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Affinity for the Dopamine D_2 Receptor Predicts Neuroleptic Potency in Decreasing the Speed of an Internal Clock

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MECK, W. H. *Affinity for the dopamine D_2 receptor predicts neuroleptic potency in decreasing the speed of an internal clock*. PHARMACOL BIOCHEM BEHAV **25**(6) 1185–1189, 1986.—For each of five neuroleptics (chlorpromazine, haloperidol, pimozide, promazine, and spiroperidol), the dose required to produce a rightward horizontal shift of 15–20% for psychophysical bisection functions that relate the percentage of *long* responses to signal duration was determined in rats for two different signal ranges (2–8 sec and 4–16 sec). Affinity for the dopamine D_2 receptor (from *in vitro* studies) predicted neuroleptic potency in producing the criterion shift of the timing functions, whereas affinity for other aminergic receptors (D_1, D_3, the α-noradrenergic receptor, S_1, and S_2) did not. The conclusion is that dopamine D_2 receptors play a major role in determining the rate of temporal integration for time estimation.

Time estimation Clock speed Neuroleptics Dopamine D_2 receptors Rat

THE decrease in subjective estimations of event duration following the administration of neuroleptics and the increase in these estimations following the administration of stimulants such as amphetamine has been considered evidence that dopamine-releasing neurons are involved in temporal integration for time estimation [14,16]. However, the conclusions that can be drawn from this evidence are compromised by the identification of at least three distinct dopamine receptor subtypes; D_1 (adenylate cyclase-linked), D_2 (non-adenylate cyclase-linked), and D_3 (presynaptic) [3, 5, 13, 22, 23, 26]. In addition, neuroleptics and amphetamines interact with other neural receptor sites such as alpha noradrenergic (NE-α) and serotoninergic sites (S_1 and S_2) [12, 24, 25]. The study we now report gives a pharmacological profile of the neuroleptic action on time estimation in the rat. For each of the five neuroleptics used in this study, the dosage required to reduce time estimations by 15–20% was correlated with its affinity for various receptor sites. Changes in time estimation were inferred from horizontal shifts in the obtained psychophysical functions that related the probability of a *long* response to signal duration. A high positive correlation would be evidence that a particular type of receptor directly mediates the neuroleptic effect upon time estimation.

The temporal bisection procedure used in this study is a discrete-trials choice procedure that is very sensitive to pharmacological interventions and can separate stimulus factors from response factors [14–16, 18]. In this procedure a stimulus of a particular duration is presented and then two response levers are inserted into a standard lever box. As an example: If a 2-sec stimulus occurred, a left *(short)* response made by the rat is reinforced by the delivery of a food pellet; if an 8-sec stimulus occurred, a right *(long)* response is reinforced. The two extreme signal durations are presented with a probability of 0.25 on each trial. On the remaining trials, one of five signals of intermediate duration is randomly presented, each with equal probability. Neither the left nor the right response is followed by food in the case of these intermediate signal durations. In this task the percentage of *long* responses rises as a function of signal duration in a sigmoidal fashion. Previous work has indicated that (a) the point of subjective equality for the two extreme signal durations is near their geometric mean, (b) the difference limen for the psychophysical function is proportional to the geometric mean of the extreme durations (i.e., Weber's law), (c) the psychophysical functions are symmetrical on a logarithmic time scale, and (d) the functions for different signal ranges are equivalent when scaled in log units relative to the geometric mean of the two extreme durations that precede reinforcement [2, 8, 16]. A quantitative model of this behavior has been developed that fits the data and relates the model parameters to psychological processes [7–10, 16].

METHOD

Subjects

The subjects were 40 experimentally naive male albino

rats of the Sprague Dawley strain (Charles River COBS-CD) about 6 months old and weighing about 400 g when the experiment began. The rats were individually housed in metal cages (Wahmann Mfg. Co.) where they had continuous access to water. They were fed a daily ration of 15 g of Agway Pro Lab Formula (RMH 3200) mixed with about 15 ml of water shortly after the daily session. A reversed light-dark cycle of 12:12 was maintained in the vivarium with fluorescent lights on from 6:00 p.m. to 6:00 a.m. eastern standard time. Training was conducted during the dark phase of the LD cycle.

Apparatus

The rats worked in 10 similar lever boxes (23×20×22 cm). The roof and side walls were transparent acrylic; the front and back walls were aluminum. The floor was 16 parallel stainless-steel bars. A pellet dispenser (Gerbrands Model D-1 or Davis Scientific Instruments Model PD-104) delivered Noyes Precision food pellets (45 mg) through an opening in the front wall to a food cup. A 140-ml glass water bottle, at least half full, hung from the back wall of the chamber. Each box contained two retractable stainless steel levers, one on each side of the food cup. The levers in Boxes 1–6 were 1.6×4.6 cm, located 3.8 cm above the grid floor (Gerbrands Model 6311). The levers in Boxes 7–10 were 2.5×5.0 cm, located 5.0 cm above the grid floor (BRS/LVE Model 123-07). Each lever box was housed in a large insulation-board chamber designed to minimize outside light or sound. Six boxes had a 7.5-W lamp attached to the middle of the back wall of the chamber; four boxes had a 6-W lamp attached to the outside of the roof of the lever box. A noise generator (Grason-Stadler Model 901B) could deliver white noise of about 80 dB (re 20 $\mu N/m^2$; General Radio Sound Meter, Model 1565-D, A scale) above background level through a 4-in. (10.2 cm) speaker mounted inside each chamber. Each chamber was equipped with a fan for ventilation and a small acrylic window for observation. A time-shared Digital Equipment Corporation PDP-12 computer controlled the experimental equipment and recorded the data.

Procedures

Pretraining. Each rat received four sessions of combined magazine and lever training. During these sessions a food pellet was delivered once each minute for 60 min (magazine training), and in addition, each lever press produced food (lever training). The left lever was inserted and 10 responses were reinforced; then the left lever was retracted and the right lever inserted; 10 right lever responses were reinforced; then the right lever was retracted and the left lever was again inserted. This alternation between levers continued until the rat had pressed each lever 60 times or 60 min had passed, whichever came first. The houselight illuminated the chamber at all times during the session.

Two-signal training (sessions 1–10). The rats were randomly assigned to four groups of 10 rats each. Each group of rats was consistently trained at the same time of day, but on randomly selected days, according to the schedule outlined below. Two daily session times were used. On each day, one of the two groups of rats assigned to each of the two session times was randomly selected to receive food-reinforced training in the lever boxes. In this way, two groups of rats were consistently trained beginning at 7 a.m. and two groups of rats were consistently trained beginning at 11 a.m. One of the groups at each of the two session times was trained to discriminate signal durations of 2 sec vs. 8 sec and the remaining two groups were trained to discriminate signal durations of 4 sec vs. 16 sec. All signal training sessions lasted 2 hr.

Half of the rats in the 2 sec vs. 8 sec Group were trained to press the left lever (*short* response) following a white noise signal of 2 sec and to press the right lever (*long* response) following a white noise signal of 8 sec. The remaining rats in the 2 sec vs. 8 sec Group had this response rule reversed. Half of the rats in the 4 sec vs. 16 sec Group were trained to press the left lever (*short* response) following a white noise signal of 4 sec and to press the right lever (*long* response) following a white noise signal of 16 sec. The remaining rats in the 4 sec vs. 16 sec Group had this response rule reversed. On each trial one of the two signals was randomly selected for presentation with a probability of 0.5. Signal presentation consisted of white noise being turned on for the selected duration. At the end of this period the signal was turned off and both levers were inserted into the box. If the rat made the correct response, a pellet of food was delivered with the probability of 0.5; if the rats made the incorrect response, no pellet was delivered. When either lever was pressed, both levers were retracted. Intertrial intervals (ITI) were 5 sec plus a geometrically distributed duration with a minimum of 0.1 sec and a mean of 40 sec. If an incorrect response had been made on the previous trial, the same signal was presented again on the next trial (correction procedure). A record was kept of the number of left and right responses following each of the two signal durations.

Seven-signal baseline training (sessions 11–25). The conditions of two-signal training were maintained except (a) there were no correction trials, (b) each of the two extreme signal durations was presented with a probability of 0.25 on each trial, and (c) on the remaining trials, one of five signals of intermediate duration was presented, each with equal probability. The intermediate signal durations were spaced at equal logarithmic intervals between the two extreme signal durations used in previous training (2.0, 2.6, 3.2, 4.0, 5.0, 6.4, and 8.0 sec for the 2 sec vs. 8 sec Group; 4.0, 5.2, 6.4, 8.0, 10.0, 12.8, and 16.0, sec for the 4 sec vs. 16 sec Group). Neither the left nor the right response was followed by food in the case of these intermediate signals. A record was kept on magnetic tape of the following characteristics of each response: (a) the subject, (b) the signal duration, (c) whether the response was left or right, and (d) the response latency.

Neuroleptic testing (sessions 26–45). The conditions of seven-signal training were maintained except that on a random half of the days during which rats received signal training they were administered an IP injection of a drug in solution with approximately 0.2 cc of physiological saline before the test session. On the remaining days, the rats received an IP injection of 0.2 cc of physiological saline 20 min before the test session.

Each group of 10 rats was evenly divided so that two rats in each group were used for the evaluation of each of five neuroleptic drugs. Each rat was used to test the effectiveness of a single drug at different doses. The dosage used in a given test session was determined by the rat's performance in the previous drug session. If a rat showed a rightward shift of its psychophysical function greater than 20%, or if it failed to lever press on more than 40% of the trials during the previous test session, the drug dosage was reduced by a factor of two. If a rat showed no shift of its psychophysical function, or if the rightward shift was less than 15%, the drug dosage was

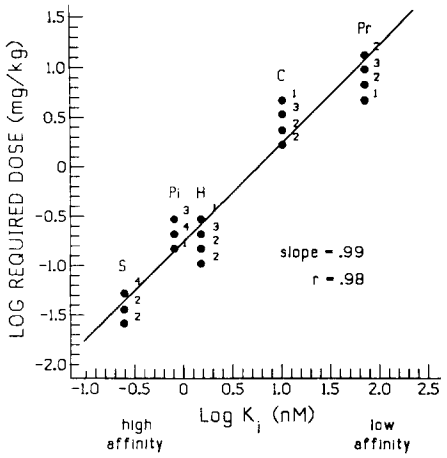

FIG. 1. The logarithm (base 10) of the neuroleptic dose (mg/kg) required to produce a 15–20% rightward shift in the psychophysical bisection functions for signal duration plotted against the logarithm of the affinity for the dopamine D_2 receptor, as measured *in vitro* [4]. K_i is proportional to IC_{50}, which is the concentration of a drug required to displace 50% of the stereospecifically bound ligand. The number beside each data point gives the number of rats for which that was the required dose. The best fitting linear regression line was computed from the logarithmic mean of the required doses for a given drug. Abbreviations: C=chlorpromazine; H=haloperidol; Pi=pimozide; Pr=promazine; S=spiroperidol.

TABLE 1

SUMMARY OF THE CORRELATIONS BETWEEN BINDING AFFINITIES FOR DIFFERENT RECEPTOR TYPES AND THE NEUROLEPTIC DOSE (LOG mg/kg) REQUIRED TO PRODUCE THE CRITERION RIGHTWARD SHIFT OF THE PSYCHOPHYSICAL BISECTION FUNCTION

Receptor Type	Correlations (r)	Significance Level (p)	References
Dopamine			
D_1*	−0.14	$p>0.1$	[11]
D_2†	0.98	$p<0.001$	[4]
D_3†	0.21	$p>0.1$	[4]
Norepinephrine			
NE-α†	−0.23	$p>0.1$	[24]
Serotonin			
S_1†	0.17	$p>0.1$	[24]
S_2‡	0.24	$p>0.1$	[12]

*Logarithm of the drugs' affinity for the receptor expressed as log IC_{50} (nM).

†Logarithm of the drugs' affinity for the receptor expressed as log K_i (nM).

‡Logarithm of the drugs' affinity for the receptor expressed as $-\log IC_{50}$ (M).

K_i is proportional to IC_{50}, which is the concentration of a drug required to displace 50% of the stereospecifically bound ligand.

increased by a factor of two. The beginning dose for all drugs was 0.025 mg/kg. Neuroleptic testing was conducted on randomly selected test days in this manner until a dose was found that produced a 15–20% rightward shift of the psychophysical bisection function. If a particular drug produced a dose effect that fell below the criterion and the next dosage increment produced an effect that fell above the criterion, the geometric midpoint between these doses was taken as the dose that satisfied the criterion. Neuroleptic testing for individual rats continued until their criterion dose was found, thereafter they received only saline injections until the criterion dose was determined for all rats. The five neuroleptics used were chlorpromazine, haloperidol, pimozide, promazine, and spiroperidol. Test sessions were initiated after a time, judging from the literature, that would be after the onset of drug action, but before the attainment of peak action. These times were 15 min for chlorpromazine, haloperidol, and promazine, 1 hr for pimozide, and 3 hr for spiroperidol.

Data Analysis

Choice responses with latencies greater than 3 sec are not included in any of the data analysis because previous work has shown that such responses are not well controlled by the reinforced stimulus dimension [14,15]. A median of 8.2±4% of the trials were discarded in this experiment by the 3-sec latency cutoff. The proportion of trials excluded from analysis did not vary reliably between neuroleptics or signal ranges. In order to evaluate the horizontal shifts in the psychophysical bisection functions a point of subjective equality (PSE) was calculated from the individual bisection functions. PSE's were obtained for each animal during each test session for both signal ranges. The calculation of the PSE was done as follows: (a) The straight line with the greatest slope, fitted by the method of least squares, relating the percentages of *long* responses to three adjacent signal durations was identified, and (b) from this straight line, the signal duration that was associated with 50% of the *long* responses was calculated and reported as the PSE. A difference limen (DL) was also estimated from the individual psychophysical functions. From the same straight lines used to estimate the PSE, the signal duration that the rat classified as *long* 75% of the time and the signal duration that the rat classified as *long* 25% of the time was found. One half of this range of signal durations is defined as the DL. The Weber fraction (WF), the DL divided by the PSE, was also calculated and serves as a relative measure of discrimination performance that can be used to compare the sensitivity of time estimation for the two different signal ranges.

RESULTS

The mean dose of a neuroleptic drug required to produce a rightward shift of 15–20% for the scaling of signal duration was calculated for each drug at each signal range. The magnitude of the rightward shift was determined by comparing PSE's obtained from seven-signal baseline training with PSE's obtained from neuroleptic testing. An analysis of variance with factors Drug (five neuroleptics) and Signal (two signal ranges) indicated the Drug effect to be significant; $F(4,30)=6.38$, $p<0.001$, while the Signal effect was found to be nonsignificant; $F(1,30)<1$. Because of the lack of a Signal effect the data from the two signal ranges were combined. The dose of each neuroleptic required to produce the criterion rightward shift was found to be strongly correlated with the drug's affinity for the dopamine D_2 receptor site, as measured *in vitro*, $r(38)=0.98$, $p<0.001$. Affinity was measured by Creese, Burt and Snyder [4] using ^{3}H-haloperidol as the radioactive ligand and calf striatal tissue. The logarithm

(base 10) of the neuroleptic dose required to produce the criterion rightward shift plotted against the logarithm of affinity for the dopamine D_2 receptor for individual rats tested under each drug is shown in Fig. 1.

The dose of a neuroleptic required to produce a 15–20% horizontal rightward shift in the psychophysical functions relating the percentage *long* response to signal duration does not correlate strongly with *in vitro* affinity for the D_1 and D_3 dopamine receptors; $r=-0.14$ and $r=0.21$ respectively. Nor does it correlate strongly with affinity for the NE-α receptor, nor with binding affinity for the S_1 and S_2 serotonin receptors; $r=-0.23$, $r=0.17$ and $r=0.24$ respectively. Affinity data for the D_1 dopamine receptor are from [11] with the ^{3}H-cis (2)-flupenthixol ligand and rat striatal tissue. Affinity data for the D_3 dopamine receptor are from [4] with the ^{3}H-dopamine ligand and calf striatal tissue. Affinity data on the NE-α receptor are from [25] with the ^{3}H-WB-4101 ligand and rat whole brain. Affinity data for the S_1 serotonin receptor in the cortex and are from [24] with the ^{3}H-serotonin ligand and rat cortical tissue. Affinity data for the S_2 serotonin receptor are from [12] with ^{3}H-spiroperidol ligand and rat frontal cortex. A summary of the correlations (r values) that relate the binding affinities of the neuroleptics for different receptor types to their potency in producing a criterion rightward shift of the timing functions are shown in Table 1.

The median psychophysical functions relating percentage *long* response to signal duration for the rats in both signal ranges during neuroleptic testing are shown in Fig. 2 for saline test days (closed circles) and drug test days (open circles). The drug data were taken from the sessions where the neuroleptic dose that produced the criterion shift was in effect for each rat and then averaged over rats. Saline data were first averaged over all saline sessions during the neuroleptic test phase for each rat and then averaged over rats. For the 2 sec vs. 8 sec Group the mean PSE under saline was 4.10 ± 0.1 sec, the mean DL was 0.81 ± 0.19 sec, and the mean WF was 0.19 ± 0.02. The mean PSE for the criterion rightward shifts under neuroleptics was 4.82 ± 0.31 sec, an average increase of $17.6\pm1.57\%$ from saline sessions, the mean DL was 1.0 ± 0.24 sec, and the mean WF was 0.21 ± 0.03. Fourteen of twenty rats had a higher WF while under the influence of a neuroleptic as compared to saline. For the 4 sec vs. 16 sec Group the mean PSE under saline was 8.13 ± 0.43 sec, the mean DL was 1.49 ± 0.11 sec, and the mean WF was 0.18 ± 0.02. The mean PSE for the criterion rightward shifts under neuroleptics was 9.53 ± 0.52 sec, an average increase of $17.3\pm1.71\%$ from saline sessions, the mean DL was 1.88 ± 0.30 sec, and the mean WF was 0.20 ± 0.03. Sixteen of twenty rats had a higher WF while under the influence of a neuroleptic as compared to saline. A comparison of the PSE's obtained during baseline training with the PSE's obtained during saline test sessions indicated that there were no reliable differences for either group; $t(19<1$, ns. The numbers reported above are means $\pm$ the standard deviations.

DISCUSSION

The conclusions of this report are in no way compromised by the fact that the nomenclature used for dopamine receptors is somewhat controversial. While the D_2 site is accepted by most investigators, certain investigators believe that the D_1 and D_3 sites may be identical. Among the receptors for biogenic amines for which neuroleptic affinity data were compared with neuroleptic effects on time estimation,

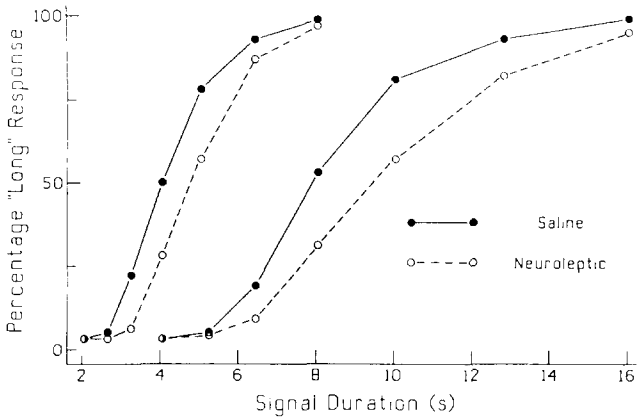

FIG. 2. Median percentage *long* response as a function of signal duration for the two signal ranges—2 sec vs. 8 sec and 4 sec vs. 16 sec. Closed circles are for sessions with saline; open circles are for sessions with neuroleptics.

only the affinity for the dopamine D_2 receptor reliably predicted the dose required to produce the criterion rightward shift in the PSE. The dose of a neuroleptic required to produce the 15–20% criterion rightward shift for the 2 sec vs. 8 sec signal range was the same dose required to produce the criterion rightward shift for the 4 sec vs. 16 sec signal range. This finding is consistent with the proposal that neuroleptic drugs affect time estimation by decreasing the rate at which a pacemaker emits pulses [1, 10, 16]. If psychophysical judgements of time are based on the accumulation of these pulses, then variation in the mean rate of the pacemaker should influence time estimations. A decrease in the speed of the pacemaker would be expected to decrease time estimations by a constant percentage of the duration to be timed rather than a constant number of seconds. Therefore, if neuroleptics decrease the speed of an internal clock, a fixed dose of a neuroleptic should produce rightward shifts of a constant percentage for timing functions obtained across a range of signal durations. This is the result that was observed. Similar proportional effects have been observed for drugs that increase the effective level of brain dopamine (e.g., amphetamine) but as predicted, the observed horizontal shifts were in the opposite direction (i.e., leftward) [15].

Although beyond the scope of the present paper, Meck [16] has shown how changes in the internal clock can be separated from changes in temporal memory using temporal bisection procedures similar to those described in this report. Meck and Church [19–21] have employed double dissociation methods with different timing tasks in order to demonstrate the generality of the effects produced by changes in the speeds of internal clock and memory storage processes.

As a final note it is worth mentioning that binding affinity for the dopamine D_2 receptor not only predicts a neuroleptic's potency for clinical treatment of schizophrenic symptoms [4] and its potency for decreasing the speed of an internal clock, but also its efficacy in blocking the reinforcing effect of electrical stimulation of the medial forebrain bundle [6]. Taken together, these results suggest that the physiological mechanisms involved in the quantification of reward magnitude and stimulus duration are quite similar [17] and that the symptoms of schizophrenia should include both the misperception of hedonics and time.

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