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Serotonin 5-HT_{1A} Receptor-Mediated Hypothermia in Mice: Absence of Spare Receptors and Rapid Induction of Tolerance

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MELLER, E., M. CHALFIN AND K. BOHMAKER. *Serotonin 5-HT_{1A} receptor-mediated hypothermia in mice: Absence of spare receptors and rapid induction of tolerance.* PHARMACOL BIOCHEM BEHAV 43(2) 405–411, 1992. – The mixed 5-hydroxytryptamine$_{1A}$ (5-HT_{1A}) receptor agonist/antagonist 8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspirol-[4.5]-decane-7,9-dione (BMY 7378) (5 mg/kg) did not significantly depress body temperature, but pretreatment with BMY 7378 blocked hypothermia induced by the selective 5-HT_{1A} agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT). In contrast, another partial 5-HT_{1A} agonist, pindolol (10 mg/kg), slightly but significantly depressed body temperature by itself but did not attenuate hypothermia elicited by 8-OH-DPAT. Attempts to identify the synaptic locus of the receptor were unsuccessful because depletion of central serotonin (5-HT) by treatment with para-chlorophenylalanine (PCPA; 3 × 150 mg/kg) did not alter the hypothermic response to 8-OH-DPAT. Partial, irreversible 5-HT_{1A} receptor inactivation by *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (1 mg/kg) reduced the maximal hypothermic effect of 8-OH-DPAT (to 53% of control) without altering its ED_{50} (0.96 mg/kg). Analysis of the data indicated a linear relationship between 5-HT_{1A} receptor occupancy and hypothermic response, that is, absence of receptor reserve. When groups of mice were treated with each of five different doses of 8-OH-DPAT (0.04, 0.16, 0.63, 2.5, and 10 mg/kg) 48 h apart, there was a significant reduction in hypothermic response after the second injection, but only at the three highest doses. The results demonstrate that 8-OH-DPAT-induced hypothermia in mice is mediated by a 5-HT_{1A} receptor whose synaptic localization is uncertain but that has no receptor reserve. In addition, tolerance is observed after only a single agonist treatment.

5-HT_{1A} receptors Hypothermia Receptor reserve Desensitization
8-Hydroxy-2-(di-*n*-propylamino)tetralin *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline

HYPOTHERMIA is a relatively nonspecific response that can be elicited by drugs of many different classes (6). Nevertheless, it can be a useful functional parameter for assessing drug interactions, especially when induced by a known agonist of defined selectivity and specificity. Hypothermia elicited by the selective 5-hydroxytryptamine$_{1A}$ (5-HT_{1A}) agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) has been extensively investigated as an easily measured and sensitive end point of 5-HT_{1A} receptor-mediated functional response (10, 13,14,28). However, a number of controversies exist in the literature regarding this effect. First, while most reports support a postsynaptic localization for the 5-HT_{1A} receptor mediating this response in both rats (14,16) and mice (21), others suggest that it is mediated by somatodendritic autoreceptors in the raphe nuclei (10) or that mice and rats differ fundamentally in this regard (3). Second, important species differences in pharmacology may exist between rats and mice. Thus, in rats, pindolol (a mixed 5-HT_{1A}, 5-HT_{1B}, and β-receptor antagonist) (15) elicits *hyper*thermia by itself and blocks the hypothermia induced by 8-OH-DPAT (1,13) and other 5-HT_{1A} agonists (buspirone, gepirone, and ipsapirone) (19), but it does not block 8-OH-DPAT-induced hypothermia in mice (12). A putatively selective 5-HT_{1A} antagonist, NAN-190, has been reported to be both effective (24) and ineffective (25) in attenuating 8-OH-DPAT-induced hypothermia in rats; in mice, however, there is agreement that it does not block the response to 8-OH-DPAT and elicits hypothermia by itself (24,29). On the other hand, a third agent, 8-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-8-azaspirol[4.5]-decane-7,9-dione (BMY 7378), attenuates the effect of 8-OH-DPAT in both rats and mice (24).

A third controversy revolves around the effects of chronic treatment with 8-OH-DPAT. Kennett et al. (18) and Beer et al. (2) reported that a single pretreatment with 8-OH-DPAT

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resulted in the desensitization of several 5-HT_{1A} receptor-mediated responses attributable to somatodendritic autoreceptor activation in the raphe nuclei, but not postsynaptic receptor responses. In contrast, Larsson et al. (20) found just the opposite: Postsynaptic responses desensitized readily, whereas autoreceptor-mediated responses did not. Of particular interest in the latter study was the observation that a single dose of 8-OH-DPAT resulted in a robust loss of response to the hypothermic effect of 8-OH-DPAT when administered 48 h later. Electrophysiological studies after chronic gepirone treatment, on the other hand, indicated selective desensitization of somatodendritic autoreceptors (4).

The anxiolytic 5-HT_{1A} agonists (i.e., buspirone, gepirone, and ipsapirone) display differential efficacy at pre- and postsynaptic 5-HT_{1A} receptors: full agonism for responses mediated by 5-HT_{1A} autoreceptors, but partial agonism at postsynaptic receptors [reviewed in (23)]. We have shown that a difference in the efficiency of receptor/effector coupling (i.e., extent of receptor reserve) may account for this: There is a large receptor reserve at the somatodendritic autoreceptor (23) but none at the postsynaptic 5-HT_{1A} receptor (e.g., that mediating inhibition of forskolin-stimulated adenylate cyclase in the hippocampus) (31). In view of the controversies discussed above, in the present studies we sought to determine whether 8-OH-DPAT-induced hypothermia in mice is: a) mediated by pre- or postsynaptic receptors; b) associated with a receptor reserve; c) blocked by putatively selective 5-HT_{1A} receptor antagonists; and d) readily desensitized by prior exposure to drug.

METHOD

Animals and Drug Treatments

Male Swiss-Webster mice (Taconic, Germantown, NY), 22–25 g, were housed four to five per cage under conditions of constant temperature (22 ± 1°C), humidity, and light cycle (light/dark 7:00 a.m./7:00 p.m.) for at least 1 week before use. They were given access to food and water ad lib. Mice were injected subcutaneously with various doses of drugs in a volume of 0.1–0.2 ml. Drugs used and their sources were: 8-OH-DPAT HBr (Research Biochemicals, Inc., Natick, MA); (±)pindolol (free base) (Sandoz, Ltd., Basel, Switzerland); BMY 7378 H_2Cl (Bristol-Myers Squibb Co., Wallingford, CT); and *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) and para-chlorophenylalanine methyl ester (PCPA) (Sigma Chemical Co., St. Louis, MO). 8-OH-DPAT, BMY 7378, and PCPA were dissolved in physiological saline; pindolol was dissolved in a minimal quantity of acetic acid and diluted with saline; EEDQ was dissolved in absolute ethanol and sequentially diluted with propylene glycol and water (1 : 1 : 3).

Temperature Measurements

Colonic temperature was measured at various times after drug treatment by gently inserting a petrolatum-coated thermistor probe (model YSI 402; Yellow Springs Instrument Co., Yellow Springs, OH) 2.5 cm into the rectum. The probe was attached to a digital thermistor thermometer (Digi-Sense, model 8522-10; Cole-Parmer, Chicago, IL); the temperature was recorded after allowing the probe to reach equilibrium (approximately 15 s). All temperature measurements were made at an ambient temperature of 22 ± 1°C.

Analysis of Brain 5-HT

Tissue samples were homogenized in 0.1 N perchloric acid containing 0.001% ascorbic acid and analyzed by high-performance liquid chromatography (HPLC) with electrochemical detection exactly as described previously (23).

Data Analysis

Dose–response curves for 5-HT_{1A} agonist-induced hypothermia were fit using the ALLFIT computer program (7) as described previously (22,23). Following partial 5-HT_{1A} receptor inactivation with EEDQ, equieffective agonist doses were utilized to construct double reciprocal plots and occupancy vs. response plots according to the method of Furchgott and Bursztyn (9) as described previously in detail (22,23). One- and two-way repeated-measures analysis of variance (ANOVA) or Student's *t*-test were used for statistical comparison of data.

RESULTS

Effect of PCPA on 8-OH-DPAT-Induced Hypothermia

Depletion of neuronal 5-HT with PCPA has been commonly used to assess the pre- or postsynaptic localization of receptors mediating a particular drug's response. A reduction in response after PCPA indicates a dependence upon endogenous 5-HT stores; a presynaptic receptor localization, affecting 5-HT synthesis and/or release, is therefore inferred. Conversely, if the receptor is postsynaptic a reduction in transmitter availability might be expected to result in an adaptive receptor upregulation, yielding a supersensitive response. Figure 1 shows that pretreatment with three doses of PCPA (150 mg/kg, IP, 72, 48, and 24 h before) did not alter the hypothermic response to 8-OH-DPAT (2 mg/kg). Despite the unchanged hypothermic response, PCPA treatment significantly reduced brain 5-HT content by 37–45% (Table 1). Additional experiments with somewhat different treatment protocols (3 × 100 mg/kg PCPA, 2 mg/kg 8-OH-DPAT challenge; 3 × 150 mg/kg PCPA, 0.5 mg/kg 8-OH-DPAT

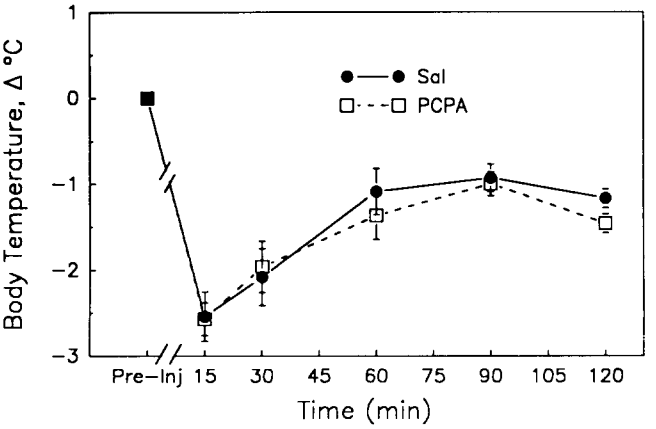

FIG. 1. Effects of PCPA on 8-OH-DPAT-induced hypothermia. Mice were treated 72, 48, and 24 h before testing with either saline (Sal) or PCPA (150 mg/kg, IP) and then challenged with 2 mg/kg 8-OH-DPAT (SC). Basal body temperature (preinjection), measured 1–2 h before the start of this and all subsequent experiments, was 37.35 ± 0.07°C (saline pretreated) and 37.63 ± 0.10°C (PCPA pretreated). Each point is the mean (±SEM) of 10 mice.

TABLE 1

EFFECTS OF PCPA ON BRAIN 5-HT CONTENT IN MICE

Brain Region	5-HT (ng/g wet wt.)	
	Saline	PCPA
Cortex	684 ± 30	431 ± 37* (−37%)
Hippocampus	751 ± 48	414 ± 34* (−45%)

*$p < 0.001$ compared to saline pretreatment, Student's t-test.

Mice were treated once daily with saline or PCPA (150 mg/kg, IP) for 3 days and killed 24 h after the last injection. Each value is the mean ± SEM of 5–6 mice.

challenge) yielded similar results (data not shown). Although the lack of a reduction in hypothermic response after depletion of 5-HT suggests that the response is not likely to be mediated presynaptically, the absence of a supersensitive response, while not obligatory, does not allow a definitive conclusion to be reached that the response is postsynaptic.

Blockade of 8-OH-DPAT-Induced Hypothermia

Pretreatment with the 5-HT$_{1A}$ partial agonist BMY 7378 (23,30) markedly attenuated the hypothermic response to 8-OH-DPAT (1 mg/kg) (Fig. 2). In a subsequent experiment, the effects of BMY 7378 and pindolol alone on body temperature, and the effects of pretreatment with these drugs on 8-OH-DPAT-induced hypothermia, were assessed (Fig. 3). A two-way repeated-measures ANOVA on the data shown in Fig. 3 yielded significant overall pretreatment, $F(4, 28) = 8.90, p < 0.0002$, repeated-measures, $F(2, 56) = 37.98, p < 0.0001$, and interaction, $F(2, 56) = 11.14, p < 0.0001$, effects. Subsequent one-way ANOVA analyses for repeated-measure effects of each of the treatments shown were carried out. Neither BMY 7378 alone, $F(2, 12) = 0.49, p > 0.05$, nor BMY plus 8-OH-DPAT treatment, $F(2, 12) = 0.27, p > 0.05$, yielded significant effects, indicating that BMY 7378 alone did not elicit hypothermia while it blocked the effects of 8-OH-DPAT. Pindolol itself elicited a small but

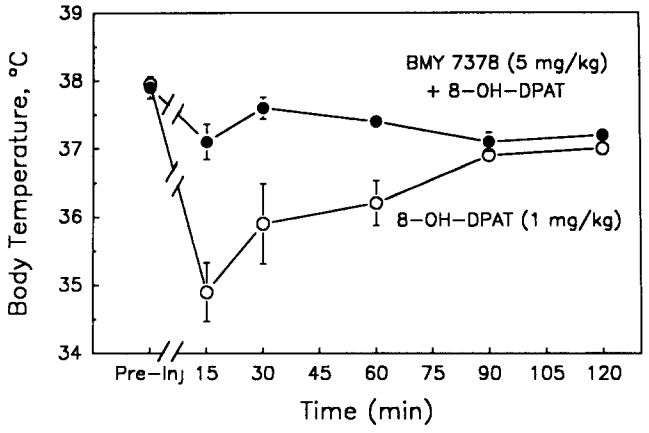

FIG. 2. Blockade of 8-OH-DPAT-induced hypothermia by BMY 7378. BMY 7378 (5 mg/kg, SC) was administered 30 min before 8-OH-DPAT. n = 4–5 mice per group.

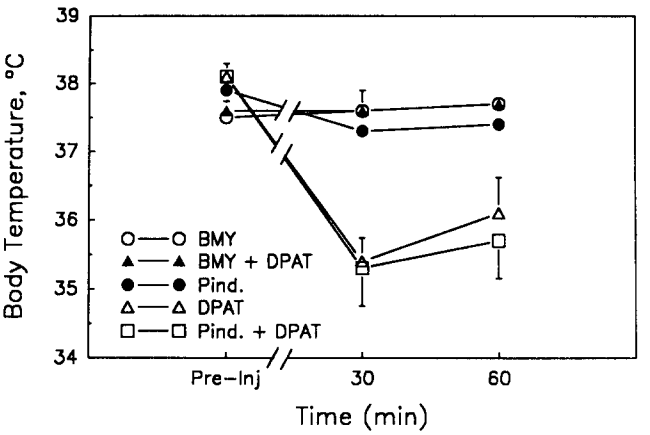

FIG. 3. Effects of BMY 7378 and pindolol on 8-OH-DPAT-induced hypothermia. BMY 7378 (5 mg/kg, SC), pindolol (10 mg/kg, SC), or saline were administered 30 min prior to saline or 8-OH-DPAT (3 mg/kg, SC). Body temperature was measured 30 and 60 min after the second injection (saline or 8-OH-DPAT). Each symbol is the mean (± SEM) of 5–7 mice.

significant hypothermia, $F(2, 12) = 31.07, p < 0.001$, but it did not attenuate the effect of 8-OH-DPAT because the repeated-measures effect was highly significant, $F(2, 12) = 13.32, p < 0.002$. Thus, BMY 7378 and pindolol clearly differed in their ability to antagonize 8-OH-DPAT-induced hypothermia, as reported previously (12,24).

Determination of Receptor Reserve for 8-OH-DPAT-Induced Hypothermia

BMY 7378 is a weak partial agonist that behaves as an agonist with full intrinsic activity in the presence of a large receptor reserve (23), but acts an antagonist (30) at 5-HT$_{1A}$ receptors where there is no receptor reserve (31). The results shown in Figs. 2 and 3 demonstrate that BMY 7378 has little intrinsic ability to elicit hypothermia and in fact antagonizes the hypothermia elicited by 8-OH-DPAT, suggesting that the 5-HT$_{1A}$ receptors mediating this effect have little receptor reserve. This was directly tested by subjecting 5-HT$_{1A}$ receptors to partial irreversible inactivation with EEDQ (23,31) (Fig. 4, left). Simultaneous ALLFIT analysis indicated that such treatment reduced the maximal hypothermic effect of 8-OH-DPAT (to 53% of vehicle-pretreated rats) without altering the ED_{50} or slope factor. Equieffective doses of 8-OH-DPAT required to elicit hypothermia in control and EEDQ-treated mice at five different levels of response (30–70% of the maximal effect obtained in EEDQ animals) were subjected to a double reciprocal plot as described previously (22,23,31) (data not shown). The pseudoactivation constant (K_A value) obtained from this plot (1.27 mg/kg) was used in conjunction with the mass-action equation to calculate fractional receptor occupancy for each of the experimental doses of the control curve (22,23,31). A plot of percent receptor occupancy for each of these doses against observed body temperature is shown in Fig. 4 (right). It can be seen that the relationship is strictly linear, indicating that there is no receptor reserve for 8-OH-DPAT-induced hypothermia (22,23,31).

Effects of Prior Agonist Exposure on 8-OH-DPAT-Induced Hypothermia

Groups of mice were treated twice, 48 h apart, with one of five different doses of 8-OH-DPAT. The time courses of the

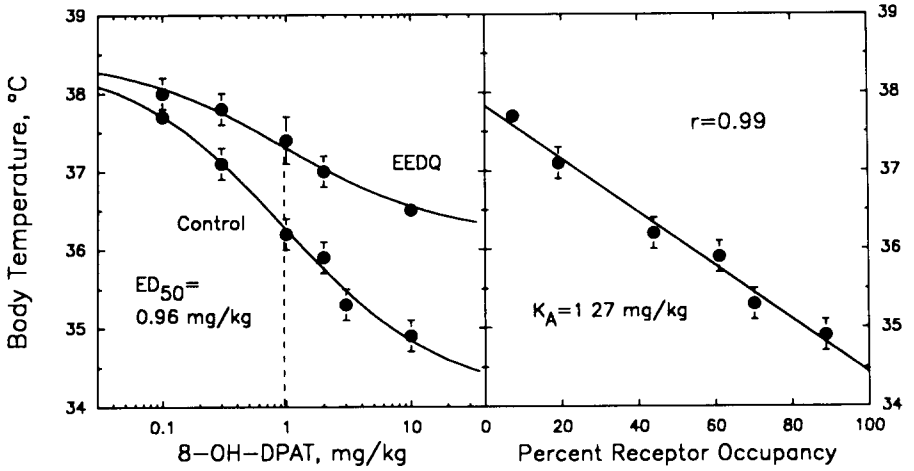

FIG. 4. Effect of partial irreversible 5-HT_{1A} receptor inactivation with EEDQ on 8-OH-DPAT-induced hypothermia. EEDQ (1 mg/kg, SC) was administered 24 h prior to 8-OH-DPAT challenge; body temperature was measured 30 min later. Mean data (±SEM) from 4 (control, n = 16–18) or 2 (EEDQ, n = 11–13) separate experiments are shown. The curves were simultaneously fit by ALLFIT as described in the text. The pseudo-K_A value (1.27 mg/kg) and the mass-action equation [$f = (A)/(A) + K_A$] were used to calculate fractional receptor occupancy (f) for each dose [(A)] used in the control experiment.

hypothermic response to each of these doses after the first and second exposures to agonist are shown in Fig. 5. It is readily apparent that a reduced maximal hypothermic response was obtained on retest, but the effect was most clear at the three highest doses. Dose-response curves were constructed for the test-retest results at the time of maximal response (30 min) and are shown in Fig. 6. ALLFIT analysis indicated that the curves could share the same ED_{50} and slope factor, but not maximal response, without a significant degradation in fit. A two-way repeated-measures ANOVA yielded obvious and highly significant dose and repeated measures effects ($p < 0.0001$ for each); there was also a significant interaction effect, $F(1, 45) = 5.40, p < 0.002$, indicating that differences in the repeated measure were dose dependent. Subsequent one-way repeated-measures ANOVA corroborated that the hypothermic response differed only at the three highest doses [0.63 mg/kg, $F(1, 9) = 36.86$, $p < 0.001$; 2.5 mg/kg, $F(1, 9) = 12.88$, $p < 0.01$; 10 mg/kg, $F(1, 9) = 33.13$, $p < 0.001$].

DISCUSSION

In our hands, treatment of mice with the 5-HT depletor PCPA did not alter their sensitivity to the hypothermic effects of 8-OH-DPAT (Fig. 1), thereby preventing any firm conclusion regarding the locus of the 5-HT_{1A} receptor mediating this response. Some investigators have reported a supersensitive response after 5-HT depletion in both mice (21) and rats (14,16), suggesting a postsynaptic site of action. One group, however, has reported that PCPA treatment abolished the hypothermic effect of 8-OH-DPAT in both mice (10,12) and rats (11,12). As pointed out by Hutson et al. (16), this discrepancy may reflect the use of a different and more vigorous protocol for PCPA administration (200 mg/kg for 12 days) than that used routinely by us and others (100–150 mg/kg for 3 days). A recent report (3), however, suggests a differential localization of the 5-HT_{1A} receptors mediating hypothermia in these rodent species: presynaptic in mice and postsynaptic in rats. Our own results differ yet again in that we were unable to observe any effect of PCPA on hypothermic response. It should be noted that different mouse strains were utilized in the various laboratories, which may underlie the highly variable results obtained. At this time, it appears that the receptor site of action is indeterminate.

The weak partial 5-HT_{1A} receptor agonist BMY 7378 (30) blocked 8-OH-DPAT-induced hypothermia but did not itself elicit a reduction in body temperature (Figs. 2 and 3). Moser (24) reported that BMY 7378 was an effective antagonist in both rats and mice, although, in contrast to our results, it produced a slight hypothermia by itself in both species. Pindolol, at a relatively high dose of 10 mg/kg, was ineffective in our hands, corroborating the results of Goodwin et al. (10,12). Propranolol, another β-receptor antagonist with a pharmacological profile similar to that of pindolol (except that it also has relatively high affinity for 5-HT_{1B} receptors) (15), was also found to antagonize hypothermia in rats but not in mice (10–12). NAN-190 is another agent that shares this differential ability to antagonize hypothermia in these two rodent species (24,29). It seems likely that the relatively high affinity of these drugs for receptors other than 5-HT_{1A} may be responsible for this marked species difference. BMY 7378 would appear, from these studies, to be the antagonist of choice regardless of species. Further work is necessary to determine the mechanism for the distinct species differences in pharmacology observed.

As mentioned above (see the Results section), the ability of BMY 7378 to act as an antagonist of 8-OH-DPAT-induced hypothermia suggested that this response is mediated by 5-HT_{1A} receptors that are not very efficiently coupled to their effectors (i.e., do not display a receptor reserve). This is consistent with the response being mediated by a receptor with a coupling efficiency characteristic of postsynaptic 5-HT_{1A} receptors, which we have previously found do not display a receptor reserve (31) and at which BMY 7378 acts as a very weak partial agonist with low efficacy (30). In contrast, BMY 7378 demonstrates strong intrinsic activity at somatodendritic 5-HT_{1A} autoreceptors that display a large receptor reserve

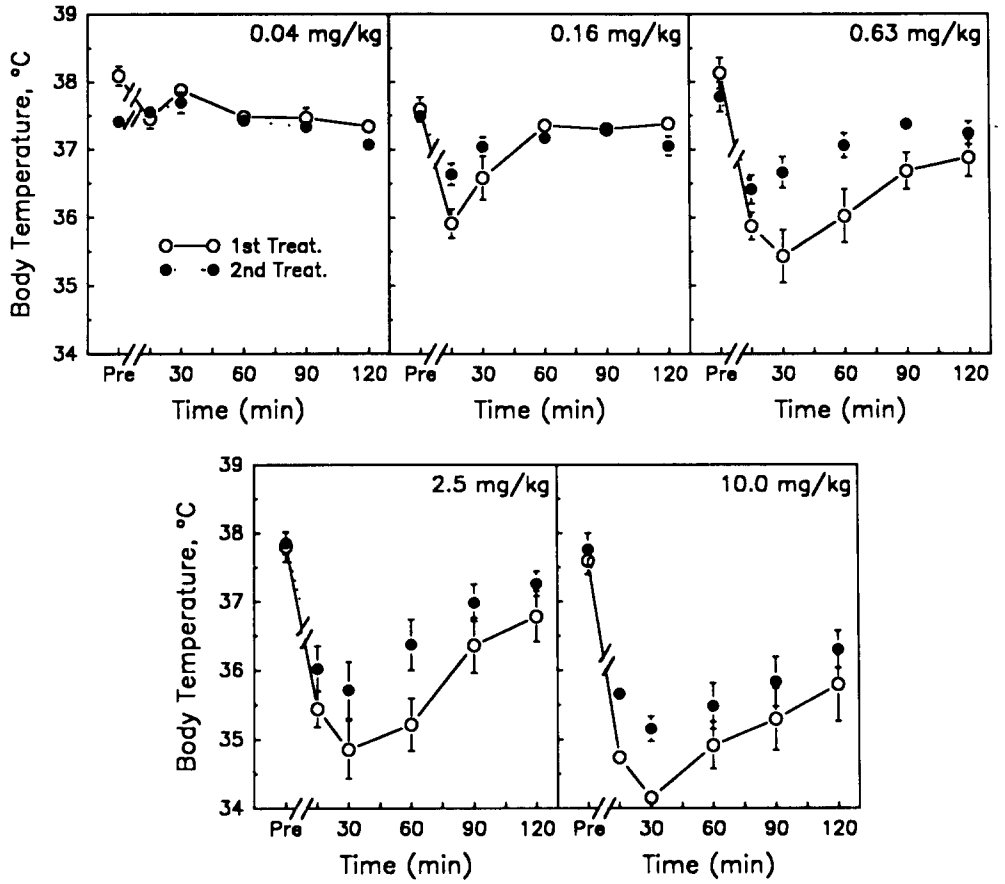

FIG. 5. Time course for 8-OH-DPAT-induced hypothermia after the first or second (48 h later) exposure to various doses of agonist. n = 10 animals per group.

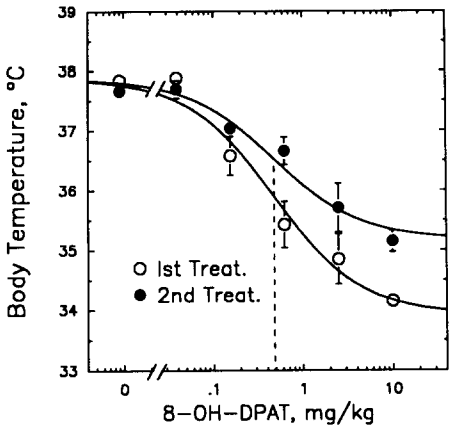

FIG. 6. Dose-response curves for hypothermia induced by 8-OH-DPAT after the first and second challenges. Data are from the 30-min time points shown in Fig. 5. ALLFIT analysis indicated that the curves could share the ED_{50} (0.48 mg/kg) and slope factor without a significant degradation in fit. However, the maximal effect after the second treatment (68% of control) was significantly different ($p < 0.05$). Note that the effects of repeated treatment are qualitatively similar to the effects of receptor inactivation (Fig. 4).

(23). The absence of a receptor reserve for hypothermia induced by the full agonist 8-OH-DPAT was corroborated by directly determining its extent utilizing the classical method of partial irreversible receptor inactivation as described by Furchgott and Bursztyn (9) (Fig. 4). This technique produced a loss of maximal response to 8-OH-DPAT without a significant shift in ED_{50}; in contrast, when this method was applied to 8-OH-DPAT-induced inhibition of 5-HT synthesis (a response mediated by somatodendritic 5-HT$_{1A}$ autoreceptors) a large rightward shift in ED_{50} (six- to eightfold) with only a modest reduction in maximal response was obtained (23). This difference in receptor/effector coupling efficiency is manifested in a large difference between the ED_{50} dose for 8-OH-DPAT-induced hypothermia (0.5–1 mg/kg; Figs. 4 and 6) and inhibition of 5-HT synthesis (15–30 μg/kg) (23).

An interesting aspect of the present studies was the corroboration (in mice) of the findings of Larsson et al. (20) (in rats) that a single treatment with 8-OH-DPAT results in a clear desensitization or tolerance to the hypothermic response of a second treatment 48 h later (Figs. 5 and 6). Qualitatively, the alteration in dose-response (Fig. 6) is similar to that after receptor inactivation (Fig. 4). Thus, irrespective of the mechanism for reducing the efficiency of receptor/effector coupling (see below) the pattern of response is the same. De Souza et al. (8) previously noted tolerance to this response (in mice) after 7 and 14 days of treatment with 8-OH-DPAT, but had not examined the response after only a single treatment. A

similar effect was noted with regard to 8-OH-DPAT-induced hyperphagia (18), although this response was characterized as being mediated by somatodendritic 5-HT_{1A} autoreceptors. Larsson et al. (20), however, examined a number of both pre- and postsynaptic functional responses and concluded that postsynaptic receptor-mediated responses were readily desensitized upon repeated treatment but presynaptic responses were not. Components of the 5-HT behavioral syndrome mediated by stimulation of postsynaptic 5-HT_{1A} receptors, including forepaw treading and flat-body posture, appear to be readily desensitized after repeated agonist treatment (20,27). In electrophysiological studies, however, 5-HT_{1A} autoreceptor responses reportedly desensitized after treatment with anxiolytic agonists [e.g., gepirone (4) and ipsapirone (26)], whereas postsynaptic responses (e.g., in the hippocampus) did not (4). Further complicating this issue, biochemical measures of autoreceptor function have generally been found to be resistant to desensitization (20,26); however, we recently demonstrated reduced sensitivity of autoreceptor-mediated function under appropriate experimental conditions (5).

The discrepant results regarding sensitivity changes in pre- and postsynaptic 5-HT_{1A} receptor function noted above may reflect, as suggested by Larsson et al. (20), a promiscuous coupling of 5-HT_{1A} receptors with various effectors through specific subtypes of G proteins (17). The various functional responses mediated by pre- and postsynaptic 5-HT_{1A} receptors may therefore be differentially affected by repeated agonist treatment as a consequence of their being coupled to different effectors and/or *via* different G proteins. The differences in receptor reserve for various 5-HT_{1A} receptor-mediated effects described above are consistent with such postulated differences in coupling characteristics. The changes in sensitivity may in fact not be at the level of the receptor because Larsson et al. (20) found no change in [^{3}H]8-OH-DPAT receptor binding parameters after repeated 8-OH-DPAT treatment, although others have found such alterations (2).

In summary, despite ambiguity regarding the synaptic localization of the 5-HT_{1A} receptors involved the present results indicate that, in mice, 8-OH-DPAT-induced hypothermia is preferentially antagonized by BMY 7378, displays no receptor reserve, and is readily desensitized even after a single prior exposure to the agonist. It is apparent, however, that an unusual degree of complexity is associated with the regulation of 5-HT_{1A} receptor-mediated function. Much additional work will be needed to unravel the mechanistic basis for this complexity.

ACKNOWLEDGEMENT

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