ANALGESIC EFFECT OF SOME MONOAMINE OXIDASE INHIBITORS*

A. C. JAUHARI AND S. K. BAPAT

Department of Pharmacology,
M. L. N. Medical College, Allahabad

Catecholamines (adrenaline, noradrenaline) in the central nervous system have been implicated in analgesia. It is a common experience that pain may not be felt during acute injuries, and this has been attributed to a sympathetic stimulation, resulting in an increased secretion of catecholamines both peripherally and centrally (11). Adrenaline injected into carotid artery or intracisternally causes a long lasting analgesia in cats and dogs (7, 12). These findings suggest that the basic mechanism of analgesia may be related to the concentrations of catecholamines at central sites.

Since the monoamine oxidase (MAO) inhibitors cause an increase in the concentration of catecholamines in rat, rabbit and mouse brain (3,4,9,14,20), and also potentiate the analgesic effect of narcotic analgesics (2), it was thought worthwhile to observe if MAO inhibitors are analgesics themselves.

MATERIALS AND METHODS

The radiant heat method using the hot nichrome wire analgesiometer as described by Davies *et al.* (5) and modified by Gujral and Khanna (10) was employed in this study. Albino rats of either sex, weighing 50-100 *g* and maintained on a diet recommended by the Indian Council of Medical Research (vide Circular No. 1/55/66-R of April 27, 1968) were allowed free access to food and water, except during the performance of the test. No animal was used more than twice a week and not more than five times in all. Preliminary screeing was done to select rats which showed a reaction time of 5 sec initially. The animals in groups of 10 were tested again at various times after the drug treatment; rats that now showed a reaction time of 10 sec or more were taken to be analgized or protected.

The drugs used in the present study were, tranylcpromine, iproniazid, isocarboxazid and nialamide. All drugs were used as pure bases and their doses refer to the base.

All the drugs except iproniazid, were suspended in gum acacia and administered by intragastric intubation in graded doses, to separate groups of animals. Iproniazid was dissolved in distilled water and administered by intragastric intubation to the animals. At least five

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dose levels giving analgesic effect between 0% to almost 100% were determined for each drug. ED_{50} was calculated by the log-dose probit response method of Finney (8).

The analgesia was also tested in animals treated with reserpine 5 *mg/kg* ip 24 hr earlier followed by a single dose of each of the MAO inhibitors. Other groups of animals received dihydroxyphanylalanine (DOPA, 20 *mg/kg*) or 5-hydroxytryptophan (5-HTP, 15 *mg/kg*) intravenously immediately after the MAO inhibitor and the test for analgesia was repeated 30 min later.

In two additional groups of the animals, isocarboxazid, was administered 30 min prior to reserpine and tetrabenazine; test for analgesia was done immediately and after varying intervals.

RESULTS

From the plot of regression lines for the analgesic effect of MAO inhibitors, ED_{50} values were computed. The most potent analgesic was isocarboxazid (ED_{50}, 2.240 *mg/kg*); the least potent was iproniazid (ED_{50}, 88.50 *mg/kg*). The ED_{50}'s of tranylcypromine and nialamide were 6.78 and 13.46 *mg/kg* respectively. Table I shows the onset, peak and duration of the analgesic action of the MAO inhibitors used in doses reported to cause a maximum MAO inhibition. Table II shows that analgesia does not occur in reserpine pretreated animals, but administration of DOPA restores the analgesic effect of MAO inhibitors. Table III shows the effects of reserpine and tetrabenazine in the same animals pretreated with isocarboxazid. The analgesia was potentiated by both, more so by tetrabenazine.

TABLE I

The onset, peak and duration of analgesic action of MAO inhibitors in rats.

Drugs	*% of animals analgized***									*Period of maximum MAO inhibition*
	15 *min*	30 *min*	1 *hr*	2 *hr*	3 *hr*	4 *hr*	5 *hr*	6 *hr*	7 *hr*	
Tranylcypromine (5 mg/kg*, orally)	20	30	30	30	20	0				1 hr (16)
Iproniazid (100 mg/kg*, orally)	20	30	30	30	40	50	30	20	0	4 hr (13)
Isocarboxazid (2 mg/kg*, orally)	40	50	40	30	20	0				1/2 hr (18)
Nialamide (10 mg/kg*, orally)	40	40	50	30	20	0				1 hr (13)

*This dose has been reported to be causing maximum MAO inhibition (see references 13, 16 and 18).
**Reaction time increased by 5 sec (control time, 5 sec).

TABLE II

The analgesic effects of MAO inhibitors in reserpine-treated rats and reserpine-treated rats given DOPA (20 mg) or 5-HTP (15 mg/kg, iv)

Drugs (peak time of MAO inhibition in parentheses)	*Peak analgesic effects in normal animals (time of effect in parentheses)*	*Peak analgesic effect in reserpinized animals*	*Effect of DOPA on reserpine treated animals*	*Effect of 5 HTP on reserpine-treated animals*
Tranylcypromine 5 *mg/kg*, (1 hr)	30% (After 1 hr)	0%	30%	0%
Iproniazid 100 *mg/kg*, (4 hr)	50% (After 4 hr)	0%	50%	0%
Isocarboxazid 2 *mg/kg*, (1/2 hr)	50% (After 1/2 hr)	0%	50%	0%
Nialamide 10 *mg/kg*, (1 hr)	50% (After 1 hr)	0%	50%	0%

TABLE III

Effect of reserpine and tetrabenazine on isocarboxazid (2 mg/kg, orally) induced analgesia.

Initial analgesia	*Reserpine 5 mg/kg, ip 1/2 hr later*	*Tetrabenazine 50 mg/kg, ip 1/2 hr later*	*Duration of analgesia*
50%	70%	90%	6 hr.

DISCUSSION

The neurohumoral basis of analgesia is still a matter for speculation. However, various workers have suggested the role of catecholamines in analgesia. Adrenaline has been known to be analgesic (7, 12). Morphine causes a decrease in the concentration of catecholamines, specially noradrenaline in the brain (6, 21) and it can be suggested that the analgesic effect of morphine may be due to a release of noradrenaline in the CNS. Similarly agents causing a decrease in the concentration of catecholamines in the CNS antagonize morphine analgesia (1, 19) and agents increasing the concentration of catecholamines potentiate morphine analgesia (17).

In the present study we have used drugs that can increase the concentration of catecholamines in the CNS by inhibiting the MAO which is the main enzyme responsible for the

degradation of catecholamines at this site. All the MAO inhibitors showed analgesic effects and remarkably the maximum analgesia was observed at a time which coincided with the reported time of peak MAO inhibitory effect of each drug as is clear from Table I. Moreover, isocarboxazid which is the most potent MAO inhibitor (18) showed the most potent analgesic effect.

Prior treatment of animals with reserpine resulted in disappearance of the analgesic effects of all the MAO inhibitors. Reserpine has been reported to antagonise morphine analgesia as well (19). Such an effect could be due to the depletion of the catecholamines in the CNS, brought about by reserpine.

Analgesia was restored after DOPA but not after 5-HTP, suggesting that noradrenaline, adrenaline, dopamine, or DOPA could serve as neurohumoral substance(s), but not 5-HTP or 5-hydroxytryptamine (5-HT). Reserpine and tetrabenazine in isocarboxazid treated animals induced marked analgesic effects. This is probably due to an acute reserpine and tetrabenazine induced noradrenaline release; the released noradrenaline being now protected from destruction by the blockade of MAO.

SUMMARY

1. Tranylcypromine, iproniazid, isocarboxazid and nialamide were tested for analgesic activity by employing the radiant heat method using the hot nichrome wire analgesiometer as described by Davies *et al.* (5).

2. All the drugs were found to possess analgesic activity of varying degree and duration.

3. Prior treatrnent of the animals with reserpine abolished the analgesia; however, the analgesic effect was restored following administration of DOPA in these animals. The administration of 5-HTP had no such effect.

4. Reserpine and tetrabenazine, potentiated the analgesic effects of MAO inhibitors.

5. Our findings suggest that the MAO inhibitors owe their analgesic activity to increased levels of catecholamines in the C.N.S.

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REFERENCES

1. Bapat, S.K. and V. Chandra. Effect of tetrabenazine on morphine analgesia in rats. *Ind. J. Physiol. Pharmac.*, **12** : 106, 1968.

2. Bapat, S.K. and A.C. Jauhari. Potentiation of morphine analgesia by MAO and COMT inhibitors. *Ind. J. Pharmac.*, **1** : 4, 1969.

3. Berther, A. Effect of reserpine on the storage of catecholamines in brain and other tissues. *Acta. Physiol. Scand.*, **51** : 75, 1961.

4. Crout, J.R., C.R. Creveling and S. Udenfriend. Norepinephrine metabolism in rat brain and heart. *J. Pharmac. Exp. Ther.*, **132** : 269, 1961.

5. Davies, O.L., S.J. Raventos and A.L. Walpole. Method for evaluation of analgesic activity using rats. *Br. J. Pharmac. Chemother.*, **1** : 255, 1946.

6. Elliott, T.R. (1912) Quoted from Progress in Medicinal Chemestry, Vol. II. Ed. Ellis G.P. and G.B. West. London. Butterworths 1962, p. 216.

7. Feldberg, W. and S.L. Sherwood. Injection of drugs into the lateral ventricle of cats. *J. Physiol. (Lond.)*, **123** : 148, 1954.

8. Finney, D.J. Probit Analysis, 2nd Ed., University Press, Cambridge, 1962.

9. Green, A.F., P.A. Young and F. Caplfrey, (1951). Quoted from Screening Methods in Pharmacology, Turner, R.A., Academic Press. 1965 P. 306.

10. Gujral, M.L. and B.K. Khanna. Comparative evaluation of some of the narcotic analgesics. *J. Sci. Ind. Res.*, **168** : 11, 1956.

11. Hotz, P. and E. Westermann (1965). Quoted from Physiologicol Pharmacology Vol. II. Ed. Root and Hoffman, Academic Press, 1965, p. 227.

12. Leimdorfor, A. The action of sympathomimetic amines on central nervous system and the blood sugar relation of chemical structure to mechanism of action. *J. Pharmac. Exp. Ther.*, **98** : 62, 1950.

13. Laroche, M.J. and B.B. Brodie. Lack of relationship between inhibition of monoamine oxidase and potentiation of hexobarbital hypnosis. *J. Pharmac. Exp. Ther.*, **130** :134, 1960.

14. Pletscher, A. Weikung Von Isoprophylisomcotin saurehydrazid aub den Stoffewechsel Von catecholaminen und 5-Hydroxytryptamine. In Gehirn Schwechsel Wacher, **67** : 1532, 1957.

15. Quinn, G.P., P.A. Shore and B.B. Brodie. Biochemical and pharmacological studies of Ro 1-9569 (Tetrabenazine) a non indol tranquillizing agent, with reserpine like effects. *J. Pharmac. Exp. Ther.*, **127** : 103, 1959.

16. Robson, J.M. and R.S. Stacey. Recent Advances in Pharmacology, London, J.A. Churchill Ltd. 1961.

17. Schaumann, W. Beeinfluss Ung der analgesischen Wirkung des Morphine durch Reserpin. *Arch. Exp. Path. Pharma.*, **235** : 1, 1958.

18. Schuwartz, M.A. The metabolism of isocarboxazid in the rats. *J. Pharmac. Exp. Ther.*, **130** : 157, 1960.

19. Sigg, F.B., G. Caprio and J.A. Schneider. Synergism of amines and anatagonism of reserpine to morphine analgesia. *Proc. Soc. Exp. Biol. Med.*, **197** : 97, 1958.

20. Spector, S.P., A. Shore and B.B. Brodie. Biochemical and pharmacological effect of monoamineoxidase inhibitors - iproniazid, JB 516, and JB 835. *J. Pharmac. Exp. Ther.*, **128** : 15, 1960.

21. Vogt, M. The concentration of sympathin in different parts of the central nervous system under normal conditions and after administration of drugs. *J. Physiol.*, (*Lond.*), **123**: 451, 1954.