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Attenuation by electroconvulsive shock and antidepressant drugs of the 5-HT_{1A} receptor-mediated hypothermia and serotonin syndrome produced by 8-OH-DPAT in the rat

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Abstract. The hypothermia and motor behavioural syndrome produced in rats by injection of the 5-HT_{1A} ligand 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) has been studied following administration of electroconvulsive shock under halothane anaesthesia (ECS) and during the administration of antidepressant drugs. Repeated ECS attenuated the hypothermic response to 8-OH-DPAT (0.1 mg/kg SC) immediately after the last of five shocks given spread out over 10 days with a maximal effect 21 days after the final shock. A single ECS was without effect. The serotonin syndrome produced by 8-OH-DPAT (0.75 mg/kg SC) was also attenuated, although simple motility was increased.

Zimeldine (20 mg/kg) and desipramine (20 mg/kg), when given once daily for 14 days also attenuated the hypothermia and the serotonin syndrome provoked by 8-OH-DPAT. The hypothermic response was somewhat reduced 24 h after a single injection of zimeldine but not 45 min after zimeldine (5 mg/kg IP). At a high dose (20 mg/kg) tranylcypromine clearly attenuated both responses 24 h after a single injection. Tranylcypromine (6 mg/kg IP) showed a smaller effect after a single injection but attenuated the behavioural syndrome on repeated administration. Repeated injection of flurazepam (10 mg/kg IP) was without effect on either the behavioural or hypothermic response to 8-OH-DPAT.

These findings are consistent with the view that responses mediated via the 5-HT_{1A} receptor may be involved in the mechanism of action of antidepressant treatments.

Key words: 5-Hydroxytryptamine (5-HT) – 5-HT_{1A} receptor – Electroconvulsive shock – Antidepressants – 8-OH-DPAT – Zimeldine – Desipramine – Tranylcypromine – Flurazepam

Antidepressant treatments have marked effects upon the biochemistry and function of 5-hydroxytryptamine (5-HT) neurones in brain. With the sub-division of 5-HT receptors into two broad subtypes 5-HT_1 and 5-HT_2 (Peroutka et al. 1980), interest was immediately centred on which was the more likely candidate for possible mediation of antidepressant effects. Peroutka and Snyder (1980) described reduced binding to 5-HT_2 receptors after a variety of drug treatments, while binding to 5-HT_1 sites was unaffected except following administration of monoamine oxidase inhibitors (MAOI). Reduced 5-HT_2-mediated head twitch behaviour in the mouse was also described following the chronic and continuing administration of antidepressant drugs (Friedman et al. 1983) but electroconvulsive shock (ECS) increased both 5-HT_2 binding in the rat (Kellar et al. 1981) and head-twitch behaviour in the mouse (see Green et al. 1983), a response considered to be mediated by 5-HT_2 receptors (see Green and Heal 1985). Re-examination of both the binding and the behaviour in the mouse confirmed the opposing effects of ECS and drug treatments (Goodwin et al. 1984) but in some ways this result weakened the association between 5-HT_2 function and antidepressant effects (Green et al. 1986), particularly since diazepam produced a similar increase in 5-HT_2 function to that produced by ECS (Green et al. 1985).

Functional correlates of 5-HT_1 receptor activation have been identified only recently. The most selective ligand so far available is 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) which binds primarily to 5-HT_{1A} sites (Middlemiss and Fozard 1983) and shows low affinity for other receptors (Leysen 1985). In the rat 8-OH-DPAT produces a hypothermic response probably mediated by pre-synaptic receptors (Goodwin and Green 1985; Goodwin et al. 1987 and a serotonin syndrome probably mediated by post-synaptic receptors (Hjorth et al. 1982; Tricklebank et al. 1984; Goodwin and Green 1985; Goodwin et al. 1987). The rat therefore allows the study of the effects of antidepressant drugs on both a pre-synaptic and a post-synaptic 5-HT_{1A}-mediated functional response. The purpose of the present work was to examine the effects of several antidepressant treatments on post-synaptic 5-HT_{1A}-mediated behaviour in the rat. However, the 8-OH-DPAT-induced hypothermic response was also examined at the same time, since previous observations in the mouse had suggested that attenuation of the hypothermic response to 8-OH-DPAT might be a common property of ECS and drug treatments (Goodwin et al. 1985b). The results in the rat confirm this finding and show, in addition, attenuation of key components of the serotonin syndrome by the same antidepressant treatments. It will be argued, therefore, that 5-HT_{1A} receptor function may provide an important mechanism for the action of antidepressant treatments.

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Materials and methods

Animals. Sprague-Dawley derived male rats weighing 150–250 g were housed in groups under conditions of controlled temperature (20° C ± 1) and lighting (dark period 19.00 hours to 07.00 hours). Food (41 B pellets) and water were freely available.

Drugs. The following drugs were used (abbreviation if any and source shown in parentheses): 8-hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT; Research Biochemicals, Wayland, MA); desipramine hydrochloride (DMI, Ciba-Geigy, Basel); zimeldine dihydrochloride (Astra Pharmaceuticals, Södertälje); tranylcypromine sulphate (TCP, Smith Kline & French, Welwyn); flurazepam (Roche, Welwyn). All were dissolved in 0.9% saline and injected intraperitoneally (IP), except where stated otherwise. Doses given refer to the salt.

Electroconvulsive shock. Animals were anaesthetised with halothane (ICI Pharmaceuticals, Alderley Edge) and an electroconvulsive shock (50 Hz, 140 V for 1 s) applied via ear-clip electrodes from a Theratronics small animal electroplexy unit. Shocks were applied on five occasions over 10 days (Mon, Wed, Fri, Mon, Wed.) at the same time of day (morning). Control animals received halothane only.

Temperature and behaviour. Temperature was measured by insertion of a probe lubricated with hand-cream 2–3 cm into the rectum, with the rat loosely restrained by the tail; the reading was displayed on a digital thermometer.

Rats show an increase in temperature on handling. Thus, in all experiments, animals were manually transferred in groups from home cages to testing cages in which a preliminary temperature reading was taken; the animals were then allowed to settle for 15 min and the starting temperature as shown in Results was obtained before injection of 8-OH-DPAT.

The serotonin syndrome when present was scored by a practised observer, where possible blind to the treatment conditions. The method described by Deakin and Green (1978) was followed, in which individual components of the syndrome (motility, forepaw-treading, head-weaving, flat body posture, hind-limb abduction, reactivity) were scored on a scale of severity 0–3 (0-absent, 1-just present, 2-definitely present, 3-extreme) at particular times after the injection of 8-OH-DPAT.

Data is presented throughout from treatment and control groups studied simultaneously.

Hypothermic responses to injection of 8-OH-DPAT were determined at doses of 0.1 and 0.75 mg/kg SC for all treatment conditions. As illustrated in Goodwin et al. 1987, the lower dose produces no definite motor syndrome and is therefore preferred for the examination of the temperature effects. However, attenuation of the response, where it occurred, was invariably seen at both doses. In addition, although presented as the nadir of the response at 30 min after injection of 8-OH-DPAT, temperatures were also recorded at 10, 20, 45 and 60 min. Where significant differences were observed at 30 min, the same direction of effect was also present at the other time points. In other words, attenuation of the response occurred at all times sampled and did not result from an advanced or retarded response profile.

Statistics. Temperature changes were compared by planned comparison of mean values 30 min after injection of 8-OH-DPAT employing Student's *t* test (2-tailed). Behavioural scores for individual animals were added for successive time points at 10, 20 and 30 min after 8-OH-DPAT to produce an estimate of the total behavioural response. These totals were averaged to obtain mean responses and compared again using the *t* test (2-tailed).

Results

The effect of electroconvulsive shock on the hypothermic response to 8-OH-DPAT. Following administration of repeated ECS, there developed an attenuation of the hypothermic response to 8-OH-DPAT (Fig. 1) which was most pronounced 2 weeks after the final ECS but was not studied beyond this time. Animals administered ECS had slightly higher basal temperatures when tested 1 and 5 days after the final ECS, but this was no longer present by the time attenuation of the response was seen in the ECS group. Thus while a baseline change in temperature could have obscured effects at the early times, it cannot be invoked to account for the attenuated hypothermic response seen subsequently.

The effect of antidepressant drugs on the hypothermic response to 8-OH-DPAT. Administration of either zimeldine (20 mg/kg) or desipramine (20 mg/kg) once daily in the morning for 14 days effectively abolished the hypothermic response to 8-OH-DPAT (Table 1). The effect was not seen 24 h after a single dose of desipramine (20 mg/kg) but was clearly already present for zimeldine treated animals (Table 1), although interestingly 45 min after injection of zimeldine, given at the lower dose of 5 mg/kg in the hope of mimicking plasma levels found 24 h after the higher dose, no attenuation of the hypothermic response to 8-OH-DPAT (0.1 mg/kg) was observed. Zimeldine administration did not change basal temperature (Table 1), while desipramine-treated animals tended to show slightly lowered basal temperatures after 14 days (Table 1).

Tranylcypromine (20 mg/kg) elevated body temperature measured 24 h later and attenuated the hypothermic response to 8-OH-DPAT. The effect was more marked following administration of this high dose daily for 14 days (Table 2).

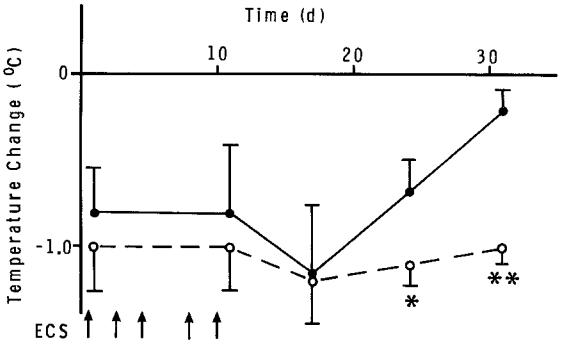

Fig. 1. The hypothermic response to 8-OH-DPAT (0.1 mg/kg SC) during and after repeated electroconvulsive shock (ECS) (*arrows*). Response is mean ± SD at nadir 30 min after injection of 8-OH-DPAT (*n* at least 5). ECS group (●); controls (○) received halothane alone. * $P<0.05$, ** $P<0.01$

Table 1. The effects of zimeldine and desipramine upon the hypothermic response to 8-OH-DPAT

Treatment	n	Rectal temperature (°C)		
		T_0	T_{30}	ΔT
Saline + 45 min	5	39.1 ± 0.2	37.9 ± 0.3	−1.2 ± 0.2
Zimeldine (5 mg/kg) + 45 min	5	38.8 ± 0.3	37.8 ± 0.4	−1.1 ± 0.2
Saline + 24 h	5	38.5 ± 0.1	37.6 ± 0.2	−0.9 ± 0.2
Zimeldine (20 mg/kg) + 24 h	5	38.3 ± 0.3	38.0 ± 0.2	−0.3 ± 0.2*
Saline daily for 14 d	5	38.5 ± 0.3	37.5 ± 0.2	−1.0 ± 0.3
Zimeldine (20 mg/kg) daily for 14 d	5	38.3 ± 0.3	38.2 ± 0.1	−0.1 ± 0.3*
Saline + 24 h	5	38.7 ± 0.2	37.9 ± 0.3	−0.8 ± 0.2
Desipramine (20 mg/kg) 24 h	5	38.7 ± 0.3	38.1 ± 0.3	−0.6 ± 0.2
Saline daily for 14 d	5	39.0 ± 0.3	38.0 ± 0.3	−0.9 ± 0.3
Desipramine (20 mg/kg) daily for 14 d	5	38.5 ± 0.4	38.9 ± 0.4	+0.3 ± 0.4*

Rats were injected with saline (0.1 ml/100 g), zimeldine or desipramine (all IP), doses as in table, either once or daily for 14 days. Responses to 8-OH-DPAT (0.1 mg/kg SC) were determined 45 min or 24 h following a single injection or 24 h after the last of 14 daily injections of saline or drug. Rectal temperature is shown as mean ± SD immediately before 8-OH-DPAT (T_0) and 30 min later (T_{30}). ΔT is mean ± SD for ($T_{30} - T_0$) calculated from the observations on each rat. * $P < 0.01$

Table 2. The effects of tranylcypromine and flurazepam upon the hypothermic response to 8-OH-DPAT

Treatment	n	Rectal temperature (°C)		
		T_0	T_{30}	ΔT
Saline + 24 h	5	38.9 ± 0.4	37.8 ± 0.4	−1.1 ± 0.2
Tranylcypromine (20 mg/kg) + 24 h	5	39.4 ± 0.2	38.6 ± 0.3	−0.6 ± 0.4
Saline daily for 14 d	5	38.7 ± 0.3	37.7 ± 0.3	−1.0 ± 0.2
Tranylcypromine (20 mg/kg) daily for 14 d	5	39.1 ± 0.6	39.0 ± 0.7	−0.1 ± 0.5*
Saline daily for 14 d	5	38.8 ± 0.1	37.8 ± 0.1	−1.0 ± 0.1
Flurazepam (10 mg/kg) daily for 14 d	5	38.9 ± 0.2	38.0 ± 0.3	−0.9 ± 0.2

Rats were injected with saline (0.1 ml/100 g), tranylcypromine or flurazepam (all IP) doses as in table. Responses to 8-OH-DPAT (0.1 mg/kg SC) were determined 24 h following a single injection or the last of 14 daily injections. Rectal temperature is shown as mean ± SD immediately before 8-OH-DPAT (T_0) and 30 min later (T_{30}). ΔT is mean ± SD for ($T_{30} - T_0$) calculated from the observation on each rat. * $P < 0.01$

The effect of flurazepam on the hypothermic response to 8-OH-DPAT. Administration of flurazepam (10 mg/kg) daily for 14 days did not attenuate the hypothermic response to 8-OH-DPAT (Table 2).

The effects of electroconvulsive shock on the serotonin syndrome produced by 8-OH-DPAT. Following repeated ECS, but not after a single shock, there was marked attenuation of the behavioural scores for forepaw treading, head weaving, flat body posture and hindlimb abduction. The mean total scores for these components of the motor syndrome produced by 8-OH-DPAT (0.75 mg/kg SC) following different treatments are shown in Fig. 2. Attenuation of the syndrome was also evident 5 days after the final shock (Fig. 2); it was still apparent after a further 10 days.

In contrast to its effect on the most characteristic components of the serotonin syndrome, ECS enhanced simple motor activity following injection of 8-OH-DPAT (Fig. 2). Since this change did not occur following administration of drugs that, like ECS, reduced the other components of the syndrome (see Fig. 3), it is not simply related to inhibition of stereotypy and postural flattening.

The effects of antidepressant drugs on the serotonin syndrome produced by 8-OH-DPAT. Repeated administration of zimeldine (20 mg/kg daily) or desipramine (20 mg/kg daily) for 14 days attenuated the forepaw treading, head weaving, flat body posture and hindlimb abduction produced by 8-OH-DPAT (0.75 mg/kg SC) (Fig. 3). In contrast, a single dose of these antidepressant drugs was without effect (Fig. 3).

A single injection of tranylcypromine (20 mg/kg) markedly suppressed the syndrome when injected with 8-OH-DPAT 24 h later and the same result was obtained after 7 days treatment (Table 3). Even at a lower dose (6 mg/kg) tranylcypromine significantly attenuated the motor response after a single or repeated administration (Table 3).

The effect of flurazepam on the serotonin syndrome produced by 8-OH-DPAT. Repeated administration of flurazepam

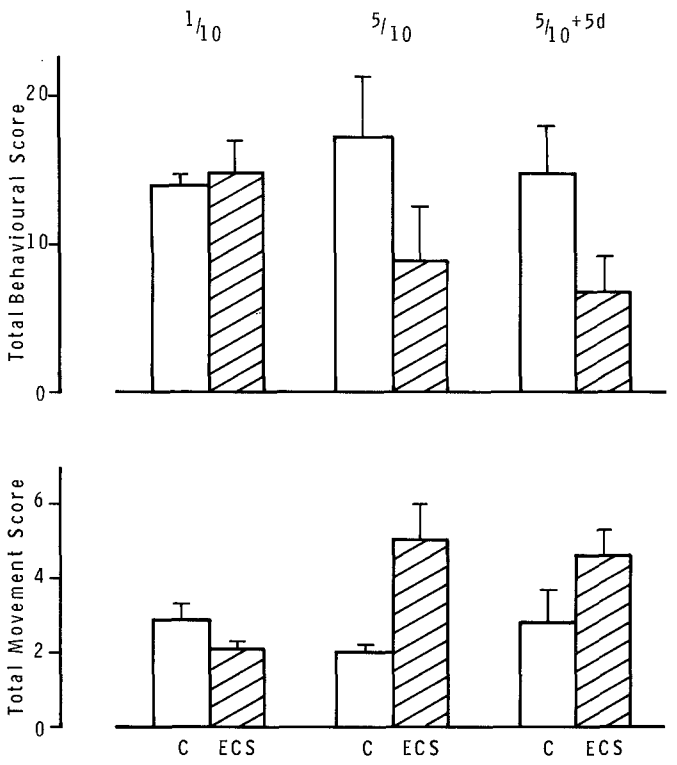

Fig. 2. The motor behavioural responses to 8-OH-DPAT (0.75 mg/kg SC) following ECS: 1/10, single shock tested next day; 5/10, five shocks over 10 days and tested next day; 5/10 + 5d, five shocks over 10 days and tested after 5 days. *Upper columns* show total scores (mean ± SD) for forepaw treading, head weaving, flattening of body posture and hind-limb abduction at 10, 20 and 30 min summed for ECS-treated animals (*hatched*) and halothane treated controls (*open columns*). *Lower columns* show for corresponding responses the summed scores (mean ± SD) for motility alone

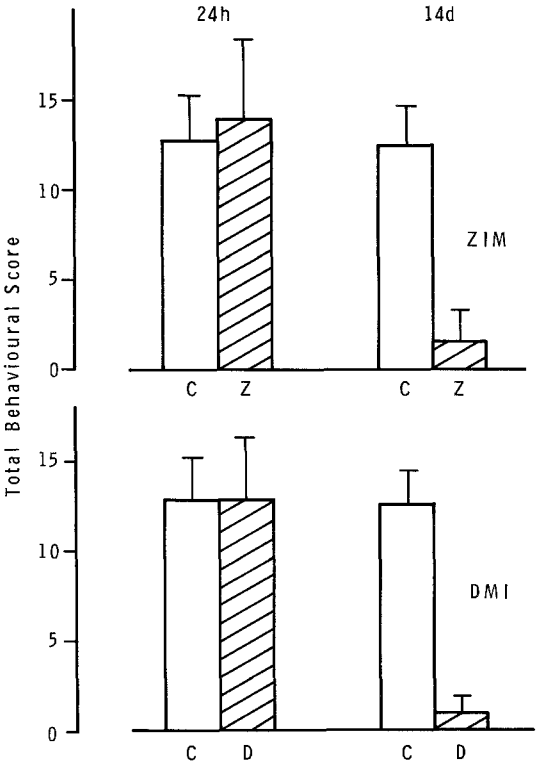

Fig. 3. The behavioural response to 8-OH-DPAT (0.75 mg/kg SC) 24 h after a single injection or following repeated daily injection (IP for 14 days) of zimeldine (*Z*) or desipramine (*D*) at a dose of 20 mg/kg. Total scores (as mean ± SD) shown by total sum for forepaw treading, head weaving, flattening of body posture and hind-limb abduction at 10, 20 and 30 min after injection of 8-OH-DPAT. Responses after 14 d are attenuated in Z-and D-treated groups compared with saline injected (0.1 ml/100 g) controls (*C*): $P < 0.025$

(10 mg/kg daily) was without effect on the serotonin syndrome produced by 8-OH-DPAT (0.75 mg/kg SC) (Table 3).

Discussion

The hypothermic response to 8-OH-DPAT in the mouse is attenuated by a range of antidepressant drugs and ECS (Goodwin et al. 1985b). In the mouse the hypothermic response is not complicated by a behavioural syndrome and is clearly abolished by neurotoxic lesioning of central 5-HT neurones (Goodwin et al. 1985a). In the rat 8-OH-DPAT also produces a dose-related hypothermia that is attenuated by 5-HT depletion (Goodwin et al. 1987) and can be studied in the absence of a clear-cut behavioural response by employing low doses of agonist. The present results essentially confirm the findings in the mouse. Thus ECS attenuated the hypothermia, with a peak effect 1–2 weeks after the final shock (studies in the mouse suggest that this attenuation can last for around 1 month after the last treatment), and desipramine and zimeldine attenuated the response during continuing administration. In fact, a clear effect was present 24 h after a single injection of zimeldine and in vitro there is some evidence for an acute interaction between the terminal autoreceptor and the 5-HT transporter system (Galzin et al. 1985). However, an explanation along these lines is made less likely by the present finding that acute

Table 3. The effects of tranylcypromine and flurazepam upon the motor behavioural responses to 8-OH-DPAT

Treatment	Total behavioural score	
	24 h	7 days
Saline	14.5 ± 3.0	13.8 ± 5.2
Tranylcypromine (6 mg/kg)	7.8 ± 3.7	3.1 ± 1.7*
Tranylcypromine (20 mg/kg)	5.0 ± 1.4	0.8 ± 1.0*
	24 h	14 days
Saline	ND	13.5 ± 5.0
Flurazepam (10 mg/kg)	ND	13.1 ± 5.0

Rats were injected with saline (0.1 ml/100 g), tranylcypromine or flurazepam (all IP), doses as in table. Behavioural scores following injection of 8-OH-DPAT (0.75 mg/kg SC) are shown as mean ± SD. Scores obtained by summing ratings as described in methods and legend to Fig. 2. Responses tested 24 h after saline or drug (acute) and after 7 days (tranylcypromine) or 14 days (flurazepam) administration (chronic). * $P < 0.01$

administration of zimeldine, which produces a blockade of 5-HT re-uptake (Ross and Renyi 1977), did not produce an immediate attenuation of the response to 8-OH-DPAT. More obviously relevant is the electrophysiological finding of a dramatically reduced rate of discharge in raphe cells 24 h after administration of zimeldine (Blier and de Mon-

tigny 1983). Further inhibition of cell firing by 8-OH-DPAT under these conditions may not be possible, and could underlie the acute attenuation of the hypothermic response.

Previous work showed an attenuation of the serotonin syndrome produced by the 5-HT agonist 5-methoxy-N, N-dimethyltryptamine (5-MeODMT) in the rat following a variety of antidepressant drug treatments (Stolz et al. 1983). At the time the behavioural effects were compared with reduced levels of binding to 5-HT_2 receptors produced by the same treatments. It is now clear, first, that the serotonin syndrome can be produced by the action of the much more selective drug 8-OH-DPAT at 5-HT_{1A} sites and, second, that 5-MeODMT also has high affinity for, and probably produces its motor effects by acting at, 5-HT_1 sites (Lucki et al. 1984; Sills et al. 1984). The present findings support those of Stolz et al. (1983) and make it difficult to understand the failure of Lucki and Fraser (1982) to find reduced motor responses to 5-MeODMT following the administration of desipramine or chlorimipramine.

There nevertheless remains a problem in discussing the data obtained with ECS. This treatment apparently enhances the serotonin behavioural syndrome induced by tranylcypromine/L-tryptophan, 5-MeODMT and quipazine (see Green and Nutt 1987 for review). Most studies only measured the behaviour using automated activity instruments and from the evidence of the current study simple enhancement of locomotion may have played a part. However, one of us (ARG) was much involved in these early studies and retains the opinion that behaviours such as forepaw treading were enhanced. Certainly the individual behavioural ratings were enhanced following quipazine (Cowen 1984). Furthermore, treatments given before ECS which blocked the enhanced behaviour also stopped the increase in 5-HT_2 binding (see Green and Nutt 1987). Given the fact that the behaviour can apparently be produced by stimulation of 5-HT_1 or 5-HT_2 receptors (Goodwin and Green 1985), perhaps the simplest explanation is that when 5-HT_1 and 5-HT_2 receptors decrease (after antidepressant drugs) the behaviour always decreases, whilst when the changes conflict (5-HT_1 receptor number down, 5-HT_2 receptor number up) the behavioural change seen is dependent on the agonist used. The increased motility to 8-OH-DPAT after ECS contrasts with the reduction in stereotyped responses. In fact, (±) propranolol does not antagonize the motility response to 8-OH-DPAT (Goodwin et al. 1987). Thus the identity of the receptors involved in this response are different from those mediating the stereotyped components of the serotonin syndrome. The response may nevertheless offer a clue to the properties of ECS that are distinct from other antidepressant treatment, and may contribute to the increased responses to 5-HT precursors following ECS.

Tranylcypromine at a dose of 6 mg/kg produced an attenuated serotonin syndrome; this finding complements the report of Lucki and Fraser (1982) of suppression of the motor response to 5-MeODMT following administration of nialamide (40 mg/kg), phenelzine (10 mg/kg) and pargyline (25 mg/kg) daily for 7 days. Some caution in the interpretation of these results is required, however, because the effects of a higher dose of tranylcypromine (20 mg/kg) were clearly seen 24 h after a single injection. This high dose of tranylcypromine (20 mg/kg) is required to produce monoamine oxidase inhibition sufficient to allow behavioural responses to L-tryptophan even 12 h later (Green et al. 1977); however, the hyperactivity to precursor loading with L-dopa is still present 24 h later. Differential effects of monoamine oxidase inhibitors on different monoamine systems may therefore depend on both dose and time of testing. It appears possible that high doses of MAOIs produce attenuation of motor effects by behavioural competition rather than by a direct effect on receptor number as proposed by Lucki and Fraser (1982). Thus, Dickinson and Curzon (1983) described inhibition of the serotonin syndrome by apomorphine and MAO inhibition may achieve an analogous effect by facilitating dopamine transmission. The amphetamine-like pharmacology of tranylcypromine may be an additional and particular complication in the present experiments.

The benzodiazepine flurazepam was without effect on either hypothermic or motor responses to 8-OH-DPAT. This negative result helps support the hypothesis that 5-HT_{1A} function provides a focus for the action of antidepressant treatments. The finding that diazepam had similar effects upon 5-HT_2 function to those of ECS helped to undermine the idea that this particular mechanism was likely to account for the unusual efficacy of electroconvulsive therapy in the treatment of depressive illness (Green et al. 1986).

The fact that the hypothermic response is attenuated fairly rapidly on antidepressant drug administration would not in itself undermine the idea that it may be involved in the action of antidepressant drugs. Presumably, some changes must occur rapidly as a part of the therapeutic process which lead to the observed therapeutic effect. What does weaken the view that the change is seminal is the observation that repeated administration of 8-OH-DPAT also leads to an attenuation of the hypothermic response (De Souza et al. 1986). 8-OH-DPAT is pharmacologically similar to buspirone, gepirone and ipsapirone and these drugs so far have only been suggested to be anxiolytic not antidepressant.

Nevertheless, the results of the present study contribute to the remarkable shift in attention currently taking place in 5-HT pharmacology. Despite the early emphasis described in the Introduction upon 5-HT_2 receptors and their functional effects, the most consistent changes in function following antidepressant treatment now appear to be mediated by 5-HT_1 receptors and in particular those subgroups of both pre- and post-synaptic receptor for which 8-OH-DPAT has high affinity. Further study of the post-synaptic function of 5-HT_{1A} receptors after psychoactive drugs should clearly be undertaken.

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References

Blier P, de Montigny C (1983) Electrophysiological investigations on the effect of repeated zimeldine administration on serotonergic neurotransmission in the rat. J Neurosci 3:1270–1278

Cowen PJ (1984) The effects of antidepressant treatment on pineal β-adrenoceptor function and on 5-HT-mediated behaviours in the rat. MD Thesis, University of London

Deakin JFW, Green AR (1978) The effects of putative 5-hydroxytryptamine antagonists on the behaviour produced by administration of tranylcypromine and L-tryptophan or L-dopa to rats. Br J Pharmacol 64:201–209

De Souza RJ, Goodwin GM, Green AR, Heal DJ (1986) Effect

of chronic treatment with 5-HT_1 agonist (8-OH-DPAT, RU 24969) and antagonist (isapirone) drugs on the behavioural response of mice to 5-HT_1 and 5-HT_2 drugs. Br J Pharmacol 89:377–384

Dickinson SL, Curzon G (1983) Roles of dopamine and 5-hydroxytryptamine in stereotyped and non-stereotyped behaviour. Neuropharmacology 22:805–812

Friedman E, Cooper TB, Dallob A (1983) Effects of chronic antidepressant treatment on serotonin receptor activity in mice. Eur J Pharmacol 89:69–76

Galzin AM, Moret C, Verzier B, Langer SZ (1985) Interaction between tricyclic and non-tricyclic 5-hydroxytryptamine uptake inhibitors and the presynaptic 5-hydroxytryptamine inhibitory autoreceptors in the rat hypothalamus. J Pharmacol Exp Ther 235:200–211

Goodwin GM, Green AR (1985) A behavioural and biochemical study in mice and rats of putative agonists and antagonists for 5-HT_1 and 5-HT_2 receptors. Br J Pharmacol 84:743–753

Goodwin GM, Green AR, Johnson P (1984) 5-HT_2 receptor characteristics and 5-HT_2 receptor-mediated head-twitch behaviour following antidepressant treatment to mice. Br J Pharmacol 83:235–242

Goodwin GM, De Souza RJ, Green AR (1985a) The pharmacology of the hypothermic response in mice to 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT): a model of presynaptic 5-HT_1 function. Neuropharmacology 24:1187–1194

Goodwin GM, De Souza RJ, Green AR (1985b) Presynaptic serotonin receptor-mediated response in mice attenuated by antidepressant drugs and electroconvulsive shock. Nature 317:531–533

Goodwin GM, De Souza RJ, Green AR, Heal DJ (1987) The pharmacology of the behavioural and hypothermic responses of rats to 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT). Psychopharmacology 91:506–511

Green AR, Heal DJ (1985) The effects of drugs on serotonin-mediated behavioural models. In: Green AR (ed) Neuropharmacology of serotonin. Elsevier, Amsterdam, pp 326–365

Green AR, Nutt DJ (1987) Psychopharmacology of repeated seizures: possible relevance to the mechanism of action of electroconvulsive therapy (ECT) In: Iversen LL, Iversen SD, Snyder SH (eds) Handbook of psychopharmacology. Plenum, New York (in press)

Green AR, Heal DJ, Goodwin GM (1986) The effects of electroconvulsive therapy and antidepressant drugs on monoamine receptors in rodent brain – similarities and differences. Ciba Foundation Symposium 122, Wiley, Chichester (in press)

Green AR, Heal DJ, Johnson P, Laurence BE, Nimgaonkar VL (1983) Antidepressant treatments: effects in rodents on dose-response curves of 5-hydroxytryptamine- and dopamine-mediated behaviours and 5-HT_2 receptor number in frontal cortex. Br J Pharmacol 80:377–385

Green AR, Johnson P, Mountford JM, Nimgaonkar VL (1985) Some anticonvulsant drugs alter monoamine-mediated behaviour in mice in ways similar to electroconvulsive shock: implications for antidepressant therapy. Br J Pharmacol 84:337–346

Green AR, Mitchell BD, Tordoff AFC, Youdim MBH (1977) Evidence for dopamine deamination by both type A and type B monoamine oxidase in rat brain in vivo and for the degree of inhibition of enzyme necessary for increased functional activity of dopamine and 5-hydroxytryptamine. Br J Pharmacol 60:343–349

Hjorth S, Carlsson A, Lindberg P, Sanchez D, Wikstrom H, Arvidsson L-E, Hacksell U, Nilsson JLG (1982) 8-Hydroxy-2-(di-*n*-propylamino)tetralin, 8-OH-DPAT, a potent and selective simplified ergot congener with central 5-HT-receptor stimulating activity. J Neural Transm 55:169–188

Kellar KJ, Cascio CS, Butler JA, Kurtzke RN (1981) Differential effects of electroconvulsive shock and antidepressant drugs on serotonin-2 receptors in rat brain. Eur J Pharmacol 69:515–518

Leysen JE (1985) Characterisation of serotonin receptor binding sites. In: Green AR (ed) Neuropharmacology of serotonin. Elsevier, Amsterdam, pp 790–116

Lucki I, Frazer A (1982) Prevention of the serotonin syndrome in rats by repeated administration of monoamine oxidase inhibitors but not tricyclic antidepressants. Psychopharmacology 77:205–211

Lucki I, Nobler MS, Frazer A (1984) Differential actions of serotonin antagonists on two behavioural syndromes of serotonin receptor activation in the rat. J Pharmacol Exp Ther 228:133–139

Middlemiss DN, Fozard JR (1983) 8-hydroxy-2-(di-*n*-propylamino) tetralin discriminates between subtypes of the 5-HT_1 recognition site. Eur J Pharmacol 90:151–153

Peroutka SJ, Lebovitz RM, Snyder SH (1980) Two distinct central serotonin receptors with different physiological functions. Science 212:827–829

Peroutka SJ, Snyder SH (1980) Long term antidepressant treatment decreases spiroperidol-labelled serotonin receptor binding. Science 210:88–90

Ross SB, Renyi AL (1977) Inhibition of the neuronal uptake of 5-hydroxytryptamine and noradrenaline in rat brain by (Z)- and (E)-3-(4-bromopheny)-N, N-dimethyl-3-(3-pyridyl)allylamines and their secondary analogues. Neuropharmacology 16:57–63

Sills MA, Wolfe BB, Frazer A (1984) Determination of selective and non-selective compounds for the 5-HT_{1A} and 5-HT_{1B} receptor subtypes in rat frontal cortex. J Pharmacol Exp Ther 231:480–487

Stolz JF, Marsden CA, Middlemiss DN (1983) Effect of chronic antidepressant treatment and subsequent withdrawal on [^{3}H]-spiperone binding in rat frontal cortex and serotonin receptor mediated behaviour. Psychopharmacology 80:150–155

Tricklebank MD, Forler C, Fozard JR (1984) The involvement of subtypes of the 5-HT_1 receptor and of catecholaminergic systems in the behavioural response to 8-hydroxy-2-(di-*n*-propylamino)tetralin in the rat. Eur J Pharmacol 106:271–282

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