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Differential Response of Amygdaloid Neurons to Clozapine and Haloperidol: Effects of Repeated Administration

GLENN D. ANDERSON AND GEORGE V. REBEC[1]

Department of Psychology, Indiana University, Bloomington, IN 47405

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ANDERSON, G. D. AND G. V. REBEC. *Differential response of amygdaloid neurons to clozapine and haloperidol: Effects of repeated administration.* PHARMACOL BIOCHEM BEHAV 24(6) 1561–1566, 1986.—Rats were pretreated with saline or with behaviorally equivalent doses of clozapine (10.0 mg/kg) or haloperidol (1.0 mg/kg) twice daily for six consecutive days. On the following day, amygdaloid neurons in clozapine-pretreated rats responded to a challenge injection of this drug with a significantly greater increase in firing rate than saline controls. In contrast, amygdaloid neurons generally remained unresponsive to haloperidol even when pretreatment with this drug was extended to 13 days. Neither clozapine nor haloperidol pretreatment, however, altered the response of amygdaloid neurons to d-amphetamine administered after a four-day washout period. Amphetamine inhibited amygdaloid activity to a comparable extent in all rats. Taken together, these results implicate the amygdaloid complex as an important site of action of clozapine and related antischizophrenic drugs.

Amygdaloid complex Clozapine Haloperidol Repeated administration Amphetamine Unit activity

ALTHOUGH both clozapine and haloperidol reduce schizophrenic symptoms, a large body of evidence suggests that these drugs do not share the same mechanisms of action. Clinically, clozapine is administered at doses 10–20 times higher than those of haloperidol, yet haloperidol is much more likely to produce motor side effects [1, 2, 7, 16, 41]. In fact, clozapine is virtually devoid of the parkinsonian symptoms commonly associated with haloperidol. Other symptom differences have been reported, including an anxiolytic action of clozapine not shared by haloperidol and related compounds [10, 15, 42]. Experimental animals also respond differently to these drugs. Rats treated with haloperidol display muscular rigidity and catalepsy, but clozapine fails to produce such effects even at relatively high doses [38,47]. Moreover, despite their antischizophrenic action, these drugs exert different effects on the behavioral response to amphetamine, which has been used as an animal model of both drug-induced and idiopathic paranoid psychosis [21,28]. Haloperidol, for example, virtually abolishes the amphetamine response, whereas clozapine has been reported to attenuate some of the behavioral effects of amphetamine [14,37] and to enhance others [36].

Data obtained in our laboratory indicate that the amygdaloid complex is a promising site for research designed to elucidate the neuronal mechanisms underlying the differential actions of these antischizophrenic drugs [27,31]. Recordings from more than 90 neurons in the amygdaloid complex of the rat have shown that whereas 60% of these cells increase their firing rate to clinically relevant doses of clozapine (10.0–20.0 mg/kg), less than 15% respond to comparable doses of haloperidol (1.0–2.0 mg/kg). Moreover, clozapine, but not haloperidol, reverses the depression of amygdaloid activity produced by amphetamine [26]. Thus, even at doses known to elicit dramatic behavioral and therapeutic effects, amygdaloid neurons are largely unresponsive to haloperidol but generally excited by clozapine.

In clinical settings, these drugs are administered for prolonged periods. In fact, maximal therapeutic effects often are not achieved unless drug therapy persists for several days or weeks [1, 24, 25, 44, 46]. Although an increasing number of studies have focused on this aspect of antipsychotic treatment, no information is available on the effects of long-term administration in the amygdaloid complex. In the present series of experiments, therefore, we extended our single-unit recordings to examine the effects of multiple injections of clozapine and haloperidol using clinically relevant doses that, when administered acutely, had significantly different effects on amygdaloid activity. We were interested in determining if these differences persist with long-term treatment and if they are associated with a change in the sensitivity of amygdaloid neurons to amphetamine.

METHOD

Experiments were conducted on 78 male, Sprague-Dawley rats, weighing between 250–400 g. The animals,

[1]Requests for reprints should be addressed to George V. Rebec.

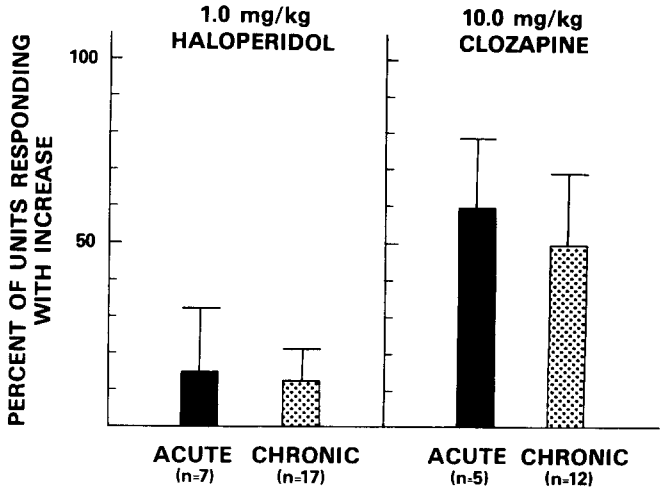

FIG. 1. Percent of amygdaloid neurons responding with an increase in firing rate to a challenge injection (IP) of 1.0 mg/kg haloperidol or 10.0 mg/kg clozapine. Note that although clozapine accelerates a greater proportion of amygdaloid units than haloperidol, 6-day pretreatment does not alter the number of neurons responding to either drug.

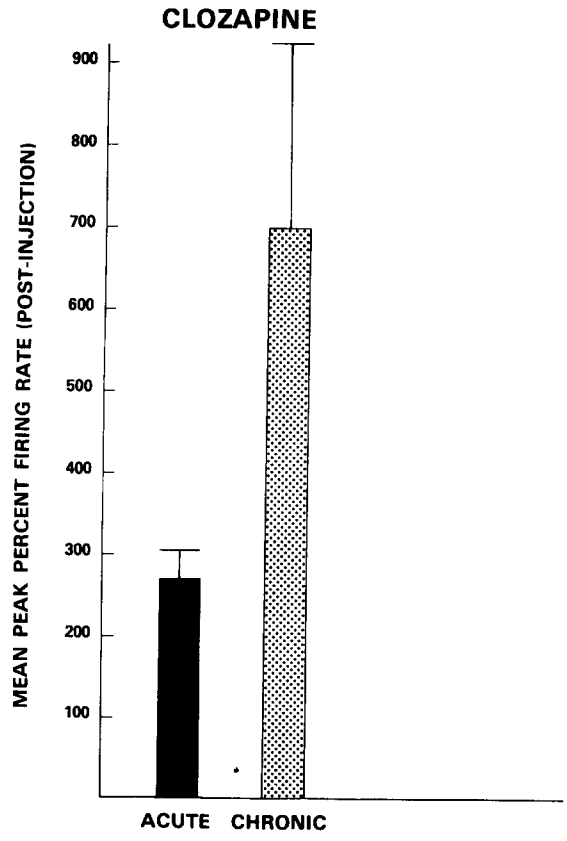

FIG. 2. Mean peak firing rate after an IP injection of 10.0 mg/kg clozapine, expressed as percentage of the 100% baseline rate. Note the significant enhancement of the response following 6-day pretreatment.

housed individually under standard laboratory conditions, were removed from their cages twice daily for six days to receive intraperitoneal (IP) injections of 1.0 mg/kg haloperidol (McNeil), 10.0 mg/kg clozapine (Sandoz), or an equivalent volume of saline. The clozapine vehicle has been shown elsewhere to exert no effect on neuronal activity [27]. In some cases, animals received twice daily injections of 1.0 mg/kg haloperidol for 13 days.

Following a withdrawal period of 1 or 4 days, the animals were prepared for single-unit recording. Surgical and anesthetic procedures were performed as described previously [17, 29, 34]. Tubocurarine chloride (Lilly) was administered (IP) to relax all skeletal muscles. Artificial respiration, provided by a rubber cone fitted snugly over the snout and attached to a small animal respirator, was adjusted to maintain an end-tidal carbon dioxide content of 4.0±0.5% as measured by a Beckman Medical Gas Analyzer. Heartbeat was displayed continuously on an oscilloscope, and body temperature was maintained at 37±0.5°C.

Tungsten microelectrodes, having an impedance of approximately 10 megohms, were lowered bilaterally into the amygdaloid complex according to the coordinates of König and Klippel [18]: 4.5 mm anterior and 4.75 mm lateral to stereotaxic zero and 7.0 mm ventral to the dural surface. Neuronal activity, recorded from both hemispheres, was amplified and displayed by conventional means. Single-unit discharges, having a signal-to-noise ratio of 3:1 or more, were counted by a neuronal spike analyzer in conjunction with a high-speed printer-counter. Spontaneous firing rates were recorded for at least 30 min to insure a stable level of baseline activity.

During single-unit recording on the first withdrawal day, rats were challenged with the same antipsychotic drug that they received during the 6- or 13-day treatment phase; saline controls received either 1.0 m/kg haloperidol or 10.0 mg/kg clozapine. Each drug was administered via a catheter implanted in the peritoneal cavity. Rats that had been withdrawn from treatment for 4 days were challenged with d-amphetamine sulfate (Smith, Kline and French). These animals were implanted with an intravenous (IV) catheter and, following the isolation of single-unit discharges, received IV injections of 0.2 mg/kg d-amphetamine (free base) at 2-min intervals.

In each case, the baseline firing rate was calculated during the 20-min period immediately preceding the drug injection and was defined as 100%. Drug-induced changes in firing rate were expressed in terms of the 100% 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 at least 50% of the baseline rate was excluded from further analysis; without such a precaution it would be impossible to rule out cellular injury, electrode drift, or other non-drug factors that could influence our results during a prolonged recording session.

Upon completion of each experiment, each animal received a lethal dose of sodium pentobarbital (Abbott), and the accuracy of the injection was verified by administering methylene blue through the catheters and inspecting each injection site. To mark the recording sites, current was passed through each electrode to make a small lesion. Following a transcardial perfusion with normal saline and 10% formalin, the brain was frozen, sectioned, and stained with cresyl violet for histological analysis.

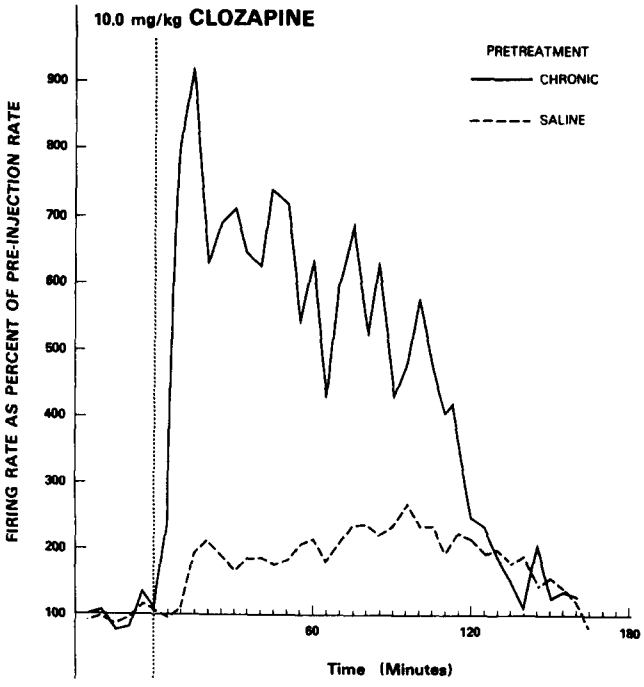

FIG. 3. Illustrative examples of the excitatory response to 10.0 mg/kg clozapine in saline- and clozapine-pretreated rats. Neuronal activity is plotted at 5-min intervals as a percentage of the 100% baseline rate. Although the onset and duration of the response are comparable in both rats, the magnitude is dramatically enhanced following chronic treatment.

RESULTS

Data were obtained from a total of 105 amygdaloid neurons located in the central nucleus (n=28), the corticomedial complex (n=52), and the basolateral complex (n=25). Units in all areas displayed a wide range of firing rates but no regional differences were observed. The mean baseline rate of all neurons sampled was 205±26 discharges/min, and there were no differences in mean firing rate across treatment groups.

Neuronal Responses to Clozapine or Haloperidol

We have shown previously that whereas an acute injection of clozapine accelerates the firing rate of 26 of 43 amygdaloid neurons by more than 150% above the baseline rate, only 6 of 49 cells respond to haloperidol [27]. We replicated these findings in saline controls and then examined the effects of multiple drug injections. As shown in Fig. 1, the percentage of neurons excited by 10.0 mg/kg clozapine or 1.0 mg/kg haloperidol did not change with long-term treatment. Thus, whereas approximately 60% of amygdaloid neurons were excited by clozapine, only 15% showed a similar response to haloperidol.

In all cases, the clozapine-induced increases in firing rate began between 5 and 20 min after the IP injection and persisted for approximately 150 min. Neither the onset nor the offset of this response changed significantly with multiple injections. As shown in Fig. 2, however, the magnitude of the increase was enhanced markedly. In fact, statistical analysis revealed a significant effect of clozapine pretreatment both with the present data alone, $t(7)=1.90$; $p<0.05$, and with the present data combined with our previous data [26] on acute increases to clozapine, $t(17)=2.95$; $p<0.005$. Thus, consistent with previous reports [27,28], the acute response approached 300% of the baseline rate and never exceeded 500%, whereas multiple clozapine injections typically doubled this response; in fact, some responses exceeded 1000% of the baseline rate. Representative examples of the increase to acute and chronic clozapine are shown in Fig. 3. Note the clear difference in response magnitude despite comparable onset and offset times.

Unlike clozapine, haloperidol produced no noticeable differences in amygdaloid activity with multiple injections. Thus, the large majority of neurons (15 of 17) failed to respond; firing rate did not deviate by more than 50% from the baseline rate at any time after the injection. In those two cases in which an increase in firing rate was observed in the chronic group, neither the onset, offset, nor magnitude of the response differed from the single excitation observed in the control group. In fact, no differences were observed even when rats were pretreated with haloperidol for 13 days. In this group, 2 of 8 neurons were excited by the drug and, again, the parameters of this response resembled those obtained from the control excitation; the remaining neurons in this sample were unresponsive.

As we have reported previously [26], some neurons were inhibited, rather than excited, by clozapine. However, only 3 such responses were recorded from both groups combined, making it impossible to determine if this response changed with chronic treatment. No inhibitions were recorded in response to haloperidol.

TABLE 1

EFFECTS OF PRETREATMENT WITH ANTIPSYCHOTIC DRUGS ON THE NEURONAL RESPONSE TO IV d-AMPHETAMINE IN THE AMYGDALOID COMPLEX

	Inhibition by d-Amphetamine	
Pretreatment	Number of Cells	ED50*
Saline	7 of 13	0.66 (0.08)
Clozapine	15 of 22	0.80 (0.06)
Haloperidol	10 of 21	0.64 (0.08)

*Mean effective dose (mg/kg) of d-amphetamine (IV) for producing a 50% inhibition of firing rate; numbers in parentheses refer to the standard error of the mean.

Neuronal Responses to Amphetamine

Separate groups of animals were treated for 6 days with saline, clozapine, or haloperidol as described above, and challenged 4 days later with IV injections of 0.2 mg/kg d-amphetamine separated by 2-min intervals. The amphetamine injections continued until firing rate decreased by at least 50% from the baseline rate or until the cumulative dose reached 1.2 mg/kg, whichever came first. In all groups, the characteristic response to this drug was an inhibition of firing rate between the second and sixth injections. Both the

mean effective dose for inhibiting neuronal activity and the number of neurons that showed this response were unaffected by pretreatment with either clozapine or haloperidol. These data are presented in Table 1.

Note that in all groups some amygdaloid neurons failed to respond to amphetamine. The number of unresponsive cells, however, did not change significantly with pretreatment. In no case did amphetamine increase amygdaloid activity.

DISCUSSION

Our results confirm and extend our previous finding that IP injections of clozapine, but not haloperidol, regularly accelerate the firing rate of neurons in the amygdaloid complex. With repeated administration, these differences become even more pronounced: the magnitude of the clozapine response is enhanced, whereas haloperidol remains largely without effect. These results are especially surprising since both behaviorally and clinically our dose of haloperidol equals or exceeds our dose of clozapine. It is unlikely that our results are unique to these doses since amygdaloid neurons are differentially responsive to acute injections of clozapine and haloperidol over a wide dose range [26,31]. Moreover, the number of neurons accelerated by these drugs was not altered with chronic treatment; only the magnitude of the response to clozapine changed, suggesting that rather than recruit progressively more neurons, multiple injections of this drug simply exert a greater effect on the population of cells that respond to acute administration. It also is unlikely that the enhanced excitation reflects a change in the pharmacokinetics or metabolism of the drug since neither the onset nor the duration of the response changed significantly with repeated injections.

Our results also revealed that pretreatment with neither clozapine nor haloperidol had an effect on the neuronal response to amphetamine. This finding is surprising since an acute injection of clozapine, but not haloperidol, is very effective in reversing the amphetamine-induced depression of amygdaloid activity [26,32]. Moreover, in behavioral tests, the amphetamine response is enhanced in rats withdrawn from antipsychotic drugs that block this response acutely [33]. The potentiation of the amphetamine behavioral response presumably reflects a compensatory increase in the sensitivity of receptors blocked by the antipsychotic drugs [39]. Thus, to the extent that clozapine blocks amygdaloid receptors that are influenced by amphetamine, one would expect a rebound supersensitivity to this drug in the amygdaloid complex of clozapine-pretreated rats. That no such effect was observed argues against an effect of clozapine on the same neuronal systems that respond to amphetamine. In fact, clozapine may reverse the amphetamine neuronal response in the amygdala via a glutaminergic or other independent neuronal system (e.g., [40]) that, when activated, simply masks the amphetamine-induced depression.

The four-day withdrawal period should be sufficient time for both clozapine and haloperidol to be cleared from the system, making it unlikely that our results with amphetamine reflect some residual interaction between this drug and the antipsychotics. In fact, the behavioral response to amphetamine is significantly enhanced in rats withdrawn from haloperidol pretreatment for only 2 days, and this effect persists for at least one week [33]. Thus, the failure of multiple injections of haloperidol to produce any change in the response of amygdaloid neurons to amphetamine suggests that the behavioral supersensitivity that accompanies long-term treatment with haloperidol cannot be explained by a direct action on neurons in this structure.

Neurons that are responsive to clozapine appear to be located throughout the amygdaloid complex. Approximately equal numbers of clozapine-induced excitations have been reported in the basolateral, central and corticomedial amygdaloid nuclear groups [26,27]. Similarly, our histological analysis of the excitations that occured in rats pretreated with the drug revealed no regional differences. Such uniformity may seem surprising in view of the heterogenous distribution of suspected neurotransmitters within the amygdaloid complex. Clozapine, however, has been reported to be an effective antagonist of cholinergic [38,43], noradrenergic [3,5], and serotonergic [13, 19, 20] receptors, all of which have been identified in the amygdala [4, 6, 12, 22]. Moreover, some amygdaloid neurons receive dopaminergic input [4,6] and, although less potent than haloperidol, clozapine also blocks dopaminergic transmission [8, 9, 39]. The actions of clozapine in the amygdaloid complex, therefore, might be explained best by an interaction among several different neuronal systems (e.g., [35]).

Haloperidol, on the other hand, is a potent blocker of dopaminergic receptors with considerably less affinity for other receptor sites [23, 37, 39, 43]. Thus, the large number of amygdaloid neurons that fail to change their firing rate in response to this drug is surprising since over 60% of these cells are known to respond to dopamine agonists [29,32].

Our results support a growing body of evidence that the differential actions of clozapine and haloperidol are enhanced with chronic treatment [11, 27, 33, 45]. That this enhancement occurs in the amygdala is especially significant since this appears to be the only forebrain site that is differentially responsive to an acute injection of these compounds. Our results also suggest, however, that clozapine is acting independently of the mechanisms that are responsible for the amphetamine-induced inhibition in this site. Finally, our results may extend to a wide range of antischizophrenic drugs that, like clozapine, are devoid of motor side effects. We already have shown that an acute injection of thioridazine, which mimics the behavioral and clinical profile of clozapine, also accelerates amygdaloid activity, whereas pimozide, a haloperidol-like antischizophrenic agent, is without effect [27,28]. It seems likely, therefore, that the amygdaloid complex will become an important site for further investigations of the neuronal systems underlying the effects of long-term treatment with clozapine and related antischizophrenic drugs.

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