The effects of RX 336M and RX 5050M on tests for antidepressant activity in mice

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Recent experiments in our laboratories have indicated that narcotic agonists, partial agonists and, to a limited extent, narcotic antagonists, possess certain pharmacological properties similar to those of (+)-amphetamine, desmethylimipramine and isocarboxazid, although they do not fit into any single category of known antidepressant (Doggett, Reno & Spencer, 1974).

Since cyclazocine has already been shown to have clinical antidepressant activity (Fink, Simeon, Itil & Freedman, 1970), we have investigated two synthetic partial agonists RX 336M (7,8-dihydro-5′,6′-dimethylcyclohex-5′-eno [1′, 2′, 8, 14] codeinone) and RX 5050M (*N*-cyclopropylmethyl-7α-(1-hydroxy-1-methylethyl) 6,14-*endo*ethano-6,7,8,14-tetrahydronorthebaine) in order to characterize further the antidepressant activity of this class of compound in experimental animals.

Groups of 10 male and female albino mice of an ICI strain, weighing 18-20 g and housed at a constant temperature of 21 ± 1°C, were used. A dose of 5 mg/kg s.c. of each RX compound was used throughout.

Both RX 336M and RX 5050M showed activity against reserpine. They reversed both the established hypothermia and ptosis induced by 3 h pretreatment with reserpine (2.5 mg/kg i.p.), although they were not able to prevent hypothermia from developing if given 1 h before this dose of reserpine. The use of tetrabenazine (25 mg/kg i.p.) as an alternative laboratory model of depression, however, revealed a difference in activity between RX 336M and RX 5050M. Whereas both reversed the hypothermia induced by 1 h tetrabenazine pretreatment, only RX 336M could prevent this hypothermia from developing if given 1 h before tetrabenazine.

In addition to investigating their activity against the more specific models of depression, other experimental procedures in which established antidepressants have a known effect were used. Both RX 336M and RX 5050M produced a two-fold increase in spontaneous locomotor activity (measured over a 2 h period), which was accompanied by an increase in core temperature (approx. 1°C max at 30 min). Also they both potentiated the number of convulsions induced by picrotoxin (3.6 mg/kg i.p.) and, to a lesser degree, those produced by leptazol (100 mg/kg i.p.) when administered in each case 1 h before the convulsive agent. Finally, when given 30 min beforehand, they had no significant effect upon the incidence of head twitches observed after injection of 5-hydroxytryptophan (200 mg/kg i.p.).

Thus, both RX 336M and RX 5050M are active in a variety of laboratory procedures designed to detect antidepressant activity. Furthermore, as previously reported for morphine and cyclazocine (Doggett, Reno & Spencer, 1974), this activity cannot be placed in any classically recognized group.

All the narcotic agonists and partial agonists so far investigated are effective in opposing at least one aspect of the reserpine depressive syndrome, an established method of evaluating potential antidepressant activity. However, their pharmacological profiles in other tests (originally developed to demonstrate the antidepressant activity of monoamine oxidase inhibitors, tricyclics and sympathomimetics) differ significantly, both from each other and from those of the established antidepressants. This observation adds further weight to the hypothesis that the narcotic agonists and partial agonists may represent a novel class of antidepressant compounds.

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References

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