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NS-49, an α_{1A}-adrenoceptor agonist, selectively increases intraurethral pressure in dogs

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Abstract

The effects of NS-49 ((*R*)-(−)-3′-(2-amino-1-hydroxyethyl)-4′-fluoromethane sulfonanilide hydrochloride), an α_{1A}-adrenoceptor-selective agonist, on intraurethral pressure and blood pressure were investigated in anesthetized dogs. In addition, the contractile effects of NS-49 on the isolated dog urethra and carotid artery were compared with those of non-selective α_1-adrenoceptor agonists. Intravenously (i.v.) administered NS-49 at 0.3 μg/kg or more significantly increased intraurethral pressure in a dose-dependent manner. Much higher doses of NS-49 were needed to increase blood pressure. In contrast, ST-1059 (1-(2′,5′-dimethoxyphenyl)-2-aminoethanol) (an active metabolite of midodrine) at 30 μg/kg or more significantly increased both intraurethral pressure and blood pressure. NS-49 was 11-fold more selective for intraurethral pressure than ST-1059. NS-49, ST-1059, phenylephrine and noradrenaline caused concentration-dependent contraction of the isolated dog urethra. NS-49 caused only a slight contraction of the dog carotid artery even at high concentrations, whereas the reference drugs caused contractions of the artery with high efficacy. The α_{1A}-adrenoceptor-selective antagonists 5-methylurapidil and WB-4101 also showed high affinity for α_1-adrenoceptors in the dog urethra in inhibiting [^{3}H]prazosin binding. In conclusion, the α_{1A}-selective agonist NS-49 selectively increased intraurethral presure in dogs, and produced selective contraction of the dog urethra. These results suggest that the α_{1A}-adrenoceptor subtype is responsible for the contraction of the urethra and the regulation of intraurethral pressure, and that NS-49 might be useful for the treatment of stress incontinence with little effect on the cardiovascular system.

Keywords: NS-49; α_1-Adrenoceptor, subtype; Intraurethral pressure; Blood pressure

1. Introduction

Oral administration of α_1-adrenoceptor agonists, including norephedrine (Ek et al., 1978; Öbrink and Bunne, 1978) and midodrine (Jonas, 1977), is effective in the treatment of female stress incontinence. These agonists work by increasing the tone of the smooth muscle in the lower urinary tract. However, these drugs also have adverse effects on the cardiovascular system due to their sympathomimetic activities (Öbrink and Bunne, 1978).

The most recent nomenclature for α_1-adrenoceptor recognizes three subtypes, α_{1A}, α_{1B} and α_{1D}, that have been cloned, as well as an additional α_{1L} subtype that has not yet been cloned (Ford et al., 1994; Bylund et al., 1994; Ruffolo et al., 1994; Hieble et al., 1995). However, the function of these subtypes in urethral contraction and in the cardiovascular system has not yet been elucidated.

NS-49 ((*R*)-(−)-3′-(2-amino-1-hydroxyethyl)-4′-fluoromethanesulfonanilide hydrochloride) (Fig. 1), which is under development for the treatment of stress incontinence, has a selective agonistic activity on the α_{1A}-adrenoceptor subtype (Obika et al., 1995) or on both the α_{1A} and the α_{1L} subtypes (Muramatsu et al., 1995).

We have now investigated the contractile responses to NS-49 of isolated dog urethra and carotid artery, and we have compared the effects of NS-49 on the intraurethral pressure and blood pressure in anesthetized dogs. The aim of the study was to determine the selectivity of NS-49 for the urethra over the artery, as well as to identify the

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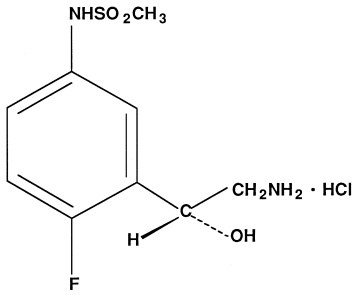

NS-49

Fig. 1. Chemical structure of NS-49, (*R*)-(−)-3′-(2-amino-1-hydroxyethyl)-4′-fluoromethanesulfonanilide hydrochloride.

α_1-adrenoceptor subtype primarily responsible for the contraction of the urethra.

2. Materials and methods

2.1. Drugs

NS-49 and ST-1059 (1-(2′,5′-dimethoxyphenyl)-2-aminoethanol) were synthesized in our laboratories. *dl*-Norephedrine hydrochloride was purchased from Tokyo Kasei (Tokyo, Japan); *l*-phenylephrine hydrochloride, *l*-noradrenaline bitartrate and atropine sulfate were from Sigma (St. Louis, MO, USA); propranolol hydrochloride was from Nacalai Tesque (Kyoto, Japan); phentolamine mesylate was from Ciba-Geigy Japan (Takarazuka, Japan); and [^{3}H]prazosin (2.93 TBq/mmol) was from New England Nuclear (Boston, MA, USA).

2.2. Measurement of intraurethral pressure and blood pressure in dogs

Female Beagle dogs weighing 8.0–11.0 kg were fasted for 24 h and anesthetized by combined treatment with urethane (600 mg/kg, i.v.) and α-chloralose (60 mg/kg, i.v.), then placed in a supine position on a heating pad (K-20, American Pharmaseal, Valencia, CA, USA). To maintain stable anesthesia, a mixture of urethane (90 mg/ml) and α-chloralose (9 mg/ml) was continuously infused into the left femoral vein at a rate of 1.5–3 ml/kg/h via a polyethylene catheter (size 5; Hibiki, Tokyo, Japan) throughout the experiments. A midline incision was made in the lower abdomen, the urinary bladder was exposed, and the urine was completely drained out through a Nelaton's catheter (10-Fr., Terumo, Tokyo, Japan) inserted via the external urethra. Polyethylene tubes (PE-90, Clay Adams, Parsippany, NJ, USA) were inserted into the bilateral ureters to drain urine from the kidneys. A 5-Fr. microtip pressure transducer (MPC-500, Millar, Houston, TX, USA) with a 5×7 mm saline-filled balloon at the tip was introduced into the bladder via the external urethra. Then the transducer was slowly withdrawn using an apparatus for monitoring the urethral pressure profile (KU-601G, AU-601G, Nihon Kohden, Tokyo, Japan), and it was positioned in the proximal urethra 0.5–1 cm from the bladder neck, because the proximal urethra is not a maximal pressure site, but the most sensitive site to α_1-adrenergic stimulation. Intraurethral pressure signals were conveyed to a carrier amplifier (AB-621G, Nihon Kohden) through a pressure transducer control unit (TC-500, Nihon Kohden). For recording the blood pressure, the left femoral artery was cannulated with a polyethylene catheter (size 9; Hibiki), which was connected to an amplifier (AP-621G, Nihon Kohden) through a pressure transducer (TP-400T, Nihon Kohden). All parameters were continuously recorded on a pen recorder (RJG-4124, Nihon Kohden). After all parameters had become stable, test drugs (dissolved in saline) were injected into the femoral vein non-cumulatively at 30 min intervals. Four animals were used for each drug. Changes in each parameter were statistically compared with pre-drug value by means of Student's paired *t*-test ($P < 0.05$).

2.3. Measurement of contractile effects

Female Beagle dogs weighing 8.5–10.6 kg were anesthetized with pentobarbital (30 mg/kg, i.v.) and killed by exsanguination. The proximal urethra and carotid artery were immediately removed. The urethra was opened by a midline incision and the circular urethral strips 10–15 mm long and 2–3 mm wide were made. The carotid artery was cut helically. Each preparation was suspended with a load of 1 g in a Magnus bath (maintained at 37°C and aerated with 95% O_2 and 5% CO_2) containing modified Krebs solution (120.5 mM NaCl, 5.9 mM KCl, 2.5 mM $CaCl_2$, 1.2 mM $MgCl_2$, 1.2 mM NaH_2PO_4, 15.5 mM $NaHCO_3$ and 11.5 mM glucose, pH 7.4). The preparations were allowed to stabilize for about 60 min. The tension of the strips was measured with an isometric transducer (T7-30-240, Toyo Baldwin, Japan) and recorded on a pen recorder (RJG-4124, Nihon Kohden) via a strain pressure amplifier (RMP-6008, Nihon Kohden). All experiments were conducted in modified Krebs solution containing propranolol (1 μM) and atropine (1 μM). The pD_2 value (the negative logarithm of EC_{50}) of each agonist was estimated from the concentration-response data by Hill plot analysis. The maximal contractile effect of each drug was calculated as its ratio to the maximal contractile effect of noradrenaline.

2.4. [^{3}H]Prazosin binding in dog urethra, rat submaxillary gland and liver

The submaxillary glands and livers were removed from male Sprague-Dawley rats (400–500 g; SLC, Hamamatsu, Japan), and weighed. The dog urethra and rat submaxillary glands were homogenized in 10 volumes of 50 mM Tris-HCl, pH 7.4, with a Polytron homogenizer (PT-3000,

Kinematika, Littau, Switzerland). The homogenate was filtered through two layers of gauze and centrifuged at 40 000 × *g* for 20 min, after which the pellet was resuspended in the same buffer and centrifuged again. The final pellet was suspended in 2 volumes for the dog urethra or 10 volumes for the submaxillary gland of the same buffer and stored at −80°C. Livers were homogenized in 10 volumes of 0.32 M sucrose with a glass-Teflon homogenizer. The homogenate was centrifuged at 1000 × *g* for 10 min, and the supernatant was decanted and centrifuged at 48 000 × *g* for 20 min. The resulting pellet was suspended in 50 mM Tris-HCl buffer and centrifuged again at 48 000 × *g* for 20 min, after which the final pellet was resuspended in 8 volumes of the same buffer and stored at −80°C. Each of the frozen membrane preparations was thawed and diluted 10-fold before use.

Each membrane preparation (0.4 ml) was incubated for 30 min at 25°C with [^{3}H]prazosin (0.2 nM for the displacement assay and 0.02–1 nM for the saturation assay) and various concentrations of an antagonist in a total volume of 0.5 ml. The binding reaction was terminated by the addition of 3 ml of ice-cold 50 mM Tris-HCl buffer, and the reaction mixture was immediately filtered through a glass fiber filter (GF/B, Whatman, Maidstone, UK) presoaked in 0.1% polyethylenimine. The filter was washed three times with 3 ml of ice-cold Tris buffer, and the radioactivity bound to the filter was measured with a liquid scintillation counter (Tri-Carb 4640, Packard, Downers Grove, IL, USA). Specific binding was determined by subtracting the nonspecific binding (binding in the presence of 10 μM phentolamine) from the total binding (binding in the absence of any test compound). All experiments were performed in duplicate.

3. Results

3.1. Effect of NS-49 on intraurethral pressure and blood pressure in dogs

The effects of NS-49 were compared with those of ST-1059 (Fig. 2). The baseline values of intraurethral pressure and blood pressure were 4.94 ± 0.26 and 150 ± 4 mmHg, respectively. NS-49 at 0.3 μg/kg or more significantly increased intraurethral pressure in a dose-dependent manner (Fig. 2A), and 3 μg/kg of NS-49 markedly increased it to 33.5 ± 1.8 mmHg. Much higher doses were needed for the increase in blood pressure (Fig. 2B). ST-1059 at 30 μg/kg or more significantly increased both intraurethral pressure and blood pressure. The difference in the positions of the log dose-response curves for NS-49 and ST-1059 in producing increases in intraurethral pressure indicates that NS-49 increased intraurethral pressure 51-fold more potently than ST-1059. The corresponding difference in producing increases in blood pressure indicates that NS-49 increased blood pressure 4.6-fold more

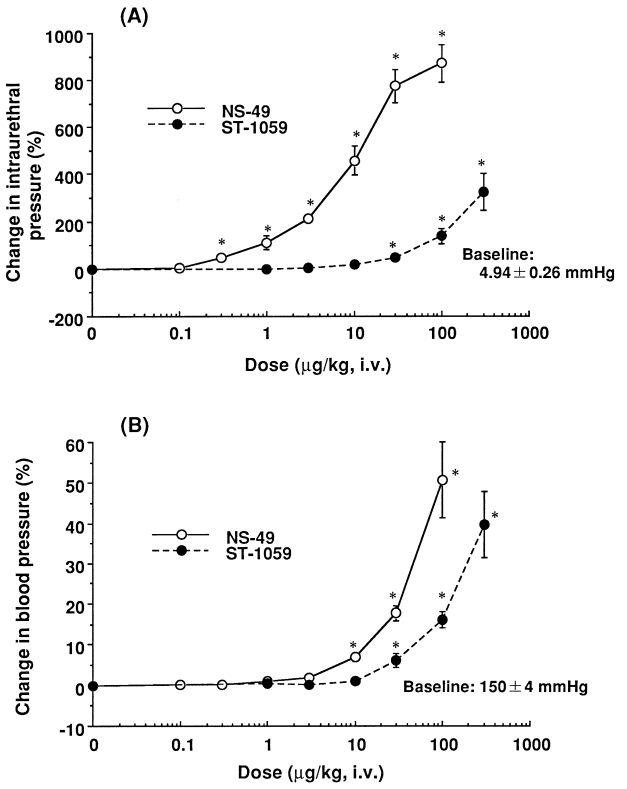

Fig. 2. Effects of NS-49 and ST-1059 on the intraurethral pressure (A) and blood pressure (B) in anesthesized dogs. Each value shows the mean ± S.E. of 4 experiments. Significantly different from pre-drug value: * $P < 0.05$ (paired *t*-test).

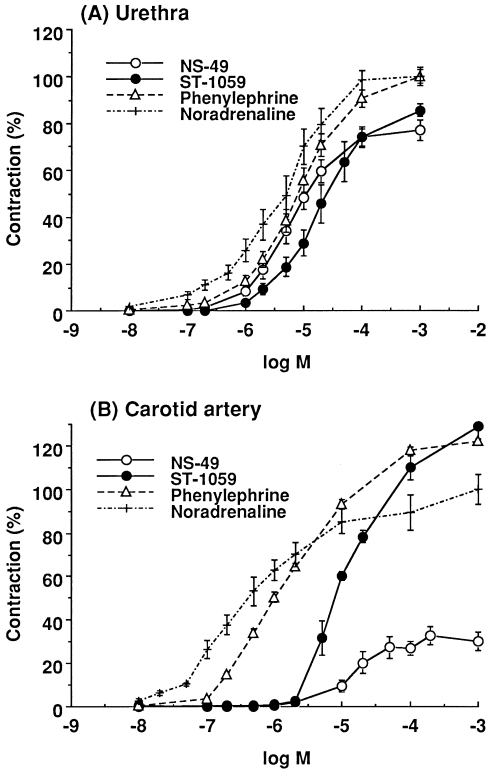

Fig. 3. Contractile responses to NS-49 and reference drugs in the dog urethra and carotid artery. Each value shows the mean ± S.E. of the percentage of the maximal response to noradrenaline.

Table 1
Comparison of the pD_2 values and the maximal contractile responses to NS-49 and reference drugs in the isolated dog urethra and carotid artery

Drugs	Urethra		Carotid artery	
	pD_2	Maximal response (%)	pD_2	Maximal response (%)
NS-49	5.20 ± 0.08	78 ± 8	4.62 ± 0.21	36 ± 3
ST-1059	4.65 ± 0.10	86 ± 5	4.90 ± 0.06	142 ± 16
Phenylephrine	5.09 ± 0.09	101 ± 3	5.77 ± 0.05	132 ± 12
Noradrenaline	5.41 ± 0.14	100	6.44 ± 0.18	100

The experiments were conducted in a modified Krebs solution containing propranolol (10^{-6} M) and atropine (10^{-6} M). The maximal response to each drug was estimated as its ratio to the maximal contractile response to noradrenaline. Each value represents the mean ± S.E. of 5 experiments.

potently than ST-1059. The comparison of the relative potency in producing increases in intraurethral pressure with that in blood pressure indicates that NS-49 was 11-fold more selective for intraurethral pressure than ST-1059.

3.2. Contractile responses of isolated dog urethra and carotid artery

NS-49, ST-1059, phenylephrine and noradrenaline all caused contraction of the isolated dog urethra in a concentration-dependent manner (Fig. 3A), and the pD_2 values were 5.20, 4.65, 5.09 and 5.41 respectively (Table 1). In contrast, NS-49 caused only a slight contraction of dog carotid artery (Fig. 3B), with a maximum response of 36% of that of noradrenaline (Table 1), whereas ST-1059 and phenylephrine caused contractions with respective maximal responses of 142% and 132% of that of noradrenaline.

3.3. [^{3}H]Prazosin binding to membrane preparations from dog urethra, rat submaxillary gland and liver

The dissociation constants obtained from the saturation curves for [^{3}H]prazosin binding to membranes prepared from the dog urethra, rat submaxilary gland and liver were 533, 83 and 53 pM, respectively (Table 2), indicating that prazosin had lower affinity for the α_1-adrenoceptors in the dog urethra than it had for those in the rat submaxillary gland and liver.

Table 2
Affinities of [^{3}H]prazosin, 5-methylurapidil and WB-4101 for α_1-adrenoceptors in dog urethra, rat submaxillary gland and liver

Tissues	K_d for [^{3}H]-prazosin (pM)	pK_i	
		5-Methylurapidil	WB-4101
Dog urethra	533 ± 72	8.78 ± 0.02	9.10 ± 0.10
Rat submaxillary gland	83 ± 4	9.05 ± 0.03	9.28 ± 0.07
Rat liver	53 ± 18	7.33 ± 0.01	8.16 ± 0.08

K_d values were determined by the saturation analysis of [^{3}H]prazosin binding to membrane preparations from the dog urethra, rat submaxillary gland (α_{1A}) or liver (α_{1B}). pK_i values were determined from data on the displacement of [^{3}H]prazosin binding to each membrane preparation by 5-methylurapidil or WB-4101. Values are shown as the mean ± S.E. of three experiments.

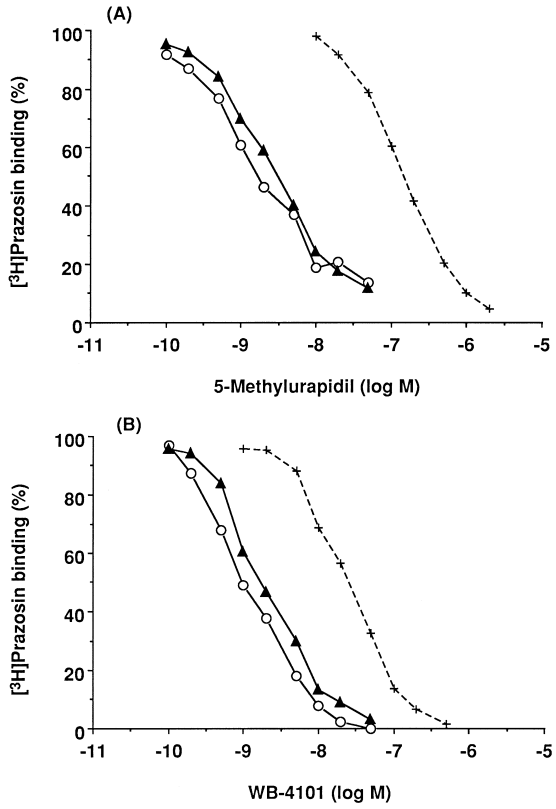

Fig. 4. Inhibition of [^{3}H]prazosin binding to membrane preparations from drug urethra, rat submaxillary gland and rat liver by 5-methylurapidil (A) and WB-4101 (B). (○) Dog urethra; (▲) rat submaxillary gland; (+) rat liver.

The α_{1A}-adrenoceptor-selective antagonists 5-methylurapidil and WB-4101 inhibited [^{3}H]prazosin binding to membranes from the dog urethra, rat submaxillary gland and liver (Fig. 4). The affinities of these α_{1A}-selective antagonists for α_1-adrenoceptors in the dog urethra were very close to those in the rat submaxillary gland and were higher than those in the rat liver (Table 2).

4. Discussion

α_1-Adrenoceptor agonists, including norephedrine (Ek et al., 1978; Öbrink and Bunne, 1978) and midodrine (Jonas, 1977; Nito, 1994), are effective in ameliorating female stress incontinence; they work by increasing the tone of the smooth muscle of the bladder base and urethra. Similar findings have been obtained in dogs with midodrine (Takahashi et al., 1991) and norephedrine (Raz and Caine, 1972). Moreover, ST-1059, an active metabolite of midodrine, arrested the urine leakage induced by electrical stimulation of abdomen of rabbits (Kontani et al., 1992).

The present study was conducted to evaluate the effects of NS-49 on intraurethral pressure and blood pressure in dogs. NS-49 caused a significant increase in intraurethral pressure at doses which did not change blood pressure; thus high urethral selectivity was observed. This urethral selectivity was confirmed in vitro: NS-49 caused strong contraction of the isolated dog urethra, but not of the carotid artery; in contrast, ST-1059, phenylephrine and noradrenaline caused contractions of both tissues with high efficacy. Comparison using only the pD_2 value may provide the possibility that the selectivity of NS-49 for urethral action is apt to be underestimated. The selectivity of an agonist should be determined not only by its affinity but also by its efficacy. In fact, the efficacy of NS-49 is substantially low in the carotid artery contraction. Therefore, NS-49 is highly selective for the urethral contraction with a high affinity and a high efficacy as compared with the carotid artery contraction.

The International Union of Pharmacology has recommended a classification of α_1-adrenoceptor into three subtypes, α_{1A}, α_{1B} and α_{1D}, that have been defined by molecular biological techniques, as well as an additional subtype, α_{1L}, that has been defined by pharmacological techniques only (Ford et al., 1994; Bylund et al., 1994; Ruffolo et al., 1994; Hieble et al., 1995).

NS-49 is a novel α_1-adrenoceptor agonist selective for the α_{1A} (Obika et al., 1995) or for both the α_{1A} and the α_{1L} subtypes (Muramatsu et al., 1995), and it has only a very weak efficacy for the α_{1B} subtype (Obika et al., 1995; Muramatsu et al., 1995). In contrast, ST-1059, phenylephrine and noradrenaline showed high efficacy for all α_1 subtypes (Obika et al., 1995). Thus, the α_{1A} selectivity of NS-49, unlike ST-1059, phenylephrine or noradrenaline, might contribute to its urethral selectivity as demonstrated in this study. In addition, the α_{1A} subtype might be primarily responsible for the increase in intraurethral pressure, and the α_{1B} and α_{1D} subtypes for the increase in blood pressure.

To confirm α_1-adrenoceptor subtypes present in the dog urethra, we compared the binding properties of [^{3}H]prazosin and the inhibitory effects of the α_{1A}-selective antagonists 5-methylurapidil and WB-4101 on [^{3}H]prazosin binding in the dog urethra with those in the rat submaxillay gland and liver, which are known to express exclusively the α_{1A} and the α_{1B} subtype, respectively (Michel et al., 1989; Bylund et al., 1994; Ford et al., 1994). These antagonists showed higher affinity for α_1-adrenoceptors in the dog urethra as well as in the rat submaxillary gland than for those in the rat liver, indicating that the α_1-adrenoceptor subtype predominantly present in the dog urethra is the α_{1A} subtype. However, [^{3}H]prazosin showed lower affinity for α_1-adrenoceptors in the dog urethra than for those in the rat submaxillary gland and liver. Therefore, α_1-adrenoceptors present in the dog urethra might have properties of the α_{1L} subtype which has low affinity for prazosin.

The relative amounts of the α_1-adrenoceptor subtypes in the prostate and in arteries have been estimated by radioligand binding assays and molecular biological techniques, i.e., the α_{1a} subtypes are predominantly expressed in human prostate, and the α_{1b} and α_{1d} subtypes in human arteries (Weinberg et al., 1994; Price et al., 1994). Hatano et al. (1994) demonstrated that the α_{1A} and α_{1B} subtypes are primarily responsible for the contraction of human urethra and internal iliac artery, respectively, in a study using α_1-adrenoceptor antagonists. However, because of a lack of α_1 subtype-selective agonists, the function of α_1 subtypes in intraurethral pressure and blood presure have not yet been elucidated. By using the α_{1A}-adrenoceptor-selective agonist NS-49, we now provide evidence that the α_{1A} subtype is primarily responsible for the control of intraurethral pressure in dogs. In fact, tamsulosin, an α_{1A}-adrenoceptor-selective antagonist (Kawabe et al., 1994; Michel and Insel, 1994) with little effects on blood pressure, is now in clinical use for the relief of the difficulty in urination caused by benign prostatic hyperplasia (Kawabe et al., 1990). However, Ford et al. (1996) reported that the contractile responses to noradrenaline in human lower urinary tissues in which the α_{1A} subtype is predominant, are mediated not by typical α_{1A} but by the α_{1L}, atypical form of α_{1A}. Because NS-49 is selective for both the α_{1A} and the α_{1L} subtypes (Muramatsu et al., 1995), the α_{1L} subtype is also considered to be responsible for the control of intraurethral pressure.

In conclusion, the α_{1A}-adrenoceptor-selective agonist NS-49, in contrast to ST-1059, produced an increase in intraurethral pressure with little effect on blood pressure. This result suggests that the α_{1A}-adrenoceptor subtype is responsible for the control of intraurethral pressure. Furthermore, because of its high urethral selectivity and minimal effect on the cardiovascular system, NS-49 might be useful in the treatment of stress incontinence.

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