

## Effects of Selective Serotonin Reuptake Inhibitors (SSRIs) on the Vasoconstriction of Isolated Rat Aorta

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선택적 Serotonin 재흡수 억제제가 흰쥐 대동맥의 수축에 미치는 영향

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국문초록

연구배경 :

serotonin, norepinephrine, 35 mM K<sup>+</sup>, 20, trazodone, imipramine, amitriptyline, norepinephrine, serotonin, fluoxetine, sertraline, 3.29 μM, amine oxidase, moclobemide, norepinephrine, Ca<sup>2+</sup>, . 결 과 : Fluoxetine, IC<sub>50</sub>가, mono-amine oxidase, moclobemide, norepinephrine, serotonin, trazodone, Ca<sup>2+</sup>

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중심 단어 :

### Introduction

Tricyclic antidepressants (TCAs) have been widely

used for the treatment of depression for over 40 years.<sup>1)</sup> However, they also elicited serious cardiovascular side effects, which could potentially limit their therapeutic

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value.<sup>2)</sup> The most frequent side effect of TCAs is orthostatic hypotension.<sup>3)</sup> It can be caused by impaired vasoconstriction and decreased myocardial contractility.<sup>4)</sup> The side effect was elicited at therapeutic doses required for psychiatric treatment, thus it could be dangerous when administered to elderly patients or patients with preexisting heart disease.<sup>3)</sup>

Selective serotonin reuptake inhibitors (SSRIs) have become the most commonly used drugs for treatment of depression, because of significantly fewer side effects than TCAs.<sup>3)5)</sup> However, the animal study for the side effects of SSRIs has not been widely conducted. Until recently, the majority of studies about the cardiovascular side effects of antidepressant treatment are clinical reports, with most investigations concentrated on TCAs.<sup>6)</sup> It had been reported that TCAs inhibited the norepinephrine-induced vasoconstriction in isolated aorta.<sup>7)</sup> This effect might be due to  $\alpha_1$ -adrenergic blocking action, which inhibits compensatory mechanism for maintaining blood pressure.<sup>8)</sup> In addition, several reports suggested that they also had a blocking action for calcium entry, and inhibited depolarization-induced vasoconstriction.<sup>7)9)</sup>

The purpose of our study was to investigate whether SSRIs could affect the vascular contraction induced by norepinephrine or high concentration of potassium ion. We also compared the effects of SSRIs on adrenergic receptor activation- and depolarization-induced vasoconstriction with that of other antidepressants.

## Materials and Methods

Male Sprague Dawley rats ( $250 \pm 50$  g) were anesthetized with sodium thiopental (50 mg/Kg) via intraperitoneal cavity. The abdomen was opened through a midline incision. The inferior vena cava was exposed and heparin (500 IU/Kg) was injected *i.v.* After opening the thoracic cavity, the descending thoracic aorta was rapidly excised and transferred into cold Tyrode solution of the following composition (in mM) : NaCl 140, KCl 5.4,  $\text{CaCl}_2$  2.0,  $\text{NaH}_2\text{PO}_4$  0.3,  $\text{MgCl}_2$  1.0, HEPES 10, glucose 10, pH 7.4 titrated with NaOH. Aortic rings (3 - 4 mm) were cleaned of loose connective tissue with special care taken not to injure

the endothelium. The rings were placed in water-jacketed baths containing Tyrode solution (37 °C, gassed with 100%  $\text{O}_2$ ), and suspended between two fine L-shaped stainless steel wires. One of the wires was connected to a force transducer (FTO3C, Grass Instruments, Quincy, MA, U.S.A.) and isometric tensions were recorded on a polygraph (7E, Grass Instruments). Rings were allowed to equilibrate for 60 min before each experiment under a resting tension of 1 g. During the equilibration period, the solution was replaced every 15 min.

Vasoconstriction caused by norepinephrine (100 nM) or KCl (35 mM) was examined two or three times in quiescent rings until successive responses remained constant. When KCl was administered, osmotic adjustment was carried out by replacing the same concentration of NaCl with KCl. After pretreatment with various concentrations of antidepressant for 20 min, we applied norepinephrine or KCl again.

The effects of antidepressants on norepinephrine- or KCl-induced vasoconstriction were expressed as means of percent inhibition  $\pm$  S.E.M. The concentration-response curves and  $\text{IC}_{50}$  values were obtained from least-squares non-linear regression.  $\text{IC}_{50}$  is defined as the concentration of antidepressant in the presence of which the maximal effect of norepinephrine or KCl is reduced by 50%.

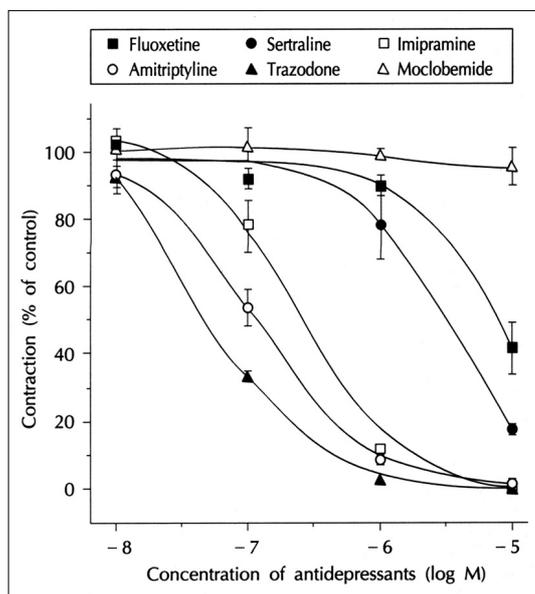
Antidepressants used in experiments were kindly donated from as follows : imipramine and amitriptyline from Myung-In (Seoul, Korea), fluoxetine from Dae-Woong Lilly (Seoul), sertraline from Korea Pfizer (Seoul), trazodone from Kuk-Je (Seoul) and moclobemide from Korea Roche (Seoul). Other drugs were obtained from Sigma Chemical (St. Louis, MO, U.S.A.). All drugs were dissolved in distilled deionized water.

## Results

The function of the endothelium was checked at the beginning of experiment with 1  $\mu\text{M}$  acetylcholine in rings precontracted with 100 nM norepinephrine.<sup>10)</sup> We discarded rings showing less than 80% relaxation, which was interpreted as endothelial damage. In endothelium-intact aortic rings with resting tension,

contractile response to 100 nM norepinephrine was  $1.11 \pm 0.27$  g. After pretreatment with antidepressant for 20 min, norepinephrine-induced vasoconstriction was decreased in a concentration-dependent manner.

Among various antidepressants, trazodone (atypical antidepressant) inhibited norepinephrine-induced vasoconstriction most potently (Fig. 1). The  $IC_{50}$  value of trazodone was 55 nM, which is lower than therapeutic plasma concentration. TCAs (amitriptyline and imipramine) also potently inhibited norepinephrine-induced



**Fig. 1.** The effects of antidepressants on the responses to norepinephrine (NE) in isolated rat aorta. After pretreatment with antidepressant for 20 min., vasoconstriction induced by NE was measured and expressed as a percent of control response. The data represents mean  $\pm$  S.E.M. from 4 - 6 aortae.

**Table 1.**  $IC_{50}$  values of antidepressants to norepinephrine (NE)- and high  $K^+$ -induced vasoconstriction

Antidepressants	100 nM NE <sup>a</sup>	35 mM $K^+$ <sup>a</sup>	NE / $K^+$ <sup>b</sup>
Fluoxetine	$8.65 \times 10^{-6}$	$3.29 \times 10^{-6}$	2.63
Sertraline	$2.44 \times 10^{-6}$	$5.75 \times 10^{-6}$	0.42
Imipramine	$2.10 \times 10^{-7}$	$5.45 \times 10^{-6}$	0.04
Amitriptyline	$1.10 \times 10^{-7}$	$1.31 \times 10^{-5}$	0.008
Trazodone	$5.49 \times 10^{-8}$	-	-
Moclobemide	-	-	-

<sup>a</sup> : The concentration ( $IC_{50}$ ) of antidepressant in the presence of which the maximal effect of NE or KCl is reduced by 50%

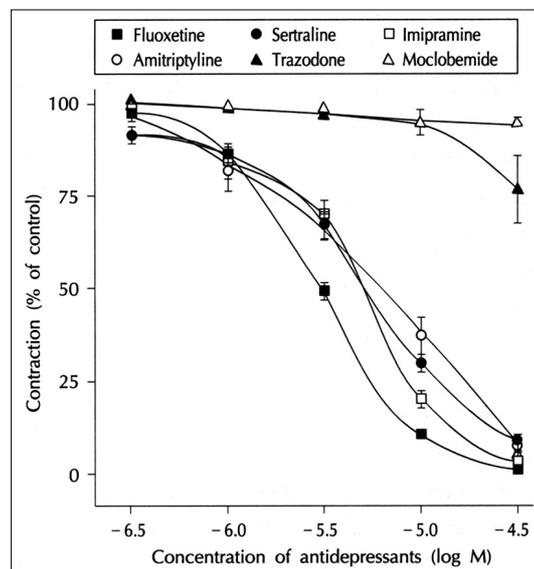
<sup>b</sup> : The ratio of  $IC_{50}$  values of NE-induced to KCl-induced vasoconstriction

vasoconstriction, and  $IC_{50}$  values were 110 and 210 nM (Table 1). SSRIs (fluoxetine and sertraline) showed less inhibitory effects than TCAs on norepinephrine-induced vasoconstriction, and moclobemide did not elicit any effect.

Vasoconstriction induced by 35 mM  $K^+$  ( $1.55 \pm 0.23$  g), which produces depolarization of vascular smooth muscle, was also attenuated by pretreatment with antidepressants (Fig. 2). Fluoxetine and sertraline were potent inhibitors and  $IC_{50}$  value of fluoxetine on depolarization-induced vasoconstriction was  $3.29 \mu M$  (Table 1). The effects of imipramine and amitriptyline were less than that of SSRIs, and the  $IC_{50}$  values were 5.5 and  $13.1 \mu M$  (Table 1). However, trazodone and moclobemide did not influence the vasoconstriction induced by depolarization.

## Discussion

The actions of various kinds of antidepressants on rat isolated aorta were examined using norepinephrine, which produces contraction by activating  $\alpha_1$ -adrenergic receptor,<sup>11)</sup> and high  $K^+$  concentration, which produces



**Fig. 2.** The effects of antidepressants on the responses to high  $K^+$  in isolated rat aorta. After pretreatment with antidepressant for 20 min., vasoconstriction induced by 35 mM  $K^+$  was measured and expressed as a percent of control response. The data represents mean  $\pm$  S.E.M. from 3 - 6 aortae.

contraction by membrane depolarization.<sup>12)</sup> The results of present study show that TCAs and trazodone blocked norepinephrine-induced vasoconstriction potently. But only high concentration of TCAs could block the high K<sup>+</sup>-induced vasoconstriction. Their IC<sub>50</sub> values for high K<sup>+</sup>-induced vasoconstriction were 30 - 100 times higher than those for norepinephrine-induced vasoconstriction.

In the meanwhile, SSRIs inhibited high K<sup>+</sup>-induced vasoconstriction more potently than NE-induced vasoconstriction. Depolarization caused by high K<sup>+</sup> concentration opens voltage-operated Ca<sup>2+</sup> channels (VOCC) of vascular smooth muscle. So the inhibitory effect on high K<sup>+</sup>-induced vasoconstriction could be correlated with blocking VOCC. Until now, blocking activity profiles of antidepressants to VOCC of vascular smooth muscle had not been reported. However, we compared the inhibitory actions of antidepressant on L-type VOCC of cardiac myocyte (unpublished), and IC<sub>50</sub> values of fluoxetine and sertraline on Ca<sup>2+</sup> inward current (2.8 μM and 2.3 μM) were similar to the results of this study. This can be interpreted as evidence that SSRIs inhibit high K<sup>+</sup>-induced vasoconstriction by blocking VOCC.

Another reports on human brain tissue, TCAs and trazodone had potent blocking action for α<sub>1</sub>-adrenergic and muscarinic receptor.<sup>13)</sup> These effects are related to certain adverse effects in depressive patients. As discussed above, the concentration range of TCAs and trazodone to block norepinephrine-induced vasoconstriction was lower than that used clinically (0.57 - 1.07 μM).<sup>6)</sup> The concentrations of SSRIs to block depolarization-induced vasoconstriction were slightly higher than therapeutic plasma levels. However it is difficult to relate the in vivo plasma concentrations to those of isolated aorta.<sup>14)</sup> It has been known that TCAs and SSRIs are lipophilic drugs, so they have a greater affinity for tissues, where they may reach higher concentrations than in plasma.<sup>6)15)</sup> Further, antidepressants are typically prescribed to depressed patients for an extended period of time, so it is possible that the inhibitory effects of SSRIs could be elicited at a lower concentrations if drug exposure were lengthened.

In conclusion, our results indicate that antidepressants

have differential effects on receptor activation-induced and depolarization-induced vasoconstriction. On the contrary to TCAs and trazodone, SSRIs have potent inhibitory effects on depolarization-induced contraction and those actions could be caused by blocking Ca<sup>2+</sup> entry through L-type Ca<sup>2+</sup> channel.

## Summary

**Background :** One of the most common side effects of antidepressant medication is orthostatic hypotension, which can be caused by impaired vasoconstriction. This study was designed to compare the inhibitory effects of antidepressants, including selective serotonin reuptake inhibitors (SSRIs), on the contractile responses to α<sub>1</sub>-adrenergic receptor activation and depolarization in isolated rat aorta.

**Methods :** Vascular rings were suspended for the measurement of isometric tension in a water-jacketed bath filled with Tyrode solution. After pretreatment with antidepressant for 20 min, vasoconstriction induced by norepinephrine (NE) or 35 mM K<sup>+</sup> was measured and compared to the control response.

**Results :** Whereas trazodone and tricyclic antidepressants (TCAs) selectively inhibited NE-induced vasoconstriction, SSRIs inhibited depolarization-induced vasoconstriction more potently. The IC<sub>50</sub> value of fluoxetine on depolarization-induced vasoconstriction was 3.29 μM, which is consistent with the previous results on L-type Ca<sup>2+</sup> currents of cardiac myocyte. Moclobemide, a monoamine oxidase inhibitor, had no effect on vasoconstriction induced by either α<sub>1</sub>-adrenergic receptor activation, or depolarization.

**Conclusion :** These results suggest that SSRIs, different from TCAs and trazodone, have potent inhibitory actions to depolarization-induced contraction that may be due to blocking Ca<sup>2+</sup> entry through L-type Ca<sup>2+</sup> channel.

**KEY WORDS :** Selective serotonin reuptake inhibitor · Antidepressant · Vasoconstriction.

## REFERENCES

- 1) Kuhn R. *The treatment of depressive state with G 22355*

- (*imipramine hydrochloride*). *Am J Psychiatry* 1958;115:459-64.
- 2) Amsterdam J, Brunswick D, Mendels J. *The clinical application of tricyclic antidepressant pharmacokinetics and plasma levels. Am J Psychiatry* 1980;137:653-62.
  - 3) Glassman AH, Preud'homme XA. *Review of the cardiovascular effects of heterocyclic antidepressant. J Clin Psychiatry* 1993;54 (suppl 2):16-22.
  - 4) Glassman AH, Bigger JT Jr, Giardina EGV. *Clinical characteristics of imipramine-induced orthostatic hypotension. Lancet* 1979;1:468-72.
  - 5) Roose SP, Glassman AH. *Antidepressant choice in the patient with cardiac disease; Lessons from the cardiac arrhythmia suppression trial studies. J Clin Psychiatry* 1994;55:83-7.
  - 6) Marshall JB, Forker AD. *Cardiovascular effects of tricyclic antidepressant drugs: Therapeutic usage, overdose, and management of complications. Am Heart J* 1982;103:401-14.
  - 7) Auguet M, Clostre F, DeFeudis V. *Effects of antidepressants on receptor-activated and Ca<sup>2+</sup>-activated contractions of rabbit isolated aorta. Gen Pharmac* 1986;17:607-10.
  - 8) Baldessarini RJ. *Drugs and the treatment of psychiatric disorders. In: The pharmacological basis of therapeutics. Gilman AG, Rall TW, Nies AS, Taylor P, 8th ed. p409-410, New York, Pergamon Press, 1991.*
  - 9) Perez-Vizcaino F, Carron R, Delpon E, Duarte J, Tamargo J. *Effects of (S)-nafenodone on  $Ca^{2+}$  fluxes and contractions in rat isolated vascular smooth muscle. Eur J Pharmacol* 1993;232:105-11.
  - 10) Furchgott RF, Zawadzki JV. *The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine. Nature* 1980;288:373-6.
  - 11) Apperley E, Humphrey PPA, Levy GP. *Receptors for 5-hydroxytryptamine and noradrenaline in rabbit isolated ear artery and aorta. Br J Pharmac* 1976;58:211-21.
  - 12) Van Breemen C. *Calcium requirement for activation of intact aortic smooth muscle. J Physiol Lond* 1977;272:317-29.
  - 13) Rachelson E, Nelson A. *Antagonism by antidepressants of neurotransmitter receptors of normal human brain in vitro. J Pharmacol Exp Ther* 1984;230:94-102.
  - 14) Delpon E, Tarmago J, Sanchez-Chapula J. *Further characterization of the effects of imipramine on plateau membrane currents in guinea-pig ventricular myocytes. Naunyn-Schmiedeberg's Arch Pharmacol* 1991;344:645-52.
  - 15) Elonen E, Linnolia M, Lukkari I, Mattila MJ. *Concentration of tricyclic antidepressants in plasma, heart and skeletal muscle after their intravenous infusion to anesthetized rabbits. Acta Pharmacol Toxicol* 1975;37:274-81.