Studies on Interactions Involving Antidepressive and other Drugs with Tetrabenazine and Noradnamine on Locomotor Activity in Mice, Including Details of the Experimental Design and Statistical Analysis

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Received May 19, 1970

Abstract. A method for the measurement of drug interactions on locomotor activity in mice has been described. The experiments were designed on a factorial basis and the data obtained were subjected to variance analysis. Using the principles described, the effects of various drugs on the hypoactivity induced by noradnamine or tetrabenazine were studied. Twenty potential drug interactions were examined, but only seven of these exhibited statistically significant interaction. Tetrabenazine hypoactivity was antagonised by nortriptyline, amitriptyline, nialamide and noradnamine. The latter also potentiated the effect of a low dose of tetrabenazine. Hypoactivity induced by noradnamine was antagonised by amitriptyline and nortriptyline, potentiated by atropine but unaffected by nialamide. The significance of these findings is discussed.

Key-Words: Noradnamine — Tetrabenazine — Locomotor Activity — Drug Interactions — Statistical Analysis.

It has been suggested that the biochemical disturbance underlying the onset of depressive reactions in man might be decreased activity of brain catechol-O-methyl transferase (COMT) with the subsequent conversion of the excess deaminated metabolites of noradrenaline likely to occur under these conditions to noradnamine (5-aminomethyl-2,3,7,8-tetrahydroxydibenzo[a,e]cycloheptatriene) (Roberts and Broadley, 1965). It was proposed that this compound might be the mediator of the depression and would be competitively antagonised by the structurally related imipramine-like antidepressant drugs; the antidepressant monoamine oxidase (MAO) inhibitors would prevent the formation of noradnamine from noradrenaline. It was subsequently pointed out that dopamine might also be able to produce this postulated depressive catabolite (Fuller and Marshall, 1965).

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We have been especially interested, therefore, in comparing the pharmacology of noradnamine with that of reserpine-like agents which have been considered to produce a useful animal model of depression (Sulser, Watts and Brodie, 1962). Such a comparison is also of special interest since reserpine-like agents have been shown to cause depletion of brain catecholamines predominantly via MAO (Glowinski and Axelrod, 1966) and as has been already suggested (Broadley and Roberts, 1967a; Cowell, 1969) it is therefore possible that some of the effects of reserpine could be mediated through the production of noradnamine.

Differences between the effects of noradnamine and reserpine have already been demonstrated on barbiturate induced narcosis (Chambers, Redfern and Roberts, 1967), leptazol induced convulsions (Jones and Roberts, 1968) and in the susceptibility of the hypothermia produced by either drug to reversal by chlorpromazine (Cowell, 1969).

We have now extended our comparison to include spontaneous locomotor activity since, unlike some of the other effects of reserpine-like agents, the observed hypoactivity is more readily antagonised by 3,4-dihydroxyphenylalanine than by 5-hydroxytryptophan (Smith and Dews, 1962), an observation which might indicate that the reduction in locomotor activity is related to depletion of catecholamines rather than to 5-hydroxytryptamine depletion.

The difficulties associated with the use of such a variable parameter as locomotor activity have been satisfactorily overcome by using large numbers of animals coupled with a sensitive statistical technique.

**Methods**

Male albino Swiss mice (18—24 g) were used throughout. Locomotor activity was recorded using a modification of the method described by Bastian and Hill (1957) employing tilt cages. Each of the ten cages used consisted of a circular plastic container (18 cm diameter, 13 cm high) attached at its base to an aluminium disc. A small depression in the centre of each disc facilitated location of a central pivot (a vertical steel pin fixed firmly to the bench) and two lateral pins completed the pivoting system; the cage was thus pivoted across a diameter at three points. At right angles to this diameter and on either side were two electrical contacts which were alternately closed by tilting the cage back and forth; a digital counter recorded each closure. The total angle through which each box tilted was adjusted to 2°. The sides of the cages were painted matt black so that light could enter only through the perforated lids; artificial lighting was maintained throughout the experiments and direct sunlight was excluded. The environmental temperature was maintained between 20 and 22°C. In use, each cage contained a single mouse and activity was recorded for 30 min.