Pharmacology Biochemistry & Behavior, Vol. 8, pp. 467–474. Printed in the U.S.A.

Alterations of Spontaneous Neuronal Activity in the Caudate-Putamen, Nucleus Accumbens and Amygdaloid Complex of Rats Produced by D-Amphetamine[1]

THEODORE R. BASHORE,[2] GEORGE V. REBEC[3] AND PHILIP M. GROVES

Department of Psychology, University of Colorado, Boulder, CO 80309

(Received 6 September 1977)

BASHORE, T. R., G. V. REBEC AND P. M. GROVES. *Alterations of spontaneous neuronal activity in the caudate-putamen, nucleus accumbens and amygdaloid complex of rats produced by d-amphetamine.* PHARMAC. BIOCHEM. BEHAV. 8(4) 467–474, 1978. – Changes in spontaneous neuronal activity in the caudate-putamen, accumbens nucleus and amygdaloid complex of immobilized, locally anesthetized rats were recorded following intraperitoneal injection of 2.5 mg/kg d-amphetamine sulfate. In each site, d-amphetamine typically produced a prolonged depression of firing rate which, in most cases, occurred after an initial, brief potentiation of activity. However, the onset of the amphetamine-induced depression occurred significantly later in the amygdala. Subsequent IP administration of either 5.0 mg/kg chlorpromazine or 2.0 mg/kg haloperidol reversed, to varying degrees, the amphetamine-induced depression of neuronal activity in each area. These results are discussed in terms of the known biochemical effects of amphetamine on catecholaminergic transmission and the alleged role of the nigro-neostriatal and mesolimbic dopamine systems in the amphetamine behavioral response.

Amygdala Nucleus accumbens Caudate putamen Amphetamine Neuronal activity

AMPHETAMINE elicits a dose-dependent sequence of behavior that in the rat includes an increase in locomotor activity and stereotyped sniffing, licking, gnawing and repetitive head movements [11, 29, 35]. The dopaminergic nigro-neostriatal pathway, which projects from the substantia nigra, pars compacta to the ipsilateral caudate-putamen [26], may be responsible, in part, for the psychomotor stimulant effects of amphetamine [14]. Recent evidence, however, suggests that the amygdaloid complex, parts of which receive dopaminergic innervation from the pars compacta, and the accumbens nucleus, which is part of the mesolimbic dopamine system and receives innervation from the mesencephalic ventral tegmental area may mediate some components of the amphetamine behavioral response [9, 10, 22, 28, 33].

Intraperitoneal injections of d-amphetamine typically produce a prolonged depression of firing rate of spontaneously active neurons in the caudate-putamen that is usually preceded by an initial, brief potentiation of neuronal activity [17, 30, 31]. The amphetamine-induced depression of neostriatal firing rate, which may be significantly related to some behavioral effects of the drug [15], appears to reflect the postsynaptic accumulation of dopamine [16], an alleged inhibitory transmitter [24]. d–Amphetamine administration also slows the firing rate of dopaminergic neurons in the substantia nigra, pars compacta [6, 18, 30] and in the ventral tegmental area [1]. The amphetamine-induced depression of activity in these sites is reversed by the administration of dopamine receptor blocking agents which also antagonize the behavioral response to amphetamine.

In the present study, we characterized and compared amphetamine-induced changes in neuronal activity in areas of the brain that receive dopaminergic innervation from the nigro-neostriatal or mesolimbic pathways. Our results indicate that under conditions designed to approximate the behavioral time-course of action of amphetamine, the drug produced qualitatively similar effects on neuronal activity in the caudate-putamen, accumbens nucleus and amygdaloid complex.

METHOD

Data were collected from 64 adult, male Sprague-Dawley rats, supplied by Simonsen Laboratories (Gilroy, CA), weighing between 250 and 470 g at the time of experimentation. The surgical procedure has been described in detail elsewhere [17]. Briefly, animals were anesthetized by ether inhalation and placed in a stereotaxic instrument

[1] Reprint requests should be addressed to: Philip M. Groves, Department of Psychology, University of Colorado, Boulder, CO 80309.
[2] Present address: Department of Psychology, Union College, Schenectady, NY 12308.
[3] Present address: Department of Psychology, Indiana University, Bloomington, IN 47401.

Copyright © 1978 ANKHO International Inc.—0091-3057/78/0804-0467$00.90

having blunt atraumatic ear bars. A short midsagittal scalp incision exposed the calvarium. The areas in and surrounding the wound were thoroughly infiltrated with procain hydrochloride (Novocain) and points of stereotaxic contact were treated with a local anesthetic ointment (Xylocaine). Supplemental applications of Novocain were administered periodically throughout the experiment. Commercial eyedrops (Visine) were applied intermittently to prevent discomfort from corneal drying. After small bilateral holes were drilled in the skull overlying the accumbens nuclei (approximately 9.4 mm anterior and 1.0 mm lateral stereotaxic zero), amygdaloid complex (approximately 4.8 anterior and 3.5 mm lateral to stereotaxic zero) or the caudate-putamen (approximately 8.10 mm anterior and 2.5 mm lateral to stereotaxic zero), the dura was removed, and ether anesthesia discontinued. Bilateral coordinates for each area were determined according to Koenig and Klippel [23]. Each animal was then immobilized with 2.0 mg/kg d-tubocurarine chloride (Abbott) with supplemental injections given at approximately hourly intervals. The preparation was artificially respired by means of a Harvard Instruments rodent respirator. Respiration rate and volume were adjusted to maintain a carbon dioxide concentration in the expired air of approximately 3.75% which was measured by a Beckman Instruments LB2 electronic carbon dioxide analyzer. Heartbeat was displayed continuously on the face of an oscilloscope and body temperature (YSI telethermometer) was maintained between 36.0 and 37.5°C by means of a recirculating hot-water heating pad (Tempump).

Following a period of approximately 30 min, glass-coated tungsten microelectrodes, having a tip dia. of approximately 1 μm and impedance of from 0.5 to 2.5 mΩ, were lowered into the target areas on each side of the brain and the search for spontaneous neuronal activity was begun. Single unit discharges were passed through a high-impedance amplifier and displayed on an oscilloscope. Unit activity was monitored on the audio monitor and, in some instances, was also photographed on 35 mm film. Isolated extracellular action potentials meeting a signal-to-noise criterion of 3 to 1 or more, were counted by means of amplitude discriminators attached to a digital printer (Newport Model 810) which provided a minute-by-minute printout of neuronal firing rates throughout the experiment. Spontaneous unit activity was monitored on a minute-by-minute basis for several minutes prior to an experiment to insure that a consistent rate of firing was established. The mean spontaneous firing rate/min for a 10 min period immediately prior to drug injection was used to define a mean preinjection control firing rate for each neuron. Preinjection firing rates fluctuated on a minute-by-minute basis within no more than 40% of this value. Each animal received an intraperitoneal (IP) injection of 2.5 mg/kg d-amphetamine sulfate (Smith, Kline and French) in saline. Some animals also received an IP injection of either 5.0 mg/kg chlorpromazine hydrochloride in saline or 2.0 mg/kg haloperidol (McNeil) 50 min after d-amphetamine.

Upon completion of each experiment, the animal received a lethal dose of sodium pentobarbital (Nembutal), the placements of the electrode tips were marked by passing current through the microelectrodes (Grass DC Constant Current Lesion Maker), and the preparation was perfused intracardially with normal saline followed by 10% Formalin and the brain removed. Each brain was frozen, sectioned and stained with cresyl-violet to verify electrode tip placements. Subsequent examination of the histological material revealed electrode tip locations which were then transferred to composite histological drawings of representative brain sections [23].

RESULTS

The mean spontaneous firing rates for all neurons sampled from the caudate-putamen, nucleus accumbens and amygdaloid complex are given in Table 1. An analysis of variance revealed that spontaneous activity did not differ significantly across brain sites. Intraperitoneal injection of 2.5 mg/kg d-amphetamine sulfate produced a depression of activity in a large majority of neurons encountered in all three brain regions (60 of 73 cells, see Table 1) although in some cases we observed prolonged increases in neuronal discharges following injection of the drug. Unit activity was considered to be depressed by d-amphetamine if its rate of firing declined to 60% of the preinjection baseline value and remained below that level for at least 15 min. Conversely, an increase in activity following d-amphetamine treatment was defined by a change in firing rate that reached 140% of the predrug control value and maintained that frequency for a minimum of 15 min. These atypical responses could not be predicted on the basis of preinjection firing rates or electrode tip location within each nucleus and are discussed separately below.

In some cases, the d-amphetamine-induced depression was followed by a rebound potentiation of activity, which was defined as an increase of firing rate that attained 140%

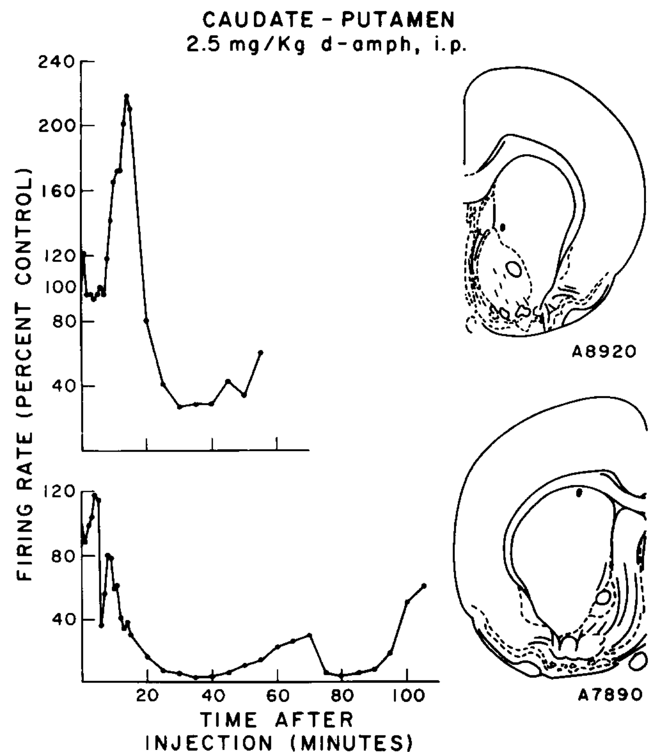

FIG. 1. Changes in neuronal activity recorded from the caudate-putamen following d-amphetamine administration. Two individual examples are shown. The positions of the electrode tips are illustrated to the right of each graph. The drug was administered at time zero.

TABLE 1

MEAN SPONTANEOUS NEURONAL ACTIVITY IN EACH REGION EXPRESSED AS SPIKES PER MIN

	Pre-Injection Firing Rate		
	Caudate-Putamen	Nucleus Accumbens	Amygdaloid Complex
	91 spikes/min (SEM ± 30) n=25; A=23	51 spikes/min (SEM ± 10) n=26; A=24	71 spikes/min (SEM ± 11) n=22, A=17
d-Amphetamine induced alterations			
Depression	18	23	19
Excitation	7	3	3
Initial potentiation	10	7	8
Rebound recovery	2 (7)	6 (9)	3 (7)
Neuroleptic blockage			
Depression			
Chlorpromazine	5 (7)	5 (9)	3 (6)
Haloperidol	3 (4)	4 (5)	5 (6)
Excitation			
Chlorpromazine	2 (4)	1 (1)	
Haloperidol	2 (3)	1 (1)	

SEM = standard error of the mean; n = number of cells; A = number of rats from whom cell population sampled. d-Amphetamine induced alterations: expressed as the number of cells in each nuclear group from the total sample that responded to the drug with either a decrease or an increase in firing rate. Also includes the number of cells whose activity depressed and this depression was preceded by an initial increase in firing rate, and the number of neurons that recovered from being depressed by d-amphetamine with a rebound potentiation. In the latter case, the numbers in parentheses represent the total number in that treatment group. Neuroleptic Blockade: number of cells in each condition whose depression or excitation in response to d-amphetamine was blocked by treatment with either chlorpromazine or haloperidol. Numbers in parentheses refer to total number of cells in that group.

of the predrug injection rate and persisted for at least 5 min. A significant proportion of neurons in each nuclear group responded to d-amphetamine with an initial, brief potentiation of firing rate that preceded the prolonged depression we observed in the majority of our sample. This alteration was defined by an increase in discharge rate that reached 140% of the preinjection value and lasted for no less than 5 min but no longer than 20 min. The number of cells in each brain site whose activity was altered in the above described ways is shown in Table 1.

The ability of the neuroleptic drugs, chlorpromazine (5.0 mg/kg) and haloperidol (2.0 mg/kg), to antagonize the d-amphetamine-induced alterations of firing rate was assessed in 46 of the 73 cells that we encountered. Each neuroleptic was administered 50 min after d-amphetamine and reversal of the d-amphetamine effect was judged to have occurred if the firing rate returned to the pre-amphetamine injection level with in 15 min. Table 1 lists the number of neurons in each condition that met this criterion.

Figure 1 illustrates two individual examples of the amphetamine-induced depression of activity in the caudate-putamen. Firing rate in this and all other figures is expressed as percent of control firing rate with 100% defined as the mean preinjection control firing rate per minute for a 10 min period prior to drug injection. Postinjection neuronal activity is reported on a minute-by-minute basis for the first 15 min and then as mean firing rate for 5 min blocks until firing rate returned to at least 60% control firing rate. Neuronal activity that did not return to this level of responsiveness was excluded from the sample. Corresponding electrode tip placements are shown to the right of each graph.

Note that in the caudate-putamen the depression of firing rate, which in the lower graph persists for approximately 100 min after amphetamine administration, is quite dramatic and, in some cases, was preceded by a marked initial potentiation of activity, as revealed clearly by the example in the upper graph. In 10 of 18 caudate-putamen neurons that subsequently decreased firing rate to d-amphetamine administration, an initial potentiation of activity occurred that ranged in magnitude for individual neurons from 150 to 550% control firing rate (see Table 1). The onset of the amphetamine-induced depression of firing rate began at approximately 20 min in 7 caudate-putamen neurons in which the response to d-amphetamine without a subsequent neuroleptic injection was monitored and persisted (below 60% control firing rate) for periods of from 45 to 155 min after injection with a mean duration of 81 min (SEM ± 10).

A qualitatively similar response occurred in the nucleus accumbens following an intraperitoneal injection of 2.5 mg/kg d-amphetamine. Representative samples of this response are illustrated in Fig. 2. Note again that following

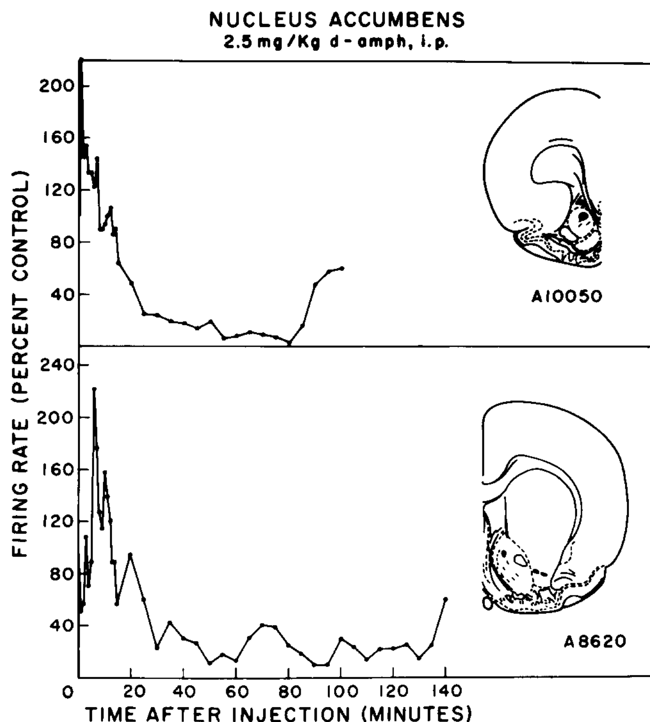

FIG. 2. Changes in neuronal activity recorded from the nucleus accumbens following d-amphetamine administration. Two individual examples are shown with the positions of the microelectrode tips illustrated to the right of each graph. The drug was administered at time zero.

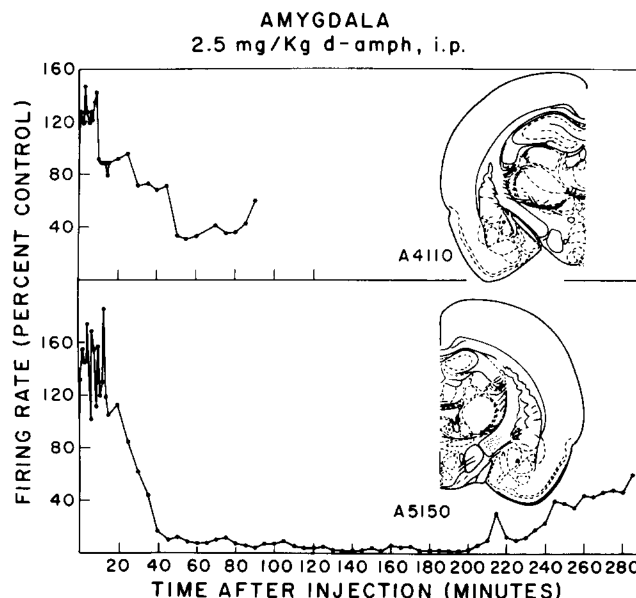

FIG. 3. Changes in neuronal activity recorded from the amygdala following d-amphetamine administration. Two individual examples are shown. The positions of the microelectrode tips are illustrated to the right of each graph. The drug was administered at time zero.

a brief potentiation of activity, firing rate was markedly inhibited, and in the case of the lower graph, this effect lasted for approximately 2 hr before returning to pre-injection control firing rate. In 7 nucleus accumbens neurons (see Table 1), an initial protentiation of activity was observed that ranged in magnitude from 220 to 305% control firing rate. Recordings from 9 neurons in which d-amphetamine was the only drug administered revealed that the onset of the amphetamine-induced depression of activity occurred at approximately 20 min and the return to control firing rate ranged for individual neurons from 35 to 180 min with a mean duration of 109 min (SEM ± 15).

In neurons variously located in the amygdaloid complex, an IP injection of 2.5 mg/kg d-amphetamine produced effects qualitatively similar to those described for the caudate-putamen and nucleus accumbens. Figure 3 illustrates amphetamine-induced changes in unit activity in two different amygdaloid neurons which exemplify the variability in response duration. In both cases, an initial potentiation of firing rate preceded the depression of activity which, as shown in the upper graph, persisted for 70 min after the injection. This effect was much more prolonged in some neurons, as revealed by the example shown in the lower graph, where the depression of activity lasted for 250 min from the time of injection. Note that both recordings were obtained from the central amygdaloid nucleus. As shown in Table 1, of 19 amygdaloid neurons that subsequently decreased firing rate to amphetamine administration, an initial potentiation of activity was apparent in 8 that ranged in magnitude from 147 to 175% of control firing rate. The amphetamine-induced depression, which in the amygdala typically occurred at 40 min after drug injection, ranged in duration for 7 individual neurons treated only with amphetamine from 75 to 305 min with a mean duration of 171 min (SEM ± 36).

Statistical analyses revealed that the magnitude of the initial potentiation of activity and the amphetamine-induced depression of firing rate did not differ significantly across brain sites, $F(2,53) = 1.94$, nor was there a consistent relationship, on an individual basis, between the duration and magnitude of the initial increase in activity and that of the subsequent depression of firing rate, $F(2,21) = 1.82$. Nevertheless, the overall duration of the drug-induced response, defined as the time from the amphetamine injection to a return to at least 60% control firing rate, was significantly longer in the amygdala than in the other two sites, $F(2,21) = 8.10$, $p<0.05$. This difference was attributable to a significant delay in onset of the amphetamine induced depression in the amygdala, $F(2,57)$, $p<0.05$. Interestingly, neurons in each site spent a comparable amount of time below 60% control rate, $F(2,21) = 1.62$.

When unit activity was monitored beyond the return to recovery criterion, a secondary or rebound increase in activity was recorded from several neurons (see Table 1). This phase of the amphetamine response, which was observed to occur in neurons in each site, was of variable magnitude and duration. The increase in activity following the amphetamine-induced depression in one amygdaloid neuron, located in central nucleus, is illustrated in Fig. 4. This unit responded to d-amphetamine with a prolonged depression of activity that persisted for over 300 min and was followed by a rebound potentiation of firing rate lasting approximately 125 min.

Attempts to reverse the d-amphetamine-induced depression in the caudate-putamen (n = 11), nucleus accumbens (n = 14) and amygdaloid complex (n = 12) with an IP injection of either chlorpromazine (5.0 mg/kg) or haloperidol (2.0 mg/kg) were successful to varying degrees.

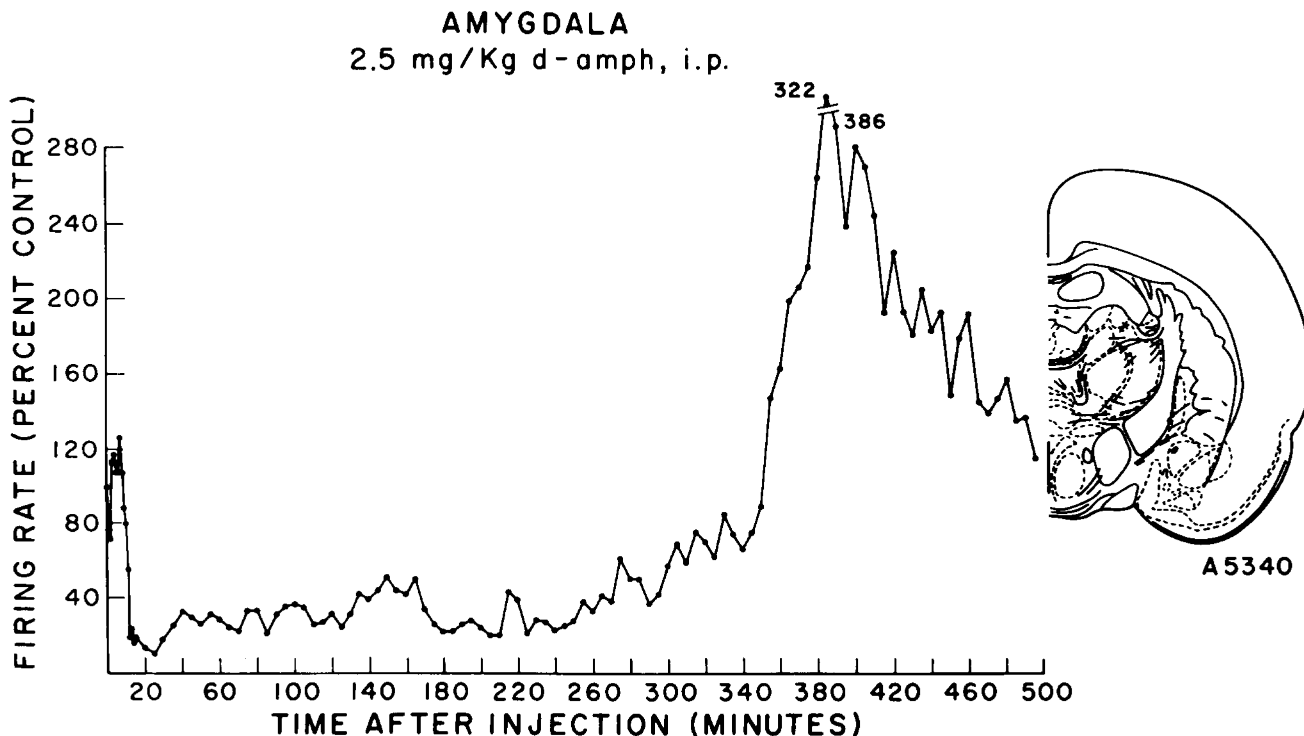

FIG. 4. The change in firing rate for one neuron recorded from the amygdaloid complex illustrating the rebound increase in firing rate that often follows the prolonged depression of activity produced by drug administration.

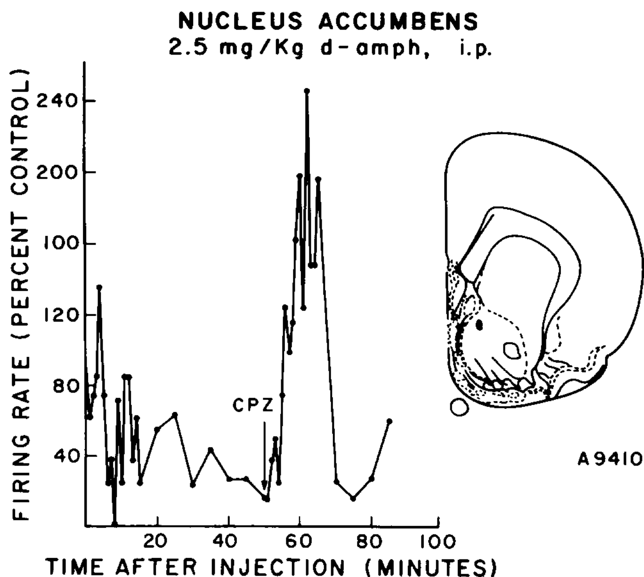

FIG. 5. Reversal of the d-amphetamine induced depression of firing rate for one neuron in nucleus accumbens by subsequent administration of chlorpromazine (5.0 mg/kg IP). Amphetamine was administered at time zero, chlorpromazine 50 min later. The position of the microelectrode tip is illustrated to the right of the graph.

In a majority of the neurons (68%) an apparent blockade occurred within 15 min of the injection. However, in a substantial proportion (32%) of the sample activity returned to the control level later than 15 min after the injection of chlorpromazine or haloperidol and therefore any subsequent increase in firing rate could not be attributed to an effect of drug administration. Table 1 shows the antagonistic effects of each neuroleptic for the respective nuclei and it is apparent that they were undifferentially effective.

Figure 5 illustrates the rapid reversal of the amphetamine response produced by chlorpromazine for one nucleus accumbens neuron. Following a depression of firing rate, chlorpromazine produced an increase in activity that surpassed control rate for several minutes. Note that this reversal was followed by a subsequent depression of activity. An example of the rapid reversal by haloperidol of the amphetamine effect in the amygdala is shown in Fig. 6. In this unit, located in the basolateral nucleus, haloperidol caused a dramatic increase in firing rate well above control level which lasted for several minutes.

A small proportion of our total sample of neurons (18%) responded to an IP injection of 2.5 mg/kg d-amphetamine with a prolonged increase in activity (see Table 1). This atypical response ranged in magnitude for individual neurons from 200 to 800% control firing rate and persisted in some cases for nearly 2 hr or more. In some of these cases, we attempted to block this prolonged increase with an IP injection of 5.0 mg/kg chlorpromazine or 2.0 mg/kg haloperidol at 50 min after d-amphetamine administration. Both drugs appeared to reverse this amphetamine-induced excitation. An example of the haloperidol blockade of this response in the caudate-putamen is depicted in Fig. 7. Subsequent administration of either chlorpromazine or haloperidol also reversed the amphetamine excitation in the nucleus accumbens but no attempts were made to block this atypical response in the amygdala.

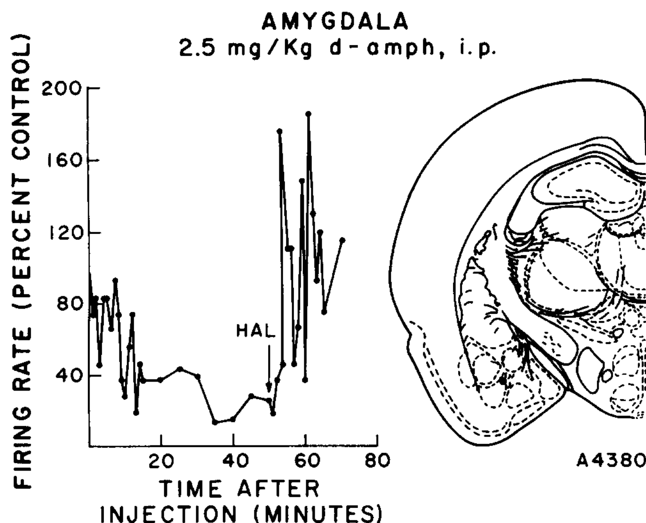

FIG. 6. Reversal of the d-amphetamine induced depression of firing rate for one neuron in the amygdaloid complex by subsequent administration of haloperidol (2.0 mg/kg IP). Amphetamine was administered at time zero, haloperidol 50 min later. The position of the microelectrode tip is illustrated to the right of the graph.

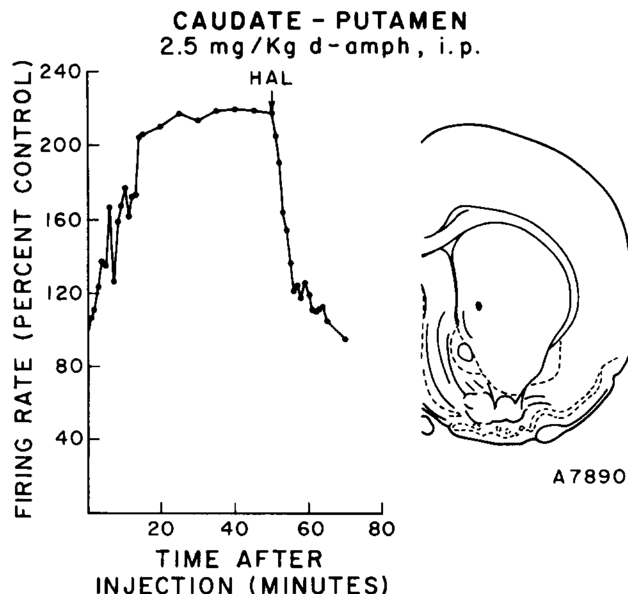

FIG. 7. An atypical, marked increase in neuronal firing rate for a neuron recorded in the caudate-putamen following d-amphetamine administration at time zero. This excitatory effect could also be blocked by subsequent haloperidol administration (2.0 mg/kg IP).

DISCUSSION

The IP administration of d-amphetamine elicited in the large majority of neurons in the caudate-putamen, nucleus accumbens and amygdaloid complex a marked depression of activity which was often preceded by an initial, brief potentiation of firing rate. These results, which are consistent with previous reports on amphetamine-induced alterations in the caudate-putamen [14, 17, 30, 31, 32], suggest that amphetamine has qualitatively similar effects on neuronal activity in those areas of the brain that receive dopaminergic innervation from the substantia nigra, pars compacta and ventral tegmental area. It is unlikely that these drug-induced changes in unit activity are secondary to peripheral effects since they are not correlated with changes in body temperature, expired carbon dioxide concentration or heart rate. We have previously reported that mephentermine, a weak central nervous system stimulant with peripheral effects comparable to those of amphetamine [20], does not significantly alter firing rate in the caudate-putamen or mesencephalic reticular formation [16,30]. In contrast to the effects of amphetamine on neuronal activity in sites of termination of dopaminergic afferents, a marked increase occurs in the reticular formation and substantia nigra pars reticulata following intraperitoneal amphetamine administration [15, 17, 30].

The initial, brief potentiation of activity which was observed in many cases prior to a depression of firing rate probably does not represent an effect of dopaminergic transmission. Lesions of the nigro-neostriatal bundle, which reduce telencephalic dopamine levels, attenuate the amphetamine-induced depression of activity in the caudate-putamen but have no significant effect on the initial potentiation [16]. That the depression of firing rate involves a dopaminergic component is supported by evidence that the subsequent administration of haloperidol, a dopamine receptor blocking agent, reverses this response to amphetamine in the caudate-putamen [17]. Our results are consistent with these reports and suggest further that an amphetamine-induced release of dopamine may also account for the slowing of firing rate in the nucleus accumbens and amygdala, although a noradrenergic influence cannot be ruled out. In most cases, both haloperidol and chlorpromazine were effective in rapidly blocking the depression of activity in the caudate-putamen, nucleus accumbens and amygdala produced by d-amphetamine. Although haloperidol is generally considered to be a relatively more specific dopamine receptor blocking agent than chlorpromazine, both agents, at the doses in this study, may have noradrenergic blocking properties as well [2]. Both dopamine and norepinephrine are present in the nucleus accumbens, and dopaminergic and noradrenergic nerve terminals have been identified in the amygdaloid complex [3,19]. Iontophoretic application of either dopamine, norepinephrine or amphetamine has been reported to produce a depression of unit activity in the nucleus accumbens, amygdala and caudate-putamen [5, 13, 24, 37, 40].

Although the return to control firing rate following the amphetamine-induced depression occurred significantly later in the amygdala than in the other two sites, this difference was apparently due to a significant delay in onset of the depression and not to an overall increase in the duration of the drug response. The total amount of time that unit activity in each site was depressed by amphetamine did not differ nor was the magnitude of the depression significantly different across brain sites, although a floor effect would undoubtedly obscure the latter. Further, the duration and magnitude of the initial amphetamine-induced potentiation of activity were not significantly different between the brain areas. The relatively late onset of the depression in the amygdala may reflect a number of pharmacokinetic and neurophysiological factors, which were not addressed by our experiments. It is interesting to note, however, that despite the heterogeneity of the neuronal population of the

amygdaloid complex [38] the depression of firing rate following amphetamine administration was relatively widespread and did not appear to be confined to a specific nucleus or region within the amygdala.

Some neurons whose activity was monitored beyond the return to control firing rate recovered from the amphetamine-induced depression with a secondary or rebound increase in activity. A similar response has been reported to occur in the caudate-putamen following systemic amphetamine administration [30] or stimulation of the substantia nigra [7,12]. Such secondary increases may reflect a reduction in in the availability of catecholamines for release which, in the case of amphetamine administration, could result from a drug induced reduction of dopamine biosynthesis [4].

A small sample of neurons in the caudate-putamen, nucleus accumbens and amygdaloid complex responded to d-amphetamine administration with a prolonged increase of activity. Such atypical responses to amphetamine have been reported previously for some neurons in the caudate-putamen [30,32]. In the amygdala, intravenous administration of amphetamine has also been reported to elicit an incrase in firing rate [40]. It is difficult to speculate on the mechanisms underlying these atypical increases in activity. Although there is some evidence that two different populations of dopamine receptors mediating synaptic inhibition and excitation could be differentially distributed in the neostriatum and nucleus accumbens (see Cools [8]), we were unable to find a consistent topographical distribution of neurons excited by amphetamine. Nevertheless, consistent with such a dual receptor idea is our evidence that both chlorpromazine and haloperidol blocked the amphetamine-induced excitation in the caudate-putamen and nucleus accumbens.

A growing body of behavioral evidence suggests that both the neostriatal and mesolimbic dopamine systems, in part, mediate the behavioral response to amphetamine. The administration of dopamine receptor blocking agents reverses the psychomotor stimulant effects of amphetamine [34,39]. 6–Hydroxydopamine lesions of the nucleus accumbens and neostriatum, which substantially reduce forebrain dopamine levels, attenuate amphetamine-induced locomotion and stereotypy, respectively, in rats [21,22]. The role of the amygdala in the amphetamine behavioral response is less clear. Amygdaloid mediation of emotional expression is well documented (see Leaton [25]) and this area may be of significance to the mood alterations produced by amphetamine [27,36]. Electrolytic lesions of the amygdala have been reported to reduce the intense components of the amphetamine-induced stereotypy in rats [9,10].

Our results indicate that amphetamine is capable of producing dramatic changes in unit activity in the caudate-putamen, nucleus accumbens and amygdaloid complex. Such changes in firing rate in areas that receive considerable dopaminergic innervation lend additional support to the notion that these sites play an important role in the behavioral response to amphetamine and amphetamine-like agents.

ACKNOWLEDGEMENT

We thank Patricia Wilson and Stephen J. Young for their skilled technical assistance, and Smith Kline and French Laboratories for supplying the d-amphetamine sulphate. This work was supported in part by grant DA 01467 from the National Institute on Drug Abuse and Research Scientist Development Award K02 MH 70706 from the National Institute of Mental Health to P. M. G.

REFERENCES

1. Aghajanian, G. K. and B. S. Bunney. Pre- and post-synaptic feedback mechanisms in central dopaminergic neurone. In: *Frontiers in Neurology and Neuroscience Research, 1974,* edited by P. Seeman and G. M. Brown. Toronto: University of Toronto Press, 1974, pp. 4–11.
2. Andén, N. E., H. Corrodi and K. Fuxe. Effects of neuroleptic drugs on central catecholamine turnover assessed using tyrosine- and dopamine-β-hydroxylase inhibitors. *J. Pharm. Pharmac.* **24:** 177–182, 1972.
3. Beni-Ari, Y., R. E. Zigmond and K. E. Moore. Regional distribution of tyrosine hydroxylase, norepinephrine and dopamine within the amygdaloid complex of the rat. *Brain Res.* **87:** 96–101, 1975.
4. Besson, M. J., A. Cheramy and J. Glowsinski. Effects of some psychotropic drugs on dopamine synthesis in rat striatum. *J. Pharmac. exp. Ther.* **177:** 196–205, 1971.
5. Bunney, B. S. and G. K. Aghajanian. Dopamine and norepinephrine innervated cells in the rat prefrontal cortex: Pharmacological differentiation using microiontophoretic techniques. *Life Sci.* **19:** 1783–1792, 1976.
6. Bunney, B. S., J. R. Walters, R. H. Roth and G. K. Aghajanian. Dopaminergic neurons: Effect of antipsychotic drugs and amphetamine on single cell activity. *J. Pharmac. exp. Ther.* **185:** 560–571, 1973.
7. Connor, J. D. Caudate nucleus neurones: Correlation of the effect of substantia nigra stimulationwith iontophoretic dopamine. *J. Psychol.* **208:** 691–703, 1970.
8. Cools, A. R., H. A. J. Struyker Boudier and J. M. Van Rossum. Dopamine receptors: Selective agonists and antagonists of functionally distinct types within the feline brain. *Eur. J. Pharmac.* **37:** 283–293, 1976.
9. Costall, B. J. and R. J. Naylor. Extrapyramidal and mesolimbic involvement with the stereotypic activity of d- and l-amphetamine. *Eur. J. Pharmac.* **25:** 121–129, 1974.
10. Costall, B. J. and R. J. Naylor. The nucleus amygdaloideus centralis and neuroleptic activity in the rat. *Eur. J. Pharmac.* **25:** 138–146, 1974.
11. Ellinwood, E. H. and R. L. Balster. Rating the behavioral effects of amphetamine. *Eur. J. Pharmac.* **28:** 25–41, 1974.
12. Feltz, P. and D. Albe-Fessard. A study of an ascending nigro-caudate pathway. *Electroenceph. clin. Neurophysiol.* **33:** 179–193, 1972.
13. Feltz, P. and J. De Champlain. Enhanced sensitivity of caudate neurones to microiontophoretic injections of dopamine in 6-hydroxydopamine treated cats. *Brain Res.* **43:** 601–605, 1971.
14. Groves, P. M. and G. V. Rebec. Biochemistry and behavior: Some central actions of amphetamine and antipsychotic drugs. *Ann. Rev. Psychol.* **27:** 91–127, 1976.
15. Groves, P. M. and G. V. Rebec. Changes in neuronal activity in the neostriatum and reticular formation following acute or long-term amphetamine administration. In: *Cocaine and Other Stimulants,* edited by E. H. Ellinwood and M. M. Kilbey. New York: Plenum Press, 1977, pp. 269–301.
16. Groves, P. M., G. V. Rebec and J. A. Harvey. Alteration of the effects of (+)–amphetamine on neuronal activity in the striatum following lesions of the nigrostriatal bundle. *Neuropharmacology* **14:** 369–376, 1975.
17. Groves, P. M., G. V. Rebec and D. S. Segal. The action of d-amphetamine on spontaneous activity in the caudate nucleus and reticular formation of the rat. *Behav. Biol.* **11:** 33–47, 1974.

18. Groves, P. M., C. J. Wilson, S. J. Young and G. V. Rebec. Self-inhibition by dopaminergic neurons. *Science* **190**: 522–529, 1975.
19. Hedreen, H. C. and J. P. Chalmers. Neuronal degeneration in rat brain induced by 6-hydroxydopamine: A histological and biochemical study. *Brain Res.* **47**: 1–36, 1972.
20. Innes, I. R. and M. Nickerson. Drugs acting on postganglionic adrenergic nerve endings and structures innervated by them (sympathomimetic drugs). In: *The Pharmacological Basis of Therpaeutics,* edited by L. S. Goodman and A. Gilman. New York: MacMillan, 1970, pp. 478–523.
21. Iversen, S. D. Neural substrates mediating amphetamine responses. In: *Cocaine and Other Stimulants,* edited by E. H. Ellinwood and M. M. Kilbey. New York: Plenum Press, 1977, pp. 31–45.
22. Kelly, P. H., P. W. Seviour and S. D. Iversen. Amphetamine and apomorphine responses in the rat following 6–OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res.* **94**: 507–522, 1975.
23. Koenig, J. F. R. and R. A. Klippel. *The Rat Brain: A Stereotaxic Atlas of the Forebrain and Lower Parts of the Brain Stem.* Baltimore: Williams and Wilkins, 1963.
24. Krnjevic, K. Electrophysiology of dopamine receptors. In: *Advances in Neurology,* Vol. 9, edited by D. B. Calne, T. N. Chase and A. Barbeau. New York: Raven Press, 1975, pp. 13–24.
25. Leaton, R. N. The limbic system and its pharmacological aspects. In: *An Introduction to Psychopharmacology,* edited by R. H. Rech and K. E. Moore. New York: Raven Press, 1971, pp. 137–174.
26. Lindvall, O. and A. Bjorklund. The organization of the ascending catecholamine neuron systems in the rat brain. *Acta physiol. scand.* (Suppl. **412**), 1974.
27. Matthysee, S. Implications of catecholamine systems of the brain in schizophrenia. In: *Brain Dysfunction in Metabolic Disorders, Res. Publ. Assoc. Nerv. Ment. Dis.,* edited by F. Plum. New York: Raven Press, 1974, pp. 305–315.
28. Pijenburg, A. J., W. M. M. Honig and J. M. Van Rossum. Effects of antagonists upon locomotor stimulation induced by injection of dopamine and noradrenaline into the nucleus accumbens of nialamide-pretreated rats. *Psychopharmacologia* **41**: 175–180, 1975.
29. Randrup, A. and E. Munkvad. Pharmacology and physiology of stereotyped behavior. *J. Psychiat. Res.* **11**: 1–10, 1974.
30. Rebec, G. V. and P. M. Groves. Differential effects of the optical isomers of amphetamine on neuronal activity in the reticular formation and caudate nucleus of the rat. *Brain Res.* **83**: 301–318, 1975.
31. Rebec, G. V. and P. M. Groves. Apparent feedback from the caudate nucleus to the substantia nigra following amphetamine administration. *Neuropharmacology* **14**: 275–282, 1975.
32. Rebec, G. V. and P. M. Groves. Enhancement of effects of dopaminergic agonists on neuronal activity in the caudate-putamen of the rat following long-term d-amphetamine administration. *Pharmac. Biochem. Behav.* **5**: 349–357, 1976.
33. Roberts, D. G. S., A. P. Zis and H. C. Fibiger. Ascending catecholamine pathways and amphetamine-induced locomotor activity: Importance of dopamine and apparent non-involvement of norepinephrine. *Brain Res.* **93**: 441–454, 1975.
34. Rolinski, Z. and J. Scheel-Kruger. The effect of dopamine and noradrenaline antagonists on amphetamine-induced locomotor activity in mice and rats. *Acta pharmac. toxic.* **33**: 385–399, 1973.
35. Segal, D. S. and A. J. Mandell. Long-term administration of d-amphetamine: Progressive augmentation of motor activity and stereotypy. *Pharmac. Biochem. Behav.* **2**: 249–255, 1974.
36. Stevens, J. R. An anatomy of schizophrenia? *Arch. gen. Psychiat.* **29**: 177–189, 1973.
37. Straughan, D. W. and K. T. Legge. The pharmacology of amygdaloid neurones. *J. Pharm. Pharmac.* **17**: 675–677, 1965.
38. Tombol, T. and A. Szafranska-Kosmal. A Golgi study of the amygdaloid complex in the cat. *Acta neurobiol. exp.* **32**: 835–848, 1972.
39. Wallach, M. B. Drug-induced stereotyped behavior: Similarities and differences. In: *Neuropsychopharmacology of Monoamines and Their Regulatory Enzymes,* edited by E. Usind. New York: Raven Press, 1974, pp. 241–260.
40. Wepsic, J. G. and G. M. Austin. The neurophysiological effects of amphetamine upon the cat amygdala. In: *The Neurobiology of the Amygdala,* edited by B. E. Eleftheriou. New York: Plenum Press, 1972, pp. 623–635.