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Reward Summation and the Effects of Dopamine D_1 and D_2 Agonists and Antagonists on Fixed-Interval Responding for Brain Stimulation

GLENN E. HUNT,*†[1] DALE M. ATRENS‡ AND DAVID M. JACKSON†[2]

*Departments of *Psychiatry, †Pharmacology, and ‡Psychology, University of Sydney, Sydney, New South Wales, Australia*

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HUNT, G. E., D. M. ATRENS AND D. M. JACKSON. *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**(4) 853–862, 1994.—The effects of dopamine D_1 and D_2 agonists and antagonists on fixed-interval (FI) self-stimulation were investigated using a reward-summation model, trading off frequency with train duration. The D_1 antagonist SCH 23390 (0.005–0.02 mg/kg) decreased FI self-stimulation and the inhibition was reversed by increasing stimulation frequency. Moreover, amphetamine (0.5 mg/kg) reversed the inhibition by a low dose of SCH 23390 (0.005 mg/kg) but not after a higher dose (0.02 mg/kg). The D_2 antagonist spiperone (0.05 mg/kg) also decreased FI self-stimulation, but unlike SCH 23390, this inhibition could not be dissociated from a performance deficit. There was no significant interaction between low doses of spiperone and SCH 23390 when coadministered that could not be predicted from their effects when given individually. Self-stimulation was inhibited by the D_1 agonist SKF 38393 (5 mg/kg). When coadministered with amphetamine, SKF 38393 partially blocked amphetamine's facilitation. The D_2 agonist bromocriptine (10 mg/kg) produced an extraordinary enhancement of performance that was also evident after a lower dose (5 mg/kg) when it was combined with amphetmaine. This enhancement of performance showed little extinction when stimulation was no longer available, suggesting it was a novel form of stereotypy. These results support the concept that D_1 dopamine receptors play a critical role in modulating the reinforcing consequences of lateral hypothalamic stimulation. The involvement of D_2 receptors on reinforcement processes remains contentious due to their effects on performance and insensitivity of responding to coincide with changes in reinforcement magnitude.

Self-stimulation Dopamine SCH 23390 Spiperone SKF 38393 Bromocriptine Amphetamine Fixed-interval (FI) Stereotyped behavior

ONE of the chief problems in studying the effects of dopamine on self-stimulation is dissociating changes in the reinforcing value of the stimulation from changes in motor function (1,11,18,32,35,48,51,57). Different procedures have been employed to try to circumvent the motor dysfunction produced by neuroleptics. Some of these procedures have included using different operants, varying the stimulation parameters, using rate-independent measures, and partial reinforcement schedules (32). Others have analyzed response decrement patterns within a test session or compared responding after a neuroleptic to that in extinction (12). The present study addresses some of the problems dissociating reward from performance effects of drugs by using a reward-summation procedure under fixed-interval (FI) reinforcement. FI self-stimulation permits a microanalysis of drug-induced changes compared to rats responding under continuous reinforcement (20,21,36,46).

The effect of a drug can be evaluated over a range of

[1] Requests for reprints should be addressed to Glenn E. Hunt, University of Sydney Clinical Sciences Block, Department of Psychiatry, Concord Hospital, Concord, New South Wales, 2139, Australia.
[2] Present address: Research Laboratories, Astra Alab AB, Södertäje, Sweden.

responding using brain stimulation because the experimenter can control the amount of stimulation per reinforcement. Plotting the behavioral output for a given level of stimulus input results in a reward-summation function (48). It is claimed this procedure permits the dissociation of changes in the rewarding value of the stimulus from changes in performance (16,17,32,49). However, this paradigm still relies on an uncontaminated response measure to quantify changes in reinforcement magnitude. Using a reward-summation paradigm under continuous reinforcement does not solve the intrinsic problems with this schedule because higher rates increase the number of reinforcements per unit time. This means that there is a greater contribution in responding from priming and stimulation aftereffects at the upper end of the curve where the interreinforcement interval is short, compared to the lower end where the interreinforcement interval is long.

The present study examines the effect of drugs on reward-summation by trading off frequency and train duration. In a previous study using this paradigm, lowering stimulation frequency produced parallel shifts in the reward-summation curve (21). Clonidine decreased, whereas amphetamine increased, self-stimulation by shifting the reward-summation curves in opposite directions. Thus, a change in reward was indicated by parallel shifts in the curves. In contrast, the inhibition produced by pimozide produced a flat reward-summation curve, which suggests a performance effect.

The purpose of the present series of experiments was to investigate the effects of selective D_1 and D_2 agonists and antagonists on self-stimulation to assess their involvement on reinforcement processes. The D_1 agonist SKF 38393 (47) and the D_2 agonist bromocriptine were used to assess the effects of dopamine agonists, and the D_1 antagonist SCH 23390 (23) and the D_2 antagonist spiperone were used to assess the effects of dopamine antagonists in the same rats so that their effects could be more easily compared. Due to the functional interaction between dopamine D_1 and D_2 receptors (7,37,45), the two agonists and the two antagonists were combined to test for drug interactions. All testing was completed using a reward-summation procedure under a FI 20-s schedule of reinforcement.

METHOD

Subjects, Surgery, and Histology

Nine male Wistar rats were implanted with 254-μm-diameter monopolar electrodes aimed at the medial forebrain bundle of the lateral hypothalamus as previously described (20). The rats were housed individually in a temperature-controlled room (20°C) and had free access to food and water. All testing was completed during light hours of a 15 L : 9 D cycle. At the conclusion of the experiments, electrode sites were verified using a histology procedure as previously described (20).

Procedure

Rats were run twice weekly using a reward-summation model that has been described and calibrated elsewhere (21). The first test session for each week was used to check for baseline stability and the second was used for drug effects. The square-wave cathodal pulses were delivered under a FI 20-s schedule of reinforcement. The pulse width (200 μs) and amplitude (individually determined, range 150–250 μA) for each rat remained constant throughout the experiment. The reward-summation procedure consisted of testing the rats under different combinations of frequency and train duration. Each session consisted of at least nine blocks of 30 trials in which train duration was adjusted to deliver a fixed number of pulses per reinforcement at 100 and 200 Hz. The six train durations that produced 10, 20, 30, 50, 100, and 200 pulses per reinforcement at 100 Hz were 0.1, 0.2, 0.3, 0.5, 1.0, and 2.0 s. The three train durations that produced 20, 50, and 100 pulses per reinforcement at 200 Hz were 0.1, 0.25, and 0.5 s. During the testing of high doses of dopamine antagonists, an extra block of trials was conducted using 1.0-s duration at 200 Hz. During the testing of the dopamine agonists, an extra block of trials was investigated with the stimulator turned off to examine extinction (0 pulse condition). The first 10 trials in each 30-trial block were considered warm-up and were not included in the analysis. The blocks of trials were arranged so that the rats received either 100 or 200 Hz of ascending or descending pulse number followed immediately by ascending or descending pulses of the other frequency. Every 3 weeks the order of presentation was changed for each rat and counterbalanced for drug effects.

The apparatus was programmed so that in the event of a rat not pressing the lever within 60 s, the stimulation was automatically delivered. If the rat did not complete the 30 reinforcements for a condition within 20 min, the trial was stopped, the data were saved for subsequent analysis, and the next block using different stimulation parameters was commenced.

Drugs

All drugs were injected IP at volumes of 1.0 ml/kg b.wt. and spaced 1 week apart. All the drugs were injected 30–60 min prior to testing except for bromocriptine, which was injected 90 min prior to testing. The drugs and dose order were randomized within each of the parts outlined below. All doses refer to the salt.

Dopamine Antagonists

In the first part of this experiment, nine rats received three doses of the D_1 antagonist SCH 23390 (0.005, 0.010, 0.020 mg/kg) and three doses of the D_2 antagonist spiperone (0.010, 0.020, 0.050 mg/kg). Saline was used as a control. Because both SCH 23390 and spiperone can also block 5-HT_2 receptors (3), the 5-HT_2 antagonist ketanserin (1 mg/kg) was used for comparison (15). These rats also received domperidone (2.5 mg/kg), a peripheral D_2 antagonist that does not readily cross the blood-brain barrier (5). To investigate the possible interaction between D_1 and D_2 antagonists, two doses of SCH 23390 (0.005, 0.020 mg/kg) were combined with two doses of spiperone (0.010, 0.020 mg/kg). All of the rats received all of the above treatments, except rat 238 did not receive 0.05 mg/kg of spiperone. All the drugs were given in randomized order and the doses were selected from previous studies using spiperone (55), SCH 23390 (39), ketanserin (33), and domperidone (29).

After completing part 1, the same rats were given amphetamine (0.5 mg/kg) alone and combined with SCH 23390 (0.005 and 0.020 mg/kg). The dose of amphetamine was selected from a previous study (21).

SCH 23390 maleate (Schering Corporation, Keniworth, NJ) was dissolved in 0.01% tartaric acid and spiperone (Janssen Pharmaceutica, Beerse, Belgium) was dissolved in a few drops of glacial acetic acid and the solution was diluted in 0.01% tartaric acid. Ketanserin tartate (Janssen Pharmaceutica) was dissolved in 0.1% tartaric acid, domperidone (Jans-

sen Pharmaceutica) was dissolved in 0.4 M lactic acid, and *d*-amphetamine sulfate (Faulding, Adelaide, Australia) was dissolved in saline.

Dopamine Agonists

In the next part, eight rats were given saline, the D_1 agonist SKF 38393 (5 mg/kg), the D_2 agonist bromocriptine (5 mg/kg), and the combination of SKF 38393 (5 mg/kg) plus bromocriptine (5 mg/kg). The doses were selected from previous studies using SKF 38393 (9) and bromocriptine (10,24). The same eight rats given 5 mg/kg SKF 38393 also received 0.5 mg/kg amphetamine and the combination of amphetamine plus SKF 38393. In the last part, six rats previously given 5 mg/kg bromocriptine and amphetamine also received bromocriptine (10 mg/kg) and the combination of bromocriptine (5 mg/kg) plus amphetamine (0.5 mg/kg).

SKF 38393 HCl (Research Biochemicals, Natick, MA) was dissolved in 0.01% ascorbic acid and bromocriptine mesylate (Sandoz, Sydney, Australia) was dissolved in 0.1% tartaric acid.

Analysis

Response measures included lever-press rate (responses per minute), the postreinforcement pause (in seconds), and the percentage of responding within each quartile of the interreinforcement interval. These measures have been fully described elsewhere (20,21,36). The index of curvature was calculated from the distribution of responding within the interreinforcement interval using the method described by Fry et al. (14). This index expresses the FI response pattern that is independent of response rate.

The data were analyzed in two stages. The first stage used a three-factor ANOVA with repeated measures on all factors. The three factors were treatment (drug/dose), stimulation frequency (100 and 200 Hz), and number of pulses per reinforcement (20, 50, and 100 pulses). These three pulse numbers were chosen because the response rates usually increase in a linear manner at this portion of reward summation curve and they are spaced 0.3 log units apart. This analysis is useful to assess overall treatment effects on FI performance and to compare the effects of drugs on the slopes of the reward-summation curves (21). Post hoc tests on differences between pairs of means used the Newman-Keuls method. Probability levels less than 0.05 were considered to be significantly different.

The second part of the analysis used nonlinear regression analysis to calculate the number of pulses required for each rat to maintain half-maximal rate (locus of the rise) as described by Coulombe and Miliaressis (8). The advantages of this method are that all of the data points are included in the nonlinear model instead of selecting only a portion of the curve for a linear type of fit. The model used the sigmoidal equation of Gompertz [rate = A * exponential(−exponential(B − C * pulses per reward))] to estimate three parameters that characterize the line of best fit. The constant A represents the maximal response rate, B is related to the intercept of the curve with the y axis, and C is related to the rate at which y increments. The locus of the rise was calculated for each rat and treatment-frequency combination by taking the log(10) of $\{B + 0.3665\}/C$ (8). The SYSTAT (Evanston, IL) statistical package was used for the nonlinear regression analysis (56). Changes in maximal and half-maximal rates from saline/vehicle were assessed by ANOVA with repeated measures.

RESULTS

Histology

Histological analysis of the brains of the nine rats indicated that all of the electrode tips were located within the boundaries of the medial forebrain bundle. Because there was no indication of any anatomical differentiation within treatment effects, all the data for each treatment effect were pooled for analysis.

SCH 23390 and Spiperone

Both dopamine antagonists decreased FI 20-s response rates whereas ketanserin (1 mg/kg) and domperidone (2.5 mg/kg) had no significant effects. Although both antagonists inhibited self-stimulation, the dose-response curves were different, as were the reward-summation curves (Figs. 1 and 2, bottom panels).

The SCH 23390 dose-response curve showed a progressive

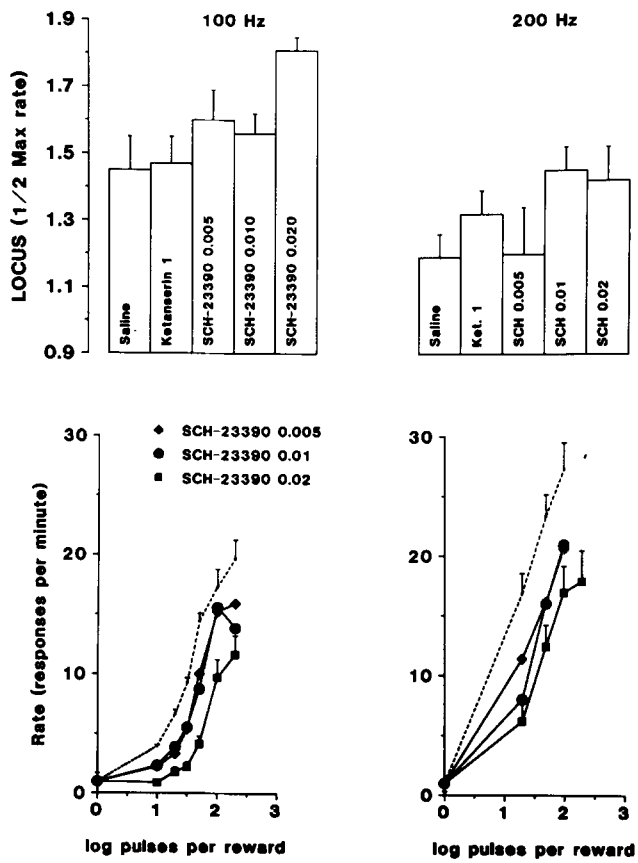

FIG. 1. Effects of SCH 23390 and ketanserin on self-stimulation rates under FI 20-s reinforcement. Top panels show the locus of the rise for each treatment at 100 Hz (left) and 200 Hz (right). An increase in the locus of the rise [defined as the number of (log) pulses required to reach half-maximal rate] indicates a decrease in the rewarding aspects of the stimulation. Vertical bars in this and subsequent figures represent 1 SEM. Bottom panels: effects of SCH 23390 on reward summation (n = 9). Dotted lines in this and subsequent figures indicate saline values. Train duration was traded off with frequency to deliver 10, 20, 30, 50, 100, or 200 pulses per reward at 100 Hz (left) or 20, 50, 100, and 200 pulses at 200 Hz (right).

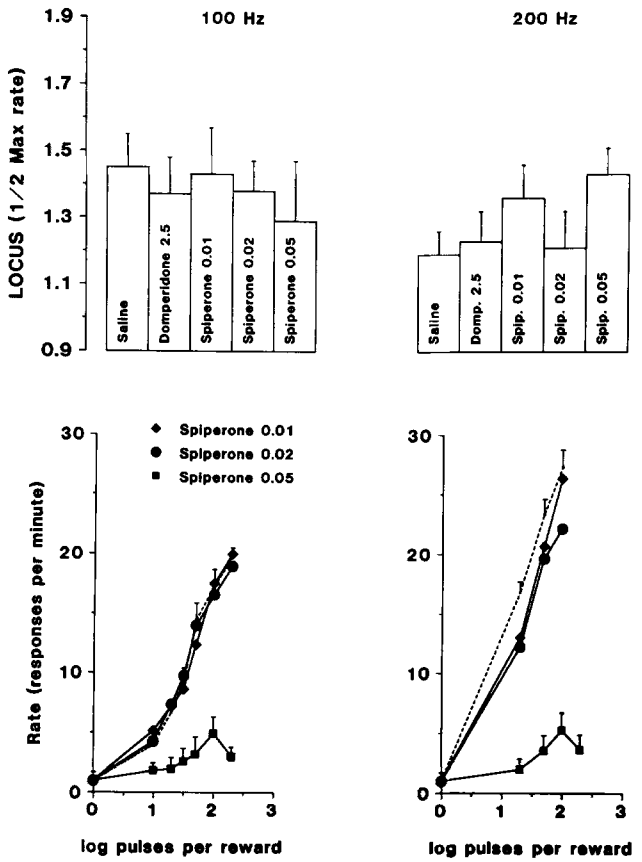

FIG. 2. Effects of spiperone and domperidone on self-stimulation rates under FI 20-s reinforcement. Top panels show locus of the rise for each treatment at 100 Hz (left) and 200 Hz (right). The locus of rise could not be calculated for 0.05 mg/kg spiperone for three rats at 100 Hz and two rats at 200 Hz because they did not lever press at all under any condition. Bottom panels: effects of spiperone on reward summation at 100 Hz (lower left) or 200 Hz (lower right panel) (n = 9).

inhibition of responding between 0.005 and 0.02 mg/kg (Fig. 1, bottom panels). In contrast, the spiperone dose-response curve was very abrupt. There was no significant difference between saline and 0.010 or 0.020 mg/kg spiperone, whereas 0.050 mg/kg virtually eliminated responding (Fig. 2, bottom panels). Visual inspection of the cumulative recordings showed that some of the rats lever pressed normally when first placed in the test chamber after 0.05 mg/kg spiperone. However, after a short time (typically within 10 reinforcements), responding ceased even at higher stimulation inputs.

Results from the three-factor ANOVA revealed that the inhibition of responding produced by SCH 23390 was partially reversed by delivering more pulses per reinforcement or doubling the stimulation frequency. There were no significant differences in the two-way interaction terms between treatment (TR) and frequency (Freq) or treatment and pulse number (PN) after SCH 23390 [$F(3, 24) = 0.511$ and $F(6, 48) = 2.108$, respectively]. In contrast, both interaction terms (TR × Freq and TR × PN) were significantly different after spiperone [$F(3, 23) = 6.32$, $p < 0.005$, and $F(6, 46) = 7.44$, $p < 0.001$]. This reflects the nonparallel slopes between 0.05 mg/kg spiperone and the three other slopes. These differences between SCH 23390 and spiperone indicate that changes in stimulus input differentially affected responding. The inhibition produced by SCH 23390 was surmountable by increasing stimulation input, whereas the inhibition following the high dose of spiperone was not surmountable by increasing stimulation input.

Results from the nonlinear regression analysis revealed that 0.02 mg/kg SCH 23390 significantly increased the locus of the rise at both frequency conditions (Fig. 1, upper panels). The shift of 0.3 log units at 100 Hz indicates that 0.02 mg/kg SCH 23390 produced a specific inhibition of reward. However, it should be noted that the reward-summation curve and locus of rise were not significantly different between 0.02 mg/kg SCH 23390 at 200 Hz (1.42 log pulses) and saline at 100 Hz (1.45 log pulses). Figure 3 further illustrates that the inhibition of self-stimulation produced by 0.02 mg/kg SCH 23390 at 100 Hz could be surmounted by doubling stimulation frequency. Moreover, the reward summation curve at the higher frequency following SCH 23390 was nearly identical to baseline responding at 100 Hz for the same number of pulses per reinforcement. The close similarity of these trade-off functions suggests that SCH 23390 decreased the rewarding value of the stimulation by 50%.

In contrast to SCH 23390, the reward-summation curve after 0.05 mg/kg spiperone was flat, indicating a nonspecific effect of this dose of spiperone on self-stimulation (Fig. 2). Smaller doses of spiperone or 2.5 mg/kg domperidone did not significantly affect the locus of the rise.

In addition to decreasing rate of responding, the microanalysis showed that SCH 23390 (0.01 and 0.02 mg/kg) and spiperone (0.05 mg/kg) increased the postreinforcement pause and decreased the percentage of responding in the third quartile of the interreinforcement interval (data not shown). In

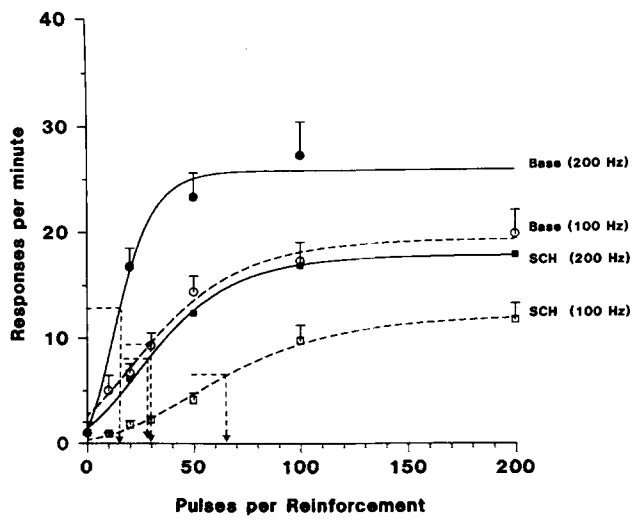

FIG. 3. The effect of 0.02 mg/kg SCH 23390 (squares) on reward summation compared to baseline responding (circles). Each point represents the mean of nine rats. Reward summation curves were constructed by plotting mean response rate against number of pulses per reinforcement using nonlinear regression analysis (see the Method section for more detail). Horizontal dotted lines indicate half-maximal rate and the vertical dotted lines dropped to the absissa represent locus of the rise. The locus of rise is the number of pulses required to reach half-maximal rate and is a measure of the reward value of the stimulation.

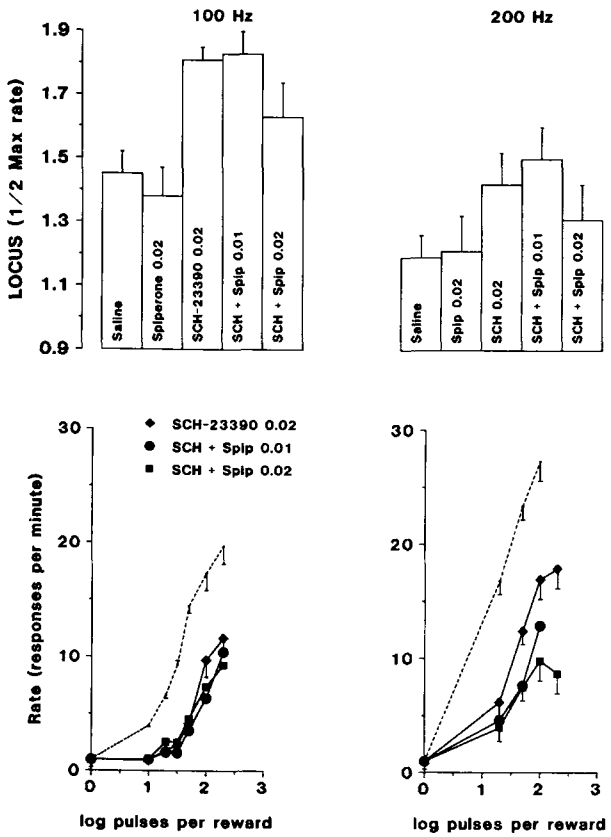

FIG. 4. Effects of SCH 23390 combined with spiperone on self-stimulation rates under FI 20-s reinforcement. Top panels show the effect of 0.02 mg/kg SCH 23390 alone and after coadministration of spiperone (0.01, 0.02 mg/kg) on locus of the rise (n = 9). Bottom panels show the reward-summation curves for the three treatments at 100 Hz (left) and 200 (Hz). Data are not shown for a lower dose of SCH 23390 (0.005 mg/kg) combined with spiperone (0.01, 0.02 mg/kg) because there were no significant differences between SCH 23390 given alone compared to when it was combined with spiperone.

several cases after 0.050 mg/kg spiperone, the postreinforcement pause exceeded 60 s, in which case the brain stimulation was initiated automatically. In two rats the locus of the rise could not be determined after the high dose of spiperone because they did not respond even at 1-s trains at 200 Hz. The low percentage of responding in the first two quartiles of the interreinforcement interval after SCH 23390 and spiperone and the longer postreinforcement pauses suggest that the inhibited responding was still under FI schedule control.

The next part of this experiment examined the effects of combining SCH 23390 (0.005, 0.020 mg/kg) with two low doses of spiperone (0.010, 0.020 mg/kg). These doses of spiperone had no significant effect on FI self-stimulation. There were no significant differences between 0.005 mg/kg of SCH 23390 and the rates after the addition of either dose of spiperone (mean rate for TR block = 13.1 responses/min for SCH 23390 by itself compared to 11.1 and 10.6 with the addition of spiperone). There was a significant difference in overall response rates between 0.02 mg/kg SCH 23390 given separately (8.5 responses/min) and when combined with 0.01 and 0.02 mg/kg spiperone [6.0 and 5.8 responses/min, $F(2, 16) = 5.15$, $p < 0.05$]. The higher dose combination decreased the maximal response rates at 200 Hz compared to SCH 23390 alone (Fig. 4, bottom right panel). Neither dose of spiperone further increased the locus of rise when combined with SCH 23390 (Fig. 4, upper panels). However, it is important to note that the combination of 0.02 mg/kg of spiperone and 0.02 mg/kg SCH 23390 did not mimic the blockade produced by 0.050 mg/kg of spiperone (Fig. 2) because responding increased as more pulses were delivered per reinforcement (Fig. 4, lower panels).

SCH 23390 and Amphetamine

Figure 5 shows the effect of combining a low dose of amphetamine (0.5 mg/kg) with SCH 23390 (0.005, 0.020 mg/kg) on self-stimulation. This dose of amphetamine produced a mild facilitation of self-stimulation compared to saline controls, as evidenced by the decrease in the locus of the rise. There was a competitive interaction between SCH 23390 and amphetamine. SCH 23390 dose-dependently blocked the facilitation of amphetamine and, conversely, amphetamine lowered the number of pulses required to maintain half-maximal responding (locus of the rise) compared to when SCH 23390 was given alone. The repeated-measures ANOVA revealed a significant treatment effect between amphetamine and amphetamine plus 0.005 and 0.02 mg/kg SCH 23390, $F(2, 16) = 68.57$, $p < 0.001$. The mean response rate for the treatment block after amphetamine was 19.3 responses/min com-

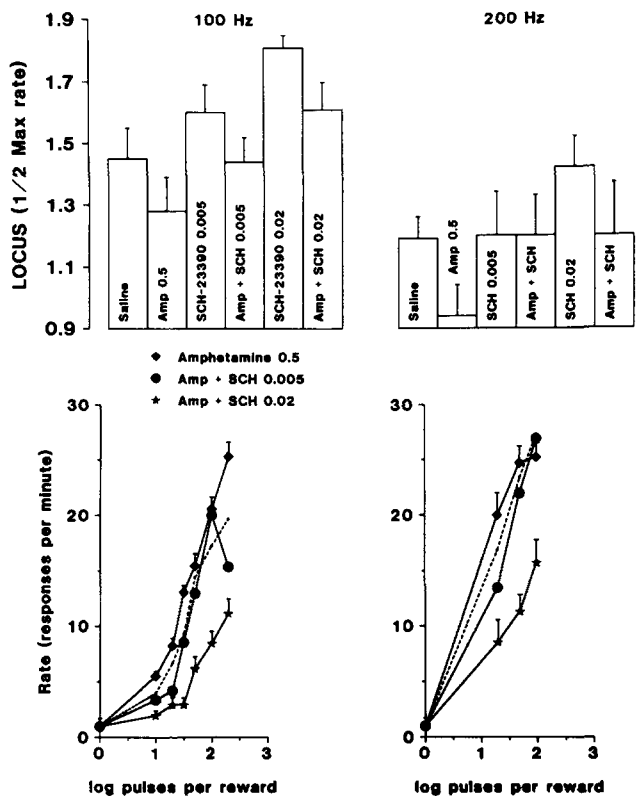

FIG. 5. Effects of SCH 23390 and amphetamine (Amp) on FI 20-s self-stimulation compared to saline responding on locus of the rise (upper panels) and reward summation (lower panels). Amphetamine (0.5 mg/kg) reversed the inhibition after 0.005 mg/kg SCH 23390 but did not reverse the inhibition after 0.020 mg/kg SCH 23390.

pared to 16.6 and 8.8 responses/min following the two doses of SCH 23390. Amphetamine did not significantly reverse the inhibition of self-stimulation produced by the higher dose of SCH 23390 when given by itself (Fig. 5 and Fig. 1).

SKF 38393 and Bromocriptine

Figure 6 shows the effects of the D_1 agonist SKF 38393, the D_2 agonist bromocriptine, and their combination on FI response rate compared to saline. When given separately, SKF 38393 (5 mg/kg) decreased responding and bromocriptine (5 mg/kg) had little effect. Neither drug significantly shifted the locus rise. The lower panels of Fig. 6 show that responding during extinction (0 pulse condition) was increased after bromocriptine compared to saline controls. When equal doses of the agonists were coadministered, the rates were not significantly different from those after SKF 38393 alone. Results from the ANOVA revealed a significant treatment effect, $F(3, 21) = 4.95$, $p < 0.01$. Compared to saline rates (17.4 responses/min), SKF 38393 lowered responding (10.2), but there was no significant change with the addition of bromocriptine (11.8 responses/min). Neither agonist alone nor the combination significantly affected the postreinforcement pause or index of curvature, suggesting that the responding was still under schedule control.

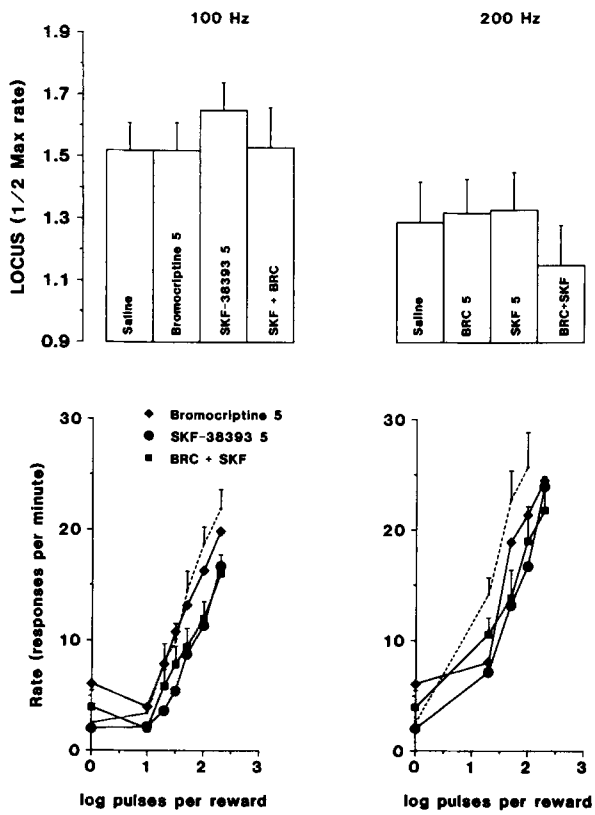

FIG. 6. Effects of SKF 38393, bromocriptine, and their combination on FI 20-s self stimulation compared to saline responding on locus of the rise (upper panels) and reward summation (lower panels). Eight rats received saline, the D_1 agonist SKF 38393 (SKF) (5 mg/kg), the D_2 agonist bromocriptine (BRC) (5 mg/kg), or their combination (SKF + BRC). SKF was given 30 min and BRC was given 90 min before testing. Extinction trials (0 pulses) were conducted with the stimulators turned off.

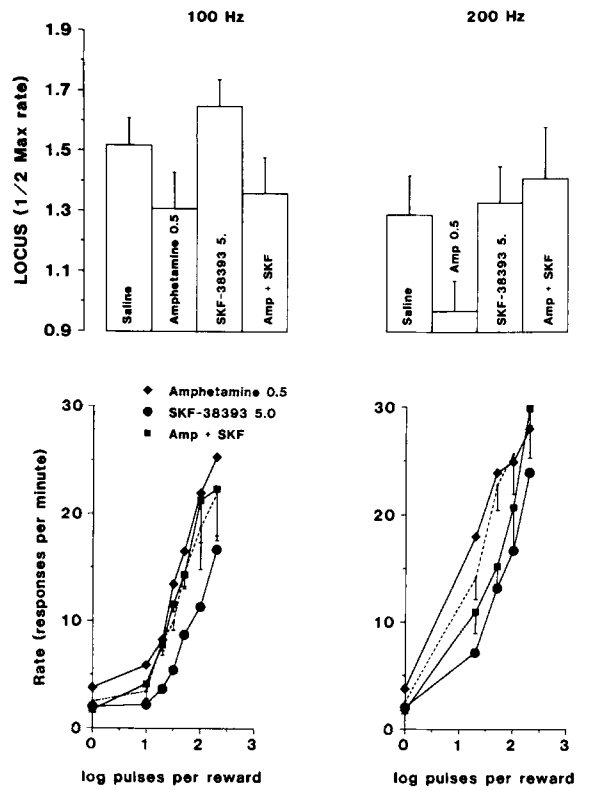

FIG. 7. Effects of amphetamine, SKF 38393, and their combination on FI 20-s self stimulation compared to saline responding on locus of the rise (upper panels) and reward summation (lower panels). Eight rats received saline, amphetamine (AMP) (0.5 mg/kg), SKF 38393 (5 mg/kg), or SKF 38393 plus amphetamine (SKF + AMP) 30 min prior to testing.

Although there was no significant interaction when 5 mg/kg of each drug was coadministered, a higher dose of bromocriptine (10 mg/kg) combined with SKF 38393 (5 mg/kg) produced marked stereotyped behavior in six rats (data not shown). The rats did not approach the lever for up to 2 h, even after priming or hand shaping. Moreover, the rats did not lever press even if placed in front of the lever on continuous reinforcement. The competitive nature of the stereotyped behavior (slow circling, intense sniffing, and licking) produced by this agonist combination suggests that rats lacked coordinated movement required to lever press.

SKF 38393 and Amphetamine

Figure 7 illustrates the effect of SKF 38393 (5 mg/kg) when combined with amphetamine (0.5 mg/kg). The reward-summation curves show that amphetamine fully restored the inhibition of responding produced by SKF 38393 at 100 Hz stimulation (lower left panel) and partially restored responding for 200 Hz stimulation (lower right panel). None of the treatments significantly increased responding during extinction (0 pulses) above saline controls.

Bromocriptine and Amphetamine

Figure 8 illustrates the effect of bromocriptine (5 and 10 mg/kg), amphetamine (0.5 mg/kg), and the coadministration

of 5 mg/kg of bromocriptine plus amphetamine. The higher dose of bromocriptine or the combination of bromocriptine plus amphetamine produced an extraordinary facilitation of lever pressing. After the higher dose of bromocriptine (10 mg/kg), most of the rats were postured over the lever and pressed continuously over the entire test session. In one rat the combination of bromocriptine plus amphetamine produced marked stereotyped sniffing, licking, and turning that interfered with responding. Consequently, this rat did not lever press over the entire test session. This contrasts with another rat that continuously pressed at a rapid rate over the entire session after this combination.

The lower panels of Fig. 8 show the reward-summation curves after two doses of bromocriptine and the bromocriptine-amphetamine combination. Although responding increased as more pulses were delivered after all three drug treatments, the high rates during extinction (0 pulses) casts doubt on the interpretation of the reinforcing value of the stimulus after 10 mg/kg bromocriptine or the combination of 5 mg/kg bromocriptine plus amphetamine. The high rates after these two treatments during extinction suggests that responding was

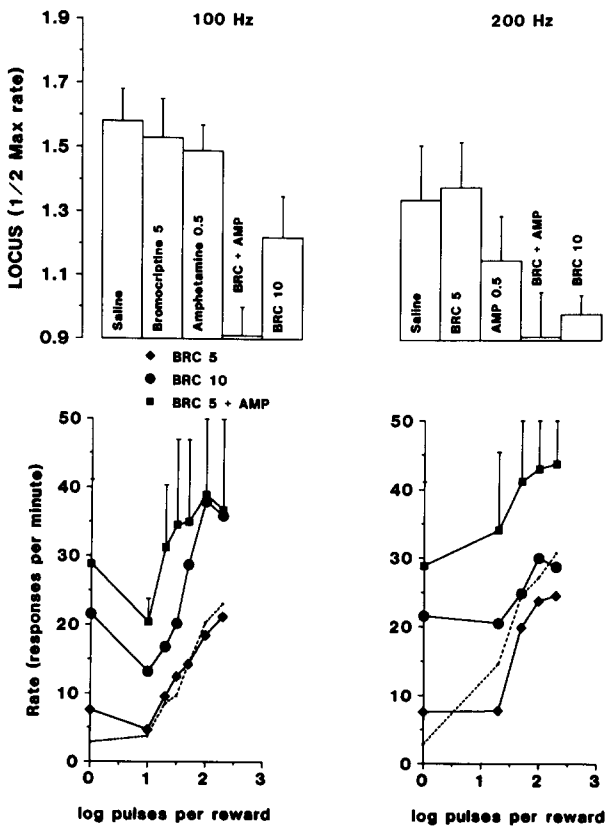

FIG. 8. Effects of bromocriptine, amphetamine, and their combination on FI 20-s self stimulation compared to saline responding on the locus of rise (upper panels) and reward summation (lower panels). Six rats received saline, amphetamine (AMP 0.5 mg/kg), bromocriptine 5 mg/kg (BRC 5) and 10 mg/kg (BRC 10), and amphetamine plus 5 mg/kg bromocriptine (BRC + AMP). Bromocriptine was injected 90 min and AMP 30 min prior to testing. Note the high response rates during extinction for BRC 10 and the BRC 5 + amphetamine combination.

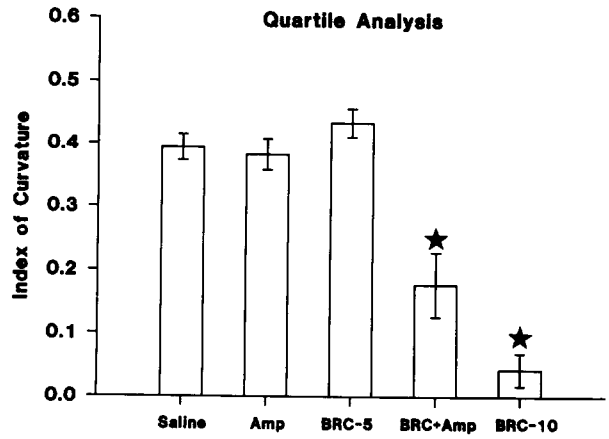

FIG. 9. The effects of bromocriptine, amphetamine, and their combination on the index of curvature (n = 6). This index reflects the pattern of responding over the fixed interval. A curvature value of zero indicates that responding was constant over the interval. Each value was averaged over six conditions (20, 50, and 100 pulses per reinforcment at 100 Hz and 200 Hz). Stars indicate values significantly different from saline control ($p < 0.05$, Newman-Keuls).

no longer under schedule control or contingent on the stimulation.

Extinction rates for several rats were so high after these two treatments that they were sometimes higher than baseline responding when the stimulation was at its maximal. These rats continued to lever press even when the leads were disconnected from the electrode connectors by the experimenter. To test the rats' ability to approach the lever, the rats were occasionally removed from the lever and placed at the opposite end of the chamber. The rats slowly returned to the lever and began pressing again even though the stimulation was not available. This preservation of lever pressing contrasts with the stereotyped movements and no responding described previously when 5 mg/kg of SKF 38393 was combined with 10 mg/kg of bromocriptine.

The unusual response pattern after 10 mg/kg bromocriptine or the combination of 5 mg/kg bromocriptine and amphetamine was most apparent in the distribution of responding in the interreinforcement interval. Normally, the percentage of responding is less than 10% in the first two quartiles. The percentage of responding was significantly higher in the first two quartiles after 10 mg/kg of bromocriptine (>20%) and after the combination of amphetamine plus 5 mg/kg of bromocriptine (15–20%). Figure 9 shows that the index of curvature was decreased by these two treatments. The low values indicate that response rate was almost constant over the fixed interval, which suggests that lever pressing was no longer under FI schedule control.

DISCUSSION

The present series of experiments demonstrates that low doses of centrally active dopamine antagonists have large effects on lateral hypothalamic self-stimulation under FI reinforcement. The D_1 antagonist SCH 23390 (23) produced dose-dependent decreases in FI response rates. The doses of SCH 23390 (0.01, 0.02 mg/kg) that inhibited self-stimulation are lower than those shown to decrease locomotor activity (19) or produce catalepsy (6,50). This inhibition was partially sur-

mounted by increasing stimulation frequency or delivering more pulses per reinforcement. This suggests that the inhibition of self-stimulation produced by SCH 23390 represents an inhibition of the reinforcing effects of the stimulation and not a performance deficit.

In contrast, the dose of spiperone (0.050 mg/kg) that inhibited self-stimulation has been shown to decrease rearing in an open field test, inhibit amphetamine-induced gnawing, and produce mild catalepsy (25,53). The dose of spiperone that inhibited FI self-stimulation in this study is similar to the dose (0.040 mg/kg) that decreases self-stimulation using continuous reinforcement (55). Although a dose of spiperone between 0.02 and 0.05 mg/kg may have produced a specific decrement in reward summation, the inhibition following 0.05 mg/kg spiperone could not be surmounted by increasing stimulation frequency or train duration over the wide range of values tested (10–200 pulses per reinforcement). These results are similar to findings using another dopamine D_2 antagonist, pimozide (21). Pimozide produced a very steep dose–response curve and the inhibition after a low dose (0.25 mg/kg) produced a flat reward–summation curve. Thus, unlike the D_1 antagonist SCH 23390, the inhibition of self-stimulation produced by D_2 antagonists could well be due to impaired motor performance. This is consistent with previous studies showing that D_2 antagonists decrease self-stimulation and inhibit numerous other operant, exploratory, and appetitive behaviors (1,11,57,58).

The doses of SCH 23390 required to inhibit self-stimulation are well below those required to block central 5-HT_2 receptors (3). Moreover, the present study shows that ketanserin, a 5-HT_2 antagonist (15), has no significant effect on self-stimulation. This is consistent with other studies demonstrating that 5-HT_2 antagonists do not affect self-stimulation (13,39). Thus, given the selective receptor binding profile of SCH 23390 (6), it seems likely that SCH 23390 inhibits reinforcement by blocking D_1 receptors.

These findings confirm and extend previous self-stimulation studies using continuous reinforcement (9,39,40). Other studies have reported that SCH 23390 also decreases responding for food, water, and saccharin (2,38). This suggests either that there may be a unitary system mediating diverse types of reinforcement or that there is, at least, a common D_1-mediated element of reinforcers (7,37).

To further explore the interaction between D_1 and D_2 receptors, two doses of spiperone (0.010 and 0.020 mg/kg) that did not significantly affect self-stimulation were combined with 0.005 or 0.020 mg/kg of SCH 23390. Combining the two antagonists produced additive effects, but no combination mimicked the inhibitory effect produced by a higher dose of spiperone (0.05 mg/kg).

The present study showed that SCH 23390 can block amphetamine's facilitation of self-stimulation. These data are in agreement with other studies showing that SCH 23390 blocks amphetamine self-administration, conditioned place preference, drug discrimination, and its enhancement of motility (27,28,31,45). They also show that amphetamine can reverse the inhibitory effects of low doses of SCH 23390. This is in agreement with the finding that blockade of dopamine uptake can also reverse the inhibitory effects of SCH 23390 on self-stimulation (44).

The selective D_1 agonist SKF 38393 (47) inhibited self-stimulation, whereas 5 mg/kg of the D_2 agonist bromocriptine had little effect. These data are consistent with previous reports showing that SKF 38393 decreased (9,40) and bromocriptine had no effect on self-stimulation (10). One reason why SKF 38393 decreased self-stimulation may be that it is classified as a partial agonist and not a full D_1 agonist (7,37,47).

The present study showed that equal doses (5 mg/kg) of the agonists produced additive effects on self-stimulation. The combined effects on self-stimulation were qualitatively similar to the effects produced when the drugs were given individually. In contrast, a higher dose of bromocriptine (10 mg/kg) combined with 5 mg/kg of SKF 38393 produced marked stereotyped behavior that abolished lever-press responding for several hours. The lack of responding cannot be considered as representing a decrement in reinforcement because the rats appeared to lack the coordinated movement needed to lever press.

When combined with amphetamine (0.5 mg/kg), bromocriptine (5 mg/kg) enhanced, whereas SKF 38393 (5 mg/kg) inhibited, self-stimulation. Moreover, a higher dose of bromocriptine (10 mg/kg) by itself or the amphetamine-bromocriptine combination enhanced responding even during extinction testing. However, analysis of FI pattern showed that lever pressing was no longer reinforcement related after 10 mg/kg of bromocriptine or the combination of 5 mg/kg bromocriptine plus amphetamine.

The vigor and persistence of the drug-modified self-stimulation, particularly during extinction, is strongly suggestive of a stereotypy. This is apparent in the dramatically altered temporal and qualitative characteristics of the behavior. However, there is a significant difference between this behavior and the commonly reported stereotypies such as head bobbing, circling, and gnawing such as those observed in this study after 5 mg/kg SKF 38393 was combined with 10 mg/kg bromocriptine. Common stereotypies disrupt operant responding and may be elicited irrespective of the reinforcement history of the animal, whereas stereotyped lever pressing clearly requires a history of being reinforced for lever pressing (41,42). Lever pressing would never be elicited by drugs in a naive animal. This hypothesis requires the assumption that learning modifies the susceptibility of behavior to stereotyping. This is not an unreasonable assumption because stereotypies frequently involve learned behaviors (34,41–43).

Furthermore, the noncontingent responding cannot be easily explained by increased resistance to extinction produced by greatly enhanced reinforcement. The drugged rats lever pressed with largely undiminished vigor after the stimulator was turned off. In some rats, the extinction rates were higher than any produced during undrugged self-stimulation. This would be easily the highest resistance to extinction ever reported in any laboratory species. The vigor of normal operant behavior declines dramatically in extinction. The drugged rats were clearly behaving in a most unusual way. They gave no indication of being able to discriminate between the presence or absence of the brain stimulation.

Leith (30) reported that 0.3 mg/kg of the mixed D_1/D_2 agonist apomorphine increased self-stimulation under continuous reinforcement, but responding was insensitive to changes in current intensity. Others have reported that apomorphine increased self-stimulation in some rats and noted that extinction could not be demonstrated as long as the drug was active (4,52). Moderate to high doses of the D_2 agonists quinpirole and CV 205-502 produced motor deficits at high-frequency stimulation, and a continuation of steadily paced responding when the stimulators were turned off (40). A similar profile for 10 mg/kg of bromocriptine was observed in this study under FI reinforcement. These data indicate that D_2 agonists like bromocriptine or mixed D_1/D_2 agonists like apomorphine amplify on-going behavior and produce an insensitivity to

changes in the motivational properties of brain stimulation. Thus, responding appears to be unrelated to reinforcement after high doses of apomorphine, bromocriptine, or amphetamine (22,30,52,54,55).

Although there may be several neurochemical explanations for the repetitive behavior following the above drugs, an obvious explanation of the noncontingent responding for brain stimulation is that the receptor activation produced by the drugs may have mimicked that produced by the electrical stimulation. However, this does not address the question of why the rats continued to lever press if the electrical stimulus was made redundant by the drug. A definitional characteristic of operant behavior is that it is under control of the reinforcer (26). When the behavior becomes irrelevant to producing the reinforcement it should gradually extinguish.

It should be noted that the above discriminations between normal and stereotyped self-stimulation could not be made using continuous or variable-interval reinforcement schedules because they produce temporally uniform responding. The use of a reward-summation paradigm that includes extinction trials along with qualitative and quantitative measures of FI performance greatly increases the power of this approach to distinguish between the different patterns of responding.

In conclusion, the D_1 antagonist SCH 23390 produced a specific decrement in the rewarding aspects of self-stimulation. In contrast, spiperone abolished responding and produced a flat reward-summation curve, suggesting it produced a motor deficit. The inhibitory effect of SCH 23390 was reversed by a low dose of amphetamine but not after a higher dose of SCH 23390. This indicates that part of the facilitation after amphetamine can be attributed to D_1 activity and supports the concept that both receptor subtypes need to be operational, otherwise dopamine neurotransmission is interrupted (37). The partial D_1 agonist SKF 38393 inhibited self-stimulation, and this effect was partly reversed by amphetamine. A high dose of the D_2 agonist bromocriptine increased FI responding, but further analysis showed that lever pressing was no longer under schedule control. A similar profile was observed after a lower dose of bromocriptine was combined with amphetamine. These data indicate that D_2 agonists amplify on-going behavior, but produce an insensitivity to cues that usually signal changes to the motivational properties of brain stimulation, and induce stereotypy behavior so that responding no longer coincides with changes in reinforcement magnitude. The present study supports the concept that dopamine D_1 receptors play a critical role in the modulation of the rewarding component of hypothalamic self-stimulation. However, these data should not be interpreted as excluding a significant role for other receptors or neurotransmitters.

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