AN ANALYSIS OF THE CENTRAL VASOMOTOR EFFECTS OF MONOAMINE OXIDASE INHIBITOR, MODALINE SULPHATE

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Received for publication March 6, 1972

Modaline, 2-methyl-3-piperidinopyrazine derivative, was found to inhibit monoamine oxidase (MAO) (1, 2) and showed therapeutic anti-depressant activity (3). This compound potentiated convulsions induced by tryptamine and hyperthermia induced by dopa similar to other MAO inhibitors (2). Moreover, it also antagonised reserpine induced hypothermia like imipramine (2). Gyllys et al. (4) showed that peripheral administration of modaline resulted in hypotension due to ganglionic blockade. Both imipramine and MAO inhibitors viz. pheniprazine and iproniazid were found to inhibit the excitability of the hypothalamic and brain stem vasomotor loci (5, 6). On the other hand, modaline potentiated the facilitation of monosynaptic spinal reflexes induced by stimulation of brain stem reticular formation (7). Therefore, investigation of the central vasomotor effects of modaline after injection into the lateral cerebral ventricle in dogs was carried out.

METHODS

The experiments were done on 26 adult mongrel dogs of both sexes weighing between 8 to 18 kg. The animals were anaesthetised with pentobarbitone sodium (30 mg/kg i.v.), bilaterally vagotomized and maintained on positive pressure artificial ventilation. A polythene tube was passed into the femoral vein. The blood pressure was recorded from the femoral artery through a mercury manometer on smoked kymograph paper. In some experiments, the blood pressure was monitored on Grass Model P 5 Polygraph using P 23 Statham pressure transducer. A cannula was implanted into the lateral cerebral ventricle according to the technique of Bhargava and Tangri (8) for intracerebroventricular administration of drugs. The excitability of the central vasomotor loci was assessed by eliciting reflex vasomotor responses obtained by electrical stimulation of the central cut end of right vagus nerve using Grass Model S 4 stimulator delivering square wave pulses (Parameters of stimulation: 10-20 cycles/sec, pulse duration 1 msec, 5-8 Volts) and by bilateral carotid arterial occlusion. The drugs used in this study were modaline sulphate (W-3207B-Warner Lambert, U.S.A.) hemicholinium, carbachol chloride, phenoxybenzamine hydrochloride, propranolol hydrochloride, tetrabenazine methanesulphonate and atropine sulphate. All the doses refer to their salts except hemicholinium which was used as a base. The volume
of fluid injected into lateral cerebral ventricle did not exceed 0.5 ml at any one time.

RESULTS

Vasomotor effect of intracerebroventricular (i.c.v.) injection of modaline sulphate

The effects of graded doses (5–15 mg) of modaline sulphate injected into the lateral cerebral ventricle were investigated on the blood pressure and reflex vasopressor responses induced by bilateral carotid arterial occlusion and by stimulation of the central cut end of vagus nerve in 8 dogs. Fig. 1 shows results of such a study. Modaline sulphate (10 mg i.c.v.) consistently produced a biphasic pressor response. The initial phase of the pressor response appeared immediately after injection of the drug, the magnitude of rise being 50 mm Hg (range 30–60 mm Hg). The blood pressure returned to normal within 5 min. The delayed phase of the pressor response to i.c.v. modaline sulphate appeared after 75 min of drug administration and reached a peak (60 mm Hg, range 40–70 mm Hg) in 240 min. This was associated with potentiation of the pressor responses to carotid arterial occlusion and afferent vagal stimulation. Furthermore, both the initial and delayed pressor responses to i.c.v. modaline sulphate were found to be dose dependent.

Effect of repeated i.c.v. injections of modaline sulphate

Modaline sulphate was injected into the lateral cerebral ventricle repeatedly at regular

![Graph](image-url)

Fig. 1. Effect of intracerebroventricular (i.c.v.) injection of modaline sulphate (10 mg) on blood pressure and reflex pressor responses evoked by stimulation of central cut end of vagus (CV) and by carotid arterial occlusion (CO) in 13.5 kg dog. Note, the biphasic pressor response, the initial phase appearing immediately after modaline injection which disappeared within 5 min and the delayed phase reaching its peak in 240 min and associated with the facilitation of CV and CO induced pressor response.
intervals and the effect was observed on the blood pressure in 3 dogs. Results are shown in Fig. 2. The initial phase of the pressor response to i.c.v. modaline sulphate (10 mg) revealed tachyphylaxis as the magnitude of the pressor response with successive injections of the drug at 30 and 60 min intervals was found to be reduced. However, it was again observed when i.c.v. injection of modaline sulphate was made at an interval of 120 min.

**Effect of i.c.v. atropine pretreatment on the initial pressor response of modaline sulphate**

The effect of i.c.v. pretreatment of atropine (1.0 mg) was studied on the initial pressor response of i.c.v. modaline sulphate and carbachol in 3 dogs. Results are shown in Fig. 3.

Pressor responses to both i.c.v. modaline sulphate (5 mg) and carbachol (100 μg) were found to be blocked after atropine pretreatment.

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**Fig. 2.** Effect of repeated i.c.v. administration of modaline sulphate (10 mg) on blood pressure in 14.0 kg dog. Note the tachyphylaxis of initial phase of pressor response when the drug was repeated at 30 and 60 min intervals.

**Fig. 3.** Effect of i.c.v. atropine (1 mg) on the initial pressor response to i.c.v. modaline sulphate (5 mg) and carbachol (100 μg) in 9.0 kg dog. Note the blockade of modaline sulphate and carbachol induced pressor responses after atropine pretreatment.
Effect of i.c.v. modaline sulphate on the blood pressure in hemicholinium pretreated dogs

The effect of modaline sulphate injected into the lateral cerebral ventricle was investigated on the blood pressure before and after 5 hr of i.c.v. pretreatment with hemicholinium (2 mg) in 4 dogs (Fig. 4). The initial pressor response induced by i.c.v. modaline sulphate (10 mg) was found to be inhibited after hemicholinium pretreatment.

Effect of atropine, phenoxybenzamine, propranolol and tetrabenazine pretreatment on the delayed pressor response to i.c.v. modaline sulphate

The effects of i.c.v. pretreatment with atropine (1 mg) phenoxybenzamine (10 mg) and propranolol (1.0 mg) and intraperitoneal pretreatment with tetrabenazine (70 mg/kg i.p.) were investigated on the modaline sulphate (10 mg i.c.v.) induced delayed pressor response and facilitation of centrally mediated reflex vasomotor responses in 8 dogs. Modaline sulphate still induced a delayed rise in the blood pressure associated with potentiation of pressor responses evoked by carotid arterial occlusion and afferent vagal stimulation in animals pretreated 1 hr before with i.c.v. atropine, phenoxybenzamine and propranolol and 18 hr before with i.p. tetrabenazine.

DISCUSSION

Modaline sulphate, a monoamine oxidase (MAO) inhibitor was found to induce a dose dependent biphasic pressor response in dogs after intracerebroventricular (i.c.v.) adminis-
tration in the present study. It produced an immediate short lived rise in blood pressure followed by a delayed pressor phase appearing 75 min after i.c.v. injections of the drug and reaching the peak in 240 min (see Fig. 1). The fact that the initial pressor response to i.c.v. modaline sulphate showed tachyphylaxis on repeated administration suggests that there was a release of some neurotransmitter in the central nervous system (CNS). Pretreatment with hemicholinium (i.c.v.) which depleted acetyl choline in CNS by inhibiting its synthesis (9), blocked the initial pressor response to i.c.v. modaline sulphate. This blockade could not be due to an inhibitory action of hemicholinium on the central vasomotor loci which was observed on peripheral administration (10) since i.c.v. hemicholinium failed to alter reflex vasomotor responses to carotid arterial occlusion and medullary stimulation (10). This observation suggests that i.c.v. modaline sulphate released acetyl choline in the CNS in order to induce this initial pressor response. Furthermore, an involvement of muscarinic receptor in this response was demonstrated since it was blocked by i.c.v. pretreatment with anti-muscarinic agent, atropine in a dose which also blocked pressor response to i.c.v. carbachol (see Fig. 3). The direct effect of atropine on postsynaptic membrane (11) could not be ruled out from this study regarding the blockade of the pressor responses. Demonstration of an excitatory role of acetylcholine in the central vasoregulatory mechanisms (12, 13) further confirmed this contention. Moreover, i.c.v. tyramine induced pressor response was also shown to be mediated through a release of acetylcholine in the CNS (14).

On the contrary, the delayed phase of the pressor response to i.c.v. modaline sulphate appeared unrelated to its MAO inhibitory activity since it was still obtainable in animals pretreated (i.c.v.) with alpha and beta adrenoceptor blocking agents viz. phenoxybenzamine and propranolol and with tetrabenazine which depleted catecholamines centrally. Gylys and Muccia (15) also demonstrated a delayed stimulant effect of modaline sulphate on the CNS independent of MAO inhibition since it increased locomotor activity in the animals pretreated with reserpine. Moreover, other MAO inhibitors like iproniazid and pheniprazine were found to inhibit hypothalamic and brain stem vasomotor loci (6). Furthermore, this delayed stimulant effect of modaline sulphate on the central vasomotor loci was not due to its imipramine like activity on the CNS (2) since imipramine was found to inhibit medullary vasomotor loci (5). Similarly, an activation of cholinergic mechanism in CNS for this delayed rise in the blood pressure was unlikely as it was not blocked by prior central atropinization. Thus, it may be suggested that modaline sulphate directly stimulated the central vasomotor loci. The observation that i.c.v. modaline sulphate potentiated the centrally mediated vasomotor reflexes, also suggests an increase in the excitability of central vasomotor loci following drug administration. Also, Dhasmana et al. (7) demonstrated a stimulant effect of modaline sulphate on brain stem reticular formation. The latency of onset of this direct stimulant effect of i.c.v. modaline sulphate could be due to a release of an active metabolite of the drug in the CNS (1, 2).
SUMMARY

Modaline sulphate injected intracerebroventricularly (i.c.v.) induced a biphasic pressor response consisting of initial and delayed phases. The delayed phase was associated with facilitation of the reflex vasomotor responses elicited by afferent vagal stimulation and carotid arterial occlusion. The initial phase of the pressor response appears to be due to a release of acetylcholine in the central vasomotor loci while the delayed phase of the pressor response seems to be a direct central stimulant effect.

Acknowledgements: The authors are grateful to Council of Scientific and Industrial Research, New Delhi for financial assistance and to Warner Lambert (U.S.A.) for the generous supply of modaline sulphate (W-3207B).

REFERENCES