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Effects of LM 5008, a selective inhibitor of 5-hydroxytryptamine uptake, on blood pressure and responses to sympathomimetic amines

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1 LM 5008 (4-[2-(3-indolyl)ethyl]piperidine) (10, 20 and 50 mg kg^{-1}) had no significant effect on pressor responses to noradrenaline or tyramine in rats anaesthetized with urethane. Desmethylimipramine (1 mg kg^{-1}) blocked the response to tyramine but chlorimipramine (5 mg kg^{-1}) had no significant effect on responses to noradrenaline or tyramine.

2 In the rabbit, anaesthetized with chloralose, LM 5008 (5 mg kg^{-1}) had no effect on pressor responses to noradrenaline, tyramine or angiotensin II, while desmethylimipramine (0.25 mg kg^{-1}) inhibited responses to tyramine and potentiated those to noradrenaline.

3 LM 5008 (10 mg kg^{-1}) had no effect on resting blood pressure of conscious normotensive or DOCA-saline hypertensive rats.

4 Tranylcypromine (5 mg kg^{-1}) produced a fall in blood pressure in conscious normotensive and in DOCA hypertensive rats.

5 Treatment with a combination of LM 5008 (10 mg kg^{-1}) and tranylcypromine (5 mg kg^{-1}) resulted in the appearance of a behavioural hyperactivity syndrome, but blood pressure was not different from that of animals treated with tranylcypromine alone.

6 These results further demonstrate the selectivity of LM 5008 for 5-hydroxytryptamine as opposed to catecholamine uptake.

Introduction

LM 5008 (4-[2(3-indolyl)ethyl]piperidine) is a selective inhibitor of 5-hydroxytryptamine (5-HT) uptake in brain synaptosomes and platelets both *in vitro* and *in vivo* (Le Fur & Uzan, 1977) which has been developed as a potential antidepressant. Tricyclic antidepressant drugs in present clinical use suffer from side effects, such as potentiation of the peripheral effects of catecholamines, orthostatic hypotension, myocardial depression and anticholinergic effects (Stimmel, 1979). Selective inhibitors of 5-HT uptake, such as zimelidine (Ross, Ogren & Renyi, 1976) CGP 6085 (Waldmeier, Baumann & Maitre, 1979) trazodone (Kellams, Klapper & Small, 1979) and LM 5008 may possess an advantage over the tricyclic antidepressants in being free from certain of these effects.

In recent years, evidence has accumulated that a bulbospinal 5-hydroxytryptaminergic pathway plays an important role in blood pressure control (Chalmers & Wing, 1975). However, the experimental data on central cardiovascular effects of 5-HT have been confusing, because of variations in response between animal species, use of anaesthetics and of a variety of agonistic or antagonistic drugs. Thus intracerebroventricular injection of 5-HT caused a pressor response in rats anaesthetized with urethane (Lambert, Friedman, Buchweitz & Gershon, 1978; Krstic & Djurkovic, 1980), but a depressor effect in anaesthetized cats (Baum & Shropshire, 1975; Nava-Felix & Hong, 1979). In conscious normotensive or hypertensive rats (Henning & Rubenson, 1971; Fuller, Holland, Yen, Bemis & Stamm, 1979; Echizen & Freed, 1982), anaesthetized cats (Florez & Armijo, 1974; Tadepalli, Mills & Schanberg, 1977) and anaesthetized dogs treated with a monoamine oxidase (MAO) inhibitor (Antonaccio & Robson, 1973), central or peripheral administration of 5-hydroxytryptophan (5-HTP) produced a lowering of blood pressure, which was potentiated by the 5-HT uptake blocker, fluoxetine (Fuller *et al.*, 1979). How-

ever, a rise in blood pressure was reported following 5-HTP administration in conscious dogs (Dunkley, Sanghri, Friedman & Gershon, 1972). Thus both pressor and depressor effects have resulted from stimulation of central 5-HT receptors, while depressor effects resulted from abolition of central 5-hydroxytryptaminergic function by administration of 5,6-dihydroxytryptamine or *p*-chlorphenylalanine in hypertensive rats (Finch, 1975; Jarrott, McQueen, Graf & Louis, 1975; Buckingham, Hamilton & Robson, 1976; Gothert & Klupp, 1978). In contrast to these results, Browning, Bramlet, Myers, Bundman & Smith (1981) failed to observe any effect on the blood pressure of normotensive or spontaneously hypertensive rats (SHR) following treatment with *p*-chlorphenylalanine, 5,7-dihydroxytryptamine or lesion of the raphe nucleus. Fuller, Yen & Stam (1981) found that 5-HT receptor agonists (quipazine and 1-[*m*-trifluoromethylphenyl]piperazine) or a 5-HT releasing agent (fenfluramine) lowered blood pressure of SHR, whereas methergoline (antagonist at 5-HT receptors) increased blood pressure in these animals. On the other hand, the selective 5-HT antagonist, ketanserin, produced a fall in blood pressure of hypertensive humans (Wenting, Man in'TVeld, Woittiez, Boomsma & Schalekamp, 1982).

Drugs which inhibit 5-HT uptake may, therefore, affect blood pressure by enhancing the effective postsynaptic 5-HT concentrations at the bulbospinal locations mediating the above described responses. The present study was designed with two aims in mind: (a) to compare the effect of LM 5008 on modification of pressor response to tyramine and noradrenaline with that of desmethylimipramine and chlorimipramine, and (b) to investigate the effects of LM 5008 on blood pressure. The combination of LM 5008 with an inhibitor of MAO produces a behavioural syndrome in rats characteristic of stimulation of 5-HT receptors (Ashkenazi, Finberg & Youdim, 1983). Alterations in systemic blood pressure were, therefore, followed in this experimental situation.

Methods

Anaesthetized animals

Male rats (Sprague-Dawley) weighing 200–250 g were anaesthetized with urethane (1.5 g kg^{-1} i.p. Blood pressure was recorded from a carotid artery by means of a Statham transducer coupled to a Brush-Gould or Beckman physiological recorder. Drugs were injected via a jugular vein cannula in a volume not greater than 0.05 ml and washed in with 0.2 ml of 0.9% w/v NaCl solution (saline). A 5 min interval was maintained between injections of pressor substances. Rectal temperature (measured with a mercury thermometer) was maintained at 37°C by covering the animal and warming as necessary using a small electric heating pad.

Two or three control responses were obtained for each of two submaximal doses of noradrenaline and tyramine, and one submaximal dose of angiotensin II. The doses used had been previously determined to be approximately 20% or 40% maximal (noradrenaline, tyramine) or 50% maximal (angiotensin II). The same doses of the agonists were repeated in duplicate after slow intravenous (10 and 20 mg kg^{-1}) or intraperitoneal (50 mg kg^{-1}) injection of LM 5008 or intravenous injection of desmethylimipramine (1 mg kg^{-1}) and chlorimipramine (1 mg kg^{-1}, 5 mg kg^{-1}). Each dose level of LM 5008, desmethylimipramine or chlorimipramine comprised a separate experiment.

Pressor responses to the agonists following administration of uptake inhibitors were expressed as a ratio of the average control response for that experiment, and the response ratio compared with that obtained in control experiments (saline injected instead of uptake inhibitor) using Student's *t* test.

Rabbits (2 to 5 kg) of either sex were anaesthetized with a mixture of thiopentone sodium (40 mg kg^{-1}) followed by α-chloralose (80 mg kg^{-1}) by intravenous injection. Respiration was in most cases voluntary, but was assisted as necessary with a Palmer animal respirator. The respiration pump was adjusted so that arterial P_{O_2}, P_{CO_2} and pH values were maintained within the normal physiological range. Blood pressure was measured as above from a carotid artery. Drugs were injected via a femoral vein catheter in a volume not greater than 0.5 ml and washed in with 2 ml saline. Rectal temperature was maintained at 39°C as described above. Doses of tyramine, noradrenaline and angiotensin II were found which gave pressor responses of the order of 30 to 40 mmHg. These doses were repeated after intravenous injection of LM 5008 (5 mg kg^{-1}) or desmethylimipramine (0.25 mg kg^{-1}). The doses used were: 5 to 20 μg (noradrenaline), 0.5 to 2 mg (tyramine) and 0.5 to 2 μg (angiotensin II). Response ratios in animals treated with LM 5008 or desmethylimipramine were compared with those in control animals using Student's *t* test.

Conscious rats

Polyethylene cannulae were implanted for chronic blood pressure measurement in either left carotid or tail artery of normotensive or DOCA-hypertensive rats under ether anaesthesia. The cannulae were pulled through the subcutaneous tissue to an exit point on the dorsal surface of the neck, filled with heparin (500 iu ml^{-1}) in isotonic saline solution and

plugged with steel wire. Blood pressure was recorded continuously the following day, for 90 min before drug injection and for up to 4 h afterwards. The arterial cannula was connected to a Statham P23Db pressure transducer via an 80 cm length of PP50 tubing, and the animals were unrestrained in their cages. Mean blood pressure was determined as diastolic pressure plus one third of the pulse pressure. Blood pressure values were measured at 30 min intervals, using the average values of diastolic and systolic pressures measured over a 5 min period. Statistical significance of conscious blood pressure values was determined by comparing post-injection values with control values using the paired *t* test. Control values for this purpose were the average of 2 separate 30 min periods before drug administration. Heart rate was measured in some experiments by counting pulsations from the blood pressure trace run temporarily at a rapid rate (10 mm s^{-1}). Behavioural activity was measured with Animax monitors as described previously (Ashkenazi *et al.*, 1983).

DOCA-hypertension was produced by unilateral nephrectomy, substitution of 1% NaCl for drinking water, and three times weekly subcutaneous injections of desoxycorticosterone acetate (10 mg/kg) for six weeks essentially as described by Green, Saunders, Wahlgren & Craig (1952).

Drugs

LM 5008 (Pharmuka) was dissolved in 0.1 M HCl and partially neutralized to pH 6 before injection. Tyramine HCl and noradrenaline acid tartrate were obtained from Sigma. Angiotensin II (Hypertensin) was supplied by Ciba-Geigy. (±)-Tranylcypromine SO_4 was obtained from Smith, Kline and French, desmethylimipramine HCl and chlorimipramine HCl from Ciba-Geigy.

Results

Modification of tyramine, noradrenaline and angiotensin responses by LM 5008 in anaesthetized rats and rabbits

Intravenous administration of LM 5008 caused a brief (10 min) fall in blood pressure, followed by return to control levels. No further change in resting

Table 1 Modification of pressor responses to tyramine, noradrenaline and angiotensin II in rats anaesthetized with urethane by LM 5008, desmethylimipramine and chlorimipramine

		Response ratio $\left(\frac{experimental}{control}\right)$				
	No. of experiments	*Noradrenaline* 50 ng	100 ng	*Tyramine* 25 μg	50 μg	*Angiotensin II* 25 ng
Control	7	1.00 ±0.10	0.98 ±0.08	0.87 ±0.09	0.90 ±0.08	1.02 ±0.03
LM 5008 10 mg kg^{-1}	5	1.09 ±0.21	1.13 ±0.27	0.69 ±0.17	0.69 ±0.15	1.04 ±0.14
LM 5008 20 mg kg^{-1}	5	1.14 ±0.18	1.00 ±0.20	0.86 ±0.22	0.69 ±0.17	1.11 ±0.18
LM 5008 50 mg kg^{-1}	5	0.87 ±0.07	—	0.52 ±0.18	0.57 ±0.16	0.61 ±0.10 *
Desmethylimipramine 1 mg kg^{-1}	5	1.14 ±0.14	—	0.09 ±0.03 **	—	1.08 ±0.21
Chlorimipramine 1 mg kg^{-1}	5	1.00 ±0.30	1.23 ±0.31	0.93 ±0.21	0.92 ±0.27	0.96 ±0.21
Chlorimipramine 5 mg kg^{-1}	5	1.17 ±0.54	1.07 ±0.24	—	0.89 ±0.18	1.16 ±0.20
Mean control pressor responses (mmHg) $n = 7$						
		24.6 ±3.1	32 ±3.4	22.9 ±2.6	38.6 ±6.9	22.2 ±2.1

Values are mean ± s.e.mean.
*$P < 0.005$; **$P < 0.001$ for difference between treated animals and control animals.

Table 2 Modification of pressor responses to tyramine, noradrenaline and angiotensin II by LM 5008 and desmethylimipramine in rabbits anaesthetized with chloralose

	No. of experiments	*Response ratio* $\left(\frac{experimental}{control}\right)$ *Noradrenaline*	*Tyramine*	*Angiotensin II*
LM 5008 ($5\ mg\ kg^{-1}$)	4	1.27 ±0.16	0.95 ±0.16	0.91 ±0.04
Desmethylimipramine ($0.25\ mg\ kg^{-1}$)	4	1.74* ±0.28	0.24* ±0.085	1.10 ±0.19
Control	4	1.0 ±0.06	1.54 ±0.34	0.89 ±0.09

Values are mean ± s.e.mean.
*$P < 0.05$ for difference from control.

blood pressure was seen over the course of the experiment (2–3 h). No significant change occurred in responses to noradrenaline, tyramine or angiotensin II following injection of 10 or $20\ mg\ kg^{-1}$ LM 5008 in urethane-anaesthetized rats (Table 1). At $50\ mg\ kg^{-1}$ LM 5008, there was a tendency for reduction in all pressor responses, although only the reduction in angiotensin II response was statistically significant, indicating a non-specific blocking action of LM 5008 at this high dose level. By contrast, desmethylimipramine ($1\ mg\ kg^{-1}$) produced a powerful suppression of the tyramine response, with no significant effect on the noradrenaline or angiotensin responses (Table 1). No alteration in resting blood pressure occurred following injection of desmethylimipramine. Chlorimipramine had no significant effect on pressor responses or on resting blood pressure at the doses used. Higher doses of chlorimipramine were toxic and produced profound hypotension and death of the animals.

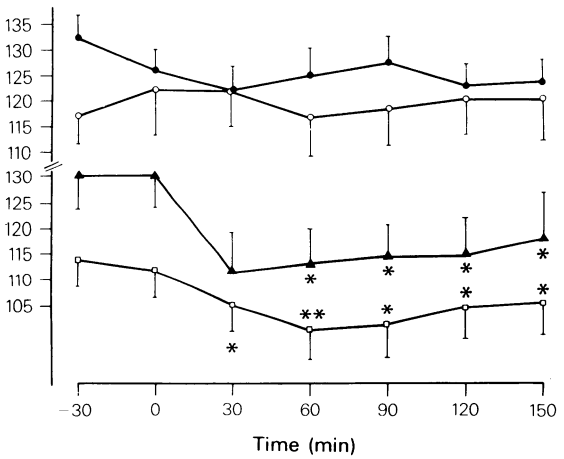

Figure 1 Mean arterial blood pressure (BP) of conscious, normotensive rats. (○) Control group ($n = 7$) injected with saline at +5 min; (●) injected with LM 5008 ($10\ mg\ kg^{-1}$ i.p.) at +5 min ($n = 5$); (▲) injected with tranylcypromine ($5\ mg\ kg^{-1}$ i.p.) at +5 min followed by saline i.p. at +35 min ($n = 7$); (□) injected with tranylcypromine ($5\ mg\ kg^{-1}$ i.p.) at +5 min followed by LM 5008 ($10\ mg\ kg^{-1}$ i.p.) at +35 ($n = 10$). Average BP values shown; vertical lines indicate s.e.mean. *$P < 0.05$, **$P < 0.01$ for difference from pre-injection values (mean of −30 and 0 time determinations).

Essentially similar results were obtained in chloralose-anaesthetized rabbits (Table 2), however, in this preparation, desmethylimipramine ($0.25\ mg\ kg^{-1}$) caused a significant suppression of the tyramine response with potentiation of the noradrenaline response, whereas no significant change in pressor response to any of the three agonists was seen after LM 5008 ($5\ mg\ kg^{-1}$).

Change in blood pressure of normotensive, conscious rats

Intraperitoneal injection of LM 5008 ($5\ mg\ kg^{-1}$) produced a transient fall in blood pressure of 25 to 40 mmHg. Blood pressure returned to control levels within 5 to 10 min, and there was no further significant alteration in blood pressure up to 4 h after the injection (Figure 1). The transient fall in blood pressure immediately following LM 5008 injection has been omitted from the averaged results shown in the figures. A significant reduction in blood pressure, of the order of 15 to 20 mmHg, occurred following the intraperitoneal injection of tranylcypromine ($5\ mg\ kg^{-1}$, Figure 1), which developed within 10 to 15 min and was maintained over the period measurements were carried out (4 h). When LM 5008 was

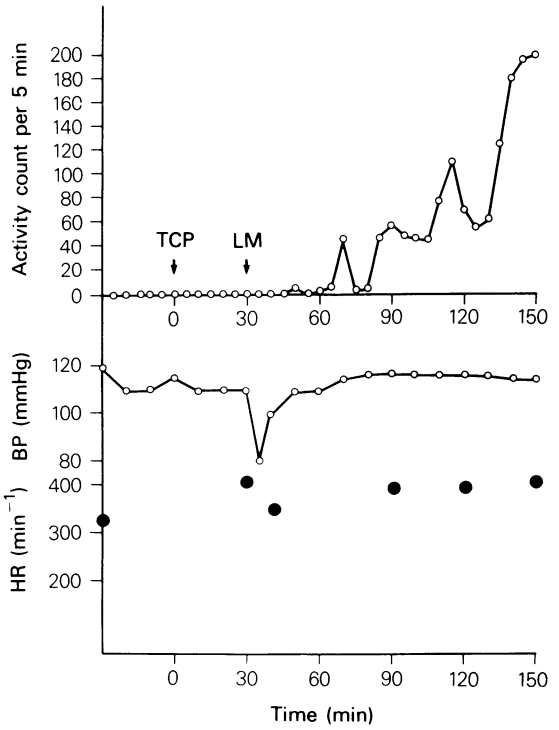

Figure 2 Results from a single experiment in a conscious normotensive rat, in which mean arterial blood pressure (BP), heart rate (HR) and activity were measured simultaneously. Tranylcypromine (TCP) was injected at +5 min, and LM 5008 (LM) at +35 min. In this case, no reduction in blood pressure resulted from injection of TCP, although in about half of the group of normotensive rats receiving TCP alone, a fall in BP occurred, resulting in a significant reduction in blood pressure for the whole group (see Figure 1).

injected 30 min after tranylcypromine, a characteristic behavioural syndrome, involving side-to-side head movement, hind limb splaying and locomotor hyperactivity developed within 45 to 60 min as described elsewhere (Ashkenazi *et al.*, 1983). Despite the marked behavioural hyperactivity, no further change in blood pressure was seen in 10 animals, which was significantly different from the reduction in blood pressure produced by tranylcypromine alone (Figures 1 and 2). In 4 of these rats treated with tranylcypromine and LM 5008, behavioural activity was monitored in conjunction with blood pressure and heart rate measurement, and an example of such an experiment is shown in Figure 2. No significant change in heart rate was observed in any of these 4 animals. All of the rats referred to above survived the experiment, and were alive and apparently normal the next day. In 4 other rats, also treated with tranylcypromine and LM 5008, a marked elevation in blood pressure occurred, reaching 35 mmHg above pre-injection levels, by 2–3 h after injection of LM 5008. These rats developed dyspnoea, cyanosis, and died 3 to 4 h after receiving LM 5008, although the initial behavioural effects of the drug combination were no different from those of the animals surviving the experiment. The blood pressure values of the rats which developed a marked toxic reaction have been excluded from the data shown.

Change in blood pressure of DOCA-hypertensive rats

Injection of LM 5008 (10 mg kg^{-1}) in DOCA hypertensive rats produced no significant alteration in blood pressure, other than the transient depressor effect mentioned above. Tranylcypromine (5 mg kg^{-1}) administration produced a significant fall in blood pressure of the order of 30 to 40 mmHg (Figure 3), although blood pressure did not reach normotensive levels. Injection of LM 5008 30 min after tranylcypromine resulted in the appearance of the behavioural reaction described above, but the blood pressure of rats treated with the combination of LM 5008 and tranylcypromine was not significantly different from those treated with tranylcypromine alone. All of the DOCA-hypertensive animals given

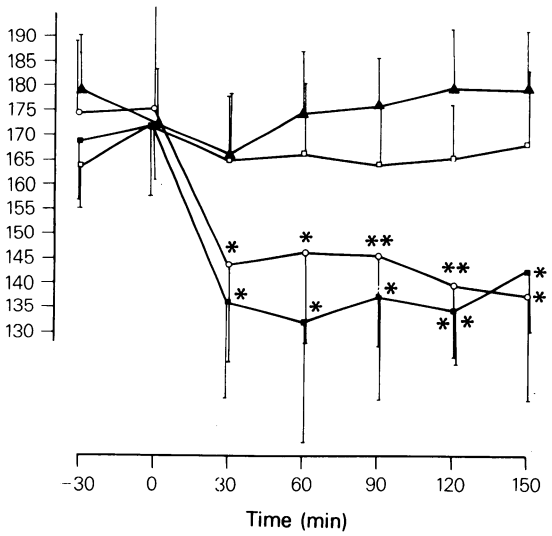

Figure 3 Mean arterial blood pressure (BP) of DOCA-saline hypertensive rats. (□) Control group injected with saline only at time +5 min ($n = 5$); (▲) injected with LM 5008 (10 mg kg^{-1} i.p.) at time +5 min ($n = 5$); (○) injected with tranylcypromine (5 mg kg^{-1} i.p.) at +5 min and saline at +35 min ($n = 7$); (■) injected with tranylcypromine (5 mg kg^{-1} i.p.) at +5 min and LM 5008 (10 mg kg^{-1} i.p.) at +35 min ($n = 5$). Average BP values shown; vertical lines indicate s.e.mean. $*P < 0.05$, $**P < 0.01$, for difference from pre-injection values (mean of −30 and 0 time determinations).

the drug combination survived the experiment for at least 24 h, and none developed the toxic respiratory syndrome referred to above.

Discussion

Modification of pressor responses to tyramine and noradrenaline has been used previously to assess the pharmacological profile of antidepressant drugs *in vivo* (Ghose, 1980). Drugs such as amitriptyline, which block neuronal uptake of noradrenaline, normally potentiate responses to noradrenaline and inhibit responses to tyramine. The lack of antagonism to the tyramine pressor response, or potentiation of the noradrenaline response, by LM 5008 in anaesthetized rats and rabbits is further evidence for the selectivity of this compound for the 5-HT uptake system. Only a slight reduction in the tyramine response was seen in the rat at 50 mg kg^{-1} LM 5008, although more than 75% inhibition of 5-HT uptake in brain synaptosomes occurred after administration of 10 mg kg^{-1} (Le Fur & Uzan, 1977). In this study, no potentiation of pressor responses to noradrenaline was seen in the rat following acute administration of desmethylimipramine, although responses to tyramine were strongly suppressed. One reason for the non-potentiation of noradrenaline by desmethylimipramine may be the known α-adrenoceptor blocking properties of desmethylimipramine (Thoenen, Hurlimann & Haefely, 1964). The net effect of desmethylimipramine on noradrenaline response is, therefore, the resultant of potentiation (uptake blockade) and inhibition (α-adrenoceptor blockade). The fact that desmethylimipramine potentiated pressor responses to noradrenaline in the rabbit may be due to a relatively smaller blocking effect of desmethylimipramine on vascular α-adrenoceptors in this animal. The lack of effect of chlorimipramine on both noradrenaline and tyramine pressor responses in the rat is consistent with the relative selectivity of this compound for 5-HT rather than noradrenaline uptake systems (Ross & Renyi, 1975).

Another factor which is known to modify catecholamine responses following administration of tricyclic antidepressants is the duration of treatment. In a study in human subjects (Larochelle, Hamet & Enjalbert, 1979), a single dose (25 mg) of imipramine did not affect pressor responses to tyramine, although daily administration of this dose for several days reduced responses to tyramine and potentiated those to noradrenaline. In the same study it was shown that trazodone did not affect pressor responses to the sympathomimetic amines. In spite of the fact that ED_{50} levels were not determined in this work (due to the lack of effect of LM 5008 on pressor responses to sympathomimetic amines), the data presented here clearly show that LM 5008 is a much less active drug than desmethylimipramine on catecholamine uptake, and are in accord with other results showing the selectivity of LM 5008 for the 5-HT uptake system (Le Fur & Uzan, 1977).

Kuhn, Wolf & Lovenberg (1980) reviewed the evidence for participation of central 5-hydroxytryptaminergic neurones in blood pressure control, and concluded that 5-HT probably does not play a primary, tonic role in maintaining blood pressure in the rat, although it may behave as a neuromodulator affecting sympathetic outflow at the level of the brain stem or spinal cord. Rats exhibiting behavioural symptoms of central 5-HT receptor stimulation, following administration of tranylcypromine and LM 5008, did not show any alteration in resting blood pressure (apart from that due to tranylcypromine itself), except for those animals in which a lethal toxicity was produced. The rise in blood pressure seen in the latter animals appeared to be associated with the toxic effect of the drug combination on the respiratory system, and this result is in agreement with the findings of Lambert *et al.* (1978), that the pressor effect of intracerebroventricularly administered 5-HT in rats anaesthetized with urethane is related to an alteration in respiration. Krstic & Djurkovic (1980), however, showed that this response was also present in artificially respired rats.

One reason for a lack of effect of systemic LM 5008 on blood pressure in the conscious rat may be that a generalised effect on all 5-hydroxytryptaminergic neurones is produced by this type of treatment, so that opposing effects exerted on different brain centres could balance themselves out. The cardiovascular effects of 5-HT injected into the cerebral ventricles may differ, since following intraventricular injection, initial distribution of 5-HT in brain tissue is unequal, resulting in relatively greater stimulation of areas close to the ventricular space. A pressor effect of 5-HT was also seen following local injection in the anterior hypothalamus (Smits & Struyker-Boudier, 1976).

The present experiments, therefore, while demonstrating the absence of effect of LM 5008 on blood pressure in conscious normotensive and hypertensive animals, do not discount a role of 5-HT in central control of blood pressure.

The pronounced fall in blood pressure seen following tranylcypromine administration in the rat is interesting in view of the fact that this drug is associated with hypertensive reactions in man (Lesse, 1978) and caused a powerful hypertensive effect following intravenous injection in the dog (Rao, Einzig, Reddy & White, 1979). Tranylcypromine possesses amphetamine-like pharmacological effects of inhibition of amine uptake and facilitation of release in

addition to its ability to inhibit MAO (Hendley & Snyder, 1968; Glowinski, Hamon, Javoy & Morot-Gandry, 1972). The net result of these various actions is, therefore, dependent on a complex balance between central and peripheral effects, and would require separate investigation in order to achieve understanding.

While the combination of LM 5008 with a MAO inhibitor appears to be potentially toxic, it should be noted that the doses of both agents used in this study were relatively large. The combination of MAO inhibitors with tricyclic antidepressant drugs is also known to produce a toxic reaction in animals, including behavioural stimulation and body temperature changes (Loveless & Maxwell, 1965). However, judiciously chosen doses of both agents in combination have been found highly effective in the treatment of depression in humans, without serious side effects (Sethna, 1974; Young, Lader & Hughes, 1979). The results of our studies, therefore, do not exclude the possibility that a carefully chosen combination of MAO inhibitors and LM 5008 could be useful in treatment of depression.

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