Pharmacology Biochemistry & Behavior, Vol. 5, pp. 349–357.

Enhancement of Effects of Dopaminergic Agonists on Neuronal Activity in the Caudate-Putamen of the Rat Following Long-Term d-Amphetamine Administration[1]

GEORGE V. REBEC[2] AND PHILIP M. GROVES[3]

Department of Psychology, University of Colorado, Boulder

(Received 24 April 1976)

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(3) 349–357, 1976. – Amphetamine- and apomorphine-induced changes in the activity of neurons in the caudate-putamen of paralyzed, locally anesthetized rats were recorded in animals pretreated with 2.5 mg/kg d-amphetamine sulphate for 6, 18 or 36 days, or in animals pretreated with saline for 36 consecutive days. In saline-pretreated animals, 2.5 mg/kg d-amphetamine sulphate (IP) produced an initial, brief potentiation of neuronal firing that was followed by a marked depression of neuronal activity lasting for approximately 35 to 110 min after injection. In amphetamine-pretreated animals, this depression of neuronal activity to the same dose of the drug was markedly prolonged, especially in animals given 36 consecutive days of d-amphetamine pretreatment. A similar enhancement occurred in response to 0.25 mg/kg apomorphine (IP) in animals pretreated with amphetamine for 36 days compared to saline-pretreated control animals. These results are discussed in relation to the known behavioral and biochemical effects of acute and long-term amphetamine administration.

Amphetamine Apomorphine Caudate-putamen Neuronal activity

IN a wide variety of species, administration of amphetamine produces an increase in locomotor behavior and, depending on the dose, a bout of repetitive or stereotyped behaviors [6, 25, 36]. Considerable evidence has accumulated to suggest that transmission in the nigro-neostriatal bundle, a dopaminergic fiber projection from the substantia nigra pars compacta to the neostriatum [1], is important for the expression of the psychostimulant effects of amphetamine, especially amphetamine-induced stereotypies [4, 11, 17, 22].

When amphetamine is administered to experimental animals for periods of days or weeks, tolerance develops to its anorexigenic, cardiovascular and hyperthermic effects [3, 5, 14, 22, 24, 33]. However, tolerance does not develop to all of the actions of the drug [16, 20, 23]. Interestingly, the hyperactivity and stereotyped behaviors produced by an injection of amphetamine are not reduced following long-term exposure to amphetamine, but rather appear to be progressively enhanced [29]. In addition to an enhancement of d-amphetamine induced stereotypies, stereotyped behavior induced by apomorphine, a direct-acting dopamine agonist, is also enhanced following long-term pretreatment with amphetamine [18].

In the locally anesthetized, paralyzed rat, an intraperitoneal injection of amphetamine produces a marked slowing of neostriatal neuronal activity lasting from one to several hours. At doses of the drug that produce both locomotor activity and stereotyped behavior in unparalyzed animals, this depression of spontaneously active neurons is preceded by a brief, initial increase in neuronal firing [13,26]. The slowing of caudate-putamen neuronal firing rates has been attributed to the amphetamine-induced release of dopamine from terminals of the nigro-neostriatal pathway [12] which acts as an inhibitory neurotransmitter in this region of the brain [21].

Segal and Mandell [29] have shown that 2.5 mg/kg d-amphetamine given once daily to rats for 36 consecutive days results in a progressive augmentation of the locomotor

[1] Supported in part by grant MH 19515 and Research Scientist Development Award K02 MH 70706 to PMG from the National Institute of Mental Health. Data presented here are also being submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Psychology at the University of Colorado by GVR, and were presented in preliminary form at the Conference on Current Issues in Stimulant Research, Duke University School of Medicine, Durham, North Carolina, November 10–12, 1975.

[2] Present address: Department of Psychiatry, School of Medicine, University of California at San Diego, La Jolla, California 92093.
[3] Reprints may be obtained from Philip M. Groves, Department of Psychology, University of Colorado, Boulder, Colorado 80309.

and stereotyped behaviors produced by this dose of amphetamine. The purpose of the present investigations was to determine if similar pretreatment for periods varying from 6–36 days would affect the responsiveness of spontaneously active caudate-putamen neurons to subsequent administration of d-amphetamine or apomorphine, indirect and direct-acting dopamine agonists respectively.

METHOD

Animals and Surgery

Experiments were carried out on 48 adult, male, Sprague-Dawley rats (supplied by Simonsen Laboratories, Gilroy, California), maintained on a 12 hr light/dark cycle with the light cycle beginning at 6:30 a.m. The animals were removed from their cages for a 2-min period at approximately 10:30 a.m. and received an intraperitoneal (IP) injection of 2.5 mg/kg d-amphetamine sulfate [Smith, Kline and French] for 6, 18 or 36 consecutive days, or an equivalent volume of 0.9% saline for 36 days. On the day immediately following the appropriate pretreatment period, the animal, weighing from 300–500 g was anesthetized with ether and placed in a stereotaxic instrument having atraumatic ear bars (Kopf Instruments). Areas of the external auditory meatus which came into contact with the blunted ear bars and the area to contact the incisor bar were pretreated with a local anesthetic ointment (Xylocaine). A short, midsagittal scalp incision exposed the calvarium. Small holes were drilled in the skull overlying the caudate-putamen (approximately 8000 microns anterior and 2500 microns lateral to stereotaxic zero of König and Klippel, [19] and the dura was slit.

The areas in and surrounding the wound were thoroughly infiltrated with procaine hydrochloride without epinephrine (Novocain) and Xylocaine was topically applied to all cut edges. Supplemental applications of local anesthetic were administered every 60–90 min throughout the experiment. Commercial eyedrops (Visine) were applied intermittently to prevent discomfort from corneal drying. Each animal was immobilized with 2.0 mg/kg d-tubocurarine chloride (Lilly) and ether anesthesia was discontinued. Supplemental injections of the paralytic were given at approximately hourly intervals. Animals were artificially respired by means of a Harvard Instruments Rodent Respirator attached to a rubber cone fitted snugly over the snout, eliminating any need for tracheal intubation. Respiration rate and volume were adjusted to maintain a carbon dioxide concentration in the expired air of 4 ± 0.5% throughout the experiment, as measured by a Beckman Instruments LB2 Gas Analyzer. Heartbeat was displayed continuously on the face of an oscilloscope and served, along with other standard clinical signs, as an indication of the condition of the preparation. Rectal temperature, measured with the aid of a YSI telethermometer, was maintained at 37 ± 0.5°C by means of a recirculating hot-water heating pad (Tempump) placed under the animal.

Apparatus and Procedure

Glass coated tungsten microelectrodes having tip diameters of approximately 1 micron and impedances of from 1 to 2 megohms were lowered into the target area on one or both sides of the brain, thus permitting, in several cases, the simultaneous recording of 2 different neurons from one animal. Extracellularly recorded action potentials of spontaneously active single neurons in the neostriatum were isolated to a criterion of 3:1, signal-to-noise ratio, utilizing Tektronix 122 or Grass P15 preamplifiers, and 3A9 differential amplifiers in a Tektronix 565 oscilloscope. Action potentials were displayed continuously on the face of the oscilloscope and were passed through an audio monitor. On-line firing rates were counted by means of an amplitude discriminator and high-speed printer-counter (Newport Digital Printer, Model 810) and were printed on a minute-by-minute basis. Following isolation of single neuron discharges, activity was monitored for a period of 30 min or more to insure a stable baseline firing rate. Animals then received an intraperitoneal injection of 2.5 mg/kg d-amphetamine sulfate or 0.25 mg/kg apomorphine and drug-induced deviations in firing rate were expressed in terms of percent of predrug baseline firing rate. In an additional sample of animals pretreated with amphetamine for 36 days, a single injection of haloperidol was administered 60 min after 2.5 mg/kg d-amphetamine. Since action potentials were monitored on the oscilloscope continuously, changes in signal amplitude or waveform could be detected and data in such cases could be eliminated from the sample.

Upon completion of each experiment animals were given a lethal dose of sodium pentobarbital (IP) and the positions of the electrode tips were marked by passing current through the electrodes to produce a small lesion (Grass Constant Current Lesion Maker). After perfusion with normal saline followed by Formalin, brains were removed, frozen, sectioned and stained with cresyl-violet for localization of electrode tip placements.

RESULTS

Daily injections of amphetamine resulted in a decline of body weight during the first week of drug treatment, although tolerance to amphetamine-induced weight loss emerged within the first two weeks of drug administration. Figure 1 illustrates the effects of d-amphetamine on the activity of neostriatal neurons for groups of animals pretreated with saline or amphetamine for varying periods of time. In this and similar figures, alterations in firing rate are based upon the percent change from the mean of a 10 min sample of activity immediately prior to drug injection for each recording. In addition, since alterations in neuronal activity continue beyond the effects described here [26] a criterion is chosen beyond which further data from individual neurons are deleted. For all groups, a return to 65% of control firing rate following drug-induced decreases in neuronal firing is used as this criterion and is indicated for each neuron by a slash. Cells not returning to this level of responsiveness were excluded from the sample, since in such cases it is impossible to distinguish drug-induced depressions of neuronal firing from deterioration of the recording and/or cell loss.

As shown in Fig. 1, in animals pretreated with saline for 36 consecutive days, d-amphetamine produced an initial potentiation of firing rate followed by a marked depression lasting from 1 to 2 hr from the time of injection. Pretreatment with amphetamine appeared to prolong the effects of a subsequent injection, especially in animals pretreated with amphetamine for 36 consecutive days. In this group, the amphetamine-induced depression of neostriatal firing rates lasted for periods ranging from approxi-

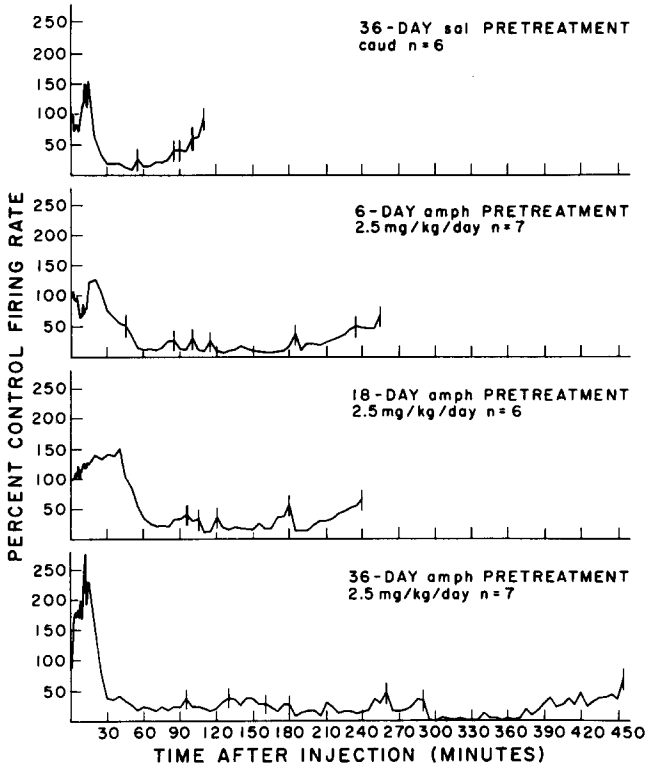

FIG. 1. Changes in neuronal firing rates in the caudate-putamen following an intraperitoneal injection of 2.5 mg/kg d-amphetamine sulphate at time zero, in animals pretreated with 36 saline injections, or 6, 18 or 36 days of d-amphetamine sulphate, from top to bottom respectively. The numbers following the letter n refer to the number of observations in each sample. The slashes indicate recovery to 65% of control firing rate for each neuron and points at which data from each neuron are deleted from subsequent averaged values.

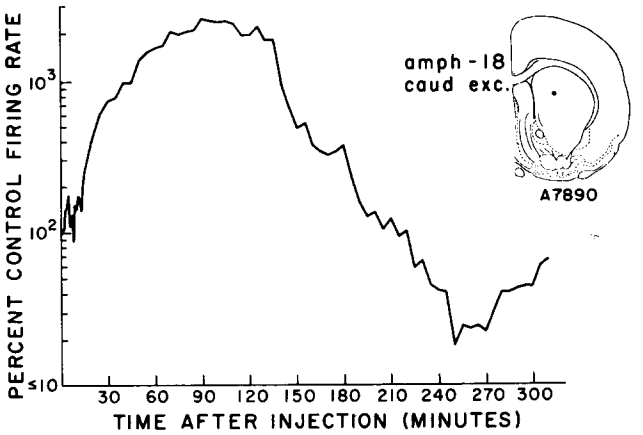

FIG. 2. An atypical, sustained increase in neuronal activity of a single neuron in the caudate-putamen of one animal pretreated with amphetamine for 18 days. The electrode tip placement is illustrated by the black dot in the histological drawing. The coronal sections in this and all subsequent figures and their identifying numbers are after König and Klippel [19].

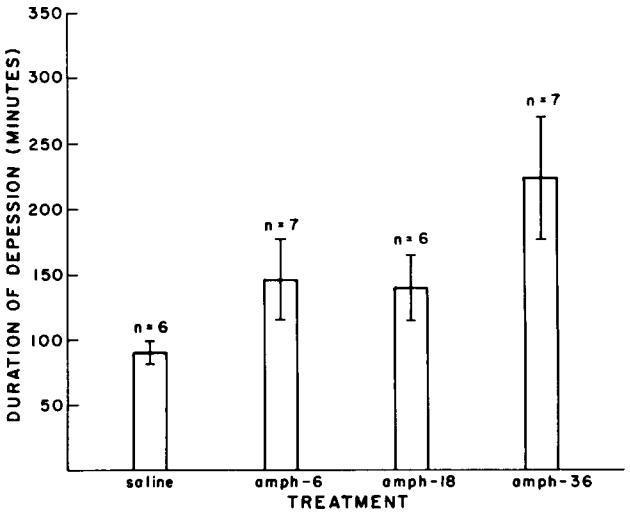

FIG. 3. The duration of decreased firing in neostriatal neurons in animals pretreated with saline, or with amphetamine for 6, 18 or 36 consecutive days. The standard error above and below the mean is indicated by the brackets at the top of each bar, and the number of observations in each group is indicated by the n.

mately 90 min to beyond 7 hr. Two exceptions to these effects, not included in Fig. 1, occurred in animals pretreated with amphetamine for 18 or 36 days in which amphetamine injection was followed by a prolonged increase in neuronal firing rate, as illustrated for 1 of those animals in Fig. 2.

The mean duration of the amphetamine-induced depression of neuronal activity in the 4 different pretreatment groups is illustrated in Fig. 3. The duration of depression for each neuron was defined by the time from injection that firing rate remained below 65% of control rate after falling below this level for 5 min or more. A trend analysis revealed a significant linear component in the effect of days of amphetamine pretreatment on the duration of the amphetamine-induced depression of neuronal activity, $F(1,22) = 7.89$, $p<0.05$. In addition, within the overall analysis, a significant difference in duration was revealed between the saline pretreated animals and those pretreated with amphetamine for 36 consecutive days, $F(1,22) = 8.61$, $p<0.05$. The effects of 6 and 18 days pretreatment, however, while of intermediate duration were not significantly different from those obtained in saline pretreated animals or animals given 36 days pretreatment with d-amphetamine. Despite some variability among individual neurons, the amphetamine-induced initial potentiation of firing rate also appeared to be enhanced by long-term treatment. A Mann-Whitney U test revealed a significant difference in the magnitude of this response between the 36 day treatment group and saline controls ($p<0.05$). Mean spontaneous firing rates for all groups were also compared. These ranged from 64 spikes/min to 142 spikes/min with no statistically significant differences between groups. Electrode tip placements where neuronal activity was recorded in 4 pretreatment groups are illustrated in Fig. 4. No apparent differences in electrode tip placements could be discerned when these data were compared to cases in which atypical increases in neuronal firing rates followed amphetamine administration, although a larger sample might have revealed such differences.

Attempts were made to block the amphetamine-induced

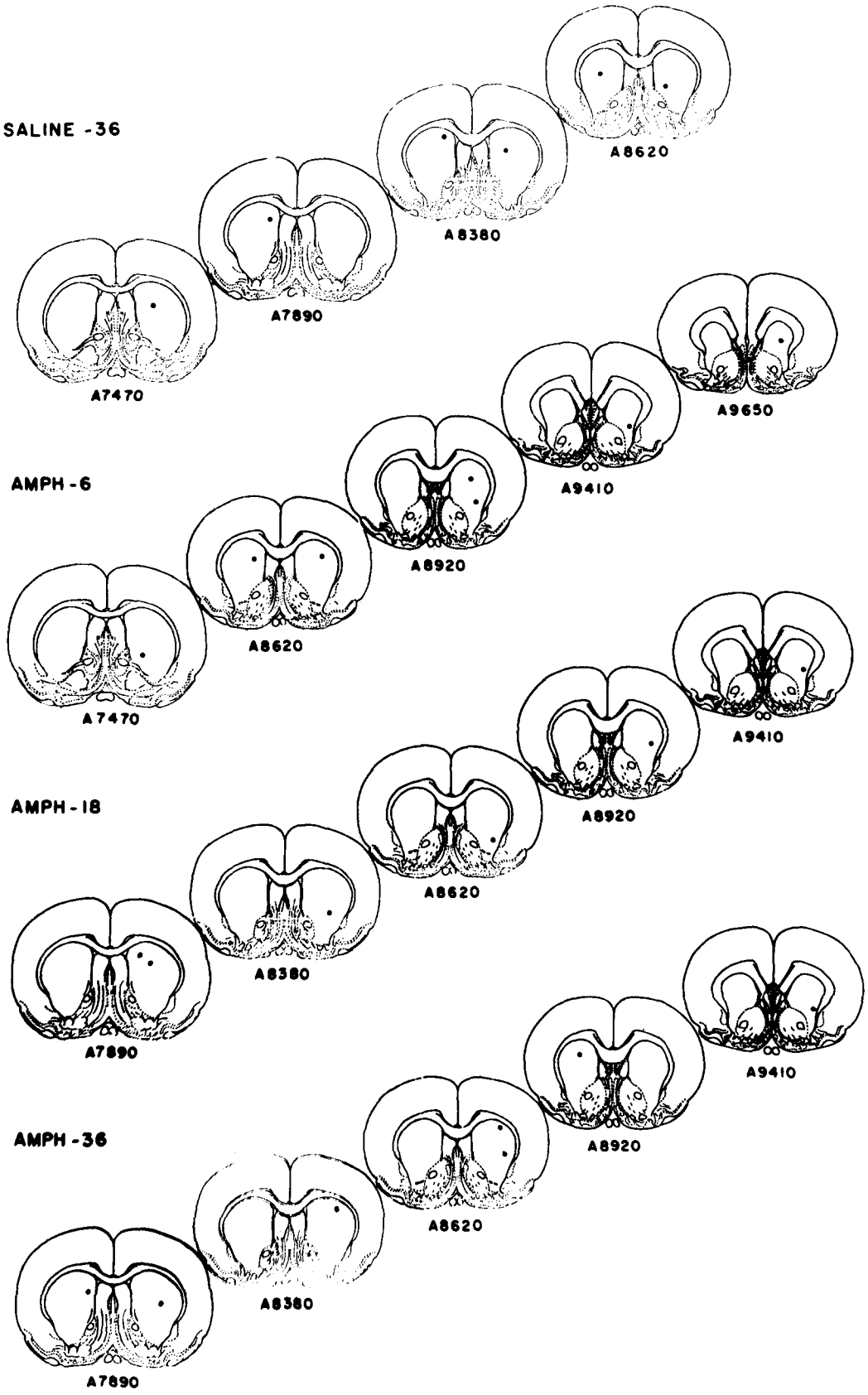

FIG. 4. Electrode tip placements, illustrated by black dots, where caudate-putamen neuronal activity shown in Fig. 1 was recorded for animals pretreated with saline for 36 days, or with d-amphetamine for 6, 18 or 36 days from top to bottom respectively.

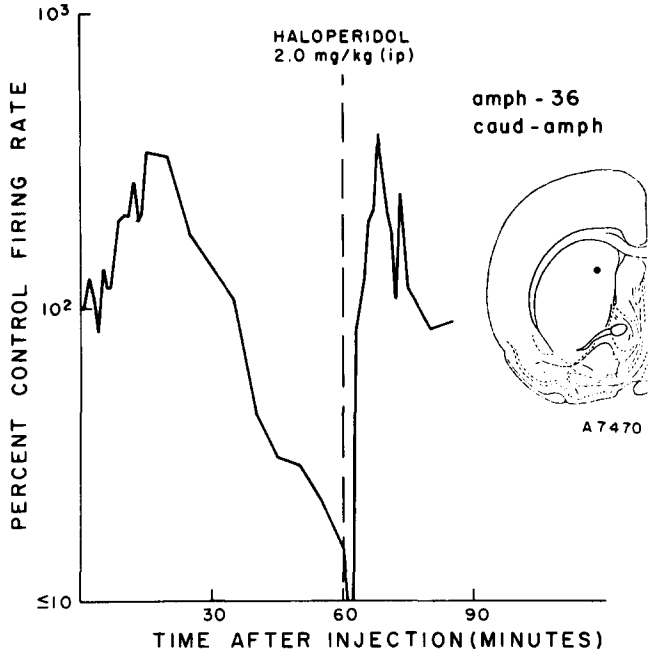

FIG. 5. Changes in the firing rate of a single neuron in the caudate-putamen recorded from an animal pretreated with d-amphetamine for 36 days. An intraperitoneal injection of haloperidol 60 min after d-amphetamine reversed the depression of firing rate. The approximate position of the recording electrode tip is illustrated to the right of the graph.

depression of firing in an additional 3 animals pretreated with amphetamine for 36 days. The result typical of all animals is illustrated in Fig. 5, in which 2.0 mg/kg haloperidol administered 60 min after d-amphetamine produced a rapid reversal of the depression of neuronal activity in this 36 day amphetamine-pretreated animal.

Apomorphine-induced changes in neostriatal neuronal activity were also markedly affected in animals pretreated with d-amphetamine for 36 days, when compared to animals pretreated with saline for a similar period. Changes in neuronal activity in the caudate-putamen in these 2 groups of animals are illustrated in Fig. 6. In saline-pretreated animals, 0.25 mg/kg apomorphine elicited an initial potentiation of firing rate that began within 10 min after the injection. This increase in activity was followed by a slowing of firing rate the mean duration of which, as defined previously, was 139 min, with the duration for individual neurons in different animals ranging from 85–220 min. In animals pretreated with amphetamine for 36 days, the initial potentiation of firing was higher, but not significantly, $F(1,14) = 1.85$, $p>0.05$. However, the duration of the apomorphine-induced depression of neuronal activity in this sample of neurons ranged from 125–455 min, with a mean value of 246 min. An analysis of variance on the duration of depression revealed a significant difference between the two groups, $F(1,14) = 6.13$, $p<0.05$. In addition, the degree of depression produced by apomorphine, defined for each neuron as the lowest mean firing rate for a 5 min period following drug injection and prior to recovery, was significantly more

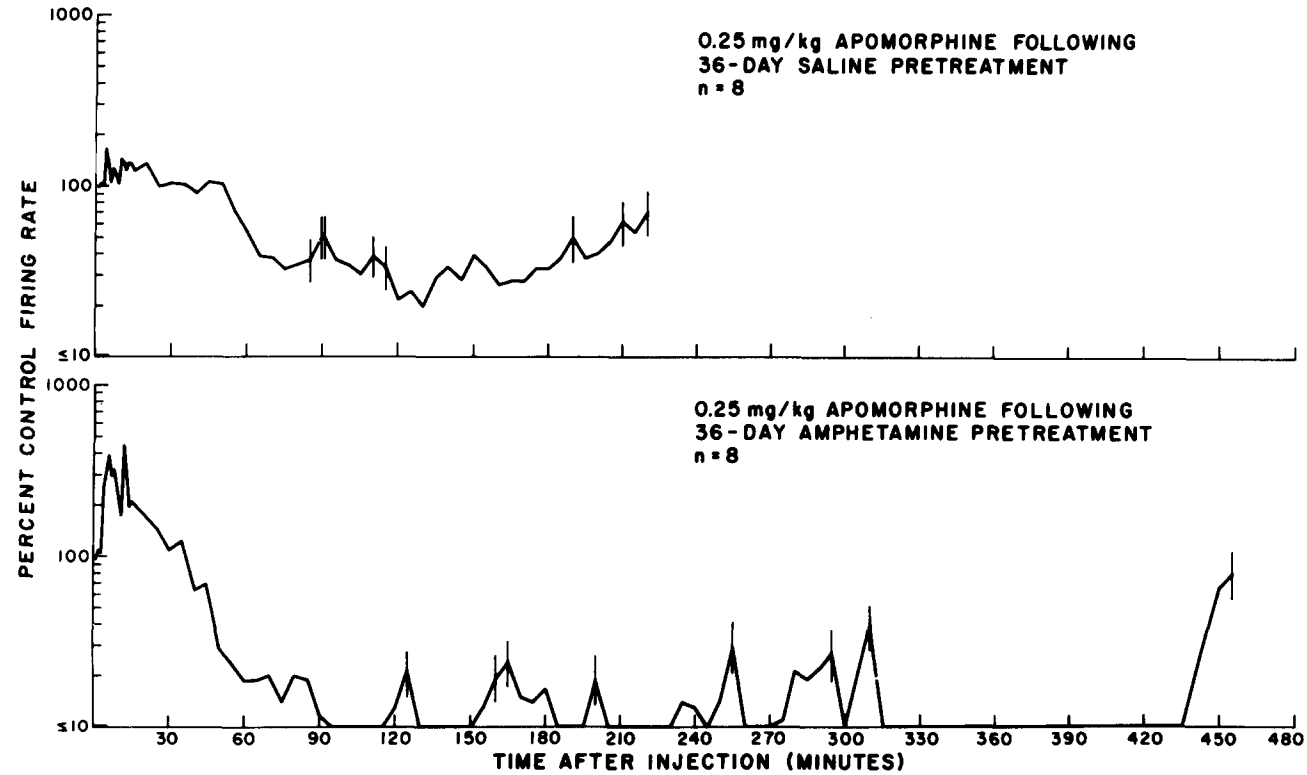

FIG. 6. Alterations produced by apomorphine in the spontaneous firing rates of single neurons in the caudate-putamen of 8 rats following pretreatment with d-amphetamine sulphate (lower graph) or saline (upper graph). Neuronal activity in amphetamine-pretreated animals was depressed to a greater extent and for longer periods of time than in saline-pretreated control animals.

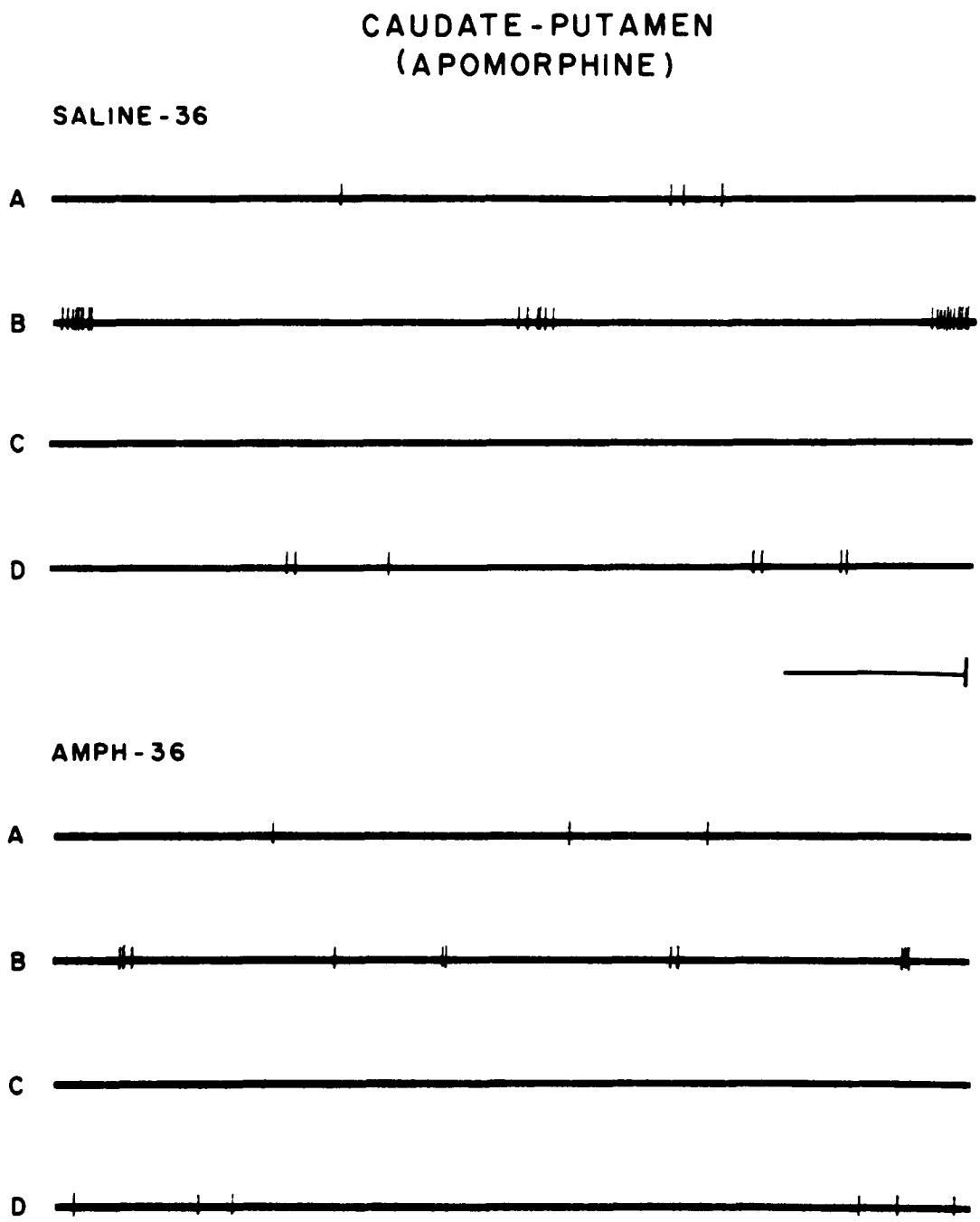

FIG. 7. Photographic records of the firing of single neurons in the caudate-putamen of the rat. The upper 4 traces illustrate spontaneous neuronal firing in an animal pretreated with saline for 36 days prior to an injection of apomorphine (A), the initial increase in firing rate approximately 10 min after injection (B), the depression in firing rate 60 min after injection (C) and recovery to predrug firing rate 90 min after injection (D). The activity of a single neuron in an amphetamine-pretreated animal is illustrated in the lower 4 traces prior to apomorphine injection (A), approximately 10 min after the injection (B), during the marked depression of neuronal firing 250 min after injection (C), and recovery to predrug firing rate 310 min after injection (D). The calibration marks indicate 2 sec (horizontal) and 100 μv (vertical).

pronounced for neurons in the 36 day amphetamine pretreated group than in saline pretreated control animals, $F(1,14) = 5.47, p<0.05$.

Two examples of the apomorphine-induced alterations in caudate neuronal firing rate, photographed directly from data film, are illustrated in Fig. 7. The upper 4 traces illustrate the spontaneous firing of a single caudate-putamen neuron in a saline pretreated animal immediately before an injection of apomorphine (A), the potentiation of activity 10 min after the drug injection (B), the depression of activity at approximately 60 min after injection (C) and the return to baseline firing rate at approximately 90 min

after apomorphine (D). The neuronal activity illustrated in the lower 4 traces was recorded from the neostriatum in an animal pretreated with amphetamine for 36 days and depicts spontaneous firing prior to an injection of apomorphine (A), the potentiation of activity 10 min after apomorphine (B), the subsequent depression of activity which, in this case, was still pronounced at 250 min after the injection (C) and the recovery of responsiveness at 310 min after apomorphine (D).

Histological analysis revealed that electrode tip placements in these two groups of animals were confined to the right of left neostriatum and are illustrated in Fig. 8.

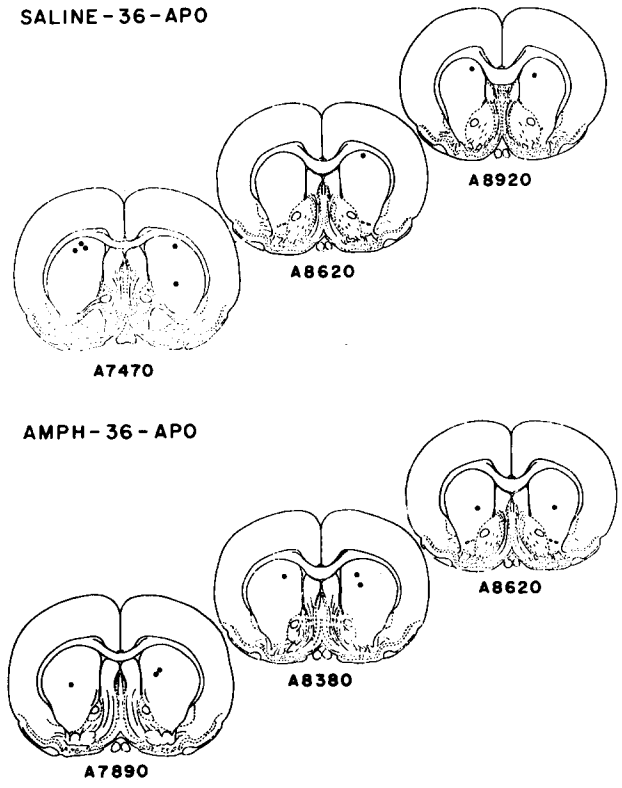

FIG. 8. Electrode tip placements in the neostriatum where neuronal activity was recorded in response to apomorphine in animals pretreated with saline for 36 consecutive days (top) or amphetamine (bottom).

DISCUSSION

The response of neostriatal neurons to an injection of 2.5 mg/kg d-amphetamine in saline pretreated animals is consistent with previous reports of the effects of a single injection of the drug in naive rats. The mechanisms underlying the initial potentiation of neuronal activity that typically precedes the marked inhibition of neuronal firing in the neostriatum, as well as those underlying the atypical, sustained acceleration in firing rate encountered in several animals remain to be elucidated [13,26]. The amphetamine-induced depression of neuronal activity has been attributed to the drug-induced release of dopamine since this aspect of the amphetamine response is blocked following lesions of the nigro-neostriatal bundle [12] or the administration of haloperidol, a dopamine antagonist [13]. The apomorphine-induced depression of firing rate in the caudate-putamen may be presumed to reflect a direct action of this drug on post-synaptic dopamine receptors [21].

When we measured the response of neostriatal neurons in rats pretreated with 2.5 mg/kg d-amphetamine for 36 days on the day following this pretreatment regimen, our results revealed an apparent enhancement of the effects of d-amphetamine and apomorphine on the activity of spontaneously active caudate-putamen neurons, especially the depression of neuronal firing rate caused by both drugs. The depression of neuronal firing rates produced by d-amphetamine and apomorphine was markedly prolonged and/or enhanced in animals pretreated with the drug for 36 consecutive days. The responses to amphetamine in animals pretreated with the drug for 6 and 18 days were also suggestive of a progressive enhancement of the effects of amphetamine following repeated exposure to it. Similar pretreatment leads to a progressive augmentation of the hyperkinesia and sterotyped behaviors produced by comparable doses of these dopaminergic agonists [18,29]. The enhanced effects of amphetamine on neostriatal neuronal firing rates and behavior in animals pretreated with amphetamine for 36 days is probably not solely due to any peripheral action of amphetamine since many of these effects show tolerance following long-term administration [3, 5, 14, 22, 23, 24, 33]. Indeed, the development of tolerance to amphetamine-induced weight loss observed in our experiments is identical to previous reports by other investigators [23]. In addition, mephentermine sulfate, a peripheral sympathomimetic drug without the prominent central effects of amphetamine [15] does not affect neuronal firing rates in the caudate-putamen significantly at a dose that produces an increase in heart rate similar to 2.0 mg/kg d-amphetamine [13]. Finally, these changes were not correlated with alterations in expired carbon dioxide, body temperature or heart rate, when these variables were monitored continuously during the experiments. In addition, consistent with a probable involvement of central dopaminergic systems in the amphetamine-induced depression, we found that subsequent administration of haloperidol blocked this response in the 36 day experimental group.

It has been suggested that the enhanced amphetamine-induced behavioral effects observed following long-term treatment may involve a functional change in central catecholaminergic transmission [8,29]. Ellinwood *et al.* [8] suggested that the reduction in central catecholamine levels following long-term amphetamine administration [7] could result in increased catecholamine receptor sensitivity, perhaps analagous to disuse or denervation [30,31]. Our results with amphetamine and apomorphine in chronically pretreated animals are compatible with this view, although other interpretations are possible. For example, while current evidence suggests that an altered metabolism of d-amphetamine following prolonged administration cannot account for the augmentation of its behavioral effects [9,22] such a mechanism could play a role in the augmentation of the effects of apomorphine on neostriatal neuronal activity and sterotyped behavior. However, there is a great deal of indirect support for the view that the sensitivity of elements postsynaptic to dopaminergic nigro-neostriatal neurons is altered by functional denervation. For example, the proportion of spontaneously active neurons in the caudate-putamen depressed by ionto-

phoretically applied dopamine is significantly greater after 6-hydroxydopamine pretreatment [10], or following long-term haloperidol administration [28,37]. Further, significantly lower ejection currents of dopamine and apomorphine are required to depress caudate unit activity following denervation of dopaminoceptive neurons [35]. Behavioral evidence also supports the notion that neostriatal dopaminoceptive elements are altered by various forms of denervation or disuse [11, 17, 31, 34].

The finding that the effects of amphetamine and apomorphine are enhanced following long-term pretreatment with amphetamine is thus compatible with a wide variety of evidence suggesting that the behavioral effects of such treatments may involve alterations in catecholaminergic transmission in the central nervous system. Further, our data provide additional evidence relevant to the neuronal mechanisms underlying the behavioral effects of amphetamine in experimental animals which have been used as an experimental model for some forms of human thought disorders [2,32].

ACKNOWLEDGEMENTS

We thank Patricia Wilson and Stephen J. Young for their skilled technical assistance. We also thank David S. Segal from the Department of Psychiatry, University of California at San Diego Medical School for helpful advice and assistance. We are grateful to Smith, Kline and French for supplying the d-amphetamine sulphate.

REFERENCES

1. Andén, N. -E., A. Carlsson, A. Dahlstrom, K. Fuxe, N. A. Hillarp and K. Larsson. Demonstration and mapping out of nigro-neostriatal dopamine neurons. *Life Sci.* 3: 523–530, 1964.
2. Angrist, B. and S. Gershon. Dopamine and psychotic states: Preliminary remarks. In: *Neuropsychopharmacology of Monoamines and Their Regulatory Enzymes,* edited by E. Usdin. New York: Raven Press, 1974, pp. 211–219.
3. Brodie, B. B., A. K. Cho and G. L. Gessa. Possible role of p-hydroxynorephedrine in the depletion of norepinephrine induced by d-amphetamine and in tolerance to this drug. In: *International Symposium on Amphetamines and Related Compounds. Proceedings of the Mario Negri Institute for Pharmacological Research, Milan, Italy,* edited by E. Costa and S. Garattini. New York: Raven Press, 1970, pp. 217–230.
4. Costa, E., A. Groppetti and M. K. Naimzada. Effects of amphetamine on the turnover rate of brain catecholamines and motor activity. *Br. J. Pharmac.* 44: 742–751, 1972.
5. Cowan, F. F., C. Cannon, T. Koppanyi and G. D. Maengwyn-Davies. Reversal of phenylalkylamine tachyphylaxis by norepinephrine. *Science* 134: 1069–1070, 1961.
6. Ellinwood, E. H., Jr. and R. L. Balster. Rating the behavioral effects of amphetamine. *Eur. J. Pharmac.* 28: 35–41, 1974.
7. Ellinwood, E. H., Jr. and O. Escalante. Behavior and histopathological findings during chronic methedrine intoxication. *Biol. Psychiat.* 2: 27–39, 1970.
8. Ellinwood, E. H., Jr., A. Sudilovsky and L. M. Nelson. Evolving behavior in the clinical and experimental amphetamine (model) psychosis. *Am. J. Psychiat.* 130: 1088–1093, 1973.
9. Ellison, T., R. Okun, A. Silverman and M. Siegel. Metabolic fate of amphetamine in the cat during development of tolerance. *Archs int. Pharmacodyn.* 190: 135–149, 1971.
10. 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, 1972.
11. Groves, P. M. and G. V. Rebec. Biochemistry and behavior: Some central actions of amphetamine and antipsychotic drugs. *A. Rev. Psychol.* 27: 91–127, 1976.
12. 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. *Neuropharmac.* 14: 369–376, 1975.
13. 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.
14. Harrisson, J. W. E., C. M. Ambrus and J. L. Ambrus. Tolerance of rats toward amphetamine and methamphetamine. *J. Am. Pharmac. Ass.* 41: 539–541, 1952.
15. Innes, I. R. and M. Nickerson. Drugs acting on postganglionic adrenergic nerve endings and structure innervated by them (sympathomimetic drugs). In: *The Pharmacological Basis of Therapeutics,* edited by L. S. Goodman and A. Gilman. New York: Macmillan, 1970, pp. 478–523.
16. Kalant, H., A. E. LeBlanc and R. J. Gibbins. Tolerance to, and dependence on, some non-opiate psychotropic drugs. *Pharmac. Rev.* 23: 135–191, 1971.
17. 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.
18. Klawans, H. L., P. Crossett and N. Dana. Effect of chronic amphetamine exposure on sterotyped behavior: Implications for pathogenesis of L-dopa induced dyskinesias. In: *Advances in Neurology,* edited by D. B. Calne, T. N. Chase and A. Barbeau. New York: Raven Press, 1975, 9: 105–112.
19. König, 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.
20. Kosman, M. E. and K. R. Unna. Effects of chronic administration of the amphetamines and other stimulants on behavior. *Clin. Pharmac. Ther.* 9: 240–254, 1968.
21. Krnjevic, K. Electrophysiology of dopamine receptors. In: *Advances in Neurology, Vol. 9, Dopaminergic Mechanisms,* edited by D. B. Calne, T. N. Chase and A. Barbeau. New York: Raven Press, 1975, pp. 13–24.
22. Lewander, T. A mechanism for the development of tolerance to amphetamine in rats. *Psychopharmacologia* 21: 17–31, 1971.
23. Lewander, T. Effect of chronic treatment with central stimulants on brain monoamines and some behavioral and physiological functions in rats, guinea pigs, and rabbits. In: *Neuropsychopharmacology of Monoamines and Their Regulatory Enzymes,* edited by E. Usdin. New York: Raven Press, 1974, pp. 221–240.
24. Magour, S., H. Coper and C. H. Fahndrich. The effects of chronic treatment with d-amphetamine on food intake, body weight, locomotor activity and subcellular distribution of the drug in rat brain. *Psychopharmacologia* 34: 45–54, 1974.
25. Randrup, A. and I. Munkvad. Pharmacology and physiology of stereotyped behavior. *J. psychiat. Res.* 11: 1–10, 1974.
26. Rebec, G. V. and P. M. Groves. Differential effects of the optical isomers of amphetemine on neuronal activity in the reticular formation and caudate nuclesu of the rat. *Brain Res.* 83: 301–318, 1975.
27. Roberts, D. C. 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.

28. Schelkunov, E. C. Adrenergic effect of chronic administration of neuroleptics. *Nature* **214**: 1210–1212, 1967.
29. 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.
30. Sharpless, S. Reorganization of function in the nervous system – Use and disuse. *A. Rev. Physiol.* **26**: 357–388, 1964.
31. Sharpless, S. Supersensitivity-like phenomena in the central nervous system. *Fedn Proc.* **34**: 1990–1997, 1975.
32. Snyder, S. H., S. P. Banerjee, H. I. Yamamura and D. Greenberg. Drugs, neurotransmitters and schizophrenia. *Science* **184**: 1243–1253, 1974.
33. Tormey, J. and L. Lasagna. Relation of thyroid function to acute and chronic effects of amphetamine in the rat. *J. Pharmac. exp. Ther.* **128**: 201–209, 1960.
34. Ungerstedt, U. Postsynaptic supersensitivity after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. *Acta physiol. scand. Suppl.* **367**: 69–73, 1971.
35. Ungerstedt, U., T. Ljungberg, B. Hoffer and G. Siggins. Dopaminergic supersensitivity in the striatum. In: *Advances in Neurology, Vol. 9, Dopaminergic Mechanisms,* edited by D. B. Calne, T. N. Chase and A. Barbeau. New York: Raven Press, 1975, pp. 57–66.
36. Wallach, M. B. Drug-induced stereotyped behavior: Similarities and differences. In: *Neuropsychopharmacology of Monoamines and Their Regulatory Enzymes,* edited by E. Usdin. New York: Raven Press, 1974, pp. 241–260.
37. Yarbrough, G. G. Supersensitivity of caudate neurones after repeated administration of haloperidol. *Eur. J. Pharmac.* **31**: 367–369, 1975.