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Effects of ketanserin on blood pressure variability in conscious spontaneously hypertensive rats[1]

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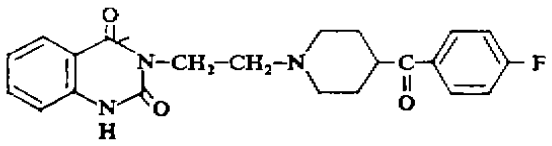
ABSTRACT Computerized analysis of blood pressure (BP) was used to study for the effects of ketanserin (Ket) on BP and blood pressure variability (BPV). Rats were instrumented chronically and BP was sampled every 4 ms by a computer from 2 · 00 to 14 : 00. Then a single dose of Ket (3 mg kg $^{-1}$) was given iv. BP and heart period (HP) were recorded for the next 30 min. The results showed that Ket lowered systolic BP (26.7 kPa to 21.1 kPa), diastolic BP (20.5 kPa to 15.8 kPa), and systolic BPV (1.3 kPa to 0.94 kPa). Otherwise, a positive relationship was found between antihypertensive effects of Ket and BPV. These findings may be of importance in antihypertensive treatment.

KEY WORDS blood pressure; ketanserin; inbred SHR rats

Blood pressure variability (BPV) is a new concept arising from the development of techniques designed for continuous blood pressure (BP) monitoring in the past decade. BPV, now considered as a new parameter of cardiovascular activity, is related to the incidence and severity of target-organ damages in hypertensive patients[1]. Ketanserin (Ket), as a new anti-hypertensive drug, can selectively block the S2 serotonistic receptor, and partially lower BP by an α_1-antagonistic action[2] Many studies were performed on its antihypertensive effects, but there was no informations available about its effects on BPV in spontaneously hypertensive rats (SHR). In the present study, we used computer analysis of BP in conscious unrestrained SHR to study the effects of Ket on BP and BPV. The relationship between BPV level and the antihypertensive effects of Ket was also investigated.



Ketanserin

MATERIALS AND METHODS

Rat and drug Male 18~ 22 wk-old SHR (296 ± *s* 22 g) from the animal house of our Department, were used. They were housed in controlled conditions and fed a standard rat chow and water *ad Lib*. Ket was provided by Janssen Company (Belgium).

BP recording The rats were anesthetized ip with a combination of ketamine (40 mg · kg^{-1}) and diazepam (6 mg · kg^{-1}). A floating polyethylene catheter (PE_{10}, 0.21 mm ID) was inserted into the distal abdominal arota from the femoral artery for BP measuring, and another catheter (PE_{50}, 0.58 mm ID) was inserted into jugular vein for iv injections. The catheters were exteriorized and fixed on the nucha. For the recording sessions, the rats were placed in cylindrical cages with controlled temperature (21 ± 1℃) and lighting (8 : 00~20 : 00) and dark (20 : 00 ~ 8 : 00) condition. The aortic catheter was connected to a BP transducer by means of a rotating swivel and a three-way stopcock that allowed continuous perfusion of the arterial catheter with heparinized (25 IU · ml^{-1}) isotonic glucose (0.6 ml · h^{-1}). With the

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swivel, rats could freely move about. The BP signals, transmitted to the electric signals by transducer, were digitized and processed by a personal computer (ALR DART). The following parameters were calculated on line: systolic BP, diastolic BP, and heart period (HP). These values were sampled beat to beat and stored on hard disc for off-line graphical treatment and statistical analysis.

Protocol One day after operation, the rats were connected to the system and let to adapt themselves to the circumstances. BP was continuously monitored for 12 h (from 2 : 00 to 14 : 00). Then Ket (3 mg · kg^{-1}) was injected iv. Systolic BP, diastolic BP, and HP were recorded for 30 min (14 : 05~ 14 : 35). In off-line analysis, the means and standard deviations of systolic BP, diastolic BP, and HP were calculated for 3 periods: basal period (2 : 00~ 14 : 00), 30 min pre-Ket (13 : 30~ 14 : 00), and 30 min post-Ket (14 : 05~ 14 : 35). BPV was expressed by standard deviations of BP recorded during these periods.

Statistical analysis The *t* test for paired data was used to compare the values obtained 30 min pre- and post-Ket. The relationship between BPV and antihypertensive effects of Ket was evaluated by means of linear regression analysis.

RESULTS

Basal values of BP and BPV in conscious unrestrained SHR Systolic BP and diastolic BP were 26.8 kPa (201 mm Hg) and 20.4 kPa (153 mm Hg) respectively in SHR. Systolic BPV and diastolic BPV were 1.7 kPa (12.75 mm Hg) and 1.4 kPa (10.5 mm Hg) (Tab 1).

Effects of Ket on BP and BPV After iv Ket, BP decreased significantly (systolic BP from 26.8± 2.7 kPa to 21.1± 2.4 kPa, $P<0.01$). On the other hand, there was no significant difference of HP between pre-Ket and post-Ket ($P>0.05$). But Ket markedly lowered systolic BPV in all rats (pre-Ket 1.3± 0.3 kPa, post-Ket 0.9± 0.2 kPa, $P<0.01$) (Tab 1). Fig 1 shows an example for the effect of Ket on systolic BPV.

Tab 1. Effects of ketanserin on blood pressure, blood pressure variability, and heart period in conscious freely moving spontaneously hypertensive rats. $n=14$, $\bar{x}\pm s$. $^{*}P>0.05$, $^{**}P<0.05$, $^{***}P<0.01$ *vs* **pre-Ket.**

	Basal values (2:00–14:00)	Pre-ketanserin (13:30–14:00)	Post-ketanserin (14:05–14:35)
SBP / kPa	26.8 ± 2.59	26.7 ± 2.67	21.1 ± 2.38***
DBP / kPa	20.4 ± 2.15	20.5 ± 2.25	15.8 ± 2.09***
HP / ms	164 ± 25	165 ± 29	167 ± 34*
SBPV / kPa	1.7 ± 0.46	1.3 ± 0.33	0.94 ± 0.16***
DBPV/kPa	1.4 ± 0.33	0.96 ± 0.16	0.85 ± 0.24*

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HP: Heart period; SBPV: Systolic blood pressure variability; DBPV: Diastolic blood pressure variability.

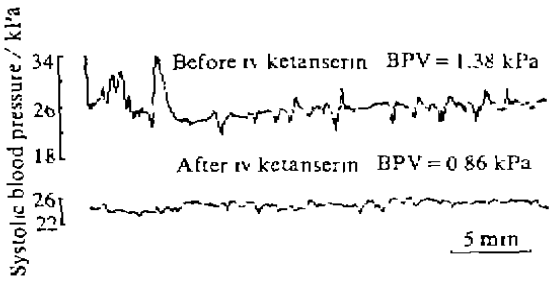

Fig 1. Recording before and after iv ketanserin 3 mg · kg^{-1} in a spontaneously hypertensive rat (SHR).

The relationship between BPV and antihypertensive effects of Ket The basal BPV was positively related to the antihypertensive effects of Ket (Fig 2). The more unstable the BP (greater BPV) was, the greater the antihypertensive effects of Ket would be. This relationship was more significant for systolic BPV than for diastolic BPV.

DISCUSSION

Computerized analysis of BP in conscious

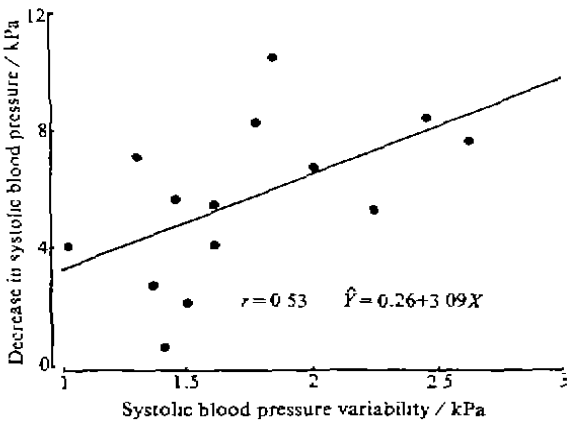

Fig 2. Relationship between basal blood pressure variability and blood pressure effects of ketanserin in SHR. $n=14$, $P<0.05$.

unrestrained rats[3,4], undoubtedly, was the most accurate measurement for BP now available. The technique made it possible to measure each individual beat over 48 h continuously, that was an ideal method for physiologic and pharmacologic studies.

Ket significantly lowered BP in hypertensive patients and in SHR, but only slightly, if any, in normotensive patients[2]. There was no significant concomitant tachycadia in SHR after administration of Ket[5]. Our results, here and previously reported[6], supported them. But the interesting finding in this study was that Ket could significantly lower BPV in SHR, just as same as the effect of Ket on BPV in male Sprague-Dawley rat[6]. As a positive relationship exists between BPV and target-organ damages in hypertension[1], it will be interesting to know if the inhibitory effect of Ket on BPV could play a substantial role in the prevention of hypertensive target-organ damages apart from its antihypertensive effect, that might sometimes be advantageous to hypertensive patients. But its mechanisms remained unknown. The regulation of BPV was in different levels (central and peripheral) and was related to multiple factors (hemodynamic, neural, and humoral mechanisms)[7,8]. In cats, Ket caused a reduction in sympathetic impulses of cardiac nerves which was attributed to central α_1-blockade[9] and an interference with the baroreflex-mediated tachycardia which was compatible to a 5-HT S_2-receptor-mediated vagal stimulation[10]. On the other hand, direct effects of this agent cannot be excluded[11]. From the other results of our laborary Ket could enhanced arterial baroreflex-blood pressure control and baroreflex-heart period control[12]. It is known that there was negative relationship between baroreflex and BPV in rats (unpublished data) and BPV increased after sinoaortice denervation[13]. Thus it is possible that the effect of Ket on baroreflex might contribute to the decrease in BPV. Ket inhibited the central sympathetic action and potentiated the excitatory of effect of noradrenaline on the spontaneous discharge of the solitary tract nucleus neurons in the slice study[14]. Therefore, it suggested that the inhibitory action of Ket on BPV might be mediated by baroreflex at the solitary tract nucleus level.

Another interesting finding was that the antihypertensive effects of Ket were positively associated with basal BPV, ie Ket had greater antihypertensive effects in rats with more marked BPV. This relationship, according to analysis of multiple linear regression, was not related to the level of systolic BP. On the contrary, our previous report indicated that the hypotensive effects of Ket in male Sprague-Dawley rats were negatively related to basal BPV[6]. Ket had no effect or slightly increased BP in those with lower BPV. These findings indicated that the physiological significance of BPV might be different in hypertensive rats and normotensive rats.

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酮舍林对清醒自发性高血压大鼠血压波动性的影响

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提要 本文用计算机化清醒大鼠血流动力学测定技术研究酮舍林(ketanserin)对清醒自由活动自发性高血压大鼠血压波动性的影响. 结果表明酮舍林能显著降低自发性高血压大鼠的血压、收缩压从 26.7 降到 21.1 kPa; 舒张压从 20.5 降到 15.8 kPa, 收缩压波动性从 1.3 降到 0.94 kPa. 酮舍林的降压效应与大鼠的收缩压波动性基础值呈正相关.

关键词 血压; 酮舍林; 近交 SHR 大鼠

卫生部药典委员会编

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