醉, 先经左侧股动脉将 $PE_{10}$ 导管插入腹主动脉, 用于血压监测. 后行一侧颈外静脉插 $PE_{50}$ 导管用于 iv. 术后 2 d 将大鼠置于实验装置内. 动脉导管经一转动装置连接压力换能器, 转动装置保证大鼠在笼内自由活动而不影响血压监测. 压力信号转换成电信号后, 经放大器和 A/D 信号采集板, 由微型计算机(ALR DART)实时计算每次心搏的收缩压、舒张

压和心动周期[3,4].

**ABR-BP 的测量方法** 设想在去除 ABR 前后机体对某一升压药(或降压药)的升(或降)压反应的差别即为 ABR-BP. 本文采用 iv Ang II 25 ng · kg$^{-1}$ 升高血压. 计算血压升高的曲线下面积. 设面积$_1$($A_1$)为 ABR 功能完整时对 Ang II 反应的大小, 面积$_2$($A_2$)为 ABR 去除后对 Ang II 反应的大小, 则

$$ABR\text{-}BP = (A_2 - A_1) / A_2 \times 100\%$$

去除 ABR 采用化学切除自主神经以阻断 ABR 反射弧的传出通路[5]. 具体方法为 iv 胍乙啶 10 mg · kg$^{-1}$ 45 min 后再 iv 5 mg · kg$^{-1}$、20 min 后 iv 甲基阿托品 1 mg · kg$^{-1}$. 为避免误差, 实验由一人操作, 给 Ang II 时给药速度均匀, 并重复 2 次, 取其均值. 面积计算法可重复性好, 在不阻断传出神经而代之以 iv 生理盐水(NS)时, Ang II 升压面积前后误差 <5%. 结果表明: SD 和 WKY 大鼠 ABR-BP 的基础值分别为 75 ± 4% 和 73 ± 10%.

**ABR-BP 的测量方法**[6-8] iv Ang II 25 ng · kg$^{-1}$, 同时记录收缩压和心动周期, 以收缩压和心动周期变化作线性回归分析, 直线的斜率即为 ABR-HP.

**实验设计** 大鼠连上记录系统后适应 20 h, 治疗组大鼠 iv Ket 3 mg · kg$^{-1}$, 对照组 iv 等体积 NS. 用计算机记录给药前后 30 min 收缩压、舒张压和心动周期, 计算 30 min 的均值, 作为基础值和药物的效应. 尔后用上述方法分别测定 ABR-BP 和 ABR-HP. 实验中为保持大鼠体内 Ket 的有效浓度, 根据 Ket 的半衰期, 每隔 1 h 补充 0.6 mg · kg$^{-1}$.

**统计学处理** 结果以 $\bar{x} \pm s$ 表示. Ket 对收缩压、舒张压和心动周期的影响用配对 $t$ 检验. Ket 对 ABR-HP 和 ABR-BP 的效应分别用非配对 $t$ 检验及 Wilcoxon 两样本法检验. 相关性研究采用直线回归法.

## RESULTS

**Ket 对基础血压和心动周期的影响** Ket 能明显地降低 SHR 和 RVHR 的收缩压(SHR 由 27.3 ± 2.5 到 20.5 ± 2.5 kPa, RVHR 由 24.5 ± 3.9 到 20.9 ± 1.9 kPa 和舒张压(SHR 由 22.9 ± 3.1 到 15.8 ± 2.2 kPa, RVHR 由 18.4 ± 3.3 到 14.9 ± 1.4 kPa Ket. 使 SHR 的心动周期延长, 由 156 ± 26 到 176 ± 34 ms, 即心率减慢, 而使 RVHR 的心动周期缩短, 由 150 ± 19 到 127 ± 17 ms, 即心率加快 (Tab 1).

**Ket 对 ABR-BP 和 ABR-HP 的影响** 无论是在 SHR 还是 RVHR. Ket 均能非常显著地 ($P<0.01$)增强 ABR-BP (SHR 由 51 ± 12 到 74 ± 8%, RVHR 由 59 ± 9 到 77 ± 7%)和 ABR-HP (SHR 由 1.8 ± 0.98 到 7 ± 3.8 ms · kPa$^{-1}$; RVHR 由 3.1 ± 1.05 到 8 ± 3.2 ms · kPa$^{-1}$ (Tab 2).

**Tab 1. Effects of ketanserin (ket) on 30-min systolic & diastolic blood pressure (SBP & DBP) and heart period (HP) in conscious unrestrained hypertensive rats. $\bar{x} \pm s$. $^{\triangle}P>0.05$, $^{\triangle\triangle}P<0.05$, $^{\triangle\triangle\triangle}P<0.01$ *vs* before iv ketanserin 3 mg · kg$^{-1}$ or saline 0.5 ml · kg$^{-1}$.**

| | Pre-saline | Post-saline | Pre-Ket | Post-Ket |
|---|---|---|---|---|
| Spontaneously hypertensive rats (SHR) | | | | |
| *n* | 7 | | 12 | |
| SBP / kPa | 26.5 ± 3.5 | 26.9 ± 4.2$^{\triangle}$ | 27.3 ± 2.5 | 20.5 ± 2.5$^{\triangle\triangle\triangle}$ |
| DBP / kPa | 19.7 ± 5.1 | 19.8 ± 5.3$^{\triangle}$ | 22.9 ± 3.1 | 15.8 ± 2.2$^{\triangle\triangle\triangle}$ |
| HP / ms | 163 ± 9 | 161 ± 10$^{\triangle}$ | 152 ± 26 | 176 ± 34$^{\triangle\triangle\triangle}$ |
| Renovascular hypertensive rats (RVHR) | | | | |
| *n* | 8 | | 10 | |
| SBP / kPa | 23.2 ± 3.7 | 23.9 ± 3.5$^{\triangle}$ | 24.5 ± 3.9 | 20.9 ± 1.9$^{\triangle\triangle\triangle}$ |
| DBP / kPa | 17.5 ± 2.5 | 18.2 ± 2.8$^{\triangle}$ | 18.4 ± 3.3 | 14.9 ± 1.4$^{\triangle\triangle\triangle}$ |
| HP / ms | 136 ± 18 | 133 ± 20$^{\triangle}$ | 150 ± 19 | 127 ± 17$^{\triangle\triangle\triangle}$ |

**Tab 2. Effects of ket (iv 3 mg · kg$^{-1}$) on arterial baroreflex-heart period control (ABR-HP) and arterial baroreflex-blood pressure control (ABR-BP) in conscious unrestrained hypertensive rats (SHR, RVHR).** $\bar{x} \pm s$. $^{*}P > 0.05$. $^{**}P < 0.05$, $^{***}P < 0.01$ *vs* saline.

| | Treatment | $n$ | ABR-BP / % | ABR-HP / ms · kPa$^{-1}$ |
|---|---|---|---|---|
| SHR | Saline | 8 | 51 ± 12 | 1.8 ± 1.0 |
| | Ket | 11 | 74 ± 8$^{***}$ | 6.8 ± 3.8$^{***}$ |
| RVHR | Saline | 8 | 59 ± 9 | 3.1 ± 1.1 |
| | Ket | 10 | 77 ± 7$^{***}$ | 7.6 ± 3.2$^{***}$ |

**Ket 对 ABR-BP 与基础血压相关性的影响** 两种高血压大鼠的收缩压与 ABR-BP 呈负性相关，即收缩压越高，大鼠的 ABR-BP 越低(SHR: $r = -0.81$, $P < 0.05$; RVHR: $r = -0.7$, $P < 0.05$)，而用 Ket 处理的大鼠，这种关系不再出现(SHR: $r = -0.17$, $P > 0.05$; RVHR: $r = 0.21$, $P > 0.05$). 此外，在收缩压与 ABR-HP 间则无相关性(Fig 1).

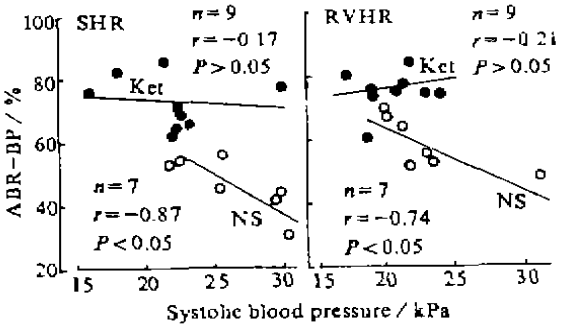


**Fig 1. Relationship between systolic blood pressure and arterial baroreflex-blood pressure control (ABR-BP) in conscious hypertensive rats (spontaneously hypertensive rats, SHR and renovascular hypertensive rats, RVHR) pretreated by ketanserin (iv 3 mg · kg$^{-1}$).**

## DISCUSSION

在抗高血压药物研究中，ABR 的功能或敏感性常被作为一项重要的观察指标. 英国 Sleight 实验室首先提出一种测定人 ABR 敏感性的方法[7]. 此后，有一些类似或改进的方法，可适用于鼠类小动物的测量，如 Struyker-Boudier 等[8]和我们的工作[3,6]. 但这些方法均有一明显的缺陷，即只能观察 ABR-HP，而不能观察 ABR-BP. 本文介绍的方法正是为弥补这一缺陷而设计. 它可用于测定 ABR-BP. 该方法的缺点是用其作药理研究时，由于胍乙啶作用时间长，很难作自身对照，即不能比较给某一降压药前后 ABR-BP，而只能作组间比较，如本文所作.

本文发现 Ket 能显著增强两种高血压大鼠的 ABR-BP. 同时发现，在基础血压和 ABR-BP 之间存在明显的负性相关，但这种负性相关在用 Ket 后不复存在. Ket 可同时使血压降低和 ABR-BP 升高. 至于血压降低和 ABR-BP 升高之间的关系，以下两种情况可能同时存在：即一是血压降低后使 ABR-BP 恢复正常，二是 ABR-BP 增强参与了 Ket 的降压机制.

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# 三七总皂甙、维拉帕米、去甲肾上腺素对大鼠和兔脑循环的作用比较[1]

伍杰雄、孙家钧 (中山医科大学药理教研室，广州 510089，中国)

R 965.2

**Comparative effects of *Panax notoginseng* saponins, verapamil, and norepinephrine on cerebral circulation in anesthetized rats and rabbits[1]**

WU Jie-Xiong, SUN Jia-Jun
*(Department of Pharmacology, SUN Yat-Sen University of Medical Sciences, Guangzhou 510089, China)*

**ABSTRACT** In urethane-anesthetized New Zealand rabbits, mean blood pressure (MBP) and cerebrovascular resistance (CVR) fell by 27–47% and 11–17% ($P<0.05$), respectively after *Panax notoginseng* saponins (PNS) 20–80 mg · kg$^{-1}$ iv. Verapamil (Ver) 30 μg · kg$^{-1}$ iv showed similar effects, but norepinephrine (NE) 30 μg · kg$^{-1}$ iv showed opposite effects. PNS and Ver reduced the MBP and CVR in sodium pentobarbital-anesthetized Wistar rats. The actions of PNS and Ver on cerebral blood flow (CBF) were related to the animal species, i.e. PNS increased CBF in rats but reduced that in rabbits, Ver increased CBF in rabbits but had no effects on that in rats. In isolated ring segments of New Zealand rabbit basilar arteries, PNS 1 and 3 mg · ml$^{-1}$ non-competitively inhibited the contractions induced by KCl with the $pD_2'$ value 2.69 ± 0.20 (−lg g · ml$^{-1}$). The results indicate that PNS and Ver are vasodilators of brain blood vessel, which would be beneficial to cerebral circulation, while NE is a vasoconstrictor of brain blood vessel.

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**KEY WORDS** ginseng; saponins; verapamil; norepinephrine; potassium chloride; basilar artery; vascular resistance

**提要** 三七总皂甙(PNS) 20–80 mg · kg$^{-1}$ iv 使麻醉兔 MBP 和 CVR 下降 27–47%和 11–17%. Ver 表现出类似效应，NE 则相反. PNS 和 Ver 也使麻醉大鼠的 MBP 和 CVR 明显下降. 对 CBF，PNS 和 Ver 的作用呈明显动物种属差异性. 对 KCl 诱发的兔基底动脉环收缩反应，PNS 1, 3 mg · ml$^{-1}$ 表现出非竞争性抑制作用，其 $pD_2'$为 2.69 ± 0.20 (−lg g · ml$^{-1}$). 表明 PNS、Ver 为脑血管扩张药，而 NE 为脑血管收缩药.

**关键词** 人参；皂甙类；维拉帕米；去甲肾上腺素；氯化钾类；基底动脉；血管阻力

三七总皂甙(*Panax notoginseng* saponins, PNS)对脑血栓性疾病有较好疗效[1]，对实验性家兔和沙土鼠急性脑缺血具保护作用[2,3]，是否与 PNS 对脑循环的影响有关？为此，本文用大鼠和家兔进行脑血流动力学测定，研究 PNS 对不同动物脑循环的影响. 同时，与维拉帕米(verapamil, Ver)，去甲肾上腺素(norepinephrine, NE)进行比较. 并在离体兔基底动脉环上，研究 PNS 对氯化钾(KCl)诱发的血管平滑肌收缩反应的影响. PNS 对脑循环的作用研究，迄今，仅见一篇文献报道[4]. 而且，该文用未结扎二侧椎动脉的狗的颈内动