Korean J. of Pharmacology
Vol. 25, No. 1, pp.67-74, 1989

Influence of Endogenous Catecholamines on Guanabenz-Induced Inhibition of Micturition Reflex in Rats

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ABSTRACT

The effect of guanabenz on volume-induced micturition reflex contraction (VIMRC) in urethane-anethetized female rats was examined under adrenalectomy, chemical-sympathectomy, ganglionectomy, alpha-1, or alpha-2 blockade.

Intracerbroventricular administration of guanalberz had little effect on VIMRC, but topical application suppressed amplitude and frequency of VIMRC. Guanabenz intravenous injection dose-dependently suppressed amplitude and frequency of VIMRC, with complete inhibition at dose of 100 μg/kg, but phenylephrine had no effect on VIMRC.

Intravesicular peak pressure and amplitude of VIMRC were increased by 6-hydroxydopamine (6-OHDA) treatment when compared with control value, but yohimbine-, prazosin-, hexamethonium-treatment and adrenalectomy did not show changes in VIMRC.

Dose-response curve of guanabenz on amplitude and frequency of VIMRC shifted significantly to the right by treatment of yohimbine and 6-OHDA, and adrenalectomy. Median inhibitory dose (μg/kg) of guanabenz to amplitude of VIMRC showed 27.3 in control group, 381.6 in yohimbine, 294.1 in 6-OHDA and 54.1 in hexamethonium, and 38.8 in prazosin. Those of guanabenz to frequency of VIMRC showed 41.7 in control group, 571.1 in yohimbine, 410.8 in 6-OHDA, 141.4 in adrenalectomy, 59.6 in hexamethoinum and 31.4 in prazosin.

These results suggest that guanabenz inhibits VIMRC through alpha-2 receptor stimulation rather than alpha-1 receptor stimulation and that catecholiamines released from sympathetic nerve ending and adrenal gland play a role in the inhibition.

Key Words: Micturition reflex, Guanabenz, Endogenous catecholamines

Abbroviation: 6-OHDA; 6-hydroxydopamine, VIMRC; volume-induced micturition reflex contraction

INTRODUCTION

Micturition reflex is caused by bladder distension which leads to increase in parasympathetic outflow (De Groat and Ryall, 1969; De Groat, 1975; De Groat and Saum, 1976), depression of sympthetic excitatory outflow to the bladder (De Groat and Theobald, 1972; 1976 De Groat, 1975), and depression of the somatic efferent input to the external urethral sphincter (De Groat, 1975).

Depression of spontaneous or evoked bladder contraction is antagonized by beta-adrenergic blocking agent in normally innervated as well as decerebrated unsitmulated bladder preparation, and the inihibition occurred in the parasympathetic ganglia on the surface of the urinary bladder affected by alpha-blocking agents, not by beta-blocking agents (De Groat and Saum, 1972; De Groat, 1975).

In urethral smooth muscle of rabbit and man, the fractional release of ^{3}H-noradrenaline induced by electrical field stimulation increases in the presence of rauwolscine, but decreases in the presence of clonidine (Mattiasson *et al.*, 1984). Clonidine exerts biphasic effects, excitatory and inhibitory action on bladder motility (Santicioli *et al.*, 1983), producing similar effect on micturition reflex (Maggi *et al.*, 1985). Guanabenz is known as an antihypertensive drug (Baum and Shrophsire, 1976; Wendt, 1980) and acts at both pre-and post-synaptic alpha-2 receptor in isolated pulmonary artery, atrium and ileum (Sakakibara, 1981;

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Misu *et al.*, 1982).

Guanabenz is a more selective than clonidine in peripheral neuroeffector junctions (Langer, 1981; Roach *et al.*, 1883; Hong and Sohn, 1984). From this point, guanabenz was considered as a selective drug in generation of inhibition on micturition reflex.

Therefore, present study was undertaken to investigate the effect of alpha-1 agonist phenylephrine or alpha-2 agonist guanabenz on micturition reflex contraction in anesthetized rats, and the influence of alpha-receptor blockers or endogenous catecholamines.

MATERIALS AND METHODS

Female Sprague-Dawley rats weighing 190-200 g were anesthetized with urethane (1.0 g/kg, i.p.). After 30 min, the urinary bladder was catheterized via the urethra using polyethlene tube (i.d. 0.51 mm). This preparation for the investigation to bladder contratction was modified Dray methods (1985). The tube was usually tied in place with a ligature around the external urethral orifice, and it was connected to a pressure transducer (Narco Biosystems, P-1000 B) via strain gage coupler, and then intravesicular pressure was recorded on physiograph (Narco Biosystems, MK-IV-P). The bladder was initially emptied as far as possible, then was filled via the recording tube by incremental 0.1 ml volumes of warmed (37℃) 0.9 % saline until bladder contractions occurred spontaneously.

In order to minimize the gradual increase in intravasicular pressure through the continuous production of urine, the bladder was routinely emptied during the recovery from the effeccts of drug, and then refilled as described earlier until reflex contraction occured again.

The changes of amplitude and frequency on micturition reflex contraction in each group were shown in percentage to control.

Route of administration

(a) Intravenous administration; guanabenz or phenylephrine was injected via jugular vein with the volume adjusted to 1 ml per kg.

(b) topical application; guanabenz 3, 10 or 30 μg was dropped on the surface of bladder by a Hamilton syringe.

(c) Intracerebroventricular (i.c.v.) injection; the head was fitted into a stereotaxic instrument (Gokyo Co.), the skull was exposed, and then polyethylene tube was pushed into lateral ventricle (1 mm lateral, 1 mm posterior, 4 mm deep from the bregma), and cemented by vertex (Dentimex Co.): After experiments, rats were sacrified 5 min after methylene blue injection, followed by rapid removal of brain, and were confirmed the dye deposition in an around the ventricular system.

Experimental group

(a) Control group; guanabenz alone was administered without operation with the dose increase.

(b) Adrenalectomy group; after anesthesia with ketamine (15 mg/kg i.p.) under light ether anesthesia, bilateral glands with ligated vein and artery were denervated and then 5 mg/kg of hydrocortisone was intraperitoneally injected 24 hours prior to experiment.

(c) Chemical sympathectomy group; 30 mg/kg of 6-hydroxydopamine was injected twice 5 and 4 days before.

(d) Yohimbine group; 1 mg/kg of yohimbine was intravenously injected 30 min before.

(e) Prazosin group; 0.1 mg/kg of prazosin was intravenously injected 30 min before.

(f) Hexamethonium group; 3 mg/kg was intravenously injected 20 min before.

The results are expressed as M±SEM. The statistical significance of the difference between control and treatment group was examined by Student's unpaired *t*-test and P values less than 0.05 were taken as significant.

Drug used were guanabenz, phenylephrine, yohimbine, hexamethonium bromide, 6-hydroxydopamine (Sigma Co.), hydrocortisone sodium succinate (Upjohn Co.), and prazosin (Pfizer Co.). 6-Hydroxydbpamine was dissolved in 0.5% ascorbic acid solution, prazosin and yohimbine were dissolved in distilled water, and other drugs were dissolved in 0.9% saline solution. All dose was calculated on the basis of weight of drug base.

RESULTS

Change of micturition reflex contraction following guanabenz or phenylenphrine

As shown in fig 1, when bladder was filled by

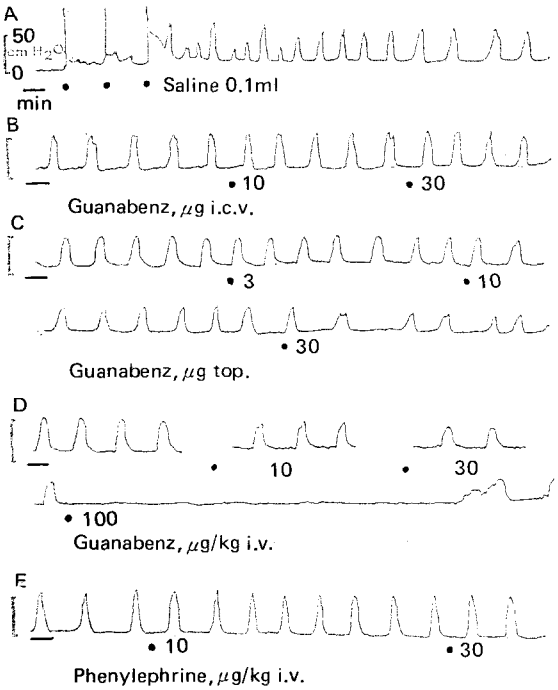

Fig. 1. Effect of guanabenz and phenylephrine on the volume-induced reflex contraction in anesthetized rats.

In A, the spontaneous rhythmic contraction recorded at the micturition threshold. In B, guanabenz intracerebroventricular injection (i.c.v., 10 and 30 μg). In C, guanabenz topical application (top., 3, 10 and 30 μg). In D, guanabenz i.v. (10, 30 and 100 μg/kg). In E, phenyle-phrine i.v. (10 and 30 μg/kg).

incremental 0.1 ml volume of 0.9% saline, the rhythmic contraction occurs (Fig. 1-A), and guanabenz i.c.v. (1-B, 10 or 30 μg) did not alter the micturition reflex contraction, but topical application (1-C, 3, 10 or 10 μg) inhibited the amplitude and frequency of micturition reflex contraction. and guanabenz i.v. (1-D and Table 1, 10 or 30 μg/kg) also inhibited the peak pressure, amplitude and frequency of micturition reflex contraction, especially 100 μg/kg i.v. ceased the reflex contraction, the cessation was sustained 20 min over. In contrast, phenylephrine i.v. injection (1-E and Table 1) with increase in dose did not influence the micturition reflex contraction.

Effect of adrenalectomy, 6-hydroxydopamine (6-OHDA)-, yohimbine-, prazosin-, or hexamethonium treatment on the micturition reflex contraction

We examined whether five factors on volume-induced micturition reflex contraction (VIMRC) is affected by adrenalectomy, 6-OHDA-, yohimbine-, prazosin-, or hexamethonium-treatment.

The VIMRC was not altered by either adrenalectomy (24 hour before) or yohimbine (1 mg/kg i.v.), or prazosin (0.1 mg/kg i.v.), or hexamethonium (3mg/kg i.v.). However, 6-OHDA treament (twice 5 and 4 days before, 30 mg/kg i.p.), when compared with the control values, significantly increased peak pressure and amplitude of VIMRC to 72.4±4.5 vs 58.8±4.6 and 57.8±5.4 vs 41.0±5.4 cm H_2O, respectively.

Table 1. Effect of guanabenz or phenylephrine on volume-induced micturition reflex contraction (VIMRC) in rats

Angists	n	Dose (μg/kg, IV)	IVP (cm H_2O)	PP (cm H_2O)	AP (cm H_2O)	FR (/min)	DR (sec)
Guanabenz	9	0	17.1±1.1	58.8±4.6	41.0±5.4	0.65±0.06	28.3±1.4
		10	17.8±1.0	46.5±4.5**	28.7±4.2**	0.55±0.06*	27.2±1.5
		30	21.0±0.8**	39.8±2.4**	19.0±2.8**	0.44±0.05**	27.8±1.7
		100	cessation (260±2.0, min)				
Phenylephrine	6	0	12.6±2.2	66.4±6.6	53.8±5.9	0.52±0.04	28.0±2.0
		3	13.4±2.2	64.4±6.6	53.8±5.9	0.54±0.02	30.0±0.0
		10	13.8±2.8	63.0±5.0	49.6±4.3	0.52±0.06	30.0±0.0
		30	14.6±3.3	61.0±3.8	47.6±2.9	0.50±0.06	30.0±0.0

IVP; Intravesicular pressure, PP; Intravesicular peak pressure, AP; Amplitude, FR; Frequency, DR; Duration. Guanabenz or phenylephrine was intraveonously administered for one minute at intervals of 15 to 20 minutes. n;number of rats. Each value means M±SEM. Number in parenthesis is the period during which VIMRC was completely suppressed. *;$p<0.05$, **; $p<0.01$ (significantly different from control value).

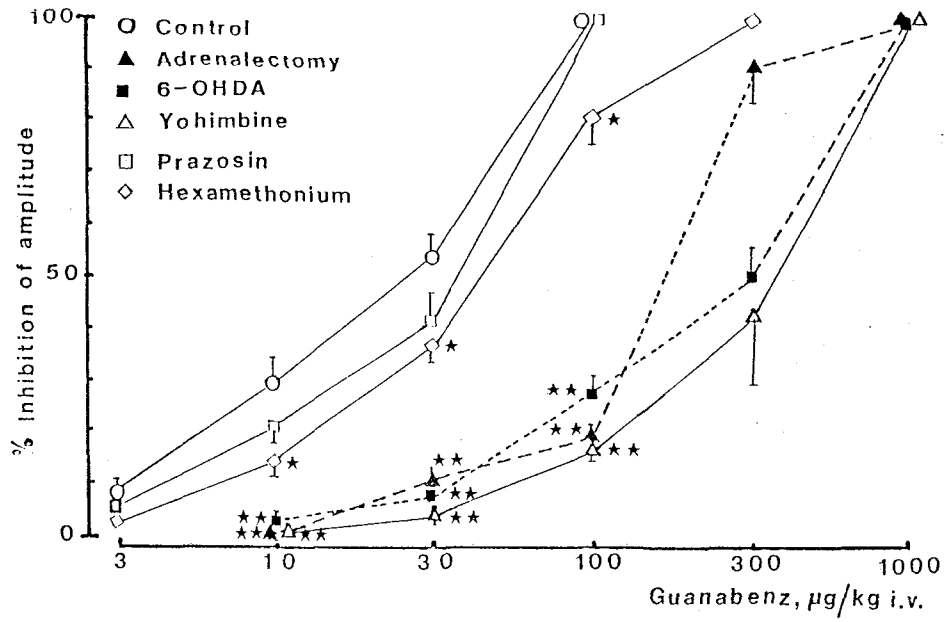

Fig. 2. Effect of guanabenz under adrenalcetomy, 6-OHDA, yohimbine-, prazosin- and hexamenthonium-treatment on amplitude of micturition reflex in anesthetized rats.
The explanation of each group is the same as table 2 written previously. % inhibition= | (A-B)/B | ×100: A, respective value after guanabenz adminstration, and B, value before initial guanabenz administration. * ; $p<0.05$, ** ; $p<0.01$.

Table 2. Effect of adrenalectomy, 6-hydoxydopamine (6-OHDA)-, yohimbine-, prazosin-, and hexamethonium treatment on the volume-induced micturition reflex contraction

Groups	n	IVP (cm H_2O)	PP (cm H_2PO)	FR (/min)	DR (sec)
Controls	9	17.1±1.1	58.8±4.6	41.0±5.4	0.65±0.06	28.3±1.4
Adrenalectomy	10	14.7±1.7	66.5±5.1	52.2±4.6	0.63±0.07	26.0±1.5
6-OHDA	7	15.7±1.6	72.4±4.6*	57.8±5.4*	0.66±0.03	26.5±1.3
Yohimbine	6	18.6±0.4	63.6±2.2	50.0±3.8	0.60±0.03	25.0±3.2
Prazosin	5	18.0±1.8	57.2±6.0	39.2±3.8	0.60±0.05	28.3±1.7
Hexamethonium	6	16.3±1.1	59.0±4.0	42.2±4.6	0.70±0.03	27.5±2.5

IVP; Intravesicular pressure, PP; Intravesicular peak Pressure, AP; Amplitude, FR; Frequency, DR; Duration. n: numbers of animals tested. Each value represents M±SEM. Adrenalectiomy was one 24 hours before and then hydrocortisone was injected 5 mg/kg (i.p.). 6-OHDA was twice injected 3 mg/kg (i.p.) 5 and 4 days before. Yohimbine or prazosin was iniected 1 or 0.1 mg/kg (i.p.) 30 min before respectively. Hexamethonium was injected 3 mg/kg (i.v.) 20 min before. * :$p<0.01$ (significntly different from control value).

Effect of guanabenz under adrenalectomy, 6-OHDA-, yohimbine-, Prazosin-, and hexamethonium- treatment on VIMRC

As the experiment shows, guanabenz inhibit the amplitude and frequency of VIMRC. So, we investigate whether ampliude and frequency is affected by alpha-receptor blockade and endogenous catecholiamines.

Change of amplitude on VIMRC: 3, 10, or 30 μg/kg i.v. of guanabenz inhibited in dose-related

Table 3. AP_{50} and FR_{50} of volume-induced micturition reflex contraction (VIMRC) and dose ratio in adrenalectomy, 6-OHDA-, yohimbine-, prazosin- and hexamethonium-treatment group on control group in rats

Group	AP_{50} (μg)	Dose ratio	FR_{50} (μg)	Dose ratio
Control	27.3		41.7	
Adrenalectomy	184.1	6.7	141.4	3.4
6-OHDA	294.1	10.7	140.8	9.9
Yohimbine	381.6	14.0	571.1	13.7
Prazosin	38.8	1.4	31.4	0.8
Hexamethonium	54.1	2.0	59.6	1.4

AP_{50} value expressed as dose (μg/kg) of guanabenz produced 50% inhibition compared with basal value of amplitude on VIMRC. FR_{50} value expressed as dose (μg/kg) of guanabenz produced 50% inhibition compared with basal value of frequency on VIMRG. Dose ratio = AP_{50} or PR_{50} in each group/AP_{50} in control group.

manners (Fig. 2), the percentage was 8.2, 30.5, or 53.1% respectively. The inhibitory values with guanabenz (10, 100, 1000 μg/kg) were 1.6%, 19.5 %, or 100% in adrealectomy, 3.5, 27.1, or 100% in 6-OHDA, 0.9, 17.3 or 100% in yohimbine, and 16. 0, 80.0 or 100% in hexamethonium group, respectively

And the median inhibitory dose (AP_{50}, μg/kg) was 27.3 in control, 184.1 in adrenalectomy, 294.1 in 6-OHDA, 381.6 in yohimbine, 38.8 in prazosin, or 54.1 in hexamethonium group, respectively (Table 3). The order of potency to the inhibition of amplitude on VIMRC was yohimbine > 6-OHDA > adrenalectomy > hexamethonium > prazosin.

Change of frequency on VIMRC: The inhibitory value which was exhibited in dose-related manners tended to attenuate in adrenalectomy, 6-OHDA or yohimbine treatment, whereas the inhibitory value remained the same with prazosin- or hexamethonium-treatment (Fig. 3).

The median inhibitory dose of guanabenz (FR_{50}, μg/kg) was 141.4 in adrenalectomy, 410.8 in 6-OHDA; 571.1 in yohimbine, 31.4 in prazosin, 59.6 in hexamethonium (Table 3). The order of

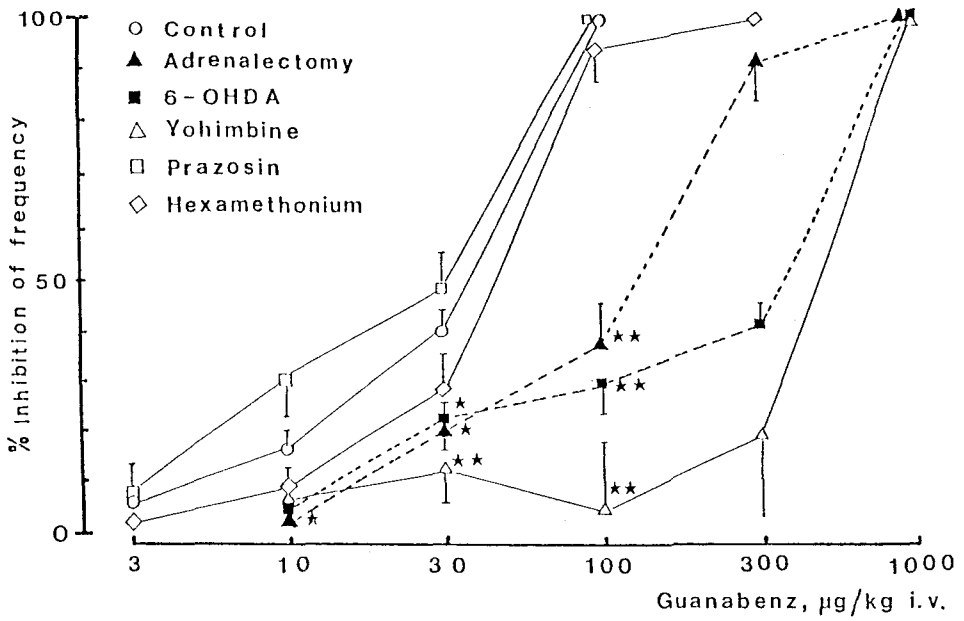

Fig. 3. Effect of guanabenz under adrenalectomy, 6-OHDA, yohimbine-. prazosin- and hexamethonium-treatment on frequency of micturition reflex in anesthetized rats. * : $p<0.05$, **; $p<0.01$

potency in inhibiting the frequency was yohimbine > 6-OHDA > adrenalectomy > hexamethonium > prazosin.

DISCUSSION

Micturition reflex is positively regulated by parasympathetic nerve fibers, and is negatively regulated by sympathetic nerve fibers (Kuru, 1965; De Groat and Ryall, 1969; De Groat, 1975; De Groat and Saum, 1976; De Groat and Theobald, 1972, 1976).

Alpha-1 receptor mediates the contraction of vacular smooth muscle, the inotropic action of heart, activation of glycogen phosphorylase in liver, and alpha-2 receptor involves in the aggregation of platelet, inhibition of insulin secretion and contraction of some vascular smooth muscle (Hoffman *et al.,* 1979; Langer, 1980; Yamaguchi and Kopin, 1980; Langer, 1981; Starke, 1981). Recently, it has been documented that alpha-1 and alpha-2 receptor are present in trigone and proximal urethra; alpha-1 receptor is distributed in the dome of urinary bladder (Ueda *et al.,* 1984; Andersson *et al.,* 1984). It is not clear on which inhibition of micturition reflex is selectively mediated by alpha-1 or alpha-2 receptor. Phenylephrine is known as alpaha-1 agonist (Docherty *et al.,* 1979; van Meel *et al.,* 1981; Carrier and White, 1985), and guanabenz is known as alpha-2 agonist (Misu *et al.,* 1982; Kobinger and Pichler, 1980; Roach *et al.,* 1983).

In this study, phenylephrine did not have an effect on VIMRC, whereas guanabenz inhibited it by i.v. administration, attenuating it by topical administration. This indicates that alpha-2 receptor activation rather than alpha-1 activation plays a critical role in inhibiting the micturition relflex, and that dircet action on bladder surface plays a minor role. The indications show that presynaptic effect may be involved in the inhibition. This inhibition by guanabenz may be caused by urethra contraction. This explanation is supported by the findings that in isolated urethra, ^{3}H-noradrenaline efflux reduced by clonidine and increased by rauwolscine (Mattiasson *et al.,* 1984) and that female rabbit urethra contain alpha-1 25% and alpha-2 receptor 75% (Andersson *et al.,* 1984).

And inhibitory action on VIMRC by guanabenz is significantly attenuated by yohimbine, not by prazosin. This result also suggests that the inhibition can be caused by alpha-2 receptor activation, presumably due to alpha-2 receptor locating pre-and post-synaptic membrane (Langer, 1974, 1980, 1981).

Ganglionic blocker hexamethonium treatment attenuated the inhibition of amplitude regardless of frequency, suggesting that the inhibition may result from ganglionic stimulation. This finding is similar to the result by Baum *et al.,* (1970) that bradycardia induced by guanabenz administration may be caused by vagal reflex and ganglionic stimulation. And the result is related to the facts that detrusor has intrinsic tone elicited from intramural ganglia (Ellioitt, 1907) and that alpha-receptor mediates inhibition of neurotransmission at pelvic ganglia level and beta-receptor mediates inhibition of neurotransmission at pelvic ganglia level and beta-receptor mediates inhibition of detrusor muscle contractility (De Groat, 1975; De Groat and Theobald, 1976; De Groat and Booth, 1980).

The inhibitory action by guanabenz was significantly suppressed under the treatment with 6-OHDA. This result indicates that the inhibition of guanabenz may be induced by indirect action elicited from the release of endogenous catecholamines. This is supported by that exogenous and endogenous catecholamines inhibit the micturition reflex (De Groat and Saum, 1972, 1976). Adrenalectomy also attenuated the inhibitory action on VIMRC by guanabenz. According to recent studies, alpha-2 receptor predominates extrasynaptically and is activated by circulation catecholamines released from adrenal medulla, or by exogenously applied catecholamines (Yamaguchi and Kopin, 1980; Wilffert *et al.,* 1982).

So, our result suggests that guanabenz-induced inhibition of VIMRC result from extrasynaptic alpha-2 receptor activation and circulatory catecholamines partially participate in the activation.

And our result showed that the duration of inhibition of micturition by guanabenz was longer than that by clonidine, and that guanabenz decreased frequency and amplitude. Other investigators showed that clonidine decreased frequency only on micturition reflex (Maggi *et al.,* 1985). It is assumed that guanabenz selectively acts at alpha-2 receptor in mediating inhibition of micturition reflex.

Taken as a whole, the results suggest that the inhibition of micturition reflex by guanabenz is related to alpha-2 receptor rather than alpha-1 activation, and that endogenous catecholamines released from adrenal medulla and sympathetic

nerve endings partially participate in the inhibition.

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= 국문초록 =

Guanabenz 투여에 의한 흰쥐의 배뇨반사억제작용에 미치는 내인성 Catecholamines의 영향

경북대학교 의과대학 약리학교실

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배뇨반사수축에 미치는 α-수용체 및 내인성 catecholamine의 영향을 검토하기 위하여 체중 190~220 g의 암컷흰쥐를 사용하여 부신절제 및 6-OHDA, yohimbine, prazosin 그리고 hexamethoium 처치시의 guanabenz에 의한 배뇨반사 수축을 비교 관찰하였든 바 그 결과는 다음과 같다.

Guanabenz 3, 10 및 30 μg/kg를 정맥주사하였을 때 용량증가에 따라 배뇨 반사수축의 크기와 횟수가 감소되었으며 100 μg/kg 투여시에는 완전히 억제되었다. 국소적용시에는 약하였고, 측뇌실내투여시에는 거의 나타나지 아니하였다. 그리고 phenylephrine은 배뇨반사수축에 아무런 영향을 주지 않았다.

6-OHDA를 처치시 방광최고내압과 수축크기가 유의성있게 증가 되었으나, 부신절제나 yohimbine, prazosin, hexamethonium 투여로는 방광수축에 거의 변화가 없었다.

Guanabenz의 배뇨반사수축의 크기와 횟수의 억제에 대한 용량반응곡선이 hexamethonium, 부신절제, 6-OHDA-, yohimbine 처치시 오른쪽으로 이동하였다. Guanabenz에 의한 억제작용이 yohimbine 처치>6-OHDA>부신절제>hexamethonium 순으로 약화되었으나 prazosin처치로는 약화되지 아니하였다.

이상과 같은 결과로 미루어 guanabenz에 의한 배뇨반사수축의 억제작용은 α_1-수용체와는 관계없이 α_2-수용체흥분작용에 기인되며, 이 억제작용은 부신수질 및 교감신경말단에서 유리되는 catecholamines이 관여된 것으로 사료된다.