Short communication

Low-dose amphetamine elevates movement-related firing of rat striatal neurons

Mark O. West a,*, Laura L. Peoples a, Andrew J. Michael b, John K. Chapin c, Donald J. Woodward d

a Department of Psychology, Rutgers University, New Brunswick, NJ 08903, USA
b Department of Cell Biology and Anatomy, University of Texas Southwestern Medical School, Dallas, TX 75235, USA
c Department of Physiology and Biophysics, Hahnemann University, Philadelphia, PA 19102, USA
d Department of Physiology and Pharmacology, Bowman Gray School of Medicine, Winston-Salem, NC 27157, USA

Accepted 8 October 1996

Abstract

To study the striatal role in amphetamine’s stimulant effects on motor behavior, single neurons were recorded in the dorsolateral striatum of unrestrained rats before and after amphetamine injection (0.5 or 1.0 mg/kg, i.p.). Comparisons of firing were made between similar motor behaviors before and after injection. Mean locomotor firing rates increased 5% to 276% within 30 min after injection and reversed within 2 h. Firing related to specific head- or forelimb-movements, which were similar in all measured parameters before and after injection, was elevated several hundred percent after injection and then reversed, the time course paralleling that of the stimulant effect on these movements. Elevation of movement-related striatal firing rates by low doses of the psychomotor stimulant is in line with established increases in firing rate normally observed for striatal neurons related to motor behavior.

Keywords: Motor behavior; Psychomotor stimulant; Amphetamine; Single unit recording; Striatum; Rat

The importance of the striatum to motor behaviors induced by amphetamine has been documented by results of microinjection studies [14,23], depletion of striatal dopamine [6,15], and measures of striatal activity [9,18,24,31]. A missing link is the characterization of striatal single-cell activity during amphetamine-induced motor behavior. Whereas striatal neurons related to movement increase firing rate in relation to movement [1,3,7,16,20,30,36], amphetamine consistently decreases striatal firing rates in anesthetized or immobilized animals [19,25,26]. This discrepancy may relate to the absence of motor behavior and/or depression characteristic of striatal activity during anesthesia [2,39].

These concerns are avoided in freely moving animals, in which amphetamine has produced both increases and decreases in striatal activity [10,11,28,33]. However, a concern not consistently addressed is to control for potential pre- vs. post-drug alterations in firing related to movement alone. The present design was to obtain a pre-drug assessment of each neuron’s activity during a movement similar to that studied after injection.

Adult Long–Evans rats (eight female, one male) were prepared for chronic recording [8,37]. Each animal was used in only one experiment (which followed surgery by >1 week), except in two cases in which the second experiment followed the first by >3 weeks. As the electrode was advanced into the striatum, the first stable cell encountered was selected. Following intraperitoneal (i.p.) injections, window discrimination of the neuronal waveform was carefully monitored. Any change in amplitude suggestive of electrode drift during the 2–3 h experiment aborted it (necessitated for 5 of 16 neurons in five animals not included), leaving 11 neurons reported, all histologically localized to the dorsolateral striatum at the level of the anterior commissure.

The Plexiglas recording chamber was positioned above a treadmill (TM) which was periodically activated (30 s on/30 s off) and moved at a walking speed of 12 cm/s [36]. All animals learned to walk the TM within the first few 60-s cycles, after which the experiment was typically begun. The experiment began with an i.p. injection of 0.9

* Corresponding author. Fax: +1 (908) 445-2263; E-mail: markwest@rci.rutgers.edu

0006-8993/97/$17.00 Copyright © 1997 Elsevier Science B.V. All rights reserved.
PH S0006-8993(96)01215-2
Fig. 1. For each striatal neuron (n = 9), bars (left to right) show mean firing rate (Hz) during rest (Saline TM-off), locomotion pre-drug (Saline TM-on), and locomotion post-drug (Amph. TM-on). Shaded bars represent 20-min blocks, in sequence, following amphetamine injection. Neurons numbered according to ascending firing rate during Saline TM-off. Percent saline (0.2–0.4 ml), followed by 20 to 30 min collection of control firing rates (Saline phase). Then dexamphetamine sulfate (Sigma) was injected i.p. in 0.2–0.4 ml saline at a dose of 1.0 mg/kg (9 neurons) or 0.5 mg/kg (2 neurons) according to its salt weight; data were pooled. Firing rates across the sample showed a skewed distribution with some values near zero; therefore, for repeated measures ANOVA, firing rate (Hz) was transformed (log, pp. 218–222) to log (Hz + 1).

Using a computerized videotape system [4,36], frames in which a particular type of movement was initiated were selected off-line as nodes for constructing PEHs displaying neuronal activity time-locked to that movement. Distance and duration, from beginning to end of that movement, were used to calculate average velocity for movements exhibiting smooth trajectory.

Firing rates of nine neurons were studied during TM-off and TM-on (Fig. 1). In the Saline phase, locomotion was...
associated with increased firing rate (relative to TM-off) for 7 of the 9 neurons and a decreased firing rate for the remaining two. During TM-off, all rats exhibited long periods of rest and little or no locomotion, thus confounding general comparisons between firing rates pre- and post-drug due to motor behavioral differences. During TM-on, rats showed primarily straight-ahead locomotion in order to keep pace with the TM in both the Saline and Amphetamine phases, allowing general comparisons of firing. Compared with saline control, TM locomotor firing rates of all nine neurons increased (range 5 to 276%) in the first 20 min post-drug \( F(1,8) = 24.3, P < 0.01 \). Thereafter, firing rates of some neurons increased further, but the final 20-min block was not significantly different \( F(1,6) < 1.0 \) from control rates for the seven neurons that could be followed 60–120 min post-injection, a time course similar to that of the drug’s effects on motor behavior (see below).

TM-on locomotion, while serving to substantially limit pre- vs. post-drug behavioral variability, lacked the specificity of a behavioral ‘clamp’ which more rigorously limits motor variability. To address whether elevated firing rates post-drug reflected motoric differences from control, four experiments were videotaped. Video-generated PEHs of firing during only homogeneous, straight-ahead TM locomotion (neuron no. 9 in Fig. 1) showed a post-drug elevation (79%) comparable to that (96%) shown in Fig. 1. This suggests that differences in locomotion did not significantly account for the elevated firing rates post-drug shown in Fig. 1.

A further refinement in clamping motor behavior is to express pre- vs. post-drug differences in firing rate during the specific movement to which that neuron’s firing is time-locked. In three animals, the recorded neurons were related specifically to vertical head movement or to ipsilateral forelimb stance during locomotion. The individual movements used as nodes to construct the PEHs of Fig. 2 showed no pre- vs. post-drug differences in mean distance, duration, or velocity (Fig. 2A) of head or limb movements, in the angle (not shown) of head movements, or in the number of step cycles per TM epoch. In contrast, mean firing rates (Fig. 2B) related specifically to these movements were markedly elevated, relative to control, for all three neurons 5 to 30 min post-drug, by 1030% (from 0.33 to 3.4 Hz, left), 529% (from 2.1 to 11.1 Hz, middle) and 217% (from 2.4 to 5.2 Hz, right). Post-drug elevations of firing related to head movement were confirmed both with more rigorous, and with less rigorous, behavioral clamps (not shown). Thus, the elevations in firing rate post-drug cannot be attributed to differences in pre- vs. post-drug movement parameters. PEHs synchronized to periods of non-movement (> 1.0 s; TM-off) as a behavioral clamp (video-generated PEHs, > 50 nodes, not shown) showed slightly smaller post-drug elevations of 423%, 141%, and 173%, respectively. Likewise, these elevations cannot be attributed to pre- vs. post-drug differences in observable motor behavior.

For both neurons related to head movement, the elevation in firing post-drug coincided with an increased frequency of head movement. The parallel between the two measures was clear in one case (Fig. 3, right) but less so in the other (Fig. 3, left), in which the elevation reversed sooner than the behavior (cf. striatal DA [18]). These data may provide insight into neural mechanisms mediating amphetamine’s effects on motor behavior, in light of (1) the relation of these neurons to head movement, which is induced by amphetamine, and (2) their location in the lateral striatal region thought critical for these motoric effects. This study goes beyond previous reports in providing a model for future analysis of this important issue, using larger samples (in preparation). It may be tentatively suggested that, at low doses, amphetamine-induced elevations in firing rate may influence motor behavior via mechanisms analogous or similar to the natural mecha-

![Fig. 3.](image_url) For two neurons (Fig. 2, left, middle), time course of head movement frequency (•) and mean firing rate time-locked to head movement (○) are plotted as % of mean Saline value (horizontal dashed line at 100%). For each 10-min block, (1) mean firing rate per individual head movement was measured from a PEH constructed as for Fig. 2, and (2) all head movements > 1 cm in amplitude were counted. PEHs each contained from 10 to 69 nodes (mean = 43). Increase from control (30 min Saline) to first block post-amphetamine is shown as broken line. Actual mean values during Saline phase: frequency of head movement, 8.4/min (left) and 4.1/min (right); mean firing rate, 0.3 Hz (left) and 1.6 Hz (right).
nisms through which their movement-related increases in firing rate contribute to motor behavior. The general elevations in striatal firing rate (11 of 11 neurons) across different behaviors (1) suggests that these signals may ‘compete’ at premotor areas in the selection of movement, and (2) supports the general theory of Lyon and Robbins [21], emphasizing the similarity of amphetamine’s effects across different behaviors, which depend “upon a single factor, the consistent increase in activation of neurons involved in motor activity (p. 89).”

Systemically injected amphetamine’s widespread effects on monoaminergic activity may exert direct and indirect effects on striatal activity. Nevertheless, it remains important to characterize striatal activity during systemic amphetamine’s induction of motoric effects that have been attributed to its actions in the striatum. The prediction based on what is known about DA receptor-mediated effects in acute preparations is that firing rates would decrease [2,5,12,13,19,25,26,34]. The present findings, however, confirm and extend those of Trulson and Jacobs [32]: within the active circuits of a freely moving animal, elevated striatal firing rates predominate [10,11,28,33,35], particularly those related to movement. This elevation may involve interactions between receptor-mediated effects and sensorimotor processing during behavioral stimulation by amphetamine. Our elevated movement-related activity and other results [22,33] are consistent with the hypothesis that enhanced corticostriatal transmission contributes to the motoric effects of stimulants [38,41]. Whether the increase occurred in corticostriatal afferent signals or post-synaptic responsiveness [17,27,29,42] remains to be determined.

Acknowledgements

This work was supported by DA-04551, DA 06886, BNS-8708523 and RR-07058 grants to M.O.W., and DA-02338, AA3901 and the Biological Humanities Foundation grants to D.J.W.

References


