Behavioral/Systems/Cognitive

Selective Encoding of Cocaine versus Natural Rewards by Nucleus Accumbens Neurons Is Not Related to Chronic Drug Exposure

Regina M. Carelli and Joyce Wondolowski
Department of Psychology, The University of North Carolina at Chapel Hill, Chapel Hill, North Carolina 27599-3270

We reported previously that subsets of nucleus accumbens (Acb) neurons differentially encode information about goal-directed behaviors for "natural" (food and water) versus cocaine reward in animals well trained to self-administer the drug (Carelli et al., 2000). Here, we examined whether repeated exposure to cocaine is the crucial determinate of the selective encoding of cocaine versus water reinforcement by Acb neurons. Acb cells were recorded during a water–cocaine multiple schedule from the first day of cocaine exposure as well as during repeated sessions. Specifically, animals were initially trained to press a lever for water and were then surgically prepared for extracellular recording in the Acb. After 1 week, Acb cells were recorded during acquisition of the water–cocaine multiple schedule. Because behavioral responding for water was already established, training on the multiple schedule was divided into three components corresponding to acquisition of self-administration: (1) "initial" (day 1 of self-administration), (2) "reliable" (self-administration behavior was present but erratic), and (3) "stable" (cocaine responding was stable). During the initial component, the percentage of water-selective neurons was high compared with cocaine neurons. However, this became approximately equal with repeated self-administration experience (i.e., during the stable component). Remarkably, the percentage of neurons showing overlapping (similar) neuronal firing patterns during initial exposure to cocaine was low (<8%) and remained low during reliable and stable components. These findings support the view that separate neural circuits in the Acb differentially encode information about cocaine versus natural reward, and that this functional organization is not a direct consequence of chronic drug exposure.

Key words: **accumbens; addiction; drug abuse; reward; self-administration; water**

Introduction

The nucleus accumbens (Acb) is crucially involved in mediating the reinforcing properties of "natural" rewards and abused substances (Kelley, 1999; Koob and LeMoal, 2001; Wise, 1982, 1997, 1998). Electrophysiological recordings in behaving animals support this view by showing that a subset of Acb neurons exhibit four types of patterned discharges within seconds of the reinforced response for intravenous cocaine (Carelli and Deadwyler, 1994; Carelli, 2000). Three of those four cell types were also observed during water reinforcement. To address whether cocaine "taps into" a neural circuit that normally processes information about natural reinforcers, we completed a series of studies that tracked the activity of the same Acb neurons during multiple schedules for either two natural reinforcers (e.g., water and food), or one of those natural reinforcers and intravenous cocaine (Carelli et al., 2000). The results showed that the majority of neurons exhibited similar overlapping neuronal firing patterns across the two natural reinforcer conditions. In contrast, only 8% of Acb cells displayed similar firing patterns relative to responding for water (or food) versus cocaine. These findings indicate that distinct populations of Acb neurons exhibit "reinforcer-selective" activity and differentially process information about cocaine versus natural rewards.

However, the aforementioned study was completed in animals that were well trained to self-administer cocaine (i.e., after 2–3 weeks of training). A number of reports indicate that repeated administration of cocaine results in cellular "neuroadaptations" in the Acb (Henry and White, 1991; White et al., 1995; Xi et al., 2002) that have been generalized to awake behaving animals (Peoples et al., 1999). It is therefore possible that neuroadaptations in the Acb, which are a consequence of repeated cocaine self-administration (SA), may underlie Acb reinforcer-selective patterned discharges observed both in our initial report and previously (Bowman et al., 1996). For example, repeated exposure to cocaine may alter the responsiveness of Acb cells to cortical or subcortical inputs that may define how particular subsets of Acb neurons encode reinforcer-selective information in the behaving animal (Pennartz et al., 1994; Carelli, 2002b). Therefore, it may be the case that cocaine initially taps into a neural circuit in the Acb that normally processes information about natural (water) reward, but that this circuit is reorganized through chronic drug exposure to selectively encode information about cocaine.

To examine this possibility, Acb neurons were recorded here

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Correspondence should be addressed to Dr. Regina M. Carelli, Department of Psychology, The University of North Carolina at Chapel Hill, CB 3270, Davie Hall, Chapel Hill, NC 27599-3270. E-mail: rcarelli@unc.edu.

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during a water–cocaine multiple schedule from the first session of cocaine exposure rather than after extensive self-administration training. It was hypothesized that if reinforcer-selective cell firing is dependent on chronic exposure to cocaine, Acb cells should exhibit similar firing patterns across both reinforcer conditions during initial exposure to the drug. In this case, previously documented reinforcer-selective patterned discharges should develop progressively over days with repeated self-administration experience. Alternatively, if neurons that encode information about cocaine are not the same cells that process information about water reward irrespective of drug history, reinforcer-selective activity should be observed as early as Session 1 of the multiple schedule (i.e., during initial cocaine exposure).

Materials and Methods

Water reinforcement training. Male Sprague Dawley rats (Harlan Sprague Dawley, Indianapolis, IN), ~90–120 d old and weighing 275–350 gm, were used as subjects ($n = 8$). Animals were housed individually and maintained at ≥85% of their preoperative body weight by regulation of water intake. Specifically, animals were given 10–15 ml of water per day (in addition to 1.0–1.5 ml of water consumed during the session) throughout the duration of the experiment. Experimental sessions were conducted in a 43 × 43 × 53 cm Plexiglas chamber (Med Associates, St. Albans, VT) housed within a commercial sound-attenuated cubicle (Fibrocrete, Crandall, GA). One side of the chamber contained two retractable levers (Coulbourn Instruments, Allentown, PA) located 17 cm apart with a water receptacle between the levers (7 cm from each lever and 2.5 cm from the bottom of the chamber).

Animals were trained initially to press a lever in the chamber for water reinforcement on a fixed ratio 1 (FR1) schedule of reinforcement. Each lever depression resulted in the delivery of water (0.05 ml) into the receptacle signaled by retraction of the lever (20 sec) and the onset of a clicking tone stimulus (10 clicks/sec; 80 db; 800 Hz; 20 sec).

Surgery. After 2–3 weeks of water training, animals were anesthetized with ketamine hydrochloride (100 mg/kg) and xylazine hydrochloride (20 mg/kg) and were surgically prepared for self-administration and extracellular recording in the Acb within the same surgery using established procedures. For self-administration, a catheter was implanted into the jugular vein and then routed subcutaneously to the back and attached to a coupling assembly (Caine et al., 1993; Carelli and Deadwyler, 1994). Animals were also prepared for chronic extracellular recording in the Acb as described previously (Carelli and Deadwyler, 1994). Electrodes were custom designed and purchased from a commercial source (NB Labs, Denison, TX). The array consisted of eight microwires (diameter, 50 μm) arranged in one row with a tip separation of ~0.25 mm. The entire array spanned an approximate rostral–caudal distance of ~2 mm. In some cases ($n = 4$ rats), a second type of array described previously (Carelli et al., 2000) was used. This array consisted of "bundles" of eight microwires (diameter, 50 μm) arranged in three rows. The first row contained two wires with a tip separation of ~0.25 mm. The second and third rows contained three wires (tip separation, ~0.25 mm). The entire array spanned a distance of ~0.35–0.65 mm anteroposterior (AP) and 0.35–0.65 mm mediolateral (ML). Each array also contained a ground wire that was inserted 3–4 mm into the brain ipsilateral to the array and ~5 mm caudal to bregma. Arrays were permanently implanted bilaterally into the Acb (AP, +1.7 mm; ML, 1.5 mm; dorsoventral, 6.0–7.5 mm, relative to bregma, level skull).

Water–cocaine multiple schedule. One week after catheter and electrode implantation, presurgical behavioral performance was reestablished for water reinforcement. Neuronal activity was recorded during all subsequent behavioral sessions that incorporated a multiple schedule of water and cocaine reinforcement. The same parameters used for water reinforcement described above were used in the multiple schedule. In this case, however, animals had access to the water-reinforced lever for 8–10 min, followed by a 20 sec timeout period (no lever extended) and extension of a second spatially distinct lever associated with cocaine reinforcement (2 hr). The beginning of the self-administration portion of the multiple schedule was signaled by the onset of a cue light positioned 6.5 cm above the second lever and lever extension. Lever depression on a FR1 schedule resulted in intravenous cocaine delivery (0.33 mg per infusion; dissolved in sterile heparinized saline vehicle) over a 6 sec period via a computer-controlled syringe pump (Model PHM-100; Med Associates). Each drug infusion was signaled immediately by retraction of the lever (20 sec) and the onset of a tone stimulus (65 db; 2900 Hz) presented over a 20 sec interval (14 sec beyond the pump duration).

Electrophysiological recordings. Electrophysiological procedures have been described in detail previously (Carelli and Deadwyler, 1994; Carelli et al., 2000). Briefly, before the start of each session, the subject was connected to a flexible recording cable attached to a commutator (Med Associates), which allowed virtually unrestrained movement within the chamber. The headstage of each recording cable contained 16 miniature unity-gain field effect transistors. Acb activity was typically recorded differentially between each active and inactive (reference) electrode from the permanently implanted microwires. The inactive electrode was examined before the start of the session to verify the absence of neuronal spike activity and served as the differential electrode for other electrodes with cell activity. On-line isolation and discrimination of neuronal activity was accomplished using a neurophysiological system that was commercially available (multichannel acquisition processor, MAP System; Plexon, Dallas, TX). Multiple window-discrimination modules and high-speed analog-to-digital signal processing in conjunction with computer software enabled isolation of neuronal signals on the basis of waveform analysis. The neurophysiological system incorporated an array of digital signal processors (DSPs) for continuous spike recognition. The DSPs provided a continuous parallel digital output of neuronal spike events to a computer. Another computer controlled behavioral events of the experiment (Med Associates) and sent digital outputs corresponding to each event to the MAP box to be time stamped along with the neural data. The neurophysiological system has the capability of recording up to four neurons per microwire using real-time discrimination of neuronal action potentials. However, in the present study, typically one to two neurons were recorded per microwire (Chang et al., 1994; Nicolelis et al., 1997). Criteria for identifying different neurons on a single wire has been described in detail previously (Chang et al., 1994; Nicolelis et al., 1997; Nicolelis, 1999; Carelli et al., 2000). Briefly, discrimination of individual waveforms corresponding to a single cell was accomplished using template analysis procedures, time-voltage boxes, or the "off-line sorter" program provided by the neurophysiological software system (MAP system; Plexon). The template analysis procedure involves taking a "sample" of the waveform and building a template of that extracellular waveform. Subsequent action potentials that "match" this waveform were included as the same cell. When using time-voltage boxes, a sample of the waveform is taken and then the experimenter superimposes two boxes onto it (typically one on the ascending limb and the other on the descending limb of the extracellular waveform). Subsequent sampled neurons are accepted as valid when they pass through both boxes. The parameters for isolation and discrimination of single-unit activity were determined and saved using the neurophysiological software and modified before each session as needed (for example, to discriminate "new" neurons that appeared on a given microwire electrode or to change the inactive electrode). The off-line sorter program allows sorting of spike waveforms corresponding to the activity of individual neurons after completion of the experiment. This sophisticated program uses a variety of methods to isolate individual waveforms including manual cluster selection of waveforms in three-dimensional space using principal component projections (Plexon).

Data analysis. Behavioral responding was characterized by cumulative response records showing the lever press response patterns during the water–cocaine multiple schedule. During initial self-administration sessions when animals did not respond regularly or frequently for the drug, neural activity was characterized via stripcharts showing firing rates for individual neurons over time. In other cases, raster displays and perievent histograms (PEHs) were completed showing the activity of each cell during a 20 sec time interval that bracketed the water- or cocaine-reinforced lever press. Types of patterned discharges [preresponse (PR), reinforcement excitation (RFe), reinforcement inhibition (RFi), and

PR+RF] have been described in detail previously and were characterized by differential mean firing rates within four time epochs in each PEH (Carelli and Deadwyler, 1994; Carelli et al., 2000). The four time epochs within each PEH were (1) baseline, defined as the time period (−10 to −7.5 sec) before the initiation of the reinforced lever press response, (2) response, defined as the time period (−2.5 to 0 sec) immediately before and during the execution of the reinforced response, (3) reinforcement, defined as the time period (0–2.5 sec) immediately after the response, and (4) recovery, defined as the time period (7.5–10 sec) after the reinforced response.

Criteria for classifying each neuron into one of the four types of patterned discharges have been described in detail previously (Carelli et al., 2000). Briefly, a neuron was classified as type PR if it showed a ≥40% increase in firing rate within a 1 sec period of maximal discharge during the response epoch only, compared with its respective baseline activity. If a neuron exhibited a 40% increase in activity that began in the response phase and extended without interruption into the reinforcement phase, it was also classified as a PR neuron. A neuron was classified as RFe if it showed a ≥40% increase in cell firing within a 1 sec period of maximal discharge during the reinforcement phase only (i.e., short-duration RFe cells), or if it exhibited a 40% increase in firing during both the reinforcement and recovery phases (long-duration RFe cells), compared with its respective baseline activity. Neurons classified as RFi had a ≥40% decrease in firing rate within a 1 sec period during the response and reinforcement epochs, compared with its respective baseline firing rate. A neuron was categorized as PR+RF if it displayed a ≥40% increase in activity during a 1 sec period within both the response and reinforcement epochs (but not the recovery phase), compared with its respective baseline rate. In addition, neurons classified as PR+RF had to exhibit a reduction in activity to baseline levels between the two peak discharges. Nonphasic (NP) neurons exhibited similar firing rates across the four time epochs without the 40% changes in activity characteristic of the four types of patterned discharges described above. Statistical confirmation of the above cell type classification was accomplished using a *t* test for dependent samples that compared mean peak (PR, RFe, PR+RF) or trough (RFi) firing rates for all neurons of a given type to their respective baseline rates.

Population histograms of normalized cell firing were generated for all phasically active neurons during the 20 sec time interval, which bracketed the water- or cocaine-reinforced response using procedures described previously (Carelli et al., 2000). Briefly, neuronal firing patterns of all PR, RFe, RFi, and PR+RF cells recorded during the multiple schedule for water and cocaine reinforcement were presented as composite PEHs summed over all cells of a specific type and normalized relative to the overall mean firing rate of each neuron. Normalization of cell firing allowed for an examination of changes in the activity of populations of cells regardless of differences in overall rates of firing between individual neurons (Carelli and Deadwyler, 1994).

Histology. After the completion of the last experiment, animals were anesthetized with sodium pentobarbital (50 mg/kg), and a 10 μA current passed for 6 sec through all recording electrodes. The rat was perfused with 4% paraformaldehyde and the brain was removed, blocked, and sectioned (50 μm) throughout the rostral–caudal extent of the Acb. Sections were stained for thionin and counterstained with Prussian blue to reveal a blue dot reaction product corresponding to the location of the marked electrode tip (Green, 1958; Carelli and Deadwyler, 1994). The procedure used to reconstruct electrode placements was as follows. Serial sections were examined under a light microscope, and the locations of marked electrode tips were plotted for all subjects on coronal sections taken from the stereotaxic atlas of Paxinos and Watson (1997). The position within the various regions of the Acb (core, shell, and rostral pole) and boundaries between these regions were determined by examination of marked electrode tip locations in relationship to (1) the borders of the stain at the level of the rostral pole and caudal Acb regions, (2) precise "landmarks" in the brain (for example, the anterior commissure), and (3) the anatomic arrangement of the Acb as depicted in the stereotaxic atlas of Paxinos and Watson (1997).

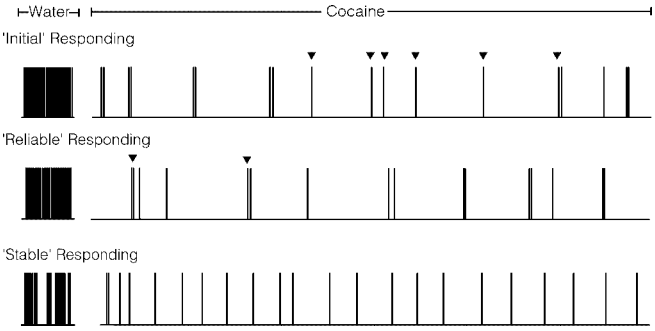

Figure 1. Cumulative records showing the behavioral (lever press) response pattern for a single animal during acquisition of self-administration in a water–cocaine multiple schedule. During the first session of cocaine exposure (initial), the animal completed 28 responses for water with a mean INT of 22.19 sec. During the self-administration phase, water was placed on the cocaine lever three times (indicated by open arrowheads), and the animal was primed several times (indicated by closed arrowheads). During the first session of reliable responding, lever pressing for water remained stable (16 presses; INT, 22.08), and responding for intravenous cocaine was present but erratic. During the stable component (day 7), behavioral responding was stable for both water (21 responses; mean INT, 42.85 sec) and cocaine (22 responses; mean INT, 6.13 min).

Results

Behavior

Animals were initially trained to press a lever for water reinforcement and then Acb cell firing was recorded during acquisition of cocaine self-administration within a water–cocaine multiple schedule. Thus, behavior on the multiple schedule was divided into three components (initial, reliable, and stable) on the basis of behavioral response patterns during the self-administration phase of each session. Note that in well trained animals (Fig. 1, bottom), self-administration behavior is characterized by a "burst" of responding at the start of the session followed by regularly responding with mean interinfusion intervals (INTs) of ~5 min. An example of behavioral response patterns across the three components is shown for one representative animal in Figure 1.

The first component (initial) included the first multiple schedule session. Across all animals, behavioral responding for water reinforcement was stable (mean responses, 22.25 ± 1.3; mean INT, 32.75 ± 5.77 sec). However, during the initial self-administration phase, behavioral responding for intravenous cocaine either did not occur or was erratic. Typically, the experimenter had to prime the animals with multiple infusions of cocaine. Priming was not limited to the start of the session but was given often throughout the session. In some cases, a drop of water was placed on the cocaine lever on several trials to initiate movement toward that lever.

The next 2–6 d of training on the multiple schedule were classified as the reliable component, reflecting less erratic (but not yet stable) self-administration behavior. During the first reliable session across all animals, responding for water reinforcement remained stable (mean responses, 22.38 ± 1.12; mean INT, 24.92 ± 1.40 sec). During the self-administration phase, the experimenter still needed to prime the animal with no more than three infusions of cocaine to initiate responding for the drug (water was never placed on the cocaine lever). In some cases, priming infusions were not necessary, but behavior was still erratic. Unlike the first day of cocaine exposure, all animals responded for the drug at this stage of training. Across all animals, the mean number of responses for cocaine was 20.50 ± 1.81, with a mean INT of 4.04 ± 1.07 min.

After 6–9 d of training, animals exhibited stable responding during both phases of the multiple schedule. Specifically, water-reinforced responding was characterized by 21.38 ± 1.21 responses, with a mean INT of 30.75 ± 3.57 sec. Stable responding for intravenous cocaine consisted of the following requirements. First, drug primes were not necessary to initiate responding. Second, animals typically exhibited a burst of responding at the start of the self-administration phase ("load-up" behavior) followed by regularly spaced responding. Across all animals ($n = 8$), the mean number of load-up responses was 2.75 ± 0.49, with a mean INT of 0.76 ± 0.15 min. After load-up, the animals exhibited regularly spaced responding with a mean number of responses of 18.87 ± 1.29 and a mean INT of 6.42 ± 0.17 min.

Nucleus accumbens cell firing during the initial (first) session of the water–cocaine multiple schedule

A total of 97 neurons was recorded (eight rats) during the first multiple schedule session (i.e., day 1 of cocaine exposure). Of the 97 cells, 24 neurons (25%) exhibited one of three types of patterned discharges relative to the water-reinforced response as described previously (Carelli et al., 2000). Briefly, a subset of neurons exhibited an increase in firing rate within seconds, preceding the reinforced response, and was classified as PR cells ($n = 5$ cells; 21%). Other neurons showed increased firing immediately after the response, RFe ($n = 15$ cells; 62%), or an inhibition in cell firing immediately before or after the response, RFi ($n = 4$ cells; 17%). Examples of the three types of neuronal firing patterns are shown in Figure 2.

As noted above, cocaine self-administration was very erratic on day 1 of the multiple schedule and often included drug primes to initiate responding. Nevertheless, in several cases, animals began to lever press for intravenous cocaine on the first day of training. Remarkably, for those animals, Acb patterned discharges relative to lever pressing for cocaine "emerged" within this first session of cocaine exposure. An example of one such neuron is shown in Figure 3. The session began with a water reinforcement phase (23 trials) during which the Acb cell exhibited no change in firing rate relative to the water-reinforced response (i.e., classified as NP; data not shown). The activity of the same Acb cell during the self-administration phase is shown in the stripcharts in Figure 3. The behavioral response pattern during the self-administration phase is shown in the cumulative record (each upward deflection indicates a cocaine-reinforced response). At the start of the SA phase, the rat lever-pressed eight times in relatively quick succession (Lever Presses: Start of SA). During this period, the Acb cell continued to exhibit nonphasic firing (Fig. 3; top left stripchart) (four of eight responses are indicated by arrows). Thereafter, the animal exhibited a pause in responding and was given a total of five experimenter-delivered cocaine-priming infusions within the next 30 min period. As expected, the cell exhibited nonphasic firing relative to the priming infusions (top middle PEH; two of five primes are shown). Shortly thereafter, the animal lever-pressed without any primes and completed 27 additional cocaine-reinforced responses. By the end of the first session of self-administration training, the animal was beginning to exhibit reliable lever-pressing behavior, and an RFe patterned discharge emerged. Specifically, RFe firing was present during the last six trials of the 2 hr self-administration phase. This finding is illustrated for the last four trials of the session in the bottom right stripchart in Figure 3.

Another example of reinforcer-selective cell firing on day 1 of the multiple schedule is shown in Figure 4. In this case, the animal lever-pressed 28 times for water reinforcement (mean INT, 21.19 ± 0.28 sec). As shown in the top PEH–rasters in Figure 4, the Acb cell exhibited RFe activity relative to water-reinforced lever presses. At the initiation of the self-administration phase, the animal immediately began responding on the cocaine lever. The same neuron continued to exhibit RFe firing during the first three trials of the self-administration phase and then shifted to nonphasic activity (indicated by the arrow in the raster). After a total of eight presses, the animal stopped lever pressing and was then primed five additional times with intravenous cocaine paired with the tone-houselight stimulus. Note that the Acb cell was not activated by the cocaine primes (see section of raster labeled primes). Thereafter, the animal completed another seven responses without additional priming infusions. Although behavioral responding for cocaine was present at the end of the session, the cell continued to exhibit nonphasic activity.

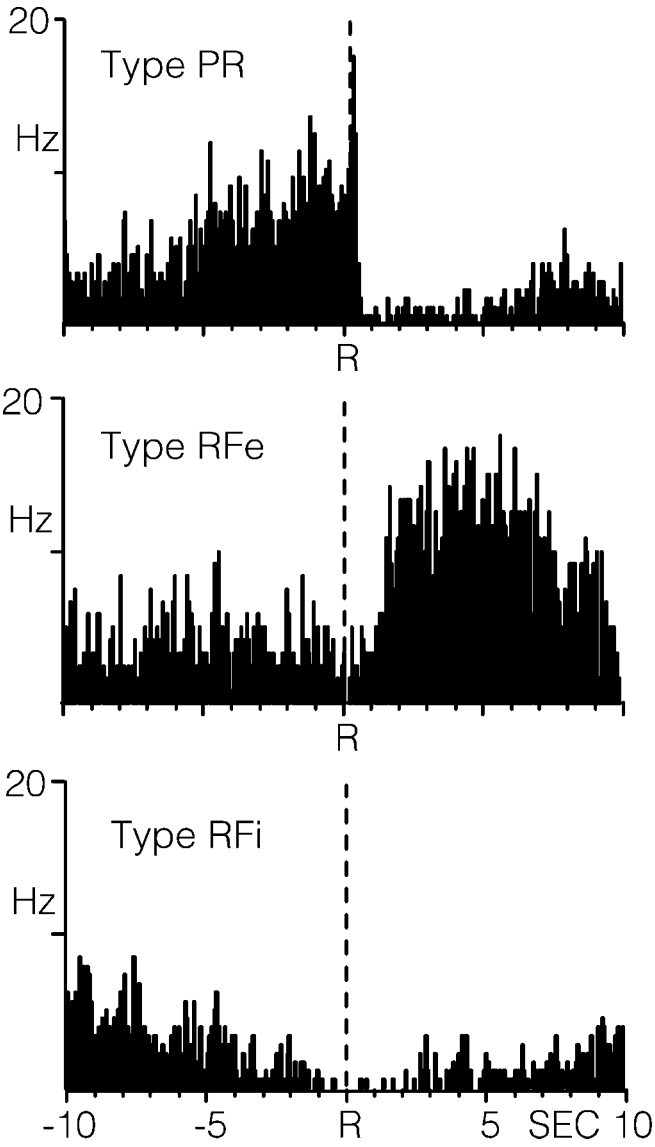

Figure 2. PEHs showing three types of neuronal firing patterns observed within seconds of the lever-press response (FR1) for water reinforcement. Top, Example of an Acb neuron displaying increased firing rates within seconds preceding the reinforced response (PR). Middle, Another neuron showing increased firing immediately after response completion (RFe). Bottom, A third Acb cell displaying a marked inhibition in background firing rates within seconds before and after the response (RFi). R, Reinforced responses. Each PEH contains 250 bins here and in subsequent figures.

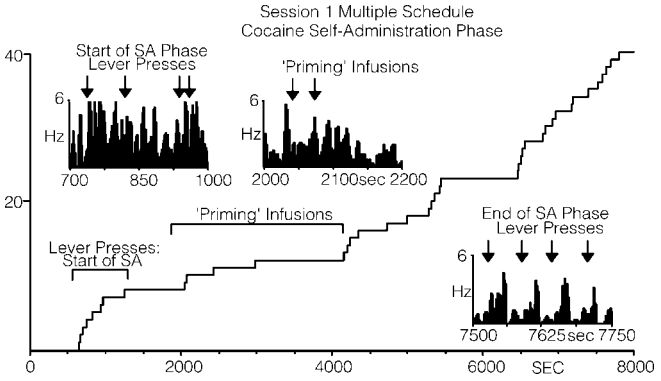

Figure 3. Emergence of cocaine-selective Acb patterned discharge during the initial exposure to cocaine in the water– cocaine multiple schedule. Cumulative record shows behavioral response patterns during the cocaine self-administration component on day 1 of the multiple schedule. Note that the animal responded quickly for intravenous cocaine at the start of the phase followed by several priming infusions. Thereafter, behavioral responding for cocaine was observed, although somewhat erratic. Stripcharts show Acb cell firing relative to lever-press responding at the start of the self-administration component (top left, indicated by arrows) during priming infusions of cocaine (top center, indicated by arrows) and relative to the last four lever-press responses in the session (bottom right, indicated by arrows). Note the onset of RFe patterned activity during the end of the session. The same neuron exhibited NP firing relative to water-reinforced responding (data not shown).

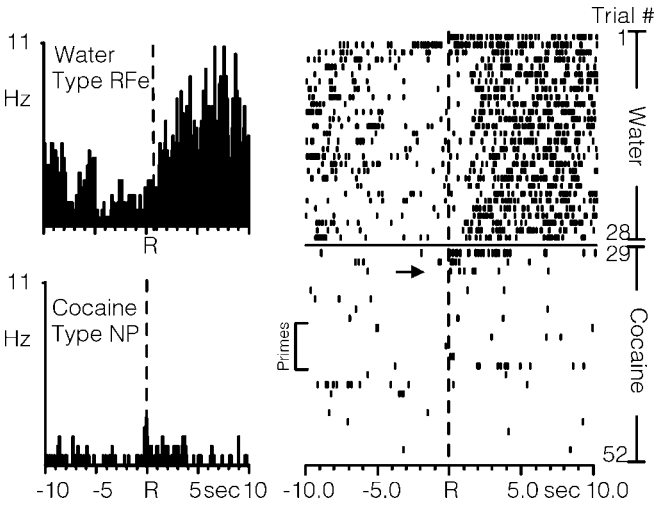

Figure 4. An example of water-selective cell firing during Session 1 of the multiple schedule. Left, PEHs show that the Acb cell exhibited RFe activity relative to the water-reinforced response (top). The same Acb cell exhibited NP activity relative to the cocaine-reinforced response (bottom). Right, Raster display shows the activity of the same neuron shown in the PEHs across all trials of the session. The cell exhibited RFe activity during the water reinforcement phase and within the first three trials of responding for cocaine. This was followed by a shift to nonphasic activity that continued during priming infusions (indicated by primes in raster) and during the remainder of the self-administration phase.

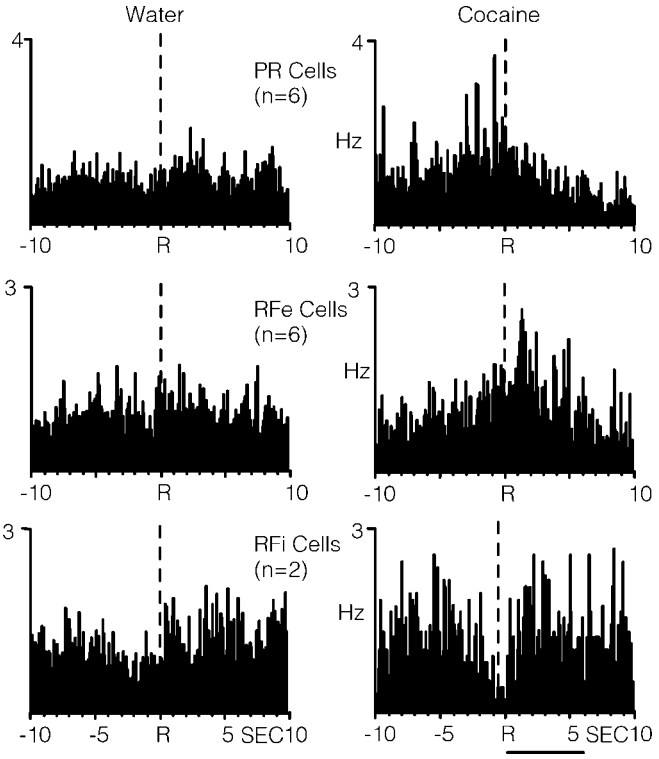

Figure 5. Composite PEHs of normalized firing of all neurons exhibiting patterned discharges relative only to the cocaine-reinforced response during the first day of the multiple schedule. Left, PEHs show that populations of neurons exhibited NP activity relative to the reinforced response for water. Right, The same cells exhibited one of three well defined types of patterned discharges (PR, RFe, RFi) relative to the cocaine-reinforced response.

To summarize the activity of Acb neurons during day 1 of cocaine exposure, cell firing was analyzed relative to reinforced responding for water versus those trials in which each animal responded on their own (no primes given) for intravenous cocaine. Because animals were not well trained, the number of cocaine-reinforced responses was relatively small (mean, 12.25 ± 3.92 responses). Nevertheless, a clear pattern of activity emerged from this analysis. Of the 97 cells recorded during the first multiple schedule session, 42 neurons exhibited patterned discharges relative to water- or cocaine-reinforced responding. Of the 42 cells, only three neurons (7%) showed similar types of neuronal discharges relative to reinforced responding for water and cocaine. The remaining 39 neurons (93%) exhibited one of three types of patterned discharges (PR, RFe, RFi) relative to the water-reinforced response ($n = 24$ cells) or cocaine-reinforced response ($n = 14$) but not both. The remaining neuron exhibited patterned discharges under both reinforcer conditions but of different types.

The composite PEHs in Figure 5 show a summary of normalized firing for cocaine-selective neurons across both reinforcer conditions. Note that this population of Acb neurons exhibited nonphasic activity relative to lever-press responding for water reinforcement (left PEHs). In contrast, although the patterned discharges were not very robust, the same Acb neurons showed one of the three types of patterned discharges (PR, RFe, RFi) relative to the lever-press response for cocaine (left PEHs). Because cocaine primes were often given on day 1 of self-administration training (Figs. 1, 3), the activity of these same neurons was also examined relative to those primes (response-independent cocaine infusions paired with the tone-houselight stimulus). No significant differences were observed in mean firing rates 5 sec before versus 5 sec immediately after cocaine primes for PR (mean rate before, 4.45 ± 2.18; mean rate after, 3.28 ± 1.77; $p > 0.05$), RFe (mean rate before, 2.55 ± 0.68; mean rate after, 1.56 ± 0.60; $p > 0.05$), or RFi cells (mean rate before, 1.75 ± 0.45; mean rate after, 2.40 ± 0.46; $p > 0.05$).

As noted above, a second population of Acb neurons exhibited the opposite pattern of activity during the multiple schedule for water and cocaine. The composite PEHs in Figure 6 summarize the activity of all neurons exhibiting patterned discharges specific to water-reinforced responding. Unlike cocaine neurons shown in Figure 5, Acb neurons illustrated in Figure 6 exhibited

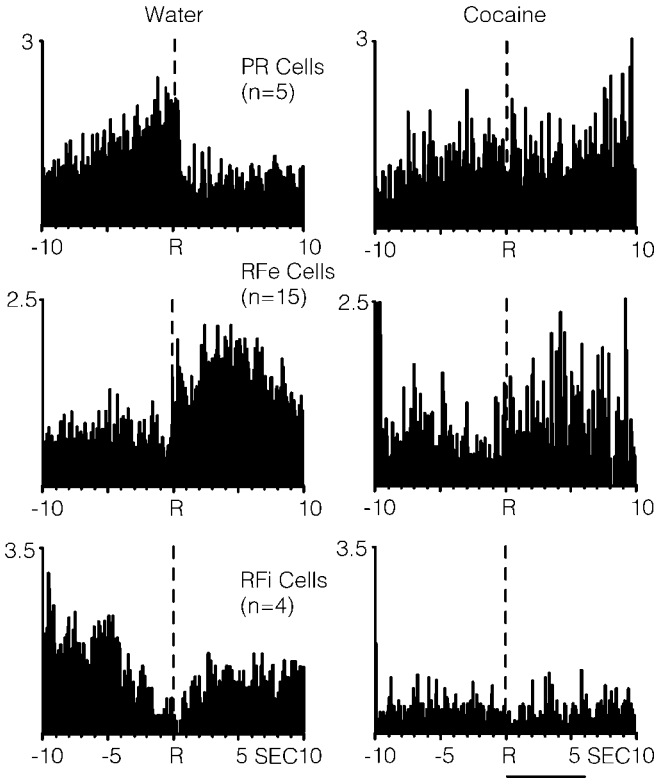

Figure 6. Composite PEHs of normalized firing of all neurons exhibiting patterned discharges relative only to the water-reinforced response during the first day of the multiple schedule. Left, PEHs show that populations of neurons exhibited three types of patterned discharges (PR, RFe, RFi) relative to the reinforced response for water. Right, The same cells exhibited NP activity relative to cocaine-reinforced responding.

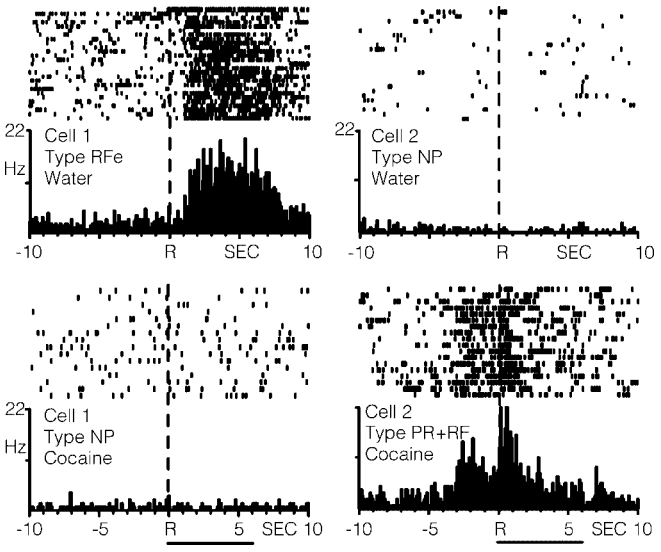

Figure 7. PEHs showing water-selective (left) and cocaine-selective (right) neurons during reliable responding on the water–cocaine multiple schedule. Left, PEHs show a single Acb neuron (cell 1) exhibiting an increase in firing rate immediately after the reinforced response for water (RFe; top) and nonphasic firing relative to the reinforced response for cocaine (bottom). Right, Another Acb neuron (cell 2) recorded in a second animal exhibited nonphasic firing during the water-reinforcement phase and a shift to PR+RF activity during self-administration.

much more robust discharge patterns relative to the goal-directed behavior for water, likely resulting from the extensive training for water as opposed to cocaine. Importantly, this population of neurons showed phasic firing relative to the reinforced response for water but nonphasic activity relative to trials in which the animals responded for cocaine.

Nucleus accumbens cell firing during reliable self-administration responding during the water–cocaine multiple schedule

Acb cell firing was also examined during the first session in which each animal exhibited reliable (although still somewhat erratic) self-administration behavior during the multiple schedule. Of the 89 cells, 42 neurons exhibited patterned discharges relative to the water- or cocaine-reinforced response. However, of the 42 responsive neurons, only five neurons (12%) showed similar types of neuronal discharges relative to reinforced responding for water and cocaine. The remaining 37 neurons exhibited one of three types of patterned discharges (PR, RFe, RFi) relative to the water-reinforced response ($n = 24$ cells) or one of four types of patterned discharges (PR, RFe, RFi, PR+RF) during the cocaine self-administration component of the multiple schedule ($n = 11$) but not both. The two remaining neurons exhibited patterned discharges under both reinforcer conditions but of different types.

Of the 42 responsive neurons, 24 cells (57%) exhibited one of three types of patterned discharges relative to water-reinforced responding (PR, $n = 4$; RFe, $n = 9$; RFi, $n = 11$). An example of a water-selective neuron is shown on the left in Figure 7. Although behavioral responding was still somewhat erratic for cocaine, a second somewhat smaller population of neurons selectively encoded information about cocaine-reinforced responding during the multiple schedule. In this case, eight cells exhibited one of the three types of patterned discharges described above relative to the reinforced response for cocaine (PR, $n = 2$ cells; RFe, $n = 3$ cells; RFi, $n = 3$ cells). In addition, a fourth type of neuronal firing pattern previously reported to be unique to cocaine reinforcement, PR+RF (Carelli and Deadwyler, 1994), was observed during the first day of reliable responding for cocaine ($n = 3$ cells). PR+RF neurons are characterized by two distinct peaks in cell firing, one immediately preceding the reinforced response and terminating at response completion (like PR cells) and a second peak immediately after the response (like RFe cells) with an inhibitory period between the two peaks (like RFi cells). An example of one such neuron is shown on the right in Figure 7.

Nucleus accumbens cell firing during stable self-administration responding during the water–cocaine multiple schedule

Acb cell firing was also examined during the first session in which each animal exhibited stable self-administration behavior during the multiple schedule (7–9 d of training). Of the 102 cells recorded during the first stable session, 46 cells exhibited patterned discharges relative to the water- or cocaine-reinforced response. Consistent with previous findings (Carelli et al., 2000), of the 46 responsive neurons, only four neurons (9%) showed similar types of neuronal discharges relative to reinforced responding for water and cocaine. The remaining 42 neurons exhibited one of three types of patterned discharges (PR, RFe, RFi) relative to the water-reinforced response ($n = 22$ cells) or one of four types of patterned discharges (PR, RFe, RFi, PR+RF) during the cocaine self-administration component of the multiple schedule ($n = 20$ cells) but not both. Mean firing rates for water-selective and cocaine-selective neurons are shown in Tables 1 and 2, respectively.

Table 1. Mean (SEM) of Acb neurons exhibiting phasic cell firing relative to the water— but not cocaine-reinforced response during stable self-administration behavior on the multiple schedule

	Type PR ($n = 7$)		Type RFe ($n = 6$)		Type RFi ($n = 9$)	
Epoch (sec)	Water	Cocaine	Water	Cocaine	Water	Cocaine
Baseline						
−10 to −7.5	3.76 (0.49)	3.13 (0.52)	1.37 (0.14)	0.60 (0.08)	3.03 (0.33)	0.99 (0.10)
Response						
−2.5 to 0	6.06 (0.77)[a]	3.43 (0.48)	0.98 (0.09)	0.51 (0.06)	1.59 (0.15)	0.88 (0.08)
Reinforcement						
0–2.5	3.50 (0.48)	4.14 (0.56)	2.59 (0.10)[a]	0.60 (0.09)	1.08 (0.12)[a]	0.80 (0.08)
Recovery						
7.5–10	3.34 (0.55)	3.52 (0.56)	2.54 (0.27)	0.57 (0.10)	2.94 (0.33)	0.90 (0.09)

[a]Forty percent change compared with baseline within the same column; significant difference ($p < 0.05$) compared with baseline within the same column.

Table 2. Mean (SEM) of Acb neurons exhibiting phasic cell firing relative to the cocaine— but not water-reinforced response during stable self-administration behavior on the multiple schedule

	Type PR ($n = 9$)		Type RFe ($n = 4$)		Type RFi ($n = 5$)		Type PR + RF ($n = 2$)	
Epoch (sec)	Water	Cocaine	Water	Cocaine	Water	Cocaine	Water	Cocaine
Baseline								
−10 to −7.5	2.09 (0.18)	3.12 (0.32)	0.65 (0.20)	1.03 (0.10)	1.62 (0.22)	1.17 (0.20)	3.98 (2.31)	2.23 (1.27)
Response								
−2.5 to 0	1.78 (0.18)	5.52 (0.52)[a]	0.90 (0.15)	1.12 (0.16)	1.63 (0.13)	0.76 (0.12)	3.46 (1.95)	4.19 (1.99)[a]
Reinforcement								
0–2.5	1.36 (0.17)	2.31 (0.24)	0.76 (0.13)	2.09 (0.18)[a]	1.23 (0.14)	0.30 (0.05)[a]	4.16 (2.25)	6.50 (0.16)[a]
Recovery								
7.5–10	1.44 (0.13)	1.94 (0.23)	0.75 (0.17)	1.18 (0.11)	1.02 (0.15)	0.57 (0.09)	3.56 (2.06)	3.38 (0.38)

[a]Forty percent change compared with baseline within the same column; significant difference ($p < 0.05$) compared with baseline within the same column.

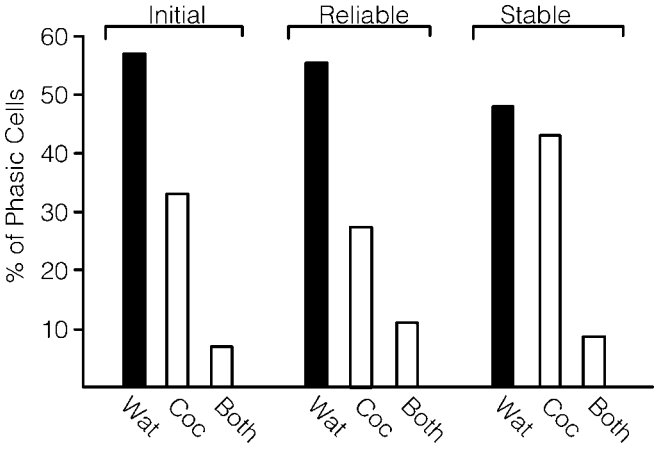

Figure 8. Distribution of water-selective versus cocaine-selective neurons during acquisition of self-administration during the water–cocaine multiple schedule. Percentage of phasic cells is plotted as a function of cell type classification across the three components (initial, reliable, stable) of self-administration training during the multiple schedule. Wat, Neurons that exhibited one of three types of patterned discharges relative only to water-reinforced responding; Coc, neurons that exhibited one of four types of patterned discharges relative only to cocaine-reinforced responding; Both, neurons exhibiting similar, overlapping neuronal firing patterns across the two reinforcer (water and cocaine) conditions.

Summary of water-selective versus cocaine-selective cell firing across three components (initial, reliable, stable) of water–cocaine multiple schedule

Figure 8 shows a summary of the distribution of reinforcer-selective neurons during the three components of self-administration training during the water–cocaine multiple schedule. The percentage of phasically active neurons that exhibited water-selective (Fig. 8, water), cocaine-selective (Fig. 8, cocaine), or similar firing patterns across both reinforcer conditions (Fig. 8, both) are plotted as a function of training component (initial, reliable, or stable). Note that during the first day of cocaine exposure (initial), the majority of phasically active neurons (57%) were related to reinforced responding for water, whereas a smaller percentage of neurons (33%) exhibited phasic firing only during the self-administration phase. Most importantly, only a small percentage of neurons (7%) showed similar, overlapping neuronal firing patterns across the two reinforcer conditions. During the second component of self-administration training (reliable), the percentage of neurons exhibiting patterned discharges specific to water-reinforced responding was similar to that on day 1 of the multiple schedule (56%), and the percentage of cocaine-selective neurons remained relatively low (26%). Again, the percentage of neurons exhibiting similar, overlapping neuronal firing patterns across the two reinforcer conditions remained low (12%). Finally, consistent with our previous findings, the percentage of water (48%) versus cocaine-selective (43%) neurons was approximately equal during stable responding on the multiple schedule, and the percentage of neurons showing overlapping neuronal firing patterns remained low (9%). Collectively, these findings show that neurons that display patterned discharges relative to water-reinforced responding do not convert to one of the phasic firing patterns observed during cocaine self-administration but instead represent a separate population of Acb neurons.

Histology

Histological reconstruction of electrode positions revealed that the neurons recorded during the test sessions were in the rostral pole, core, and shell subregions of the Acb, as defined by Zahm and Brog (1992). Electrode placements spanned a rostral–caudal distance of 2 mm, ranging from 2.7 to 0.7 mm rostral to bregma and from 0.5 to 2.5 mm lateral to midline. Cases in which wires were not positioned in the Acb were excluded from the data analysis.

Discussion

We reported previously that distinct populations of Acb neurons selectively encode information about goal-directed behaviors for cocaine versus natural (food and water) reinforcement (Carelli et al., 2000), consistent with results reported for primates (Bowman et al., 1996). However, those results were obtained in animals that were well trained to self-administer cocaine (i.e., after 1–3 weeks of training). A number of studies indicate that repeated administration of psychomotor stimulants results in cellular neuroadaptations in the Acb (Henry and White, 1991; White and Kalivas, 1998; White et al., 1998; Robinson and Kolb, 1999; Xi et al., 2002) and elsewhere (Ungless et al., 2001; Fagergren et al., 2003; Saal et al., 2003). To test whether chronic cocaine experience may underlie reinforcer-selective activity observed in previous reports, Acb neurons were recorded here during a water–cocaine multiple schedule from the first session of cocaine exposure rather than after extensive self-administration training. We hypothesized that if reinforcer-selective cell firing is dependent on repeated exposure to cocaine, the majority of Acb cells should exhibit similar, overlapping neuronal firing patterns across water versus cocaine reinforcement conditions during initial exposure to the drug. However, the present findings revealed that Acb neurons exhibited reinforcer-selective activity as early as Session 1 of the multiple schedule. These findings support the view that separate neural circuits in the Acb differentially encode information about cocaine versus natural reward, and that this functional organization is not a direct consequence of chronic drug exposure.

Distinct populations of Acb neurons selectively encode information about cocaine versus water during initial exposure to cocaine

In the present study, Acb cell firing was recorded during acquisition of cocaine self-administration within a water–cocaine multiple schedule. During training, self-administration behavior was initially erratic but stabilized with repeated self-administration experience. Nevertheless, distinct populations of Acb neurons were recorded as early as day 1 of self-administration training that differentially encoded information about goal-directed behaviors for cocaine versus water reinforcement. Remarkably, patterned discharges emerged by the end of the cocaine self-administration phase (Fig. 3) or disappeared (for water-selective neurons) during self-administration (Fig. 4). These findings are consistent with the view that separate neural circuits exist in the Acb that selectively encode information about cocaine versus natural rewards that is not dependent on chronic (over one or more weeks) drug experience.

Another important aspect of the present findings is the distribution of water-selective versus cocaine-selective neurons across training sessions. As illustrated in Figure 8, the majority of phasically active neurons during the first session encoded information about goal-directed behaviors for water, likely because animals were initially trained to respond for water reward before implementation of the multiple schedule. However, the percentage of water-selective versus cocaine-selective neurons became approximately equal with the establishment of stable self-administration behavior. Importantly, throughout all components of training, there were relatively few neurons that exhibited similar, overlapping neuronal firing patterns across the two reinforcer conditions. Collectively, these findings illustrate the dynamic nature of Acb cell firing in behaving animals in that within just one session, patterned discharges specific to cocaine reinforcement emerged and that, with additional training, more neurons were recruited in the Acb to selectively encode cocaine-related information.

We reported previously that a fourth type of neuronal firing pattern, cocaine-specific or PR+RF, is observed only during cocaine self-administration and not water reinforcement sessions (Carelli and Deadwyler, 1994; Carelli, 2002a). Interestingly, PR+RF neurons were not observed during initial exposure to the drug but emerged after several days of training. It has recently been reported that cellular neuroadaptations within the brain reward circuit result from repeated cocaine administration (Henry and White, 1991; White et al., 1995; White and Kalivas, 1998; Xi et al., 2002). Thus, PR+RF neurons may reflect an activation of a discrete subset of Acb neurons that only occurs with repeated exposure to cocaine. Nevertheless, it is important to note that like other cell types, PR+RF neurons exhibit nonphasic activity relative to water-reinforced responding and therefore do not reflect a subset of neurons that encode goal-directed behaviors for water.

The present findings are also consistent with previous reports showing that specific populations of Acb neurons are activated by stimuli associated with cocaine delivery (Carelli, 2000, 2002) as well as cocaine availability (Ghitza et al., 2003). For example, we have shown that response-independent presentations of audiovisual stimuli previously paired with cocaine delivery during self-administration sessions activates distinct populations of Acb neurons. Specifically, neurons that discharge within seconds after response completion for intravenous cocaine (RFe, RFi, and PR+RF) are activated in this context. In the present study, we show that Acb neurons are not activated by priming infusions of cocaine paired with this same stimulus when presented during initial training sessions (Session 1). This finding is consistent with the view that the activation of Acb neurons by cocaine-associated stimuli documented in previous studies (Carelli, 2000) represents a learned association between the stimuli and cocaine administration in well trained animals.

Implications for the functional organization of the nucleus accumbens

The selective activation of Acb neurons during goal-directed behaviors for natural versus cocaine reinforcement provides important insight into the functional organization of this structure. Anatomic studies show that the Acb receives convergent synaptic inputs from a variety of cortical and subcortical structures including portions of the prefrontal cortex, subiculum of the hippocampus, basolateral amygdala, and the ventral tegmental area (Groenewegen et al., 1987,1991; Zahm and Brog, 1992; Brog et al., 1993; Heimer et al., 1995, 1997; Wright et al., 1996). It has been proposed that the striatum is part of a larger system of functionally segregated circuits that link the basal ganglia and cortex, and that processing of information within and between these circuits is primarily parallel in nature (Alexander et al., 1986; Alexander and Crutcher, 1990; Groenewegen et al., 1996). Furthermore, numerous studies indicate that the Acb is one component of a larger circuit subserving reinforcement-related processing including the initiation of goal-directed behaviors (Wise, 1998; Pennartz et al., 1994; Carelli, 2002b). The present findings expand those views by showing that within this larger system exists a separate "microcircuit" (at least at the level of the Acb) in which discrete populations of Acb neurons selectively encode goal-directed behaviors for natural (food and water) versus cocaine reward. This selective activation is likely a consequence of afferent activation (from cortical and subcortical structures) of discrete subsets of Acb neurons. Furthermore, the present study

shows that this system appears to be an innate functional feature of the Acb and is not a direct consequence of chronic cocaine exposure.

The present findings are consistent with a theoretical view of the functional organization of the Acb proposed by Pennartz et al. (1994). Those authors proposed that the Acb consists of a collection of neuronal "ensembles" or groups of cells with different functional properties. The activation of specific neuronal ensembles is modifiable and depends on reward-related learning processes. Here and in previous studies, animals completed the same behavioral response (lever press) for drug or natural reward, yet subsets of Acb neurons were responsive only under specific reinforcer circumstances. Furthermore, the present findings show that the activation of specific populations of neurons occurs rapidly and is observed within the first self-administration session. These findings illustrate the dynamic nature of Acb cell firing in behaving animals and the ability of single Acb neurons to reorganize their activity related to reinforcer-specific conditions after initial experience with a reward.

Conclusion

Electrophysiological studies of behaving animals support the critical role of the Acb in reinforcement-related processing by showing that Acb neurons encode the important features of goal-directed behaviors for natural as well as drug reward (Carelli and Deadwyler, 1994; Chang et al., 1994, 1998; Peoples and West, 1996; Peoples et al., 1998; Carelli, 2000; Schultz, 2000). We have shown previously that discrete subsets of neurons in the Acb selectively encode information about cocaine versus natural (food and water) rewards. Here, we expand those findings by showing that this selective encoding of reinforcer-specific information is not the direct consequence of chronic drug exposure but occurs as early as the first self-administration session. However, the factors underlying and controlling this activity remain to be determined. For example, it is not known whether cocaine taps into a more generalized neural system involved in processing, e.g., incentive motivational factors associated with positive reinforcement (Stewart et al., 1984; Robinson and Berridge, 2003). Alternatively, cocaine may be activating neurons that normally process information about sexual behaviors, because the Acb has been functionally linked with this process (Everitt, 1990; Wenkstern et al., 1993; Hull et al., 1999; Kippin et al., 2003). It is also possible that cocaine may activate a population of neurons that remain "idle" until exposed to a potentially rewarding stimulus in the environment (Grigson, 2002). Regardless of its functional origin, the present findings indicate that Acb neurons are recruited to encode goal-directed behaviors for cocaine almost immediately after initial exposure to the drug. An important and clinically related issue will be to determine whether this activation remains evident after abstinence from drug use.

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