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