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Dopamine D3 Receptor Mutant and Wild-Type Mice Exhibit Identical Responses to Putative D3 Receptor-Selective Agonists and Antagonists

MING XU,[1] TIMOTHY E. KOELTZOW,[2] DONALD C. COOPER,[2] SUSUMU TONEGAWA,[1] AND FRANCIS J. WHITE[3]*

[1]*Howard Hughes Medical Institute, Center for Learning and Memory, and Department of Biology, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139*

[2]*Department of Neuroscience, Finch University of Health Sciences/The Chicago Medical School, North Chicago, Illinois 60064-3095*

[3]*Department of Cellular and Molecular Pharmacology, Finch University of Health Sciences/The Chicago Medical School, North Chicago, Illinois 60064-3095*

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ABSTRACT Previous studies using a variety of drugs with different affinities for the dopamine (DA) D3 receptor suggested that this receptor is involved in regulating motor activity and hypothermia. However, the in vivo selectivity of many of these compounds has been repeatedly questioned. To examine the precise roles of the DA D3 receptor in motor activity and hypothermic responses, we used mutant mice lacking the DA D3 receptor to evaluate the in vivo effects of several putative D3 receptor-selective agonists and antagonists. Using automated photocell activity chambers, we observed that the decreases in locomotor activity produced by putative D3 receptor-selective agonists as well as increases in locomotor activity produced by putative D3 receptor antagonists are identical in D3 receptor mutant and wild-type mice. In addition, the hypothermia produced by the putative D3 receptor-selective agonist PD 128907 is identical in both groups of mice. Based on these findings, we propose that D3 receptors are unlikely to be involved in these effects and we caution that the putative D3 ligands that have been used to reach conclusions regarding the functional roles of D3 receptors lack the necessary in vivo selectivity to support such conclusions. **Synapse 31:210–215, 1999.**

INTRODUCTION

Suggestions regarding possible behavioral functions mediated by dopamine (DA) D3 receptors were based primarily on the reduction in locomotor activity produced by agonists with apparent moderate preference for D3 receptors, e.g., 7-OH-DPAT (Daly and Waddington, 1993; Svensson et al., 1994b), and the induction of motor hyperactivity by antagonists with moderate selectivity for D3 receptors (Waters et al., 1993b; Sautel et al., 1995). Although DA autoreceptors have long been implicated in these behavioral effects (see Clark et al., 1985, for review), some investigators began to attribute these effects to postsynaptic D3 receptors because they were observed in the absence of neurochemical alterations known to be mediated by DA autoreceptors, i.e., DA release or synthesis (Waters et al., 1993a,b, 1994; Svensson et al., 1994a,b; Sautel et al., 1995). A second function that has been attributed to postsynaptic D3 receptors is the hypothermic response produced by D2-class receptor agonists (Millan et al., 1994, 1995a,b). Although early studies with 7-OH-DPAT attributed hypothermia to D2 receptor stimulation (Ahlenius and Salmi, 1994), recent results indicate that the doses at which D2-class agonists produce hypothermia correlate better with binding affinities for D3 as opposed to D2

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Current address for M. Xu: Department of Cell Biology, Neurobiology and Anatomy, University of Cincinnati College of Medicine, Cincinnati, Ohio 45267-0521.

*Correspondence to: Francis J. White, Ph.D., Department of Cellular and Molecular Pharmacology, The Chicago Medical School, 3333 Green Bay Rd., North Chicago, IL 60064-3095. E-mail: whitef@mis.finchcms.edu

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receptors (Millan et al., 1995). In addition, the hypothermic response to D2-class agonists were prevented by the putative selective D3 receptor antagonist S 14297 ((+)-7-(N,N-dipropylamino)-5,6,7,8-tetrahydro-naphtho (2,3b) dihydro,2,3-furane) (Millan et al., 1994, 1995b).

A major drawback with these studies on D3 receptor functions is that they are based solely on moderate selectivity of ligands for the D3 as opposed to the D2 receptor, as determined by binding affinities to cloned receptors expressed in various transfected cell systems. Such affinities often do not accurately reflect functional affinities even in the same cell systems (Sokoloff and Schwartz, 1995). Therefore, we have taken advantage of the recently described D3 receptor mutant mouse to determine possible roles of D3 receptors in motor behavior and thermoregulation (Xu et al., 1997). These mice lack the DA D3 receptor but exhibit otherwise normal dopaminergic systems. We compared the D3 receptor mutant mice to their wild-type litter-mates in both locomotor and hypothermia tests using compounds with proposed preferential affinities for the D3 receptor. We reasoned that if the in vivo effects of these drugs are mediated by D3 receptors, they should be absent or significantly reduced in the D3 receptor mutant mice. Our results suggest that these two functions previously proposed to be mediated by the DA D3 receptor are more likely mediated by other members of the D2-class receptor subfamily.

MATERIALS AND METHODS

D3 receptor mutant mice

D3 mutant mice were generated as described by Xu et al. (1997). Mutant mice and their wild-type litter-mates were bred at the Massachusetts Institute of Technology and were shipped to the Chicago Medical School. All mice were allowed 7–8 days to acclimate to the new environment prior to experimental testing. D3 mutant and wild-type mice were housed separately in groups of three to four with food and water available ad libitum in a temperature- and humidity-controlled room with a 12-h light/dark cycle.

Procedures

Locomotor activity experiments were conducted in a separate room within the vivarium during the light portion of the light/dark cycle. Standard 30 × 50 cm propylene cages were placed inside adjustable frames equipped with two sets of infrared photobeam detectors (San Diego Instruments, Inc., San Diego, CA). The lower set of detectors was placed for the detection of horizontal locomotor activity, whereas the higher set recorded rearing behaviors. For each cage, all beam breaks were relayed by an interface to a 286-based microcomputer with custom software (PASF, San Diego Instruments). The configuration allowed detection of three dependent variables, including total number of beam breaks, sequential beam breaks (ambulations), and rearing. All results presented in this study reflect the total number of beam breaks, i.e., ambulations plus repetitive breaks of a single lower photobeam plus rearing. Careful analysis of the individual components of this measure indicated nearly identical results for each dependent variable.

Prior to behavioral testing, animals were allowed to habituate to the testing environment for at least 30 min except when noted. Drugs were administered i.p. in volumes of 1 ml/100 g immediately following the habituation period. Tests were generally conducted for 1 h, with the exception of the nafadotride experiments, because of published reports indicating a longer duration of action of this drug (Sautel et al., 1995). All drugs were dissolved in physiological saline. To determine the behavioral effects of PD 128907 (0.01, 0.05, 0.1, 0.5 mg/kg) and nafadotride (0.03, 0.3, 3.0 mg/kg), dose–response curves were generated using experimenter-blind, randomized designs. For U99194A, separate groups of mice were tested with saline, 3.9 and 7.8 mg/kg. To maximize the locomotor stimulant effects of putative D3 receptor-selective antagonists, longer habituation periods of 60 min were used to ensure that mice were well habituated. In each experiment, saline was injected on the first day and locomotor activity was assessed to establish baseline levels. On subsequent test days, spaced 1 week apart (except when noted), each animal was randomly exposed to each challenge dose until each subject had been assessed with all doses. Core body temperature was measured prior to and 15 min after injection of PD 128907.

Statistical analysis

Differences between D3 mutant and wild-type mice in behavioral tests were conducted either with independent *t*-tests (single tests) or repeated measures analysis of variance (ANOVA) for dose–response determinations. Individual planned comparisons following ANOVAs were conducted with Dunnett's test with $\alpha = 0.05$.

RESULTS

Suppression of locomotor activity by putative D3 receptor agonists is identical in D3 receptor mutant and wild-type mice

Several investigators have suggested that DA D3 receptor stimulation leads to a decrease in motor activity (see Introduction). However, these studies were based on pharmacological ligands with questionable selectivity for D3 receptors. To determine the influence of the D3 receptor on motor activity in vivo, we compared the responses of D3 receptor mutant and wild-type mice to the putative D3 receptor agonist PD 128907, which reportedly exhibits the greatest selectivity for D3 over D2 receptors (Sokoloff and Schwartz, 1995).

Using a randomized design, we tested groups of eight mice for their responses to saline and four doses of PD 128907 (0.01–0.5 mg/kg). This agonist caused a significant dose-dependent suppression of locomotor activity ($F_{3,42} = 8.26$, $P = 0.0002$), which was equivalent in the D3 receptor mutant and the wild-type mice ($F_{1,42} = 0.12$, $P = 0.74$, Fig. 1A). To discern whether higher doses of this drug might cause locomotor stimulation, as reported in rats (Pugsley et al., 1995; Bristow et al., 1996), we tested two additional doses of PD 128907 (1.5 and 3.0 mg/kg) in a separate group of D3 receptor mutant and wild-type mice. Both doses produced further decreases in locomotor activity (Fig. 1A, inset) and the two groups of mice responded in a nearly identical manner ($F_{1,23} = 1.50$, $P = 0.23$). These findings cannot be attributed to some unusual property of PD 128907 because we observed similar decreases in locomotor activity in response to two other agonists with in vitro selectivity for D3 receptors, quinpirole (0.05 mg/kg) and 7-OH-DPAT (0.01 mg/kg). For both drugs, there were no differences between the two groups of mice with respect to the suppression of basal motor activity ($t_{10} = 1.41$, $P = 0.18$ for quinpirole; $t_{14} = -0.53$, $P = 0.6$ for 7-OH-DPAT). Thus, D3 receptor mutant and wild-type mice exhibit identical behavioral responses to these putative D3 receptor-selective agonists.

Induction of locomotor activity by putative DA D3 receptor-selective antagonists is identical in D3 receptor mutant and wild-type mice

The putative D3 receptor-selective antagonists that have been identified and tested to date exert inverted-U shaped dose–response effects on locomotor activity, increasing locomotion at low doses and decreasing it at higher doses (see Introduction). The increase is observed in well-habituated rodents and has been attributed to preferential antagonism of postsynaptic D3 receptors. This implies that under tonic conditions, DA activates D3 receptors to inhibit locomotor activity. Decreases in locomotor activity produced by higher, non-D3 preferring doses of putative D3 receptor-selective antagonists are presumed to reflect D2 receptor antagonism. Based upon this reasoning, we would expect that low doses of D3 preferring antagonists would increase locomotor activity in wild-type mice but not in the D3 receptor mutants.

We tested the behavioral effects of two putative D3 receptor-selective antagonists, U 99194A (5,6-di,methoxy-2-(dipropylamino) indan HCl) and nafadotride, in the D3 mutant and wild-type mice. U 99194A produced a dose-dependent biphasic effect on locomotion in that a low dose produced a greater increase than a higher dose (Fig. 1B). Nafadotride produced only locomotor activation (Fig. 1C), which was considerably less pronounced than that observed with U 99194A and which was not dose-dependent. Most importantly, we observed no differences between D3 mutant mice and their wild-type litter-mates with respect to the effects of either U99194A ($F_{1,53} = 0.86$, $P = 0.36$) or nafadotride ($F_{1,42} = 0.01$, $P = 0.94$). These findings indicate that the motor responses produced by these structurally dissimilar compounds are more likely to result from actions other than at D3 receptors.

Hypothermia induced by PD 128907 is identical in DA D3 receptor mutant and wild-type mice

PD 128907, at the relatively high dose of 0.5 mg/kg, produced hypothermia (Fig. 2). However, there were no differences in the hypothermic responses of D3 receptor mutant and wild-type mice. Thus, hypothermia is likely to be mediated by other members of the D2-class receptor family, most likely the D2 receptor itself.

DISCUSSION

Elucidation of the in vivo functions mediated by the DA D3 receptor has been hampered by the lack of ligands with sufficient selectivity for this receptor subtype. To overcome this problem, we used mutant mice lacking the D3 receptor and focused on two specific functions that have been speculated to involve the D3 receptor, alterations in locomotor activity and hypothermia. We found that the suppression of locomotor activity and induction of hypothermia by putative D3 receptor-selective agonists, as well as activation of locomotion by putative D3 receptor-selective antagonists, are completely normal in mice lacking D3 receptors. Since detailed histological analysis indicates that there were no detectable changes in the mesostriatal dopamine systems of the D3 receptor mutant mice (Xu et al., 1997), our findings raise questions about certain claims regarding the in vivo functions of D3 receptors based on studies using these ligands.

Reduction of locomotor activity by putative DA D3 receptor-selective agonists is likely mediated by DA D2 receptors

Unlike rats, in which dopamine D2-class receptor agonists cause a dose-dependent bi-phasic suppression/enhancement of locomotor activity, mice show a monophasic suppression of locomotor activity across a broad dose range when tested with most dopamine D2-class receptor agonists (bromocriptine appears to be an exception—see Jackson et al., 1989). The suppression of locomotor activity has been attributed either to a reduction of synaptic DA levels as a result of D2 autoreceptor stimulation (Clark and White, 1987; Jackson et al., 1989) or to the activation of a postsynaptic D2-class receptor that is inhibitory upon locomotion. The D3 receptor has been implicated as such a postsynaptic receptor based on two major findings. First, in one laboratory locomotor suppression in rats could be observed at doses of putative D3 receptor agonists that did not appear to decrease in vivo microdialysate concentrations of DA, i.e., no autoreceptor stimulation (Svensson et al., 1994a,b). Second, putative D3 receptor

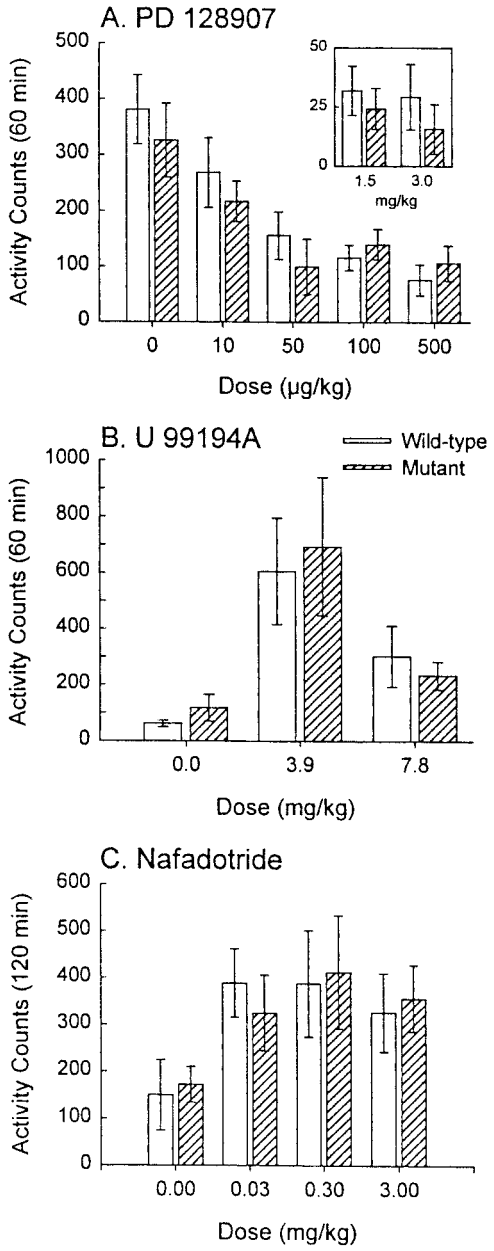

Fig. 1. Effects of putative D3 receptor-selective ligands on locomotor activity. **A:** Dose–response curves illustrating the locomotor suppressant effects of the putative D3 receptor-selective agonist PD 128907 in D3 receptor mutant and wild-type mice (n = 8/group). The inset graph shows results obtained from separate groups of mice (mutant mice n = 7 and wild-type mice n = 8 at 1.5 mg/kg; n = 6 for both groups at 3.0 mg/kg). These results are shown as an inset because they were from mice that were not included in the randomized dose–response experimental design. Note that the inhibitory effects of PD 128907 were identical in mutant and wild-type mice. The '0' dose refers to a saline injection. All results are expressed as mean ± SEM. **B:** Dose–response curves illustrating the locomotor-activating effects of the putative D3 receptor-selective antagonist U 99194A in D3 receptor mutant and wild-type mice. Sample sizes for the wild-type and D3 mutant mice are 12 and 11 for saline (0), 7 and 6 for 3.9 mg/kg and 11 and 12 for 7.8 mg/kg. **C:** Dose–response curves illustrating the locomotor-activating effects of the putative D3 receptor-selective antagonist nafadotride (n = 8 per group at all doses) in D3 mutant and wild-type mice. This test was conducted for 2 h and a separate analysis of the results for each hour also revealed no difference between D3 mutant and wild-type mice. For both graphs, the '0' dose refers to a saline injection and bars represent means ± SEM.

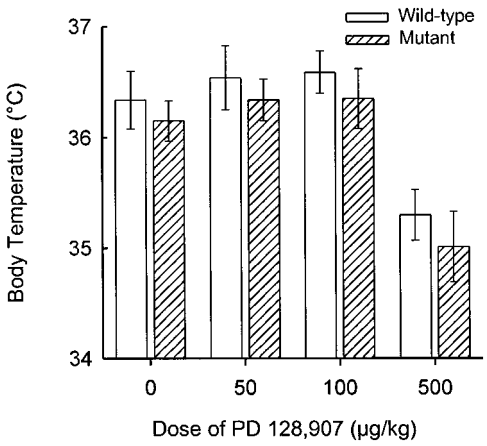

Fig. 2. Effects of PD 128907 on core body temperature. Note that PD 128907 induces hypothermia only at the highest dose tested and did so equally well in D3 receptor mutant and wild-type mice (n = 8 per group). The '0' dose refers to a saline injection. Each bar represents mean ± SEM.

antagonists increase locomotor activity, also at doses that did not appear to increase DA release as measured by in vivo microdialysis (Waters et al., 1993b, 1994; Sautel et al., 1995). However, our findings question the involvement of D3 receptors in these behavioral effects.

Mice lacking the DA D3 receptor exhibited reductions in locomotor activity in response to three putative D3 receptor agonists, PD 128907, quinpirole, and 7-OH-DPAT, which were identical to those observed in their wild-type littermates. Thus, it is unlikely that this effect is the result of D3 receptor stimulation. Taken together with the results of our previous studies indicating that D3 receptors do not appear to exert significant DA autoreceptor actions (Koeltzow et al., 1998), it is clear that PD 128907, like quinpirole and 7-OH-DPAT (Liu et al., 1994; Large and Stubbs, 1994; Gonzalez and Sibley, 1995), exerts potent DA D2 receptor actions in vivo. Although it might be argued that D2 receptors have compensated for the lack of D3 receptors in the mutant mice, the density and affinity of DA D2 receptors are normal both qualitatively and quantitatively in these mutant mice, suggesting that there is no significant upregulation of D2 receptor systems in D3 receptor mutant mice (Accili et al., 1996; Xu et al., 1997). Combined with the fact that many investigators (Gilbert and Cooper, 1995; Gilbert et al., 1995; Pugsley et al., 1995; Gainetdinov et al., 1996) do not see the dissociation between suppression of locomotion and DA release during administration of putative D3 receptor-selective agonists, as reported by Svensson and colleagues (1994a,b), we believe that D2 autoreceptor stimulation is more likely to underlie the decrement in locomotor activity observed with these drugs. According to this view, DA autoreceptor stimulation would greatly reduce levels of synaptic DA, thereby denying postsynaptic D1-class receptors their endogenous ligand. Without D1 receptor activation, occupation of postsynaptic

D2 receptors by the exogenous agonists would be rendered behaviorally inconsequential, because stimulation of both D1 and D2 receptors is required for the locomotor activation. This would directly lead to a decrease in locomotor activity (for reviews, see Clark and White, 1987; Waddington and Daly, 1993; White and Hu, 1993). In support of this possibility, we have demonstrated that the three agonists tested in this study all potently stimulate impulse-modulating DA autoreceptors leading to a suppression of activity of dopamine neurons in both D3 mutant and wild-type mice (Koeltzow et al., 1998). This would lead to a decrease in DA release, as would stimulation of nerve-terminal regulating modulating DA autoreceptors, as we have demonstrated in D3 receptor mutant mice using in vivo microdialysis (Koeltzow et al., 1998).

Locomotor activation by preferential DA D3 receptor antagonists may not be mediated by D3 receptors

The second basis for the hypothesis that postsynaptic D3 receptors mediate suppression of motor activity is the production of hyperactivity by putative D3 receptor-selective antagonists. We tested two compounds that have been reported to exert preferential actions as D3 receptor antagonists. U 99194A exhibits a 20-fold preference for D3 over D2 receptors expressed in cell lines (Waters et al., 1993b). Nafadotride exhibits approximately 10-fold selectivity for D3 over D2 receptors in both binding and functional assays in vitro (Sautel et al., 1995). Both U 99194A and nafadotride have been shown to produce locomotor activation in habituated rats in the absence of detectable increases in DA release (Waters et al., 1993b; Sautel et al., 1995), leading to the hypothesis that postsynaptic D3 receptors are tonically inhibitory on motor activity. However, in our studies increases in locomotor activity produced by U99194A and nafadotride were identical in D3 receptor mutant and wild-type mice, indicating that the effect is unlikely to be mediated by a blockade of D3 receptors. Perhaps these drugs also exhibit poor in vivo selectivity and thereby increase activity by selectively blocking DA D2 autoreceptors. Alternatively, and perhaps more likely, they may activate locomotor activity through as yet unidentified actions that are not necessarily identical for the two compounds.

Hypothermia induced by PD 128907 is not mediated by DA D3 receptors

It has been previously demonstrated that putative D3 receptor-selective agonists (Millan et al., 1994), like other D2-class agonists with high receptor efficacy (Sánchez and Arnt, 1992), produce hypothermia in rodents. Here, we have demonstrated that at relatively high doses the putative D3 receptor-selective agonist PD 128907 induced significant hypothermia, but that it did so equally well in mice with and without functional D3 receptors. Accordingly, this effect must be caused by PD 128907 acting at other, presumably D2, receptors.

CONCLUSIONS

Our findings demonstrate that D3 receptors are unlikely to be involved in thermoregulation or in modulation of motor activity under normal circumstances. We found that putative D3 receptor-selective agonists suppress ongoing motor activity equally well in normal mice and mice lacking D3 receptors, clearly demonstrating that these drugs are not D3-selective in vivo. We propose that the effect is due to activation of D2 autoreceptors, which decreases levels of synaptic DA, leading to hypoactivity. Our results also question the proposal that under normal conditions occupation of D3 receptors by endogenous DA dampens locomotor activity. The similar abilities of putative D3 receptor antagonists to promote locomotion in D3 receptor mutant and wild-type mice question the involvement of D3 receptors in the effect. We do not mean to imply that D3 receptors are not involved in motor behavior. Our recent findings from the D3 receptor mutant mice suggest that D3 receptors play an important dampening role on motor and motivational functions when DA transmission through both D1 and D2 receptors is enhanced (Xu et al., 1997). Additional studies will be necessary to ascertain what other aspects of behavior are also modulated by D3 receptors, but we will need better drugs with true in vivo selectivity to establish the functional roles of D3 receptors. Finally, an important consideration that must be acknowledged is a possible species difference between mouse and rat with respect to D3 receptor function. Certainly, these species respond differently to D2-class receptor agonists; whether this is a reflection of species differences in D2 or D3 receptors or their respective interactions with D1 receptors will be an important area for future research.

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