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Effects of Antipsychotic Drugs on Brain-Stimulation Detection: Preliminary Observations[1,2]

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WHEELING, H. S. AND C. KORNETSKY. *Effects of antipsychotic drugs on brain-stimulation detection: Preliminary observations*. PHARMACOL BIOCHEM BEHAV 21(4) 645–649, 1984.—The effects of two antipsychotic drugs, haloperidol and clozapine, on the detection of electrical brain stimulation were investigated. Rats were trained to make an instrumental response to a brain stimulation cue delivered via an electrode implanted in one of several forebrain or midbrain loci. A response to this stimulation was reinforced by the delivery of a rewarding electrical stimulus via a second electrode implanted in the hypothalamus. By varying the current intensity of the cue stimulus, a detection threshold was determined in each subject both prior to and after administration of various doses of haloperidol or clozapine. Compared to changes on vehicle control days, both drugs produced a dose-related elevation of the detection thresholds. Although haloperidol was more potent than clozapine in most subjects, the minimal effective doses of haloperidol for affecting detection from forebrain loci were lower than for affecting detection from midbrain loci. A reverse differential sensitivity was observed after clozapine administration. Concurrent effects of these two drugs on latency to respond, as well as on both task defined strength of responding and ability to inhibit responding not only indicated the specificity of threshold elevations, but provided additional behavioral information concerning the actions of the two antipsychotic agents. It is proposed that the method employed in this experiment is suitable for measuring the effects of drugs on the discriminative or perceptual properties of electrical brain stimulation and may indicate central sites of drug action.

Detection thresholds Electrical brain stimulation Antipsychotic drugs Psychophysics-animal

NUMEROUS studies reviewed by Doty [3] have provided evidence that the ability of an animal to discriminate or detect an electrical brain stimulation cue can be used to delineate functional relationships among brain loci or between brain loci and peripheral sensory signals. It has even been suggested that brain-stimulation detection thresholds may represent a ". . . brain excitability state" [12]. However, relatively few studies concerning the effects of drugs on brain-stimulation detection have been reported.

We have previously described a method for measuring detection thresholds which distinguishes the discriminative or perceptual from the motivational properties of intracranial stimuli [9]. In this earlier experiment, it was observed that detection thresholds were substantially lower than reward thresholds measured from the same lateral hypothalamic loci in the same subjects. Further, cocaine differentially affected the discriminative and motivational properties of electrical stimulation.

The single electrode method we employed previously has been modified such that detection stimuli are presented to one brain site while responding is maintained with rewarding stimulation to the posterior hypothalamus [17]. This technique is similar to that described by Bass [1]. The present report represents our initial attempt to determine the effects of drugs on detection thresholds measured with this technique. We decided to test for the possible differential effects of a prototypical and an atypical antipsychotic agent, haloperidol and clozapine, respectively, on brain-stimulation detection from several brain sites.

METHOD

Subjects

Eleven male CDF strain rats (Charles River Laboratories, Wilmington, MA), weighing between 275 and 350 g, were stereotaxically implanted with bipolar stainless steel electrodes (Plastic Products, Roanoke, VA). Electrodes were insulated except at the tips (0.13 mm dia.). One electrode in each subject was aimed at the site from which detection thresholds were to be measured (see below). A second electrode was aimed at the posterior hypothalamus.

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Apparatus

Subjects were trained and tested in plastic experimental chambers (20×20×36 cm) enclosed within light and sound attenuating cabinets. A cylindrical manipulandum (15 cm long and 7.5 cm in dia.) was mounted within one wall of the chamber. Four equally spaced cams operated a microswitch when the manipulandum was rotated.

A constant current stimulator generated 0.5 sec trains of biphasic square waves of 0.2 msec duration with an intervening delay of 0.2 msec between positive and negative phases. Detection stimuli were presented at a pulse frequency of 20 Hz, while rewarding stimulation was maintained at 160 Hz. Programmed contingencies and data collection were controlled by a microcomputer (Sunrise Systems, Pembroke, MA). The electrical parameters were routinely checked with an oscilloscope.

Procedure

The procedure for determining detection thresholds was based on a discrete trial task in which the presentation of a non-contingent stimulus (S1) to the detection site acted as a cue for the initiation of a trial [17]. If the subject responded to the cue, a contingent rewarding stimulus (S2) was immediately delivered via the hypothalamic electrode. The intensity of S2 for each subject was three times the reward threshold for the hypothalamic site (see below).

According to a modification of the psychophysical method of constant stimuli, current intensities of S1 were presented in a quasi-random order alternating above and below an estimated threshold intensity. The range of intensities included eight steps, 4 above and 4 below the estimated threshold in 1 μA gradations. If the subject responded to an intensity below the estimated threshold or failed to respond to an intensity above the estimated threshold, the entire range of S1 current intensities shifted downward or upward, respectively. Thus, the subject's responding adjusted the magnitude of the range of test stimuli such that the midpoint of the range was estimated as the threshold on each trial. The detection threshold for any time period was the mean of these trial-by-trial estimated thresholds. This procedure allowed continual tracking of the threshold over time.

Trials began on the average of one every 15 sec (range: 7.5 to 21.6 sec). A response, i.e., one-quarter turn of the manipulandum, within 5 sec after the onset of S1 resulted in the immediate delivery of S2. Additional microswitch closures which occurred within 3.5 sec after a correct response were defined as extra-correct responses. Responses made during an intertrial interval instituted a 30 sec delay in the onset of the next trial. Intertrial responses occurring within 2 sec of each other defined a single intertrial cluster. Drug induced changes in extra-correct responses and intertrial clusters indicated effects on strength of responding and ability to inhibit responding, respectively. In addition, the mean latency to respond based on all correct responses for a session was computed. Changes in these latter performance variables provided additional measures of drug effect.

Reward thresholds for the hypothalamic site in each subject were measured prior to training on the detection task, and were defined as the mean of 5 consecutive determinations, each 60 min in duration, for which the coefficient of variation was less than 15 percent. Reward thresholds were measured in a fashion similar to that for determining detection thresholds except that both non-contingent and contingent stimuli were delivered via the same hypothalamic electrode and covaried in current intensity. In the detection task, contingent rewarding stimulation was fixed at an intensity approximately equivalent to three times the reward threshold for each subject, up to a limit of 250 μA at a frequency of 160 Hz.

Once a subject learned the detection task, the following test schedule was instituted. The subject was tested for 30 min of which the last 20 min was used to calculate a pre-injection (PRE) threshold. At this point, an intraperitoneal injection (1 ml/kg b.wt.) of either vehicle (control) or drug solution was administered. Fifteen min later, a 60 min post-injection (POST) session, consisting of 6 consecutive 10 min periods, was begun. Detection thresholds for each 10 min POST period were computed. The major dependent variable was the difference between the threshold for each 10 min POST period and the PRE threshold on that same day. For each subject, the mean and standard deviation of the threshold changes corresponding to each 10 min POST period were calculated for control days.

From 3 to 10 days of vehicle injections preceded the initiation of drug testing. A minimum of 2 days, usually vehicle test days, intervened between drug test days. Not all preparations remained viable to complete testing of both drugs, but an attempt was made to balance the order of drug administration between subjects. At least one week of vehicle test days separated dose-response determinations for those subjects in which the effects of the two drugs were tested.

Data Analysis

Since the threshold changes after vehicle for each of the six 10 min POST periods relative to the PRE session showed no systematic trends, the mean of these threshold changes (POST period minus PRE thresholds) was used for comparing data from drug treatment days. If the threshold change for any POST period after drug administration exceeded the mean change after vehicle injection by 2 standard deviations (95 percent confidence limits), that drug induced threshold change was considered statistically different from control data. On the basis of this analysis, the minimal dose of drug which produced a significant alteration in detection during any POST period was determined. Also, we estimated the times to onset, peak and duration of effect as the time from injection of the minimal effective dose to the midpoint of the 10 min POST periods exhibiting significant effects.

For the analysis of changes in latency to respond, strength and efficiency of responding, the difference between the values for the PRE session and the entire 60 min POST session were employed. The number of extra-correct responses were divided by the number of correct responses within the same session to account for differences in length of sessions and in day-to-day performance. The number of intertrial clusters for a PRE session (20 min) was multiplied by 3 for comparison with the corresponding POST session (60 min).

Drugs

Haloperidol and clozapine were dissolved in slightly acidic saline solutions which were adjusted to pH 5.6 with NaOH. The vehicle alone was administered on control test days. Doses are expressed in terms of the base form of the drugs.

Histology

At the completion of testing, subjects were sacrificed with

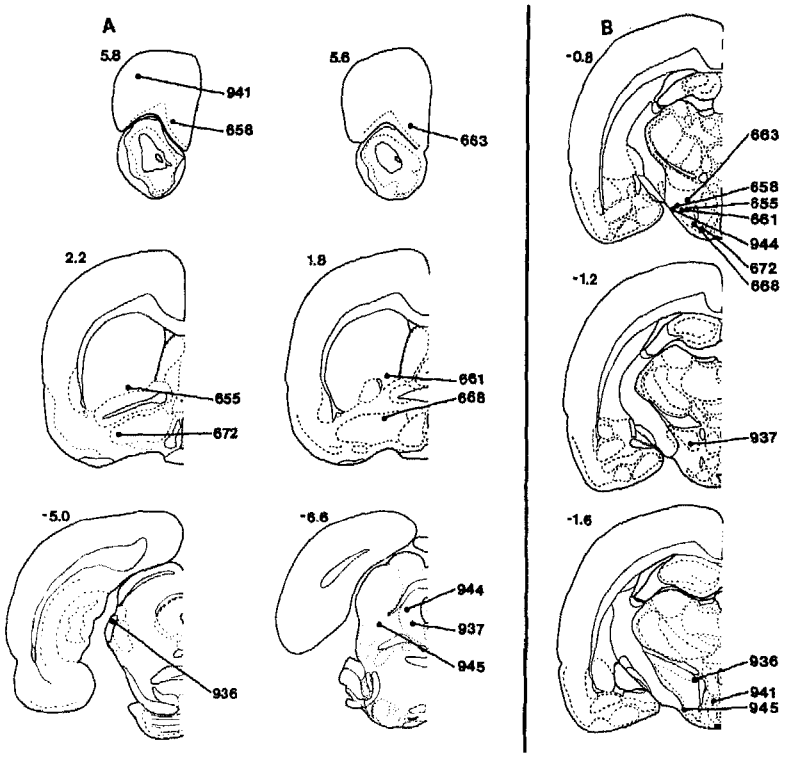

FIG. 1. Reconstruction of the tips of (A) detection and (B) corresponding hypothalamic reward electrodes for each subject on sagittal sections. The distance in mm from bregma are indicated in reconstructions adapted from Pellegrino, *et al.* [11].

an overdose of anesthetic and perfused intracardially with formalin. Brains were removed, further fixed, sectioned (40 μm) and stained.

RESULTS

Electrode Placements

Detection electrode placements are reconstructed in Fig. 1A. Forebrain detection sites consisted of the lateral preoptic area (N=2), the ventral neostriatum (N=2), the medial (N=2) and the lateral (N=1) frontal cortices. A group of midbrain detection placements included the brachium of the inferior colliculus (N=1), the reticular formation (N=1) and the periaqueductal gray (N=2).

The hypothalamic sites to which contingent rewarding stimulation was delivered are reconstructed in Fig. 1B and listed in Table 1 according to the corresponding detection loci for each subject. These sites ranged from the lateral hypothalamus, within or near the medial forebrain bundle (N=6), the zona incerta (N=2), the ventral (N=2) and dorsal (N=1) premammillary nuclei. Despite this variability in the sites to which rewarding contingent stimulation was delivered, neither the rewarding value of this contingent stimulation nor the findings concerning brain-stimulation detection were attributable to this variability (see below).

Control Thresholds

The mean PRE detection threshold for each subject is listed in Table 1. Overall detection thresholds measured from forebrain sites were significantly lower than thresholds measured from midbrain sites ($t=3.09$, $p<0.02$). The present sample was derived for the purpose of pharmacological testing from a larger group of subjects described elsewhere [17].

The mean and standard deviation of the six 10 min POST period detection threshold changes from control days for each subject are also presented in Table 1. Control detection threshold changes were not significantly correlated with the magnitude of PRE detection thresholds ($r(9)=0.40$). Also, hypothalamic reward thresholds (Table 1) were not correlated with detection thresholds from the same subjects ($r=0.22$).

Drug Effects

Both haloperidol and clozapine caused dose-related elevations of detection thresholds from all sites. For each subject the minimal doses of haloperidol and clozapine which produced a significant threshold change during at least one 10 min POST period are presented in Table 2. The range of minimal effective doses of haloperidol for affecting detection from forebrain loci was between 0.0125 and 0.05 mg/kg for 6 of 7 subjects. In one subject (941) detecting stimulation to the lateral frontal cortex the minimal effective dose was 0.075 mg/kg, a dose which completely abolished responding in that subject. The relative insensitivity to the effects of haloperidol in this latter subject was similar to that observed in two subjects detecting stimulation to the periaqueductal gray.

In contrast, detection from forebrain loci was less sensitive than detection from midbrain loci to the effects of

TABLE 1

CONTROL DETECTION THRESHOLD DATA AND CORRESPONDING HYPOTHALAMIC REWARD THRESHOLDS

Subject	Detection Site*	Detection Threshold†	Control Detection Threshold Changes§	Reward Site¶	Reward Threshold#
			Forebrain		
668	LPA	11.4 (21)	+0.2 (2.35)	PMV	43.9
672	LPA	13.6 (11)	−0.4 (1.13)	PMV	45.9
655	NS	11.6 (30)	+0.6 (2.54)	LH	37.3
661	NS	14.5 (23)	+0.8 (3.16)	LH	113.1
658	MFC	30.3 (12)	+2.2 (5.38)	LH	48.3
663	MFC	11.5 (18)	−0.4 (3.37)	LH	20.1
941	LFC	6.9 (11)	−5.9 (3.71)	PMD	34.9
	mean (SEM)	14.3 (2.82)			49.0 (11.26)
			Midbrain		
936	BIC	25.2 (15)	−2.6 (5.40)	ZI	50.9
945	RF	32.0 (12)	+0.4 (5.02)	LH	56.7
937	PAG	24.7 (31)	−0.1 (4.53)	ZI	97.3
944	PAG	25.0 (37)	−0.8 (5.59)	LH	32.4
	mean (SEM)	26.7 (1.76)			59.3 (13.68)

*Abbreviations for sites of detection electrodes; BIC—brachium of the inferior colliculus; LFC—lateral frontal cortex; LPA—lateral preoptic area; MFC—medial frontal cortex; NS—neostraitum; PAG—periaqueductal gray; RF—reticular formation.

†The mean PRE detection threshold in μA at a frequency of 20 Hz and the number of test days on which the threshold was based in parentheses.

§Mean (SEM) of detection threshold changes from control test days—based on 6 ten min POST period thresholds comprising each POST session.

¶Abbreviations for sites of hypothalamic reward electrodes: LH—lateral hypothalamus within or adjacent to medial forebrain bundle; PMD—dorsal premammillary nucleus; PMV—ventral premammillary nucleus; ZI—zona incerta.

#Mean reward threshold in μA at a frequency of 160 Hz for hypothalamic sites to which contingent stimulation was delivered.

TABLE 2

MINIMAL DOSE PRODUCING ELEVATION OF DETECTION THRESHOLD BY SITE AND BY DRUG

Subject	Site*	Haloperidol†	Clozapine†
		Forebrain	
668	LPA	0.05	2.5
672	LPA	0.025	—
655	NS	0.0125	1.0
661	NS	0.05	0.5
658	MFC	0.0125	4.0
663	MFC	0.025	4.0
941	LFC	0.075§	—
		Midbrain	
936	BIC	—	1.0
945	RF	—	0.25§
937	PAG	0.075	0.125
944	PAG	0.075	0.05

*Abbreviations for sites of detection electrodes same as in Table 1.

†Minimal effective dose (mg/kg, IP) for elevating detection thresholds.

§Animal ceased responding after administration of this dose.

clozapine. Doses of clozapine from 0.05 to 0.25 mg/kg elevated detection thresholds from the periaqueductal gray and the reticular formation, whereas doses from 0.5 to 4 mg/kg were required to affect detection from forebrain sites. The one exception was animal 936 whose electrode was in the midbrain and had a minimal effective dose which was within the range of minimal doses for animals with forebrain electrodes. For haloperidol, the times to onset of effect and peak effect appeared to be a function of specific brain site rather than of neuraxial level. Detection thresholds from the neostriatum and lateral frontal cortex were elevated by 20 min after injection of their respective minimal doses of haloperidol, while the onset of threshold elevations from other forebrain or from midbrain loci occurred at approximately 50 min after injection. In contrast, the times to onset of effect and peak effect for clozapine were from 20 to 30 min after injection and were generally unrelated to the site of the detection electrode, despite the wide range of minimal doses represented. With few exceptions, the duration of minimal effects were from 10 to 20 min. In two cases, subject 941 after administration of haloperidol and subject 945 after administration of clozapine, the obtained minimal effective dose completely abolished detection behavior during the entire 60 min POST session. However, for most subjects times to onset and times to peak effect decreased while durations of effect increased with increasing doses of either drug.

Besides drug induced changes in detection threshold other effects were observed. Doses of haloperidol from 0.0125 to 0.05 mg/kg and of clozapine from 0.05 to 4 mg/kg reduced intertrial responding. Thus, both drugs enhanced the ability to inhibit unreinforced responding. These effects occurred both independent of and in conjunction with alterations in detection. In addition, clozapine in doses from 0.1 to 0.5 mg/kg, but not haloperidol at any dose, often produced significant increases in extra-correct responding, that is, increased strength of responding. The mean latency to respond, was rarely affected by doses of either drug. In only one case, subject 668, did the minimal effective dose of clozapine (2.5 mg/kg) both increase latency to respond and concomitantly decrease the number of intertrial clusters.

DISCUSSION

Our results indicate that single doses of haloperidol and clozapine specifically elevate current intensity thresholds for the detection of electrical brain stimulation. Both antipsychotic drugs produced dose-related attenuations of the cueing property of central discriminative stimuli without general depressant, incoordinating or disruptive effects. Further, haloperidol and clozapine altered detection differentially depending on the sites to which stimuli were delivered. Generally, detection from forebrain sites was more sensitive to the effects of haloperidol and less sensitive to the effects of clozapine than was detection from midbrain sites. On the basis of minimal effective doses for subjects tested with both drugs, haloperidol was from 10 to 160 times more potent than clozapine at forebrain sites but only 1 or 2 times more potent at periaqueductal gray sites.

Both drugs produced additional effects which were unrelated to changes in detection thresholds. Thus, haloperidol and clozapine enhanced the ability to inhibit inappropriate, i.e., intertrial, responding. Since the task we employed required the subject to attend to the signaled onset of a trial, the decreases of intertrial responding may represent a facilitated focusing of selective attention. This interpretation is similar to that in previously reported studies in which chlorpromazine facilitated performance in the presence of distracting brain stimulation in the rat [4,8]. The administration of low doses of clozapine, but not haloperidol, produced increases in extra-correct responding in several subjects. In as much as extra-correct responses indicate behavioral activation, the changes might be analogous to increased overall rates of responding in mice and squirrel monkeys [15] and to increased local rates of responding in rats [2] reported to occur after administration of low to moderate doses of clozapine.

Speculations concerning possible mechanisms underlying drug induced changes in detection need not necessarily presume that the site of the effects are coincident with the sites of the detection electrodes although this may be the case. In part, this reflects an uncertainty regarding the neuroanatomical substrates of detection per se [17]. However, most of the forebrain loci which were studied are reported to receive substantial dopaminergic innervation [6,7]. In addition, the relative potencies of haloperidol and clozapine on detection from these forebrain sites are not dissimilar from reported *in vitro* affinities for dopaminergic postsynaptic receptors [10,14]. Even the differential times to onset of the effects of haloperidol between neostriatal and most other forebrain loci, as well as the lack of such distinctions by brain site after clozapine administration parallel the time course of enhanced single unit activity and increased dopaminergic metabolite levels observed after administration of these drugs [5, 13, 16]. Thus, it is possible that a blockade of dopaminergic receptors may subtend threshold elevations from the forebrain loci. The insensitivity of detection from periaqueductal gray and lateral frontal cortex sites to the effects of haloperidol may be due to a relative dearth of such innervation or the lack of importance on detection of whatever dopaminergic innervation exists at those sites. On the other hand, it is not possible at present to begin to suggest neurochemical mechanisms responsible for the enhanced sensitivity of detection from most midbrain loci to the effects of clozapine. Obviously, there is a need for further neuropharmacological investigation of brain-stimulation detection as a phenomenon distinct from other stimulation induced or mediated behaviors.

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