Differential Changes in Signal and Background Firing of Accumbal Neurons During Cocaine Self-Administration

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INTRODUCTION

Learning theories of drug addiction propose that the disorder reflects pathologically strong conditioned (learned) behaviors and conditioned stimulus control thereof. The abnormally strong behavior and stimulus control are proposed to be due, at least in part, to acute drug effects that either mimic or amplify reward-related learning mechanisms during periods of drug self-administration (for review and related proposals, see DiChiara 1998, 2002; Everitt et al. 2001; Robbins and Everitt 1999; Robinson and Berridge 1993; Stewart 1992; Stewart et al. 1984; White 1996). These acute drug effects are proposed to occur with each drug self-administration experience so that ultimately facilitation of drug-seeking behavior by drug-associated cues becomes irresistible and drug-seeking behaviors become compulsive and uncontrollable.

Several lines of evidence are consistent with possible contributions of drug-learning interactions to addiction and additionally provide clues as to the neural mechanisms that might mediate them. Consistent with a possible role for drug-learning interactions, animal studies show that addictive drugs amplify the influences of conditioned stimuli on instrumental behavior directed toward natural rewards and may facilitate reward-related learning (Harmer and Phillips, 1998; Killcross et al. 1997; Krivane and McGaugh 1969; Robbins 1978; Robbins et al. 1983, 1989; Taylor and Horger, 1999; Taylor and Robbins 1986; Wyvell and Berridge 2000). Both of these effects of addictive drugs appear to be transduced, at least in part, by dopamine (DA)-mediated actions in the accumbens. Studies of drug reward indicate that the accumbens also makes important contributions to the acquisition and the expression of drug-reward-related behavior (for review, Koob et al., 1998; Lesher and Koob 1999; Wise and Bozarth 1987; also see Cornish and Kalivas 2000). Finally, studies of natural rewards show that the nucleus accumbens mediates aspects of drug reward-related learning and the influence of that learning on behavior (for review, see Cardinal et al. 2002; Hall et al. 2001; Parkinson et al. 1999; Smith-Roe and Kelley 2000). These data are consistent with the proposal that addictive drugs may impact mechanisms that are normally involved in reward-related learning and behavior and may thereby contribute to aberrant drug-reward-related learning. Moreover, the data indicate that this drug-learning interaction, and the contribution of this interaction to drug addiction may be mediated by drug effects on the accumbens.

Extracellular recordings of accumbal firing patterns during
intravenous drug self-administration sessions are consistent, at least to some extent, with the hypothesis that drug effects on the accumbens may be involved in mediating a drug-induced amplification of drug-reward-related learning. These studies show that some accumbal neurons exhibit excitatory phasic firing time locked to drug-reward-related events, including the drug-directed instrumental behavior and cues that predict the delivery of drug (Carelli et al. 1993; Chang et al. 1994; Janak et al. 1999; Peoples and West 1996; Uzwiak et al. 1997). Characterization of the functional role of the phasic firing patterns indicates that they are related to drug-reward-related events (Bowman et al. 1996; also see Carelli 2000; Carelli and Deadwyler 1996a; Peoples et al. 1997). Interestingly, most of these neurons, like the majority of accumbal neurons, also exhibit decreases in average firing during the self-administration session (Peoples et al. 1998b, 1999; also see Peoples and West 1996). Several lines of pharmacological and behavioral evidence indicate that the decreases in average firing rate reflect the predominant pharmacological effect of self-administered cocaine (Nicola and Deadwyler 2000; Peoples and West 1996; Peoples et al. 1994, 1998a,b; also see Nicola et al. 1996; Qiao et al. 1990; Rebec and Zimmerman 1980; Uchimura and North 1990; White 1990; White et al. 1993). That accumbal neurons exhibit responses to both drug-reward-related events and pharmacological effects of drug is consistent with the hypothesis that self-administered drug modulates accumbal processing of drug-reward-related signals (Peoples et al. 1998b, 1999).

A question to be addressed is how might the predominantly inhibitory effects of self-administered cocaine on average firing rate “amplify,” or otherwise enhance, the primarily excitatory lever-press firing patterns. One possibility is that drug has a less inhibitory effect on the drug-reward-related signals than on other, background, neural activity. Such differential changes in firing would increase the signal-to-background ratio of the reward-related signals and potentially translate into an increased impact of those signals on accumbal contributions to learning and behavior. In the present study, we investigated whether accumbal neurons exhibit firing patterns during drug self-administration sessions that are consistent with this hypothesis. Animals were trained to intravenously self-administer cocaine. Neurons that exhibited both a lever-press firing pattern and a decrease in average firing during the self-administration session were identified and analyzed for differential changes in signal and background firing over the course of a self-administration session.

 Portions of the data were presented at the Society for Neuroscience 32nd Annual Meeting (Peoples and Cavanaugh 2002).

METHODS

Subjects

The subjects (24 male Long-Evans rats) and neurons described in the present report are a subset of those included in a previously described study (Peoples et al. 1998b). Inclusion of subjects in the present study was contingent on a procedural criterion. Specifically, during the recording session, subjects had to initiate drug seeking under drug-free conditions (i.e., no priming infusion of drug). All animal care and protocols were in accordance with the Guide for the Care and Use of Laboratory Animals published by the U.S. Public Health Service and approved by the Animal Care and Use Committee of Rutgers, The State University of New Jersey.

Surgery and postoperative maintenance

Animals were anesthetized with pentobarbital sodium (50 mg/kg ip). Before surgery, subjects received injections of atropine methyl nitrate (10 mg/kg ip) and penicillin G (75,000 U/0.25 ml ip). Anesthesia was maintained with periodic injections of pentobarbitonal sodium (5–10 mg/kg ip) and ketamine hydrochloride (60 mg/kg ip). A catheter was implanted in the jugular vein and exited through a j-shaped stainless steel cannula cemented to the skull. An array of quad-Teflon-coated stainless steel wires was implanted in the accumens (between 0.7 and 2.7 mm anterior from bregma; between 0.8 and 2.2 mm lateral from bregma; and between 6.8 and 7.2 mm ventral from level skull) (Paxinos and Watson 1996). The array consisted of 12–16 microwires (diameter of each uninsulated wire tip, 50 μm) arranged in two parallel rows, which were −2 mm in length and separated from one another by 0.45–0.55 mm (wire center to wire center).

After surgery, subjects were housed in steel-grid chambers. The catheter was connected to a fluid swivel (Brown et al. 1976). A motor-driven pump perfused the catheter with 0.2 ml of heparinized bacteriostatic saline once per hour. Occasionally, outside the experimental sessions, a brief period of anesthesia was induced by intravenous administration of methohexital (10 mg/kg) to either confirm catheter patency or to facilitate attachment of the electrical harness. At least 7 days after surgery and 3 days before self-administration training, subjects were transferred to a Plexiglas chamber where they remained 24 h/day for the duration of the study. Subjects had free access to water and were fed ~15 g of food each day to maintain body weight at 350 g.

Procedures

DAILY COCAINE SELF-ADMINISTRATION SESSION. Onset of each self-administration session was signaled by a regular sequence of events that began with the illumination of a stimulus light followed by insertion of the response lever into the chamber. Once the lever was inserted animals received an intravenous infusion of saline (0.2 ml). The saline infusion was paired with a 7.5-s tone that corresponded with the duration of the syringe pump operation, and the offset of the stimulus light for 40 s. These tone and light stimulus events are the same events associated with cocaine infusions later during the self-administration session. The sequence of events that occurred between the first illumination of the stimulus light and the re-illumination of the light, at the end of the 40-s light-off period, is referred to as the discriminative stimuli (S<sup>D</sup>).

After completion of the S<sup>D</sup>, animals had the opportunity to self-administer cocaine according to a fixed-ratio 1 (FR 1) schedule of drug reinforcement. Each press of the lever was followed immediately by a 0.2-ml intravenous infusion of cocaine (0.7 mg/kg per 0.2-ml infusion), a 7.5-s tone that corresponded to duration of the syringe pump operation, and a 40-s timeout, during which the stimulus light was turned off and a lever press had no programmed consequence. Each session was limited in duration to 6 h or 80 infusions. At the end of the self-administration session, the stimulus light was turned off, and the response lever was removed from the chamber.

OVERALL SELF-ADMINISTRATION HISTORY PRIOR TO THE RECORDING SESSION. All self-administration sessions, from the first to the last, were conducted identically and according to the procedures described in the preceding section. Animals typically approached and pressed the lever on the first day of self-administration training and were self-administering drug within the first one to three sessions. Self-administration training sessions were conducted 7 days/wk. Prior to the recording study, subjects completed 12–17 days of self-administration training.
VIDEO RECORDING. During each recording session, behavior was videotaped using a JVC HR-78004 Super VHS recorder. Each video frame (30 frames/s) was sequentially time-stamped by a computer coupled with a video frame counter (Thalner Electronics VC-436). Frames were time-stamped according to the same computer clock that time-stamped each neural discharge. The camera view was oriented perpendicular to the response lever. The entire chamber was visible; thus the rat was always visible. The video system allowed us to document, off-line, the timing of behaviors completed in any area of the chamber with a temporal resolution of 33 ms.

ELECTROPHYSIOLOGICAL RECORDING SESSIONS. Phases of the recording session. A recording session started with a 20-min nondrug baseline-recording period. At the end of the 20-min period, the typical daily self-administration session was conducted. A 40-min nondrug recovery period followed the self-administration session. During the nondrug baseline and recovery periods that bracketed the self-administration session, subjects were not exposed either to the drug cues, the nondrug baseline and recovery periods that bracketed the self-administration session. During the nondrug baseline and recovery periods that bracketed the self-administration session, subjects were not exposed either to the drug cues, the nondrug baseline and recovery periods that bracketed the self-administration session.

Data analysis

CHARACTERIZATION OF THE RESPONSIVENESS OF INDIVIDUAL NEURONS TO THE OCCURRENCE OF THE LEVER PRESS AND TO THE ADMINISTRATION OF DRUG DURING THE MAINTENANCE PHASE. The statistical analyses used to test the significance of changes in firing exhibited by an individual neuron differed depending on whether firing was evaluated with respect to either an event that occurred repeatedly during the session (e.g., lever press) or an event that occurred only once. In the case of an event that occurred repeatedly during the session, firing rate (number of discharges, also referred to as counts) was calculated during two intervals per occurrence of the event, one interval that preceded the onset of the event and one interval that followed the onset of the event. Discharges during the pre- and postevent intervals were then compared using a Wilcoxon matched-pairs test (Peoples and West 1996; Peoples et al. 1997, 1998b; Schultz et al. 1992; Siegel and Castellani 1988). Analyses of neural responses to events that occurred once per session were carried out in either of two ways. First, in some cases, the total number of discharges during an interval before and after the onset of the event were simply counted and used to calculate a percent change in firing rate. Second, discharges before and after the event were compared using a Mann-Whitney test.

Although the nonparametric statistical tests are designed for comparisons between populations of subjects, they can be appropriately applied to “single-subject” data that are not autocorrelated (Kazdin 1984) across the time periods being employed in the analysis. Additionally, extensive experience in evaluating the utility of various statistical approaches has shown us that the use of the tests, in conjunction with visual inspection methods (Kazdin 1984), is a reliable and rigorous method for defining responsive neurons. There are three main categories of firing patterns exhibited by accumbal neurons during an FR 1 cocaine self-administration session. These firing patterns have been defined and characterized in a number of previous reports (e.g., Peoples and West 1996; Peoples et al. 1997, 1998a,b; Uzwiak et al. 1997). The procedures used to analyze the firing patterns are thus only briefly described herein.

Lever-press firing patterns were defined as a significant increase or decrease in average firing rate within ±3 s of the lever press, relative to firing during the −12 to −9-s prepress. To test for an increase in firing rate, discharges during the 12 s before and after each lever press (excluding the 1st 8–10 presses and any presses preceded or followed by an inter-infusion interval of <6 min) were determined using a sliding window method (i.e., 0.3-s window and 0.1-s step). Maximum firing rate in a 0.3-s window within the 3-s pre- and postpress was compared with median firing rate during −12 to −9 s prepress (Wilcoxon matched pairs test, 1-tailed, a = 0.01). Comparable methods were used to test for a decrease in firing rate time-locked to the lever press. Offset was defined as the first of three successive 0.3-s windows that showed significantly different firing from the median firing rate during −12 to −9 s prepress. Offset was defined as the first of three 0.3-s windows that showed firing rate that did not significantly differ from the same median firing rate.

An inter-infusion-interval firing pattern consisted of a change in average firing rate within the 2-min postpress, relative to the 2-min prepress. To test for this type of change, firing rate (i.e., number of discharges) during the 4 min before and after each lever press (excluding the 1st 8–10 presses and any presses preceded or followed by an inter-infusion interval of <6 min) was first calculated using a sliding window method (i.e., 0.5-min window and 0.1 min step). To test for a postpress decrease in firing, the minimum firing rate postpress was then compared with the maximum firing rate prepress (Wilcoxon matched pairs test, 1-tailed, α = 0.05). A postpress increase in firing was defined as a significant difference between maximum firing rate postpress and minimum firing rate prepress.

A session change in firing was defined as a significant change in firing rate during each of two 20-min periods during the maintenance phase of the self-administration session relative to the 20-min nondrug baseline recording period. The two self-administration periods included the first 20 min of the second hour of self-administration behavior and the last 20-min of the self-administration session. Neurons that showed significant unidirectional changes in firing rate.
during the two 20-min self-administration periods, relative to the predrug period, were defined as showing a session change in firing rate.

**ANALYSIS OF SIGNAL AND BACKGROUND.** For lever-press neurons, signal period was defined on an individual neuron basis and equaled the interval elapsing between the onset and offset of the phasic increase in firing. The background period equaled 12 to 4 s prepress for all neurons. The background period was generally longer than the signal period; however, the measures of signal and background firing rate were equated by calculating each as discharges per second (i.e., Hz). Calculation of background firing rates over the longer time period provided measures of background firing that were consistent with the overall firing rates observed during the nonsignal portions of the peri-event histograms. Signal and background firing rates were calculated on a trial-by-trial basis for each of the first 36 self-infusions for all neurons that showed the combined profile of a lever-press response and a session decrease in firing. Changes in signal and background firing were evaluated relative to two periods: the 30 s that preceded the onset of the self-administration session (referred to as the pre-SB period) and the 30 s before the first press. The ratio of signal and background firing (S:B) was also determined on a trial-by-trial basis.

As a control for nonspecific determinants of the increases in S:B, we made additional comparisons of average firing during a “signal-control” period and a background period for all neurons that showed a session decrease in firing (i.e., were tonically inhibited) but showed no lever-press response during the maintenance phase. Signal equaled the average signal period for all lever-press neurons (i.e., 0.5 s prepress to +1.5 s postpress). The background period was defined as the same period used for the lever-press neurons.

**BEHAVIORAL CONTROL ANALYSIS.** The lever-press firing patterns are closely associated with drug seeking. It was thus possible that differential changes in percent time spent in drug seeking during signal and background periods contributed to differential changes in signal and background firing. We tested for this possibility in two ways. First, we characterized the percent of time that animals spent in lever-directed locomotion during the signal and background periods. In this analysis, lever-directed locomotion was defined as locomotion that brought the animal proximal to the lever. In most cases, this meant that the animal was close enough so as to press the lever. Lever-directed locomotion increases in frequency shortly before each cocaine-reinforced lever press during ongoing drug self-administration sessions (see Peoples et al. 1998a). The extent to which the pattern of change in the lever-directed locomotion is consistent with the pattern of change in signal and background firing would therefore be indicative of whether differential changes in drug-seeking behaviors during signal and background potentially explain differential changes in firing.

Second, we conducted a behavioral clamp analysis (Peoples 2002; Rank et al. 1983). Calculations of signal and background firing rate were limited to periods in which animals were engaged in a specific behavior. For all neurons, the background firing rate was calculated during the first period within the 12 to 4 s prepress during which the animal engaged in 0.5 s of uninterrupted stereotypy (or comparable behavior such as standing in place on the non-lever side of the chamber). Signal firing rate was calculated in either of two ways, depending on the timing of the signal period. For most neurons, signal firing was calculated during drug-seeking behavior that occurred within the last 0.5 s before a reinforced lever press. Drug seeking was defined as an approach to the lever that terminated with a press of the lever. The lever approach had to be 0.5 s in duration to be included in the analysis. For other neurons, limiting calculation of signal firing to drug seeking was not possible because the signal period was exclusively postpress (4 neurons). For these neurons, signal firing was calculated during locomotion away from the lever, immediately after completion of the lever press. Limiting calculations of firing rate to these behaviorally defined periods allowed us to evaluate the possibility that differential changes in behavior, and more specifically drug-reward-related behavior, during the signal and background periods contributed to differential changes in the signal and background firing rates over the course of the self-administration session. Additionally, it allowed us to test further the hypothesis that drugs may affect differentially activity that encodes reward-related events during the self-administration session relative to other neural activity. The videotapes of one experiment were not useable. The data from that experiment (1 subject and 2 neurons) were therefore not included in the behavioral control analyses.

**Histology**

Subjects were injected with a lethal dose of pentobarbital sodium. Anodal current (50 μA for 4 s) was passed through each microwire. Animals were perfused with formalin-saline. Coronal sections (50 μm) were mounted on slides and incubated in a solution of 5% potassium ferricianide and 10% HCl to stain the iron deposits left by the recording tip. The tissue was counterstained with 0.2% solution of Neutral Red. The location of each wire tip was plotted on the coronal plate (Paxinos and Watson 1996) that most closely corresponded to its anterior-posterior position. Only those neurons verified histologically to be located within the nucleus accumbens were included in the study.

**RESULTS**

**Self-administration behavior and changes in drug level**

The patterns of self-administration behavior and the associated changes in drug level observed in the present study were consistent with those described in many previous studies (e.g., Pettit and Justice 1989; Yokel 1987). The pattern of drug intake included an initial loading phase and a subsequent maintenance phase. The initial presses of the loading phase were executed rapidly relative to all subsequent presses. After these rapidly completed self-infusions, animals slowed responding to a session low before stabilizing response rates at an intermediate rate that was maintained during the remainder (i.e., maintenance phase) of the session (Fig. 2).

Estimated drug levels rose rapidly in association with the initial presses to a session maximum (“overshoot” stage of loading phase). As response rate slowed, drug level at the time of the press first decreased from the peak that was attained...

![FIG. 2. Average inter-infusion interval and calculated drug level. For all subjects, average inter-infusion interval (●) is plotted as a function of cocaine-reinforced lever presses. Average calculated drug level (■) (cf. Pan et al. 1991) at the time of each lever press, within 0.125 min before each press, is also plotted for the same lever presses.](http://jn.physiology.org/10.1152/jn.00126.2002)
during loading (“recovery” stage of loading phase) and then remained within stable narrow limits for the duration of the session. In addition to these loading-to-maintenance changes, drug level also showed a regular oscillation between successive lever presses. Specifically, drug rapidly increased to a stable maximum shortly after each self-infusion and then slowly decreased to a stable minimum that was attained shortly before the next self-infusion (Fig. 3).

Neuron firing patterns

**AVERAGE FIRING PATTERNS DURING THE MAINTENANCE PHASE.** Phasic changes in firing during the seconds before and after the cocaine-reinforced lever press. Twenty of 68 accumbal neurons showed a phasic change in firing rate during the few seconds that bracketed cocaine-reinforced lever presses (e.g., Fig. 3B). For all but one neuron, the phasic change was an increase in firing rate around the time of the press relative to background (hereafter referred to as lever-press neurons).

Changes in firing associated with delivery of self-administered drug. The 19 excitatory lever-press neurons exhibited two types of changes in firing in response to self-administered drug. The most common type involved a stable change in average discharge rate during the maintenance phase, relative to the pre- and postdrug recording periods (henceforth referred to as a session change or a tonic change in firing). For 14/19 neurons, the session change in firing was a decrease (i.e., neurons were tonically inhibited, Fig. 3A); for 4/19 neurons, the session change was an increase (i.e., neurons were tonically excited, Fig. 4). Consistent with the predominance of decreases, average firing rate of all 19 lever-press neurons decreased during the self-administration session relative to the nondrug pre- and postdrug recording periods. This could be seen visually when average firing rate during the maintenance phase was compared with average firing during the pre- and postsession nondrug periods (Fig. 4A). The decrease in the average firing rate of the population of lever-press neurons was also evident visually and statistically when calculation of firing rate was restricted to the seconds (i.e., ±10 s) that bracketed cocaine self-infusions and firing was compared across successive self-infusions [Fig. 5, F(35,595) = 2.21, P < 0.001]. The second type of change in firing that was associated with drug delivery was exhibited by 15/19 neurons and occurred during the minutes that elapsed between successive self-infusions. Firing rate decreased during the first minute postpress and then progressively increased until the time of the next lever press (inter-infusion-interval firing pattern referred to previously as decrease + progressive reversal) (Peoples and West 1996). This firing pattern (Fig. 3C) closely mirrored the regular oscillation in drug level that occurred between successive self-infusions (Fig. 3A).

The neurons that showed no lever-press firing pattern (i.e., non-lever-press neurons) also showed changes in association with drug delivery. The number of those neurons that showed session decreases and increases were 31/48 and 14/48 (i.e., 64 and 29%) respectively. Sixteen of the 48 neurons showed inter-infusion-interval pattern.

**CHANGES IN SIGNAL AND BACKGROUND FIRING.** Examples of signal and background periods are shown for two neurons in Fig. 6. In Fig. 7 (left), average signal and background firing are plotted as a function of lever-press number for all 14 of the tonically inhibited lever-press neurons. Comparisons between the 30-s pre-SD and the signal and background for the first lever press [F(2,26) = 3.56, P < 0.05] showed that signal (Tukey test, P < 0.05) but not background (Tukey test, P > 0.05) was significantly greater than average firing pre-SD. Across the first 36 presses, average signal showed no significant change [F(35,455) < 1.0] and thus remained elevated above the pre-SD rate throughout the session. In contrast, average background decreased significantly [F(35,455) = 3.49, P < 0.01] and in a dose-related fashion (Fig. 7B, left). The differential changes in signal and background produced a significant increase in both the average ratio of signal-to-background (S:B) [F(35,455) = 1.61, P < 0.05] and the average difference between signal and background (S-B) [F(35,455) = 1.56, P < 0.05; (Fig. 7, C and D, left].

A more-detailed analysis of signal and background firing of

**Fig. 3.** The firing patterns of a single tonically inhibited lever-press neuron. A: a session decrease (tonic inhibition) firing pattern. Firing rate (counts per 0.5 min) is plotted as a function of session time. Above the plot of firing is a display of drug level [calculated as a function of 0.10-min intervals according to formulas described by Pan et al. (1991)]. Inset: the change in drug level before and after a single self-infusion (dashed line in center of inset = lever press). B: a lever-press firing pattern. Average firing rate (counts per 0.1-s bin) is plotted during the 12 s before and after all reinforced lever presses during the self-administration session. Time 0 corresponds to the time of the lever press. C: an inter-infusion-interval firing pattern. Average firing rate (counts per 0.1-min bin) is plotted during the 4 min before and after all reinforced lever presses. Time 0 equals the time of the lever press. A–C correspond to firing patterns exhibited by the same neuron during a single self-administration session.
single neurons showed that the changes in group mean firing reflected an average of two predominant patterns of signal and background change that were exhibited by 11 of the 14 neurons. For one group of six neurons (e.g., Figs. 8 and 9), both background and signal tended to be elevated above pre-SD levels at the time of the first press. Over the course of the self-administration session, the decrease in average signal was smaller in magnitude than was the decrease in average background firing rate. Therefore signal firing rate remained above the pre-SD rate throughout the self-administration session. The S:B ratio thus increased over the course of the session. For a second group of five neurons (e.g., Fig. 10), there was no
consistent trend for signal and background firing rate to be either greater than or less than pre-$S^D$ at the time of the first press, although in all cases firing was low and close to pre-$S^D$. Over the course of the self-administration session, decreases in background were small as would be expected given that the firing rates of the neurons were already low at the start of the session. The signal firing rate for this group of neurons did not consistently differ from background firing during the loading phase of the session, but subsequently increased to rates that tended to exceeded background and pre-$S^D$. The increase occurred at either of the following times: the time at which drug reached the maximum level at the end of the overshoot stage of the loading phase or around the time at which the recovery phase was ending and the maintenance phase began. After this transition, signal showed trial-to-trial variation but hovered around a stable “mean” rate that was equal to or greater than the pre-$S^D$ rate. As a consequence of this pattern of signal and background firing, S:B showed an overall increase during the maintenance phase, relative to the loading phase (Fig. 10). Despite the differences between the two predominant patterns, both were consistent in showing that signal either attained a rate or remained at a rate that exceeded pre-$S^D$ whereas background firing rate generally fell below pre-$S^D$.

BEHAVIORAL CONTROL. Analysis of videotapes showed that at the beginning of the self-administration session, animals spent time approaching the response lever during the background period as well as during the signal period. As the loading phase progressed, approaches to the response lever decreased in frequency and became restricted primarily to the signal period (Fig. 11). Time spent approaching the lever showed a greater decline during the signal period than during the background period. This pattern of differential change in the frequency of the behavior during signal and background periods is not in line with the differential changes in signal and background firing (e.g., compare Figs. 7B and 11). It is thus difficult to conclude that the changes in firing were due simply to changes in the occurrence of drug-seeking-related behaviors per se.

Nevertheless, it was possible that the decreases in background firing rate and hence the increase in S:B were due, in part, to the decrease in the frequency of drug seeking during the background period. If this interpretation were correct, eliminating periods of drug seeking from the calculation of background firing would be expected to diminish the decrease in background firing rate over the course of the session and to also reduce the increase in S:B. We tested for this possibility in the six neurons that showed increases in S:B that were attributable only to differential decreases in signal and background firing. Specifically, we limited calculations of signal to periods in which animals were engaged in drug seeking and limited calculation of background firing to periods in which animals were engaged in stereotypy (or a comparable behavior). These recalculations of signal and background did not eliminate either the decrease in background firing rate or the increase in S:B (Figs. 12 and 13). These data show that the increases in S:B did not reflect changes in drug-seeking behavior during the signal and background periods. Moreover, controlling for drug seeking during the background period increased the apparent difference between background and signal firing at trial 1 for 5/6 neurons (e.g., Fig. 13), thus confirming that the increase in S:B for those neurons reflected an amplification of firing that was present at the first press rather than an emergence of a firing pattern that was initially absent.

NON-LEVER-PRESS NEURONS THAT WERE TONICALLY INHIBITED. As a control for nonspecific determinants of the increase in S:B, we made comparisons of firing during the background period and a “signal control” period for another group of neurons. This second group of neurons included all recorded neurons that were tonically inhibited but showed no excitatory phasic response in relation to the lever press (referred to as non-lever-press neurons). For these neurons, there were no significant differences among average pre-$S^D$ firing and average signal and background firing at the time of the first press [$F(2,60) = 1.01, P < 0.05$]. Across the first 36 self-infusions, firing during the signal and background periods decreased significantly [$F(35,1050) = 2.48, P < 0.001$] and comparably [$F(35,1050) = 1.34, P > 0.05$]. There was no significant change in either the average S:B [$F(35,1050) = 1.15, P > 0.05$] or the average S:B [$F(35,1050) = 1.28, P > 0.05$ (Fig. 7, right)].

POPULATION S:B. The analyses of signal and background of the lever-press and non-lever-press neurons showed that the resistance of signal to inhibition during the self-administration session was unique compared with the firing exhibited by other
accumbal neurons. It is thus possible that the magnitude of the reward-related signals increased relative to the background firing of all accumbal neurons. Evidence consistent with this hypothesis was observed in the present study. Average signal of the lever-press neurons showed no significant change over the course of the self-administration session \( F(35, 595) < 1.0 \); whereas, average background of all recorded neurons decreased significantly \( (F(35, 2275) = 3.05, P < 0.001) \). These differential changes in signal and background were associated with a doubling of the population S:B (Fig. 14).

FIG. 7. Changes in signal and background for tonically-inhibited neurons. Left and right: tonically inhibited lever-press neurons \((n = 14)\) and non-lever-press neurons \((n = 31)\), respectively. A: average drug level at the time of each press is plotted as a function of press number. B: average log Hz during the signal (full circles) and background (empty circles) periods is plotted as a function of lever-press number. Dashed line, average firing rate during the 30-s pre-S. To the right of the plot, standard error bars are shown for the median average log Hz during presses 11–36 for the signal (full circles, left) and background (empty circles, right) periods. C: average signal-to-background ratio (S:B) is plotted as a function of lever-press number. Dotted line, a signal to background ratio of 1. To the right of the plot, standard error bars are shown for the 1st press (light gray bars, left) and the press at which we observed the median ratio during presses 11–36 (black bars, right). D: average difference between signal and background (S-B) plotted as a function of lever-press number. To the right of the plot, standard error bars are shown for the 1st press (light gray bars, left) and the press at which we observed the median S-B difference during presses 11–36 (black bars, right).
Histology

Three-quarters of the lever-press neurons were in the anterior half of the accumbens core. The other lever-press neurons were in the shell or along the shell core border. The neuron number was too small to make any definitive between-territory comparisons; although, it is interesting to note that none of the lever-press neurons that showed increases in signal were located within the shell.

DISCUSSION

Summary of major findings and conclusions

Learning theories of drug addiction propose that drug-induced amplification of accumbal mechanisms that normally mediate aspects of reward-related learning and behavior contributes to the etiology of drug addiction. Neurophysiological mechanisms that might transduce such a drug effect on accumbal mechanisms have yet to be identified. Based on previous studies of accumbal firing patterns during drug self-administration sessions and previous studies of DA modulation of striatal information flow, we hypothesized that self-administered drug may lead to aberrant amplified drug-reward-related learning, in part, by enhancing the S:B of drug-reward-related signals during drug self-administration sessions (for similar and related proposals, see Carelli et al. 1999; Nicola et al. 2000; Peoples et al. 1998a).

Given this hypothesis, in the present study, we tested whether the excitatory phasic firing responses to drug-reward-related events such as the cocaine-reinforced lever press (i.e., signal), would be less sensitive than other accumbal firing (i.e., background) to the inhibitory effects of self-administered cocaine. Trial-by-trial characterizations of signal and background firing of lever-press neurons showed that signal either remained at a rate or attained a rate during the self-administration
session that exceeded the pre-S^D firing rate, whereas, background firing rate generally fell below pre-S^D. Behavioral control analyses showed that the differential changes in firing could not be attributed to differential changes in behavior during signal and background periods. It is thus possible that the lesser inhibition of signal relative to background reflected a differential pharmacological effect of cocaine on signal and background firing. The differential changes in signal and background firing rate were associated with an increase in the ratio of signal-to-background for the individual neurons. Perhaps more importantly, the unique resistance of signal firing to the inhibitory effects of self-administered cocaine was associated with an increase in signal firing of the lever-press neurons relative to the firing of all the recorded accumbal neurons. These increases in S:B might be expected to increase the influence of the accumbal drug-reward-related signals on the state of accumbal-related neural circuits and hence on accumbal-mediated functions (e.g., learning). It is thus a mechanism by which the predominantly inhibitory effects of self-administered drug could amplify accumbal contributions to reward-related learning during drug self-administration sessions. Consistent with the proposals of learning theories of addiction, such drug effects could potentially contribute to the development of drug addiction.

Contribution of primary drug effects to the increases in S:B

The individual neuron and population increases in S:B were largely attributable to the differential inhibition of signal and background firing. It is possible that the differential inhibition reflected pharmacological mechanisms. As we have already noted, control analyses ruled out the possibility that the S:B changes were caused by differential changes in behavior during the signal and background periods. Moreover, numerous analyses in previous accumbal recordings during drug self-administration sessions show that for most neurons, the decreases in average firing are likely to be pharmacological in origin.
A pharmacological mediation of the S:B increase would be consistent with the findings of various types of electrophysiological experiments. Acute electrophysiological recording studies generally show that the primary pharmacological effect of cocaine on spontaneous firing of accumbal neurons is inhibition (Nicola et al. 1996; Qiao et al. 1990; Rebec and Zimmerman 1980; Uchimura and North 1990; White et al. 1993). Additionally, in both anesthetized animals and awake, spontaneously active animals, iontophoretic application of either cocaine or amphetamine to the accumbens (and elsewhere) inhibits tonic, spontaneous, firing to a greater degree than it inhibits evoked excitatory signals (Haracz et al. 1993; Jimenez-Rivera and Waterhouse 1991; Kiyatkin and Rebec 2000; Wang and Rebec 1993). Given these data, it appears that the contribution of inhibition to increases in the ratio of signal to background observed in the present study is consistent with, and potentially mediated by, a primary intra-accumbal pharmacological effect of cocaine.

FIG. 12. Changes in signal and background firing for neurons that showed differential decreases in signal and background firing: control for differential changes in the frequency of drug-seeking behavior. A: average log Hz during the signal (■) and background periods (○) is plotted as a function of lever press. B: average S:B is plotted as a function of lever-press number. C: average firing rate (log Hz) during drug seeking that occurred within the last 0.5 s of the signal period (■) and average firing rate (log Hz) during a 0.5-s stereotypy event that occurred during the background period (○) are plotted as a function of lever-press number. D: average ratio of firing rate during drug seeking (signal period) and firing rate during stereotypy (background period) is plotted as a function of lever-press number.

FIG. 13. Changes in signal and background firing for an individual neuron: control for differential changes in behavior. The 4 graphs correspond to the data of a single neuron. Plotted as a function of lever-press number are the following: A: signal (■) and background (○) firing rates; B: ratio of signal and background; C: firing rates during drug seeking (■) and stereotypy (○); and D: ratio of firing rate during drug seeking to firing rate during stereotypy.
accumbal DA in drug reward, it seems likely that changes in drug-reward-related accumbal firing would be mediated by DA rather than by the other monoamines.

A role of DA in mediating the S:B changes observed in the present study would be consistent with the hypothesis that DA modulates accumbal and striatal activity in a behaviorally dependent and neural activity-dependent manner. More specifically, increases in DA input are expected to enhance transmission of strong, contextually relevant, excitatory signals relative to weaker and less relevant excitatory inputs (Floresco et al. 2001; Hernandez-Lopez 1997; Kiyatkin and Rebec 1996; Levine et al. 1996; Mogenson and Yim 1991; O’Donnell and Grace 1996; Pennartz et al. 1994; Pierce and Rebec 1995; Rolls et al. 1984). This hypothesis is based primarily on the effects of experimenter-applied DA during either acute recording conditions or recordings in awake animals engaged in spontaneous behavior (although see Rolls et al. 1984). The present study shows that accumbal firing patterns consistent with the differential modulation of signal and background can be observed during a period in which subject-determined reward-relevant increases in accumbal DA regulate ongoing instrumental behavior. The data thus suggest that the S:B mechanism and the hypotheses regarding DA modulation of accumbal information flow may be applicable to reward-related accumbal DA function.

Relation to other studies

COCAINE SELF-ADMINISTRATION. The present study is the first to test for trial-to-trial changes in the signal and background firing of accumbal neurons over the course of the self-administration session. However, related analyses were conducted in a number of previous studies. Specifically, Carelli and colleagues compared average firing during the 10-s pre- and postpress for all lever presses during the loading phase to average firing pre- and postpress during the maintenance phase (Carelli and Deadwyler 1996b; Carelli et al. 1999). These researchers observed that average firing 10-s pre- and postpress was greater during the maintenance phase than during the loading phase and that this increase in average firing was associated with increased evidence of the phasic lever-press firing patterns. Based on these observations, Carelli and colleagues (Carelli and Deadwyler 1996; Carelli et al. 1999) concluded that accumbal neurons are responsive to drug-reward-related signals only after drug, and presumably DA, exceeds some threshold level. The results of the present study also show that phasic firing patterns are more apparent during the maintenance phase relative to the loading phase. However, we propose that the findings of the present study, along with other data, are consistent with alternative conclusions regarding the mechanisms that potentially mediate the enhancement of phasic firing over the course of the self-administration session.

For a significant subset of the neurons in the present study, signal firing was elevated at the time of the first press in relation to firing before the start of the self-administration session. For these neurons, signal firing either remained stable or decreased somewhat but nevertheless remained elevated relative to baseline firing rates throughout the self-administration session. On the other hand, the background firing de-
increased over the course of the self-administration session to rates that were below baseline firing rates. Indeed, average background firing of all lever-press neurons decreased over the course of the self-administration session. The same was true for the non-lever-press neurons. These findings are consistent with the interpretation that at least some accumbal neurons are responsive to afferent input related to drug-reward events at the onset of the self-administration session. Moreover, the present findings are consistent with the further conclusion that a primary effect of drug is to inhibit or cull non-drug-reward-related responses rather than to switch-in responsiveness of accumbal neurons to excitatory afferent input. These conclusions are consistent with evidence that activation of accumbal afferents can evoke drug seeking and that neurochemical changes in the accumbens correlate with the initiation of drug seeking (e.g., Cornish and Kalivas 2000; Cornish et al. 1999; Gratton and Wise 1994; Ito et al. 2000; Kiyatkin and Stein 1996; Phillips et al. 2003; Vorel et al. 2001; Weiss et al. 2000).

It is the case that there were some neurons in our study that showed increases in signal firing and average firing pre- and postpress over the course of the self-administration session. A priori, it is possible that these increases reflected a drug-induced enhancement in excitatory accumbal responses. There are a number of DA-mediated facilitative mechanisms that have been identified in acute electrophysiological studies that could potentially mediate such a drug-induced enhancement in the absolute magnitude of the signal (for review, see Nicola et al. 2000; O’Donnell 1999; Pennartz et al. 1994). However, data from several studies point to additional possible interpretations of the increases in firing. First, although there is evidence that in the majority of cases decreases in firing during drug self-administration are pharmacological in nature, there is little evidence that the increases in firing exhibited by accumbal neurons are also (for review, see Peoples 2002). Indeed, when increases in signal were observed in the present study (also in the studies of Carelli and Deadwyler 1996b; Carelli et al. 1999), the increase most often occurred abruptly at particular points in the session. This non-dose-dependent step-function change in firing is more likely to reflect a nonpharmacological neural response to a change in the state of either the environment or the animal rather than a direct pharmacological effect of the drug that influences the ability of neurons to respond to preexisting afferent input. Second, accumbal recordings made in animals engaged in sequences of behavior directed toward nondrug rewards indicate that at least some accumbal neurons exhibit phasic responses to reward-related events contingent on the proximity of the event to reward (Shidara et al. 1998). Those data suggest that context-dependent responses of some accumbal neurons to reward-related events may help to track progress through a reward-related sequence. It is possible that some of the increases in signal exhibited by lever-press neurons during a drug self-administration session reflect such tracking rather than a drug-induced change in the ability of a neuron to respond to particular afferent input.

**OTHER ADDICTIVE DRUGS**. Electrophysiological recordings conducted by other investigators show that accumbal neurons exhibit firing patterns during sessions of ethanol and heroin self-administration that are comparable to patterns exhibited during cocaine self-administration (Chang et al. 1998; Janak et al. 1999). Moreover, acute recording studies show that addictive drugs, in general, tend to decrease average firing of accumbal neurons (Criado et al. 1995, 1997; Hakan and Henricksen 1989; and references cited in the INTRODUCTION). It will thus be of interest in future studies to explore the possibility that self-administration of other drugs produce within-neuron increases in S:B and population increases in S:B that are comparable to those observed in the present study of cocaine self-administration. Given the common inhibitory effects of addictive drugs, it is possible that a drug-induced increase in drug-reward-related S:B is a common neurophysiological mechanism contributing to the reinforcing and possibly addictive effects of the drugs (discussed further in Accumbal contributions to reward-related learning and drug addiction).

**NATURAL REWARDS.** Electrophysiological recordings of striatal and accumbal firing during instrumental sessions maintained by natural rewards have not yielded reports of changes in S:B (although, see Rolls et al. 1984). There are a number of potential explanations for the absence of such reports. First, the increases in S:B ratio may be unique to drug self-administration. This explanation is plausible given that self-administered drug is likely to produce changes in accumbal neurochemistry that are distinct quantitatively, if not qualitatively, from neurochemical changes associated with instrumental behavior directed toward natural rewards. Second, it is possible that studies of natural rewards have not yet applied analyses appropriate to observing the phenomena. In regard to this latter possibility, there has been little characterization of background (tonic) firing in electrophysiological studies of nondrug rewards. It would be of interest to perform such analyses. There are many commonalities among the variables and mechanisms that influence behavior directed toward drug and nondrug rewards. It thus seems possible that the S:B changes observed in the present study are closely related to the mechanisms that normally regulate (i.e., gate) the flow of signals through the accumbens and thereby direct reward-related behavior and influence reward-related learning (discussed further in the following text).

**Accumbal contributions to reward-related learning and drug addiction**

**QUESTIONS ANSWERED AND QUESTIONS STILL REMAINING.** The present findings are relevant to understanding the involvement of accumbal neurons in learning and drug addiction. The role(s) of the nucleus accumbens in learning is not fully understood. However, microinjection and lesion studies show that dopamine-mediated accumbal mechanisms do contribute to the occurrence and expression of certain types of reward-related learning. For example, the accumbens is involved in autoshaping (Pavlovian conditioning) (e.g., Cardinal et al. 2002). The accumbens additionally modulates the impact of previously conditioned stimuli on instrumental (reward-directed) behavior (for review, see Everitt et al. 1999, 2001). Acutely administered cocaine and other psychomotor stimulants enhance the influence of previously conditioned stimuli on reward-related behavior and have been observed to facilitate some types of reward-related learning (e.g., Cardinal et al. 2000; Harmer and Phillips 1998; Killcross et al. 1997; Krivanek and McGaugh 1969; Robbins 1978; Robbins et al. 1989; Taylor and Horger 1999; Wynn and Berridge 2000). The drug effects appear to be mediated, in part, by dopaminergic modulation of accumbal
neural activity (Robbins et al. 1989; Taylor and Horger 1999; Taylor and Robbins 1986; Wyvell and Berridge 2000). These and other observations have led to the proposal that drug-induced increases in accumbal DA contribute to the development of drug addiction by amplifying accumbal mechanisms that normally contribute to reward-related learning and behavior. This facilitation of accumbal mechanisms is thought to lead to the abnormal strengthening of drug-directed behaviors and stimulus control thereof, which in turn contributes to compulsive drug-seeking (for review and related proposals, see Berke and Hyman 2000; DiChiara 1998, 2002; Hyman and Malenka 2001; Robbins et al. 1983; Robbins 1978; Robinson and Berridge 1993; Robinson and Everitt 1999; Stewart 1992; Stewart et al. 1984; White 1996).

Based on this learning view of addiction, one can make a number of predictions. One such prediction is that drug actions in the accumbens would enhance reward-related accumbal signaling during periods of drug self-administration. In contrast to this prediction, and as already described in the preceding text, we have not as of yet observed evidence that pharmacological effects of self-administered drug increase the absolute magnitude of excitatory reward-related accumbal signals. However, the present study demonstrates that self-administered drug is associated with a differential inhibition of signal and background such that there is a net enhancement of the learning view, that the increase in S:B might amplify the contribution of the accumbens to learning. To evaluate this prediction, it would be helpful to first consider the firing patterns of accumbal neurons during non-drug-reward-related learning and to understand how those firing patterns normally contribute to learning. One could then ask if the drug-induced changes in firing patterns (i.e., the enhanced S:B) potentially amplify the contribution of the accumbens. Patterns of phasic activity exhibited by accumbal neurons during reward-related sequences are consistent with the functional contributions that DA-mediated accumbal mechanisms are known to make to reward-related behavior and learning. For example, consistent with an accumbal contribution to autoshaping and an accumbal modulation of the influence of conditioned stimuli on instrumental behavior, accumbal neurons show phasic firing in relation to conditioned stimuli, instrumental behavior, and reward (e.g., Apicella et al. 1991; Bowman et al. 1996; Carelli and Deadwyler 1994; Chang et al. 1994; Lavoie and Mizumori 1994; Peoples et al. 1997; Shidara et al. 1998; Williams et al. 1989). Despite this correspondence, very little is known about the mechanisms by which the reward-related accumbal signals actually contribute to either the formation of associations or to the influence of conditioned stimuli on reward-directed behavior. Whether and how increases in the S:B of reward-related signals might facilitate accumbal contributions to learning and behavior are therefore a matter of speculation.

To make progress in addressing these questions, it is necessary to form testable hypotheses. In considering developing views of the neurophysiology of accumbal contributions to learning and behavior, in conjunction with the present findings, we have identified a possible direction for future research. In the next section, we briefly describe current views of accumbal neurophysiology and DA modulation thereof. Familiarity with these views is necessary for understanding our hypotheses, which are described in the final section.

DEVELOPING VIEWS OF THE NEUROPHYSIOLOGY OF ACCUMBAL CONTRIBUTIONS TO LEARNING AND BEHAVIOR. Electrophysiological recordings in behaving animals engaged in behavior directed toward reward show that a relatively small minority of neurons (<30%) actually respond to stimulus and behavioral events (e.g., Bowman et al. 1996; Carelli and Deadwyler 1994; Chang et al. 1994; Lavoie and Mizumori 1994; Schultz et al. 1992; Uzwiak et al. 1997; Williams 1989; Williams et al. 1993; although see Shidara et al. 1998). Moreover, these neural responses tend to be heterogeneous in terms of the particular reward-related events that evoke them and also in terms of the direction of the change in firing, although excitatory responses predominate. These data are consistent with the previously stated conclusion that “...behaviorally meaningful information in the nucleus accumbens is represented by fine-grained spatiotemporal firing patterns [of ensembles of neurons]... rather than by massive waves of activity uniformly sweeping from Acb to the ventral pallidum and related terminal fields” (Pennartz et al. 1994; p 726). The make-up of or ensembles of neurons that respond in a particular situation is unknown; however, consistent with what is understood of striatal circuitry, it has been hypothesized that an ensemble is a group of neurons that have similar afferent and efferent relationships and are closely related functionally (Pennartz et al. 1994). More specifically, ensembles may be groups of neurons defined by membership within particular cortico-striato-pallido-thalamo-cortical loops (Pennartz et al. 1994; also see Alexander et al. 1990; Groenewegen et al. 1990, 1993; Haber and McFarland, 2001). Based on acute electrophysiological studies of individual neurons, activation of ensembles is proposed to require convergent synchronous input (Pennartz et al. 1994; O’Donnell and Grace 1996; O’Donnell 1999), which is thought to derive from functionally related cortical and limbic afferents. Activation of particular accumbal ensembles is expected to lead to the activation of functionally related groups of neurons in down-stream mesencephalic, cortical (via ventral-pallido-thalamic projections), and hypothalamic targets. The activation of certain ensembles, in conjunction possibly with inactivation of others, is thought to mediate changes in sensory and cognitive processing, the internal milieu, and the motivation and behavior of the organism (see Pennartz et al. 1994). Thus the heterogeneity of accumbal responses during a reward sequence may be understood as reflecting the sequential and simultaneous activation of multiple ensembles within distinct cortico-striato-pallido-thalamo-cortical loops in response to the various components and aspects of a reward-related sequence. DA input to the accumbens is thought to refine the spatiotemporal pattern of neural activity and to thereby modulate accumbal contributions to behavior and learning (O’Donnell 1999; Pennartz et al. 1994). Acute electrophysiological evidence suggests that this DA influence on neural and ensemble activity may be mediated by multiple mechanisms (see Nicola et al. 2000; O’Donnell 1999; Pennartz et al. 1994 for review). One mechanism is firing-rate-dependent (i.e., frequency-dependent) inhibition, which is thought to contribute to the selective activation of ensembles that are most relevant to the behavioral setting (Pennartz et al. 1994). The
differential inhibition of drug-reward-related firing and background firing observed in the present study can be viewed as potentially reflecting such differential modulation of ensemble activity. This modulatory, “filtering” effect of DA on ensemble activation could contribute to directing behavior by constraining which neurons and ensembles are activated and thus able to pass signals on to downstream targets and consequently influence behavior.

The filtering effect of DA could similarly contribute to learning by narrowing the ensembles in accumbens, or downstream targets, that are available to participate in processes that mediate the development and strengthening of associations. It is also possible that a differential inhibition of reward-related and nonreward-related signals could influence learning by modulating the susceptibility of neurons to frequency-dependent cellular and synaptic plasticity (e.g., long-term potentiation and depression). Such plasticity is thought to lead to a differential strengthening and weakening of synaptic connections, neuronal responses, and, perhaps, ensemble responses and to ultimately underpin learning and selective changes in behavioral responses to environmental stimuli predictive of reward (cf. Berke and Hyman 2000; Hyman and Malenka 2001; Pennartz et al. 1994). Finally, it should be noted that shifts in DA activation that occur as a function of repeated behavioral experiences, for example, the shift in DA responses from the primary reward to stimuli that predict reward (for review, see Schultz 2000; Schultz and Dickinson 2000), may further contribute to selection and constraint of synapses and neurons that are subject to neuroplasticity and thereby further limit or cap learning (i.e., limit the extent to which certain patterns of activation are strengthened and weakened) and facilitate development and maintenance of adaptive contextually appropriate behavioral responses.

HYPOTHESES REGARDING DRUG-INDUCED AMPLIFICATION OF ACCUMBAL CONTRIBUTIONS TO LEARNING AND THE PHARMACOLOGICAL MECHANISMS THAT CONTRIBUTE TO DRUG ADDICTION. All addictive drugs elevate DA in the accumbens (for review, DiChiara 1995; DiChiara and Imperato 1988; Leshner and Koob 1998; Wise and Bozarth 1987). These drug-induced elevations in DA are likely to be substantially higher than those that occur under non-drug-reward-related conditions. It is thus likely that during drug self-administration, drug-reward-related and non-drug-reward-related patterns of accumbal neural activity are subject to abnormally strong effects of DA on ensemble selection and plasticity. Additionally, because of the direct effects of addictive drugs on DA neurons, increases in DA in relation to drug reward may not dissipate as a function of repeated experience to the same extent as occurs in relation to non-drug rewards (DiChiara 1998, 2002). It is thus possible that DA influences on learning are not subject to normal experience-related constraints. That is, additional strengthening and weakening of various synapses and neural responses may occur with each and every self-administration experience.

Given the unusual characteristics of DA input to the accumbens during drug self-administration sessions, and observations of the present study, we hypothesize that during drug self-administration sessions, DA-mediated drug effects may engender an unusually global and powerful weakening of synaptic connections and neural responses that are involved in transmission of signals unrelated to drug reward. Conversely, and simultaneously, a relatively unique sparing of drug-reward-related signals during drug self-administration may lead to an unusually selective susceptibility of the relevant synapses and neural responses to maintenance or perhaps strengthening. Thus with repeated drug self-administration, there may be a general weakening of neural responses that are unrelated to drug reward and a highly selective sparing of neural responses related to drug reward. The proposed differential weakening of synaptic connections and neural excitability could lead to a progressive decline in the throughput of non-drug-reward-related signals through accumbal circuits, including cortico-striato-pallido-thalamo-cortical loops, and a decline in the influence of non-drug-reward-related signals on behavior and learning. Simultaneously, drug-reward-related signals would exert an increasingly dominant “lone-voice” role in influencing the same. Such a narrowing of information flow in addition to contributing to the progressive and selective increase in drug-reward-related behaviors could also potentially contribute to the progressive narrowing in behavioral repertoire, anhedonia, decreased reward sensitivity, and cognitive deficits that are characteristic of drug addiction (cf. Grant et al. 2000; Koob and LeMoal 2001; Martin-Söelch et al. 2001a,b; Rogers et al. 1999; Volkow et al. 2000).

A number of observations made in our laboratory, in addition to the present findings, suggest that this proposal is worth exploring. We observed previously that accumbal neurons that are inhibited by cocaine self administration show a progressive decline in average basal firing rate as a function of repeated drug self-administration sessions (Peoples et al. 1997). This decline in average firing is consistent with evidence that repeated exposure to drug can be associated with weakening of synaptic strength in the accumbens (Thomas et al. 2001). It is also consistent with cellular plasticity that has been documented to occur in animals with a history of repeated drug exposure and that is expected to be associated with a decrease in neural excitability (e.g., Nestler 2001; White et al. 1995; Zhang et al. 1998; for a related observation, see O’Donnell and Grace 1993). Finally, preliminary analyses in our laboratory suggest that across repeated drug self-administration sessions, firing related to drug-reward-related events does not decrease to the same extent to which background firing decreases (unpublished observations, Peoples and Cavanaugh). These observations are consistent with the proposal that an increase in S:B is a neurophysiological mechanism that could mediate the drug-induced amplification of the accumbal contribution(s) to learning that is hypothesized to contribute to drug addiction.

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DISCLOSURES

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REFERENCES

Alexander GE, Crutcher MD, and DeLong MR. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, “prefrontal” and...


