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Effect of Imipramine or ECS on Central β_1 and β_2 Receptor Sensitivity in the Cardiovascular Response of Rat

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Abstract□This study was investigated the effects of imipramine (IMI) and electroconvulsive shock (ECS), which are used as antidepressant therapy, on the central β_1- or β_2 adrenergic receptor in anesthetized rats. The resting blood pressure and heart rate decreased in reserpinized group (5 mg/kg i.p., 24 hr before), but not in other 4 groups *i.e.* acute IMI (20 mg/kg i.p. 3-5 hr before), chronic IMI (Same dose, twice a day for 14 days), single ECS (sinusoidal 20 Hz, 120 V for 1 sec) and repeated ECS (same condition, daily for 12 days). The increase of heart rate and hypotension evoked by 1 or 3 μg intracerebroventricular (i.c.v.) administration of (+)dobutamine, β_1-agonist, was attenuated by chronic IMI treatment. The hypotension by salbutamol, β_2-agonist, 1 or 3 μg i.c.v. was significantly attenuatted in repeated ECS or reserpine treatment. And, the diminution of pulse pressure of salbutamol also reduced by repeated ECS. These results suggest that IMI or ECS result in attenuation on tachycardia by (+)dobutamine or on hypotension by salbutamol, presumably by which the central β_1 or β_2-receptor sensitivity may be suppressed, respectively.

Keywords□imipramine, ECS, (+)dobutamine, salbutamol, i.c.v.

Depression induced as one of its major manifestations, a disturbance of affect or mood, can be generated from reduction of noradrenaline (NA) or 5-hydroxytrytamine (5-HT)[1-4], and tricyclic antidepressants enhance NA function by inhibiting the neuronal uptake these biogenic amines[5-9].

By contrast, in recent views, depression arises from hyperactivity of NA synapse, which is downregulated by antidepressants[10,11]. In rat whole brain minus cerebellum, chronic desipramine treatment increases the dissociation constant, decreases receptor density of (^{3}H)-dihydroxyalprenolol[12]. This downregulation of β-receptor is displayed in cerebral cortex[13] and noradrenergic cyclic AMP generating system[14].

Long term administration of electroconvulsive shock (ECS) decreases adenylate cyclase activity, or maximum binding of (^{3}H)-dihydroxyalprenolol, and increases behavior response of 5-HT, NA, dopamine without altering their concentration[15-19].

Meanwhile, it had published on the existence of central β-receptor that isoproterenol i.c.v. produced increase of HR and decrease of BP, and this effect was antagonized by propranolol pretreatment[20]. (±) dobutamine has a predominant stimulatory effect on cardiac β_1-receptor, and acts α and β_2 receptor[21-25]. α_1-adrenoceptor agonist activity as inotropic agent exists in (−) enantiomer[26,27], whereas β_1-adrenoceptor agonist activity exists in (+) enantiomer[24,27]. Salbutamol has such β_2-agonist effect as dilatation of smooth muscle of uterus, bronchus and blood vessel[28,31].

As pointed out above, the significance of the reduction in β-adrenoceptor number is that most clinically affective antidepressant and ECS produce these similar effects. From these findings, it is expected that cardiovascular response *via* central route to the β-receptor will be suppressed. The confirmation of the β_1- and β_2-receptor sensitivity by imipramine or ECS might also be of importance to elucidate partially the mechanism of action.

Therefore, to examine the change of sensitivity of β_1- and β_2-receptor by imipramine or ECS, in

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anesthetized rats it was investigated as to whether or not (+) dobutamine-induced chronotropic action and salbutamol-induced hypotension induced by i.c.v. administration of them is altered by imipramine or ECS.

MATERIAL AND METHODS

Animal and drugs

Adult Sprague-Dawley rats of either sex, weighing 180-220 g, were used. Angitensin II, salbutamol, prazosin HCl, yohimbine, and atenolol were purchased from Sigma Chemical Co. in USA, and atropine sulfate were purchased from Tedia Co. in Japan. Butoxamine HCl, (+) dobutamine, and imipramine were donated from Burroughs Wellcome Co. in USA, Eli Lilly Co. in USA and Whan In Co, in Korea. All drugs were dissolved in 0.9% saline solution except for prazosin and yohimbine, which were solubilized in distilled water, and all doses were calculated on the basis of weight of drug base.

Operation and drug adimistration

Rats were anesthetized with urethane (1 g/kg, i.p.), and then atropine of 1 mg/kg were treated prior to operation. 30 min, stabilizing period, was demanded, and polyethylenetube (i.d. 0.56 mm) filled with heparin (100 units/m*l*) was cannulated into femoral artery for direct estimation of blood pressure by which strain gage coupler connected with pressure transducer (p-1000B, Narco Biosystems Inc.), and heart rate was monitored via biotachometer coupler as output to pressure transducer. And the rats were fixed in a prone position, the head was fitted into stereotaxic frame, the skull was exposed and prepared for intracerebroventricular (i.c.v.) administration (Stereotaxic instrument, Gokyo Inc.), and then placed into a lateral ventricle using following coordinates with reference to the bregma: 1 mm posterial, 1 mm lateral to the midline and 4 mm deep from the skull surface, and the polyethylene tube was pushed down the position, and cemented by Rebase (Orient Co.). One i.c.v. volume was below 3 μl. After experiment, rats were sacrified 5 min after methylene blue injection, the brain was rapidly removed, and were examined for dye deposited in and around the ventricular system.

Butoxamine or atenolol was treated via lateral ventricle 10 min before (+)dobutamine or salbutamol i.c.v., respectively. The positive chronotropic activity by (+)dobutamine and hypotension by salbutamol compared with the effects of IMI or ECS-treated group.

Table I. Influence of imipramine (IMI), electroconvulsive shock (ECS) or reserpine on diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR) in anesthetized rat

Group	n	DBP/SBP (mmHg)	HR (beats/min)
Control	16	87.6±2.8/121.8±2.6	365.0±10.1
Acute IMI	12	81.6±5.4/121.6±5.8	353.3±19.2
Chronic IMI	11	84.8+7.2/125.2+4.8	335.2+20.1
Single ECS	11	90.1+3.5/130.5+5.8	388.3+19.4
Repeated ECS	12	86.9+4.5/125.2+4.0	372.5+11.7
Reserpine	14	69.7±3.5/104.7±3.8**	328.4± 9.5**

Acute IMI or Chronic IMI; IMI of 20 mg/kg was intraperitoneally injected 4-5 hr before or twice daily for 14 days. Single or Repeated ECS; ECS (for 1 sec, 20 Hz, 120 V) was conducted 2 hr before or once a day for 12 days. Reserpine of 5 mg/kg was intraperitoneally treated 24 hr before. Each value represents mean ± SEM. n; number of rat used. ** $p<0.01$ (significantly different from control group).

Experiment group

(A) Control group; (+)dobutamine or salbutamol was 1 and 3 ug administered i.c.v., respectively. (B) Acute IMI group: Imipramine of 20 mg/kg was treated 3-5 hr before. (C) Chronic IMI group: Same dose was treated twice a day for 14 days. (D) Single ECS group: Electroconvulsive shock (sinusoidal for 1 sec, 20 Hz with 120V) was conducted 2 hr before, and then we confirmed the convulsion induced. (E) Repeated ECS group: The same ECS was conducted once a day for 12 days. (F) Reserpine treated group: reserpine of 5 mg/kg was treated i.p. 24 hr before.

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

RESULT

Influence of imipramine (IMI), electroconvulsive shock (ECS) on the level of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) prior to (+)dobutamine and salbutamol administration

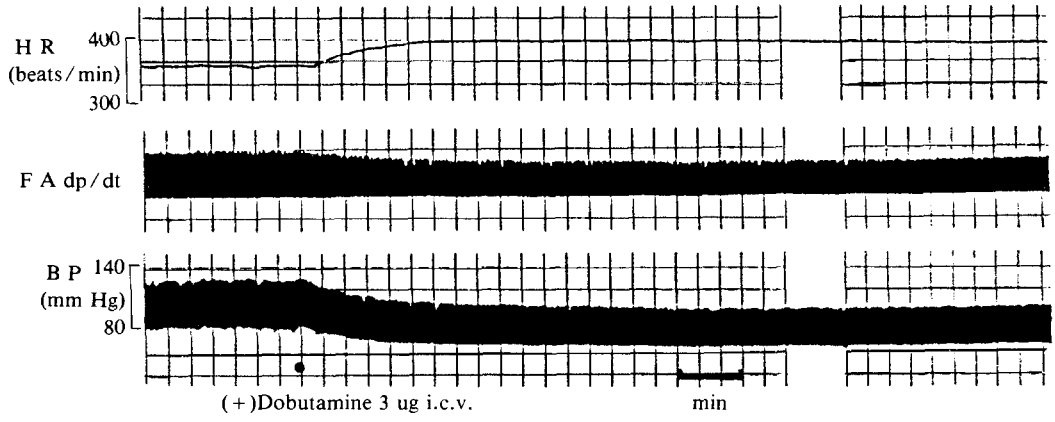

Fig. 1. Effect of 3 μg intracerebroventricular (i.c.v.) injection of (+)dobutamine on the recording of heart rate (HR), dp/dt of femoral artery (FA) and blood pressure (BP) in butomamine-pretreated rats.
Butoxamine 1 ug i.c.v. was treated 10 min before. BP was directly estimated via femoral artery.

Before drug treatment in anesthetic state, we observed the basal level of DBP, SBP and HR (Table I). As the table indicates, they showed the decrease in reserpinized group (5 mg/kg i.p., 24 hr before), but not in 4 groups *i.e.* acute IMI (20 mg/kg i.p. 3-5 hr before), chronic IMI (same dose, twice a day for 14 days), single ECS (for 1 sec,

Effect of imipramine (IMI) and electrocovulsive shock (ECS) on cardiovascular response by (+)dobutamine i.c.v.

In order to seek the pur central β_1-receptor effect of (+)dobutamine, β_2-antagonist butoxamine was administered *via* same route 10 min prior to i.c.v. of (+)dobutamine. Such treatment had little increase on BP without the change of HR, and (+)dobutamine i.c.v. of 1 or 3 μg provoked the increase of HR, and decrease of BP and FA dp/dt (Fig. 1 and Table II). In contrast, this positive chronotropic activity by (+)dobutamine appeared to be attenuated by reserpine treatment, with more attenuation by chronic IMI, but not by

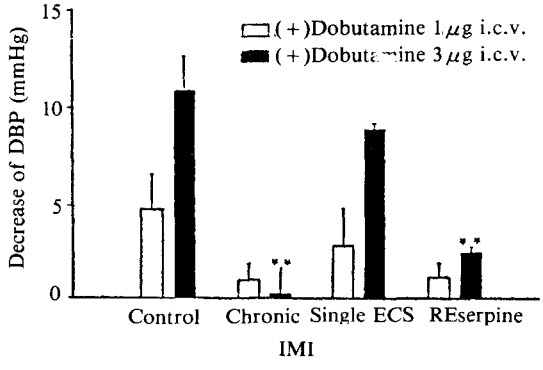

Fig. 2. Influence of IMI or reserpine on hypotension elicited from (+)dobutamine i.c.v. in butoxamine-pretreated rats.
Butoxamine 1 ug i.c.v. was treated 10 min before. Vertical bar represents mean ± SEM of 6-8 experiments. **; $p<0.01$.

Table II. Effect of imipramine (IMI), electroconvulsive shock (ECS) or reserpine on the chronotropic action induced by (+)doubtamine intracerebroventricular (i.c.v.) administration in anesthetized rats

Group	n	Increase of HR (beats/min)	
		1 μg	3 μg
Control	6	18.0 ± 1.1	35.0 ± 2.0
Acute IMI	6	25.8 ± 4.6	43.3 ± 10.1
Chronic IMI	6	1.2 ± 0.9**	6.6 ± 6.2**
Single ECS	6	12.2 ± 3.4	31.6 ± 5.2
Repeated ECS	6	13.6 ± 4.9	24.6 ± 5.6
Reserpine	7	6.4 ± 4.4**	23.4 ± 7.7

Acute IMI or chronic IMI; IMI of 20 mg/kg was intraperitoneally injected 4-5 hr before of twice a day for 14 days. Single or Repeated ECS; ECS (for 1 sec, 20 Hz, 120 V) was conducted 2 hr before or once a day for 12 days. Reserpine of 5 mg/kg was intraperitoneally injected 24 hr before. Each value represents mean ± SEM. n; number of rats used.
**; $p<0.01$ (significantly different from control). Butoxamine 1 μg i.c.v. was injected 10 min before (+)dobutamine administration.

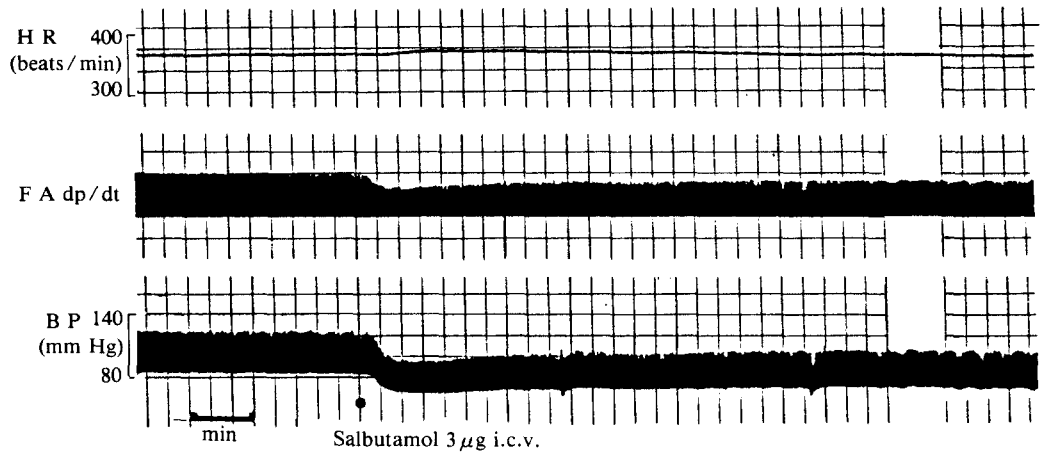

Fig. 3. Effect of 3 μg i.c.v. of salbutamol on the recording of HR, FA dp/dt and BP in atenolol-pretreated rats.
Atenolol 1 μg i.c.v. was treated 10 min before. Experimental condition and abbreviations are the same as the described in Fig. 1.

Table III. Effect of IMI, ECS or reserpine treatment on vasodepressive action induced by salbutamol i.c.v. in anesthetized rat

Group	n	Decrease of DBP (mmHg)	
		1 μg	3 μg
Control	10	10.1 ± 2.1	20.3 ± 4.3
Acute IMI	6	4.6 ± 1.8	13.3 ± 3.1
Chronic IMI	5	6.3 ± 1.5	12.5 ± 3.6
Single ECS	5	5.0 ± 1.6	13.4 ± 2.5
Repeated ECS	6	3.2 ± 1.2*	7.0 ± 3.3*
Reserpine	7	3.0 ± 1.2*	9.8 ± 2.1**

Atenolol 1 μg i.c.v. was injected 10 min before salbutamol administration (1 and 3 μg i.c.v.). Each value indicates mean ± SEM. n; number of experiment.
* ($p<0.05$), ** ($p<0.01$); significantly different from control.

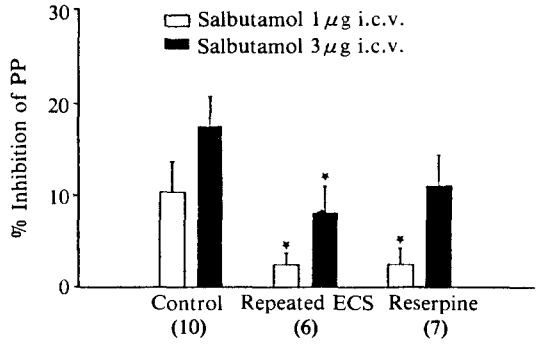

Fig. 4. Effect of repeated ECS or reserpine on salbutamol-induced % inhibition of pulse pressure (PP) in atenolol-pretrated rats.
Each value represent mean ± SEM, and the number of ( ) means number of animals. * $p<0.05$.

acute IMI, single ECS or repeated ECS. In addition, reflex hypotension following the increase of heart rate by (+)dobutamine 3 μg rather than 1 μg i.c.v. was attenuated by chronic IMI or reserpine treatment (Fig. 2).

Effect of IMI or ECS on the hypotension provoked by salbutamol i.c.v.

When atenolol, β_1-antagonist, was treated i.c.v. 10 min before, it reduced a little HR regardless of BP. Salbutamol 1 or 3 μg but not 0.1 or 0.3 μg dose dependently reduced the DBP and FA dp/dt, but increased a little HR (Fig. 3 and Table III). This hypotension induced by sabutamol both 1 and 3 μg i.c.v. was suppressed by repeated ECS or reserpine treatment, and sustained the same with either acute IMI or chronic IMI or single ECS. And the basal pulse pressure (PP, 39.4 ± 1.6) was not changed by repeated ECS (37.6 ± 1.7), or reserpine treatment (35.8 ± 1.9). The diminution of PP by salbutamol i.c.v. was inhibited by reserpine or repeated ECS treatment (Fig. 4).

DISCUSSION

Mood elevation and depression, or affective disorder is associated with the amine change of brain, and the binding of β-receptor is reduced by tricyclic antidepressants[12,13]. This down regulation of β-

receptor is also displayed by ECS[16,19].

In this study from this point, to examine the influence of IMI or ECS on cardiovasccular response by central β_1 or β_2 receptor, Butoxamine β_2-antagonist or atenolol β_1-antagonist was treated i.c.v. 10 min prior to (+) dobutamine or salbutamol, respectively. As expected, (+)dobutamine i.c.v. had a tendency to increase HR, salbutamol i.c.v. to decrease BP. This result indicates an augmentation in the intensity of chronotropic activity, and it is possible that this effect by (+)dobutamine or salbutamol might be directly related to the stimulation of β_1- or β_2-receptor.

In the group treated chronically with IMI, chronotropic action by (+)dobutamine i.c.v. was attenuated. This result is similar to the evidence that desipramine results in the diminution of low affinity β_1-receptor, but not in high affinity β_2-receptor in binding of (^{125}I)-iodohydroxybenzylpindolol[32].

Interestingly, in the group given with the chronic ECS, the hypotension of salbutamol was attenuated. These results show that the selectivity of β_1 or β_2 receptor is differentiated by IMI or ECS, respectively. Previous papers showed that tricyclic antidepressants increase the formation of cyclic AMP induced by GABA-B receptor[33], decrease those by GABA-A receptor[34], and decrease 5-HT_2 receptor[35]; ECS increase 5-HT_2 receptor[35] and the formation of inositol phosphate[36]. The papers suggest the possibility that IMI or ECS may act characteristically on different receptors. In addition, another notion is that central β_2-receptor regulate positively in presynaptic sites, thereby augmenting the release of catecholamines[37], whereas central β_1-receptor is present at postsynaptic membrane[38]. So, it was assumed that IMI or ECS is likely to act on the central postsynaptic or presynaptic membrane, respectively. And single and chronic ECS induced convulsion, but hypotension by salbutamol i.c.v. produced reduction by repeated ECS. This might be because ECS increased energy metabolism and vascular resistance, and blood brain barrier becomes more panetrable[19], which will be apt to contract the skelethal muscle in repeated treatment rather than in single treatment.

Reserpine of 5 mg/kg was treated 24 hr to confirm the indirect effect on presynaptic membrane for these cardioascular responses by (+)dobutamine or salbutamol. In this condition of depleted the catecholamines from sympathetic nerve terminal and adrenal medulla[39,40], DBP, SBP and HR prior to drug administration was significantly reduced ($p<0.01$). In reserpinized group, hypotension by salbutamol but not chronotropism by (+)dobutamine was attenuated. This indicates that positive feedback mechanism in presynaptic site may be suppressed by salbutamol, and endogenous catecholamines was partially involved in the hypotension. In the isolated aorta, vasodilatation was enhanced by reserpine[41,42], and the chronotropic effect in isolated heart was enhanced by catecholamine or calcium exposure[43,44]. This nonspecific supersensitivity in heart was not provoked in present study. This may be because reserpine single treatment of our result is different from chronic treatment, but the mechanism of action in heart remains in doubt.

In present study, the hypotension of (+)dobutamine was attenuated by chronic IMI treatment, which may be due to reduction of reflex mechanism by which chronotropic activity was already suppressed. This reduction of hypotension at high dose 3 μg of (+)dobutamine was exerted in reserpine treated group, assumed attributable to the low level of BP and HR than other group without drug treatment.

And in our result, salbutamol decrease pulse pressure and FA dp/dt, and this reduction of the pulse pressure was suppressed by repeated ECS. This result was congruent with our data intravenously injected (not published). The interpretation of this is considered that hypotension results in the reduction of venous return and left ventricular end diastoic pressure, and consequently can decrease cardiac output and pulse pressure. This phenomenon can be provoked *via* autonomic circulation in intact state of CNS mechanism. In our experiment of pithed rats (not published), pulse pressure was increased by cumulative i.v. injection of salbutamol. In fact, because of low level of BP and HR in pithed rats, we injected angiotension II with the same drugs. This indicates that salbutamol may differently act on peripheral or central pathway, despite the interaction between salbutamol and angiotensin II is not elucidated.

Taken as a whole, IMI or ECS resulted in the reduction to HR increase by (+)dobutamine i.c.v. or in the reduction to decrease of BP by salbutamol i.c.v., presumably by which the central β_1 or β_2 receptor sensitivity may be attenuated.

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LITERATURE CITED

1. Bunney, W.E., Jr. and Davis, J.M.: Norepinephrine in depressive reactions: A review. *Arch. Gen. Psychiatry* **13,** 483 (1965).
2. Schildkraut, J.J.: The catecholamine hypothesis of affective disorders: A review of supporting evidence. *Amer. J. Psychiat.* **122,** 508 (1965).
3. Schildkraut, J.J., Schanberg, S.M., Breese, G.R. and Kopin, I.J.: Norepinephrine metabolism and drugs used in the affective disorders: A possible mechanism of action. *Amer. J. Psychiat.* **124,** 54 (1967).
4. Lapin, I.P. and Oxenkrug, G.F.: Intensification of the central serotonergic process as a possible determinant of thymoleptic effect. *Lancet* **1,** 132 (1969).
5. Schidkraut, J.J. and Seymour, S.K.: Biogenic amines and emotion. *Science* **156,** 21 (1967).
6. Glowinski, J.L. and Axelrod, J.: Inhibition of uptake of tritiated noradrenaline in the intact rat brain by imipramine and structurally related compounds. *Nature* **204,** 1318 (1964).
7. Carlsson, A., Corrod, H., Fuxe, K. and Hokfelt, T.: Effects of some antidepressant drugs on the depletion of intraneuronal brain 5-hydroxytryptamine stores caused by 4-methyl-α-ethyl-metatyramine. *Eur. J. Pharmacol.* **5,** 357 (1969a).
8. Carlsson, A., Corrod, H., Fuxe, K. and Hokfelt, T.: Effects of some antidepressant drugs on the depletion of intraneuronal brain catecholamine stores caused by H-α-dimethyl-meta-tyramine. *Eur. J. Pharmacol.* **5,** 367 (1969b).
9. Koe, K.B.: Molecular geometry of inhibitors of catecholamines and serotonin in synaptosomal preparations of rat brains. *J. Pharmacol. Exp. Ther.* **100,** 649 (1976).
10. Sulser, F., Vetulani, J. and Mobley, P.L.: Mode of action of antidepressant drugs. *Biochem. Pharmacol.* **27,** 257 (1978).
11. van Praag, H.M.: Depression and CNS disease. *Lancet* **2,** 1259 (1982).
12. Banerjee, S.P., Kung, L.S., Riggi, S.J. and Chana, S.K.: Development of β-adrenergic receptor subsensitivity by antidepressants. *Nature* **268,** 455 (1977).
13. Sarai, K., Frazer, A., Brunswick, D. and Mendels, J.: Desmethyl imipramine-induced decrease in beta-adrenergic receptor binding in rat cerebral cortex. *Biochem. Pharmacol.* **27,** 2179 (1978).
14. Vetulani, J., and Sulser, F.: Action of various antidepressant treatments reduces reactivity of noradrenergic cyclic AMP generating system in limbic forbrain. *Nature* **257,** 495 (1975).
15. Green, A.R., Heal, D.J. and Grahame-Smith, D.G.: Futher observation on the effect of repeated electroconvulsive shock on the behavioral responses of rats produced by increases in the functional activity of brain 5-hydroxytryptamine and dopamine. *Psychopharmacology.* **52,** 195 (1977).
16. Vetulani, J., Stawarz, R.J., Pingell, J.V. and Sulser, I.: A Possible common mechanism of action of antidepressant treatments. *Naunyn-Schmiedeb. Arch. Pharmacol.* **293,** 109 (1976).
17. Bergstrom, D.A. and Kellar, K.J.: Effect of electroconvulsive shock on monoaminergic receptor binding sites in rat brain. *Nature* **278,** 464 (1979).
18. Lerer, B. and Belmarker, R.H.: Receptors and the mechanism of action of ECT. *Biol. Psychiatry* **17,** 497 (1982).
19. Small, I.F., Small, J.G. and Milstein, V.: Electroconvulsive therapy. In *American Handbook of Psychiatry.* ed. by Berger, P.A. and Brodie, H.K.H., Basic Books Inc., New York, p.999 (1986).
20. Bhargava, K.P., Mishra, M. and Tangri, K.K.: An analysis of central adrenoceptors or control of cadiovascular function. *Br. J. Pharmacol.* **45,** 596 (1972).
21. Robie, N.W., Nutter, D.O., Moody, C. and McNay, J.L.: *In vivo* analysis of adrenergic receptor activity of dobutamine. *Cir. Res.* **34,** 663 (1974).
22. Ruffolo, R.R.Jr., Spradlin, T.A., Pollock, G.D., Waddel, J.E. and Murphy, P.J.: Alpha and beta-adrenegic effects of the stereoisomers of dobutamine. *J. Pharmacol. Exp. Ther.* **219,** 447 (1981).
23. Ruffolo, R.R.Jr., Messick, K. and Horng, J.S.: Interaction of three inotropic agents, ASL-7022, dobutamine and dopamine with alpha and beta-adrenoceptors *in vitro. Naunyn-Schmiedeb. Arch. Pharmacol.* **326,** 317 (1984).
24. Ruffolo, R.R.Jr. and Messik, K.: Systemic hemodynamic effects of dopamine, (±)-do-

butamine and the (+) and (−) enantiomers of dobutamine in anesthetized normotensive rats. *Eur. J. Pharmacol.* **109,** 173 (1985).
25. Kenakin, T.P.: An *in vitro* quantitative analysis of the α-adrenoceptor partial agonist activity of dobutamine and its relevance to inotropic selectivity. *J. Pharmacol. Exp. Ther.* **216,** 210 (1981).
26. Wagner, J. and Brodde, O.E.: On the presence and distribution of α-adrenoceptors in the heart of various mammalian species, *Naunyn-Schmiedeb. Arch. Pharmacol.* **302,** 239 (1978).
27. Ruffolo, R.R.Jr. and Yaden, E.L.: Vascular effects of the stereoisomers of dobutamine. *J. Pharmacol. Exp. Ther.* **224,** 46 (1983).
28. Brittain, R.T., Farmer, J.R., Jack, D., Martin, L.E. and Simpson, N.T.: α-[(t-butylamino)methyl]-4-OH-m-xylene-α_1, α_3-diol (AH 3365): a selective beta-adrenergic stimulant. *Nature* **219,** 862 (1978).
29. Wasserman, M.A. and Levy, B.: Cardiovascular and bronchomotor responses to selective beta-adrenergic receptor agonists in the anesthetized dog. *J. Pharmacol. Exp. Ther.* **189,** 445 (1974).
30. Wilffert, B., Gouw, M.A.W., Timmermans, P.B.M.W.M. and van Zwieten, D.A.: Interaction between beta-2 adrenoceptor-mediated vasodilatation and alpha-1 adrenoceptor-mediated vasoconstrictionin the pithed normotensive rat. *J. Cardiovasc. Pharmacol.* **5,** 829 (1983).
31. Ahrens, R.C. and Smith, G.D.: Albuterol: An adrenergic agents for use in the treatment of asthma. Pharmacology, pharmacokinetics and clinical use. *Pharmacotherapy.* **4,** 105 (1984).
32. Minneman, K.P., Dibner, M.D., Wolfe, B.B. and Molinoff, P.B.: Beta-1 and beta-2 adrenergic receptor in rat cerebral cortex are independently regulated. *Science* **220,** 866 (1979).
33. Suzdak, P.D. and Gianutsos, G.: Effect of chronic imipramine or baclofen on GABA-B binding and cyclic AMP production in cerebral cortex. *Eur. J. Pharmacol.* **131,** 129 (1986).
34. Suzdak, P.D. and Gianutsos, G.: Parallel changes in GABAergic and noradrenergic receptor sensitivity following chronic administration of antidepressant and GABAergic drugs: A possible role for GABA in affective disorders. *Neuropharmacology.* **24,** 217 (1985).
35. Kellar, K.J., Cascio, C.S., Butler, J.A. and Kurtzke, R.N.: Differential effects of electroconvulsive shock and antidepressant drugs on serotonin-2 receptors in rat brain. *Eur. J. Pharmacol.* **69,** 515 (1981).
36. Newman, M.E., Miskin, I. and Lerer, B.: Effect of single and repeated electoconvulsive shock administration on inositol accumulation in rat brain slices. *J. Neurochem.* **49,** 19 (1987).
37. Dhalof, C., Englberg, G. and Svensson, T.H.: Effect of beta-adrenoceptor antagonists on the firing ate of noradrenaline neurons in the locus coerulus of the cat. *Naunyn-Şchmiedeb. Arch. Pharmacol.* **317,** 26 (1981).
38. Handley, S.L. and Singh, L.: The modulation of beta-twich behaviour by drugs acting on beta-adrenoceptors: evidence for the involvement of both beta-1 and beta-2 adrenoceptors. *Psychophamacology.* **88,** 320 (1986).
39. Shore, P.A.: Transport and storage of biogenic amines. *Ann. Rev. Pharmac. Toxicol.* **12,** 209 (1972).
40. Stitzel, R.E.: The biological fate of reserpine. *Pharmacol. Rev.* **28,** 179 (1977).
41. Cohen, M.L. and Berkowitz, B.A.: Decreased vascular relaxation in hypertension. *J. Pharmacol. Exp. Ther.* **196,** 396 (1976).
42. Cauvin, C.A., Devia, C.J. and Kirkendol, P.L.: Effect of reserpine pretreatment on *in vivo* femoral arterial responses to vasodilator agents. *J. Pharmacol. Exp. Ther.* **216,** 447 (1981).
43. Hawthorn, M.H. and Broadley, K.J.: Reserpine induced supersensitivity occurs for β-adrenoceptor-mediated responses of heart and trachea but not of the uterus and lug. *Eur. J. Pharmacol.* **105,** 245 (1984).
44. Westfall, D.P. and Fleming, W.W.: Sensitivity changes in the dog heart to noradrenaline, calcium and aminophylline resulting from pretreatment with reserpine. *J. Pharmacol. Exp. Ther.* **159,** 98 (1968).