THE MECHANISM OF HYPOTENSIVE ACTION OF N-[2-(2-METHOXYPHENOXY) ETHYL]-3-(2, 5-DIMETHOXYPHENOXY) PROPYLAMINE HYDROCHLORIDE

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Compounds possessing a methoxy benzene structure have been synthesized and screened pharmacologically by a large number of workers (3, 5, 7). Recently Augstein and coworkers (2) synthesized a series of compounds and tested their hypotensive activity. Out of these compounds N-[2-(2-methoxyphenoxy) ethyl]-3-(2, 5-dimethoxyphenoxy) propylamine hydrochloride (MBII) which showed profound hypotensive action has been studied for its mechanism of action.

MATERIALS AND METHODS

Studies on blood pressure :

Mongrel dogs, either sexs weighing between 8 and 15 *kg* were employed. The anaesthetic agent always used was pentobarbital sodium (35 *mg/kg* i.v.), unless otherwise mentioned. The blood pressure was recorded from the common carotid artery or femoral artery using a mercury manometer. Trachea was exposed and respiration was recorded through a Marey's tambour. Groups of 3 dogs were employed for each experiment. For studying the onset, degree and duration of hypotensive action, the dogs were anaesthetized with chloralose (80 *mg/kg* i.v.) or pentobarbital sodium (35 *mg/kg* i.v.). Dogs were pretreated with atropine (3 *mg/kg*) or pheniramine (5 *mg/kg*) in order to test cholinergic or histaminic activity of MBII. The antiangiotensin effect was studied by infusing angiotensin (1 *mcg/ml* in 5% glucose normal saline) continuously at the rate which raised the blood pressure of the dog by about 25%. Response to the administration of adrenaline, noradrenaline and isopropylnoradrenaline 5 *mcg/kg* each was studied in drug treated dogs to find out the adrenergic receptor blocking activity. Influence of the drug on the rise of blood pressure due to bilateral carotid artery occlusion and stimulation of central cut end of vagus was studied as described by Plummer *et al.* (6).

The effect of drug on spinal dog and the influence on the contraction of nictitating membrane due to administration of adrenaline (5*mcg/kg*) and the stimulation of pre and post ganglionic fibres of the cervical sympathetic trunk was studied according to the technique of Burn (4). The cats were anaesthetized with chloralose (80 *mg/kg* i.p.). All drugs were injected through the cannulated femoral vein.

Studies on heart :

Experiments were performed on the dog heart *in situ*. The chest was opened in an anaesthetized dog and the contractions of auricle and ventricle were recorded directly. Electrocardiogram was recorded with Grass ink writing oscillograph using the conventional bipolar lead II.

Studies on the peripheral blood vessels :

Influence of the drug on hind limb perfusion of dog was studied according to the method described by Agarwal and Dandiya (1).

OBSERVATIONS

Blood pressure :

MBII, when administered in a dose of 200 *mcg/kg* in dogs anaesthetized with chloralose caused a mean fall of 55 *mm* of Hg. (50 to 60) which lasted for about 2½ hours. The heart rate was markedly increased. The respiration became shallow and rapid. In dogs anaesthetized with pentobarbital sodium similar effects were produced when a dose of 1 *mg/kg* was given (Table I).

TABLE I

Effect of MBII on the blood pressure of anaesthetised dogs

S. No.	Drug and dose	Anaesthesia used	No. of observation	Blood pressure in mm of Hg mean (Range)				Heart rate per minute mean (Range)			
				Before	After	Change	Duration of action	Before	After	Change	Duration of action
1	MBII 200*mcg/kg*	Chloralose 80*mg/kg* i.v.	3	140 (130-155)	85 (70-90)	55 (40-60)	150 (140-164)	136 (116-144)	230 (210-255)	94 (82-106)	120 (100-135)
2	MBII 1*mg/kg*	Pentobarbitone sodium 35*mg/kg* i.v.	9	125 (110-135)	65 (60-75)	60 (45-70)	170 (155-180)	154 (140-164)	216 (212-248)	62 (58-98)	90 (70-100)

The influence of MBII on various procedures is shown in Table II. The rise in blood pressure due to bilateral carotid artery occlusion, the stimulation of central cut end of vagus and administration of adrenaline and noradrenaline was antagonized by pretreatment with MBII whereas the effect of isopropyl noradrenaline was unaltered. In spinal dogs MBII did not show any hypotensive action in a dose of 200 *mcg/kg* but when the dose was increased to 1 *mg/kg* a slight and transient fall was observed. This fall in blood pressure was insignificant when compared to normotensive dogs.

Both atropine and pheniramine did not prevent the hypotensive action of the drug. The rise in blood pressure due to angiotensin infusion was also not antagonized by MBII.

MBII prevented the contraction of nictitating membrane of cat due to administration of adrenaline (5 *mcg/kg*) and the stimulation of pre and post ganglionic fibres of cervical sympathetic trunk (Fig. 2).

Action on the dog heart (in situ) :

On dog heart *in situ* the rate and the force of auricular and ventricular contraction was markedly increased in a dose of 1 *mg/kg* (Fig. 1). In the electrocardiogram, it increased the amplitude of P and QRS waves as well as the heart rate.

TABLE II

Influence of MBII on the alteration in blood pressure of dogs due to various procedures

Procedure adopted	*Dose of MBII*	*No. of observations*	*Alteration in the blood pressure response in mm of Hg mean (Range)*	
			Before	*After*
Carotid occlusion	1 *mg/kg*	3	40 (35-50)	5 (5-10)
Central vagal stimulation	1 *mg/kg*	3	50 (45-55)	15 (10-25)
Adrenaline (5*mcg/kg*)	1 *mg/kg*	3	30 (25-35)	...
Noradrenaline (5 *mcg/kg*)	1 *mg/kg*	3	35 (25-40)	...
Isopropyl noradrenaline (5 *mcg/kg*)	1 *mg/kg*	3	—60 (—50 to —70)	—60 (—50 to —70)
Spinal dog††	200 *mcg/kg*	3	..	—†
	1 *mg/kg*	3	..	—10 (—5 to —15)

†The effect did not last for more than 3 minutes.
††The blood pressure in these dogs ranged between 90 and 100 *mm* of Hg.

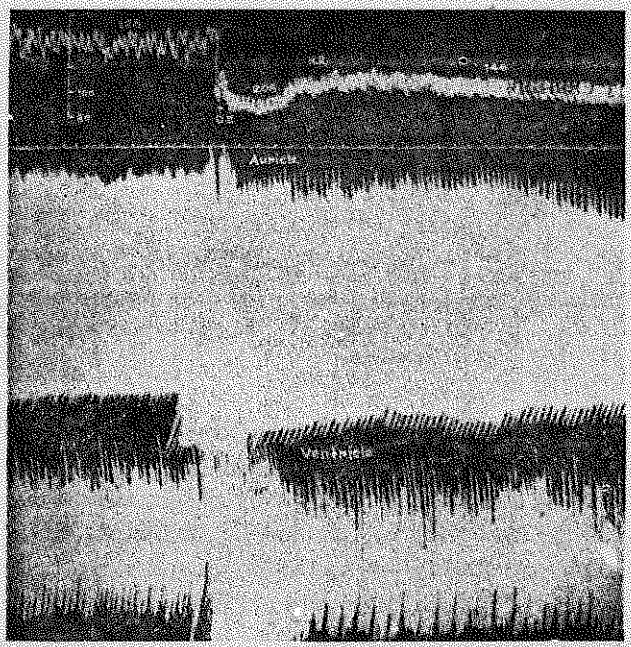

Fig. 1 Record showing the effect of MBII on blood pressure, auricular and ventricular contraction of dog (*in situ*)

Time 30 seconds
DI MBII 1 *mg/kg*
D Drum stopped for
H.R. Heart rate

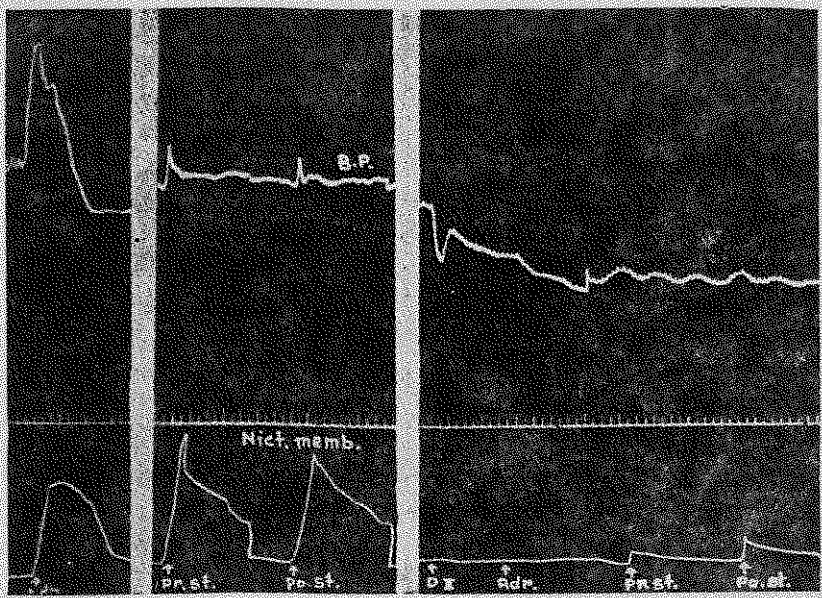

Fig. 2 : Record showing the influence of MBII on the contraction of nictitating membrane and blood pressure of cat due to the administration of adrenaline and stimulation of pre and post ganglionic fibres of cervical sympathetic trunk

DII	MBII (1*mg*/*kg*) Male cat, 2 *kg*.
Adr.	Adrenaline
Pr St	Pre-ganglionic nerve stimulation
Po St	Post-ganglionic nerve stimulation
Anaesthesia	Chloralose (80 *mg*/*kg*)
Time	30 seconds

Blood vessels :

Hind limb perfusion of dog did not show any change when the drug was administered in a dose of 100 *mcg*.

DISCUSSION

The potent hypotensive action of MBII is in conformity with the finding of Augstein *et al.* (2). In the present study an attempt has been made to elucidate its mechanism of action. The hypotensive action of MBII could not be blocked by pheniramine or atropine, indicating that it is not acting through the histaminic or cholinergic mechanism. MBII also did not affect the angiotensin induced hypertension showing thereby that it was devoid of any antiangiotensin activity. The blockade of the rise in blood pressure due to the administration of adrnaline and noradrenaline confirmed the alpha receptor blocking properties of the compound as shown by Augstein *et al.* (2). The effect of isopropylnoradrenaline was not influenced by this drug, indicating that it blocks only alpha adrenergic receptors. Like reserpine (6) this drug also reduced the rise in blood pressure due to bilateral carotid artery occlusion and stimulation of central cut end of vagus, indicating a central component in its mechanism of action. Absence of the hypotensive effect in spinal dogs in a dose of 200 *mcg*/*kg* and a slight but insignificant fall

in a dose of 1 *mg/kg* further supports the evidence of central component in its mechanism of hypotensive action. The blockade of contraction of nictitating membrane of cat due to the administration of adrenaline and the stimulation of pre and post ganglionic fibres of cervical sympathetic trunk confirms its alpha receptor blocking properties.

On the dog heart (*in situ*) MBII when injected in a dose of 1 *mg/kg* increased the heart rate and force of auricular and ventricular contraction. Electrocardiogram confirmed these findings and also ruled out the possibility of production of any cardiac abnormality. The increase in the rate and force of contraction of the heart may be due to the uninhibited beta receptors as it has a selective alpha receptor blocking activity.

Studies on the hind limb perfusion of dog revealed that this drug has no direct action on the blood vessels.

SUMMARY

(1) The mode of hypotensive action of N [2-(2-methoxyphenoxy) ethyl]-3-(2, 5-dimethoxyphenoxy) propylamine hydrochloride (MBII) has been investigated.

(2) The mechanism by which MBII exerts its hypotensive action appears to be central as well as peripheral.

(3) The drug does not seem to be suitable for clinical study as it also, like other alpha receptor blocking drugs, causes reflex tachycardia and palpitation since the beta receptors are unaffected.

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REFERENCES

1. Agarwal, S.L. and P.C. Dandiya. Chemical & preliminary pharmacological investigations of premine hydrochloride. *Indian Pharmacist*, **9**:120, 1954.
2. Augstein, J., W.C. Austin, R.J. Boscott, S.M. Green and C.R. Worthing. Some cardiovascular effects of a series of aryloxyalkylamines. *I.J. Med. Chem.*, **8**:356, 1965.
3. Borsy, J., E. Csanyi and I. Lazar. A method of assaying tranquilizing drugs on the inhibition of oriental hypermotility. *Arch. Int. Pharmacodyn.*, **124**:180, 1960.
4. Burn, J.H. *Practical Pharmacology*, Blackwell Publications, Oxford, 1952, p. 57.
5. Dandiya, P.C., P.K. Sharma and M.K. Menon. Studies on central nervous system depressants: Part IV—Structure activity relationship of some locally synthesized trimethoxybenzene derivatives. *Indian J. Med. Research*, **50**:750, 1962.
6. Plummer, A.J., A. Earl, J.A. Schneider, J. Trapold and W. Barret. Pharmacology of Rauwolfia alkaloids including reserpine. *Ann. N.Y. Acad. Sci.*, **59**: 8, 1954.
7. Sharma, J.D. and P.C. Dandiya. Studies on central nervous system depressants (I). General pharmacological properties of trimeglamide. *Arch. Int. Pharmacodyn. Ther.*, **137**:218, 1962.