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ORIGINAL INVESTIGATION

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Brain stimulation and morphine reward deficits in dopamine D2 receptor-deficient mice

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Abstract *Rationale:* The rewarding effects of lateral hypothalamic brain stimulation, various natural rewards, and several drugs of abuse are attenuated by D1 or D2 dopamine receptor (D1R or D2R) antagonists. Much of the evidence for dopaminergic involvement in rewards is based on pharmacological agents with limited or "relative" selectivity for dopamine receptor subtypes. Genetically engineered animal models provide a complementary approach to pharmacological investigations. *Objectives:* In the present study, we explored the contribution of dopamine D2Rs to (1) brain stimulation reward (BSR) and (2) the potentiation of this behavior by morphine and amphetamine using D2R-deficient mice. *Methods:* Wild-type (D2Rwt), heterozygous (D2Rhet), and D2R knockout (D2Rko) mice were trained to turn a wheel for rewarding brain stimulation. Once equivalent rate–frequency curves were established, morphine-induced (0, 1.0, 3.0, and 5.6 mg/kg s.c.) and amphetamine-induced (0, 1.0, 2.0, and 4.0 mg/kg i.p.) potentiations of BSR were determined. *Results:* The D2Rko mice required approximately 50% more stimulation than the D2Rwt mice did. With the equi-rewarding levels of stimulation current, amphetamine potentiated BSR equally across the three genotypes. In contrast, morphine potentiated rewarding stimulation in the D2Rwt, had no effect in the D2Rhet, and antagonized rewarding stimulation in the D2Rko mice. *Conclusions:* D2R elimination decreases, but does not eliminate, the rewarding effects of lateral hypothalamic stimulation. After compensation for this deficit, amphetamine continues to potentiate BSR, while morphine does not.

Keywords Amphetamine · Reinforcement · Knockout · Depolarization · Mice · Opioid · ICSS · Addiction · Neuroleptic

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Introduction

The mesolimbic dopamine system has been implicated in the rewarding effects of lateral hypothalamic brain stimulation, psychomotor stimulants, and in the rewarding effects of more natural incentives such as food, water, and sexual interaction (Wise 1982; Wise and Rompre 1989). Each of these incentives elevates extracellular dopamine levels. Lateral hypothalamic brain stimulation elevates extracellular dopamine levels largely through the trans-synaptic stimulation of mesolimbic dopamine fibers (Yeomans et al. 1993). Psychomotor stimulants, such as cocaine and amphetamine, increase the amount of endogenous mesolimbic dopamine available to stimulate dopamine receptors by inhibiting dopamine reuptake. The neuropharmacological effects of psychomotor stimulants summate with the effects of lateral hypothalamic stimulation to significantly potentiate brain stimulation reward (BSR). The central reward-potentiating effects of psychomotor stimulants occur in mesolimbic dopamine regions where they are self-

injected, suggesting common mechanisms within this system for drug reward and the potentiation of BSR (Wise 1996). Further confirmation of mesolimbic dopamine's importance in brain stimulation and psychomotor stimulant reward is the evidence that each incentive is ineffective as a reward when dopamine receptors are blocked (Gallistel and Karras 1984; see Wise 2004).

Two facts suggest that the dopamine system is also at least partially involved in the rewarding effects of opiates (Wise 1989). First, self-administered doses of opiates disinhibit the dopamine system (Johnson and North 1992), causing elevations of dopamine in nucleus accumbens (NAS) and presumably other dopamine terminal fields (Wise et al. 1995a). Second, similar elevations of NAS dopamine (Hurd et al. 1989; Pettit and Justice 1989; Wise et al. 1995b) mediate the rewarding actions of other drugs of abuse (Yokel and Wise 1975; De Wit and Wise 1977; Roberts et al. 1977; Lyness et al. 1980; Ettenberg et al. 1982; Loh and Roberts 1990). It is difficult to imagine how the elevations in dopamine level, caused by rewarding intravenous heroin injections, would not contribute to the rewarding effects of that drug when similar increases are responsible for the rewarding effects of cocaine and amphetamine.

Opiates can activate reward circuitry in at least three ways (Wise 1989; Dockstader et al. 2001; Laviolette et al. 2004). Opiates have dopamine-independent psychomotor stimulant effects in the NAS (Kalivas et al. 1983) and are directly self-administered into the NAS (Olds 1982; Goeders et al. 1984; David and Cazala 2000; David et al. 2002), where they are thought to act to inhibit the medium spiny neurons that are the target of synaptically released dopamine. They also have dopamine-dependent and dopamine-independent rewarding actions in the ventral tegmental area (VTA) (Laviolette et al. 2004). The dopamine-dependent rewarding actions involve μ opioid receptor mediated disinhibition of the dopamine system, either by actions on γ-aminobutyric acid (GABA)ergic interneurons (Johnson and North 1992) or on GABAergic projection neurons that send collaterals to their dopaminergic neighbors (Tepper et al. 1995). There is also a δ opioid receptor mediated rewarding action of opiates in the VTA (Jenck et al. 1987; Devine and Wise 1994); the relative potencies of μ and ∂ agonists as rewards (Devine and Wise 1994) are proportional to the ability of these agents to activate the mesolimbic dopamine system (Devine et al. 1993).

Much of the evidence for dopaminergic involvement in reward fuction was based on pharmacological agents with limited selectivity for dopamine receptor subtypes. The purpose of the present study was to explore the contribution of the D2 dopamine receptor (D2R) to the rewarding effects of lateral hypothalamic brain stimulation and to the ability of morphine or amphetamine to potentiate such stimulation. We assessed the rewarding effectiveness of lateral hypothalamic brain stimulation under drug-free conditions and under conditions of morphine and amphetamine treatment in D2R knockout, heterozygous, and wild-type mice. We used a BSR paradigm that allows quantitative comparisons (Gallistel 1987; Gallistel and Freyd 1987) between mice with 100, 50, or 0% of the normal complement of D2Rs and between drug and nondrug conditions.

Materials and methods

Animals

Adult male D2R knockout (D2Rko, *N*=8), heterozygous (D2Rhet, *N*=7), and wild-type (D2Rwt, *N*=7) mice, backcrossed to C57BL/6J for ten generations, were used. The mice were 60–120 days old and weighed approximately 21–30 g at the start of the experiment. All animals were experimentally naive, housed in groups of two to five in a temperature-controlled room (21°C) with a 12-h light–dark cycle, and given free access to Purina Laboratory Chow and tap water before the start of the experimental procedure. The facilities were fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC), and the studies were conducted in accordance with the *Guide for Care and Use of Laboratory Animals* provided by the National Institutes of Health (NIH).

The homologous recombination techniques used and the mice's genealogy are described in detail in previous reports (Kelly et al. 1997, 1998). Briefly, a vector in which the 5′ half of exon 8 was eliminated (sequences encoding the sixth transmembrane domain through the carboxy terminus) was electroporated into a D3 embryonic stem (ES) cell line (129/Sv-derived). Positive clonal ES cells were injected into C57BL/6J blastocysts. Subsequently, D2R heterozygous mice were backcrossed to wild-type C57BL/6J mice for a number of generations. The mice used in the current study were from the tenth generation. Heterozygous matings and polymerase chain reaction (PCR)-based identification were used to generate and genotype the mice used in the current study.

Apparatus

Seven mouse operant conditioning chambers were used (Coulbourn Instruments, Allentown, PA, USA). Each operant conditioning chamber was equipped with one mouse wheel operandum that consisted of two 5-cm (diam.) disks connected by 30 rungs interposed between the two disks at the outer edge (MedAssociates, Vermont) and one commutator (Plastics One, Florida). The edge of the wheel protruded 1.6 cm into the operant conditioning chamber and registered a response using infrared photo beams following one-quarter rotation of the operandum. Mice typically faced the operandum and pressed down on the rungs to register a response, or stood to the side of the operandum and gripped and turned downward to register a response. One stimulus light was located to the side of the wheel. The stimulus light was illuminated during electrical stimulation. MedAssociates stimulators were used to deliver electrical stimulation. The stimulator and stimulus lights were

controlled by an integrated Coulbourn environmental control system and a MedAssociates interface. System control and data acquisition and storage were accomplished using MedAssociates software.

Surgery

Subjects were surgically prepared with an electrode implanted in the lateral hypothalamus (a.p. −1.3, m.l. 1.1, d.v. −5.2). Surgical procedures were performed under ketamine-induced (80 mg/kg, i.p.) and xylazine-induced (16 mg/kg, i.p.) anesthesia. One stainless steel skull screw was installed opposite the electrode. An uninsulated wire that served as an anode was wrapped around the screw. Dental cement surrounded the electrode and screw.

Training

Subjects were given 1 week to recover from surgery. For training, the mice were placed in the operant conditioning chamber and allowed free access to the operandum (wheel). Each quarter-turn of the wheel produced a 200-ms train of stimulation (0.1-ms rectangular cathodal pulses at a rate of 100 Hz). During these training sessions, the current was adjusted on individual basis on an arbitrary scale to obtain maximal response rates. Three daily sessions of 30 min each were run at the current that maintained maximal response rates. In the following daily sessions, the current was adjusted down (again on a ratio scale) to a level that resulted in approximately half of the maximal responding. Once half-maximal responding was obtained, three more sessions were run at that current.

Mice were then trained under a protocol in which frequency was systematically manipulated to generate rate–frequency response curves. Nine rate–frequency trials were conducted during each session. Each of the nine trials began with five noncontingent priming trains delivered at 161 Hz. Following the five priming stimulations, the subject had a 50-s access to wheel-turn-contingent stimulations starting with 161 Hz. Stimulations were always accompanied by the illumination of a stimulus light to the left of the wheel manipulandum. At the end of the 50-s period, the frequency was decreased by 20%. The subject was then given five priming stimulations at the new frequency. Following the priming stimulations, the subject had 50-s access to wheel-turn-contingent stimulations at the new frequency. The trial continued for 19 current decrements at 20% each or until fewer than eight responses were made during two consecutive frequencies. At the end of the trial, a 10-s intertrial interval was imposed. The houselight was turned off during this period. Each trial provides a rate–frequency curve. The entire session consisted of nine rate–frequency trials as described above. A typical nondrug session would last approximately 80 min. Minor adjustments in the stimulation current were made during this training period to achieve equivalent rate–frequency response curves across genotypes. All sessions were run using the same frequency range. An average of six daily sessions were run until performance stabilized across days.

Effects of morphine and amphetamine on BSR

As soon as equivalent rate–frequency curves were established, morphine- and amphetamine-induced potentiations of BSR were assessed in each subject. Morphine dose–effect curves were determined first in approximately half of the mice from each genotype, while amphetamine dose–effect curves were determined first in the other half. Each mouse received only one dose per session. Only one session was run per day. To acclimatize the mice to the injection regimens, subcutaneous saline injections were given prior three sessions (3 days) preceding morphine testing, and i.p. saline injections were given prior three sessions preceding amphetamine testing. Saline or drug was administered immediately before sessions (i.p. saline or amphetamine), or 15 min before the sessions (s.c. saline or morphine). Doses were tested in ascending order (morphine 0, 1.0, 3.0, and 5.6 mg/kg s.c.; amphetamine 0, 1.0, 2.0, and 4.0 mg/kg i.p.). At least three saline test sessions were conducted between drug doses. The next drug dose was not tested unless the saline test session differed from the established baseline (average of the three baseline saline test sessions) by less than 12%. At least three stable saline test sessions were established between each drug assessment.

Current comparisons

At the conclusion of the experiment, in a subset of knockout and wild-type mice, the average current used to maintain approximately equivalent rate–frequency functions was switched; the knockout mice were tested with the currents previously used for the wild-type mice and vice versa. In contrast to the manipulations made during the training phase, the current was changed in discrete units (to either 122 or 66 μA) in this experiment. This experimental manipulation was used to confirm original differences observed across genotypes in the baseline assessment protocols.

Histology

After the completion of testing, the mice were perfused transcardially with saline followed by paraformaldehyde. Their brains were removed and immersed in paraformaldehyde. A day later, the brains were transferred to 18% sucrose and refrigerated. The brains were trimmed and frozen at −80°C for 1 week before being cut on a cryostat. The sections were stained with cresyl violet, and the location of the electrode tips was determined under a microscope.

Statistics

Dependent measures, half-maximal frequency, and theta zero The dependent measures in the rate–frequency portion of the study were the half-maximal frequency (HMF) and theta zero value. HMF was defined as the frequency at which half the maximal amount of responding occurred. Theta zero was defined as the minimum stimulation frequency required to support wheel turning. A rate–frequency curve was generated for the last seven of the nine trials conducted during each session by counting the responses that occurred during the 50-s period allotted during each frequency opportunity. The resulting curve was interpolated on a log scale. The two dependent measures, HMF and theta zero, were determined by linear interpolation of the points from 20 to 80% of maximal responding in the curve after transformation of the raw data to a percentage of maximal responding. The equation from the linear curve fit of this region was used to interpolate the frequency at which 50% of the responding occurred (HMF) and to determine the *x*-intercept (theta zero).

Differences across genotypes during baseline assessments and current switch Determination of statistical differences in current, HMF, and theta zero values across genotypes was conducted using a one-way analysis of variance (ANOVA). Only the wild-type and the knockout mice were included in this analysis since the current switch paradigm used only these two genotypes.

Drug effects The change in theta zero was used to determine the effects of drug administration on BSR. To determine that morphine or amphetamine had approximately the same time course across each genotype, the effects of each drug and drug dose on HMF and theta zero across trials were analyzed by repeated measures ANOVA (Genotype×Trial as a repeated measure). A two-way repeated measures ANOVA (Genotype×Drug dose) was used to determine the effects of morphine or amphetamine on lateral hypothalamic BSR. The effects of morphine and amphetamine on lateral hypothalamic BSR within a genotype were assessed using a one-way repeated measures ANOVA for each drug. A contrast analysis was done to determine which, if any, dose produced a significant change in BSR. All statistics were done using SuperANOVA software (Abacus Concepts, Berkely, CA).

Results

Each genotype learned to manually turn the operandum when each quarter-turn of the operandum was rewarded with a 200-msec train of 100-Hz lateral hypothalamic electrical stimulation. When rewarded with adequate levels of stimulation current, the animals continued to turn the wheel with little interruption or distraction. If the stimulation current was low, however, the animals lost interest in the wheel quickly, as did animals that had been turning the wheel regularly when stimulation was abruptly discontinued.

Training

Once the animals were seen to respond reliably, they were trained under a protocol in which stimulation intensity or stimulation frequency was systematically manipulated to identify minimum stimulation parameters required to maintain responding (threshold levels) and to characterize the relation between amount of reward and rate of response to generate rate–frequency response curves. First, the stimulation current was varied individually to establish, for each animal, the stimulation intensity that would equally center the rate–frequency curve at approximately the same location (90 Hz). The required intensities were 70.1 μA for D2Rwt animals, 103.2 μA for D2Rhet animals, and 129.4 μA for D2Rko animals (Fig. 1). Increasing the current increases the diameter of the effective stimulation field (Wise 1972; Ranck 1975); thus, a greater portion of the reward system had to be stimulated for stimulation to be normally effective in animals lacking D2 receptors.

Current comparisons

Inasmuch as the number of reward fibers activated is not a linear function of current intensity (Gallistel 1987), no quantitative estimate can be made from these data as to the *degree* of reward function impairment in the D2Rhet and D2Rko animals. However, we subsequently determined frequency thresholds, the minimum frequency required to sustain responding, at each of two fixed current levels (60 and 122 μA). Here, each 0.1-ms stimulation pulse activates the reward fibers it reaches only one time, and differences

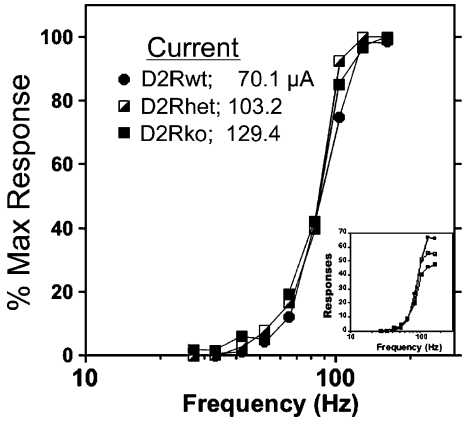

Fig. 1 Rate–frequency response curves. Percent of maximal response rate as a function of increasing stimulation frequency in D2Rwt, D2Rhet, and D2Rko mice (n=7–8/genotype, ±SEM). The current was systematically manipulated in all three genotypes in order to obtain equivalent half-maximal frequency (HMF) values. The D2Rko mice required significantly greater current than D2Rwt mice in order to maintain equivalent HMF values. *Inset*: actual response rates across increasing stimulation frequency

in stimulation frequency—since they determine differences in the number of stimulation pulses—are linearly related to reward strength (Gallistel 1987). Differences in frequency threshold indicated that the stimulation was almost 1.6 times more effective in D2Rwt as in D2Rko animals (Fig. 2) (60 μA: $F_{Genotype}$=5.3, *df*=1,8, p<0.03; 122 μA: $F_{Genotype}$=6.2, *df*=1,8, p<0.01).

Effects of morphine on BSR

Morphine potentiated rewarding stimulation in wild-type animals, shifting rate–frequency functions to the left (reducing the number of pulses required to maintain responding), whereas it antagonized the rewarding stimulation in the knockout animals, shifting rate–frequency functions to the right (Fig. 3). The rewarding potency of the stimulation in the heterozygous animals was not significantly affected by morphine. The potentiation of BSR in D2Rwt mice and the antagonism in D2Rko mice were directly related to the dose of morphine (Fig. 4) (D2Rwt: F_{Dose}=6.1, *df*=3,12, p<0.0001; D2Rhet p=0.77, n.s.; D2Rko F_{Dose}=4.3, *df*=3,15, p<0.0226). The leftward shifts in the D2Rwt mice were statistically significant at both the 3.0-mg/kg (p<0.008) and the 5.6-mg/kg (p<0.002) doses. The rightward shifts in the D2Rko mice were statistically insignificant at the 3.0-mg/kg dose (p<0.08) but statistically significant at the 5.6 mg/kg (p<0.003) dose. The qualitative difference in morphine's effects across genotypes was reflected in an overall main effect of Genotype ($F_{Genotype}$=5.6, *df*=2,16, p<0.0001) and the significant Genotype×Dose interaction ($F_{Genotype×Dose}$=3.1, *df*=6,48, p<0.013). In addition to causing a rightward shift in the rate–frequency curve, morphine depressed the maximum response rate in the D2Rko animals.

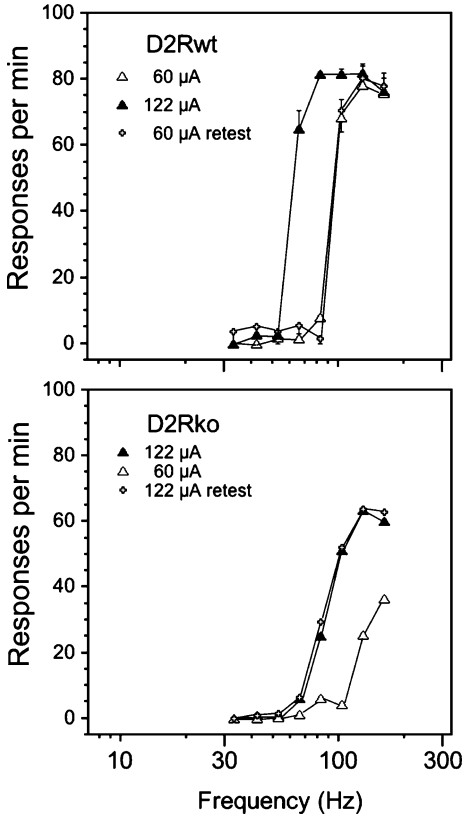

Fig. 2 Changes in current shift the rate–frequency curve in both D2Rwt and D2Rko mice. In this subset of D2Rwt and D2Rko mice (*n*=4/genotype), the current required to maintain equivalent half-maximal frequencies was 60 and 122 μA, respectively. When the current was changed from 60 to 122 μA in the D2Rwt mice, the rate–frequency curve shifted significantly to the left. When the current was changed from 122 to 60 μA in the D2Rko mice, the rate–frequency curve shifted significantly to the right

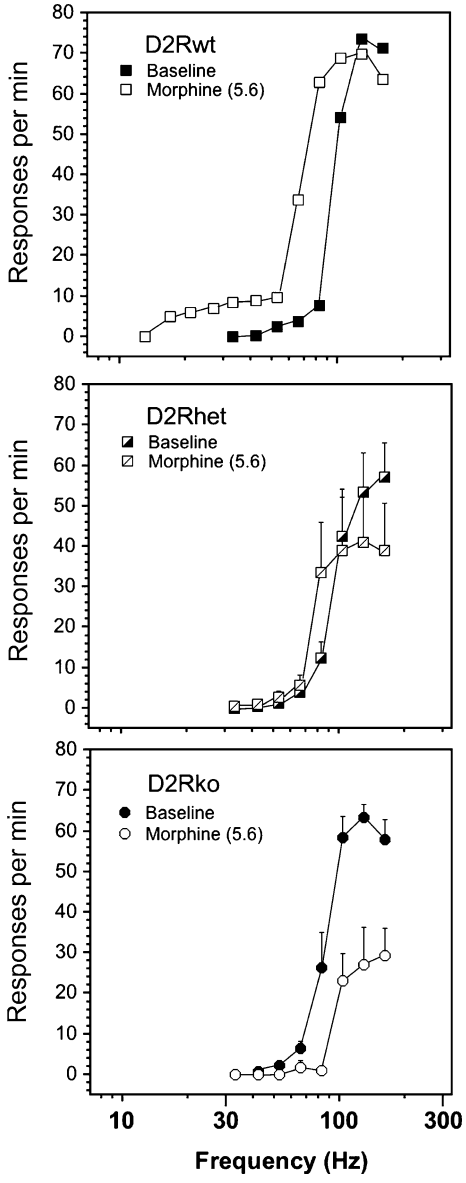

Fig. 3 Morphine-induced shifts in rate–frequency curves. Each *point* represents the mean of seven to eight mice per genotype, ±SEM

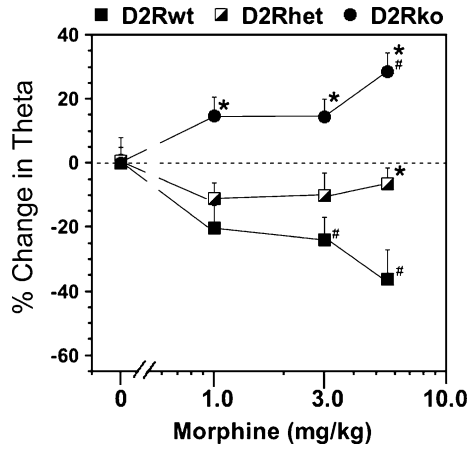

Fig. 4 Morphine-induced changes in theta zero. Each *point* represents the self-stimulation frequency thresholds defined as the minimum frequency required to maintain wheel turning (n=7–8/genotype, ±SEM). #Significantly different than saline (p<0.05). *Significantly different than D2Rwt mice (p<0.05)

Effects of amphetamine on BSR

In contrast to morphine, amphetamine caused equal, leftward shifts in the rate–frequency functions of each of the three genotypes (Fig. 5), decreasing the required threshold stimulation by approximately half in the case of the highest dose (4.0 mg/kg) (Fig. 6). There was a significant overall main effect of amphetamine Dose (F_{Dose}=87.4, df=3,45, p<0.0001), but there was no overall main effect of Genotype or a Genotype×Dose interaction (Fig. 6). Amphetamine had no effect on maximal response rate in any genotype.

Histology was used to confirm electrode placements. Only those subjects whose electrode tips were located in the lateral hypothalamic portion of the medial forebrain bundle were used (Fig. 7). Statistical analysis of the final electrode location confirmed that there were no significant differences in electrode placement across genotypes.

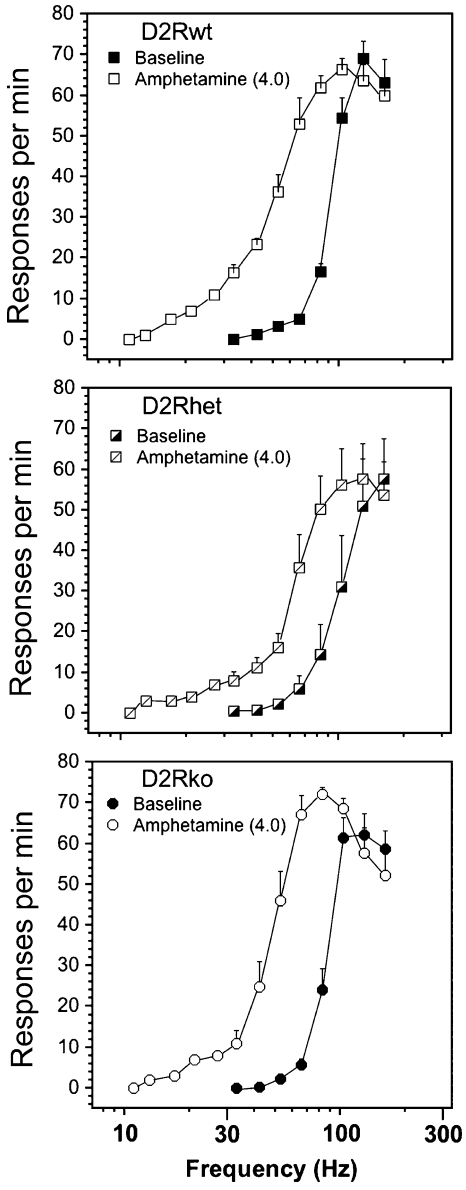

Fig. 5 Amphetamine-induced shifts in rate–frequency curves. Each *point* represents the mean of seven to eight mice per genotype, ±SEM

Discussion

The first goal of the present study was to determine if D2R elimination would alter sensitivity to rewarding hypothalamic electrical stimulation. This possibility was clearly confirmed. Two stimulation parameters were manipulated to change reward strength to test reward sensitivity: the stimulation intensity and the stimulation frequency. Increases in stimulation intensity spread the effective radius of stimulation, recruiting additional (more distant) fibers of the reward pathway (Wise 1972). Increases in stimulation frequency increase the number of action potentials in each stimulated reward fiber (Gallistel 1987). It is well known that these two factors affect reward strength, and that increases in either one can offset decreases in the other (Edmonds et al. 1974; Yeomans 1975). In this regard, the D2Rko mice required significantly greater stimulation intensities than the D2Rwt mice in order to equally center the rate–frequency curve at approximately the same location (90 Hz). When the stimulation intensity was held constant (60 or 122 μA), higher stimulation frequencies were required for the D2Rko animals than for the D2Rwt mice. The D2R knockout animals required approximately 1.6 times more stimulation pulses to maintain behavior similar to that of wild-type animals. Thus, deletion of the *D2R* gene reduced by approximately one third the rewarding effectiveness of lateral hypothalamic brain stimulation. This is not a surprising finding, as D2R-selective dopamine antagonists are well known to dramatically attenuate the rewarding effects of lateral hypothalamic stimulation (Nakajima and Baker 1989). However, the D2R knockout deficit was surmountable with increases of either current or frequency. This is a somewhat surprising finding, since dopamine antagonists, at sufficient doses, cause the complete extinction of responding for BSR

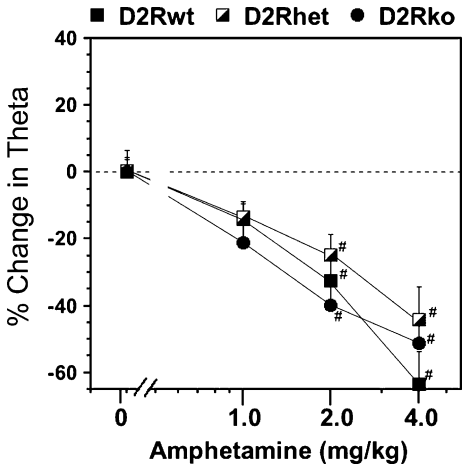

Fig. 6 Amphetamine-induced changes in theta zero. Each *point* represents the self-stimulation frequency thresholds defined as the minimum frequency required to maintain wheel turning (n=7–8/genotype, ±SEM). #Significantly different than saline (p<0.05)

that is not surmountable with increases in current or frequency (Fouriezos and Wise 1976; Fouriezos et al. 1978; Franklin and McCoy 1979; Gallistel and Freyd 1987; Nakajima and Baker 1989). Most dopamine-mediated behaviors appear to depend on cooperativity between D1-type and D2-type dopamine actions (Woolverton 1986; Carlson et al. 1987; Clark and White 1987). The fact that self-stimulation survives D2R deletion at all suggests that D1, D3, or D4 dopamine receptors may play a stronger role than previously suspected (Nakajima and Patterson 1997; Xu et al. 1999).

The effects of morphine on BSR were dramatically different in wild-type and knockout mice. Although the high dose of morphine potentiated rewarding stimulation in the D2Rwt mice, as measured by a 36% reduction in the number of rewarding pulses required to sustain half-maximal responding, it antagonized rewarding brain stimulation in the D2Rko mice, as measured by a 28% increase in the number of pulses required for minimal (theta zero) or half-maximal responding. The failure of morphine to potentiate BSR in D2Rko animals suggests that the D2 receptor is essential for the effect of morphine that summates with BSR to determine the rate of responding at different stimulation parameters. This observation is quite consistent with our previous finding that morphine fails to serve as an intravenous reinforcer in the same line of D2Rko mice (Elmer et al. 2002), and is not explained by alterations in the D3R receptor (see D3Rko; Narita et al. 2003) since these mice have normal levels of D3R (Baik et al. 1995). The deficit in reward-potentiating effects would not likely be overcome with higher morphine doses since there was a dose-dependent decrease in the rewarding value of brain stimulation in the knockout mice, and higher doses used in pilot studies nearly produced a complete cessation of responding. In addition, it is not generally true that the D2Rko mice are insensitive to morphine; morphine administration increases locomotor activity to a similar degree in D2Rwt and D2Rko mice (Smith et al. 2002; Hayward and Low, in press) and results in greater striatal dopamine release (Rouge-Pont et al. 2002) and a greater degree of analgesia (King et al. 2001) in the D2Rko mice than their wild-type counterparts.

The rightward shift in the rate–frequency function produced by morphine in the D2Rko animals is not simply explained by a decrease in reward, unless it is posited that morphine has aversive or response-limiting effects that are unmasked by D2R gene deletion. When rats are treated with the combination of lateral hypothalamic stimulation, D2R pharmacological blockade, and rewarding morphine (microinjections into the VTA), they sometimes show complete response cessation that is attributed to a depolarization inactivation of the dopamine system (Rompre and Wise 1989a). This depolarization inactivation is presumed to result from three treatments that in combination increase dopamine agonist (DA) firing beyond sustainable limits: lateral hypothalamic stimulation is thought to directly depolarize some DA fibers (Yeomans et al. 1985) and transsynaptically activate others (Wise 1980; Yeomans 1995), D2R pharmacological blockade accelerates dopamine neurons by blocking autoreceptor inhibition (Groves et al. 1975), and morphine disinhibits DA cell firing by inhibiting GABAergic afferents to the DA cells (Johnson and North 1992). The additional electrical stimulation due to the higher current used in the D2Rko mice would further exacerbate the lateral hypothalamic stimulation component in the knockouts. Support for the depolarization hypothesis is found in the fact that the normally reward-antagonizing effect of ventral tegmental muscimol reinstates responding under these conditions (Rompre and Wise 1989b) and reinstates DA cell firing in electrophysiological studies in which the dopamine system is in a depolarization block from the combination of opiates and dopamine antagonists (Henry et al. 1992). If depolarization inactivation, due to the combined effects of D2R deletion, morphine, and lateral hypothalamic stimulation, plays a role in the present study, it would appear that only part of the system goes into block under our testing conditions—a neurophysiological and behavioral state not previously described and clearly worth characterizing in more detail. Regardless of the mechanism responsible for the unusual rightward shift, the clear conclusion from the morphine studies is that the D2 receptor plays an important role in its reward-enhancing effects, just as it appears to play an important role in its direct rewarding effects (Elmer et al. 2002) and in morphine-conditioned place preference ($D2RL^{-/-}$ mice; Smith et al. 2002).

D2R deletion had no effect on the ability of amphetamine to potentiate self-stimulation. Given the demonstrated importance of D2R activation for the rewarding effects of the brain stimulation, the presumed importance of dopamine and the D2R in the potentiating effects of amphetamine on lateral hypothalamic BSR (Gallistel and Karras 1984), and the significant effects of D2R deletion on morphine potentiation of BSR, this was a surprising finding. However, lesions of the dopamine cell bodies also disrupt the reward-enhancing effects of morphine but not amphetamine (Hand and Franklin 1985). It is not easy to imagine how D2R deletion would affect the rewarding

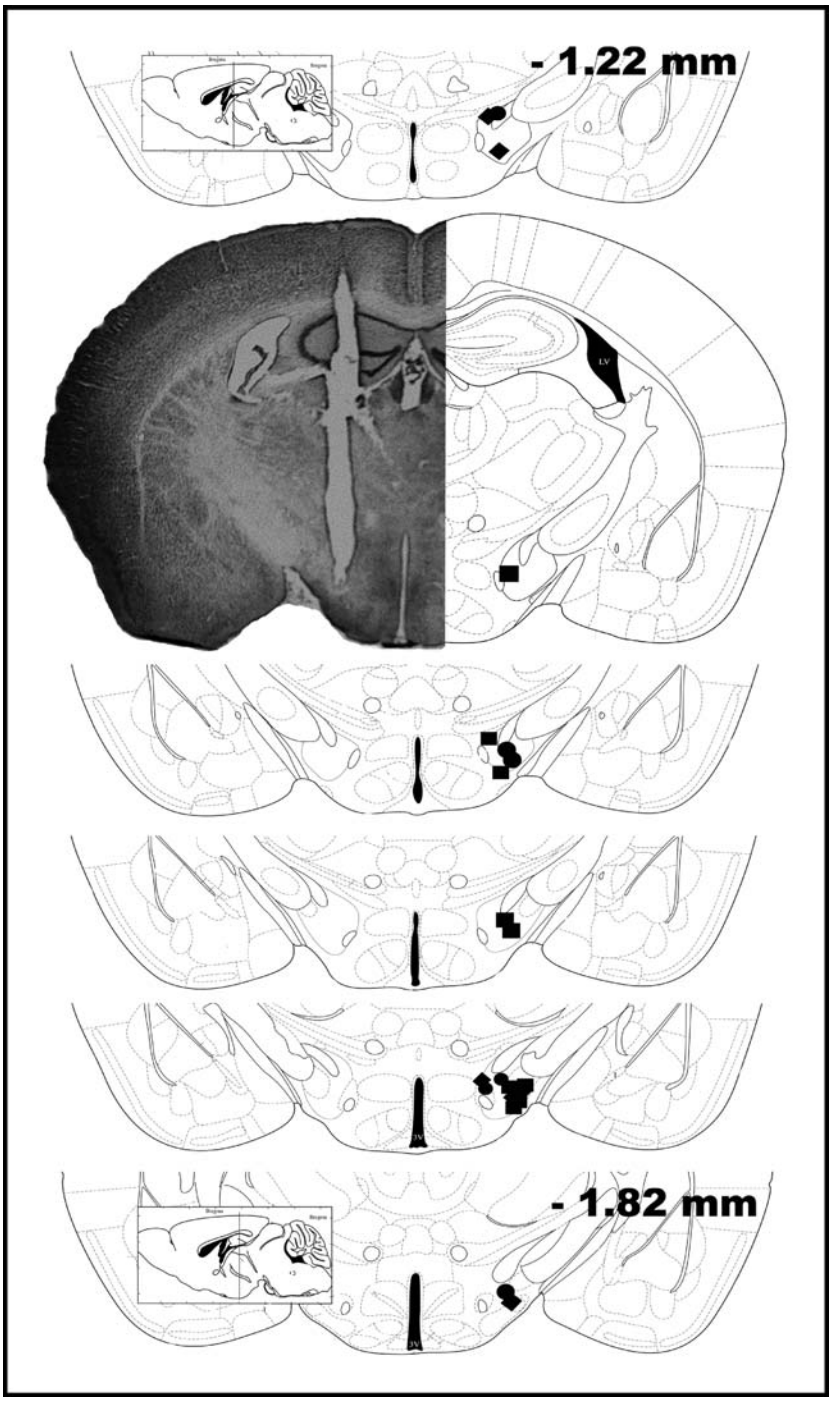

Fig. 7 Histology. Electrode locations as determined by histological verifications: ● D2Rwt, ♦ D2Rhet, ▪ D2Rko. Distances given to right in the *top* and *bottom plates* are from bregma. Some symbols overlap locations. Only those subjects with a verified lateral hypothalamic electrode location were included in the analysis. An example photomicrograph of an electrode placement is shown in the *second plate from the top*

effects of brain stimulation and the reward-potentiating effects of morphine without affecting the reward-potentiating effects of amphetamine. In these animals, the ability of amphetamine to potentiate BSR seems to depend on other dopamine receptors. D1 receptor activation is known to be rewarding in its own right (White et al. 1991; Weed and Woolverton 1995; Grech et al. 1996; Abrahams et al. 1998); indeed, D1R activation in the VTA apparently contributes to the rewarding effects of cocaine (Ranaldi and Wise 2001). Several studies provide evidence to suggest that dopamine D1R stimulation is rewarding (Self and Stein 1992) and is sufficient to potentiate lateral hypothalamic BSR (Gilliss et al. 2002). Amphetamine may increase DA levels in an impulse-independent manner, thus increasing D1 receptor stimulation in a manner sufficient to potentiate lateral hypothalamic BSR. Recent sensorimotor gating studies, using D1R and D2R knockout mice (Ralph-Williams et al. 2002, 2003), suggest a more prominent, independent role for D1R following direct DA administration. Thus, amphetamine may be acting through D2-like and D1-like mechanisms in the D2Rwt mice while acting solely or predominantly through D1 mechanisms in the

D2Rko mice. This hypothesis would predict that the administration of a D1 antagonist would not affect amphetamine potentiation of lateral hypothalamic BSR in the D2Rwt mice, but would significantly attenuate it in D2Rko mice. Deletion of the D2 receptor also fails to abolish the rewarding (Caine et al. 2002), locomotor stimulating, and discriminative stimulus effects (Chausmer et al. 2002) of cocaine that are blocked by dopamine D2R antagonists (Spealman et al. 1991; Chausmer and Katz 2001). Overall, these findings point to either a more independent role for the D1R in mice or to significant D3R or D4R contributions to behaviors that are dependent on the family of D2R-like dopamine receptors, at least in mice that have developed without the normal complement of D2Rs. Regardless of the mechanism responsible for the sustained potentiation of rewarding stimulation by amphetamine, the conclusion from the amphetamine studies is that D2R appears to play no exclusive role in the dopamine-dependent rewarding effects of this agent.

The present findings are problematic for the widely held notion (Wise and Bozarth 1987; Di Chiara and Imperato 1988; Wise 1996) that the same postsynaptic effects of dopamine are critical for both the rewarding effects of hypothalamic brain stimulation and the rewarding and reward-enhancing effects of psychomotor stimulants and opiates. While it is well established that each of these rewards causes significant elevations of extracellular dopamine levels, they do so in different ways. Brain stimulation reward is thought to activate the dopamine system transsynaptically (Yeomans et al. 1993) for the most part. The primary actions of amphetamine and cocaine on the dopamine system are to cause an impulse-independent DA release by reversing the dopamine transporter (Fischer and Cho 1979; Khoshbouei et al. 2003) and to cause an impulse-dependent dopamine accumulation by blocking the dopamine transporter (Heikkila et al. 1975), respectively. Amphetamine and cocaine also elevate the extracellular levels of norepinephrine and serotonin, and serotonin levels, in turn, may affect DA cell firing (Cameron and Williams 1994). Whatever the mechanism of activation, however, each of these rewards elevates dopamine levels in the major dopamine terminal fields, and the importance of postsynaptic D2 receptors for triggering reward should be similar in all cases. However, this situation appears not to be the case, and, in contrast, the results presented above suggest that the various dopamine receptor subtypes play active and distinct roles in the rewarding effects of different agents. This hypothesis fits with the findings that amphetamine and cocaine are most avidly self-administered into different dopamine terminal fields, and that the core and shell of one of these fields, the NAS, are differently important for the rewarding effects of opiates (Alderson et al. 2001; Hutcheson et al. 2001) and dopamine uptake inhibitors (Carlezon et al. 1995).

Genetically engineered animal models offer a complementary research tool to pharmacological agents. They are especially helpful when the pharmacological agents have limited receptor subtype selectivity, as is the case for dopamine receptor subtypes. A source of concern that must be noted in all knockout studies is the unintended consequence of neurodevelopmental alterations consequent to eliminating the gene of interest. However, electrophysiologically, all indications are that the dopamine system of the D2Rko remains intact and responds in a manner hypothesized following selective elimination of the dopamine autoreceptor (Benoit-Marand et al. 2001; Schmitz et al. 2001, 2002; Rouge-Pont et al. 2002). This is not to say that other neurobiological differences that have been observed between the D2R knockout and wild-type mice do not contribute to findings reported herein (Bozzi and Borrelli 1999; Murer et al. 2000; Zahniser et al. 2000; Cepeda et al. 2001). Although several caveats exist with embryonic gene manipulation, it is important to note that D2R knockout mice have a normal complement of μ opiate receptors (Maldonado et al. 1997) and show other opiate-mediated behaviors (Drago et al. 1999). Two additional facts further support selective D2R involvement in the current findings. First, D2R knockout mice do not have substantially altered D1R, D3R, or D4R profiles or dopamine concentrations (Baik et al. 1995; Kelly et al. 1998; Dickinson et al. 1999). Second, the changes seen in BSR and morphine potentiation of BSR were gene-dosage-dependent. Incorporating the heterozygous mice in the experimental design provided a range of receptor levels (100, 50, and 0%) to test the D2R hypotheses. In this case, the magnitude of D2R elimination's effect was highly correlated to D2R concentration. Thus, the evidence provided in this report supports the conclusions that (1) D2R elimination decreases, but does not eliminate, the rewarding effects of lateral hypothalamic stimulation, (2) D2R deletion does not alter the rewarding effects of amphetamine, thereby suggesting that the D2R is not exclusively involved in the dopamine-dependent rewarding effects of amphetamine, and (3) D2R deletion significantly alters the reward-enhancing effects morphine, just as it appears to play an important role in its direct rewarding effects (Elmer et al. 2002).

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