Pharmacology Biochemistry & Behavior, Vol. 30, pp. 451–456. Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

The Effect of 8-OH-DPAT on Temperature in the Rat and Its Modification by Chronic Antidepressant Treatments

K. M. WOZNIAK,[1] C. S. AULAKH, J. L. HILL AND D. L. MURPHY

Section on Clinical Neuropharmacology, Laboratory of Clinical Science
National Institute of Mental Health, NIH Clinical Center, Room 3D41, Bethesda, MD 20892

Received 10 August 1987

WOZNIAK, K. M., C. S. AULAKH, J. L. HILL AND D. L. MURPHY. *The effect of 8-OH-DPAT on temperature in the rat and its modification by chronic antidepressant treatments.* PHARMACOL BIOCHEM BEHAV 30(2) 451–456, 1988.—Administration of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) to rats produced a dose-dependent hypothermia. Pretreatment with the receptor antagonist methiothepin abolished this effect, and pretreatment with haloperidol, propranolol and pindolol partially attenuated it, although methiothepin and pindolol had hyperthermic actions of their own. Other receptor antagonists including ritanserin, naloxone, clonidine, phenoxybenzamine and metergoline did not significantly modify the response elicited by subsequent 8-OH-DPAT challenge. In antidepressant studies, chronic treatment (22 days) with clorgyline attenuated the hypothermic response to 8-OH-DPAT, whereas similar duration of treatment with the tricyclics clomipramine and imipramine did not significantly modify it. Also, acute treatment for three days with each of the antidepressants did not modify 8-OH-DPAT-induced hypothermia. We conclude that rat rectal temperature can be a useful model to help assess the functional state of serotonergic mechanisms, including the adaptational changes induced by long-term antidepressant treatment.

8-OH-DPAT Temperature Receptor antagonists Clorgyline Clomipramine Imipramine

THE existence of multiple 5-hydroxytryptamine (5HT) receptor subtypes in the central nervous system has previously been demonstrated by radioligand binding studies [48,50]. More recently, there has been the recognition of multiple sites with high affinity for [^{3}H]5HT, i.e., the $5HT_1$ subtypes, $5HT_{1A}$ and $5HT_{1B}$ [47], and most recently $5HT_{1C}$ and $5HT_{1D}$ [24].

8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), an ergot congener synthesized by Arvidsson *et al.* [2], has been suggested to be a selective centrally active 5HT agonist whose behavioral and neurochemical profile appears consistent with agonist activity at both pre- and postsynaptic 5HT receptors. Namely, it has been demonstrated that 8-OH-DPAT decreases brain serotonin synthesis and produces a behavioral syndrome (forepaw treading, head weaving, flat body posture) which is characteristic of postsynaptic receptor activation [27]. Also, it stimulates male rat sexual behaviors [1], depresses dorsal raphe firing [10], and reduces K^+ evoked efflux of [^{3}H]5HT from slices of rat cortex [17,22]. These findings suggest activity at presynaptic (autoreceptor) sites, although there is other evidence against this [37]. In vitro, 8-OH-DPAT shows both high affinity and selectivity for the $5HT_{1A}$ recognition site [11,40], and shows low affinity for other receptors [31].

Central serotonin systems are known to be associated with thermoregulation in several species and most of the evidence points to the preoptic area of the anterior hypothalamus as playing the most important role [23,29]. However, the exact nature of the response to serotonin is controversial [7]. Both hypothermia [6, 13, 32] and hyperthermia [8, 18, 42] have been induced in rats by serotonin or 5HT agonists. It has been proposed that the differential effects of 5HT or 5HT agonists on rat body temperature depend on the exact agent and route of administration employed [43]. However, the exact receptor subtypes involved in thermoregulation have yet to be classified, although recent theories have suggested that activation of $5HT_{1A}$ receptors by serotonin agonists may lead to decreases in body temperature whereas increases are mediated via activation of $5HT_2$ receptors [20]. Such oppos-

[1]Requests for reprints should be addressed to Dr. Krystyna Wozniak, Laboratory of Clinical Science, NIH Clinical Center, 10/3D41, Bethesda, MD 20892.

ing temperature responses following activation of different serotonin receptor subtypes may also account for the earlier discordant findings with different 5HT agonists acting predominantly on one or other receptor subtype. Hence, the current study was undertaken in order to examine the hypothermic response to the allegedly selective $5HT_{1A}$ receptor agonist, 8-OH-DPAT, and its possible alteration by putative receptor antagonists, and further, to investigate the modification of this response by short- and long-term antidepressant treatments with a view to evaluating the adaptive central mechanisms after such treatments.

METHOD

Adult male Wistar rats weighing approximately 250 g at the start of the study were used. Animals were housed in groups of six under controlled 12-hour light-dark cycles (7 a.m.–7 p.m.) and temperature (24±1.0°C), and allowed free access to food and water.

Rectal temperature measurements were recorded by means of a rectal probe and digital thermometer (Sensortek, Inc.). Each animal was habituated to the probe by several exposures prior to the experiment. The probe was inserted 2.5 cm into the colon of each rat, without its removal from the cage. During the experimental sessions, all measurements were made between 10 a.m. and 5 p.m. and at an ambient temperature of 25±1.5°C. Animals were brought into this environment and habituated for at least one hour prior to any recording.

Dose Response

A group of five animals were administered 8-OH-DPAT (0.125 mg/kg, SC) and rectal temperature recordings were made in duplicate at various time intervals for up to 120 minutes after injection as indicated in the Results section. Three and six days later these animals were challenged with 8-OH-DPAT (0.25 and 0.5 mg/kg, respectively), and rectal temperature recordings were measured similarly. Another group of five animals were given saline injections on each of the three test days and rectal temperature recordings were concurrently measured with the above experimental group.

Antagonist Studies

The possible neuropharmacological components of the temperature change induced by 8-OH-DPAT were examined utilizing various receptor antagonists. Groups of at least six animals were given a receptor antagonist (at a dose selected from previously published literature), followed 15 minutes later by saline. Rectal temperature was monitored from just prior to antagonist administration until 120 minutes after saline injection.

Several days later these animals received the same antagonist followed 15 minutes later by a test dose of 8-OH-DPAT (0.25 mg/kg, SC). This dose of 8-OH-DPAT was chosen from the dose-response portion of the study, since it produced a measurable but submaximal hypothermic response. Rectal temperature recordings were measured similarly for 120 minutes after 8-OH-DPAT administration.

Control groups of six animals receiving saline (instead of antagonist) followed by 8-OH-DPAT or additional saline were run at appropriate intervals to control for environmental and/or other influences on the response. Rectal temperature was measured in these groups as described above.

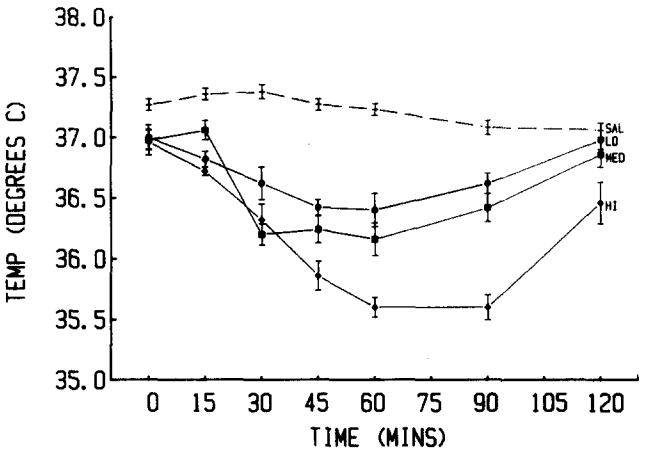

FIG. 1. The effect of 8-OH-DPAT on rectal temperature in the rat following its subcutaneous injection at time zero, where LO=0.125, MED=0.25, and HI=0.5 mg/kg of 8-OH-DPAT. Each point represents the mean temperature (°C) ±S.E.M. from 5 animals. SAL represents mean temperature recordings from concurrently run control animals receiving saline SC.

Antidepressant Studies

The ability of short- and long-term antidepressant (clorgyline, imipramine and chlorimipramine) treatments to modify the hypothermic response of rats to 8-OH-DPAT was examined. Groups of five animals were implanted with osmotic minipumps (Alza Corp.) under pentobarbital anesthesia. Each group received clorgyline (1 mg/kg/day), imipramine (5 mg/kg/day), chlorimipramine (5 mg/kg/day) or saline, the experimenter being blind to the exact treatments. Animals from each group were then challenged with a test dose of 8-OH-DPAT (0.25 mg/kg, SC) after short-term (3 days), mid-term (14 days) and long-term (22 days) antidepressant or saline treatments. Rectal temperature was monitored from 0 to 120 minutes after the 8-OH-DPAT injection.

Drugs

The following drugs were used: 8-OH-DPAT, clorimipramine, imipramine, clorgyline, clonidine, propranolol, naloxone, haloperidol, ritanserin, pindolol, methiothepin, metergoline, and phenoxybenzamine.

All drugs were dissolved in 0.9% saline except for haloperidol, ritanserin, pindolol, and metergoline which were dissolved first in 0.01 N HCl and methiothepin in 0.1 N HCl, and then normalized with NaOH.

All injections were given intraperitoneally (IP) with the exception of 8-OH-DPAT which was given subcutaneously (SC).

Statistics

The data were analyzed using repeated measures design analysis of variance accompanied by contrasts (specified a priori) of the variables. Where necessary, significant effects were further characterized using one-way analysis of variance procedures and associated *t*-tests of specific hypotheses. Analysis procedures were those of the Statistical Analysis System (SAS, Carey, NC).

RESULTS

Administration of 8-OH-DPAT to rats produced signifi-

TABLE 1

EFFECTS OF VARIOUS ANTAGONISTS ON 8-OH-DPAT-INDUCED TEMPERATURE CHANGES (°C)

Antagonist	Delta (°C) After Saline	Delta (°C) After DPAT	Net Delta (°C)	N
Saline	0.03 ± 0.09	−0.87 ± 0.09	−0.90 ± 0.11	18
Clonidine (0.05 mg/kg)	−0.12 ± 0.10	−1.15 ± 0.11	−1.03 ± 0.12	12
Phenoxybenzamine (0.5 mg/kg)	−0.09 ± 0.09	−0.82 ± 0.12	−0.73 ± 0.15	6
Naloxone (0.4 mg/kg)	−0.01 ± 0.17	−0.72 ± 0.09	−0.71 ± 0.19	6
Haloperidol (0.125 mg/kg)	0.18 ± 0.16	−0.36 ± 0.14‡	−0.53 ± 0.21§	12
Methiothepin (HI) (10 mg/kg)	1.08 ± 0.27‡	1.05 ± 0.33‡	−0.03 ± 0.36‡	6
Methiothepin (LO) (2.5 mg/kg)	0.23 ± 0.18	−0.75 ± 0.09	−0.98 ± 0.24	6
Propranolol (4 mg/kg)	−0.18 ± 0.12	−0.45 ± 0.18*	−0.28 ± 0.22†	6
Ritanserin (0.63 mg/kg)	−0.12 ± 0.16	−0.90 ± 0.08	−0.78 ± 0.12	6
Metergoline (0.5 mg/kg)	−0.07 ± 0.10	−1.37 ± 0.14†	−1.30 ± 0.195§	6
Pindolol (HI) (4 mg/kg)	0.93 ± 0.09‡	0.35 ± 0.23‡	−0.58 ± 0.19	6
Pindolol (LO) (1 mg/kg)	0.48 ± 0.15*	−1.32 ± 0.12*	−1.80 ± 0.10‡	5

Values are expressed as peak minus baseline differences [mean delta (°C) ± S.E.M.].
Values which are significantly different from their respective saline control values are represented by *$p<0.05$, †$p<0.01$, ‡$p<0.001$, and a trend, $p<0.1$, is denoted by §.

cant, $F(1,9)=30.0$, $p<0.001$, decreases in rectal temperature which were of dose-related magnitude (see Fig. 1). The effect of the highest dose (0.5 mg/kg) was significantly greater than that of the medium, $F(1,4)=8.73$, $p<0.05$, and the low, $F(1,4)=24.22$, $p<0.01$, dose. However, the effect of the medium dose (0.25 mg/kg) did not differ significantly, $F(1,4)=1.77$, $p>0.05$, from the low dose (0.125 mg/kg). The maximum effect of 8-OH-DPAT on temperature usually appeared between 45 and 60 minutes following injection and approached normal (pre-injection) values by 120 minutes following each dose of 8-OH-DPAT (see Fig. 1). The maximum effect of the highest dose (0.5 mg/kg) was maintained even at 90 minutes after injection. The control group of animals receiving saline displayed maximum deviations from the mean zero time value (37.3±0.05, n=18) over the same test period of less than 0.21°C (n.s., $p>0.05$).

Studies with receptor antagonists (Table 1) demonstrated that pretreatment of rats with haloperidol ($p<0.001$), propranolol ($p<0.05$), and high doses of methiothepin ($p<0.001$) and pindolol ($p<0.001$) significantly attenuated 8-OH-DPAT's effect on body temperature. On the other hand, pretreatment with metergoline ($p<0.01$) or a low dose of pindolol ($p<0.05$) significantly potentiated the hypothermia induced by 8-OH-DPAT relative to that seen in the saline-pretreated animals. None of the other antagonists tested significantly affected 8-OH-DPAT-induced hypothermia. When taking into account the effect of the pretreatment alone on basal temperature in calculating the net effect of 8-OH-DPAT, its modification by metergoline, haloperidol and high dose of pindolol did not quite reach significance ($p>0.05$, $p<0.1$). When administered alone, only high dose (10 mg/kg) methiothepin and both doses (4 and 1 mg/kg) of pindolol had significant effects on basal temperature as compared to saline treatment (see Table 1).

The remainder of this study was directed towards establishing whether short- (3 days) or long-term (22 days) exposure to a particular antidepressant might alter the response to 8-OH-DPAT. Short-term (Fig. 2) and long-term (Fig. 2) treatment with all three antidepressants, namely clorgyline, imipramine and clomipramine, did not significantly, $F(6,22)=1.56$, $p>0.05$, affect the baseline temperature as compared to saline treatment. Administration of 8-OH-DPAT produced hypothermia in all four groups of animals, with a significant, $F(3,11)=5.17$, $p<0.05$, time versus treatment interaction. Further analysis revealed that none of the antidepressant-treated groups differed significantly from either the saline-treated group or each other in their response to 8-OH-DPAT at Day 3 (see Fig. 2). On the other hand, at Day 22, the maximum response to 8-OH-DPAT was significantly ($p<0.05$) attenuated by about 46% in clorgyline-treated animals only as compared to saline (Fig. 2b). Similar treatment with clomipramine and imipramine failed to significantly alter the hypothermic response to 8-OH-DPAT. After 14 days of treatment, the effects of 8-OH-DPAT on temperature were similar to those at 22 days, but the attenuated response in the clorgyline-treated group (approximately 35%) failed to reach significance ($p>0.05$).

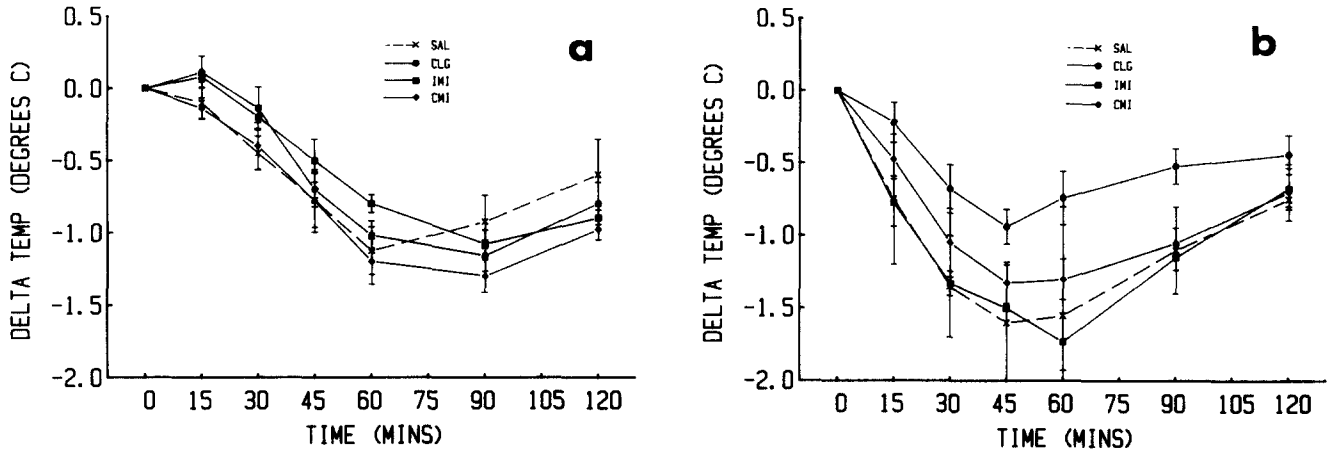

FIG. 2. The effect of 8-OH-DPAT on temperature in rats treated for 3 days (a), or 22 days (b), with an antidepressant drug [CLG=clorgyline (1 mg/kg/day), IMI=imipramine (5 mg/kg/day), CMI=clomipramine (5 mg/kg/day)], or saline (SAL). Values are expressed as mean maximum change in temperature (°C) from baseline ±S.E.M.

It is noteworthy that another group of rats receiving a full 28 days of treatment with the same antidepressants provided comparable data, in which the clorgyline-treated animals displayed a markedly attenuated response to 8-OH-DPAT (about 43% of a similar saline control group).

DISCUSSION

The present results add further support to earlier investigations demonstrating that 8-OH-DPAT produces a marked, dose-related hypothermia in rats [20, 25, 41] and mice [15].

Peripheral 5HT mechanisms have been suggested to be involved in the temperature effects of some 5HT agonists [56]. However, in the case of 8-OH-DPAT, its intracerebroventricular injection produces a full hypothermic response [15]. Similarly, blockade of peripheral 5HT systems with xylamidine does not alter the induced hypothermia [20], suggesting mediation by central 5HT mechanisms.

Various investigators have proposed that hypothermia induced by 5HT agonists in rats is $5HT_{1A}$ mediated [14, 20, 25], although it is not yet clear whether the receptors mediating the response are located pre- or postsynaptically. Administration of 8-OH-DPAT to rats induces various behaviors, some of which are characteristic of presynaptic 5HT receptor activation while others indicate activation of postsynaptic receptors. Consistent with the former, 8-OH-DPAT administration increases feeding in non-deprived rats [12] and stimulates male rat sexual behaviors [1]. Since methiothepin is generally considered to be a potent antagonist at presynaptic $5HT_1$ receptors [16,36], the attenuation of 8-OH-DPAT-induced hypothermia by methiothepin pretreatment in the present study is suggestive of a presynaptically based site of action of 8-OH-DPAT. The experimental finding that methiotepin itself was hyperthermic in rats is in agreement with an action at presynaptic 5HT autoreceptor sites, thereby increasing postsynaptic 5HT levels which could then elevate rat body temperature. However, methiotepin has also been reported to possess actions at dopaminergic and noradrenergic receptors [33], actions which could also be pertinent to this study. Potentiation of 8-OH-DPAT's effect by the postsynaptic 5HT receptor antagonist metergoline, as observed in this study (and previously noted in mice by Goodwin *et al.* [15]) is consistent with a presynaptically based site of action for 8-OH-DPAT which would then be additive with postsynaptic receptor blockade. In mice, it does appear that 8-OH-DPAT-induced hypothermia is indeed mediated, at least partially, by presynaptic $5HT_{1A}$ receptors since lesioning of 5HT terminals with 5,7-dihydroxytryptamine (5,7-DHT) or depletion of 5HT stores by parachlorophenylalanine (PCPA) prevents it [15]. There is also some in vitro evidence for a presynaptic action of 8-OH-DPAT including the demonstration of binding of ^{3}H-OH-DPAT to putative presynaptic 5HT receptor sites [17] and inhibition of K^+ evoked release of 5HT from rat cortical tissue [22]. Electrophysiological studies have shown that 8-OH-DPAT depresses dorsal raphe cell firing [10] and data from a recent ligand binding study of Markinkiewicz *et al.* [35] have led to the suggestion that the somatodendritic autoreceptors of 5HT neurones in the raphe may indeed be $5HT_{1A}$ [54].

On the other hand, 8-OH-DPAT administration to rats also induces behaviors, notably the serotonin syndrome, characteristic of postsynaptic $5HT_{1A}$ receptor activation [55]. Attenuation of 8-OH-DPAT-induced hypothermia by pretreatment with propranolol or pindolol in the present study is consistent with mediation via postsynaptic $5HT_{1A}$ activation since both of these beta-adrenoceptor antagonists also attenuate the serotonin behavioral syndrome in rats [55]. Both compounds have also been shown to be $5HT_1$ antagonists in rats in vitro [33,44]. Alternatively, propranolol and pindolol may attenuate 8-OH-DPAT's effect, at least partially, via their beta-adrenoceptor antagonist action since agonists at this site, such as clenbuterol, can enhance the hypothermic response to 8-OH-DPAT [19]. In addition, any autoreceptor antagonist properties associated with these compounds [38,39] could also modify the 8-OH-DPAT-induced response. Increased body temperature following administration of pindolol alone further suggests antagonism at presynaptic 5HT sites, although it is also possible that pindolol may be exerting an agonist action at postsynaptic 5HT receptor sites other than the $5HT_{1A}$ site. Hjorth and Carlsson [26] have recently provided some biochemical evidence to suggest that pindolol displays mixed agonist/antagonist properties at central $5HT_1$ receptors. The potentiation of 8-OH-DPAT-induced hypothermia by pre-

treatment with a low dose of pindolol and attenuation by high dose, as observed in the present study, may provide some support to their theory.

Failure of naloxone (an opiate antagonist), phenoxybenzamine (alpha$_1$-noradrenergic antagonist), clonidine (alpha$_2$ agonist), and ritanserin (a selective 5HT$_2$ antagonist) to modify 8-OH-DPAT's effect on temperature suggests that these receptors may not be involved. However, attenuation of the same response by haloperidol in the present study (an effect also noted in mice by Goodwin *et al.* [15]) suggests dopamine involvement in the mediation of 8-OH-DPAT's effect, especially since dopamine itself is hypothermic in the rat [30]. Furthermore, 8-OH-DPAT has been shown to exert dopamine agonist activity at the level of the anterior pituitary gland [53]. Alternatively, haloperidol may be exerting its effect via the 5HT$_1$ receptor site since the high affinity binding here is actually defined by displacement with another butyrophenone, spiperone [47].

Finally, in the last part of our study, it was found that 8-OH-DPAT-induced hypothermia was attenuated following long-term treatment with the selective monoamine oxidase (MAO) inhibiting antidepressant, clorgyline. Short-term treatment with clorgyline, as well as both long- and short-term treatment with the tricyclic antidepressants, clomipramine and imipramine, had no significant modifying action on 8-OH-DPAT's effect on temperature. This suggests development of a functional subsensitivity of the 5HT receptors mediating the hypothermic response following chronic treatment with the MAO inhibitor clorgyline. This is consistent with data from a variety of behavioral, electrophysiological and radioligand studies demonstrating differential effects of chronic treatment with these two classes of antidepressant drug. Thus, long-term treatment with non-selective MAO inhibitors, but not tricyclics, attenuated the serotonin behavioral syndrome in rats [34], which is thought to be mediated via 5HT$_{1A}$ mechanisms [55]. In another behavioral study, long-term imipramine treatment potentiated (Aulakh *et al.*, in press) while long-term clorgyline attenuated [5] m-CPP-induced suppression of food intake and locomotor activity in rats. Furthermore, electrophysiological studies have shown that long-term treatment with tricyclic antidepressants does not change 5HT autoreceptor sensitivity [3] but potentiates postsynaptic 5HT function [9]. On the other hand, long-term clorgyline reportedly decreases 5HT autoreceptor sensitivity [4] as well as postsynaptic 5HT function [46]. Finally, in radioligand studies, chronic, but not acute, treatment with the MAO inhibitors clorgyline, nialamide [34,52] or pargyline [49] has been shown to down-regulate the number of 5HT$_1$ receptors in rat brain, whereas the selective MAO-B inhibitor, deprenyl, and several tricyclics had no effect. This suggests that the ability of MAO inhibitors to decrease 5HT$_1$ receptor sites relates to their inhibition of MAO type A, since 5HT is metabolized preferentially by this type of MAO [28]. Although in the above studies it is not clear what proportion of the reduced 5HT$_1$ binding sites or function relates specifically to 5HT$_{1A}$ or 5HT$_{1B}$, we can say that our finding of a suppressed 5HT$_{1A}$ mediated response by chronic clorgyline treatment is consistent with the above previously reported results. However, Gudelsky *et al.* [21] did not observe attenuation of 8-OH-DPAT-induced hypothermia following clorgyline treatment for seven days, although closer inspection of their data revealed a trend towards an attenuated response. In the present study, a similar trend was noted after 14 days of treatment which became significant only after 22 days.

In summary, we conclude that changes in body temperature induced by a 5HT agonist may indeed provide a useful model to evaluate changes in 5HT receptor sensitivity, especially those induced by long-term antidepressant treatments. The decreased sensitivity of 5HT$_{1A}$ receptors (pre- and/or postsynaptic) following long-term clorgyline treatment, as observed in the present study, cannot be related to a common mechanism for therapeutic efficacy of all antidepressant drugs. Nevertheless, the present findings may have therapeutic relevance in that only long-term treatment with an MAO inhibitor induced these changes, and the clinical characteristics of patients who respond to MAO inhibitors may be different from those who generally respond to tricyclic therapy as observed by Quitkin *et al.* [51] and Nies [45].

REFERENCES

1. Ahlenius, S., K. Larsson, L. Svensson, S. Hjorth, A. Carlsson, P. Lindberg, H. Wikstrom and D. Sanchez. Effects of a new type of 5HT receptor agonist on male rat sexual behavior. *Pharmacol Biochem Behav* **15**: 785–792, 1981.
2. Arvidsson, L. E., U. Hacksell, J. L. G. Nilsson, S. Hjorth, A. Carlsson, P. Lindberg, D. Sanchez and H. Wikstrom. 8-Hydroxy-2-(di-n- propylamino) tetralin, a new centrally acting 5-HT receptor agonist. *J Med Chem* **24**: 921–923, 1981.
3. Blier, P. and C. DeMontigny. Effect of chronic tricyclic antidepressant treatment on the serotonergic autoreceptor: A microiontophoretic study in the rat. *Naunyn Schmiedebergs Arch Pharmacol* **314**: 123–128, 1980.
4. Blier, P. and C. DeMontigny. The effect of repeated administration of monoamine oxidase inhibitors on the firing activity of serotonergic and noradrenergic neurons. Abstract of 14th CINP Meeting, Florence, 1984, p. 38.
5. Cohen, R. M., C. S. Aulakh and D. L. Murphy. Long term clorgyline treatment antagonizes the eating and motor function responses to m-chlorophenylpiperazine. *Eur J Pharmacol* **94**: 175–179, 1983.
6. Cox, B. and T. F. Lee. 5-Hydroxytryptamine induced hypothermia in rats as an *in vivo* model for the quantitative study of 5-hydroxytryptamine receptors. *J Pharmacol Methods* **5**: 43–51, 1981.
7. Cox, B. and P. Lomax. Pharmacological control of temperature regulation. *Annu Rev Pharmacol Toxicol* **17**: 341–353, 1977.
8. Crawshaw, L. I. Effects of intracerebral 5-hydroxytryptamine injection on thermoregulation in the rat. *Physiol Behav* **9**: 133–140, 1972.
9. DeMontigny, C. and G. K. Aghajanian. Tricyclic antidepressants: Long-term treatment increases responsivity of rat forebrain neurons to serotonin. *Science* **202**: 1303–1306, 1978. 1978.
10. DeMontigny, C., P. Blier and Y. Chaput. Electrophysiologically identified serotonin receptors in the rat CNS. Effect of antidepressant treatment. *Neuropharmacology* **23**: 1511–1520, 1984.
11. Deshmukh, P. P., D. L. Nelson and H. I. Yamamura. Localization of 5HT$_1$ receptor subtypes in rat brain by autoradiograph. *Fed Proc* **41**: 6238, 1982.
12. Dourish, C. T., P. H. Hutson and G. Curzon. Low doses of the putative serotonin agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OHDPAT) elicit feeding in the rat. *Psychopharmacology (Berlin)* **86**: 197–204, 1985.
13. Feldberg, W. and V. J. Lotti. Temperature responses to monoamines and an inhibitor of MAO injected into the cerebral ventricles of rats. *Br J Pharmacol* **31**: 152–161, 1967.

14. Goodwin, G. M. and A. R. Green. A behavioral and biochemical study in mice and rats of putative selective agonists and antagonists for $5HT_1$ and $5HT_2$ receptors. *Br J Pharmacol* **84:** 743–753, 1985.
15. Goodwin, G. M., R. J. DeSouza and A. R. Green. The pharmacology of the hypothermic response in mice to 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT). *Neuropharmacology* **24:** 1187–1194, 1985.
16. Gothert, M. Modulation of serotonin release into the brain via presynaptic receptors. *Trends Pharmacol Sci* **4:** 437–440, 1982.
17. Gozlan, H., S. El Mestikawy, S. Bourgoin, M. Hall, L. Pichat, J. Glowinski and M. Hamon. The specific labelling of pre- and postsynaptic 5HT receptors by ^{3}H-PAT in the rat CNS. *Naunyn Schmiedebergs Arch Pharmacol* **324S:** 73, 1983.
18. Grahame-Smith, D. G. Studies *in vivo* on the relationship between brain tryptophan, brain 5HT synthesis and hyperactivity in rats treated with a monoamine oxidase inhibitor and L-tryptophan. *J Neurochem* **18:** 1053–1066, 1971.
19. Green, A. R., G. M. Goodwin, R. J. DeSouza and D. J. Heal. The $beta_2$-adrenoceptor agonists clenbuterol and salbutanol enhance the hypothermic action of 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) in mice by a central mechanism. *Neuropharmacology* **25:** 21–24, 1986.
20. Gudelsky, G. A., J. I. Koenig and H. Y. Meltzer. Thermoregulatory responses to serotonin (5-HT) receptor stimulation in the rat. *Neuropharmacology* **25:** 1307–1313, 1986.
21. Gudelsky, G. A., J. I. Koenig, H. Jackman and H. Y. Meltzer. Suppression of the hypo- and hyperthermic responses to 5-HT agonists following the repeated administration of monoamine oxidase inhibitors. *Psychopharmacology (Berlin)* **90:** 403–407, 1986.
22. Hamon, M., S. Bourgoun, H. Gozlan, M. D. Hall, C. Goetz, F. Artaud and A. S. Horn. Biochemical evidence for the 5HT agonist properties of PAT [8-hydroxy-2-(Di-n-propylamino)-tetralin] in the rat brain. *Eur J Pharmacol* **100:** 263–276, 1984.
23. Hardy, J. D. Physiology of temperature regulation. *Physiol Rev* **41:** 521–606, 1961.
24. Heuring, R. E. and S. J. Peroutka. Characterization of a novel ^{3}H-5-hydroxytryptamine binding site subtype in bovine brain membranes. *J Neurosci* **3:** 894–903, 1987.
25. Hjorth, S. Hypothermia in the rat induced by the potent serotonergic agent 8-OH-DPAT. *J Neural Transm* **61:** 131–135, 1985.
26. Hjorth, S. and A. Carlsson. Is pindolol a mixed agonist-antagonist at central serotonin (5HT) receptors? *Eur J Pharmacol* **129:** 131–138, 1986.
27. Hjorth, S., A. Carlsson, P. Lindberg, P. Sanchez, H. Wikstrom, L. E. Arvidsson, U. Hacksell and J. L. G. Nilsson. 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, 1982.
28. Jacob, J. J. and J. T. Girault. 5-Hydroxytryptamine. In: *Body Temperature. Regulation, Drug Effects and Therapeutic Implications*, edited by P. Lomax and E. Schonbaum. New York: Marcel Dekker, 1979, pp. 183–230.
29. Houslay, M. D. and K. F. Tipton. A kinetic evaluation of monoamine oxidase in rat liver mitochondrial membranes. *Biochem J* **139:** 645–652, 1974.
30. Kruk, Z. L. The effect of drugs acting on dopamine receptors on the body temperature of the rat. *Life Sci* **11:** 845–850, 1972.
31. Leysen, J. E. Characterization of serotonin receptor binding sites. In: *Neuropharmacology of Serotonin*, edited by A. R. Green. Amsterdam: Elsevier, 1985, pp. 79–116.
32. Lin, M. T., C. F. Chow, Y. F. Chern and K. M. Wu. Elevating serotonin levels in brain with 5-hydroxytryptophan produces hypothermia in rats. *Pflugers Arch* **377:** 245–249, 1978.
33. Lloyd, K. G. and G. Bartholini. The effect of methiotepin on cerebral monoamine neurones. *Adv Biochem Psychopharmacol* **10:** 305–309, 1974.
34. Lucki, I. and A. Frazer. Prevention of the serotonin syndrome in rats by repeated administration of monoamine oxidase inhibitors but not tricyclic antidepressants. *Psychopharmacology (Berlin)* **77:** 205–211, 1982.
35. Markinkiewicz, M., D. Verge, H. Gozlan, L. Pichat and M. Hamon. Autoradiographic evidence for the heterogeneity of $5HT_1$ sites in the rat brain. *Brain Res* **291:** 159–163, 1984.
36. Martin, L. L. and E. Sanders-Bush. Comparison of pharmacological characteristics of $5\text{-}HT_1$ and $5\text{-}HT_2$ binding sites and those of serotonin autoreceptors which modulate serotonin release. *Naunyn Schmiedebergs Arch Pharmacol* **321:** 165–170, 1982.
37. Middlemiss, D. N. 8-Hydroxy-2-(di-n-propylamino)tetralin is devoid of activity at the 5-hydroxytryptamine autoreceptor in rat brain. Implications for the proposed link between the autoreceptor and the [^{3}H]5HT recognition site. *Naunyn Schmiedebergs Arch Pharmacol* **327:** 18–22, 1984.
38. Middlemiss, D. N. Stereoselective blockade at [^{3}H]-5HT binding sites and at the 5HT autoreceptor by propanolol. *Eur J Pharmacol* **101:** 289–293, 1984.
39. Middlemiss, D. N. Blockade of the central 5-HT autoreceptor by beta-adrenoceptor antagonists. *Eur J Pharmacol* **120:** 51–56, 1986.
40. Middlemiss, D. N. and J. R. Fozard. 8-Hydroxy-2-(di-n-propylamino) discriminates between subtypes of the $5HT_1$ recognition site. *Eur J Pharmacol* **90:** 151–153, 1983.
41. Middlemiss, D. N., J. Neill and M. D. Tricklebank. Subtypes of the 5-HT receptor involved in hypothermia and forepaw treading induced by 8-OH-DPAT. *Br J Pharmacol* **85S:** 251, 1985.
42. Myers, R. D. Serotonin and thermoregulation: old and new views. *J Physiol (Paris)* **77:** 505–513, 1981.
43. Myers, R. D. and M. B. Waller. Thermoregulation and serotonin. In: *Serotonin in Health and Disease*, edited by W. Essman. New York: Spectrum, 1978, pp. 1–67.
44. Nahorski, S. R. and A. L. Willcocks. Interactions of beta-adrenoceptor antagonists with 5-hydroxytryptamine receptor subtypes in rat cerebral cortex. *Br J Pharmacol* **78:** 107P, 1983.
45. Nies, A. Clinical applications of MAOI's. In: *Drugs in Psychiatry, Vol 1*, edited by G. D. Burrow, T. R. Norman and B. Davies. Amsterdam: Elsevier, 1983, pp. 219–247.
46. Olpe, H. R. Differential effect of chlorimipramine and clorgyline on the sensitivity of cortical neurons to serotonin. *Eur J Pharmacol* **69:** 375–377, 1981.
47. Pedigo, N. W., H. I. Yamamura and D. L. Nelson. Discrimination of multiple [^{3}H]5-hydroxytryptamine binding sites by the neuroleptic spiperone in rat brain. *J Neurochem* **36:** 220–226, 1981.
48. Peroutka, S. J. and S. H. Snyder. Multiple serotonin receptors: differential binding of [^{3}H]5-hydroxytryptamine. [^{3}H]lysergic acid diethylamide and [^{3}H]spiroperidol. *Mol Pharmacol* **16:** 687–699, 1979.
49. Peroutka, S. J. and S. H. Snyder. Long term antidepressant treatment decreases spiroperidol-labelled serotonin receptor binding. *Science* **210:** 88–90, 1980.
50. Peroutka, S. J. and S. H. Snyder. Multiple serotonin receptors and their physiological significance. *Fed Proc* **42:** 213–217, 1983.
51. Quitkin, F., A. Rifkin and D. F. Klein. Monoamine oxidase inhibitors. *Arch Gen Psychiatry* **36:** 749–760, 1979.
52. Savage, D. D., J. Mendels and A. Frazer. Monoamine oxidase inhibitors and serotonin reuptake inhibitors: differential effects on [^{3}H]serotonin binding sites in rat brain. *J Pharmacol Exp Ther* **212:** 259–263, 1980.
53. Simonovic, M., G. A. Gudelsky and H. Y. Meltzer. Effect of 8-hydroxy-2-(di-n-propylamino)tetralin on rat prolactin secretion. *J Neural Transm* **59:** 143–149, 1984.
54. Sprouse, J. S. and G. K. Aghajanian. Serotonergic dorsal raphe neurons: electrophysiological responses in rats to $5HT_{1A}$ and $5HT_{1B}$ receptor subtype ligands. *Soc Neurosci Abstr* **11:** 47, 1985.
55. Tricklebank, M. D., C. Forler and J. R. Fozard. The involvement of subtypes of the $5\text{-}HT_1$ receptor and of catecholaminergic systems in the behavioral response to 8-hydroxy-2-(di-n-propylamino)tetralin in the rat. *Eur J Pharmacol* **106:**. 271–282, 1984.
56. Winter, J. C. Xylamidine tosylate: differential antagonism of the hypothermic effects of N,N-dimethyl-tryptamine bufotine and 5-methoxytryptamine. *Arch Int Pharmacodyn Ther* **198:** 61–66, 1972.