CENTRAL MUSCLE RELAXANT ACTIVITY OF A DOZEN CNS ACTIVE AGENTS AND A CORRELATION WITH THEIR PSYCHOTROPIC ACTIVITY

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Received for publication July 18, 1967

Tricyclic antidepressants like imipramine (IMI), desmethylinipramine (DMI) and amitriptyline (AMI) have been shown to antagonise muscle rigidity in experimental reserpine depressive syndrome (1-4) as well as in clinical depressive states. Imipramine also abolishes the rigidity associated with parkinsonism (5). We have earlier reported that these agents possess a potent central muscle relaxant activity of longer duration (6-8). Orphenadrine another structurally similar antidepressant has been reported to possess both central and peripheral muscle relaxant activity (9-11).

Chlorpromazine, a tranquillizer causes skeletal muscle relaxation in certain spastic disorders. Both supraspinal (12) and spinal (13) components have been reported for such activity. Preferential blockade of monosynaptic reflexes has been reported for major tranquillizers (14). Chlorpromazine has been shown to have less potent antistrychnine activity than mephenesin. Bhargava and Srivastava (15) also reported that chlorpromazine is less potent than mephenesin in antagonizing strychnine induced potentiation of linguomandibular polysynaptic reflex.

Like tricyclic antidepressants, MAO inhibitors also antagonize reserpine induced muscular rigidity. However, no report regarding the central muscle relaxant activity of these agents is available in the literature. The commonly employed group of drugs in the treatment of psychic disorders are antidepressants, tranquillizers and stimulants. We have earlier suggested that the central muscle relaxant activity of imipramine and allied drugs, plays an important role in their antidepressant action. The present study was undertaken with two aims; firstly to find out a potent central muscle relaxant of longer duration than mephenesin secondly to explore the role of such an inhibitory activity (central muscle relaxant activity) in the antidepressive, tranquillizing and stimulant action of the drugs.

METHODS

Thirty-five cats (2.5-4.0 kg) of either sex were employed in the present study. The animals were anaesthetized with pentobarbitone sodium, were routinely vagotomised

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and maintained on positive pressure artificial respiration. The blood pressure was recorded on smoked kymograph paper from a common carotid artery through mercury manometer. A silver cannula was implanted into a lateral cerebral ventricle according to the method of Feldberg and Sherwood (16). The linguomandibular reflex was elicited by the method of King and Unna (17) as modified by Bhargava and Srivastava (18). The inhibition of the linguomandibular reflex was taken as the criterion for the central muscle relaxant activity. Sciatic nerve stimulated contraction of the gastrocnemius muscles was taken as control for the peripheral neuromuscular transmission in all the experiments. The results were subjected to the statistical analysis by the method of Finney (19) and ED50 (mg) standard error (SE) and 95% confidence limits were calculated.

The drugs were dissolved in normal saline and given intracerebroventricularly (ICV). The total volume of the fluid injected ICV at a time never exceeded 0.25 ml.

The drugs employed in the present study were mephenesin (Myanesin, B.D.H.), imipramine (Tofranil, Geigy), amitriptyline (Elavil, M.S.D.), desmethylimipramine (Pertofran, Geigy), iproniazid (Marsalid Hoffman La Roche), phenelzine (Nardil, Warner Lambert), amphetamine (Benzedrine, S.K.F.), ephedrine, chlorpromazine (Largactil, M. & B), thioridazine (Mellaril, Sandoz), HF 2159 (Wander), chlordiazepoxide (Librium, Roche) and orphenadrine (Riker).

RESULTS

In the present study a dozen psychotropic agents were studied on the linguomandibular reflex (LMR) in cats. Intracerebroventricular administration of imipramine, desmethylimipramine and amitriptyline inhibited the linguomandibular reflex. The ED50, standard error and 95% confidence limit of these agents are shown in Table 1 and Fig. 2. Amitriptyline had longest duration of action (76 minutes), next in order was imipramine (46 minutes), while desmethylimipramine was the short acting (10 minutes). Orphenadrine, an agent having structural similarity with imipramine, has been shown to possess central muscle relaxant activity. This agent was also found to inhibit the linguomandibular reflex (activity ratio 1.73) for a longer period (27 minutes) than mephenesin.

Amongst the MAO inhibitors, iproniazid and phenelzine were studied for their effect on the linguomandibular reflex. Intracerebroventricular injection of these agents inhibited the linguomandibular reflex. Iproniazid was less potent (activity ratio 0.03) than mephenesin while phenelzine was more potent (activity ratio 3.12). The duration of action of these agents was more than mephenesin (see Fig. 2 and Table 1).

CNS stimulants, amphetamine and ephedrine were studied on the linguomandibular reflex. Lower doses of amphetamine (0.1 to 1 mg ICV) inhibited the linguomandibular reflex. However, this block could never exceed more than 30%. On the contrary higher doses (more than 2.0 mg ICV) produced facilitation of the responses. Ephedrine was found to be the weakest agent (activity ratio 0.18) amongst the agents tested. The duration of action of ephedrine at ED50 dose was 20 minutes.

Tranquillizers like chlorpromazine, thioridazine, HF 2159 and chlordiazepoxide

were also studied on the linguomandibular reflex. Amongst these agents HF 2159 (activity ratio 11.36) was the most potent. Chlorpromazine (activity ratio 6.94) thioridazine (activity ratio 3.00) and chlordiazepoxide (activity ratio 1.73) came next in the decreasing order of potency. All these agents had longer duration of action as compared to mephenesin (see Fig. 2 and Table 1). However, chlorpromazine exhibited the longest duration of action.

DISCUSSION

Increased muscle tone is a common accompaniment of various psychic disorders (20, 21). Reserpine, an amine depletor, is known to produce an experimental syndrome similar to the clinical depressive states. Clinically as well reserpine is known to produce acute psychosis in patients. Imipramine and allied drugs have been found to antagonize the increased muscle tone both in clinical depressive states and in experimental reserpine syndrome (1-4). We have earlier demonstrated that imipramine, desmethylinipramine and amitriptyline possess potent central muscle relaxant activity (6, 7). Such a central inhibitory effect on the

FIG. 1. Shows the effect of ephedrine (upper panel), iproniazid (middle panel) and thioridazine (lower panel) on the linguomandibular reflex (LMR) and blood pressure (B.P.). All the three agents inhibited the LMR. Recovery from the drug effect is shown in the figure.

FIG. 2. Central muscle relaxant activity of a dozen CNS active agents. The ED₅₀ (mg) with standard error is shown on the left and the duration of action (minutes) is shown on the right. HF 2159 was the most potent agent while chlorpromazine had the longest duration of action.

TABLE 1. Central muscle relaxant activity of psychotropic agents.

Drugs	ED50±S.E. (mg)	95% Confidence limits	Activity ratio
Mephenesin	1.25±0.01	1.27 —1.23	1.00
Imipramine	0.24±0.02	0.27 —0.21	5.20
Desmethylimipramine	0.56±0.20	0.95 —0.17	2.23
Amitriptyline	0.40±0.002	0.41 —0.39	3.12
Orphenadrine	0.77±0.001	0.778—0.774	1.62
Phenelzine	0.40±0.001	0.409—0.404	3.12
Iproniazid	4.13±0.034	4.199—4.064	0.30
Ephedrine	6.96±0.730	8.39 —5.53	0.18
Amphetamine	1 mg produced 30% inhibition of the reflex (LMR) while higher doses were either ineffective or produced facilitation of the responses		
Chlorpromazine	0.18±0.002	0.185—0.178	6.94
Thioridazine	0.416±0.02	0.455—0.377	3.00
HF 2159	0.11±0.002	0.117—0.108	11.36
Chlordiazepoxide	0.72±0.003	0.731—0.722	1.73

TABLE 2.

Drugs	Central muscle relaxant activity		Clinical efficiency as antidepressant
	ED50 (mg)	Activity ratio	
Mephenesin	1.25	1	—
Imipramine	0.24	5.20	71% (22)
Amitriptyline	0.40	3.12	65% (23)
Phenelzine	0.40	3.12	62% (24)
Desmethylimipramine	0.56	2.23	68% (25)
Orphenadrine	0.77	1.62	—
Iproniazid	4.13	0.30	54% (26)

TABLE 3.

Drugs	Central muscle relaxant activity		Forced locomotor activity		Reference
	ED50(mg)	Activity ratio	ED50(mg)	Activity ratio	
Mephenesin	1.25	1	106.4	1	(27)
Chlorpromazine	0.18	6.94	5.01	21.2	(28)
Thioridazine	0.416	3.00	15.85	6.7	(28)
HF 2159	0.11	11.36	—	—	—
Chlordiazepoxide	0.72	1.73	67.1	1.5	(27)

somatic control of these agents, might be playing an important role in relieving the increased muscle tone of various psychic disorders.

From the results of the present study it is obvious that both tricyclic antidepressants as well as MAO inhibitors possess potent central muscle relaxant activity of relatively longer duration than mephenesin. A comparison of the activity ratios of these agents

for inhibiting the linguomandibular reflex and their clinical efficacy in depressive states has been made in Table 2. From the Table it is clear that both the activities run parallel. Such a parallelism between central muscle relaxant activity and clinical efficacy suggests that the central muscle relaxant activity might be playing an important role in the antidepressant action of these agents.

Out of the two stimulants studied only ephedrine exerted some inhibitory effect on the linguomandibular reflex. Smaller doses of amphetamine have some inhibitory effect while higher doses either had no effect or potentiated the responses. As amphetamine a potent central nervous system stimulant did not have any consistent inhibitory effect on the linguomandibular reflex, it seems that this activity which may be present in some CNS stimulants like ephedrine, has no relationship with the stimulant action of the drug.

All the four tranquillizers studied in the present study showed potent inhibitory effect on the LMR.

Forced locomotor activity has been used to test the tranquillizing activity of a drug (29). A good correlation has been observed between the drug induced locomotor suppression and conditioned avoidance suppression (28, 30-32). A comparison of central muscle relaxant activity and suppression of forced locomotor activity has been made in Table 3. From the Table it is obvious that both the activities run parallel.

SUMMARY

In the present study a dozen CNS active agents have been studied on the linguomandibular reflex and an attempt has been made to correlate the central muscle relaxant activity with their antidepressant, CNS stimulant and tranquillizing activities. In the present series HF 2159 was found to be most potent (11.36 times of mephensin). Amongst the antidepressants there seemed a close correlation between the central muscle relaxant activity and the clinical efficacy of the drugs. Out of two CNS stimulants only ephedrine elicited some inhibitory effect while amphetamine had either no effect or potentiated the responses. All the four tranquillizers showed potent inhibitory effect on the LMR. A close correlation between the tranquillizing and central muscle relaxant activity is shown in Table 3.

Acknowledgement: The authors are grateful to Indian Council of Medical Research, New Delhi for financial assistance.

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