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A STUDY OF THE ROLE OF BRAIN CATECHOLAMINES IN DRUG INDUCED TREMOR

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In a recent study, Owen & Marsden (1965) have shown that adrenaline increases and that the adrenergic β-receptor blocking drugs, pronethalol and propranolol, diminish tremor in patients with Parkinson's disease. Vas (1966), however, did not observe any effect of propranolol in Parkinsonian tremor.

Friedman (1963) and Friedman, Aylesworth & Friedman (1963) have shown that tremorine lowers the noradrenaline levels in the brains of rats, mice and guinea-pigs but fails to do so in rabbits, which do not show tremor after the administration of tremorine.

These findings indicate that brain catecholamines may have a role in causing tremor and the present work was undertaken to study their role in, and the effect of, a recent adrenergic β-receptor blocking drug—namely, dextro-N-isopropyl-para-nitrophenylethanolamine (d-INPEA)—on tremorine and harmaline induced tremor in mice.

METHODS

Tremor was recorded by a modification of the method of Ahmed & Taylor (1959). A perforated plastic box 5 in × 3 in × 2 in was bolted to a 3½ in brass rod (¼ in diameter), which in turn was fixed into the position of the stylus of a high impedance (6,000 Ω) electromagnetic gramophone pick-up. Lateral movements of the box were converted by the pick-up into electrical changes, which were amplified and recorded on one channel of a Grass four channel electroencephalograph. The amplification level was kept at a minimum. The paper speed was 15 mm/sec. The whole device was kept in a sound-proof booth. Sixty male mice, weighing between 22–27 g, fed in the morning on the day of experiment, were used. They were placed in the box, one at a time, for 10–15 min before each experiment, in order to acclimatize them. This ensured a very low baseline due to reduced spontaneous activity of the mice. After a control period, one of the two tremorogenic drugs was injected intraperitoneally (tremorine 20 mg/kg and harmaline 30 mg/kg) and movements were recorded every 5 min for 60 min. After establishing that in the doses given, all the mice showed tremor after the drugs, they were divided into six groups of 10 mice.

The mice in each group received one of the drugs used in the present study, intraperitoneally, and each group then was further divided into two subgroups of five animals each, for challenging with tremorine and harmaline. The effects of these tremorogenic drugs were then followed for a period of 1 hr.

The various drugs used for modifying tremor were: reserpine (Serpasil; Ciba), alpha-methyl-meta-tyrosine (Merck, Sharp and Dohme), pargyline (Abbot), propranolol (I.C.I.), d-INPEA and l-INPEA (Selvi).

RESULTS

Tremorine

The injection of tremorine (20 mg/kg) produced a fine tremor (13–16 c/s), associated with peripheral parasympathomimetic effects, such as miosis, chromodacryorrhoea, salivation and diarrohoea. Tremor appeared after 4–6 min, reached a peak level in 20–25 min and was still present after 60 min.

Harmaline

The administration of harmaline (30 mg/kg) caused a slightly slower tremor (12–14 c/s) which was not accompanied by any parasympathomimetic effects. In some of the control animals, Straub tail phenomenon and piloerection were seen.

The effect on experimental tremor of adrenergic β-receptor blocking drugs and drugs which modify the concentration of amines in the brain are shown in Table 1 and Fig. 1.

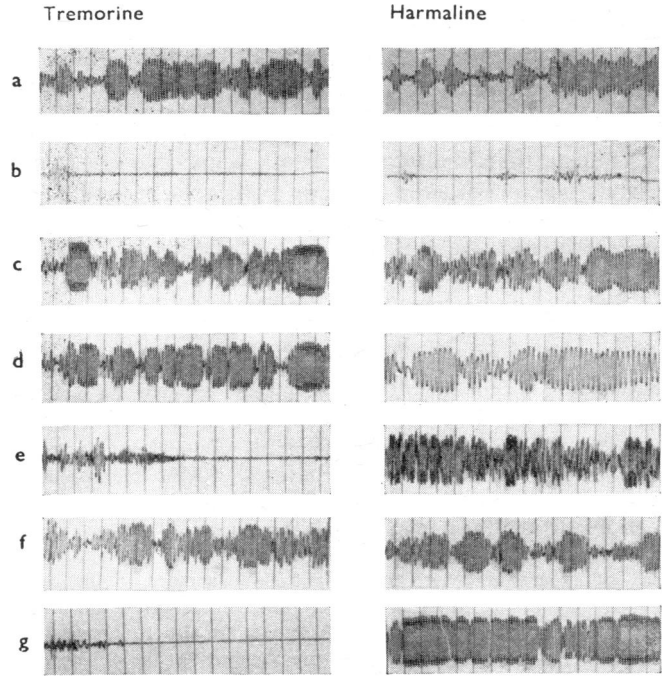

Fig. 1. Record of tremors produced by tremorine (left hand vertical panel) and harmaline (right hand vertical panel) in control animals (a), and after propranolol (b), d-INPEA (c), l-INPEA (d), reserpine (e), alpha-methyl-meta-tyrosine (f) and pargyline (g).

These show that β-adrenergic receptor blocking drug d-INPEA and the inactive isomer l-INPEA have no effect on tremor induced by harmaline or tremorine, whereas the prior administration of propranolol prevented the onset of tremor after both drugs. In addition,

TABLE 1

EFFECT ON EXPERIMENTAL TREMOR OF ADRENERGIC β-RECEPTOR BLOCKING DRUGS AND DRUGS WHICH MODIFY THE CONCENTRATION OF AMINES IN THE BRAIN

Drugs	Doses (mg/kg, i.p.)	Purpose of administration	Time of administration before tremorogenic drug (hr)	Effect on spontaneous activity	Effect on experimental tremor after	
					Tremorine (20 mg/kg, i.p.)	Harmaline (30 mg/kg, i.p.)
Propranolol	10	Adrenergic β-receptor blockade	½	Reduced; ataxia	Blocked	Not blocked
d-Inpea	40	Adrenergic β-receptor blockade	½	No effect	Not blocked	Not blocked
l-Inpea	40	Inactive isomer	½	No effect	Not blocked	Not blocked
Alpha-methyl-meta-tyrosine	100	Preferential depletion of brain catecholamines*	8	No effect	Not blocked	Not blocked
Reserpine	5	Depletion of brain catecholamines and 5-HT	48 and 24	Reduced; catatonia	Reduced; pronounced immobility, ataxia, parasympathomimetic action of tremorine unchanged, death	Increased; marked excitement humping, darting and Straub tail phenomenon
Pargyline	5	Elevation of brain catecholamines and 5-HT	48 and 24	Increased	Reduced; immobility followed by death	Increased; marked excitement and violent movements

* Brodie & Costa (1962)

treatment with reserpine or pargyline reduced the tremor seen after tremorine but increased the effect of harmaline. The tremor produced by both harmaline and tremorine was unchanged 8 hr after the administration of alpha-methyl-meta-tyrosine.

DISCUSSION

The present experiments indicate that d-INPEA has no effect on the spontaneous motility of the mice and does not prevent the tremor induced by harmaline or tremorine. Propranolol, however, decreased the spontaneous motility and blocked the drug induced tremors. These findings indicate that the anti-tremor actions of propranolol are not due to the blockade of the adrenergic β-receptors but may be due to other pharmacological actions. Propranolol has been reported to produce depression of the central nervous system (Murmann, Almirante & Saccani-Guelfi, 1966) and shows central muscle relaxant effects (Sinha, Srimal, Jaju & Bhargava, 1966). These effects may be responsible for its anti-tremor action.

Preferential depletion of the noradrenaline and dopamine content of the brain by alpha-methyl-meta-tyrosine did not induce tremor nor modify the tremor produced by tremorine and harmaline, while simultaneous depletion or increase of brain noradrenaline, dopamine and 5-HT by reserpine and pargyline respectively modified the spontaneous activity and blocked tremorine induced tremor. In spite of the anti-tremor action of reserpine and pargyline, tremorine proved to be lethal in all of the mice tested. Reserpine and pargyline were found to increase harmaline tremor. Zetler (1957), however, observed that reserpine antagonized harmine induced tremor in mice when the two drugs were given together. In the present study reserpine was administered 48 hr before harmaline, which would have caused a more marked depletion of brain 5-HT and catecholamines, when compared with the changes in the levels of brain amines which would be produced by simultaneous administration of reserpine and harmine.

The present findings indicate that catecholamines alone may not be directly concerned in the biochemical lesion in drug induced tremor but may play a permissive role, along with other neuro-hormones.

SUMMARY

1. The blockade of adrenergic β-receptors and preferential depletion of brain catecholamines were found not to modify harmaline and tremorine induced tremor in mice.

2. The catecholamine levels in brain, *per se*, did not appear to influence tremor induced by the above drugs.

3. Prior administration of drugs which cause changes in the concentration of both 5-hydroxytryptamine and catecholamines in the brain profoundly altered the tremor patterns.

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