Influence of Amineptine on Changes of Blood Pressure Evoked by Norepinephrine and Dopamine

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The influence of amineptine, an antidepressant currently employed having mainly selective dopaminergic neurochemical activity, on the pressor responses evoked by norepinephrine (NE) and dopamine (DA) was studied in anesthetized whole rats.

Amineptine at doses of 0.5, 1.5, and 5.0 mg/kg/30 min infused into the femoral vein of the rat caused a dose-related inhibition of the pressor responses of NE and DA.

The hypertensive responses of NE and DA augmented by pretreatment with reserpine, a catecholamine depletor, were also clearly depressed following the infusion of amineptine with a rate of 1.5 mg/kg/30 min.

Furthermore, the pressor responses of NE and DA potentiated by pretreatment with debrisoquin, a sympathetic neuron blocker, were markedly diminished after pretreatment with the infusion of amineptine at the above same rate (1.5 mg/kg/30 min).

These experimental results demonstrate that amineptine causes an inhibitory effect on the pressor responses evoked by NE and DA. It is thought that the amineptine effect may be due to the blockade of the peripheral adrenergic alpha-receptors in addition to the previously described uptake inhibition of dopamine.

Key Words: Amineptine, Peripheral adrenergic alpha-receptor blockade

INTRODUCTION

Amineptine (S 1694), a tricyclic derivative consisting of an imipramine tricyclic nucleus and a long, 7-carbon atom aliphatic aminoacid chain bonded to the central ring[1] is one of the most interesting second generation antidepressants, as shown in Fig. 1. It is well-known that amineptine has mainly selective dopaminergic neurochemical activity and acts specifically on the inhibition of reuptake and on the increase of dopamine (DA) release at the synaptic level[2~4] and that it affects the meso-limbic and meso-cortical dopaminergic pathways which control mood and behavioral changes, alertness, and vigilance[5].

Like other dopaminergic receptor agonists, amineptine increases locomotor activity and induces streotyped movements and hyperthermia in rats[3]. It appears to inhibit dopamine uptake[6]; it raises striatal homovanyllic acid levels[3~4] and reduces dopamine turnover[6] without significantly affecting 3, 4-dihydroxyphenyl acetic acid.

The blockade of the neuronal uptake of norepinephrine (NE) and (or) serotonin is considered to be the main mechanism of action of most antidepressant drugs[7~9]. However, the clinical efficacy of several antidepressants which increase dopaminergic transmissions suggests another possible mechanism. Among the tricyclic drugs, amineptine has been reported to display a peculiar biochemical effect as it inhibits the neuronal dopamine (DA) uptake. However, there is some controversy over the mechanism of pharmacological action induced by amineptine.

Mocaer[13] (1984) and Ceci et al[14]. (1986) have

reported that amineptine selectively inhibits the reuptake of DA with the releasing effect of it, but without any changes in level of NE or serotonin while Bonnet et al[15]. (1987) has found that amineptine inhibits DA uptake and is devoid of catecholamine effects and that it displays a relatively low affinity for the NE uptake system.

It is also known that amineptine does not show major effects on liberation or reuptake of NE at doses in which it has potent effects upon the dopaminergic pathways. Nevertheless it modifies the activity of functional beta-adrenergic postsynaptic receptors[16]. Furthermore, a number of functional as well as receptor binding studies have revealed that several of the antidepressant drugs in addition to their reuptake blockade inhibit postsynaptic receptors[17~21]. This receptor blocking action could at least theoretically counteract the beneficial effect of the reuptake inhibition and might be responsible for a number of unwanted effects and complications of prolonged treatment.

Therefore, in the present study it was attempted to investigate first, whether amineptine affects the dopaminergic and noradrenergic uptake system and also their release, and second, whether it has noradrenergic or dopaminergic postsynaptic receptor blocking activities, the influence of amineptine on the changes of blood pressure evoked by norepinephrine and dopamine was examined in the anesthetized rats.

MATERIALS AND METHODS

1. Experimental Animals

Adult normotensive rats (Sprague-Dawley) of both sexes, weighing 180 to 250 grams, were used in these experiments. The animals were housed individually in separate cages, and food (Cheil Animal Chow®) and tap water were allowed ad-libitum at least for a week to adapt to experimental circumstances. On the day of the experiment, the rats was anesthetized with 40 mg/kg pentobarbital-Na (Nembutal-Na®) intraperitoneally. A tracheotomy was performed by inserting a cannula into the trachea of the animals tied in a supine position on fixing panels to prevent movement. Body temperature was maintained at 37°-38°C in a thermostatically controlled blanket and heating lamp.

2. Measurement of Blood Pressure

In order to observe changes in arterial pressure, one of the common carotid arteries was catheterized with polyethylene tubing (outsidediameter [o.d.]: 0.45 mm). The tubing was connected to a pressure transducer (Gould Co.), and the pulse of the mean arterial blood pressure was recorded on a polygraph (Beckamn Co.) continuously. The artery tubing was filled with heparin solution (400 I.U.) to prevent blood coagulation during the experiment. Another cannulation with polyethylene tubing (o.d.: 0.35 mm) was made into a femoral vein for the administration of drugs and supplemental anesthetic agents as needed to maintain light surgical anesthesia. Each rat was left undisturbed for at least 30 minutes after completion of the operative procedures to permit cardiovascular parameters to be stabilized. Dopamine and norepinephrine were administered at intervals of 20 minutes.

3. Drugs

The sources of the drugs used in the present study are as follows: amineptine hydrochloride (Les Laboratoires Servier, France), reserpine (Azoo Pharmaceutical Co. Korea), debrisoquine sulfate (Chong Keun Dang Pharmaceutical Co., Korea), and 1-norepinephrine bitartrate and 1-dopamine hydrochloride (Sigma Chemical Co., U.S.A.).

The drugs were dissolved in 0.9% sodium chloride solution on the day of the experiment and stored in a refrigerator, except for norepinephrine and dopamine. Norepinephrine and dopamine were prepared in 0.9% acid saline (pH=4.0). A 30% ethyl alcohol-sodium chloride solution was added to the amineptine solution to facilitate dissolution. All durgs were given into a femoral vein in a volume of 0.2 ml in 0.9% saline, except for administration of amineptine, which was infused into a jugular vein at a given rate.

4. Statistical Analysis

Statistical significance between groups was determined by utilizing the Student's "t"test. Data obtained from the animals which served as the corresponding control were analyzed for the significance using the t-test for unpaired observation. A P-value of less than 0.05 was considered to represent statistically significant change, unless specifically noted in the text. Values given in the text refer to means with standard errors (S.E.) of the mean.

RESULTS

1. Effect of Amineptine on the Changes of Arterial Blood Pressure Evoked by NE and DA

The experimental rats were allowed to stabilize at least 30 min before experimental protocols were initiated. When cardiovascular parameters became
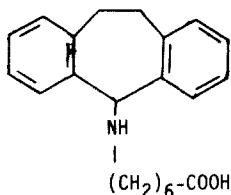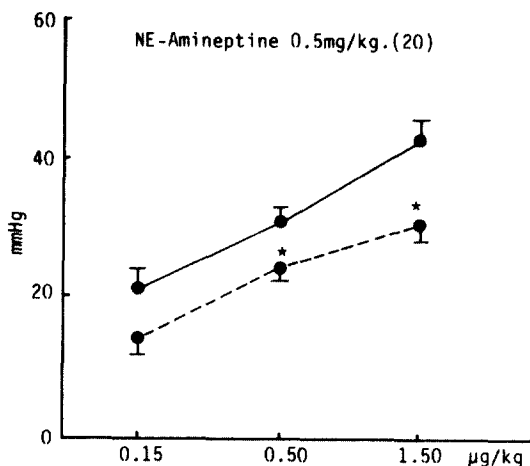

Fig. 1. *The chemical structure of amineptine*

Fig. 2. *Influence of amineptine (0.5 mg/kg.I.V.) on norepinephrine-evoked pressor responses. Amineptine was infused into a femoral vein at a rate of 0.5 mg/kg/30 min after obtaining control values of the norepinephrine-evoked pressor effects. The solid line denotes control responses before the administration of amineptine and the dotted line responses after amineptine. Abscissa: Pressor response evoked by norepinephrine in mmHg. Ordinate: Doses of norepinephrine in $\mu g/kg$. The vertical bars indicate standard error of the mean as compared with differences between the values before and after amineptine. The numeral in the upper bracket represents the number of experimental animals. *: $p < 0.05$, NE: Norepinephrine*

stabilized, drugs were injected into a femoral vein of the rat.

First, to determine the dosing schedule, amineptine with a dose of 0.5 mg/kg/30 min at a rate of 0.05 ml/min was infused. Before the infusion of amineptine, NE at doses of 0.15, 0.50, and 1.5 ug/kg injected intravenously caused a marked elevation in blood pressure of 20.7 ± 2.5, 31.1 ± 3.4 and 43.2 ± 4.3 mmHg, respectively. But after amineptine infusion, repeated administration of the same dose of NE as previously mentioned resulted in greatly reduced responses of 14.0 ± 3.9 (NS), 24.5 ± 3.8 ($p < 0.05$), and 30.8 ± 3.7 ($p < 0.05$), mmHg, respectively, from 20 rats as shown in Fig. 2.

Intravenous injection of dopamine at doses of 10.30 and 100 ug/kg before amineptine elicited increases in arterial pressure of 11.9 ± 2.3, 16.9 ± 2.8, and 22.8 ± 2.8 mmHg, respectively, while repetitive administration of the same dose as the above following injection of amineptine at a dose of 0.5 mg/kg/30 min inhibited the responses of blood pressure by 8.7 ± 2.2 (NS), 12.6 ± 1.7 ($p < 0.05$), and 16.8 ± 2.4 ($p < 0.05$)mmHg from 19 rats, respectively, as shown in Fig. 3.

Increasing the dose of amineptine to 1.5 mg/kg, the NE-evoked pressor responses at doses of 0.15, 0.5 and 1.5 ug/kg were clearly reduced to 15.0 ± 2.9 (n=20, $p < 0.01$), 24.5 ± 3.8 (n=20, $p < 0.01$), and 30.8 ± 3.7 (n=20, $p < 0.001$)mmHg, respectively, by comparing then with their control of 27.1 ± 1.9, 36.5 ± 3.9, and 51.1 ± 5.1 mmHg, respectively, as
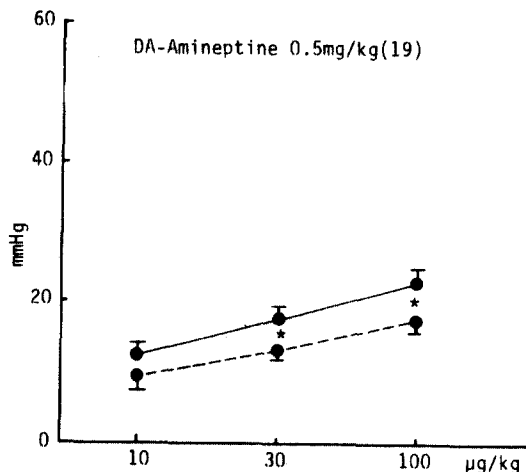

Fig. 3. *Influence of amineptine (0.5 mg/kg.I.V.) on dopamine-induced pressor responses. Other legends and methods are the same as in Fig. 2. DA: dopamine, *: $p < 0.05$*
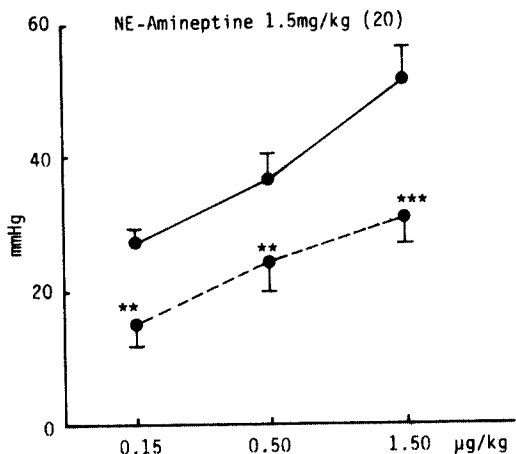
Fig. 4. Influence of amineptine (1.5 mg/kg.l.V.) on norepinephrine-evoked pressor responses. Other legends and methods are the same as in Fig. 2. **:p < 0.01, ***: p < 0.001
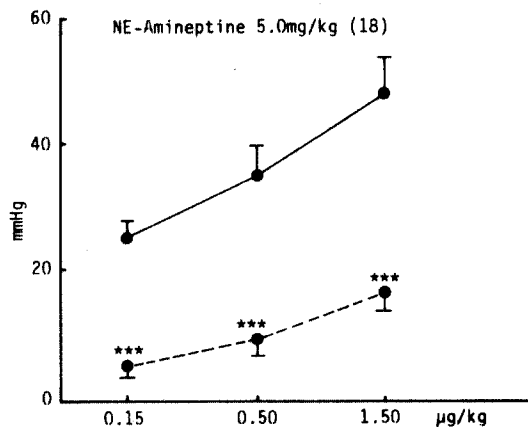

Fig. 6. Influence of amineptine on norepinephrine-evoked pressor responses. Other legends and methods are the same as in Fig. 2. ***: p < 0.001
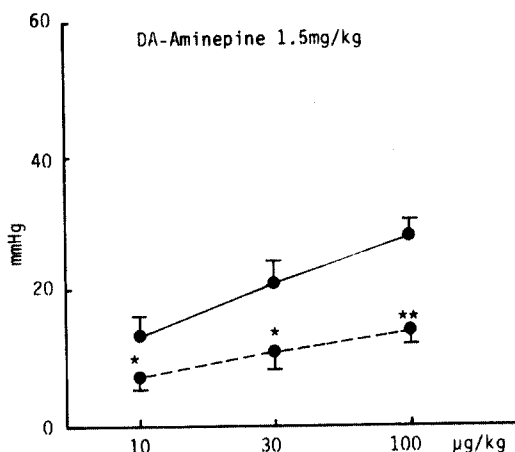

Fig. 5. Influence of amineptine (1.5 mg/kg.l.V.) on dopamine-induced pressor responses. Other legends and methods are the same as in Fig. 2. *: p < 0.05, **: p < 0.01
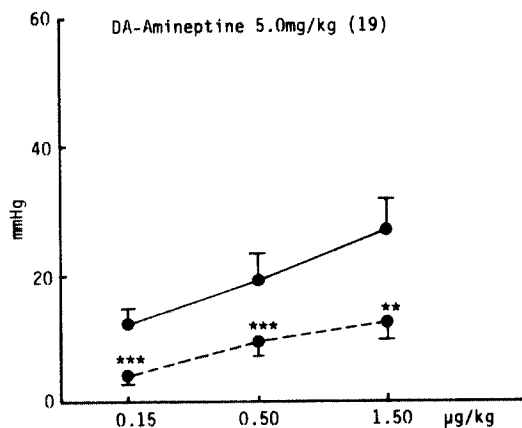

Fig. 7. Influence of amineptine (5.0 mg/kg, I.V.) on dopamine-induced pressor responses. Other legends and methods are the same as in Fig. 2. **: p < 0.01, ***: p < 0.001

shown in Fig. 4. DA-induced pressor responses at doses of 10, 30, and 100 ug/kg before amineptine were 12.7±2.7, 20.5±3.0, and 28.7±2.1 mmHg in 18 rats, respectively, but these responses after amineptine infusion were significantly inhibited to 6.7±1.0 (p < 0.05), 10.4±2.4 (p < 0.05), and 13.9± 20.9 (p < 0.01), respectively, as shown in Fig. 5.

Fig. 8 and 9 show the representative responses

of NE-and DA-evoked blood pressure following the infusion of amineptine at a dose of 1.5 mg/kg/ 30 min.

When the dose of amineptine was increased to 5.0 mg/kg, the NE-evoked pressor responses at 0. 15, 0.50, and 1.5µg/kg were much more markedly blocked by 4.4±1.3 (n=18, p < 0.001), 9.8±2.7 (n=18, p < 0.001), and 17.2±2.7 (n=18, p < 0.001), respectively, in comparison with each control response of 24.7±2.1, 35.1±4.1 and 48.6±5.1
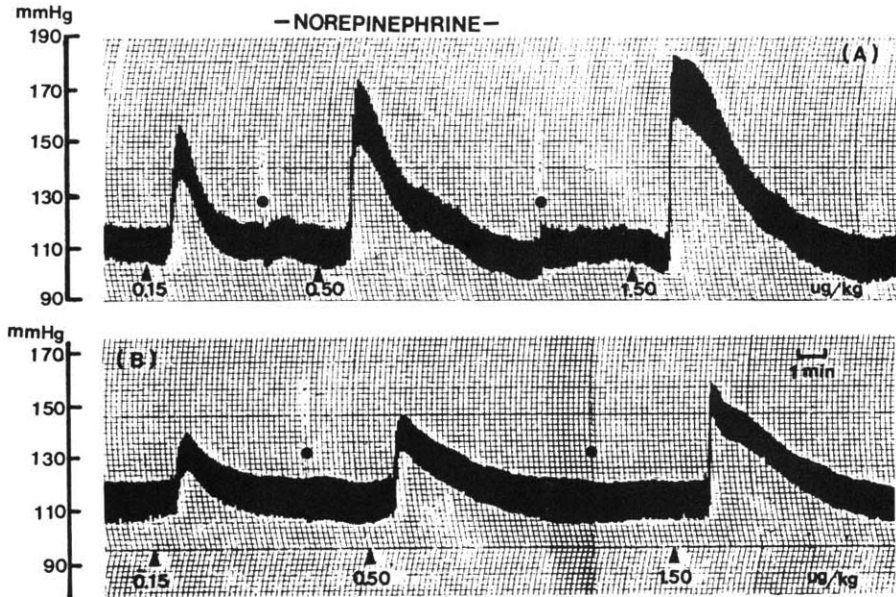
Fig. 8. *The inhibition of norepinephrine-evoked pressor responses by amineptine. At arrow marks, the indicated doses of norepinephrine (0.15, 0.50, and 1.50 μg/kg) were given intravenously at 15-minute intervals. Between (A) and (B) amineptine (1.5 mg/kg/30 min) was infused into a femoral vein. Ordinate, blood pressor responses in mmHg. Time: 1 min. The black circle represents stoppage for 15 min.*
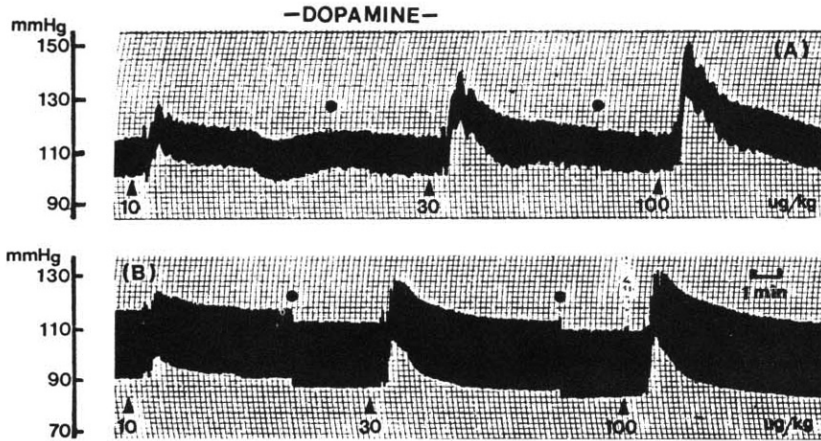

Fig. 9. *The inhibition of dopamine-evoked pressor responses by amineptine. Other methods and legends are the same as in Fig. 8.*

mmHg in 18 rats, respectively, as shown in Fig. 6. DA-induced pressor responses at 10, 30, and 100 μg/kg before amineptine treatment were 12.6±18.2, 18.8±3.8 and 26.7±4.7 mmHg from 19 experiments, respectively, but following infusion of amineptine with a dose of 5.0 mg/kg/30 min, they were clearly depressed to 4.0±0.4 (p<0.001), 9.

8±2.4 (p<0.01), and 11.2±2.5 (p<0.01) mmHg, at the above same doses, respectively. Fig. 7 shows that the pressor responses evoked by DA were inhibited by amineptine pretreatment. In all subsequent experiments, a dose of 1.5 mg/kg of amineptine was used. The effect of amineptine itself on blood pressure response at doses used in the
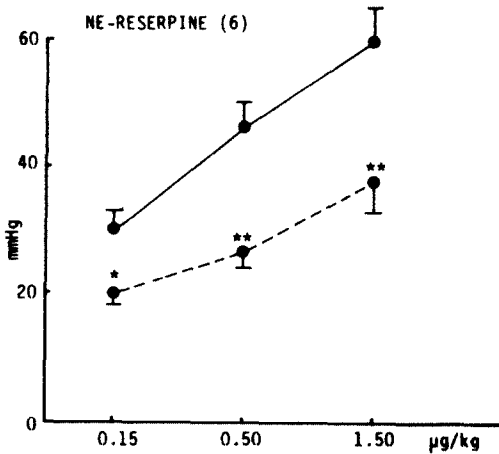
Fig. 10. *Influence of amineptine on pressor responses of norepinephrine potentiated by reserpine. Reserpine (3 mg/kg) was given intra muscularly about 48 hours before administration of amineptine. The solid line represents the response of norepinephrine 48 hours after reserpinization and the dotted line responses after amineptine (1.5 mg/kg/30 min, I.V.). Other legends and methods are the same as in Fig 2. **: p<0.01*
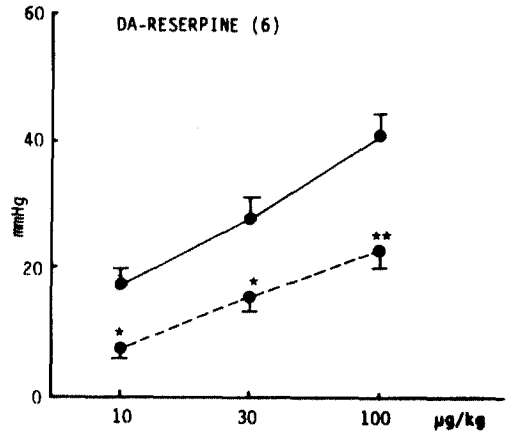
Fig. 11. *Influence of amineptine on pressor responses of norepinephrine potentiated by reserpine. Other legends and methods are the same as in Fig. 2 and 8. *: p<0.05, **:p<0.01*

present investigation was negligible (unpublished result).

2. Effect of Amineptine on NE-and DA-Evoked Pressor Responses in Reserpinized Rats

Reserpine is known to deplete stores of catecholamines and 5-HT in many organs, including the brain and adrenal medulla[22]. Therefore, it is of particular interest to examine the effect of amineptine on the pressor responses of NE and DA potentiated by pretreatment with reserpine. In the present experiment, reserpine was injected subcutaneously in the rats with a dose of 3 mg/kg about 48 hours before administration of amineptine. After reserpinization, the original arterial pressure was maintained between 50 and 70 mmHg through all the experiments.

NE-evoked arterial pressor responses at doses of 0.15, 0.50 and 1.50 μg/kg were markedly augmented to 29.3$\pm$2.7, 46.0$\pm$4.0, and 60.1$\pm$5.2 mmHg, respectively, while following the pretreatment amineptine (1.5 mg/kg/30 min) responses of NE at the same doses of amineptine as before were significantly diminished by 20.1$\pm$2.0 (N=6,

p<0.05), 27.4$\pm$2.1 (n=6, p<0.01), and 38.6$\pm$3.9 (n=6, p<0.01)mmHg, respectively, as shown in Fig. 10. In a similar fashion as the NE responses, DA-induced hypertensive responses at doses of 10, 30, and 100 μg/kg after reserpinization were greatly enhanced to 17.0$\pm$2.0, 28.2$\pm$2.7 and 40.9$\pm$3.1 mmHg in 6 rats, respectively. While following the infusion of amineptine (1.5 mg/kg/30 min), the pressor responses of DA at the above same doses were markedly inhibited to 7.2$\pm$1.1 (p<0.05), 15.4$\pm$2.2 (p<0.05), and 22.9$\pm$2.5 (p<0.01) mmHg, respectively. Fig. 11 shows that DA-induced pressure after reserpinization is definitely depressed by pretreatment with amineptine.

3. Effect of Amineptine on NE-and DA-Evoked Pressor Responses Enhanced by Debrisoquin

Since it is known that debrisoquin is a postganglionic sympathetic blocking agent whose mode of action presumably is the prevention of the release of NE from its peripherally-located stores at the neuroeffector site[23], and that it also potentiates the pressor responses evoked by NE or tyramine[24~25], it is very exciting to examine the effect of amineptine on NE-and DA-induced pressor responses augmented by debrisoquin.

Debrisoquin (3.0 mg/kg) was administered intravenously in order to block the sympathetic nerve endings and to induce catecholamine supersensitivity at least 30 min before the infusion of
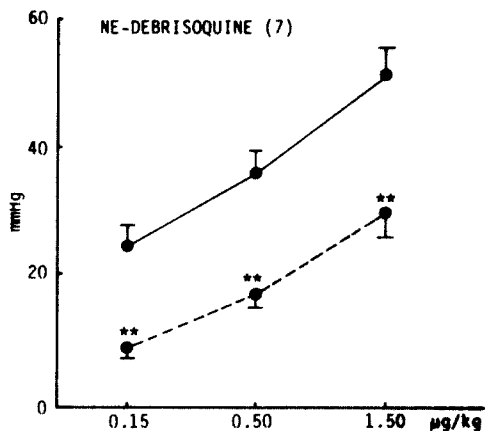
Fig. 12. *Influence of amineptine on pressor responses of norepinephrine potentiated by debrisoquine. Debrisoquine was injected intravenously about 60 min before administration of amineptine. Other legends and methods are the same as in Fig. 2. and 10.* **: $p < 0.01$
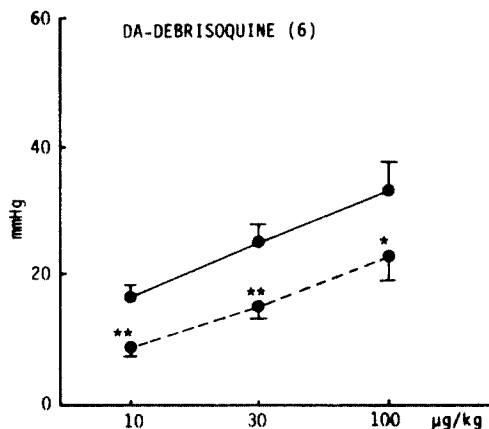

Fig. 13. *Influence of amineptine on pressor responses of dopamine potentiated by debrisoquine. Other legends and methods are the same as in Fig. 2. and 10.* *: $p < 0.05$, **: $p < 0.01$

amineptine. In 7 rats, the pressor responses evoked by NE at doses of 0.15, 0.50 and 1.5 μg/kg after pretreatment with debrisoquin were clearly potentiated to 24.4 ± 2.1, 35.2 ± 3.2, 51.4 ± 3.8 mmHg, respectively, but following the infusion of amineptine the responses of NE at the above same doses were remarkably depressed to 7.9 ± 1.0 (p <

0.01), 16.2 ± 2.7 (p < 0.01), and 29.6 ± 3.7 (p < 0.01) mmHg, respectively. Fig. 12 indicates that the pressure responses of NE enhanced by debrisoquin are considerably inhibited by amineptine administration.

In addition, dopamine-evoked pressor responses at doses of 10, 30, and 100 μg/kg, i.v. following debrisoquin (3.0 mg/kg) were distinctly augmented to 16.1 ± 2.0, 24.9 ± 2.4, and 32.7 ± 3.8 mmHg, respectively, while after pretreatment with amineptine (3.0 mg/kg) the responses of DA at the above same dose were significantly diminished to 8.1 ± 1.1 (n=6, p < 0.01), 14.9 ± 2.2 (n=6, p < 0.01), and 22.5 ± 3.4 (n=6, p < 0.05) mmHg, respectively, as shown in Fig. 13.

DISCUSSION

The present investigation demonstrates that amineptine infused into a femoral vein of the rat causes a marked reduction in the pressor responses evoked by NE and DA. It seems that this inhibitory effect of amineptine may be due to the blockade of peripheral adrenergic alpha-receptors. However, the present data do not agree with the previous results[2,13~15], of some investigators in which amineptine acts on the inhibition of reuptake and on the release of DA at the synaptic level while agreeing with functional as well as receptor binding studies revealing that several antidepressant drugs, in addition to their reuptake blockade, inhibit postsynaptic receptors[17~21]. If amineptine is a selective inhibitor of reuptake or a releasing agent of dopamine as described previously[2~4] in the present study, amineptine should potentiate the pressor responses of NE or DA. In general, the main mechanism of action of tricyclic antidepressants is thought to be due to the blockade of the neuronal uptake of NE and/or serotonin.

The supersensitivity to catecholamines has been studied mostly on the nictitating membrane where 2 types of supersensitivity may exist[26]. A "presynaptic" supersensitivity develops after surgical denervation and correlates with the degeneration of adrenergic nerve terminals. It is specific for catecholamines and related amines and develops within 48 hours after denervation. It is undoubtedly related to the absence of the catecholamine uptake mechanism. Another type of supersensitivity, which is nonspecific in that it applies not only to catecholamines but also to acetylcholine and other agonists, develops slowly after surgical denerva-

tion or decentralization. It appears to be post-synaptic and requires weeks for its development. This postsynaptic supersensitivity is a consequence of reduced levels of the transmitter. Cocaine[26~27], some antihistaminics[28~29], and tricyclic antidepressants[30~33] cause presynaptic supersensitivity as a consequence of interference with catecholamine reuptake by the adrenergic terminals. On the other hand, chronic administration of reserpine leads to a postsynaptic type of supersensitivity by chronic depletion of the transmitters.

As mentinoed above, it is thought that from the present work amineptine does not produce any enhancement of the pressor responses evoked by NE and DA, differing from the cases of other tricyclic antidepressants[30~33]. However, in the present work in view of the the fact that amineptine clearly depressed the pressor responses of DA and NE, it is felt that amineptine rather possesses the peripheral adrenergic alphareceptor blockade. In support of this idea, in the present study amineptine also markedly inhibited the pressor responses of NE and DA augmented by the pretreatment with reserpine or debrisoquine.

Generally, it is well-known that pretreatment with reserpine[26] or debrisoquin[24~25] causes the augmentation of the pressor responses evoked by catecholamines. However, in terms of the finding that amineptine rather reduced the pressor responses of NE or DA as well as those of NE or DA potentiated by the pretreatment with reserpine or debrisoquin, it is felt that amineptine possesses the activity of peripheral adrenergic alpha-receptors at the doses used in the present investigation. In confirmation of this blockade of adrenergic alpha-receptors by amineptine, it is found that same tricyclic antidepressants also have high affinities for alpha-adrenergic binding sites in the brain and that this property has been linked to the ability of these drugs to reduce psychomotor agitation and to produce sedation[18].

Differential effects on psychomotor agitation and sedation-hypotension may be related to relative alpha-noradrenergic blocking actions. In the absence of alpha-noradrenergic blocking activity, all the tricyclic antidepressants may cause a similar degree of psychomotor activation. However, the alpha-blocking properties of the tertiary amines would counteract such effects and also confer a capacity to relieve agitation and to cause sedation and hypotension[18].

In general, in experiments to study the effect of drugs on alpha-receptors in cerebral cortex in vitro, 2 different radioactive ligands are used: 1 antagonistic ([^{3}H] WB4101) and 1 agonistic ligand ([^{3}H] clonidine)[34~35].

Two ligands appear to interact with different alpha-adrenergic receptors and it has been suggested that [^{3}H] clonidine labels presynaptic receptors as well as postsynaptic receptors[36]. U'Prichard et al[37]. (1981) have also reported that most of the tricyclic antidepressants including (in order of potency) amitriptyline, clomipramine, nortriptyline, imipramine, mianserin, desipramine, and maprotiline have a high affinity for antagonistic receptors. Furthermore, they also showed that some antidepressants inhibited [^{3}H] WB4101 binding in about the same concentration as they inhibited the uptake of [^{3}H] noradrenaline. Peroutka et al[38]. (1977) have suggested that there is a significant correlation between the sedative effects of neuroleptic drugs and their ability to block alpha-adrenergic receptors.

As shown in the above previous reports, it is thought that in the present study amineptine may cause the blockade activity of peripheral adrenergic alpha-receptors, resulting in a significant inhibition of the pressor reponses evoked by norepinephrine and dopamine. However, Labrid[16] (1984) has reported that the action of amineptine is exerted purely at the presynaptic level; indeed, it does not influence the binding of specific ligands to the postsynaptic alpha 1 and 2, beta adrenergic, dopaminergic, serotonergic, gabanergic and muscarinic receptors. However, these results of Labrid[16] do not agree with that of the present experiment in which amineptine rather inhibited the pressor responses of NE and DA as well as their responses potentiated by pretreatment with reserpine or debrisoquin.

Anyway, the results of the present investigation strongly suggest that amineptine has the blocking activity of the peripheral adrenergic alpha-receptors in addition to the known inhibitory effect on catecholaminergic reuptake mechanism. A more detailed investigation to elucidate the correct mechanism of the action of amineptine using receptor binding techniques remains to be conducted.

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