Potentiation of picrotoxin-induced convulsions in mice by antidepressants. Specificity of the effect.

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The literature contains two brief reports describing the potentiation of picrotoxin-induced convulsions in rats (Barron, Hall, Natoff & Vallance 1965) and mice (Doggett, Reno & Spencer, 1974) by imipramine or potential antidepressant agents. The specificity of this test for thymoleptics has now been studied.

Groups of 10 male albino mice (LAC/A) weighing 20-24 g were individually housed in perspex boxes (20 x 10 x 10 cm). Soluble test drugs were injected subcutaneously at various times before the standard sub-threshold dose of picrotoxin (3.5 mg/kg, i.p.).

CD_{50} values (50% of the mice convulsing within 45 min) and 95% confidence limits of active drugs at the time of peak effect were: nialamide (5.6 mg/kg, 3.1-10.1, 1 h), tranylcypromine SO_4 (13.4 mg/kg, 8.2-21.9, 2 h), desmethylimipramine HCl (DMI) (14.2 mg/kg, 9.5-21.0, 2 h, imipramine HCl (15.2 mg/kg i.p., 7.5-30.7, 2 h), viloxazine HCl (Vivalan^R) (18.9 mg/kg, 10.8-33.0, 1 h) and morphine SO_4 (25.2 mg/kg, 17.6-36.1, 0.5 h).

Consistent dose-response lines were not obtained with d-amphetamine SO_4, methamphetamine HCl, apomorphine HCl, nalorphine HBr, naloxone HCl, chlordiazepoxide HCl, chlorpromazine HCl, chlorzoxazone, γ-aminobutyric acid, compound 48/80, chlorpheniramine maleate, atropine SO_4, eserine SO_4, propranolol HCl, lignocaine HCl or theophylline.

Phenytoin (4.6 mg/kg, 3.0-7.0, 4 h), in contrast to trimethadione, was active in the picrotoxin test and this result is consistent with the findings of Lotti, Torchiana & Porter (1973) in the mouse reserpine-reversal test. The weak narcotic antagonist, RX 336-M (Cowan & Macfarlane, 1974) was active (7.3 mg/mg, 4.4-11.9, 1 h) in both tests whereas dose-response lines were not obtainable with cyclazocine.

The data suggest that, in the evaluation of novel antidepressant compounds, the picrotoxin test may be a useful adjunct to the popular reserpine-reversal test particularly since representative psychomotor stimulants, major tranquillisers, anxiolytics and antihistamines are apparently inactive.

It is of interest that both α-methyl-p-tyrosine (α-MT) (250 mg/kg i.p., 2 h) and 5-hydroxytryptophan (160 mg/kg i.p., 2 h) potentiated picrotoxin convulsions whereas this effect was not demonstrated with *p*-chlorophenylalanine (*p*CPA) (300 mg/kg i.p. daily for 3 days). Preliminary interactional studies have shown that although *p*CPA does not alter the CD_{50} value of DMI, the convulsant effects of DMI and α-MT are additive.

References

BARRON, D.I., HALL, G.H., NATOFF, I.L. & VALLANCE, D.K. (1965). Pharmacological properties of 3-dimethylamino-2-methyl-1-phenyl-O-tolylpropanol (SK & F 70463-A). *J. Pharm. Pharmac.*, **17**, 509-516.

COWAN, A. & MACFARLANE, I.R. (1974). Antagonism of reserpine-induced hypothermia in mice by narcotic antagonists, with special reference to RX 336-M. In: *Temperature Regulation and Drug Action*, ed., Jacob, J., Lomax, P. & Schönbaum, E. Basel: Karger (in press).

DOGGETT, N.S., RENO, H. & SPENCER, P.S.J. (1974). The effects of RX 336M and RX 5050M on tests for antidepressant activity in mice. *Br. J. Pharmac.*, **50**, 440P.

LOTTI, V.J., TORCHIANA, M.L. & PORTER, C.C. (1973). Investigations on the action and mechanism of action of diphenylhydantoin as an antagonist of tetrabenazine and reserpine. *Arch. int. Pharmacodyn. Ther.*, **203**, 107-116.

The effect of psychotropic drugs on the Dopa potentiation test in mice

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Administration of a monoamine oxidase inhibitor (MAOI) in combination with 3,4-dihydroxyphenylalanine (Dopa) induces in mice slightly increased locomotor activity and irritability. If in addition imipramine is given between the MAOI and Dopa, these behavioural responses are greatly potentiated: the animals jump, squeak and fight (Everett, 1966). On basis of this finding, Everett (1966) concluded that the 'Dopa potentiation' test is useful in screening for anti-depressants. In accord with this view, Plotnikoff, Kastin, Anderson & Schally (1971) found that the

melanocyte stimulating hormone inhibiting factor (MIF), which has anti-depressant properties (Ehrensing & Kastin, 1974), also potentiated the Dopa-induced behavioural responses. The present investigation was undertaken to study the usefulness of Dopa potentiation as a screening tool for anti-depressants.

In each experiment 96 female Charles-River mice (19-21 g) were used. The animals were housed in plastic cages, 4/cage. They were pretreated subcutaneously with iproniazid (100 mg/kg) approximately 16 h prior to the test. One h before the test, the animals were injected intraperitoneally with either the test compound, the reference compound (imipramine), or placebo. Six groups received placebo treatment whereas three groups were used for each drug treatment. L-Dopa methylester (100 mg/kg) was administered intraperitoneally to all mice 30 min prior to the test. The behaviour of the animals was rated under 'double blind' conditions by two independent observers 30, 45 and 60 min after the administration of Dopa. The rating scale was from 0 (no locomotor activity) to 4 (all four mice hyperactive and jumping). The data were analysed by means of the two-tailed permutation test (Scheffé, 1972).

It was found that the reference compound imipramine (10 and 22 mg/kg) invariably potentiated the Dopa induced responses. Another anti-depressant, amitriptyline (10 and 22 mg/kg), yielded the same results. The new anti-depressant Org GB94 (Itil, Polvan & Hsu, 1972) potentiated the Dopa-induced responses in a dose of 32 mg/kg but to a lesser extent than imipramine. MIF (1 and 3 mg/kg) produced a slight but non-significant potentiation. Other peptides ($ACTH_{4-10}$ and desglycinamide lysine vasopressin: 1 and 3 mg/kg) had an equivocal effect.

Chlordiazepoxide (10 and 32 mg/kg) induced strong potentiation but the results obtained with diazepam (1 and 3.2 mg/kg) did not reach significance. The neuroleptics chlorpromazine (1 and 3.2 mg/kg) and haloperidol (0.1 and 0.32 mg/kg) inhibited the Dopa-induced responses. Apomorphine (1 and 3 mg/kg) moderately potentiated the action of Dopa while amphetamine (1 and 3 mg/kg) produced an almost maximal potentiation. Slight potentiation was found after treatment with methysergide (3 mg/kg) and atropine (1 and 3 mg/kg).

Whole brain concentrations of 5-HT, noradrenaline, dopamine, tyrosine, tryptophan and GABA were also determined in the groups of mice treated with imipramine, Org. GB94, chlordiazepoxide, chlorpromazine, diazepam, apomorphine and amphetamine; the highest doses of these drugs used in the Dopa potentiation test were administered. There was no significant correlation between the effects of these drugs on behaviour and their effects on the brain amines or precursors.

It can be concluded that anti-depressants are active in the Dopa potentiation test. However, as compounds which do not have anti-depressant activity are also effective, the Dopa potentiation test cannot be considered to be an adequate screening tool for anti-depressants. Everett (1966) assumed that the potentiation is caused by blocking the re-uptake mechanism for catecholamines at the presynaptic nerve ending. The present results suggest that several mechanisms are involved in the ability of drugs to potentiate the action of Dopa.

References

EHRENSING, R.H. & KASTIN, A.J. (1974). Melanocyte-Stimulating Hormone, release inhibiting hormone as an anti-depressant. *Arch. Gen. Psychiat.*, **30**, 63-65.

EVERETT, G.M. (1966). The Dopa response potentiation test and its use in screening for anti-depressant drugs. In: *Anti-depressant drugs*, ed. Garattini, S. & Dukes, M.N.G., pp. 164-167. Amsterdam: Excerpta Medica Foundation.

ITIL, T.M., POLVAN, N. & HSU, W. (1972). Clinical and EEG effects of GB-94, a 'tetracyclic' anti-depressant (EEG model for discovery of a new psychotropic drug). *Curr. Therap. Res.*, **14**, 395-413.

PLOTNIKOFF, N.P., KASTIN, A.J., ANDERSON, M.S. & SCHALLY, A.V. (1971). Dopa potentiation by a hypothalamic factor MSH release-inhibiting hormone (MIF). *Life Sci.*, **10**, Pt. 1, 1279-1283.

SCHEFFE, H. (1972). Permutation tests. In: *The analysis of variance*, p. 3. London & Sydney: John Wiley & Sons, Inc.