Published in final edited form as:

Neuroscience. 2010 February 17; 165(4): 1013. doi:10.1016/j.neuroscience.2009.11.031.

State-dependent plasticity of the corticostriatal pathway

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Abstract

Plasticity at corticostriatal synapses is thought to underlie both normal and aberrant forms of reinforcement-driven learning. Studies in brain slices have found bidirectional, spike-timing dependent plasticity in striatum; however it is not known whether similar rules govern corticostriatal plasticity in awake behaving animals. To assess whether behavioral state is a key regulator of plasticity in this pathway, we examined the effects of 5Hz cortical stimulation trains on evoked striatal field potentials, in either anesthetized or awake, unrestrained rats. Consistent with prior studies we observed long-term potentiation in intact, barbiturate-anesthetized animals. However, when an identical stimulation pattern was applied to the same animals while awake, long-term depression was observed instead. Our results demonstrate that the rules governing corticostriatal plasticity depend critically on behavioral state, and suggest that the dynamic context of cortical-basal ganglia loops must be considered while investigating synaptic mechanisms underlying reinforcement learning and neurological disorders.

Keywords

striatum; plasticity; long-term potentiation; anesthesia; barbiturate; learning

Synaptic plasticity in cortical-basal ganglia circuits is a likely core mechanism by which animals learn context-dependent action sequences leading to rewards (e.g. Houk and Wise, 1995, Schultz 1998). Dysregulation of plasticity may be critically involved in drug addiction (Berke and Hyman, 2000), dyskinesias (Graybiel et al., 2000) and Parkinson's Disease (Shen et al., 2008). Understanding the rules governing striatal plasticity is thus essential for determining how the basal ganglia contribute to both normal and pathological behaviors.

Most information flow into the basal ganglia occurs at glutamatergic synapses onto striatal medium spiny neurons (MSNs), whose spines provide a major locus of synaptic change (e.g. Robinson & Kolb 2004). Corticostriatal plasticity has been extensively investigated in brain slices, and both long-term potentiation (LTP) and long-term depression (LTD) have been observed depending on experimental conditions (for review see DiFillipo et al. 2009). Recent studies that varied the precise timing between synaptic input and post synaptic spiking revealed bidirectional spike-timing-dependent plasticity at synapses onto MSNs (STDP; Fino et al., 2005; Pawlak and Kerr, 2008; Shen et al., 2008), but different groups have obtained very different STDP functions, again possibly due to distinct experimental conditions. Studies in intact animals have also found both LTD and LTP in striatum, and a relationship to dopamine

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modulation (e.g. Charpier and Deniau, 1997; Charpier *et al.*, 1999; Reynolds and Wickens, 2000; Reynolds *et al.*, 2001; Goto & Grace 2005). However these studies were performed in anesthetized animals, and striatal physiology is very different in awake states (e.g. West 1998, Mahon et al. 2006).

We therefore directly compared corticostriatal plasticity under awake versus anesthetized conditions, using rats with chronically implanted electrodes. To facilitate investigation in freely moving animals, we made use of a cortical stimulation protocol previously shown to produce LTP in barbiturate-anesthetized animals without requiring current injection into the post-synaptic cell (Charpier *et al.*, 1999).

Experimental Procedures

Electrophysiology

All procedures were approved by the University of Michigan's University Committee on Use and Care of Animals. We used 15 adult male Long-Evans rats (350–550g). Thirteen rats were implanted with a chronic microdrive assembly containing 6 independently moveable tetrodes, each consisting of four strands of 12.5µm nichrome wire (Kanthal Palm Coast, FL, USA). Target coordinates in striatum were AP +1.0mm (from bregma), ML 2.0–4.0mm, DV 3.5–5.5mm (from brain surface). Two rats were implanted with a 4×8 array of microwires (Tucker Davis Technology, Alachua, FL, USA). Array target coordinates were AP +0.5–2.5mm, ML 2.75–4.5mm, DV 3.5–5.0mm (see Supplemental Figure 2). Each animal was also implanted with a bipolar stimulating electrode (either SNEX 200 obtained from David Kopf Instruments, Tujunga, CA or Plastics1 item # 303/3, Roanoke, VA) into contralateral motor cortex (AP +3.2mm, ML +3.3mm DV 1.6mm). Electrophysiologically-guided electrode positioning began immediately following surgery, and continued during post-surgical recovery (minimum 10 days).

Animals were housed on a 12:12 (light:dark) hour cycle and tested during the light phase. Each conditioning stimulation session was conducted with the rat placed on a familiar, elevated octagonal platform (16" diameter, walls 5.5" high). For awake sessions, animals were free to move during the course of the experiment, but tended to rest quietly. For experiments under anesthesia, animals were given an initial dose of sodium pentobarbital (66mg/kg, IP), with supplements (22mg/kg) if an animal twitched in response to hind paw pinch. Awake and anesthetized experiments were conducted on the same day, separated by 1 hour if the animal was tested first under the awake condition or a minimum of 4 hours if the animal was first tested under anesthesia. Electrodes were not moved between testing sessions.

Electrical stimulation used single, 0.1ms, biphasic square wave pulses (1mA), from an analog stimulus isolator (A-M Systems, Sequim, WA). The experimental sequence consisted of 30 minutes of baseline measurements with stimulation at 0.1Hz (180 pulses), "conditioning stimulation" at 5Hz (1000 pulses), and 60 minutes of post conditioning pulses at 0.1Hz (360 pulses). Single test pulses did not result in any overt movement or vocalization. Occasionally, 5Hz stimulation would result in repetitive neck movements that ceased immediately with stimulation offset. Electrophysiological signals were wide-band filtered (1–9000Hz) and sampled at 25–31.25kHz. Recording, visualization and stimulation were controlled and synchronized using LabVIEW software (National Instruments, Austin TX). After completion of experiments on each rat, current (20µA, 10s) was passed through each recording electrode to create marker lesions. Recording sites were not included in analyses if located outside striatum, or if the noise pattern suggested a non-functional contact.

Data Analysis

Evoked field potentials were averaged in successive sets of 10 stimulation events. For each such average, the highest amplitude positive peak within 22ms of stimulation was detected (“P1”). Electrodes were excluded if there was no P1 peak (within 22ms). Next, the most negative peak that preceded P1 (excluding 0–2ms to avoid the stimulation artifact) was detected (“N1”). The N1-P1 voltage difference was our estimate of synaptic strength. Just one single wire of each tetrode was used for field potential analyses.

For each electrode estimates of synaptic strength were compared between baseline (30min epoch just prior to conditioning stimulation) and post-conditioning (30min epoch, beginning 30min after conditioning stimulation). The null hypothesis of no change in synaptic strength was rejected if the means were significantly different (t-test, $\alpha=0.01$). If, in a given animal, no electrodes had a significant change in synaptic strength then we reported the result as no change (nc). Otherwise we reported LTP if the mean normalized post conditioning synaptic strength was above 100% and LTD if below 100%. In no cases did an individual animal show a significant increase in synaptic strength on one tetrode or electrode but a significant decrease on another.

Results

Anesthesia reverses the direction of corticostriatal plasticity

We assessed the effects of 5Hz cortical stimulation on corticostriatal synaptic strength in fifteen animals, tested while awake and unrestrained, under barbiturate anesthesia, or both (Figures 1,2; Table 1). The shape of the evoked potential was similar in both states, although we occasionally observed lower amplitude and variance in baseline measurements of synaptic strength when under anesthesia (Supplementary Figure 1.)

Of eleven animals that received the conditioning stimulation under barbiturate anesthesia, seven showed LTP and four showed no change; in no case did we observe LTD. These observations are consistent with prior findings of corticostriatal LTP in barbiturate-anesthetized rats (Charpier and Deniau, 1997; Charpier et al. 1999), even though experimental conditions were not identical (e.g. they used intracellular recording and ipsilateral stimulation). Results were very different under the awake condition, with the majority of animals (9/15) showing LTD instead; in no case did we observe LTP. The result of the experiment did not depend on the order of treatment, since the three animals which the anesthesia session was performed first displayed the same pattern of results as animals who received stimulation under the awake condition first (Figure 2).

Direction of plasticity does not strongly reflect intrastriatal location

Reports in brain slices have found evidence that synaptic plasticity may operate differently in distinct striatal subregions (Partridge et al., 2000; Smith et al., 2001). We therefore examined the contribution of intra-striatal location to our results (Figure 3). Although some possible weak trends were apparent, location was not a major factor – our overall finding of LTD in the awake state, LTP under anesthesia held across a wide range of antero-posterior, medio-lateral, and dorso-ventral coordinates.

Evoked corticostriatal field potential originates from within the striatum

Although evoked potentials are often used to assess synaptic strength they are an indirect measure, and the origin of field potentials measured in striatum is not fully clear (Berke 2005). To gain increased confidence in our measure we examined the spatiotemporal pattern of evoked potentials in two animals implanted with a three-dimensional, fixed-geometry array of 32 individual recording electrodes (Supplementary Figure 2). The largest amplitude P1

response was measured from electrodes located deep within the striatum. This is consistent with our evoked potential measure corresponding to striatal physiological events (Ryan et al. 1986), rather than (for example) volume conduction from the overlaying cerebral cortex.

Discussion

This study provides the first description, to our knowledge, of corticostriatal plasticity in intact, unrestrained animals. We found that such plasticity was strikingly dependent on the state of the animal. We confirmed observations of LTP under barbiturate anesthesia (Charpier *et al.*, 1999), but found LTD in the same animals when awake. This finding has broad implications for the study of neural plasticity, and in particular for investigations into relationships between corticostriatal synapses and reinforcement-based learning.

Evoked potentials have been widely used to study synaptic plasticity both in other brain regions and in other areas of striatum (e.g. Goto and Grace 2005). We cannot be certain which intrastriatal processes are contributing to the observed evoked potential in our experiments, although synaptic and postsynaptic currents, close to the recording electrode, are believed to be the dominant factor (Mitzdorf, 1985; Berke, 2005; Katzner *et al.*, 2009). Strong evidence that our evoked potential measure mirrors excitatory post-synaptic potentials (EPSPs) comes from combined intracellular and extracellular recordings in striatum (Ryan *et al.* 1986). They observed cortically-evoked striatal potentials with a very similar or identical time course to ours, and found that the extracellular P1 peak corresponded to intracellular EPSPs. The short latency of this peak makes it very likely to reflect monosynaptically evoked EPSPs, though we cannot entirely rule out the possibility that fast polysynaptic events in cortex are involved.

The reversal of synaptic plasticity with barbiturate anesthesia may reflect either the actions of this drug locally within the striatum, and/or drug-induced changes in the overall patterns of synaptic input to this structure. We consider the former possibility first. Barbiturate is a sedative-hypnotic drug that tends to prolong the opening of GABA_A channels (D'Hulst et al. 2009) and it is worth noting that related manipulations have previously been shown to have a profound effect on striatal plasticity. For example, Yin et al (2007) observed in brain slices that another sedative-hypnotic, ethanol, can reverse the direction of striatal plasticity in dorsomedial striatum (although this reversal was from LTP to LTD). Alterations in striatal GABA_A transmission may also be involved in the very different STDP functions described for striatum *in vitro*. Two groups (Pawlak and Kerr, 2008; Shen et al., 2008) reported a Hebbian plasticity function in the presence of GABA_A inhibitors, while a third study (Fino et al., 2005) omitted this treatment and reported an anti-Hebbian plasticity function.

Under barbiturate anesthesia cortical activity patterns are quite different to the awake state, and can drive spontaneous ~5Hz membrane potential oscillations in striatal MSNs (Charpier et al. 1999). Successful induction of corticostriatal LTP with artificial 5Hz stimulation correlates with the entrainment of large-scale cortical spindle oscillations (Charpier et al. 1999). This would result in more broadly coherent inputs to striatum, and a higher probability of postsynaptic spiking in synchrony with the directly stimulated inputs. In addition, cortical stimulation results in feed-forward inhibitory input from fast spiking interneurons (FSIs), via GABA_A receptors, onto MSNs. FSIs show marked paired pulse depression at ~100–200ms intervals (e.g. Mallet et al. 2005), so coordinated 5Hz stimulation may result in enhanced postsynaptic MSN activity via disinhibition. Further work is needed to explore the contributions of interneurons to striatal synaptic plasticity, both as coordinators of MSN timing and as a site of plasticity themselves (Fino et al. 2008).

Overall, our results support the general idea that the background patterns of cortical activity are a critical determinant of the direction of synaptic change (Mahon et al. 2004). In contrast

to prior *in vivo* results they are more consistent with LTD as a predominant form of plasticity in the awake, behaving striatum. However, our experiments have significant limitations: we also used a highly artificial form of cortical stimulation in our experiments, and cannot directly control the timing of postsynaptic spiking. Despite this, there are interesting parallels between the striatum and other structures involved in procedural learning that employ an anti-Hebbian plasticity algorithm, including the dorsal cochlear nucleus (Tzounopoulos and Kraus 2009) and cerebellum. Anti-Hebbian rules can support the formation of a “negative image” of one’s own actions, that enable their sensory consequences to be distinguished from other events (Bell et al., 2008). This may also be of great importance in striatum, which receives efference copy of corticospinal outputs as part of an overall algorithm in which unexpected outcomes drive reinforcement learning (Redgrave and Gurney, 2006).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank members of the Berke Laboratory for critical discussions. This work was funded by the University of Michigan, and the National Institute on Drug Abuse (T32 DA007281; R01 DA014318).

List of Abbreviations

LTP	long-term potentiation
LTD	long-term depression
STDP	spike-timing-dependent plasticity
GABA	gamma-aminobutyric acid
FSI	fast-spiking interneuron
EPSP	excitatory post-synaptic potential

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Figure 1.

Field potential measurement of evoked monosynaptic strength. (A) Electrical stimulation was applied in orofacial motor cortex, and evoked potentials were recorded from multiple electrodes in the contralateral striatum. (B) Illustration of stimulation protocol. (C) Monosynaptic strength was estimated as the voltage difference between the first negative (N1) and positive (P1) peaks. Trace is an average from 10 consecutive stimulation events. Stimulation artifact is at 0 ms. (D, E) Sample measurements of series averaged evoked field potentials from a single electrode recorded under both the awake state (D) and the barbiturate anesthetized state (E). Dashed lines indicate epochs used to calculate synaptic strength at baseline and following conditioning.

Figure 2.

Direction of plasticity is dependent upon brain state. Eleven animals received 5 Hz stimulation under two brain states, awake/unrestrained and barbiturate anesthesia. Closed markers indicate significant changes in each state, and horizontal lines indicate state means. A two tailed paired samples t-test reveals a significant effect of brain state on plasticity outcome ($p=0.002$). Seven animals were tested in the awake state first (circles) followed by barbiturate anesthesia. In 3 animals the order of testing was reversed (triangles).

Figure 3.

No clear relationship between intra-striatal location and plasticity direction. For each striatal tetrode tested under both awake (A–C) and anesthetized (D–F) conditions, post-conditioning synaptic strength is plotted against mediolateral (A, D), dorsoventral (B, E) and anteroposterior (C, F) position. The overall direction of change does not vary with position, although in the anesthetized state (only) there was a weakly significant ($p = 0.042$) linear correlation between synaptic change and mediolateral position, if we do not correct for multiple comparisons. This appeared to be largely due to a single outlier point.

Table 1

Summary of plasticity results for all experiments.

Awake State			Barbiturate Anesthesia								
ID#	note	n	Min.	Max.	Mean	LTD	n	Min.	Max.	Mean	
92		4/4	76.8	87.3	84.2	LTD					
93		0/3	97.8	103.2	100.1	nc					
100		4/4	77.2	87.3	81.3	LTD	4/4	110.2	119.9	114.6	LTP
107		0/4	105.2	107.2	106.4	nc	4/4	112.3	121.1	115.4	LTP
108		0/1	-	-	95.1	nc	0/1	-	-	108.8	nc
109		3/3	83.7	87.6	85.2	LTD	0/3	94.0	98.2	95.6	nc
112	a	3/3	72.2	81.9	78.5	LTD	0/3	96.7	101.5	99.6	nc
113	a	0/1	-	-	103.6	nc	0/1	-	-	95.2	nc
115	a	1/3	86.6	93.9	91.0	LTD	3/3	123.9	155.0	137.7	LTP
122	a	4/4	79.2	86.1	82.7	LTD	3/4	105.6	119.1	114.2	LTP
132	a,b	1/2	85.9	95.7	90.8	LTD	1/2	99.6	112.7	106.1	LTP
133	a,b	3/3	84.3	90.4	87.4	LTD	2/3	101.6	108.6	106.1	LTP
136	a,b	0/1	-	-	94.4	nc	1/1	-	-	108.0	LTP
138	a,c	6/14	74.6	92.0	83.8	LTD					
139	a,c	0/23	88.0	111.0	95.7	nc					

ID# indicates each animal, and n indicates the fraction of striatal electrodes where a significant change in synaptic strength was observed. The minimum, maximum and mean synaptic strength, following tetanus, is reported as a percentage of baseline for each animal with two or more tetrodes or electrodes, otherwise a single result is presented under mean change. Notes on experimental protocol:

^aThese animals had a stimulating electrode with a slightly larger tip separation (0.6 mm).

^bThese animals were tested in the barbiturate anesthetized state first.

^cThese animals were implanted with a microwire array.