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Differential Actions of Classical and Atypical Antipsychotic Drugs on Spontaneous Neuronal Activity in the Amygdaloid Complex

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REBEC, G. V., K. D. ALLOWAY AND T. R. BASHORE. *Differential actions of classical and atypical antipsychotic drugs on spontaneous neuronal activity in the amygdaloid complex.* PHARMAC. BIOCHEM. BEHAV. 14(1) 49–56, 1981.—Classical antipsychotic drugs such as haloperidol produce akinesia and catalepsy, whereas clozapine and related atypical antipsychotics fail to elicit these behaviors even at relatively high doses. Despite these behavioral differences, a cataleptic dose of haloperidol (2.0 mg/kg) produces changes in neuronal activity in the neostriatum and nucleus accumbens comparable to those produced by a non-cataleptic dose of clozapine (20.0 mg/kg). To further elucidate the brain mechanisms underlying the differential behavioral response to these drugs, an electrophysiological analysis was extended to neurons in the rat amygdaloid complex. Whereas an intraperitoneal injection of 2.0 mg/kg haloperidol generally failed to alter the firing rate of amygdaloid neurons, 20.0 mg/kg clozapine typically produced a prolonged increase in activity. Similarly, clozapine, but not haloperidol, reversed the depression of firing rate produced by 1.0 mg/kg *d*-amphetamine. The results suggest that neurons in the amygdaloid complex are more responsive to antipsychotic drugs devoid of extrapyramidal side effects than to antipsychotics which elicit parkinsonian-like motor dysfunctions.

d-Amphetamine Amygdaloid complex Clozapine Haloperidol Unit activity

THE distinction between classical and atypical antipsychotic drugs is based primarily on their behavioral effects. When used clinically, for example, classical antipsychotic drugs produce a series of parkinsonian-like motor dysfunctions, whereas the atypical antipsychotics are devoid of extrapyramidal side effects [7, 20, 45]. Similarly, in laboratory animals classical, but not atypical, antipsychotic drugs produce immobility, rigidity, and other signs of catalepsy [8, 9, 15]. These drugs have also been differentiated according to their ability to block different components of the behavioral response to amphetamine. Thus, haloperidol, a representative classical antipsychotic drug, abolishes the locomotor activity and the focused stereotyped behaviors produced by amphetamine, whereas atypical antipsychotics like clozapine block the drug-induced locomotion but not the focused stereotypy [15,26].

Despite these dramatic behavioral differences, both classes of antipsychotic drugs have been reported to block dopamine (DA) receptors in the neostriatum and nucleus accumbens. Clozapine, for example, produces changes in DA turnover in both sites comparable to those produced by haloperidol [46, 47, 51, 52]. In fact, neither clozapine nor haloperidol show any regional differences in binding to DA receptors [30]. These findings are somewhat surprising in view of the large body of evidence implicating DA afferents to the neostriatum, but not the nucleus accumbens, in Parkinson's disease [4, 11, 24], amphetamine-induced stereotypy [12, 21, 25], and other motor dysfunctions [10, 19, 33].

In order to further elucidate the brain mechanisms underlying the differential behavioral response to classical and atypical antipsychotics, we have begun an analysis of the effects of these drugs on neuronal activity. An initial series of experiments confirmed that, despite their behavioral differences, these drugs produced comparable effects on neurons in the neostriatum and nucleus accumbens [40]. We found, for example, that 2.0 mg/kg haloperidol, which elicits catalepsy in rats [9,23], mimicked the effect of a non-cataleptic dose of clozapine (20.0 mg/kg) on unit activity in both sites. In the present study, we extended our analysis of these drug doses to the amygdaloid complex, an area of the limbic system whose DA input has been implicated in the behavioral response to a wide variety of drugs [12, 14, 16]. In addition, since amygdaloid neurons are responsive to amphetamine [2,50], we also compared the ability of haloperidol and clozapine to block amphetamine-induced changes in neuronal activity. Our results indicate that although some neurons in the amygdaloid complex are responsive to both antipsychotic drugs, clozapine is significantly more effective

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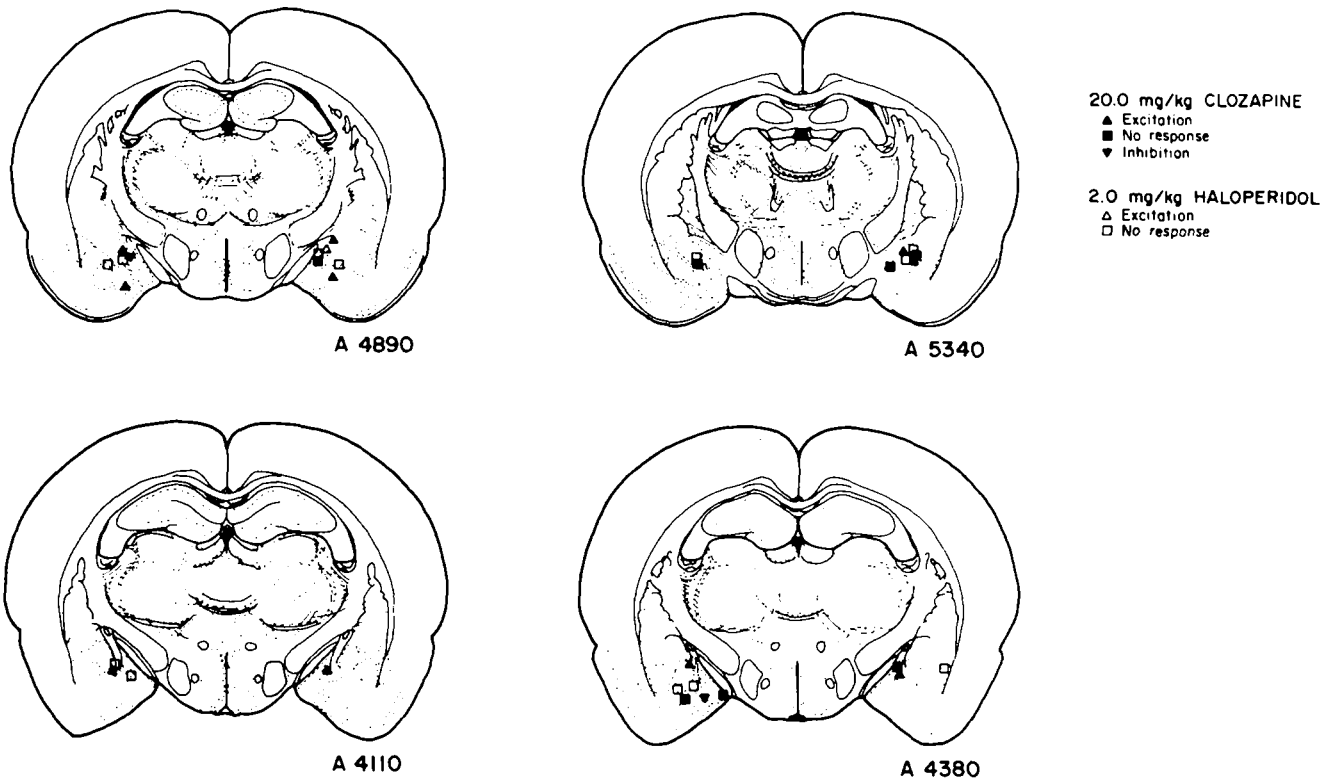

FIG. 1. Location of electrode tip placements in the amygdala for all single unit recordings following an IP injection of 20.0 mg/kg clozapine or 2.0 mg/kg haloperidol. The symbols indicate the distribution of neurons associated with an increase, decrease, or no change in firing rate as identified in the legend. Histological drawings are after König and Klippel [29].

than haloperidol both in increasing spontaneous neuronal activity and in blocking the neuronal response to amphetamine.

METHOD

Male Sprague-Dawley rats (Harlan Industries, Indianapolis, IN), weighing approximately 400 g, were prepared for single unit recording as previously described [22,41]. Briefly, the animals were anesthetized by ether inhalation and secured in a stereotaxic instrument equipped with blunt, atraumatic ear bars. After the skull was exposed, small bilateral holes were drilled over the amygdala (approximately 4.5 mm anterior and 4.0 mm lateral to stereotaxic zero) according to the coordinates of König and Klippel [29]. All points of surgical and stereotaxic contact were locally anesthetized (procaine and xylocaine); subsequent electrocorticographic recordings were dominated by large, slow waves indicating effective local anesthesia. Following surgery, the ether was withdrawn and the animal was immobilized with 2.0 mg/kg tubocurarine chloride (Lilly). Artificial respiration, provided by a Harvard Instruments Rodent Respirator, was adjusted to maintain an end expiratory carbon dioxide content of 3.5 (±0.5) % (Beckman Instruments, LB-2 Medical Gas Analyzer). Heartbeat was displayed continuously on the face of an oscilloscope, and body temperature was maintained at 37 (±0.5)°C.

Tungsten microelectrodes, having impedances of from 2.0 to 5.0 MΩ were bilaterally lowered 7 mm from the surface of the brain, and the search was begun for spontaneously active single unit discharges. Neuronal activity, recorded from both sides of the brain, was amplified and displayed by conventional means. Single unit discharges, having a signal-to-noise ratio of 3:1 or more, were counted on a minute-by-minute basis by means of a neuronal spike analyzer (Mentor N-750) in conjunction with a high-speed printer-counter (Digitec 6120). Unit activity was recorded for at least 30 min prior to the injection of experimental drugs to insure a stable firing rate. The mean firing rate/min, calculated for the 10-min period immediately preceding the drug injection, served as baseline and was defined as 100%. Drug-induced changes in firing rate were expressed in terms of the pre-injection baseline rate for each neuron sampled. Unit activity that failed to maintain a constant signal-to-noise ratio or that did not return to within 40% of the pre-injection rate was excluded from the experiment.

Each animal received an injection of either 1.0 mg/kg (free base) d-amphetamine sulfate (Smith, Kline, and French), 2.0 mg/kg haloperidol (McNeil), or 20.0 mg/kg clozapine (Sandoz) via an indwelling intraperitoneal (IP) catheter. In some animals, d-amphetamine was followed several minutes later by an IP injection of haloperidol and/or clozapine. Upon completion of each experiment, the animal received a lethal dose of pentobarbital (Abbott), and the accuracy of the IP injections was verified by administering methylene blue dye through the catheter and inspecting the peritoneal cavity. Data obtained from animals in which dye was found outside the peritoneal cavity were discarded. To mark the recording sites, current was passed through each electrode to make a small lesion. Following a transcardial perfusion, the brain was frozen, sectioned, and stained with cresyl violet for histological analysis.

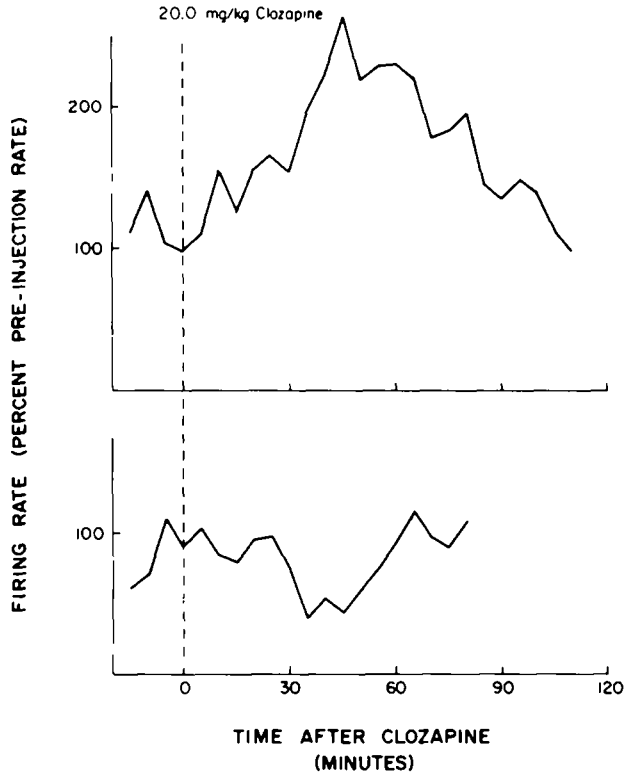

FIG. 2. Representative examples of excitatory and inhibitory responses of individual neurons in the amygdala produced by 20.0 mg/kg clozapine injected (IP) at Time 0. Unit activity, expressed in terms of the 100% pre-injection rate, is reported as the mean firing rate for 5 min intervals until activity returned to within 40% of the pre-injection rate.

RESULTS

Data were obtained from a total of 70 amygdaloid neurons recorded from 48 experimental animals. The majority of neurons were recorded from the central amygdaloid nucleus (n=38) with the remainder in the corticomedial complex (n=17) and in the basolateral group (n=15). The mean spontaneous firing rate of all neurons was 25.5 (SEM ± 2.41) discharges/min; an analysis of variance revealed no significant differences in firing rate between nuclear groups in the amygdaloid complex. In fact, a slow and steady firing pattern was characteristic of neurons in all the nuclear groups. Drug-induced increases or decreases in activity were defined as a greater than 40% change from the baseline rate for a period of at least 15 min (spontaneous pre-drug fluctuations never exceeded this value for more than 5 consecutive min). Neurons whose spontaneous activity remained within 40% of the baseline rate during the first 60 min after the drug injection were classified as unresponsive.

Differential Effects of Clozapine and Haloperidol

Figure 1 illustrates the recording location of 32 amygdaloid neurons whose activity was increased, decreased, or unchanged by the administration of 20.0 mg/kg clozapine or 2.0 mg/kg haloperidol. In 10 of 19 neurons, clozapine produced an increase in firing rate that peaked at a mean value of 275.0 (SEM ± 16.78)% of baseline and that lasted for a mean duration of 76.5 (SEM ± 18.09) min. Note that the increase was recorded from neurons in each of the nuclear groups including 5 in the central, 3 in the corticomedial and 2 in the basolateral nuclei. Although 7 neurons were unresponsive to clozapine, 2 other units were depressed by the drug. The activity of these latter neurons, both in the cortico-medial group, was slowed to below 60% of the baseline rate for a mean period of 52.5 (SEM ± 45.96) min. Representative examples of the clozapine-induced changes in amygdaloid activity are shown in Fig. 2.

In contrast, haloperidol changed the firing rate of only 1 of 13 neurons in the amygdaloid complex. The aberrant neuron, located in the central amygdaloid nucleus, increased its firing rate above 140% of the pre-injection rate for 60 min, reaching a peak response during this time of 175% of baseline. The remaining 6 neurons in the central amygdaloid nucleus, however, failed to respond to haloperidol as did 2 neurons in the cortico-medial and 4 neurons in the basolateral nuclei.

Antipsychotic Drugs and the Response to d-Amphetamine

As shown in Fig. 3, approximately 74% of the neurons (28 of 38) in the amygdaloid complex responded to an IP injection of 1.0 mg/kg d-amphetamine with a depression of firing rate. Note that this response was recorded from all the nuclear groups, including 17 units in the central, 6 in the basolateral and 5 in the cortico-medial nuclei. In some cases (n=6), the depression was preceded by an initial increase in activity that never lasted more than 15 min. Only 8% of the neurons (3 of 38) responded with a prolonged excitation, having a mean duration of 85.0 (SEM ± 19.69) min. Although this response was rare, it was observed only in the central nucleus. Unit activity in the remaining 18% of our sample (7 of 38) was not changed by the drug.

Of the 28 neurons inhibited by d-amphetamine, we monitored the entire time-course of the drug response in 11 units (Table 1) and attempted to reverse the inhibition in the remaining 17 neurons with a subsequent injection of 20.0 mg/kg clozapine or 2.0 mg/kg haloperidol (Table 2). As shown in Table 1, d-amphetamine inhibited unit activity for more than 30 min during the first hour after injection. Continued recording beyond the return to baseline revealed that a small number of neurons (n=4) responded with a rebound increase in firing rate that lasted for several min and that reached a mean maximum value of 190.5 (SEM ± 41.47)% of the pre-injection rate. Table 2 indicates that although the amphetamine-induced depression was comparable for both antipsychotic drug groups, clozapine was more effective than haloperidol in blocking this response. Statistical analysis revealed that during the 20-min period after antipsychotic drug administration unit activity was significantly higher in the clozapine group than in the haloperidol group ($t=2.94$; $p<0.025$). Furthermore, whereas a comparison of firing rate 10 min before and 20 min after clozapine revealed a significant difference ($t=3.16$; $p<0.01$), no such difference in activity was observed before and after haloperidol administration. In fact, whereas clozapine blocked the amphetamine response in all neurons tested (n=8), haloperidol failed to reverse the depression in 8 of 9 neurons (the one exception was located in the basolateral nucleus). In those cases in which haloperidol was ineffective, a subsequent injection of 20.0 mg/kg clozapine was required to return unit activity to within 40% of the baseline rate. Representative examples of the effects of clozapine and haloperidol on the

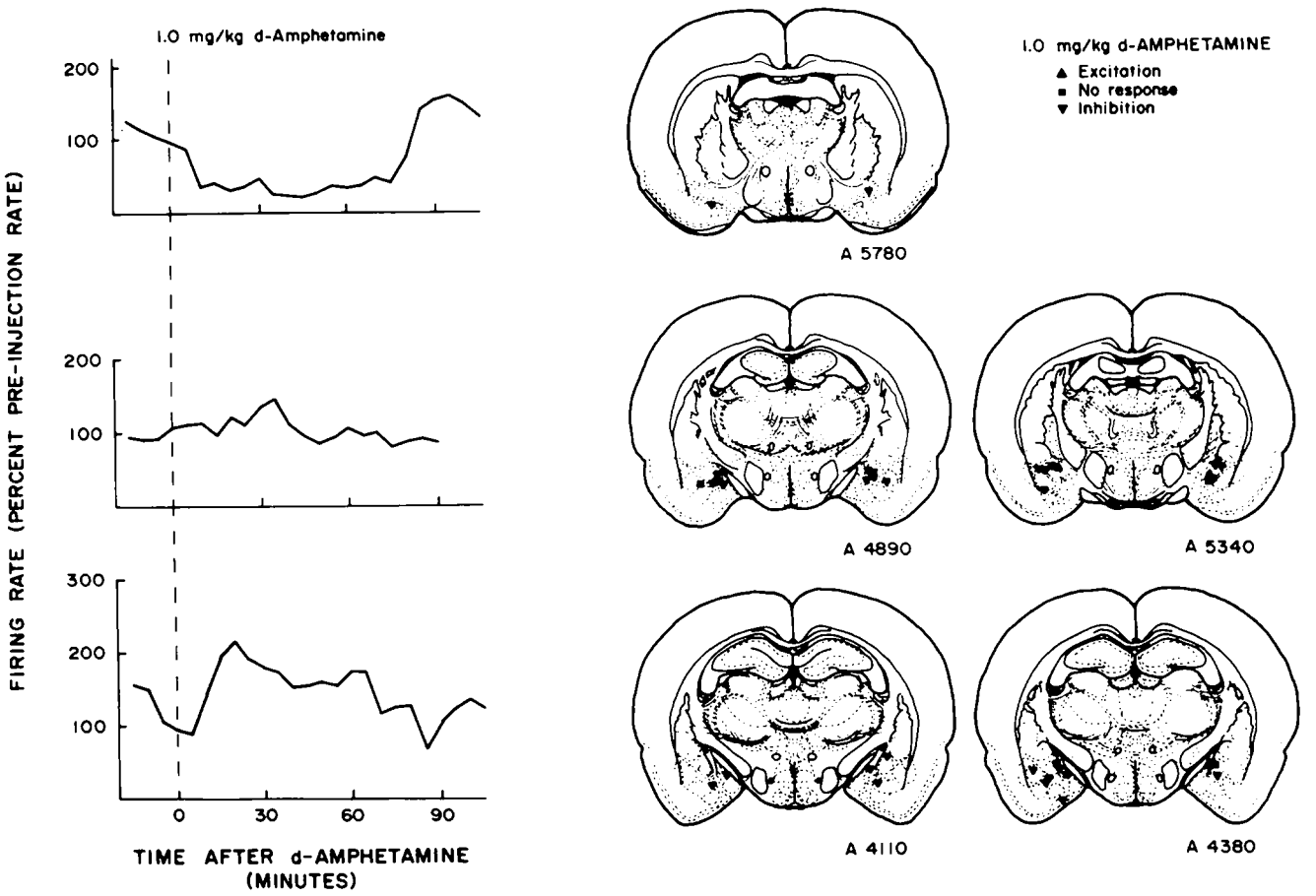

FIG. 3. Responses of individual neurons illustrating the increase, no change or decrease in firing rate produced by 1.0 mg/kg d-amphetamine injected (IP) at Time 0. Firing rate is expressed as percent of the pre-injection rate as in Fig. 2. The electrode tip placements for all amygdaloid neurons in the amphetamine group are shown at right along with their characteristic response as identified in the legend.

TABLE 1

PARAMETERS OF THE AMPHETAMINE-INDUCED DEPRESSION

Mean Onset Time (minutes after injection)	Mean Recovery Time (minutes after injection)	Mean Peak Depression (percent baseline)
24.5 (3.71)	57.7 (6.49)	32.2 (5.05)

Data were collected from 11 neurons in the amygdaloid complex. The mean onset indicates the time after an IP injection of 1.0 mg/kg d-amphetamine that unit activity first fell below 60% of the baseline rate and remained there for a period of 15 min or more. Recovery was designated as the time that firing rate first returned to 60% or more of baseline and remained there for at least the next 10 min. The mean peak depression refers to the greatest percent inhibition of activity from the baseline rate for a 5-min period for each neuron. Numbers in parentheses indicate the standard error of the mean.

amphetamine-induced inhibition of activity are illustrated in Fig. 4.

DISCUSSION

In sharp contrast to the similar effects of atypical and classical antipsychotic drugs on unit activity in the neostriatum and nucleus accumbens [40], the present results indicate that neurons in the amygdaloid complex are differentially responsive to these drugs. Thus, haloperidol, at a dose which elicits catalepsy in rats, generally failed to alter spontaneous neuronal activity, whereas clozapine, which is devoid of extrapyramidal side effects, typically produced a prolonged increase in firing rate. These results suggest that in addition to the neostriatum and nucleus accumbens, the

TABLE 2

BLOCKADE OF THE AMPHETAMINE RESPONSE BY ANTIPSYCHOTIC DRUGS

Treatment	Mean Firing Rate: 10-Min Period Before Antipsychotic	Mean Firing Rate: 20-Min Period After Antipsychotic
Clozapine (n=8)	32.5 (5.06)	101.7 (22.92)*†
Haloperidol (n=9)	23.3 (4.89)	36.0 (8.23)

Following an IP injection of 1.0 mg/kg d-amphetamine, clozapine (20.0 mg/kg) or haloperidol (2.0 mg/kg) was injected IP to block the amphetamine-induced depression (n=number of neurons in each group). Mean firing rate, expressed as percent of baseline, was calculated for the 10-min period immediately prior to the antipsychotic drug injection and for the 20-min period immediately afterwards. Numbers in parentheses refer to the standard error of the mean.

*Differs from pre-clozapine rate, $p<0.01$ (t-test).

†Differs from post-haloperidol rate, $p<0.025$ (t-test).

amygdala mediates, at least in part, the differential behavioral effects of atypical and classical antipsychotic drugs.

The neurochemical mechanisms underlying the action of the antipsychotic drugs is complicated by reports that apart from blocking DA receptors, these drugs act on a variety of neurotransmitters including acetylcholine, norepinephrine (NE), and serotonin [1, 13, 27, 28, 31, 38, 42, 43]. Since these chemicals have been identified in the amygdaloid complex [3, 6, 18, 37], any neurochemical explanation for the differential actions of clozapine and haloperidol is only speculative. It is interesting to note, however, that in the one case in which haloperidol increased amygdaloid activity, histological analysis revealed that the recording electrode was located in the central amygdaloid nucleus, an area that along with the basolateral nucleus contains the highest concentration of DA in the amygdaloid complex [32,35]. In this one instance, the haloperidol response was comparable to that produced by clozapine. Since some evidence suggests that clozapine is a more potent blocker of central NE receptors than haloperidol [5,34], it is possible that although both drugs antagonize DA transmission, clozapine, because of its strong adrenolytic effect, acts on a larger population of amygdaloid neurons than haloperidol.

This hypothesis may also explain the superior efficacy of clozapine in reversing the amphetamine-induced depression of activity. Amphetamine, for example, apart from facilitating DA transmission [12, 21, 25], has been reported to release NE from nerve terminals in the amygdaloid complex [48]. Furthermore, consistent with a putative inhibitory noradrenergic projection to the amygdala [36], iontophoretic application of NE onto amygdaloid neurons has been reported to inhibit unit activity [49]. Thus, the clozapine-induced reversal of the amphetamine response can be attributed, in part, to a blockade of NE receptors. This view is strengthened by our finding that haloperidol, a more potent DA antagonist than clozapine [17,44], failed to block the amphetamine-induced depression in all but one case. The exceptional neuron was recorded from the basolateral nucleus, suggesting that at least in this region of the amygdala DA may be involved in the neuronal response to amphetamine [2].

We have previously shown that clozapine is also more effective than haloperidol in reversing the amphetamine-induced depression in the neostriatum and nucleus accumbens [39]. In these sites, however, haloperidol blocked the amphetamine response, differing from clozapine only with respect to the onset and magnitude of this effect. In contrast, 8 of 9 amygdaloid neurons depressed by amphetamine failed to respond to haloperidol, whereas clozapine reversed the amphetamine response in every case. It is unlikely, therefore, that the neurochemical mechanisms underlying the action of the antipsychotic drugs in the neostriatum and nucleus accumbens can explain the differential action of clozapine and haloperidol in the amygdaloid complex. It is also unlikely that the inability of haloperidol to reverse the amphetamine-induced inhibition can be explained by recording from a group of amygdaloid neurons that differ in some way from those responding to clozapine, since the atypical antipsychotic blocked the amphetamine response even in the same neurons that did not respond to haloperidol. Moreover, the amphetamine-induced depression was comparable prior to the administration of either clozapine or haloperidol arguing against the possibility that any differential drug effects may be related to the degree of baseline inhibition.

The pronounced differences in unit activity produced by 2.0 mg/kg haloperidol and 20.0 mg/kg clozapine in the amygdaloid complex implicate this site in the dramatic behavioral differences produced by similar doses of the same drugs. Thus, amygdaloid neurons fail to respond to a dose of haloperidol which elicits catalepsy, but clozapine accelerates unit activity despite the fact that this and even higher doses do not cause any severe motor dysfunction. That the unique behavioral effects of the atypical antipsychotics may be explained by their action in the amygdala is supported by evidence that lesions of this structure significantly reduce the ability of clozapine, but not haloperidol, to block the behavioral activation produced by amphetamine [16]. It is conceivable, therefore, that the extrapyramidal side effects associated with the administration of the classical antipsychotic drugs are determined not only by their effects in the neostriatum and nucleus accumbens, but also by their relative inability to alter neuronal activity in the amygdaloid complex.

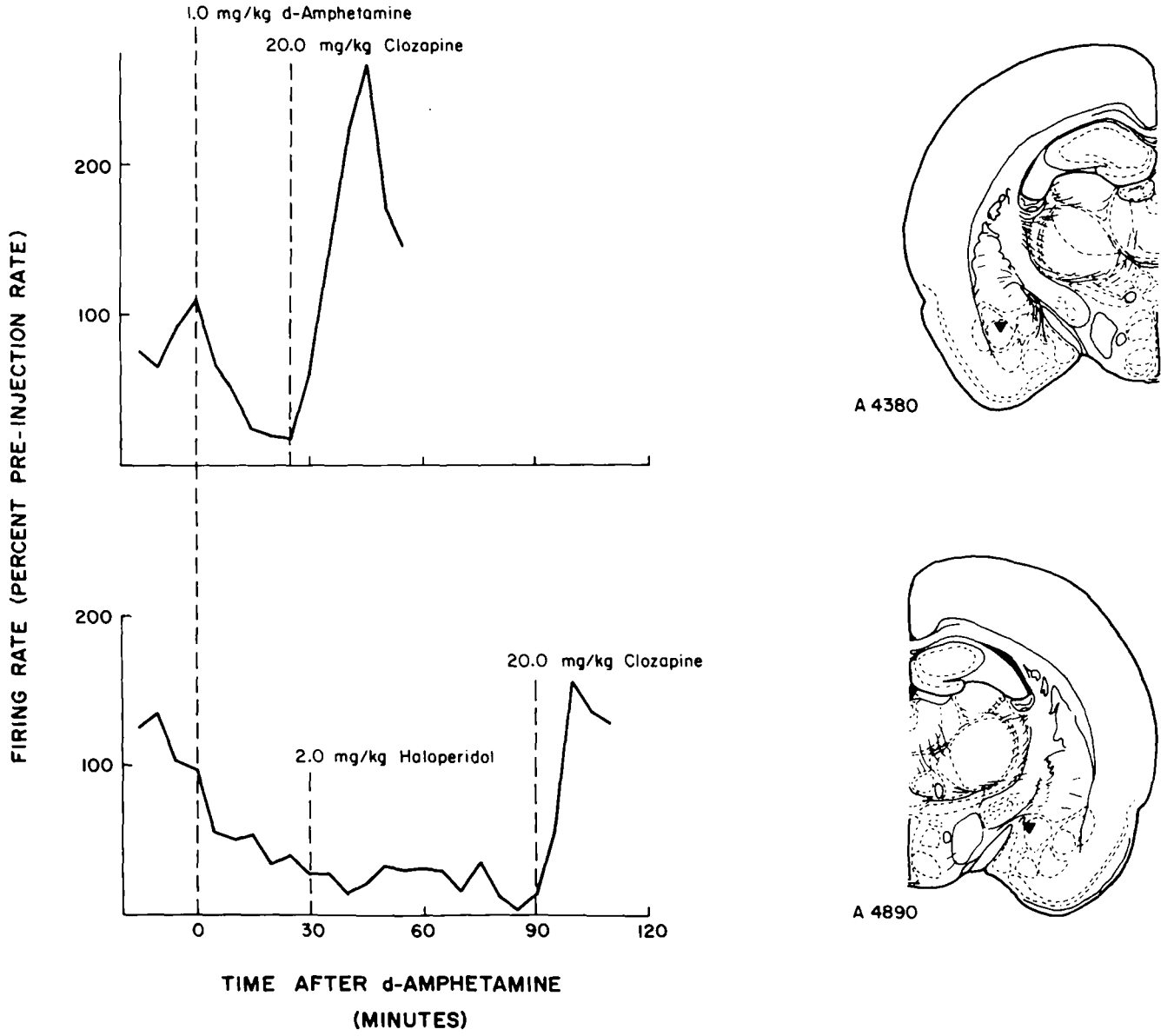

FIG. 4. Representative examples of the clozapine-induced reversal of the inhibition produced by 1.0 mg/kg d-amphetamine. The bottom graph illustrates the failure of haloperidol to block the amphetamine response. Unit activity is expressed as the percent of the pre-injection firing rate as in Fig. 2. The electrode tip placements are shown at right.

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