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A Dopamine D_1 Agonist Elevates Self-Stimulation Thresholds: Comparison to Other Dopamine-Selective Drugs

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BALDO, B. A., K. JAIN, L. VERALDI, G. F. KOOB AND A. MARKOU. *A dopamine D_1 agonist elevates self-stimulation thresholds: Comparison to other dopamine-selective drugs.* PHARMACOL BIOCHEM BEHAV. **62**(4) 659–672, 1999.—The effects of the high-efficacy D_1 receptor agonist SKF 81297 and the $D_{2/3}$ receptor agonist 7-OH-DPAT on brain stimulation reward thresholds and on response latencies in responding for the stimulation, were compared to the effects of subtype-selective receptor antagonists and a dopamine uptake blocker. SKF 81297 produced dose-dependent elevations in reward thresholds but did not alter response latencies. In contrast, 7-OH-DPAT produced inconsistent reward threshold elevations, yet dose dependently increased response latencies. Both the dopamine D_1 receptor antagonist SCH 23390 and the D_2 antagonist raclopride elevated reward thresholds, but only raclopride significantly increased response latencies. The dopamine uptake inhibitor GBR 12909 lowered reward thresholds and did not influence response latencies. The present results provide a clear demonstration that a selective, high-efficacy D_1 receptor agonist elevates brain stimulation reward thresholds without producing performance deficits. Furthermore, it was observed that the effects upon reward measures of D_1-selective compounds, but not D_2/D_3-selective compounds, are dissociable from their effects upon response latency in this task. These results are discussed with regard to a distinction between the effects of indirect and direct dopamine agonists on reward thresholds, a distinction that does not depend upon the subtype-selectivity of the direct agonists tested. © 1999 Elsevier Science Inc.

Brain stimulation reward Response latency Dopamine SKF 81297 7-OH-DPAT SCH 23390 Raclopride GBR 12909

IT has been shown that the ascending dopaminergic pathways are an important component of the neural substrate that supports the reinforcement derived from electrical stimulation of the medial forebrain bundle, ventral tegmental area, and related sites [for reviews, see (50,59)]. Among the lines of evidence for dopamine's involvement in brain stimulation reward is the well-documented finding that drugs that block dopamine neurotransmission, such as receptor antagonists, produce effects indicative of an attenuation of brain stimulation reward, such as an elevation in brain stimulation reward thresholds [e.g., (9,19,20,57,58)]. Conversely, drugs that facilitate dopamine neurotransmission indirectly by blocking reuptake or enhancing release of that monoamine, potentiate brain stimulation reward (i.e., lower thresholds) [e.g., (10,17,21, 33,40,42)]. It is presumed that the attenuation of brain stimulation reward by dopamine receptor antagonists reflects the blockade at postsynaptic receptor sites of stimulation-relevant presynaptic dopaminergic activity. In addition, it is postulated that the facilitation induced by indirect dopamine agonists reflects the interaction of pharmacologically induced augmentation of presynaptic dopamine neurotransmission with the substrate that supports brain stimulation reward. Although dopamine is clearly involved in the brain stimulation reward substrate at some level, it should be noted that dopamine neu-

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rons are likely activated transsynaptically, rather than directly, by electrical brain stimulation (7,8,68).

In contrast to the clear effects of indirect agonists on brain stimulation reward, direct dopamine receptor agonists have yielded inconsistent results. One example is the direct agonist quinpirole, which has been reported to both facilitate (51) and attenuate (16) brain stimulation reward. The factors underlying the difference between the effects of indirect dopamine agonists and direct dopamine agonists are presently unknown.

The purpose of the present study was to explore the effects of selective, direct dopamine receptor agonists, which clearly distinguish D_1-like from D_2-like receptor subtypes (23,53,54), on brain stimulation reward thresholds and motor performance (as assessed by response latency), both measured concomitantly in a rate-independent self-stimulation paradigm. The direct D_1 agonist chosen was SKF 81297, a highly selective, high efficacy agonist in rats (4,28,65), which is self-administered by primates (24,66) and has not been tested in a rat self-stimulation paradigm previously. The D_2-like agonist chosen was the $D_{2/3}$-selective agonist 7-OH-DPAT, which has a low affinity for D_1 receptors (39). The D_1-selective antagonist SCH 23390 and the D_2-selective antagonist raclopride were tested also to provide a reference, within the same self-stimulation procedure, for potential differences in receptor subtype involvement in reward and motor function, as assessed by the threshold and latency measures, respectively (23,53,54). To demonstrate proof-of-principle for the well-known threshold-lowering effects of indirect dopamine agonists, the effects of the highly selective dopamine uptake inhibitor, GBR 12909 (63), also were assessed in this study. Behaviorally active but submaximal dose ranges were chosen based on dose–effect functions obtained from self-stimulation tasks or other behavioral tasks previously described in the literature [see (1,2,13, 16,22,40,48)].

METHOD

Subjects

Subjects were male Wistar rats (Charles River, Kingston, NY) weighing 260–280 g upon arrival in the laboratory. Rats were housed in groups of two in clear plastic cages with wood-chip bedding. Food and water were available ad libitum. Animals were kept in a temperature-controlled vivarium under a 12-h light/dark cycle (lights on at 2200 h). During the dark phase of the cycle, vivarium rooms were temporarily illuminated when used with dim red lights. For the first week after their arrival, animals were allowed to habituate to their new environment without handling. After the first week, animals were handled. All procedures were in accordance with the United States National Institutes of Health's guidelines regarding the principles of animal care. Animal facilities and protocols were approved by the Institutional Animal Care and Use Committee of The Scripps Research Institute, and assessed by the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC).

Electrode Implantation

Chronic indwelling stainless steel bipolar electrodes of 0.25 cm diameter (Plastics One, Roanoke, VA) were implanted into the medial forebrain bundle at the level of the lateral hypothalamus. Rats (weighing 310–340 g at time of surgery) were anesthetized with a Halothane/oxygen mixture (for the SKF 81297, 7-OH-DPAT, and GBR 12909 experiments) or with 50 mg/kg sodium pentobarbital (administered intraperitoneally) supplemented with 0.06 mg atropine sulfate (administered subcutaneously) (for the SCH 23390 and raclopride experiments). Rats were then secured in a stereotaxic frame with the toothbar elevated 5.0 mm above the interaural line. An electrode aimed at the lateral hypothalamus (AP: −0.5 mm from bregma; ML: ±1.7 mm; DV: −8.3 from dura) was inserted through a burr-hole drilled through the skull, and cemented to four skull screws with dental acrylic (Teets Methyl Methacrylate Denture Material, Co-Oral-Lite Mfg. Co., Diamond Springs, CA). The surgical wound was flushed with a solution of saline and the antibiotic Gentamicin (0.3 ml of 40 mg/ml Gentamicin sulfate in 0.6 ml physiological saline), closed with silk sutures, and treated with Bacitracin ointment. Animals were allowed to recover for at least 1 week prior to behavioral testing.

Apparatus

Training and testing took place in eight Plexiglas operant chambers (30L × 17W × 30H cm) with wire-grid floors. The chambers were contained within sound-attenuating cabinets. Within each operant chamber, a wheel manipulandum requiring a 0.196 N force to rotate it one quarter-turn protruded from one wall. Animals were connected to the stimulation circuit by gold-contact swivel commutators and bipolar leads. Brain stimulation was administered by constant-current stimulators interfaced with a microcomputer.

Brain Stimulation Reward Threshold Procedure

Animals were trained to respond according to a modification of the discrete-trial current-threshold procedure of Kornetsky and Esposito (37,42,43). In the present task, a trial was initiated by the delivery of noncontingent current stimulation, and animals learned to turn a wheel manipulandum within 7.5 s of the delivery of that noncontingent electrical stimulation. A quarter wheel-turn resulted in the delivery of identical current stimulation. Following a variable intertrial interval (7.5–12.5 s, average 10 s), another trial was initiated with the delivery of noncontingent electrical stimulation. Failure to respond to the noncontingent stimulus within 7.5 s resulted in the onset of an intertrial interval. Responding during the intertrial interval delayed the onset of the next trial by 10 s.

Current levels were varied in alternating descending and ascending series. A set of three trials was presented at each current intensity. The first three trials of a given testing session were initiated at a superthreshold current intensity, and subsequent three-trial sets were presented at incrementally decreasing current intensities (current intensities were altered in 5-μA steps). At the point at which the animal responded to fewer than two of the three trials ("negative scores") at two consecutive current intensity levels, an ascending series of three-trial sets was initiated. The ascending series continued until the animals responded for two or more of the three trials ("positive scores") at two consecutive current intensities. In a given testing session, four alternating descending/ascending series were presented. The threshold for each series was defined as the midpoint between consecutive current intensities, which yielded "positive scores," and consecutive current intensities that yielded "negative scores." The overall threshold of the session was defined as the mean of the thresholds for the four individual series. Each testing session was approximately 30 min in duration.

In addition to the threshold measure, a performance measure, response latency, also was provided by the paradigm. Response latency was defined as the time elapsed between

the presentation of the noncontingent stimulus (i.e., onset of the stimulus), and the quarter wheel-turn response of a given trial. Mean latency for the session was defined as the mean latency of responding for all trials for which an animal responded within the 7.5 second period (i.e., "positive score" responding).

The electrical stimuli used in the present study were sinusoidal bursts of current with a frequency of 60 Hz. The stimulus duration was 100 ms for the 7-OH-DPAT, SKF 81297, and GBR 12909 experiments, and 250 ms for the SCH 23390 and raclopride experiments. Those stimulus durations were chosen so that the majority of subjects in each experiment had thresholds within a range that allowed both threshold elevations and threshold lowerings to be detected. Previous experience in our laboratory has shown that consistent and reliable drug effects are obtained at either of those two stimulus durations.

Experimental Design

Animals were trained to respond in the self-stimulation paradigm described above. Once stable responding was achieved (≤10% variation in threshold for 3 consecutive days), vehicle injections preceding the daily testing sessions were administered. When daily postvehicle thresholds stabilized (≤10% variation for 3 consecutive days), animals were subjected to drug injections administered in counterbalanced orders according to Latin square designs. An injection of vehicle was incorporated into each Latin square. Each drug was tested in a separate group of rats. Drug injections were separated by at least 3 days. On those interim days, vehicle injections were administered prior to threshold testing. The drugs tested in this study were the dopamine D_1 receptor antagonist SCH 23390 (n = 9 rats), the dopamine D_2 receptor antagonist raclopride (n = 9 rats), the dopamine D_1 receptor agonist SKF 81297 (n = 8 rats), the dopamine D_2/D_3 receptor agonist 7-OH-DPAT (n = 7 rats), and the dopamine uptake inhibitor GBR 12909 (n = 8 rats).

Drugs

SKF 81297 [(±)-6-Chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide)] and 7-OH-DPAT [(±)-7-Hydroxy-dipropylaminotetralin hydrobromide)] were obtained from Research Biochemicals International, Natick, MA.; GBR 12909 [1-(2-(bis(4-Fluorophenyl)methoxy)ethyl)-4-(3-phenylpropyl)piperazine dihydrochloride] was generously donated by Novo Nordisk A/S (The Netherlands); SCH 23390 ((+)-7-Chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride) was Schering Plough Inc. (Kenilworth, NJ); raclopride [S-(−)-3,5-dichloro-N-([1-ethyl-2-pyrrolidinyl]) methyl-2-hydroxy-6-methoxybenzamide L-tartarate] was generously donated by Astra Lakemedel AB (Sodertalje, Sweden); pentobarbital was obtained from Abbott Laboratories, Chicago, IL; and atropine sulfate was obtained from Sigma Chemical Co., St. Louis, MO. Gentamicin was obtained from Solo-Pak Laboratories, Elk Grove Village, IL.

Recent advances in the identification of novel dopamine receptor subtypes have presented certain challenges with regard to nomenclature. It is reasonable to refer to SCH 23390 as a D_1 antagonist, and to raclopride as a D_2 antagonist (although it is considerably less potent at D_4 vs. D_2 and D_3 receptors), if it is understood that those subtype designations are meant to refer to subtype classes (i.e., the "D_1-like" class and the "D_2-like" class). That nomenclature convention will be utilized in the present report for the sake of brevity, and because functional differences among the receptors within a class have not been elucidated. In the case of 7-OH-DPAT, which has been shown to exhibit between 10 and 100 fold selectivity for D_3 and D_2 receptors, claims have been made that some of its behavioral effects are specifically mediated by D_3 receptors rather than by D_2 and D_4 receptors. Nevertheless, the selectivity of 7-OH-DPAT for D_3 over D_2 receptors in vivo has been contested (11); therefore, 7-OH-DPAT will be referred to as a D_2/D_3 receptor agonist.

SKF 81297, 7-OH-DPAT, and raclopride were dissolved in physiological saline and injected subcutaneously 10 min before the testing session. GBR 12909 was dissolved in a hot saline/tartaric acid mixture (1 mg racemic tartaric acid per 5 mg GBR 12909), which was allowed to cool before injection; intraperitoneal injections of GBR 12909 were administered 20 min before the testing session. SCH 23390 was first dissolved in methanol in a volume of 1 μg/μl, and then diluted with physiological saline. SCH 23390 was administered subcutaneously 30 min before the testing session. All drugs were administered in an injection volume of 1 ml/kg.

Statistical Analyses

For each separate drug experiment, percent change from baseline threshold was calculated by expressing the drug-influenced threshold scores as a percentage of the mean threshold for the previous three baseline testing days (predrug baseline thresholds). Those percent-change scores were subjected to one-factor repeated-measures analysis of variance (ANOVA). The levels in the ANOVAs corresponded to the treatments (vehicle plus drug doses) for each drug experiment. To test for possible confounding effects of the order of drug administration, the repeated-measures ANOVAs were recalculated with the order of the treatments as the independent variable.

Predrug baseline thresholds also were subjected to one-factor repeated-measures ANOVA to assess the stability of baseline responding throughout the course of the drug treatment regimens. ANOVAs on baseline thresholds were calculated two ways for each experiment: with the temporal order of pretreatment baseline thresholds as the independent variable, and with the treatment-associated order (i.e., vehicle and drug doses in ascending order) as the independent variable. Because those two analyses yielded almost exactly the same results in each case, for the purpose of clarity, only the latter analysis is reported in this article.

Latency scores were analyzed in exactly the same fashion as the threshold scores. Two latency values were missing due to a data collection error in the SKF 81297 experiment, and in the GBR 12909 experiment. In those cases, the missing data points (two missing points out of 42 for the SKF 81297 experiment; two missing points out of 36 for the GBR 12909 experiment) were replaced by the global mean of all latency scores for that experiment.

Following significance in the overall ANOVA, post hoc comparisons among means were conducted with the Newman–Keuls test (67). The level of statistical significance was set at $p \leq 0.05$.

RESULTS

Order Effects

No effect of dose order was noted for either the reward threshold measure, Fs = 0.59–1.8, NS, or the latency measure, Fs = 0.7–3.0, NS, in any of the experiments.

Dopamine Receptor Antagonists (SCH 23390 and Raclopride)

The dopamine D_1 receptor-selective antagonist SCH 23390 produced a dose-dependent increase in brain stimulation reward thresholds, $F(4, 32) = 14.32$, $p \leq 0.0001$. Post hoc comparison among means with the Newman–Keuls test revealed that the highest dose (0.02 mg/kg) produced a threshold elevation that differed significantly from the effects of all other doses, whereas the effects of the 0.01 mg/kg dose differed significantly from the effects of the 0.0025 mg/kg dose, and vehicle (see Fig. 1A). In contrast to its effects on reward thresholds, SCH 23390 failed to alter response latencies, $F(4, 32) = 1.767$, NS (Fig. 1B). Neither pretreatment baseline reward thresholds, nor baseline response latencies, varied throughout the course of the experiment, Fs = 0.82–1.09, NS.

As shown in Fig. 2A, the dopamine D_2-receptor-selective antagonist raclopride elevated brain stimulation reward thresholds, $F(3, 24) = 6.977$, $p \leq 0.002$; post hoc comparison among means indicated that the effect of the 0.02 mg/kg dose was different from the effects of all other doses. In addition, it can be seen in Fig. 2B that raclopride significantly increased response latency, $F(3, 24) = 12.54$, $p \leq 0.001$; post hoc analysis with the Newman–Keuls test indicated that latency values for the 0.02 mg/kg dose were significantly higher than those associated with 0.01 mg/kg or vehicle, and that the 0.005 mg/kg dose produced an increase in latency scores that differed significantly from vehicle (Fig. 2B). Neither pretreatment baseline reward thresholds, nor pretreatment baseline latencies, varied over the course of the experiment, Fs = 0.55–0.83, NS.

Direct Dopamine Receptor Agonists (SKF 81297 and 7-OH-DPAT)

Brain stimulation reward thresholds were dose-dependently elevated by the direct dopamine D_1 receptor agonist SKF 81297, $F(5, 35) = 7.118$, $p \leq 0.0001$; post hoc comparison among means with the Newman–Keuls test revealed that the effect of the 1.5 mg/kg dose was significantly different from the effects of all other doses, and that the effect of the 0.75 mg/kg dose differed from the effects of 0.5, 0.25, 0.125 mg/kg, and vehicle (Fig. 3A). The slight increase over baseline thresholds for the vehicle treatment which was obtained in this study (112.7% of baseline) is well within the range of variation observed under baseline conditions. In contrast to its effects on reward thresholds, SKF 81297 failed to alter response latency at any dose tested, $F(5, 35) = 0.30$, NS (Fig. 3B). As depicted in Fig. 3A and 3B, pretreatment baseline reward thresholds, and pretreatment baseline response latencies remained stable over the course of the experiment, Fs = 1.26–1.5, NS.

The direct dopamine D_2/D_3 agonist 7-OH-DPAT failed to produce a statistically significant effect on brain stimulation reward thresholds, $F(4, 24) = 0.878$, NS (Fig. 4A). In contrast, 7-OH-DPAT significantly elevated response latency, $F(4, 24) = 4.50$, $p \leq 0.007$; post hoc analysis with the Newman–Keuls test revealed that latency scores associated with the 1.0 mg/kg dose were different from those associated with any of the other doses (Fig. 4B). In addition, baseline thresholds and response latencies were unaltered throughout the experiment, Fs = 0.26–0.57, NS.

The Dopamine Uptake Inhibitor GBR 12909

The selective dopamine uptake inhibitor GBR 12909 significantly lowered brain stimulation reward thresholds, $F(4, 24) \geq 2.772$, $p \leq 0.05$ (Fig. 5A). Post hoc comparison among means with the Newman–Keuls test indicated that the effect of the 5.0 mg/kg dose was significantly different from the effect of vehicle. GBR 12909 failed to alter response latencies, $F(4, 24) = 0.338$, NS (Fig. 5B). Pretreatment baseline thresholds and response latencies were unaltered over the course of the drug treatments, Fs = 0.38–2.3, NS.

DISCUSSION

The dopamine agonists and antagonists used in the present study produced distinct effects on reward thresholds and response latencies. First, the direct dopamine D_1 receptor agonist SKF 81297 dose-dependently elevated thresholds for rewarding electrical stimulation of the lateral hypothalamus, but did not influence response latencies. In contrast, the dopamine D_2/D_3-selective agonist 7-OH-DPAT significantly increased response latencies but had no consistent significant effect on reward thresholds, although a trend towards threshold elevation at some doses was noted. Second, both the D_1-selective dopamine receptor antagonist SCH 23390 and the D_2-selective receptor antagonist raclopride produced brain stimulation reward threshold elevations; however, of those two antagonists, only raclopride significantly elevated response latencies. Third, the selective dopamine uptake blocker GBR 12909 significantly lowered reward thresholds without influencing response latencies. The present results provide a clear demonstration that a highly selective direct D_1 receptor agonist, with high agonist efficacy, markedly elevates brain stimulation reward thresholds, an effect that is commonly interpreted as an attenuation of stimulation-derived reward. In addition, the present data indicate a difference between the effects of direct dopamine agonists (which lack threshold-lowering effects), and the effects of indirect dopamine agonists (which lower thresholds), a difference which is independent of receptor subtype. Furthermore, the results of this study provide evidence for a distinction between the ability of "D_1-like" and "D_2-like" selective compounds to produce dissociable effects on reward vs. performance measures. Specifically, compounds selective for D_1-like receptors influenced reward thresholds at doses that produced no effect on response latencies, whereas compounds selective for D_2-like receptors influenced thresholds only at doses that also increased response latency.

Since the time of the initial discovery that at least two subclasses of dopamine receptors exist, and the development of receptor antagonists that exhibited subtype selectivity, attempts have been made to discern the relative contribution of those subtypes to the function of the neural system that supports brain stimulation reward. Most brain stimulation reward studies using subtype-selective antagonists have failed to reveal a clear distinction between D_1 and D_2 receptors on brain stimulation reward [for review, see (47)]. In the present study, only the highest dose of raclopride (0.02 mg/kg) produced a significant elevation of reward threshold, an elevation that was of smaller magnitude than the effect produced by the highest dose of SCH 23390 (0.02 mg/kg). It may be that higher doses of raclopride would have produced even greater threshold elevations, but also impaired other more motor-related measures. In summary, the present results that both SCH 23390 and raclopride elevated thresholds, indicating that both D_1 and D_2 receptors are involved in the mechanism of medial forebrain bundle stimulation-derived reinforcement, are in general agreement with the literature.

The present results are also consistent with the suggestion that the two receptors may be of different relative importance in dopamine-mediated reinforcement vs. dopamine-mediated

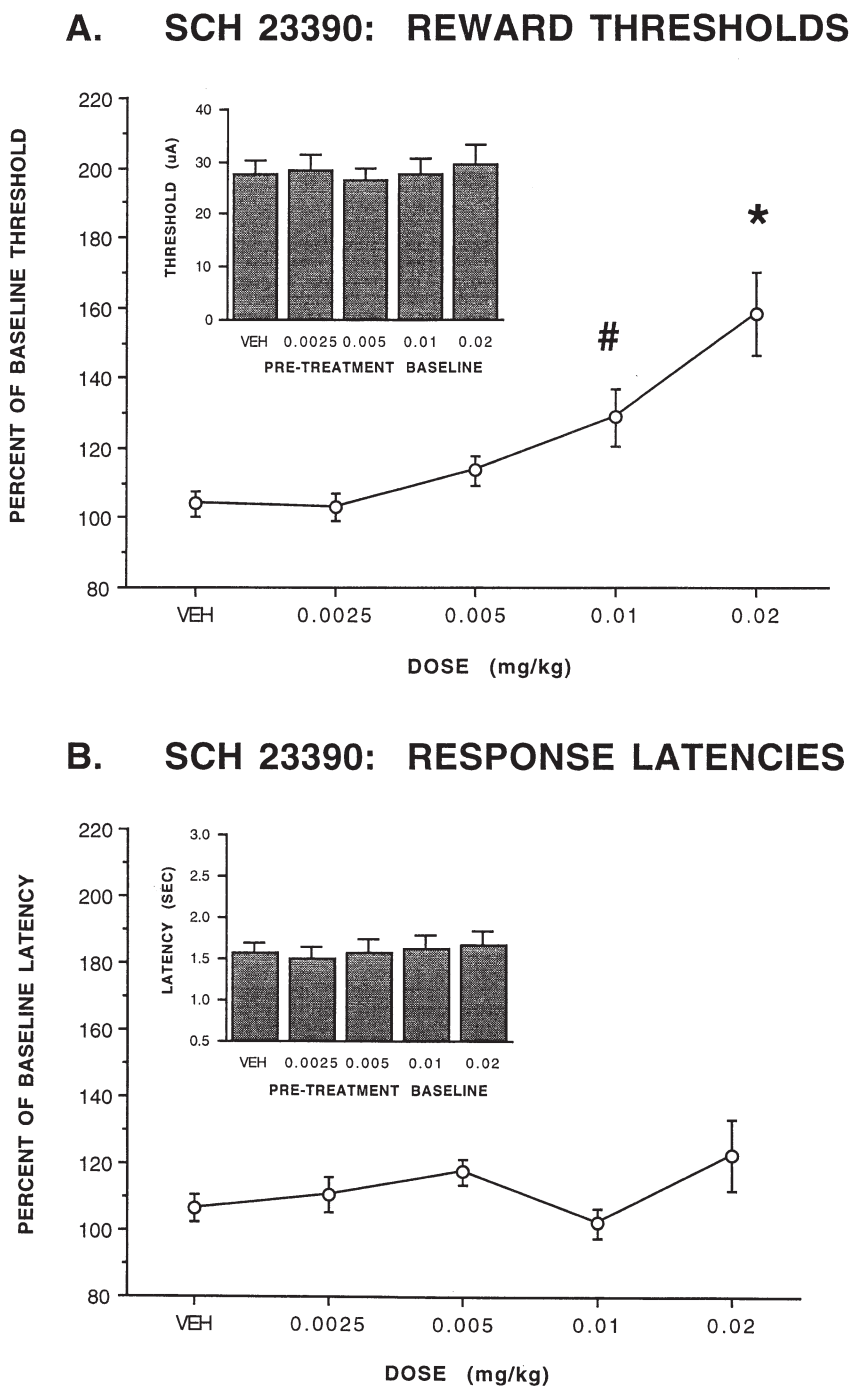

FIG. 1. (A) Effects of the dopamine D_1 receptor antagonist SCH 23390 on brain stimulation reward thresholds. Data are expressed as percent change of the treatment-influenced threshold from the mean threshold of the previous 3 baseline testing days ("pretreatment baselines"—see text). Error bars represent 1 SEM. VEH = vehicle. #$p < 0.05$ different from VEH and 0.0025 mg/kg, and *$p < 0.05$, different from all other means, by Newman–Keuls test. Inset: pretreatment baseline thresholds expressed in μAmps. Error bars represent 1 SEM. (B) Effects of SCH 23390 on percent change from baseline latency, defined as in A. Inset: pretreatment baseline latencies expressed in seconds. Error bars represent 1 SEM.

motor function (3,27). The D_1 antagonist significantly elevated brain stimulation reward thresholds at doses that did not produce an effect on response latencies. Similarly, the D_1 agonist SKF 81297 was devoid of effects on response latencies. In contrast, the D_2 antagonist raclopride and the $D_{2/3}$ agonist 7-OH-DPAT both significantly increased response latencies. Our data, therefore, suggest that D_1-like selective drugs, whether they be agonists or antagonists, may have more selective ef-

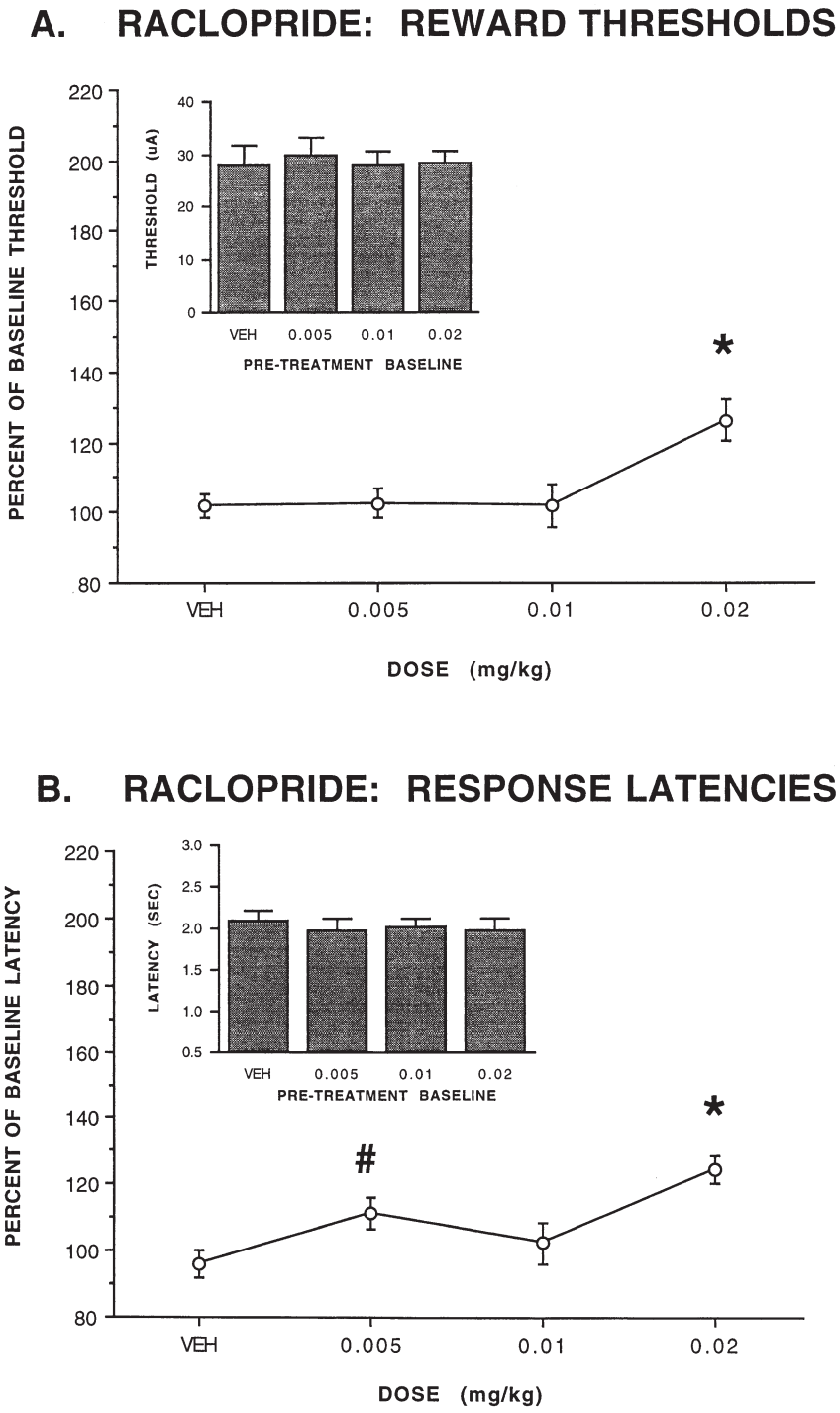

FIG. 2. (A) Effects of the dopamine D_2 receptor antagonist raclopride on brain stimulation reward thresholds. Data are expressed as percent change of the treatment-influenced threshold from the mean threshold of the previous 3 baseline testing days ("pretreatment baselines"—see text). Error bars represent 1 SEM. VEH = vehicle. *$p < 0.05$ different from all other means, by Newman–Keuls test. Inset: pretreatment baseline thresholds expressed in μAmps. Error bars represent 1 SEM. (B) Effects of raclopride on percent change from baseline latency, defined as in A. *$p < 0.05$ different from VEH and 0.01 mg/kg, and #$p < 0.05$ different from VEH, by Newman–Keuls test. Inset: pretreatment baseline latencies expressed in seconds. Error bars represent 1 SEM.

fects on reward than on motor performance in the present procedure than do D_2-like selective drugs. In this study, D_2-like selective compounds produced effects on reward, as assessed by thresholds, at doses that also produced effects on performance, as assessed by the response latency measure. That observation does not necessarily indicate that in the case of $D_{2/3}$-selective drugs, increases in the reward threshold were due to response speed impairments rather than attenuation of brain

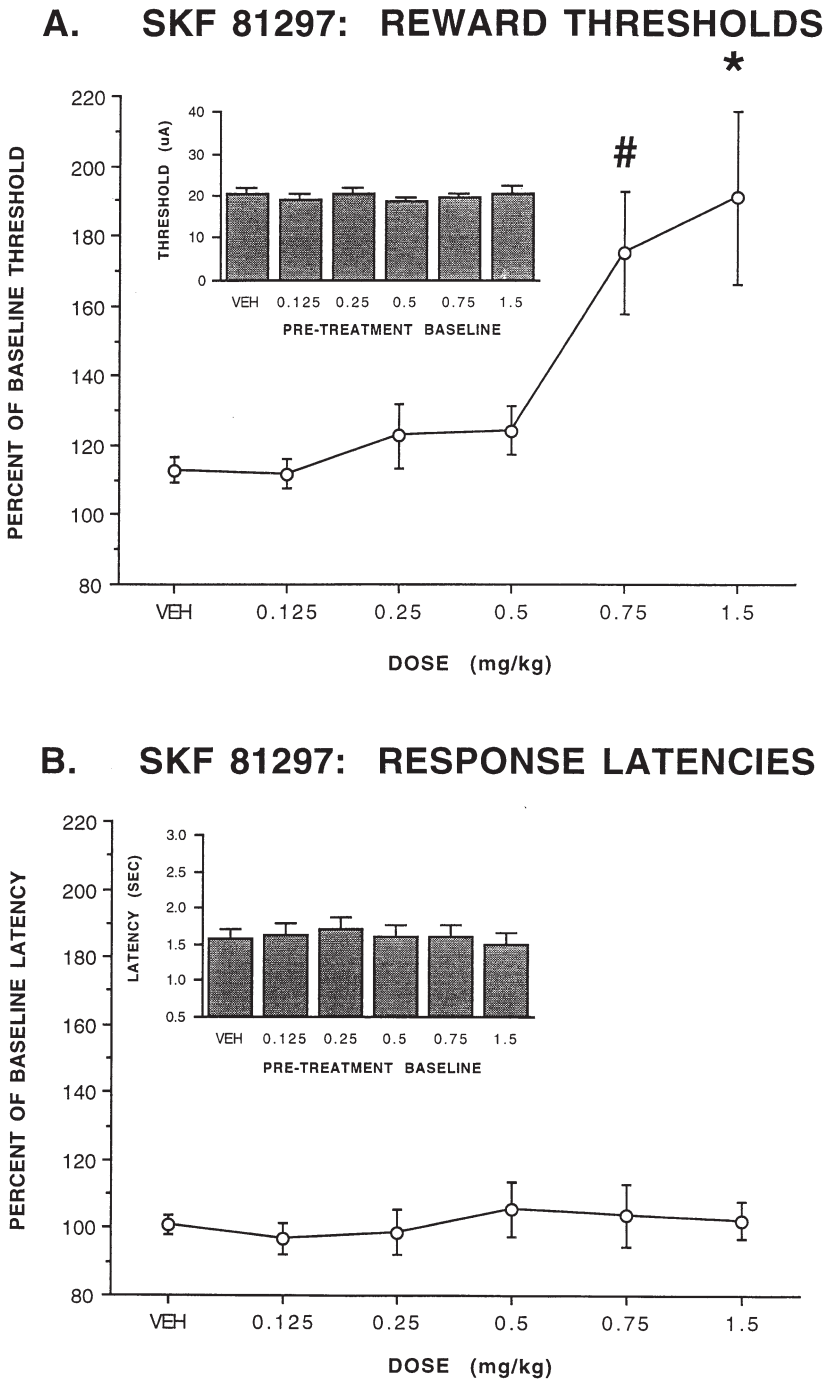

FIG. 3. (A) Effects of the direct dopamine D_1 receptor agonist SKF 81297 on brain stimulation reward thresholds. Data are expressed as percent change of the treatment-influenced threshold from the mean threshold of the previous 3 baseline testing days ("pretreatment baselines"—see text). Error bars represent 1 SEM. VEH = vehicle. *$p <$ 0.05 different from all other means, and #$p < 0.05$, different from the means associated with 0.5, 0.25, 0.125 mg/kg, and vehicle, by Newman–Keuls test. Inset: pretreatment baseline thresholds expressed in μAmps. Error bars represent 1 SEM. (B) Effects of SKF 81297 on percent change from baseline latency, defined as in A. Inset: pretreatment baseline latencies expressed in seconds. Error bars represent 1 SEM.

stimulation reward per se. Indeed, for the 1.0 mg/kg dose of 7-OH-DPAT, a dose that elevated response latencies, no close association was found between drug-induced changes on the reward threshold and latency measures ($r = 0.47$). Clearly, further work with additional subtype-selective agonists and antagonists is required to bolster the generalization that D_1 and D_2-selective drugs produce differential effects on reward vs. performance measures in this task.

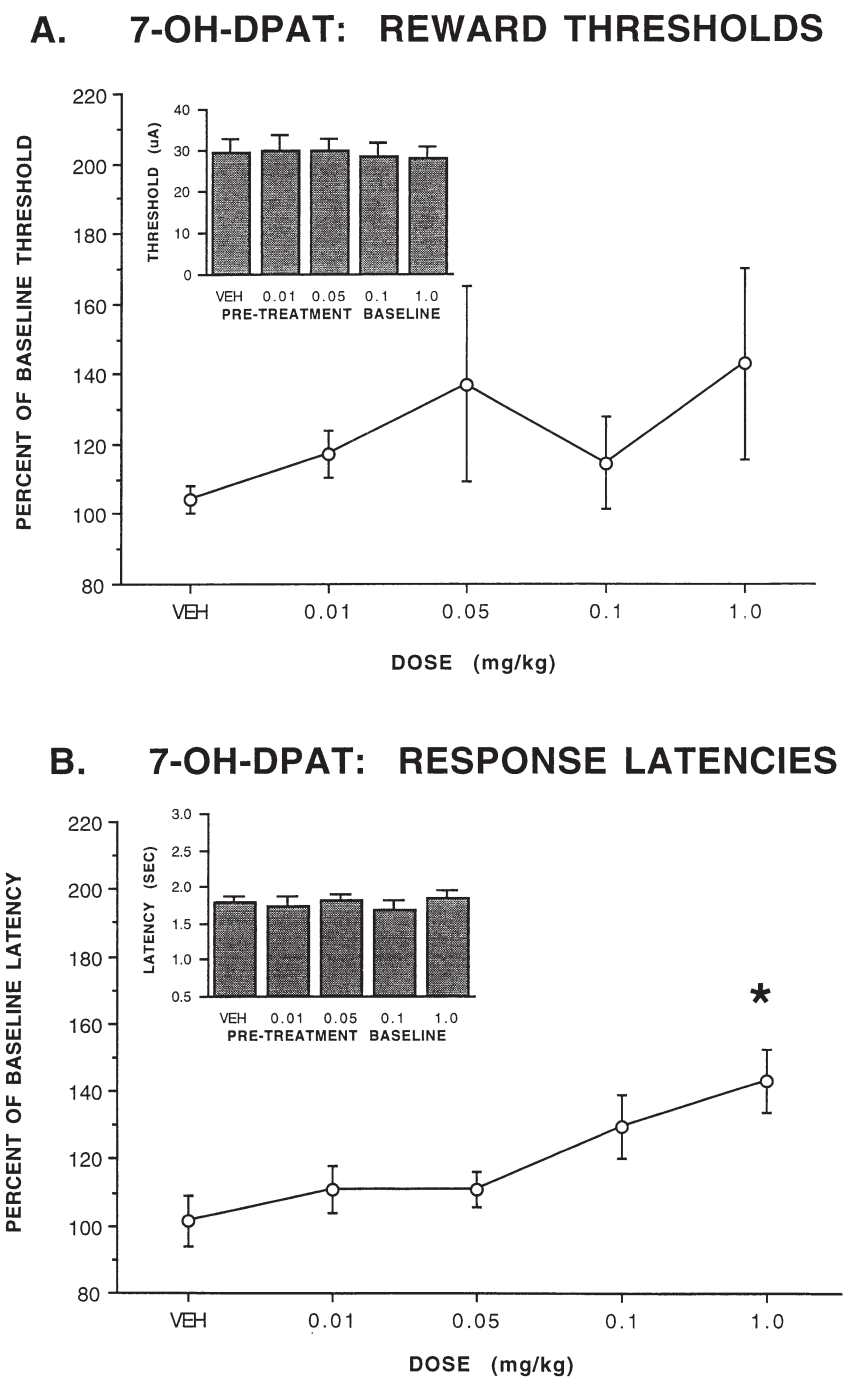

FIG. 4. (A) Effects of the direct dopamine D_2/D_3 receptor antagonist 7-OH-DPAT on brain stimulation reward thresholds. Data are expressed as percent change of the treatment-influenced threshold from the mean threshold of the previous 3 baseline testing days ("pre-treatment baselines"—see text). Error bars represent 1 SEM. VEH = vehicle. Inset: pre-treatment baseline thresholds expressed in μAmps. Error bars represent 1 SEM. (B) Effects of 7-OH-DPAT on percent change from baseline latency, defined as in A. $*p < 0.05$ different from all other means, by Newman–Keuls test. Inset: pretreatment baseline latencies expressed in seconds. Error bars represent 1 SEM.

In the present task, response latencies reflect the elapsed time between the noncontingent stimulation that signals the onset of each trial, and the performance of the operant response. Thus, response latencies in part reflect response speed and have been shown to be sensitive to manipulations that selectively impair motor performance, such as increasing the amount of force required to turn the manipulandum (42). Interestingly, studies using food-reinforced lever-release tasks

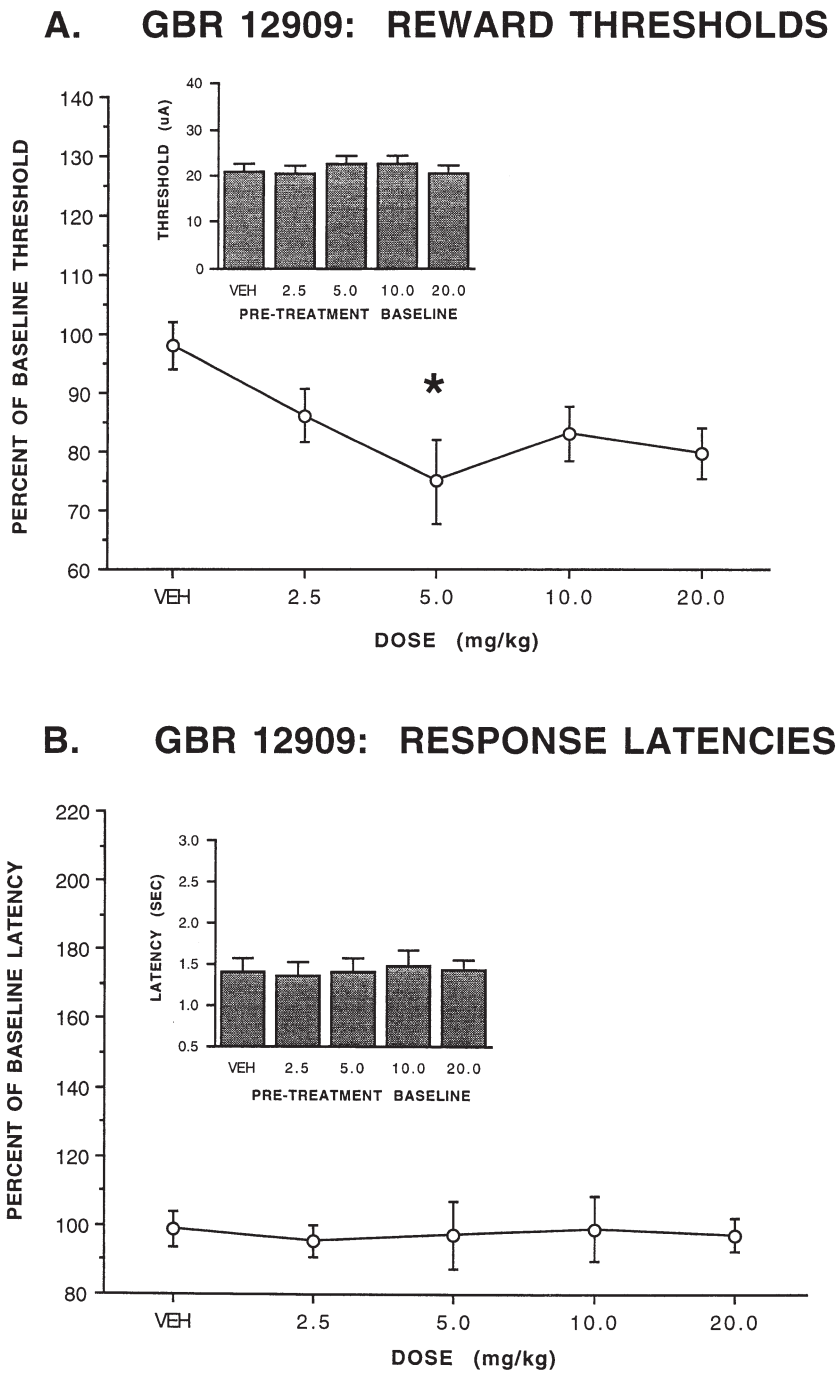

FIG. 5. (A) Effects of the dopamine uptake inhibitor GBR 12909 on brain stimulation reward thresholds. Data are expressed as percent change of the treatment-influenced threshold from the mean threshold of the previous three baseline testing days ("pretreatment baselines"—see text). Error bars represent 1 SEM. VEH = vehicle. *$p < 0.05$ different from VEH, by Newman–Keuls test. Inset: pretreatment baseline thresholds expressed in μAmps. Error bars represent 1 SEM. (B) Effects of GBR 12909 on percent change from baseline latency, defined as in A. Inset: pretreatment baseline latencies expressed in seconds. Error bars represent 1 SEM.

in rats revealed that the D_2 antagonist raclopride increased reaction time, whereas the D_1 antagonist SCH 23390 was without effect (2,44). In contrast, an investigation of the effects of SCH 23390 and spiperone (a D_2-selective antagonist) on a lever-release task reinforced by avoidance of an electrical stimulus showed that SCH 23390 increased reaction time, whereas the D_2-selective antagonist, spiperone, did not (45). Although the factors underlying the discrepancy among those

studies have not been identified, the response–latency results from the present brain stimulation reward paradigm, which is a positively reinforced task, tend to support the conclusions of the positively reinforced reaction-time tasks in rats that point to a greater involvement of D_2 receptors over D_1 receptors in reaction-time performance. It should be noted, however, that higher doses of SCH 23390 (i.e., greater than 0.02 mg/kg) may have produced increases in response latency in the current study. Nevertheless, the doses of SCH 23390 chosen were sufficient to elevate reward thresholds, and thereby clearly demonstrate a dissociation between the effects of that drug on reward thresholds and response latencies.

The 7-OH-DPAT–induced increase in response latency observed in the present study is consistent with previous findings demonstrating a depression of motor output induced by low doses of that drug, such as decreased spontaneous locomotor activity and operant lever-pressing (1,15,16,31,60). At higher doses, despite its depressant effect on extracellular dopamine levels [e.g., (22,49)], 7-OH-DPAT has been shown to produce stimulant-like effects such as increased locomotor activity and stereotypy (1,15), and facilitation of cocaine reinforcement via its agonist action at postsynaptic D_2/D_3 receptors (49). It is likely that the well-documented depressant effect of low doses of 7-OH-DPAT on motor output and dopamine release, as well as possible disruptive stimulant-like effects at the highest dose tested, both contributed to the increase in response latencies observed in the present study.

It is of interest to note that the dopamine uptake inhibitor GBR 12909 did not produce effects on the response latency measure. Because the intermediate (5 mg/kg) dose of GBR 12909 produced a lowering of reward threshold, the lack of effect on latency is not due to a failure to choose a behaviorally active dose range for GBR 12909. It is more likely that any increases in response speed induced by that psychostimulant would not be detectable in the present procedure due to the very short response latencies (i.e., approximately 1.5 s) obtained under control conditions. Thus, the lack of effect of GBR 12909 on latency could be due to a "floor" effect. In addition, the failure of GBR 12909 to influence response latencies at any dose tested indicates that the modest U-shaped dose–effect function obtained for the threshold-lowering effect of that drug was not due to disruption of responding by the higher doses of GBR 12909.

A striking paradox in the present data is the finding that both the D_1 receptor antagonist SCH 23390 and the high-efficacy D_1 receptor agonist SKF 81297 produced clear, dose-dependent increases in reward thresholds. Furthermore, the dopamine D_2/D_3 agonist 7-OH-DPAT produced inconsistent trends toward threshold elevation, in contrast to the clear threshold-lowering effects of the indirect dopamine agonist GBR 12909. Given that direct D_1 and D_2/D_3 agonists are self-administered (12,13,24,49,55,66), and that 7-OH-DPAT produces conditioned place preference (32,41), it would be reasonable to hypothesize that SKF 81297 and 7-OH-DPAT would act to facilitate, rather than attenuate, brain stimulation reward. Nevertheless, SKF 81297 induced consistent, marked threshold elevations, and 7-OH-DPAT failed to lower thresholds at any dose tested. Although the basis for direct dopamine agonist effects on brain stimulation reward are not known, several potential mechanisms may have produced the observed effects.

One possible explanation for the threshold-elevating effect of SKF 81297 is that the doses of that drug used in the present study were high enough to induce intense motor stereotypies, which would disrupt operant responding, lead to inconsistent performance in the brain stimulation reward task, and thereby result in falsely elevated threshold estimates. It is worthwhile to note in that regard that the doses of SKF 81297 required to elevate thresholds (0.75 and 1.5 mg/kg) are considerably higher than the minimal doses required to produce behavioral effects in other paradigms [e.g., (5,52)]. Furthermore, a recent study of the brain stimulation reward-related effects of another direct dopamine agonist, apomorphine, revealed that the apparent tendency of that drug to elevate thresholds in the curve–shift paradigm is likely the result of an artifact stemming from response-disrupting stereotypies (25). It could be proposed that a similar artifact may be present in the present data. However, this hypothesis is unlikely for several reasons. First, casual observation of the animals failed to reveal any obvious stereotyped behavior, even at the highest dose of SKF 81297 tested (1.5 mg/kg). Second, the doses that produced threshold elevations influenced neither the number of extra stimulation-contingent wheel revolutions performed during the self-stimulation trials, nor the number of incorrect responses emitted during the intertrial intervals (data not shown). Third, the same doses that produced clear, marked threshold elevations did not influence response latencies. Thus, during the trials in which thresholds were elevated, not only were the animals responding properly in the task, but the speed of their response was unchanged, suggesting that potential effects on motor systems did not interfere with performance in this task.

An alternative hypothesis for the discrepant effects of direct and indirect dopamine agonists in the brain stimulation reward paradigm relates to the ability of direct agonists to stimulate dopamine receptors regardless of the activity of dopamine neurons [see (6,18,26,38,64)]. In contrast, the effects of indirect agonists such as dopamine uptake blockers and releasers are more directly linked to the activity of the neurons from which the dopamine is released. Accordingly, one might predict that by directly stimulating postsynaptic dopamine receptors without regard to presynaptic dopaminergic activity, direct agonists would "uncouple" the postsynaptic dopamine signal from the behaviorally relevant neural events driving the presynaptic dopamine neurons. In contrast, indirect agonists would act to potentiate the presynaptic dopamine signal. Thus, assuming that the reward signal induced by electrical stimulation represents the critical neural event that controls behavior in the brain stimulation reward paradigm, if activity-dependent dopamine release directly conveys that stimulation-induced information across a synapse to postsynaptic dopamine receptors, one could postulate that the noncontingent, uncoupled stimulation of those postsynaptic dopamine receptors by a direct agonist would "mask" the stimulation-relevant dopamine signal. The signal would then be more difficult to detect over the "noise" induced by the direct agonist. One might additionally predict the direct agonist to produce false reward signals of its own, resulting in further loss of stimulus control [(26,38,48], but see (64)]. In either event, in the present brain stimulation reward task, higher levels of stimulation would be required to produce a reliably detectable reward signal, and thresholds would correspondingly rise. In summary, it is possible that reward threshold elevations could result from either dopamine antagonist-induced attenuation of the reward signal, or dopamine agonist-induced enhancement of the background over which the reward signal needs to be perceived.

The clearly contrasting effects in the present paradigm of the indirect dopamine agonists cocaine [e.g., (17,42)] and GBR 12909, and the direct D_1 receptor agonist SKF 81297, are con-

sistent with the reward-masking hypothesis outlined above. In addition, although the D_2/D_3 receptor agonist, 7-OH-DPAT, failed to produce reliable threshold elevations in the present study, that compound was also devoid of consistent threshold-lowering effects. These results further support the distinction between the consistent effects of indirect dopamine agonists and the inconsistent effects of direct dopamine agonists that have also been noted in other brain stimulation reward procedures (see Table 1). The present results further demonstrate that this distinction does not depend upon the subtype selectivity of the direct agonists tested.

With regard to the issue of subtype selectivity, it is important to note that the dopamine synthesis and release-regulating autoreceptors are of the D_2-like class (14,30,46,61). It is, therefore, possible that in addition to any masking effects, D_2-like agonists may influence thresholds via autoreceptor-mediated suppression on presynaptic dopaminergic function (18,35). As previously discussed, autoreceptor-like mechanisms could account for some of the effects of 7-OH-DPAT in the present study. In contrast, D_1-like agonists do not typically produce the same degree of extracellular dopamine depression as do D_2-like agonists [e.g., (62)]. On that basis, one might expect the brain stimulation reward-related effects of D_1 agonists to be predominantly due to postsynaptic receptor agonism. Nevertheless, the commonly used D_1 agonist SKF 38393 has relatively low intrinsic activity in the rat (4,28,65), and may, therefore, function as a partial agonist in rat self-stimulation studies. Aside from the present study, there has been only one other investigation of a high efficacy D_1 agonist on brain stimulation reward thresholds in the rat. In direct contrast to the present findings, it was demonstrated that A77636 lowered thresholds for ventral tegmental stimulation in a curve–shift procedure, after either systemic or intraaccumbens administration (51).

There are a number of factors that could be relevant to the discrepancies between previous results and the present data. For example, the effects of dopamine agonist-induced masking may be most apparent in discrete trial brain stimulation reward paradigms that are characterized by low densities of stimulation. For example, in the present paradigm, the availability of reward in each trial is signaled by the delivery of a single noncontingent electrical brain stimulus, and the trials are separated from one another by random intervals. For those reasons, there is a greater emphasis upon the detection of randomly occurring stimulation-derived reward signals; in some ways, the present paradigm resembles a vigilance task. In such a situation, an optimal signal-to-noise ratio is critical

TABLE 1

EFFECTS OF SUBTYPE-SELECTIVE DOPAMINE AGONISTS, ADMINISTERED SYSTEMICALLY OR INTRACEREBRALLY INTO DOPAMINE TERMINAL REGIONS, ON MEDIAL FOREBRAIN BUNDLE/LATERAL HYPOTHALAMUS, VENTRAL TEGMENTAL AREA, OR SUBSTANTIA NIGRA SELF-STIMULATION

Drug	BSR Method	BSR site	Dose Range, Site	BSR Effect	Reference
D_1-like receptor agonists					
SKF 38393	reward summation (FI schedule)	MFB	5.0 mg/kg	⇓	27
SKF 38393	freq. curve shift	MFB	0.1–0.4 mg/kg	–	48
SKF 38393	freq. curve shift	MFB or VTA	5 μg in 0.5 μl, NAcc	⇑	56
A-77636	freq. curve shift	VTA	3.0 mg/kg	⇑	51
			30 μg in 0.5 μl, Nacc	⇑	
			30 μg in 0.5 μl, CPu	—	
D_2-like receptor agonists					
(±)7-OH-DPAT	freq. curve shift	VTA	0.1–10.0 mg/kg	⇓,c	16
(±)7-OH-DPAT	rate of responding (CR schedule)	VTA	0.01–0.3 mg/kg	⇓	22
R(+)7-OH-DPAT	current curve shift	MFB	0.094–1536 nmol/kg (approx. 0.00003–0.5 mg/kg)	⇓ low doses ⇑ high doses	32
Bromocriptine	reward summation (FI schedule)	MFB	5, 10 mg/kg	–, r	27
Bromocriptine	threshold—method of limits	MFB	4–16 mg/kg	⇑	34
Bromocriptine	rate of responding (CR schedule)	SNC	5–20 mg/kg	⇑	57
Quinpirole	freq. curve shift	VTA	0.03–1.0 mg/kg	⇓,c	16
Quinpirole	freq. curve shift	MFB	0.5–2.0 mg/kg	⇑,c	48
Quinpirole	freq. curve shift	VTA	1.0 mg/kg	⇑,c	51
			0.3–10.0 μg in 0.5 μl NAcc, CPu	⇓	
Quinpirole	freq. curve shift	MFB or VTA	10.0 μg in 0.5 μl NAcc	⇓	56
CV 205-502	freq. curve shift	MFB	0.5 mg/kg	⇑,c,r	48

MFB = medial forebrain bundle/lateral hypothalamic region, VTA = ventral tegmental area, SNC = substantia nigra pars compacta, NAcc = nucleus accumbens, CPu = caudate-putamen, FI = fixed interval, CR = continuous reinforcement. ⇑ signifies a facilitation of brain stimulation reward (BSR); ⇓ signifies an attenuation of BSR; – indicates no significant effect. Note: SKF 38393 has been shown to be a partial agonist (see text). Comments: c = curve flattening was observed; r = response perseveration was observed under extinction conditions.

for the maintenance of consistent responding, and subjects might, therefore, be highly susceptible to the disruptive effects of agonist-generated dopaminergic "noise" and false reward signals. Interestingly, it has been shown that the threshold for rewarding stimulation can be dissociated from the threshold for detection of low levels of nonrewarding stimulation (9); thus, direct dopamine agonists could be masking either the perception of the stimulation as rewarding (i.e., the detection of "reward signals") or the detection of brain stimulation per se in this task. In contrast to the present task, other brain stimulation reward threshold estimation methods, such as curve–shift procedures, usually involve considerably higher response rates and corresponding densities of stimulation that may overpower the effects of direct agonist-induced masking. This hypothesis could explain the difference between the present data and previous findings (51,56). That hypothesis does not account, however, for the observation that the direct D_2 receptor agonist bromocriptine lowered reward thresholds in a self-stimulation paradigm very similar to the one used in the present study (34). It could be that the differing pharmacodynamic and behavioral profiles of bromocriptine relative to many other direct dopamine agonists may partly explain its effects on reward thresholds (29). For example, in contrast to direct agonists such as apomorphine and quinpirole, the locomotor stimulation induced by even high doses of bromocriptine is very modest, delayed in onset, and very long lasting (29). It is, therefore, possible that bromocriptine produces only low-level stimulation of postsynaptic dopamine receptors, allowing for increased dopaminergic neurotransmission, resulting from the electrical brain stimulation, to be perceived. This effect of bromocriptine differs from the postsynaptic effects of other dopamine agonists that fail to lower thresholds in the present procedure. In addition, it may be that direct stimulation of D_1 receptors is required to produce maximal agonist-induced reward masking effects, a hypothesis that is supported by the present observation that while 7-OH-DPAT produced only an inconsistent trend towards threshold elevation, SKF 81297 markedly elevated thresholds. Along those lines, the mixed D_1/D_2 direct agonist apomorphine is without threshold lowering effects in the present paradigm [(35,36); Baldo, Veraldi, Koob, and Markou, unpublished observations].

In summary, the present study provides clear evidence of a distinction between the effects on reward threshold of dopamine indirect agonists and direct agonists measured in the same rate-free brain stimulation reward procedure. That distinction was shown to be independent of the subtype-selectivity of the direct agonists tested; thus, direct agonists of both the D_1-like and D_2-like receptor classes were found to be devoid of threshold-lowering effects, whereas the selective dopamine uptake inhibitor GBR 12909 clearly lowered thresholds. Furthermore, the full-efficacy D_1-selective agonist, SKF 81297, clearly elevated reward thresholds while leaving response latencies unchanged, an effect that was hypothesized to result from the ability of that agonist to noncontingently stimulate postsynaptic dopamine receptors, resulting in a masking of the stimulation-derived reward signal. Finally, D_1-selective drugs were found to exert more selective effects on reward than on motor performance, whereas D_2/D_3-selective drugs exhibited no such selectivity.

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REFERENCES

1. Ahlenius, S.; Salmi, P.: Behavioral and biochemical effects of the dopamine D_3 receptor-selective ligand, 7-OH-DPAT, in the normal and reserpine-treated rat. Eur. J. Pharmacol. 260:177–181; 1994.
2. Amalric, M.; Berhow, M.; Polis, I.; Koob, G. F.: Selective effects of low-dose D_2 dopamine receptor antagonism in a reaction-time task in rats. Neuropsychopharmacology 8:195–200; 1993.
3. Amalric, M.; Koob, D. F.: Functionally selective neurochemical afferents and efferents of the mesocorticolimbic and nigrostriatal dopamine system. In: Arbuthnott, G. W., Emson, P. C., eds. Progress in brain research, vol. 99: Chemical signalling in the basal ganglia. New York: Elsevier; 1993:209–226.
4. Andersen, P. H.; Jansen, J. A.: Dopamine receptor agonists: Selectivity and dopamine D1 receptor efficacy. Eur. J. Pharmacol. 188:335–337; 1990.
5. Arnt, J.; Hyttel, J.; Sanchez, C.: Partial and full dopamine D_1 receptor agonists in mice and rats: Relationship between behavioural effects and stimulation of adenylate cyclase activity in vitro. Eur. J. Pharmacol. 213:259–267; 1992.
6. Beninger, R. J.; Hoffman, D. C.; Mazurski, E. J.: Receptor subtype-specific dopaminergic agents and conditioned behavior. Neurosci. Biobehav. Rev. 13:113–122; 1989.
7. Bielajew, C.; Shizgal, P.: Behaviorally derived measures of conduction velocity in the substrate for rewarding medial forebrain bundle stimulation. Brain Res. 237:107–119; 1982.
8. Bielajew, C.; Shizgal, P.: Evidence implicating descending fibers in self-stimulation of the medial forebrain bundle. J. Neurosci. 6:919–929; 1986.
9. Bird, M.; Kornetsky, C.: Dissociation of the attentional and motivational effects of pimozide on the threshold for rewarding brain stimulation. Neuropsychopharmacology 3:33–40; 1990.
10. Broekkamp, C. L. E.; Pijnenburg, A. J. J.; Cools, A. R.; Van Rossum, J. M.: The effect of microinjections of amphetamine into the neostriatum and nucleus accumbens on self-stimulation behavior. Psychopharmacologia 42:179–183; 1975.
11. Burris, K. D.; Pacheco, M. A.; Filtz, T. M.; Kung, H. F.; Molinoff, P. B.: Lack of discrimination by agonists for D_2 and D_3 dopamine receptors. Neuropsychopharmacology 12:335–345; 1995.
12. Caine, S. B.; Koob, G. F.: Modulation of cocaine self-administration in the rate through D_3 dopamine receptors. Science 260: 1814–1816; 1993.
13. Caine, S. B.; Koob, G. F.: Pretreatment with the dopamine agonist 7-OH-DPAT shifts the cocaine self-administration dose–effect function to the left under different schedules in the rat. Behav. Pharmacol. 6:333–347; 1995.
14. Clark, D.; White, F. J.: Review: D_1 dopamine receptor—The search for a function: A critical evaluation of the D_1/D_2 dopamine receptor classification and its functional implications. Synapse 1:347–388; 1987.
15. Daly, S. A.; Waddington, J. L.: Behavioural effects of the putative D_3 dopamine receptor agonist 7-OH-DPAT in relation to other "D_2-like" agonists. Neuropharmacology 32:509–510; 1993.
16. Depoortere, R.; Perrault, Gh.; Sanger, D. J.: Behavioural effects in the rat of the putative dopamine D_3 receptor agonist 7-OH-DPAT: Comparison with quinpirole and apomorphine. Psychopharmacology (Berlin) 124:231–240; 1996.
17. Esposito, R. U.; Motola, A. H.; Kornetsky, C.: Cocaine. Acute

effects on reinforcement thresholds for self-stimulation behavior to the medial forebrain bundle. Pharmacol. Biochem. Behav. 8:437–439; 1978.
18. Fouriezos, G.; Francis, S.: Apomorphine and electrical self-stimulation of rat brain. Behav. Brain Res. 52:73–80; 1992.
19. Fouriezos, G.; Wise, R. A.: Pimozide-induced extinction of intracranial self-stimulation: Response patterns rule out motor or performance deficits. Brain Res. 103: 377–380; 1976.
20. Gallistel, C. R.; Davis, A. J.: Affinity for dopaminergic D_2 receptors predicts neuroleptic potency in blocking the reinforcing effects of MFB stimulation. Pharmacol. Biochem. Behav. 19:867–872; 1983.
21. Gallistel, C. R.; Karras, D.: Pimozide and amphetamine have opposing effects on the reward summation function. Pharmacol. Biochem. Behav. 20:73–77; 1984.
22. Gilbert, D. B.; Millar, J.; Cooper, S. J.: The putative dopamine D_3 agonist, 7-OH-DPAT, reduces dopamine release in the nucleus accumbens and electrical self-stimulation to the ventral tegmentum. Brain Res. 681:1–7; 1995.
23. Gingrich, J. A.; Caron, M. G.: Recent advances in the molecular biology of dopamine receptors. Annu. Rev. Neurosci. 16:299–321; 1993.
24. Grech, D. M.; Spealman, R. D.; Bergman, J.: Self-administration of D_1 receptor agonists by squirrel monkeys. Psychopharmacology (Berlin) 125:97–104; 1996.
25. Hall, F. S.; Stellar, J. R.: Measurement issues in curve-shift analysis of apomorphine effects on rewarding brain stimulation. Pharmacol. Biochem. Behav. 53:417–423; 1996.
26. Herberg, L. J.; Stephens, D. N.; Franklin, K. B. J.: Catecholamines and self-stimulation: Evidence suggesting a reinforcing role for noradrenaline and a motivating role for dopamine. Pharmacol. Biochem Behav. 4:575–582; 1976.
27. Hunt, G. W.; Atrens, D. M.; Jackson, D. M.: Reward summation and the effects of dopamine D_1 and D_2 agonists and antagonists on fixed-interval responding for brain stimulation. Pharmacol. Biochem. Behav. 48:853–862; 1994.
28. Izenwasser, S.; Katz, J. L.: Differential efficacies of dopamine D_1 receptor agonists for stimulating adenylyl cyclase in squirrel monkey and rat. Eur. J. Pharmacol. 246:39–44; 1993.
29. Jackson, D. M.; Mohell, N.; Georgiev, J.; Bengtsson, A.; Larsson, L. G.; Magnusson, O.; Ross, S. B.: Time course of bromocriptine induced excitation in the rat: Behavioural and biochemical studies. Naunyn Schimiedebergs Arch. Pharmacol. 351:146–155; 1995.
30. Jackson, D. M.; Westlind-Danielsson, A.: Dopamine receptors: Molecular biology, biochemistry, and behavioral aspects. Pharmacol. Ther. 64:291–370; 1994.
31. Kling-Petersen, T.; Ljung, E.; Svensson, K.: Effects on locomotor activity after local application of D_3 preferring compounds in discrete areas of rat brain. J. Neural Transm. 102:209–220; 1995.
32. Kling-Petersen, T.; Ljung, E.; Wollter, L.; Svensson, K.: Effects of dopamine D_3 preferring compounds on conditioned place preference and intracranial self-stimulation in the rat. J. Neural Transm. 101:27–39; 1995.
33. Knapp, C. M.; Kornetsky, C.: The effects of amfonelic acid alone and in combination with naloxone on brain stimulation reward. Pharmacol. Biochem. Behav. 32:977–982; 1989.
34. Knapp, C. M.; Kornetsky, C.: Bromocriptine, a D_2 receptor agonist, lowers the threshold for rewarding brain stimulation. Pharmacol. Biochem. Behav. 49:901–904; 1994.
35. Knapp, C. M.; Kornetsky, C.: Low-dose apomorphine attenuates morphine-induced enhancement of brain stimulation reward. Pharmacol. Biochem. Behav. 55:87–91; 1996.
36. Kornetsky, C.; Bain, G.: Brain stimulation reward: A model for drug-induced euphoria. In: Modern methods in pharmacology, vol. 6: Testing and evaluation of drugs of abuse. New York: Wiley-Liss; 1990:211–231.
37. Kornetsky, C.; Esposito, R. U.: Euphorigenic drugs: Effects on the reward pathways of the brain. Fed. Proc. 38:2473–2476; 1979.
38. Leith, N. J.: Effects of apomorphine on self-stimulation responding: Does the drug mimic the current? Brain Res. 277:129–136; 1983.
39. Levesque, D.; Diaz, J.; Pilon, C.; Martres, M. P.; Giros, B.; Souil, E.; Schott, D.; Morgat, J. L.; Schwartz, J. C.; Sokoloff, P.: Identification, characterization, and localization of the dopamine D_3 receptor in rat brain using 7-(3H)hydroxy-N, N-di-n-propyl-2-aminotetralin. Proc. Natl. Acad. Sci. USA 89:8155–8159; 1992.
40. Maldonado-Irizarry, C. S.; Stellar, J. R.; Kelley, A. E.: Effects of cocaine and GBR 12909 on brain stimulation reward. Pharmacol. Biochem. Behav. 48:915–920; 1994.
41. Mallet, P. E.; Beninger, R. J.: 7-OH-DPAT produces place conditioning in rats. Eur. J. Pharmacol. 261:R5–R6; 1994.
42. Markou, A.; Koob, G. F.: Construct validity of a self-stimulation threshold paradigm: Effects of reward and performance manipulations. Physiol. Behav. 51:111–119; 1992.
43. Markou, A.; Koob, G. F.: Intracranial self-stimulation thresholds as a measure of reward. In: Saghal, A., ed. Behavioral neuroscience, vol II: A practical approach. New York: Oxford University Press; 1993:93–115.
44. Marrow, L.; Overton, P.; Clark, D.: Disruption of conditioned reaction time performance by dopamine receptor antagonists in the rat. Behav. Pharmacol. 4:15–29; 1993.
45. Mayfield, R. D.; Randall, P. K.; Spirduso, W. W.; Wilcox, R. E.: Selective D_1 and D_2 dopamine receptor antagonists produce differential effects on reaction time in rats. Pharmacol. Biochem. Behav. 46:759–768; 1993.
46. Mercuri, N. B.; Saiardi, A.; Bonci, A.; Picetti, R.; Calabresi, P.; Bernardi, G.; Borrelli, E.: Loss of autoreceptor function in dopaminergic neurons from dopamine D_2 receptor deficient mice. Neuroscience 79:323–327; 1997.
47. Nakajima, S.: Subtypes of dopamine receptors involved in the mechanism of reinforcement. Neurosci. Biobehav. Rev. 13:123–128; 1989.
48. Nakajima, S.; O'Regan, N. B.: The effects of dopaminergic agonists and antagonists on the frequency-response function for hypothalamic self-stimulation in the rat. Pharmacol. Biochem. Behav. 39:465–468; 1991.
49. Parsons, L. H.; Caine, S. B.; Sokoloff, P.; Schwartz, J.-C.; Koob, G. F.; Weiss, F.: Neurochemical evidence that postsynaptic nucleus accumbens D_3 receptor stimulation enhances cocaine reinforcement. J. Neurochem. 67:1078–1089; 1996.
50. Phillips, A. G.; Fibiger, H. C.: Neuroanatomical bases of intracranial self-stimulation: untangling the Gordian knot. In: Liebman, J. M.; Cooper, S. J., eds. The neuropharmacological basis of reward. New York: Oxford University Press; 1989:66–105.
51. Ranaldi, R.; Beninger, R. J.: The effects of systemic and intracerebral injections of D_1 and D_2 agonists on brain stimulation reward. Brain Res. 651:283–292; 1994.
52. Reavill, B.; Bond, B.; Overend, P.; Hunter, A. J.: Pharmacological characterization of the discriminative stimulus properties of the dopamine D_1 agonist, SKF 81297. Behav. Pharmacol. 4:135–146; 1993.
53. Schwartz, J.-C.; Giros, B.; Martres, M.-P.; Sokoloff, P.: The dopamine receptor family: Molecular biology and pharmacology. Semin. Neurosci. 4:93–108; 1992.
54. Seeman, P.; Van Tol, H. H.: Dopamine receptor pharmacology. Trends Pharmacol. Sci. 15:264–270; 1994.
55. Self, D. W.; Stein, L.: The D_1 agonists SKF 82958 and SKF 77434 are self-administered by rats. Brain Res. 582:349–352; 1992.
56. Singh, J.; Desiraju, T. R.; Raju, T. R.: Dopamine receptor subtypes involvement in nucleus accumbens and ventral tegmentum but not in medial prefrontal cortex: On self-stimulation of lateral hypothalamus and ventral mesencephalon. Behav. Brain Res. 86:171–179; 1997.
57. Steiner, M.; Katz, R. J.; Carroll, B. J.: Behavioral effects of dopamine agonists across the estrous cycle in rats. Psychopharmacology (Berlin) 71:147–151; 1980.
58. Stellar, J. R.; Kelley, A. E.; Corbett, D.: Effects of peripheral and central dopamine blockade on lateral hypothalamic self-stimulation: Evidence for both reward and motor deficits. Pharmacol. Biochem. Behav. 18:433–442; 1983.
59. Stellar, J. R.; Stellar, E.: The neurobiology of motivation and reward. New York: Springer Verlag; 1985.
60. Svensson, K.; Carlsson, A.; Waters, N.: Locomotor inhibition by the D_3 ligand R-(+)-7-OH-DPAT is independent of changes in dopamine release. J. Neural Transm. 95:71–74; 1994.

61. Tang, L.; Todd, R. D.; O'Malley, K. L.: Dopamine D_2 and D_3 receptors inhibit dopamine release. J. Pharmacol. Exp. Ther. 270:474–479; 1994.
62. Tomiyama, K.; Koshikawa, N.; Funada, K.; Oka, K.; Kobayashi, M.: In vivo microdialysis evidence for transient dopamine release by benzazepines in rat stratum. J. Neurochem. 65:2790–2795; 1995.
63. van der Zee, P.; Koger, H. S.; Gootjes, J.; Hespe, W.: Aryl 1,4-dialk(en)ylpiperazines as selective and very potent inhibitors of dopamine uptake. Eur. J. Med. Chem. 15:363–370; 1980.
64. Walker, S.; Fouriezos, G.: Integration of free pulses in electrical self-stimulation of the rat brain. Behav. Neurosci. 109:168–179; 1995.
65. Weed, M. R.; Paul, I. A.; Dwoskin, L. P.; Moore, S. E.; Woolverton, W. L.: The relationship between reinforcing effects and in vitro effects of D_1 agonists in monkeys. J. Pharmacol. Exp. Ther. 283:29–38; 1997.
66. Weed, M. R.; Woolverton, W. L.: The reinforcing effects of dopamine D_1 receptor agonists in rhesus monkeys. J. Pharmacol. Exp. Ther. 275:1367–1374; 1995.
67. Winer, B. J.: Statistical principles in experimental design, 2nd ed. New York: McGraw Hill; 1971.
68. Yeomans, J. S.: Quantitative measurement of neural post-stimulation excitability with behavioral methods. Physiol. Behav. 15: 593–602; 1975.