Effect of Ketanserin on Adrenal Sympathetic Nerve Activity in Rats

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Abstract—The present study was undertaken to clarify the site for the sympathoinhibitory action of ketanserin in anesthetized rats. Intravenous (i.v.) administration of ketanserin (0.5 and 5 mg/kg) produced a decrease in preganglionic adrenal sympathetic nerve activity (ANA) that is accompanied with hypotension and bradycardia. Intracerebroventricular (i.c.v.) administration of ketanserin (200 μg/rat) also decreased ANA, blood pressure (BP) and heart rate (HR). Intrathecal (i.t.) administration of ketanserin (200 μg/rat), on the other hand, affected neither ANA, BP nor HR. These results indicate that the site of the sympathoinhibitory action of ketanserin is the supraspinal structures, and not at the spinal cord level. In addition, the decrease in ANA after i.v. administration of ketanserin (0.5 and 5 mg/kg) was attenuated significantly with pretreatment of 5,7-dihydroxytryptamine (200 μg/rat, i.c.v.) or 6-hydroxydopamine (200 μg/rat, i.c.v.). These findings suggest that the adrenal sympathoinhibitory action of ketanserin may be centrally mediated via both serotonergic and noradrenergic pathways in rats.

Ketanserin tartrate (3-[2-[4-(p-fluorobenzoyl)-1-piperidinyl]ethyl]-2,4(1H,3H)-quinazolinedine L-tartrate) is a selective 5-hydroxytryptamine type 2 (5-HT2) receptor antagonist that has an affinity for alpha-1-adrenoceptors (1-3). It has been demonstrated that ketanserin has an antihypertensive effect that is mainly due to its peripheral action on blood vessels (4, 5).

Recently, we have reported that intravenous (i.v.) administration of ketanserin decreased postganglionic renal nerve activity (RNA), inferior cardiac nerve activity (ICNA) and preganglionic adrenal nerve activity (ANA) accompanied with hypotension and bradycardia in anesthetized rats (6). These findings suggest that the sympathoinhibitory action of ketanserin may be responsible for the hypotensive and bradycardic mechanism of this drug.

However, there have been few reports in the literature concerning the mechanism of the sympathoinhibitory action of ketanserin. McCall et al. (7, 8) suggested that ketanserin as well as prazosin inhibit cardiac sympathetic outflow via their antagonistic action at central alpha-1-adrenoceptors in baroreceptor-denervated cats. In our experiments, ketanserin's effect on sympathetic nerve activity appeared to differ from that of prazosin because prazosin did not produce a decrease in ANA and RNA at equi-hypotensive doses in buffer nerve intact rats (M. Matsumoto and H. Togashi, unpublished data).

The present study was carried out to clarify the sympathoinhibitory action of ketanserin. That is, I performed experiments to elucidate the effect of ketanserin on ANA, preganglionic sympathetic nerve activity, which was decreased by central sympathoinhibitory drugs (9, 10). In order to investigate the site of ketanserin's sympathoinhibitory action and whether this sympathoinhibitory action is mediated via 5-HT2 receptors and/or alpha-1-adrenoceptors, attention was focused on the following two points: 1) the effect of intracerebroventricular (i.c.v.) or intrathecal (i.t.) administration of ketanserin on ANA, BP and HR and 2) the effect of intravenous (i.v.) administration of ketanserin
on ANA, BP and HR in 5-HT or norepinephrine (NE) depleted rats pretreated with selective monoamine neurotoxins.

Materials and Methods

General: Normotensive male Wistar rats (320–380 g and 9–12 weeks old) were used. Rats were anesthetized with alpha-chloralose (50 mg/kg, i.p.) and urethane (500 mg/kg, i.p.). After immobilization with gallamine triethiodide (10 mg/kg, i.v.), respiration was maintained through a tracheal cannula connected to a rodent respirator (Harvard Apparatus, Millis MA; model 683). Blood pressure (BP) and heart rate (HR) were recorded continuously via the femoral artery with a pressure transducer (Nihon Kohden, Tokyo, Japan; MPU-0.5A). Rectal temperature was maintained between 37 and 38°C with a heating pad.

Intravenous (i.v.) administration was performed through a cannula inserted into the femoral vein. The volume of i.v. injection was kept constant at 0.5 ml/kg during 30 sec periods. Intracerebroventricular (i.c.v.) administration was carried with a microsyringe that was lowered to a depth of 3.5 to 4.0 mm below the surface of the dura mater and positioned at 1 mm lateral to the midline 1 mm posterior to the bregma with a stereotaxic apparatus. Intrathecal (i.t.) administration was performed via polyethylene tubing that was inserted through an incision in the atlantooccipital membrane to the caudal region of the thoracic enlargement (T-10). All i.c.v. and i.t. injections were made at a volume of 10 μl/rat/2 min. Control animals received an equivalent volume of saline. Correct placement of the i.c.v. microsyringe and the i.t. tubing was confirmed at the end of the experiments by injection of methylene blue dye.

Adrenal sympathetic nerve recordings: The left adrenal branches from the splanchnic nerve were retroperitoneally dissected free from surrounding tissue and cut near the adrenal gland. Spontaneous efferent nerve mass discharges were recorded from the central cut end of the nerve with bipolar platinum-iridium wire electrodes. Adrenal nerve activity was amplified, passed through a window discriminator and counted every 10 sec by a digital pulse counter (Nihon Kohden, Channel Selector S-1526).

Monoamine depletion: The selective 5-HT neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT) (200 μg/rat, i.c.v.) was injected 30 min after the systemic administration of desipramine (25 mg/kg, i.p.). 6-Hydroxydopamine (6-OHDA) (200 μg/rat, i.c.v.), a neurotoxin selective for noradrenergic neurons, was injected 10 min after the administration of pargyline (25 mg/kg, i.p.). Experiments were performed 14 days after the i.c.v. injection of the neurotoxins. The concentrations of brain 5-HT and catecholamine (CA) were determined in rats pretreated with these neurotoxins. Rats were sacrificed, and whole brains were rapidly dissected, frozen with liquid nitrogen and stored at −80°C for up to two weeks before assay. 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) concentrations were determined by high performance liquid chromatography with an electrochemical detector (HPLC-ECD) (Irica Co., Ltd., RF-500). CA concentrations were measured by the trihydroxyindole method (HPLC-THI) (Simadzu Co., Ltd.; RF-500).

Drugs: The following drugs and chemicals were used: ketanserin tartarate (Janssen Pharmaceutica, Beerse, Belgium) and 5,7-dihydroxytryptamine creatinine sulfate, 6-hydroxydopamine hydrochloride, pargyline and desipramine hydrochloride (Sigma Chemicals).

Statistical analysis: Statistical significance of the difference between the control and drug-treated groups was determined by Student’s t-test. P<0.05 was considered to be significant. Values obtained were expressed as means±S.E.

Results

Effects of intravenous (i.v.) administration of ketanserin on ANA, BP and HR: Ketanserin (0.5 and 5 mg/kg, i.v.) produced a significant decrease in ANA (Fig. 1B). At doses of 0.05, 0.5 and 5 mg/kg, ketanserin caused a significant and dose-dependent decrease in mean arterial pressure (MAP). With regard to HR, ketanserin (0.5 and 5 mg/kg, i.v.) produced significant decreases (Table 1).

Effects of intracerebroventricular (i.c.v.) administration of ketanserin on ANA, BP and HR: As shown in Fig. 2A, ketanserin (200 μg/
a rat, i.c.v.) produced a decrease in ANA that was gradually accompanied with hypotension and bradycardia. Thirty minutes after i.c.v. administration, significant decreases in ANA, BP and HR were observed as compared with the values of the control rats (Fig. 2B).

**Fig. 1.** Effects of intravenous (i.v.) administration of ketanserin (0.05, 0.5 and 5 mg/kg) on adrenal sympathetic nerve activity (ANA). A) Traces from top to bottom are discharge rate of ANA, actual ANA, blood pressure (BP) and heart rate (HR). B) Time course observation. The ordinate is the percentage of change in ANA from the value obtained before ketanserin administration (▲—▲, 0.05 mg/kg, n=6; ●—●, 0.5 mg/kg, n=6; ■—■, 5 mg/kg, n=9; ○—○, saline, n=6). Each point represents the mean±S.E. *P<0.05 and **P<0.01 vs. control rats.

|                  | MAP (mmHg) before | MAP (mmHg) after | HR (bpm) before | HR (bpm) after |
|------------------|-------------------|------------------|-----------------|----------------|
|                  | n  | mean | S.E. | n  | mean | S.E. | n  | mean | S.E. | n  | mean | S.E. |
| Saline           | 10 | 102.46 | 6.16 | 103.60 | 6.80 | 417.70 | 12.30 | 415.80 | 12.43 |
| Ketanserin       |    |      |      |          |      |      |      |      |      |
| 0.05 mg/kg       | 8  | 113.79 | 1.51 | 87.87* | 5.33 | 429.25 | 10.56 | 406.38 | 12.47 |
| 0.5 mg/kg        | 10 | 101.10 | 2.69 | 66.40** | 4.08 | 420.40 | 6.24 | 357.90** | 9.36 |
| 5 mg/kg          | 10 | 108.69 | 4.36 | 51.20** | 1.86 | 424.70 | 9.74 | 353.40** | 8.93 |

Data was obtained 20 min after administration of ketanserin. Each value represents the mean±S.E. *P<0.05 and **P<0.005 vs. saline-administered control rats.

Effects of intrathecal (i.t.) administration of ketanserin on ANA, BP and HR: i.t. administration of ketanserin (200 μg/rat) did not affect ANA, BP and HR (Fig. 2, A and B).

Brain 5-HT and CA concentrations in 5,7-DHT or 6-OHDA pretreated rats: In 5,7-
DHT (200 µg/rat, i.c.v.) pretreated rats, 5-HT and 5-HIAA concentrations were significantly reduced to approximately 24.6% and 17.9% of those in the non-treated control rats, respectively. NE and DA concentrations were not altered. In 6-OHDA pretreated rats, NE and DA concentrations were reduced to 18.8% and 33.2% of those in the non-treated control rats, respectively. 5-HT and 5-HIAA concentrations were not altered as compared with those in the control rats (Table 2).

**Effect of pretreatment with 5,7-DHT or 6-OHDA on the ketanserin-induced decrease in ANA, BP and HR:** The ketanserin-
induced (0.5 mg/kg, i.v.) decrease in ANA was attenuated significantly by pretreatment with 5,7-DHT or 6-OHDA (Fig. 3, A and B). The maximum decrease in ANA after ketanserin administration (0.5 mg/kg, i.v.) was 42.76±9.39% (mean±S.E.) of the initial value in the non-treated rats. In the 5,7-DHT and 6-OHDA pretreated rats, ANA was 104.7±19.83% and 85.32±6.50%, respectively. After i.v. administration of 5 mg/kg of ketanserin, ANA was 45.41±10.44% of the initial value in the non-treated rats. In the 5,7-DHT and 6-OHDA pretreated rats, ANA was 210.17±43.98% and 129.06±20.91%, respectively (Fig. 4). With regard to the decrease in MAP, there was no significant difference between the 5,7-DHT pretreated and non-treated rats. No significant difference was observed between the decreased MAP in 6-OHDA pretreated rats and that in the non-treated rats.

On the other hand, decreased HR was significantly attenuated by pretreatment with 5,7-DHT at a dose of 0.5 mg/kg (Table 3).

**Discussion**

In this experiment, i.c.v. administration of ketanserin (200 µg/rat) produced significant decreases in ANA, BP and HR, whereas i.t. administration of equivalent doses of ketanserin had no effect on ANA, BP and HR. Namely, ketanserin did not act at the spinal cord level where the origin of the preganglionic nerves, the intermediolateral cell column (IML), is located. These findings demonstrated that ketanserin acts at the supraspinal level to reduce ANA in rats. My findings coincided with previous results that showed that the decrease in ANA after i.v. administration of ketanserin disappeared after transection of the spinal cord at the C1-C2 level (11).
Fig. 4. Effects of ketanserin (0.5 and 5 mg/kg, i.v.) on adrenal sympathetic nerve activity (ANA) in 5,7-
dihydroxytryptamine (5,7-DHT) and 6-hydroxy-
 dopamine (6-OHDA) pretreated rats. Data were obtained 20 min after i.v. administration of ketanserin. Each value represents the mean ± S.E. *P < 0.025, **P < 0.01 and ***P < 0.005 vs. non-treated control rats.

Radioligand binding studies indicate that ketanserin’s highest affinity is to 5-HT2 receptors (1, 2). Laduron et al. (12) reported that i.v. administered [³H]-ketanserin bound to responsive 5-HT2 receptors in the rat brain. It has been reported that intraperitoneal administration of ketanserin modified central 5-HT2 receptor mediated behavior (13).

In this study, I found that pretreatment with 5,7-DHT significantly attenuated the ketanserin-induced decrease in ANA. Pretreatment with 5,7-DHT caused brain 5-HT and 5-HIAA concentrations to be selectively depleted, but did not alter the brain NE and DA concentrations. These findings suggest that the central serotonergic pathway may play an important role in the adrenal sympathoinhibitory action of ketanserin.

Recently, numerous investigators have obtained evidence indicating that the central serotonergic pathway facilitates sympathetic nerve activity (14–20). For instance, the descending serotonergic pathway into the IML projecting from B1 (nucleus raphe pallidus) and B3 (nucleus raphe magnus) in medullary raphe nuclei served to elevate sympathetic nerve activity and BP (15–17). Microiontophoretically applied 5-HT excited the sympathetic preganglionic neurons (18). In addition, electrical stimulation of the ascending serotonergic pathway of B7 (nucleus raphe dorsalis) and B8 (nucleus raphe medianus) in the mesencephalic raphe nuclei led to an increase in sympathetic nerve activity and BP (19, 20). However, it is unclear whether this serotonergic pathway-facilitated sympathetic nerve activity is mediated via 5-HT2 receptors or via other subtypes of 5-HT receptors (21). Recently, McCall et al. (22) have reported that 5-HT2 receptor agonists, 1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane and MK 212, increased the inferior cardiac nerve activity in cats. According to their results, 5-HT2 receptors may be related to serotonergic pathway-facilitated sympathetic nerve activity.

In this study, ketanserin’s failure to decrease the ANA in 5-HT depleted rats suggests the possibility that 5-HT2 receptors may have an important role in the adrenal sympathoinhibitory action of ketanserin. Furthermore, I have found that 6-OHDA pretreatment also significantly attenuates the ketanserin-induced decrease in ANA. In 6-OHDA pretreated rats, brain NE concentrations were selectively reduced, whereas brain 5-HT and 5-HIAA concentrations remained unchanged. These findings demonstrated that the adrenal sympathoinhibitory action of ketanserin was mediated not only via the serotonergic pathway but also via the noradrenergic pathway.

The present results differ from those of McCall et al. (7, 8) which showed that the central sympatholytic action of ketanserin resulted from the ability to antagonize alpha-1-adrenoceptors rather than 5-HT2 receptors in baroreceptor-denervated cats. This discrepancy may be attributed to three basic differences in experimental conditions: First of all, it may be the result of using a different
Table 3. Effects of intravenous (i.v.) administration of ketanserin (0.5 and 5 mg/kg) on mean arterial blood pressure (MAP) and heart rate (HR) in 5,7-dihydroxytryptamine (5,7-DHT) and 6-hydroxydopamine (6-OHDA) pretreated rats

|                          | MAP (mmHg) | HR (bpm) |          |          |          |          |          |          |          |          |          |
|--------------------------|------------|----------|----------|----------|----------|----------|----------|----------|----------|----------|----------|
|                          | initial    | decrease | initial  | decrease |          |          |          |          |          |          |          |
|                          | n          | mean     | S.E.     | mean     | S.E.     | mean     | S.E.     | mean     | S.E.     |          |          |
| Non-treated control rats | 6          | 91.60    | 8.99     | 30.17    | 8.28     | 399.17   | 10.19    | 49.17    | 7.86     |          |          |
| Ketanserin 0.5 mg/kg i.v. |            |          |          |          |          |          |          |          |          |          |          |
| 5,7-DHT pretreated rats  | 5          | 118.94   | 6.56     | 25.34    | 3.03     | 432.60   | 5.83     | 16.40*   | 10.91    |          |          |
| 6-OHDA pretreated rats   | 6          | 100.33   | 7.99     | 23.68    | 9.17     | 430.50   | 23.41    | 31.83    | 16.23    |          |          |
| Non-treated control rats | 7          | 112.89   | 6.15     | 47.89    | 8.50     | 442.57   | 5.50     | 79.00    | 22.93    |          |          |
| Ketanserin 5 mg/kg i.v.  |            |          |          |          |          |          |          |          |          |          |          |
| 5,7-DHT pretreated rats  | 6          | 117.83   | 9.77     | 57.88    | 4.22     | 433.50   | 10.77    | 79.17    | 16.56    |          |          |
| 6-OHDA pretreated rats   | 7          | 117.33   | 6.15     | 41.53    | 8.50     | 436.86   | 10.04    | 59.14    | 10.82    |          |          |

Data was obtained 20 min after administration of ketanserin. Each value represents the mean±S.E. *P<0.05 vs. non-treated control rats.
species of experimental animal. Hoyer et al. (23) reported that the affinity ratios of ketanserin for 5-HT₂ versus alpha 1-adrenoceptors were different depending on the animal species and that the highest selectivity for 5-HT₂ receptors was observed in rat brain membranes. Secondly, the monoamine neurotoxins used in this experiment were more selective than those used by the McCull group. Thirdly, the difference in results may be due to the different characteristics of the preganglionic adrenal nerves and postganglionic nerves, because adrenal medullary function seems to dissociate from the other sympathetic nerve activity (24). For these reasons, a comparison with the report by McCull et al. could not be presented.

Anatomical studies indicate that serotonergic neurons of the B7 area projected into the locus ceruleus (25, 26) or anterior hypothalamus/preoptic area (27, 28) and that the noradrenergic pathway was densely innervated to the B7 area (29, 10). Baraban and Aghajanian (31) reported that the firing activity of 5-HT cells in the B7 area was suppressed by microiontophoretically applied alpha-adrenoceptor antagonists, while it was increased by alpha-agonists. It has been demonstrated that the serotonergic pathway was in series with the noradrenergic pathway at the suprapontine level and that these pathways excited sympathetic nerve activity (32). In addition, these pathways had an antagonistic control on the sympathetic nerve activity at the bulbospinal level, i.e., the descending serotonergic pathway facilitated the sympathetic nerve activity, while the descending noradrenergic pathway inhibited sympathetic nerve activity.

In the present experiment, the site of the sympathoinhibitory action of ketanserin was shown to be on the supraspinal level, not on the spinal cord level. Moreover, the decrease in ANA may have been mediated via both serotonergic and noradrenergic pathways. Thus, ketanserin may act on the serotonergic pathway in series with the noradrenergic pathway to reduce ANA.

This experiment did not completely clarify whether or not the adrenal sympathoinhibitory action of ketanserin contributes to the cardiovascular effects of this drug. However, the ketanserin-induced decrease in MAP was not affected by pretreatment with monoamine neurotoxins despite an attenuation of the decrease in ANA. These facts suggest that the decreased ANA may not be responsible for ketanserin's hypotensive effect. Moreover, ketanserin (5 mg/kg, i.v.) increased the ANA remarkably in both 5,7-DHT and 6-OHDA pretreated rats. These findings may be due to an indirect action of ketanserin such as a baroreflex resulting from peripheral vasodilation, because 5 mg/kg of ketanserin produced a marked reduction of the aortic depressor nerve activity (ADNA), baroreceptor afferent nerve activity, which correlated well with the changes in blood pressure (6). Therefore, this increased ANA in monoamine neurotoxins pretreated rats may result from the markedly decreased ADNA. That is, at a dose of 5 mg/kg, the peripheral vasodilating action seems to be dominant over the central hypotensive action of ketanserin. Phillips et al. (33) have reported that the hypotension caused by ketanserin at low doses (0.1–0.4 mg/kg) was mediated via the inhibition of sympathetic nerve activity, while at high doses (1–4 mg/kg), it was due to the antagonistic action of the peripheral vasodilation induced by alpha-1-adrenoceptor blocking action. My findings partially coincided with their conclusion.

With regard to HR, ketanserin-induced (0.5 mg/kg, i.v.) bradycardia was attenuated by pretreatment with 5,7-DHT. This fact suggests the possibility that the serotonergic pathway-mediated ANA may be related to bradycardia induced by ketanserin. However, at a dose of 5 mg/kg, significant attenuation of bradycardia after pretreatment with 5,7-DHT was not observed. In order to elucidate the role of decreased ANA on ketanserin-induced bradycardia, further studies are required.

In summary, the present study demonstrated that ketanserin acts on the supraspinal level to decrease ANA in rats. In addition, the fact that the ketanserin-induced decrease in ANA was significantly attenuated by pretreatment with both 5,7-DHT and 6-OHDA suggests the possibility that the adrenal sympathoinhibitory action of ketanserin may be centrally mediated via blocking
actions on both 5-HT2 receptors and alpha-
1-adrenoceptors.

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