Short communication

Tonic firing of rat nucleus accumbens neurons: changes during the first 2 weeks of daily cocaine self-administration sessions

Laura L. Peoples ¹, Anthony J. Uzwiak, Fred Gee, Mark O. West

Department of Psychology, Busch Science Campus, Rutgers, The State University of New Jersey, New Brunswick, NJ 08903, USA

Accepted 17 November 1998

Abstract

Activity of single neurons in the nucleus accumbens (NAcc) of rats was recorded extracellularly on the 2nd and 15th days of intravenous cocaine self-administration. Each of the two electrophysiological recording sessions consisted of three successive phases: a pre-drug baseline recording period, a cocaine self-administration session, and a post-drug recording period. Firing of individual neurons was typically inhibited during the self-administration session, relative to the pre-drug period. The inhibition was greater on the 15th day relative to the 2nd day. Additionally, firing rates during the pre-drug period and the self-administration session were typically lower on the 15th day as compared to the 2nd day. The present data are consistent with previous acute electrophysiological findings and are in line with the hypothesis that repeated drug self-administration engenders changes in the mesoaccumbens pathway that contribute to drug addiction. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Nucleus accumbens; Cocaine; Self-administration; Addiction; Electrophysiology; Rat

It has been proposed that long-lasting changes in the mesoaccumbens dopamine pathway occur as a consequence of repeated drug self-administration and contribute to the development of drug addiction [6,7,14,28,30]. Consistent with this proposal, researchers using acute electrophysiological procedures have shown that a history of repeated experimenter-delivered injection of psychomotor stimulants can alter the activity of single nucleus accumbens (NAcc) neurons in the anesthetized rat and rat brain slice [9–11,34,37,38]. Comparable electrophysiological studies have not been conducted in the awake animal. Drug effects on neural activity can vary depending on certain electrophysiological recording conditions (e.g., presence vs. absence of anesthesia) [1,3,15,35] as well as on methods of drug administration (e.g., self-administered vs. experimenter-delivered) [5,32]. Thus, it is not known whether the findings of the acute electrophysiological studies will generalize to the awake animal with a history of drug self-administration. To begin addressing this question, the present study used chronic extracellular recording procedures to characterize the activity of single NAcc neurons across repeated cocaine self-administration sessions.

Male Long–Evans rats (maintained at 350 g; Charles River, Wilmington, MA) were chronically implanted with a catheter in the jugular vein and an array of microwires in the NAcc. Rats were placed in a Plexiglas chamber that was used for housing, self-administration sessions, and recording sessions. During the self-administration session, each press of a lever was followed by an intravenous infusion of cocaine (0.7 mg/kg/0.2 ml infusion). Daily sessions (7 days per week) were limited to 60 infusions or 6 h [cf. Ref. [24]]. Procedures were designed to minimize pain and discomfort. Animals were treated in accordance with the Guide for the Care and Use of Laboratory Animals published by the USPHS and with the protocols approved by the Animal Care and Use Committee of Rutgers, The State University of New Jersey.

Electrophysiology recording sessions. Extracellular recording procedures were conducted during the second or third self-administration session (i.e., 1st day following acquisition of the operant) (typically Day 2 and hence referred to as Day 2) and again between the 12th and 17th
sessions (typically day 15 and hence referred to as Day 15). Each extracellular recording session consisted of three successive phases: (1) a pre-drug baseline period (20 min), (2) a self-administration session, and (3) a post-drug period (40−60 min). Average drug exposure prior to Day 2 and Day 15 equaled 11.3 ± 0.5 mg and 174 ± 13.3 mg, respectively. Average number of cocaine self-infusions equaled 47.2 ± 2.2 and 725.2 ± 55.4, respectively.

Criteria for neural recordings. Post-hoc analyses (DataWave, CO) were used to discriminate populations of neural waveforms [cf. Ref. [24]]. To be included in the present study, populations of waveforms had to be consistent with four criteria. First, the population of waveforms recorded by a single microwire had to show evidence of a minimum interspike interval consistent with the refractory period of a single neuron. Second, the population of waveforms had to have been recorded by a microwire that was used successfully to record neural activity on both Day 2 and Day 15. Third, the waveforms recorded by the same microwire had to be qualitatively and quantitatively comparable between the two sessions (stability criterion). Specifically, for both days, it was necessary for neural waveforms to have been defined by the same eight discrimination parameters and by a comparable range of variation in each of those eight parameters. Comparable waveforms recorded with the same microwire were likely to correspond to the same neuron. Fourth, neural waveforms had to be sufficient in amplitude (i.e., ≥ 100 μV) on each day for the smallest discriminated waveforms to exceed the amplitude of the (typical) maximal fluctuations in the noiseband (i.e., 50 μV) (completeness criterion). This requirement for a minimum waveform amplitude allowed us to verify that our ability to detect discharges did not change between Day 2 and Day 15 (as would happen if the distance changed between the recording wire and the neuron). Given the foregoing, we interpreted a between-session difference in neural activity recorded by a given microwire to be a between-session difference in the activity (i.e., discharge rate or pattern) of a single neuron.

Effect of the cocaine self-administration session on tonic firing. For each neuron and each day, firing rate during the last 20 min of the self-administration session was compared to firing rate during the 20 min pre-drug period in a Wilcoxon Matched Pairs test (unidirectional α = 0.05). In order to conduct the test, each 20-min period was divided into (40) 0.5-min bins that were numbered consecutively. The number of discharges in comparably numbered trials from the self-administration and pre-drug periods were input as matched pairs [cf. Ref. [31]]. If firing rate during the self-administration session was significantly lower or higher during the self-administration session, relative to the pre-drug period, firing was said to have been inhibited or excited, respectively. The terms inhibited and excited referred only to the direction of the change in firing rate, not to the mechanisms that might have mediated the changes in firing.

Between-session comparisons of firing rate. The following were compared between Day 2 and Day 15: (1) firing rate during the 20 min pre-drug period (referred to as pre-drug firing rate) and (2) firing rate during the last 20 min of the self-administration session (referred to as self-administration firing rate). Comparisons were made using the Wilcoxon Matched Pairs test.

Neuron sample. On Day 2 of cocaine self-administration, 83 microwires recorded activity of single neurons. Of the 83 wires, 53 recorded neural activity on both Day 2 and Day 15. Of those 53 wires, 13 (13/53, 24.5%) yielded neural records that met the criteria of stability and completeness (Fig. 1). The 13 neurons were located primarily

---

**Fig. 1.** An individual neuron that met all criteria for inclusion in the between-session comparisons of firing. Data are shown for Day 2 (top row) and Day 15 (bottom row). The left column shows overlays of successively recorded neural waveform traces (positive voltage up). The traces displayed for each day consist of the first 1500 occurrences of the discriminated waveform. The calibration bar to the left of each overlay of waveform traces corresponds to the amplitude of the noiseband (i.e., typical background noise) which was 50 μV. The duration of the trace was 0.64 ms. The right column shows frequency histograms inclusive of all interspike intervals during the recording session that ranged between 0.1 and 25.0 ms (i.e., interspike interval histograms). The ordinate of the interspike interval histogram displays counts (i.e., number of intervals in the entire recording session); the abscissa displays duration (increments of 0.1 ms) of the interspike intervals. The lower maximum ordinate value of the Day 15 histogram reflects a reduced firing rate.
In the core of the NAcc [13,21] (10/13 neurons). None of the 13 neurons were recorded from areas that could be unambiguously identified as the shell.

Inhibition of tonic firing during the self-administration session. On Day 2, 7/13 (53.8%) neurons showed significantly inhibited firing during the self-administration ses-
sion relative to the pre-drug period (Fig. 2, left column and 3, bottom graph). The other 6/13 (46.2%) neurons did not show a significant change in tonic firing rate on Day 2.

The number of neurons that showed a significant inhibition of firing during the self-administration session was greater on Day 15 (11/13, 84.6%) than it was on Day 2. In addition, for most neurons, the magnitude of inhibition during the self-administration session was greater on Day 15 than on Day 2 (Fig. 2, left versus right column and Fig. 3, bottom graph).

Pre-drug and self-administration firing rates. For a majority of neurons (9/13, 69.2%), tonic firing rate during the last 20 min of the self-administration session was significantly lower on Day 15 than it was on Day 2. Pre-drug tonic firing rate was also lower on Day 15 than on Day 2 for most (10/13, 76.9%) neurons. The between-session decrease in self-administration firing rate (average ± S.E. = 79.4 ± 4.2%) tended to be greater than the between-session decrease in pre-drug firing rate (average = 58.9 ± 8.1%) (Fig. 3, top).

Self-administration behavior. Although the general pattern of self-administration behavior was comparable on the two recording days, the average (modal) interinfusion interval for all infusions within the session (excluding the first 10 infusions) was significantly shorter on Day 15 (7.1 ± 0.5 min) than on Day 2 (9.7 ± 1.0 min) [t(8) = 2.06, p < 0.05] (one-tailed t-test). The decrease in interinfusion interval exhibited by subjects was not significantly correlated with the decrease in neural firing rate that was recorded from those subjects [r = 0.447 (df = 12), p > 0.05] (Pearson Product Moment correlation).

Summary and conclusions. Both the NAcc firing patterns within the individual self-administration sessions [23] and subjects’ self-administration behavior [25] were prototypic of those observed in previous studies. It is thus likely that the present findings are representative of accumbal, predominantly core, neurons that exhibit firing patterns during a free-operant (FR1) limited-access cocaine self-administration session.

Numerous pharmacological and behavioral variables, including those described below, potentially contributed to the between-session changes in tonic firing. First, the between-session increases in drug intake could have made a contribution. However, several observations of the present study, including (1) the absence of a significant correlation between the changes in interinfusion interval and tonic firing and (2) the presence of decreases in pre-drug firing, indicate that increases in drug level could not have been the sole determinant [also see Refs. [10,20]]. Second, it is possible that long-lasting physiological responses or adaptations to the repeated drug administration contributed to the changes [cf. Refs. [7,8,28,36–39]]. Finally, learning, may have also played a role [see Refs. [2,4,12,16–18,26,27,29]]. It is important to note that contribution of learning would not exclude the possibility of a contribution of drug effects. It would also not preclude a possible role of the neural changes in the development of drug addiction [cf. Refs. [19,28,33]].

Previous electrophysiological studies conducted in the anesthetized rat and in the rat brain slice showed that repeated administration of cocaine enhanced the sensitivity of accumbal neurons to the inhibitory effects of those and other dopamine agonists [9,10,34,36–38]; also see Ref. [11] as well as reduced the excitatory response of NAcc neurons to glutamate [38]. The present data provide evidence that these findings may generalize to the awake rat with a history of cocaine self-administration.

Data collected using a variety of measurement techniques and experimental paradigms have led researchers to hypothesize that changes in the NAcc occur gradually over the course of repeated episodes of drug self-administration and contribute to the development of drug addiction. The present data are in line with this hypothesis and moreover suggest, as do other data [10,34], that changes in NAcc...
function that may contribute to drug addiction include a decline in efferent signal [10,34].

Acknowledgements

Mr. Anthony T. Fabbricatore and Mr. Frank X. Guyette assisted in the collection of data. Ms. Sejal Vyas and Ms. Binaifer Mohta contributed to data analysis. Ms. Linda King, Mr. Patrick Grace, and Dr. Donald MacNeil provided technical assistance. Research was supported by NIDA grant DA 06886.

References


Fig. 3. Top graph: between-session changes in pre-drug (light gray bars) and self-administration firing rates (dark gray bars). The ordinate displays the between-session percent change in the pre-drug and self-administration firing rates of individual neurons. The abscissa shows the identification number (i.e., 1–13) assigned to each of the 13 neurons. Percent change was calculated according to the equation $\frac{(A - B)}{(A + B)} \times 100$; wherein $A$ and $B$ equaled the firing rate (total number of discharges during a 20 min period) of a given neuron on Day 15 and Day 2, respectively. The ordinate is bi-directional with 0% change indicated at the midpoint of the ordinate. A between-session decrease in firing rate is represented as a negative percent change (bars that are below the zero line); a between-session increase in firing rate is indicated by a positive percent change (bars that are above the zero line). A significant between-session change in either pre-drug or self-administration firing rate of a given neuron is indicated by an asterisk. For example, Neuron 2 showed a significant between-session decrease in both pre-drug firing rate and self-administration firing rate on Day 15 and Day 2, respectively. The ordinate is bi-directional with 0% change indicated at the midpoint of the ordinate. A significant change in firing rate of a given neuron on a given day is indicated by an asterisk.


