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REPEATED EXPOSURE OF RATS TO THE CONVULSANT AGENT FLUROTHYL ENHANCES 5-HYDROXYTRYPTAMINE- AND DOPAMINE-MEDIATED BEHAVIOURAL RESPONSES

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1 Rats were convulsed once daily for 7 days by exposure to the inhalant convulsant agent, flurothyl (Indoklon, bis (2,2,2-trifluouroethyl)ether). Twenty four hours after the final convulsion the rats were injected with tranylcypromine (20 mg/kg) followed 30 min later by L-DOPA (50 mg/kg), a procedure which increases brain dopamine concentrations. The flurothyl-treated rats showed a greater locomotor activity response than rats that had not been convulsed.

2 This enhanced response appears to be due to increased postsynaptic dopamine receptor sensitivity since flurothyl-treated rats also showed enhanced locomotor responses to methamphetamine (2 mg/kg) and apomorphine (2 mg/kg).

3 Enhanced 5-hydroxytryptamine-induced activity responses following administration of tranylcypromine (20 mg/kg) and L-tryptophan (50 mg/kg) were also seen 24 h after the last of 10 daily flurothyl-induced convulsions.

4 The increased 5-hydroxytryptamine response also appears to be due to increased postsynaptic sensitivity since the flurothyl-treated rats showed increased hyperactivity following administration of tranylcypromine (20 mg/kg) and the suggested 5-hydroxytryptamine agonist, 5-methoxy *N,N*-dimethyltryptamine (2 mg/kg).

5 No change in the brain concentration of 5-hydroxytryptamine, 5-hydroxyindoleacetic acid, tryptophan, dopamine or noradrenaline was observed 24 h after the last of 10 daily flurothyl-induced convulsions, compared to untreated rats. The rate of 5-hydroxytryptamine accumulation after tranylcypromine/L-tryptophan treatment and of dopamine and noradrenaline accumulation after tranylcypromine/L-DOPA treatment was similar in both groups.

6 Repeated flurothyl convulsion has the same effects on these behavioural tests as repeated electroconvulsive shock. Since both treatments have been used successfully to treat depression, it is suggested that the mechanism of action of electroconvulsive therapy may be by increasing postsynaptic responses to the monoamine neurotransmitters.

Introduction

Despite the success of electronconvulsive therapy (ECT) in treating depression, its mechanism of action is unknown. Recently it has been demonstrated that repeated, but not single, electroconvulsive shocks (ECS), once daily for 7 or more days results in rats displaying enhanced behavioural responses to various procedures thought to stimulate central 5-hydroxytryptaminergic, dopaminergic or noradrenergic systems (Modigh, 1975; Evans, Grahame-Smith, Green & Tordoff, 1976; Green, Heal & Grahame-Smith, 1977).

There have been several reports (see Discussion) of the efficacy of the convulsant drug flurothyl (Indoklon, bis (2,2,2-trifluoroethyl)ether; $F_3C CH_2OCH_2CF_3$) in treating depression. Since the possibility exists that enhanced post-synaptic catecholamine and 5-hydroxytryptamine (5-HT) responses following ECS might be the way that ECT is working therapeutically (Evans *et al.*, 1976; Green *et al.*, 1977; Modigh, 1975; 1976) it was decided to see whether the convulsant drug, flurothyl, also produced the enhanced response to the various behavioural tests used in the previous studies.

Methods

Adult male Sprague–Dawley rats weighing 140–180 g (Anglia Laboratory Animals, Alconbury, Huntingdon) were used in the study. They were housed in groups

and given an *ad libitum* diet of 41B pellets and tap water. The room was at constant temperature (20°C) and kept on a 12 h light dark cycle of 06 h 00 min to 18 h 00 minutes.

Drugs were obtained from the following sources, tranylcypromine (Smith, Kline and French), L-tryptophan, L-DOPA, 5-methoxy *N,N*-dimethyltryptamine, methamphetamine, pentylenetetrazol (Sigma Chemical Co.), apomorphine (MacFarlan-Smith). All drugs were injected intraperitoneally dissolved in 0.9% w/v NaCl solution (saline) or in the case of L-DOPA, suspended in saline containing 1% carboxymethylcellulose.

Production of convulsions

Rats were exposed to flurothyl by placing them in a desiccator jar (volume 2.5 l) and introducing 0.04 ml flurothyl, which vaporized within 10 s producing a concentration of 23 parts/10^6 (w/v). After about 20 s the rats started to exhibit myoclonic jerks and they convulsed after approximately 30 seconds. At the onset of the convulsion they were immediately removed from the desiccator and returned to their home cage, convulsions normally lasting for about a further 10 seconds. This procedure was repeated once daily for 7 or 10 days. Twenty-four fours following the final convulsion the rats were examined by the various tests outlined below. Control rats were not exposed to flurothyl but were placed in the desiccator jar for 30 s each day.

Electroconvulsive shocks were given to rats lightly anaesthetized with halothane through earclip electrodes. A shock of 150 V (50 cycle per second sinusoidal) was given for 1 s from a portable Edison ECT unit. Control rats were given the halothane anaesthesia only.

Behavioural tests

5-HT and dopamine-induced behavioural responses were examined by measurement of the hyperactivity which follows injection of tranylcypromine and L-tryptophan or tranylcypromine and L-DOPA. These treatments raise the concentration of 5-HT and dopamine respectively in the brain and produce a series of behavioural changes including hyperactivity which was measured in groups of 3 animals on LKB Animex activity meters (sensitivity and tuning 30 μA). The degree of hyperactivity appears to be related to the rate of 5-HT or dopamine synthesis and 'spill-over' into functional activity. The behavioural changes and methods have been described elsewhere both for the 5-HT system (Grahame-Smith, 1971a; Green & Grahame-Smith, 1974) and the dopamine system (Everett, Weigland & Rinaldi, 1963; Green & Kelly, 1976).

Activity changes and behaviour following tranylcypromine and 5-methoxy *N,N*-dimethyltryptamine (5-MeODMT) were as described by Grahame-Smith (1971b) and were measured with LKB Animex meters as were the locomotor changes following methamphetamine and apomorphine.

Results of the activity were collected as movements/min and graphs show the mean of every 5 min period. The flurothyl experiments were only performed twice because of the small amount of flurothyl available, the drug not having been produced for several years. However 3 control experiments were performed and graphs show the mean values and the range obtained on two experiments (flurothyl) and 3 experiments (control) with different groups of animals. Mean total movements $\pm$ s.e.mean of both groups of animals during experimental period and Student's t test on these observations are given in the legends to the figures.

Biochemical assays

Brain tryptophan was measured by the method of Denckla & Dewey (1967). Brain 5-hydroxytryptamine and 5-hydroxyindoleacetic acid concentrations were measured by the method of Curzon & Green (1970) and noradrenaline and dopamine by that of Chang (1964).

Results

Effect of repeated flurothyl convulsions on tranylcypromine/L-DOPA-induced hyperactivity

The study of Modigh (1975) showed that catecholaminergic responses were increased after 7 daily electroconvulsive shocks. Due to the small amount of flurothyl available it was decided to try 7 daily treatments rather than 10 as in our previous studies (Evans *et al.*, 1976; Green *et al.*, 1977).

Rats were therefore convulsed daily for 7 days by flurothyl inhalation as described in Methods. On day 8, 24 h after the final convulsion the rats were given tranylcypromine (20 mg/kg) followed 30 min later by L-DOPA (50 mg/kg) and activity measured. The rats subjected to flurothyl convulsions showed enhanced responses compared to control rats not exposed to flurothyl (Figure 1a). Brain dopamine concentrations were similar in both groups 60 min after the L-DOPA injection (Table 1).

Effect of repeated flurothyl convulsions on amphetamine- and apomorphine-induced locomotor activity

The experiment with tranylcypromine and L-DOPA suggested that flurothyl-induced convulsions enhanced dopamine-mediated behavioural responses,

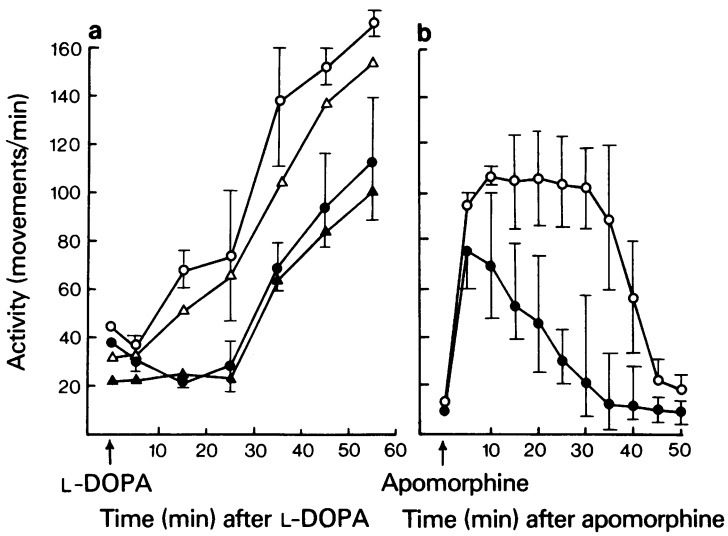

Figure 1 Hyperactivity response of rats treated with flurothyl to (a) tranylcypromine/L-DOPA and (b) apomorphine. Rats were convulsed daily for 7 days by exposure to flurothyl. Twenty-four hours after the final convulsion rats were injected with (a) tranylcypromine (20 mg/kg) followed 30 min later by L-DOPA (50 mg/kg) or (b) apomorphine (2 mg/kg). Results show activity response following L-DOPA or apomorphine. The mean and range of 3 observations (control) and 2 observations (flurothyl) is shown. (●) Control (untreated); (○) flurothyl-treated. (△) Response to tranylcypromine and L-DOPA of rats treated for 4 days with flurothyl followed by 4 days with ECS; (▲) control of this experiment, rats being untreated for 4 days followed by 4 days of halothane anaesthesia only. Both groups were given tranylcypromine (20 mg/kg) followed 30 min later by L-DOPA (50 mg/kg) 24 h after the final shock. Total movements ± s.e.mean during 60 min following L-DOPA: control, 3306 ± 428 (3); flurothyl, 6310 ± 630 (2), $P < 0.025$. Total movements ± s.e.mean during 50 min following apomorphine: control, 1670 ± 569 (3); flurothyl, 4052 ± 717 (2), $P < 0.05$.

probably by a postsynaptic change since dopamine synthesis was similar in both groups.

This view was strengthened by the observation that while the peak locomotor activity was not altered by 7 daily flurothyl induced convulsions, the time of increased activity was lengthened after either the dopamine releasing drug, methamphetamine (2 mg/kg), or the putative dopamine agonist, apomorphine (2 mg/kg) (Figures 1b and 2).

Effect of repeated flurothyl convulsions on the hyperactivity following tranylcypromine and L-tryptophan

A single ECS given once daily for 10 days enhanced the hyperactivity produced by increasing brain 5-HT concentration by administration of tranylcypromine (20 mg/kg) and L-tryptophan (50 mg/kg) (Evans *et al.*, 1976; Green *et al.*, 1977). Preliminary experiments established that an enhanced hyperactivity response to tranylcypromine and L-tryptophan was not seen 24 h after the last of 7 daily flurothyl-induced convulsions. However, a single flurothyl convulsion once daily for 10 days enhanced the tranylcypromine/L-tryptophan hyperactivity on day 11 (Figure 3a). The 5-HT accumulation in the brain was the same in both groups (Table 1) suggesting a postsynaptic change. This was confirmed by the observation that on day 11, 24 h after the last of 10 daily flurothyl convulsions the hyperactivity response to the suggested 5-HT agonist, 5-MeODMT (Grahame-Smith, 1971b) was also enhanced (Figure 3b).

Brain amine concentrations following flurothyl

Brain dopamine, noradrenaline and 5-HT concentrations were not altered 24 h after the last of 10 flurothyl-induced convulsions once daily to rats (Table 1). Brain tryptophan and 5-hydroxyindoleacetic acid concentrations were also unaltered (Table 1).

Effect of treatment with both flurothyl and ECS on tranylcypromine L-DOPA-induced activity

Enhancement of tranylcypromine/L-DOPA-induced activity is not seen 24 h after the last of 4 daily flur-

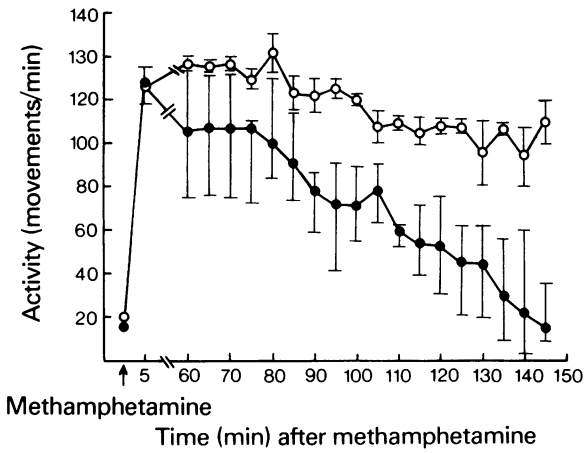

Figure 2 Hyperactivity response of rats treated with flurothyl to methamphetamine. Rats were convulsed daily for 7 days by exposure to flurothyl. Twenty-four hours after the final convulsion the rats were injected with methamphetamine (2 mg/kg). Results show mean activity response and range of 3 separate observations (control) and 2 observations (flurothyl). (●) Control (untreated); (○) flurothyl-treated. Total movements ± s.e.mean during period 60 min to 150 min after methamphetamine: control, 4993 ± 230 (3); flurothyl, 10705 ± 455 (2), $P < 0.001$.

othyl-induced convulsions or 4 treatments with ECS (unpublished observations). Rats were therefore treated for 4 days with flurothyl, followed by 4 days with a single daily ECS. On day 9 these rats showed enhancement of the hyperactivity response to tranylcypromine and L-DOPA compared to control rats (Figure 1a).

Effect of flurothyl on pentylenetetrazol-induced convulsions

In the previous study (Evans *et al.*, 1976) it was found that 24 h after the final of 10 daily ECS, rats convulsed much more rapidly than the control group after injection of pentylenetetrazol. However, 24 h after the last of 10 daily flurothyl-induced convulsions no shortening of the time to convulsion following pentylenetetrazol (65 mg/kg) was observed. The convulsion produced did appear to be more severe in the flurothyl-treated rats.

Discussion

The fact that flurothyl evokes convulsive seizures in laboratory animals when inhaled has been known for some time (Krantz & Truitt, 1957; Krantz, Truitt, Ling & Speers, 1957). It is an ether with a pleasant ethereal odour and is excreted unchanged through the

Table 1 Effect of flurothyl on brain tryptophan, 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), dopamine and noradrenaline and the accumulation of 5-hydroxytryptamine following tranylcypromine and L-tryptophan and dopamine and noradrenaline following tranylcypromine and L-DOPA

Treatment	*Compound measured*	*Concentration (μg/g brain wet wt.)* *Control*	*Flurothyl*
Saline	Tryptophan	4.85 ± 0.38 (7)	4.79 ± 0.25 (8)
	5-hydroxytryptamine	0.43 ± 0.02 (7)	0.41 ± 0.01 (8)
	5-hydroxyindoleacetic acid	0.45 ± 0.02 (7)	0.41 ± 0.01 (8)
	Dopamine	2.11 ± 0.13 (7)	1.92 ± 0.11 (8)
	Noradrenaline	0.30 ± 0.02 (7)	0.31 ± 0.02 (8)
Tranylcypromine + L-tryptophan	5-hydroxytryptamine	1.17 ± 0.14 (6)	1.16 ± 0.05 (6)
Tranylcypromine + L-DOPA	Dopamine	6.88 ± 0.82 (6)	8.55 ± 0.40 (6)
	Noradrenaline	0.57 ± 0.03 (6)	0.59 ± 0.05 (6)

Rats were convulsed daily for 10 days by exposure to flurothyl as described in Methods. On day 11, 24 h after the final convulsion the animals were killed and brain 5-HT, 5-HIAA, tryptophan, noradrenaline and dopamine measured. Brain 5-HT following tranylcypromine and L-tryptophan was measured in rats convulsed daily for 10 days. Twenty-four hours after the final convulsion, rats were injected with tranylcypromine (20 mg/kg) followed 30 min later by L-tryptophan (50 mg/kg). They were killed 90 min after the L-tryptophan when brain 5-HT was measured. Brain dopamine and noradrenaline following tranylcypromine and L-DOPA was measured in rats convulsed daily for 7 days. Twenty-four hours after the final convulsion rats were injected with tranylcypromine (20 mg/kg) followed 30 min later by L-DOPA (50 mg/kg). They were killed 60 min after the L-DOPA when brain dopamine and noradrenaline were measured. In all cases control rats received the same treatment as the experimental rats except that they had not been convulsed with flurothyl. Results show mean ± s.e.mean with number of observations in parentheses.

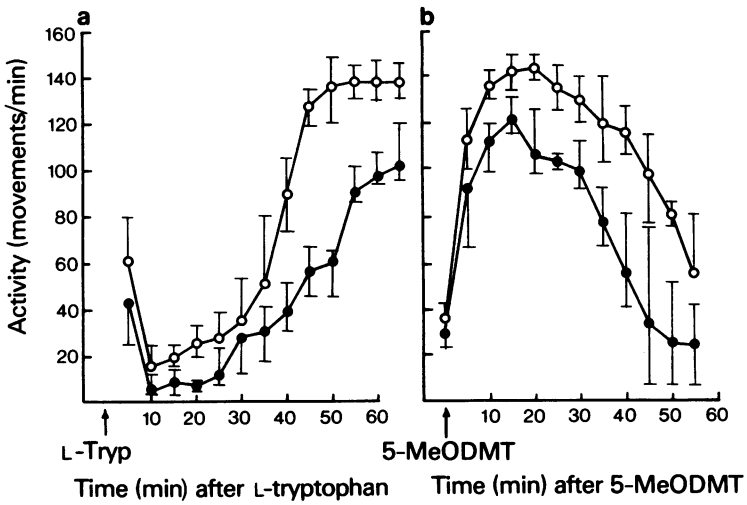

Figure 3 Hyperactivity response of rats treated with flurothyl to (a) tranylcypromine/L-tryptophan and (b) tranylcypromine/5-methoxy *N,N*-dimethyltryptamine. Rats were convulsed daily for 10 days by exposure to flurothyl. Twenty-four hours after the final convulsion the rats were injected with tranylcypromine (20 mg/kg) followed 30 min later by either L-tryptophan (L-Tryp) 50 mg/kg or 5-methoxy *N,N*-dimethyltryptamine (5-MeODMT) (2 mg/kg). Results show activity response following L-tryptophan or 5-MeODMT. The mean and range of 3 separate observations (control) and 2 observations (flurothyl) is shown. (●) Control (untreated); (○) flurothyl-treated. Total movements ± s.e.mean during 60 min after L-tryptophan: control, 2443 ± 267 (3); flurothyl, 4077 ± 352 (2), $P < 0.025$. Total movements ± s.e.mean during 60 min following 5-MeODMT: control, 4316 ± 235 (3); flurothyl, 6327 ± 487 (2), $P < 0.025$.

lungs (Krantz *et al.*, 1957). While the convulsions lasted longer than those following ECS, the animals gained weight steadily and there was no difference in the body weights of the control and experimental groups at the end of 10 days treatment. ECS, in contrast causes mice to gain weight at a slower rate than control animals (Modigh, 1975).

When rats were convulsed daily with flurothyl for 10 days they showed enhanced 5-HT-mediated behavioural responses, in a similar way to rats treated with a daily ECS for 10 days (Evans *et al.*, 1976; Green *et al.*, 1977). This change appears to be occurring postsynaptically. Similarly enhanced postsynaptic dopamine responses are elicited by a single daily convulsion for 7 or more days with flurothyl or ECS (Modigh, 1975; Evans *et al.*, 1976; Green *et al.*, 1977).

No difference between the control and flurothyl-treated groups in the peak activity following methamphetamine, 5-MeODMT or apomorphine was observed. However the activity remained elevated for longer in the flurothyl-treated groups. Previously it was observed that ECS-treated rats only showed an enhanced peak activity after 5-MeODMT when the dose of 5-MeODMT was low. At higher doses the peak activity was similar but the ECS group remained active for a longer period (Evans *et al.*, 1976). It is possible that an enhanced peak activity can only be shown when the rats are given a submaximal stimulatory dose.

The brain dopamine concentration in the flurothyl-treated rats was somewhat raised over that seen in the control group 60 min after tranylcypromine and L-DOPA (Table 1). While this value failed to reach statistical significance it may be that it indicates a flurothyl-induced alteration in dopamine synthesis. Nevertheless the results with methamphetamine and apomorphine indicate that postsynaptic changes in sensitivity are also occurring. Whether such changes are occurring at the receptor or in the neuronal systems connected to these receptors cannot be stated at this point.

Previously Green and colleagues (1977) found that 10 days of treatment with sub-convulsive electroshock did not enhance the 5-HT-induced behavioural responses. It was pointed out that it is generally believed that clinically, a shock of sufficient magnitude to cause a convulsion (had a muscle relaxant not been given) is necessary to produce mood improvement; that is, seizure activity changes consistent with a convulsion having occurred should be seen on an electroencephalogram (Cronholm & Ottosson, 1960). This clearly indicates that it is the convulsion

that is important in the production of the mood improvement rather than the passage of the electrical current and this indication is supported by clinical experience with flurothyl.

The techniques used for administration of flurothyl to humans have been described in detail elsewhere (Rose & Watson, 1967). Flurothyl convulsive therapy was suggested to be both safe and clinically effective as an antidepressant (Krantz, Esquibel, Truitt, Ling & Kurland, 1958). Comparative studies on the efficacy of flurothyl and ECT concluded there were no essential differences in the outcome between the two methods of producing convulsions (Karliner & Padula, 1959a, b; Fink, Kahn, Karp, Pollack, Green, Allan & Lefkowits, 1961; Spreche, 1964). Several studies indicated that flurothyl-induced convulsions caused less memory loss than ECT. This observation was confirmed more recently both by Small (1974) and Rose (personal communication).

The fact that flurothyl produces the same effects as ECS in the various behavioural tests used in this study suggests that they may have a common mode of action, a view strengthened by the fact that 4 days of treatment each with flurothyl and ECS causes enhancement of the dopamine-induced behaviour while 4 days of either treatment alone causes no enhancement. Mood improvement in depressed subjects has also been noted following alternate treatments with ECT and flurothyl (Freund & Warren, 1965).

However, one difference was noted between repeated treatment with ECS and flurothyl. Flurothyl-treatment did not shorten the time to the onset of pentylenetetrazol-induced convulsions. Whether this is due to the longer duration of the flurothyl-induced convulsion is not known.

In previous publications (Green *et al.*, 1977; Evans *et al.*, 1976) it was suggested that ECT might be working therapeutically by increasing the size of the postsynaptic 5-HT and dopamine responses following stimulation by the endogenous amine transmitters. The fact that flurothyl and ECS both enhanced the postsynaptic response and are both effective clinically is consistent with this suggestion

I thank Dr Louis Rose for his generous gift of Indoklon.

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