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Effects of the Preferential Dopamine Autoreceptor Antagonist (+)-AJ76 in the Intracranial Self-Stimulation Paradigm

TORBEN KLING-PETERSEN[1] AND KJELL SVENSSON

Department of Pharmacology, University of Göteborg, S-400 33 Göteborg, Sweden

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KLING-PETERSEN, T. AND K. SVENSSON. *Effects of the preferential dopamine autoreceptor antagonist (+)-AJ76 in the intracranial self-stimulation paradigm.* PHARMACOL BIOCHEM BEHAV 43(2) 495–501, 1992.—As revealed by locomotor activity experiments in rodents, *cis*-(1*S*,2*R*)-5-methoxy-1-methyl-(2-*n*-propylamino)tetralin [(+)-AJ76] is a preferential dopamine autoreceptor antagonist that produces stimulatory or weak inhibitory behavioral effects in animals that display low or high baseline activity, respectively. In the present study, the possible positive reinforcing properties of (+)-AJ76 were studied by means of the intracranial (median forebrain bundle) self-stimulation (ICSS) technique in rats. The current intensity of the electrical stimuli was used as the independent variable. The resulting rate/intensity curves were analyzed by computer, and the half-maximal response (called EC_{50}) was calculated for each animal. When starting on a suprathreshold current intensity, (+)-AJ76 dose dependently (3.1–52.0 μM/kg, SC) increased the EC_{50} without producing any apparent motor deficits like muscular rigidity or catalepsy. A clear-cut and more potent inhibitory action was also noted for haloperidol (0.033–0.133 μM/kg, SC) and the di-*N*-methyl analog of (+)-AJ76 called (+)-AJ118 (0.8–3.5 μM/kg, SC), while *d*-amphetamine (1.4 or 5.4 μM/kg, SC) decreased the EC_{50} values. In the second experiment, animals were subjected to a subthreshold current intensity for 30 min. The intensity was set to produce a response of 15% or less of maximal, shaping response rate for the respective animals. Of these 22 animals, 10 responded with a stimulation, while the ICSS response was inhibited in the others. We did not, however, get consistent results in all rats tested. In summary, this study shows that (+)-AJ76 appears to lack positive reinforcing properties comparable to those produced by classical stimulants such as *d*-amphetamine.

Intracranial self-stimulation Dopamine Preferential autoreceptor antagonists Baseline activity Positive reinforcement

SCIENTISTS have used the discovery that electrical stimulation of various parts of the brain elicits a powerful response to study catecholaminergic neurotransmission. Today, a fairly large number of techniques have been designed, often combined in the term "intracranial self-stimulation" (ICSS). Even though this technique has been used for more than 30 years, it has not received the attention once predicted (18). One explanation might be the debate over which neural system mediates brain reward: dopaminergic or noradrenergic transmission (9). Lately, scientists also question whether 5-hydroxytryptamine (5-HT) is involved (5). A further complication of this issue is that many different parts of the brain give rise to ICSS: the medial forebrain bundle (MFB) at the level of the lateral hypothalamus (25), the mecencephalic central gray (15), the ventral noradrenergic bundle (21), the ventral tegmental area (30), and several other locations in the brain. The MFB gives rise to a high degree of self-stimulation and the fact that it is a large structure within easy reach makes it an ideal target for ICSS.

A major problem with ICSS is the interpretation of the animal's response. Is the lever-pressing rate proportional to the reward value of the stimulation? Is a given drug affecting the motor response of the rat or is a change in lever-pressing rate a result of the drugs intrinsic value [see (14,19,28) for discussion]? The general consensus is that the assessment of reward should be determined through a rate-independent method (33). This can be accomplished by means of a method that eliminates the possible motor effects of a drug through an analysis of an independent parameter like threshold values. This could be achieved either by examining direct animal responses (10,13,17), by letting the animal decide for itself using the "autotitration model" (24) or an automated method for establishing an ED_{50} or "locus of rise" (1,31), or by the "Campbell broken line technique" (4). The method we employed is

[1] Requests for reprints should be addressed to Torben Kling-Petersen, Department of Pharmacology, University of Göteborg, P.O. Box 33031, S-400 33 Göteborg, Sweden.

based upon computer analysis of the raw data (see below). The left shift of sigmoidal curves (rate of responding vs. current intensity, ranging from a suprathreshold to a subthreshold intensity), indicates an increase in brain self-stimulation. A right shift indicates a subsequent decrease in stimulation. A saline rate-intensity curve is used as control.

There are, however, situations where a rate-dependent measure of reward could be used. At suprathreshold current intensities, that is, upper asymptote of a rate–intensity curve, maximal activation of the dopamine (DA) system by the drug would disrupt the contingency relationship and result in less responding. Correspondingly, at subthreshold intensities a drug that produces activation of the DA system should summate with the electrical stimulation, thereby converting that intensity into a suprathreshold value, resulting in an increase in responding (14).

cis-(+)-5-Methoxy-1-methyl-2-(*n*-propylamino)tetralin [(+)-AJ76] is a DA receptor antagonist with a preferential action on the autoreceptors (26). In contrast to classical neuroleptics, (+)-AJ76 does not produce hypomotility or catalepsy. In behavioral studies, the compound increases locomotor activity over a wide dose range. The stimulation is particularly pronounced in animals that are habituated to the activity meters (26). In vivo brain microdialysis experiments in the rat show that (+)-AJ76 increases the release and synthesis of dopamine (32). In animals pretreated with apomorphine or *d*-amphetamine, (+)-AJ76 blocks the hyperactivity down to, but not below, saline control levels (26,27). (+)-AJ76 was shown to be positive in the conditioned place preference paradigm (27); however, it is not self-administered in rats and it only partially generalizes to the cocaine discrimination cue (11). Thus, (+)-AJ76 seems to have a "normalizing" effect on animal behavior and produces a stimulation or an inhibition if the baseline activity is low or high, respectively (26).

Recently, a new DA receptor (D_3) was described (23). This receptor appears to have high density in the limbic brain areas. Interestingly, (+)-AJ76 and its di-*n*-propyl analog, (+)-UH232, were the only compounds with a higher preference for D_3 vs. D_2 receptors in a series of both classical and atypical DA antagonists tested (23). The functional role of the D_3 receptor remains to be elucidated.

The present study was aimed at investigating the possible positive reinforcing properties of (+)-AJ76 by means of ICSS. For reference purposes, we included *d*-amphetamine, haloperidol, and *cis*-(+)-(1*S*,2*R*)-1-methyl-5-methoxy-2-(dimethylamino)tetralin [(+)-AJ118]. Although (+)-AJ118 has a chemical structure similar to (+)-AJ76, the biologic profile is that of a classic DA receptor antagonists, that is, it induces strong hypomotility and catalepsy in rodents (12).

METHOD

Animals

Twenty-two male Sprague-Dawley rats (ALAB, Sollentuna, Sweden) were housed in individual, plastic cages with food and water ad lib. The colony was maintained on a reversed dark–light cycle, with the dark period starting 7 a.m. and lasting 12 h. All rats were trained and tested during the dark phase. Rats were allowed at least 2 weeks adaption time before the testing started. At the time of surgery, rats weighed from 270–390 g. A mixture consisting of ketamine (100 mg/kg) and xylazine (5 mg/kg) was administered IP to induce operational anesthesia. Each rat was stereotaxically implanted (in a Kopf instrument) with a bipolar, stainless steel electrode (Model MS 303, Plastic One, Roanoke, VA) insulated except at the tip, and fixed to the skull with two stainless steel screws and dental cement (SweTray). The electrode was lowered to the median forebrain bundle, coordinates from bregma, keeping the skull level between bregma and lambda: anterior, −4.3 mm; lateral, ±1.4 mm; and ventral, −8.7 mm from the skull surface (2). After the conclusion of the experiments, a representative number of the animals were killed and the electrode position was verified using standard histologic procedures (see below).

Self-Stimulation Equipment

Self-stimulation training and testing was performed in a 50 × 28 × 30 cm operant test cage (E10-10, Coulbourn Instruments, Inc., Lehigh Valley, PA) with a metal lever (E21-03, Coulbourn) placed 5 cm above the floor. The test cage was placed in a sound- and light-attenuating box (E10-20, Coulbourn) with ventilation and a weak houselight. The electrical brain stimulation was delivered from an isolated constant-current stimulator (E13-51, Coulbourn) through a two-channel commutator (SL2C, Plastic One). Brain stimulation consisted of cathodal, monophasic square-wave pulses of 200-μs duration. The stimulator shunts the electrode to ground to minimize capacitance build-up. the stimulation was monitored using a standard oscilloscope. Control of the stimulator and operant box was accomplished with an Apple Macintosh IIci computer equipped with an interface card (MIO 16/9 L, National Instruments, Austin, TX). The software was written using object-oriented programming (LabVIEW, National Instruments).

Experimental Procedure

After allowing rats at least 1 week postoperative recovery, they were trained to self-stimulate for a reinforcing stimuli consisting of a 0.3-s burst with a frequency of 100 Hz. The current was initially set at 100 μA and raised gradually in 0.05 log units until reliable self-stimulation was established (normally three to five 30-min training sessions). Reliable self-stimulation was defined as three or more test sessions where the animal's maximal as well as mean rate of response did not differ more than 10% when compared to three consecutive 30-min training sessions).

Experiment 1. The current intensity was lowered in 0.05 log units every third minute during the test session, starting at a suprathreshold level. The first minute of testing at each current intensity level was treated as sample/warm-up period and the data was subsequently discarded. The response for the following 2 min was recorded and the mean rate of pressing for each intensity was calculated. The experiment was stopped when the rat refrained from pressing during a whole 3-min period. The current intensity–response curve for each rat was then subjected to a modified Probit conversion according to Litchfield and Wilcoxon (16) and an EC_{50} value for each rat was calculated. The EC_{50} values were defined as the current intensity required to yield a response rate that is 50% of the maximal response. This is also called the SI_{50} by Liebman (15). A minimum of three EC_{50} measurements on different, but often consecutive, days were collected and used as comparison for the control EC_{50}. Each drug test was preceded by a control EC_{50} determination, and the following day the drug's EC_{50} was calculated. Rats were then allowed a washout period of at least 5 days before the next experiment. The control EC_{50} values were constantly monitored throughout the entire set of experiments and a rat that differed more than

0.05 log units between different control sessions was excluded from further testing.

Experiment 2A. Before the drug tests began, animals were tested two or three times to establish their respective subthreshold current intensities. This intensity was defined as the current intensity yielding approximately 15% or less of maximal response. On control days (normally the 2 days preceding the drug day), animals were administered saline and the number of lever presses were recorded for 30 min. The first 5 min of each 30-min series was treated as warm-up time and subsequently discarded. Animals were injected the following day with drug and tested in the same manner as previously described.

Experiment 2B. Animals were tested on a suprathreshold current, i.e., the same current intensity that produce a maximal response rate in Experiment 1A, and the number of lever presses were recorded for 30 min. The first 5 min of each 30-min series was treated as warm-up time and subsequently discarded. As in Experiment 2A, at least 2 control days preceded the drug test.

Drugs

The following drugs were used: *d*-amphetamine sulfate (Apoteksbolaget AB, Sweden), haloperidol (Janssen Pharmaceutica, Beerse, Belgium), (+)-AJ76 HCl (synthesized by the Upjohn Co., Kalamazoo, MI), and (+)-AJ118 HCL (synthesized by Dr. Anette Johnasson at the Department of Organic

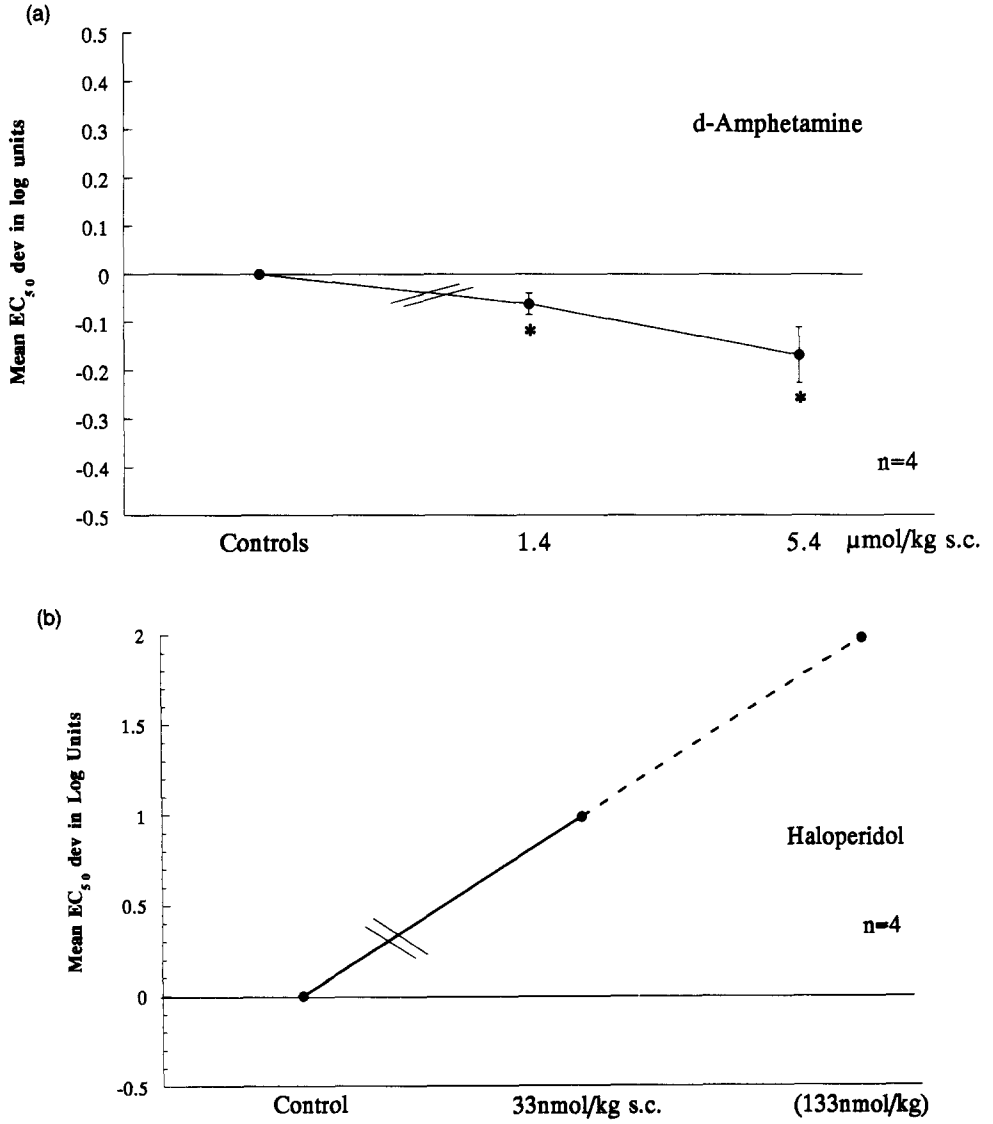

FIG. 1. Effects of compounds on ICSS in the rat. The dose-dependent stimulatory effect of *d*-amphetamine (a) and the inhibition of ICSS by haloperidol is shown as the mean deviation of EC_{50} compared to controls. A left shift of the sigmoidal curve (i.e., stimulation) results in a negative line (*d*-amphetamine) and a right shift results in a positive line (haloperidol). (b) The broken line indicates a rate of responding below 70% of maximal control rate of response and is treated as less reliable results. Haloperidol and *d*-amphetamine were administered SC 15 min prior to testing. Mean ± SEM (n = 4–8). Statistics: ANOVA followed by Fisher's PLSD (*$p < 0.05$ vs. saline-treated animals).

Pharmaceutical Chemistry, University of Uppsala, Sweden) (12). All drugs were dissolved in physiological saline except haloperidol, which was dissolved in minimal quantity of glacial acetic acid and made up to volume in a 5.5% glucose solution. The drugs were administered SC in a volume of 5 ml/kg body weight 15 min before testing.

Statistical Analysis

Statistical comparisons were performed using analysis of variance (ANOVA) followed by Fisher's PLSD test. Probability levels less than 5% were regarded as statistically significant.

Histologic Examination

After completion of the experimental series, animals were killed by an overdose of sodium pentobarbital and subjected to intracardial perfusion with saline followed by a 4% formaldehyde solution. Brains were removed and stored in 4% formaldehyde solution until 48 h before sectioning. They were then transferred to a 10% glucose solution to induce cryoprotection. The brains were cut on a cryotome with a thickness of 25 μm, placed on gelatin coated slides, and stained with cresyl violet. The slices were then examined using a standard microscope and the position of the electrodes were determined. The histology revealed that all electrode tips were within or in clear proximity to the median forebrain bundle.

RESULTS

Experiment 1

As can be seen in Fig. 1a, *d*-amphetamine dose dependently lowered the current intensity needed to produce 50% of maxi-

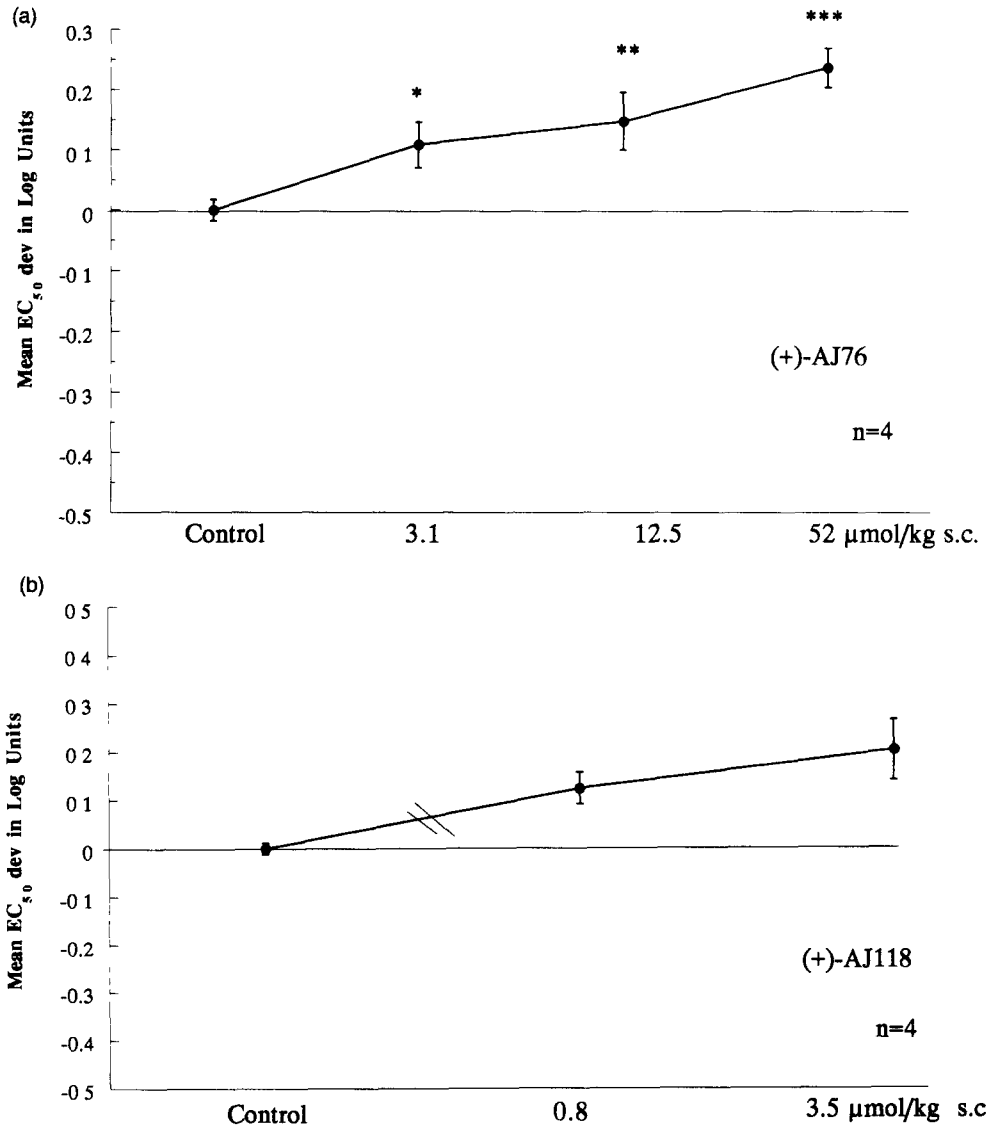

FIG. 2. (a) The inhibitory properties of (+)-AJ76 and (b) (+)-AJ118 are seen as dose-dependent increases in EC_{50} compared to controls. Both (+)-AJ76 and (+)-AJ118 were administered SC 15 min prior to testing. Mean ± SEM (n = 4–6). Statistics: ANOVA followed by Fisher's PLSD (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. saline-treated animals).

mal response (EC_{50} values), while (+)-AJ76, (+)-AJ118, and haloperidol resulted in variances in the increase in EC_{50}. In contrast, haloperidol (Fig. 1b) potently elevated the EC_{50} values and at the highest dose a clear motor deficit was observed (muscular rigidity and hypokinesia). (+)-AJ76 and (+)-AJ118 (Figs. 2a and 2b) also dose dependently inhibited the ICSS response, but were less potent and less efficacious when compared to haloperidol. Furthermore, at the doses tested these two compounds failed to induce catalepsy.

Experiment 2A

In animals exposed to a subthreshold current intensity, a low dose (3.1 μM/kg, SC) of (+)-AJ76 was inactive (Fig. 3). A higher dose (12.5 μM/Kg, SC), resulted in an increase in response rate (Fig. 3). This effect was not statistically significant due to large deviations; only 10 of the 22 animals produced an increase in response rate. Of these 10 animals, 6 were tested at both doses of which 4 showed stimulation at both doses. The general behavior of animals during the experiments included exploration of the test cage, with a prolonged time spent in proximity to the part of the cage where the lever was placed. Stimulated animals showed signs of typical dopaminergic behavior such as grooming and sniffing. Animals showing inhibition in response did not display any signs of motor impairment.

Experiment 2B

When exposed to a suprathreshold current intensity, a high dose (12.5 μM/kg, SC) of (+)-AJ76 consistently produced a decrease in the response rate (Fig. 3). The response was reduced to approximately 25% of controls (Fig. 3). This confirms the results obtained in Experiment 1.

DISCUSSION

Our results obtained with *d*-amphetamine and haloperidol conform to the literature (7,22). Furthermore (+)-AJ118, a compound with a pharmacological profile similar to that of haloperidol (12), produced a clear-cut inhibition of the ICSS response.

The results of Experiment 1 also indicate an inhibitory effect of (+)-AJ76 on the ICSS performance. The absence of a detectable stimulatory effect of (+)-AJ76 may be explained when the pharmacological actions of this preferential dopamine autoreceptor antagonist are considered (26). Whether or not (+)-AJ76 has weak stimulatory or inhibitory properties appears to be dependent upon the animal's baseline activity. A possible conclusion from Experiment 1 is that animals exposed to a relatively high current intensity exhibit a high DA nerve tone. In this situation, the postsynaptic blocking properties of (+)-AJ76 become apparent. It is important to notice the absence of stimulatory properties of (+)-AJ76 when animals display a high baseline activity. The compound blocks the stimulatory effects of *d*-amphetamine (27), apomorphine, 5,6-DiPr-ADTN (26), and cocaine (unpublished data). It is interesting to note that other weak stimulants, like caffeine, produce some detectable stimulation when given in low doses (17).

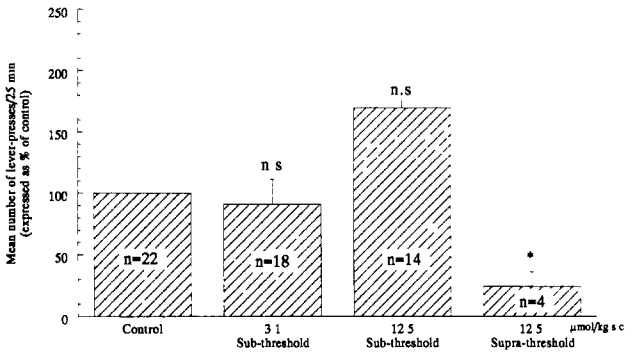

FIG. 3. Effects of (+)-AJ76 using sub- and suprathreshold current intensities. Response rates measured for 25 min after a warm-up period of 5 min. Note the increase and decrease in percent of respective controls. Saline and (+)-AJ76 were administered 15 min before testing began SC (n = 14–18 for the subthreshold experiment and n = 4 for the suprathreshold experiment). Statistics: ANOVA followed by Fisher's PLSD (*$p < 0.05$ vs. saline-treated animals).

The results from Experiment 2A indicate that the stimulatory actions of (+)-AJ76 is individual for each animal. Ten of the 22 rats tested in this model responded positively to (+)-AJ76 at either 3.1 or 12.5 μM/kg, SC. It is possible that (+)-AJ76's DA-releasing actions, summated with the weak current intensity, resulting in facilitation of the ICSS response. Of these 10 animals, some appeared stimulated by one of the two doses but not by both. The other rats did not show any indication of stimulatory actions. Rather, their response to (+)-AJ76 seemed to be inhibitory (cf Experiment 1).

The individuality in response might be derived from the current intensity levels animals were exposed to. Even though the intensities were well below the specific EC_{50} for each animal, the current might be too high in some animals to allow (+)-AJ76 to display its stimulatory effect. This response could be compared to the locomotor activity studies where some habituated animals are "more habituated than others." Furthermore, the differences in response could be a combination of unusually low baseline activity and/or a different degree of motivation, that is, "pleasure feeling." Interestingly, the partial DA receptor agonists, (−)-3PPP and SDZ 208-911, also show variation in individual response when tested in electrophysiological and behavioral experiments, respectively (6,8).

In animals exposed to a suprathreshold current, (+)-AJ76 displayed a clear-cut reduction in response rate. It is important to notice that the activity was not reduced to a nonresponding level. This is in line with the results of Experiment 1. Furthermore, no motor impairment such as catalepsy could be detected during the experiment. It has to be emphasized that although the same animals were used in several experiments they were constantly monitored by being subjected to control EC_{50} tests in between each set of experiments. The EC_{50} values for these rats did not change statistically significantly for the whole set of experiments.

To summarize, (+)-AJ76 appears to have a "normalizing" effect where it can reduce motor activity and ICSS or produce a behavioral stimulation in some animals depending upon the baseline activity. It is interesting to note that while (+)-AJ76 produces conditioned place preference (20) and partially generalizes to the subjective effects of cocaine (3) and *d*-amphetamine (D. Clark, unpublished data) it failed to be self-administered in the same species (20). The compound also antagonizes self-administration of cocaine in the rat (20). Taken together with the results from the present study, (+)-AJ76 does not seem to possess strong positive reinforcing properties in the rat. Compounds with this interesting pharmacological profile might be clinically useful, for example, as antipsychotics against positive and negative schizophrenic

symptoms, antidepressants, and in the rehabilitation of drug addicts. Theoretically, the preferential DA autoreceptor antagonists are less likely to cause excessive stimulation and dependence due to their "behavioral-normalizing" properties.

The importance of the newly described dopamine D_3 (23) and D_4 receptors (29) in the area of ICSS and reward is not known; however, the density of D_3 receptors in brain areas often associated with reward (limbic areas) is astonishing. Interestingly, (+)-AJ76 and its di-*n*-propyl analog (+)-UH232, were shown to have the highest preference for the D_3 receptor in a series of both classical and atypical neuroleptics. The importance of these subtypes of the DA receptor for the behavioral effects of (+)-AJ76 and compounds with similar pharmacological actions clearly needs further evaluation. Further experiments are warranted to clarify if these new DA receptor subtypes are of importance for the unique behavioral actions of (+)-AJ76.

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