The Basal Ganglia VIII, J, Paul Bolam, Cali.A. Ingham and Peter J. Magill (Eds.)
Advances in Behavioral Biology 56, Springer, NY

FEEDFORWARD AND FEEDBACK INHIBITION IN THE NEOSTRIATUM

James M. Tepper, Tibor Koós and Charles J. Wilson*

1. INTRODUCTION

The neostriatum is the principal input structure of the basal ganglia and as such, plays the greatest role in integrating and transducing the excitatory input that derives from the cortex and thalamus. The principal neuron, the GABAergic spiny projection neuron, comprises the majority of the striatal neurons, ranging from slightly less than 80% of all the neurons in primates (Graveland and DiFiglia, 1985) to almost 98% in rodents (Luk and Sadikot, 2001; Rymar et al., 2004). The remainder of the neuronal population consists of at least 3 distinct types of GABAergic and one cholinergic interneuron.

The somatodendritic morphology and existence of a local axonal arborization of the spiny neuron was well described in the earliest Golgi studies but the nature and full extent of the local axon collateral plexus was not completely appreciated until the advent of in vivo intracellular staining of striatal neurons with horseradish peroxidase in the late 1970s and early 1980s (Wilson, 1979; Preston et al., 1980; Wilson and Groves, 1980; Bishop et al. 1982). These studies revealed that the main axon of the spiny cell branched within a few tens of micrometers from the soma of origin to form a relatively dense and homogeneous local arborization that in most cases overlapped and extended slightly beyond the dendritic field of the parent neuron. In some cases the local collateral arborization extended for great distances beyond the parent dendritic field.

Around the same time it became clear from electron microscopic analysis of intracellularly or retrogradely labeled material that the principal targets of the spiny cell local axon collaterals were the surrounding spiny neurons (Wilson and Groves, 1980; Somogyi et al., 1981). This was not unexpected given the numerical predominance of the spiny cells in the striatum, and the finding led rather naturally to the inference that the functional organization of the neostriatum would incorporate a powerful lateral inhibitory modulation of spiny neurons by their local collaterals (Groves, 1983). Several other independent lines of evidence supported this view.

For example, most neostriatal neurons exhibited very little spontaneous activity in vivo and many did not fire spontaneously at all (Richardson et al., 1977; Levine et al., 1982), even in locally anesthetized preparations (Wilson and Groves, 1980, 1981). However, in anesthetized rats, local application of a $GABA_A$ antagonist produced a dramatic increase in the firing rate of a subpopulation of spiny neurons (Nisenbaum and Berger. 1992), providing evidence for a substantial GABAergic tone in vivo. Local stimulation in striatal slices readily elicited GABAergic IPSPs in spiny neurons presumed to be mediated by the local collaterals (Lighthall and Kitai, 1981). Stimulation of the entopedun-

* James M. Tepper, Center for Molecular and Behavioral Neuroscience, Rutgers University, Newark, NJ 07102. Tibor Koós, Section of Neurobiology, Yale University School of Medicine, New Haven, CT 06510. Charles J. Wilson, Division of Life Science, University of Texas at San Antonio, San Antonio, TX, 78249, USA

cular nucleus in decorticate and thalamic-lesioned cats, which was expected to cause antidromic activation of striatal spiny neurons, led to inhibition of striatal units in extracellular recordings in cats, an effect that could be blocked by iontophoretic application of bicuculline (Katayama et al., 1981). Finally, single action potentials evoked by depolarizing current injections in spiny neurons were found to reduce the size of EPSPs evoked by stimulation of substantia nigra, an effect that was eliminated by systemic administration of bicuculline and which was attributed to the activation of axon collaterals synapsing back onto the parent cell (Park et al., 1980).

Thus, as biologically based computational models of the neostriatum began to be applied to understanding the functioning of the basal ganglia, a common attribute of many striatal models came to be the instantiation of the spiny cell local axon collateral synapses as a "winner-take-all" lateral inhibition which acted to strengthen and sharpen the output of the most strongly excited neurons by inhibiting their neighbors which in turn would lead to disinhibition of the strongly excited cells (e.g., Wickens et al., 1995; Beiser and Houk, 1998; Redgrave et al., 1999; Wickens and Oorschot, 2000; Bar-Gad and Bergman, 2001).

Experiments designed to detect collateral inhibition directly failed to do so. Antidromic activation of spiny neurons while recording intracellularly in vivo or in vitro failed to produce a detectable IPSP but cortical stimulation subthreshold for eliciting orthodromic spikes in spiny neurons could evoke IPSPs in spiny neurons in slices (Wilson et al. 1989), in vivo in neonates (Tepper and Trent, 1993) and in neostriatal grafts (Xu et al., 1991). However, simultaneous recording of pairs of cells located within each other's axon collateral field failed to reveal synaptic responses, even with spike-triggered averaging (Jaeger et al., 1994). The difficulty in demonstrating collateral inhibition in striatum, despite the incontrovertible anatomical evidence for the existence of the synapses, although somewhat surprising to many, was strikingly consistent with results from in vivo extracellular recordings in behaving monkeys or rats where little or no correlation among spiking in nearby neurons was observed (Jaeger et al., 1995; Woodward et al. 1995) and with results from in vivo intracellular recordings which showed that although the up and down state transitions of nearby spiny neurons were highly correlated, action potentials were not (Stern et al., 1998). These data led to the suggestion that collateral interactions among spiny neurons is not a source of powerful inhibition in the striatum but that spiny cell collaterals might play a more subtle modulatory role. Therefore the strong GABAergic inhibition observed after local or cortical stimulation was likely mediated by GABAergic interneurons (Jaeger et al., 1994).

2. INTERNEURONAL GABAERGIC INHIBITION IN STRIATUM

The earliest Golgi studies that showed, in addition to the great preponderance of medium-sized spiny neurons, a large aspiny neuron and one or more medium sized aspiny neurons that clearly differed from the medium sized spiny neuron in somatic size, shape and/or dendritic arborization were present in striatum, albeit in very small proportion. The ability of medium-sized aspiny neurons to take up radiolabeled GABA showed that at least some of these were GABAergic (Bolam et al., 1983). Subsequent studies utilizing immunocytochemical labeling revealed three distinct types of GABAergic interneurons that colocalized, respectively, parvalbumin (PV), calretinin (CR) or neuropep-

tide Y (NPY), somatostatin (SOM) and nitric oxide synthase (Takagi et al., 1983; Cowan et al., 1990; Bennett and Bolam, 1993; Kawguchi, 1993; Rymar et al., 2004). Two of these (the parvalbumin and the NPY expressing neurons) have been characterized electrophysiologically and termed FS and PLTS interneurons, respectively (Kawaguchi, 1993; Koós and Tepper 1999), but no recordings have been reported from identified CR^+ interneurons. Recordings from an infrequently encountered and immunocytochemically or morphologically unidentified GABAergic interneuron, termed the LTS neuron have been reported (Koós and Tepper, 1999; 2002) which might correspond to the calretinin-containing GABAergic interneuron (Tepper and Bolam, 2004), or represent a physiological variant of SOM^+ PLTS neurons. This classification is most likely overly simplistic considering the morphological and physiological diversity of the PV interneurons (Kawaguchi, 1993; Koós and Tepper, 1999), and the comparison with cortical (Markram et. al., 2004; Monyer and Markram, 2004) and hippocampal (Freund and Buzsaki 1995) interneuron populations which is particularly relevant in the light of the shared developmental origin of certain cortical GABAergic interneurons with their striatal counterparts (Marin et al., 2000).

In recordings from brain slices, the striatal PV-expressing neuron was found to exhibit very narrow spikes with a large, rapid AHP, little or no spike frequency accommodation even at high firing rates (> 200 Hz) and intermittent firing in short bursts which arise from subthreshold membrane potential oscillations in response to lower amplitude depolarizing pulses (Kawaguchi, 1993, Kawaguchi et al., 1995; Koós and Tepper, 1999; 2002; Bracci et al., 2003). These electrophysiological characteristics are similar or identical to the so-called fast-spiking (FS) interneuron previously described in cortex and hippocampus (Freund and Buzsaki, 1995), a subclass of which also expresses parvalbumin). Similar results were obtained in striatal organotypic cell co-cultures (Plenz and Aertsen, 1996; Plenz and Kitai, 1998). The somatostatin neuron was also shown to exhibit distinguishing electrophysiological features including a low threshold spike and prolonged plateau depolarizations (Kawaguchi, 1993, Kawaguchi et al., 1995).

The expected role of these interneurons in mediating intrastriatal GABAergic inhibition was first demonstrated directly by simultaneous whole cell recordings of FS interneurons and spiny neurons in striatal slices (Koós and Tepper, 1999; 2002). These recordings revealed that action potentials in FS interneurons produced monosynaptic $GABA_A$-mediated IPSPs in roughly 25% of spiny neurons within a 250 μm radius of the presynaptic neuron. The IPSPs were notable in several respects. They were large; single spikes in a FS interneuron produced hyperpolarizing IPSPs in spiny neurons at their maximal subthreshold up state membrane potential over 1 mV in amplitude. Summation was very effective and short bursts of action potentials led to IPSPs up to 7 mV in amplitude (Koós and Tepper, 1999). The IPSP was also very effective at delaying or even abolishing evoked spikes in postsynaptic spiny neurons; single presynaptic spikes produced a delay of almost 6 ms in spiny cell spike timing and short bursts could completely block spiking (Koós and Tepper, 1999). The IPSP was also extremely reliable, showing an overall failure rate of less than 1% (Koós and Tepper, 1999; Tepper et al., 2004). In addition, the FS interneurons were also found to be electrotonically coupled, as predicted by the electron microscopic visualization of gap junctions (Kita et al., 1990), and therefore presumed to form a sort of syncytium of GABAergic interneurons that could act to generate IPSPs in a large number of spiny neurons simultaneously.

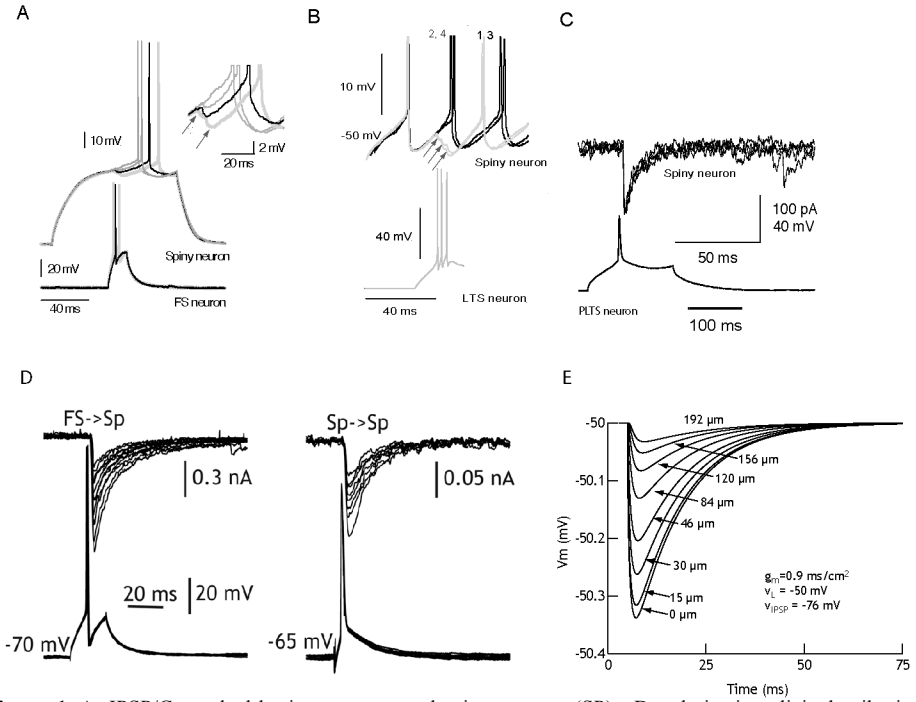

Figure 1. **A**. IPSP/Cs evoked by interneurons and spiny neurons (SP). Depolarization-elicited spike in a spiny neuron (2 upper light gray traces) is delayed by IPSPs evoked by single spikes (lower black trace) or a spike doublet (lower gray trace) of an FS interneuron. Inset shows IPSPs and spike delays at higher gain. **B**. Burst of three spikes evoked in a LTS neuron delays firing of depolarization-induced spiking of a spiny neuron. The LTS evokes compound IPSPs (upper gray traces 1, 3) that prevent the firing of the spiny neuron (black traces 2, 4). **C**. Single spike in a PLTS neuron elicits an IPSC in a spiny neuron. **D**. Comparison of IPSCs evoked in spiny neurons by spiny cells (Sp->Sp) and by fast spiking cells (FS->Sp). Typical IPSCs in whole cell recordings after replacement of K^+ by Cs^+. The time course of the IPSCs are similar, but the FS-evoked IPSP is about 6 times larger than the Sp->Sp IPSC. Note difference in scales. **E**. Computer simulation of spiny cell IPSPs with the synapse at varying distances from the somatic recording site.

Similarly powerful and effective IPSPs in spiny neurons were elicited by spiking in LTS neurons (Koós and Tepper, 1999; 2002)., Although also monosynaptically connected to spiny neurons, PLTS neurons may primarily provide dendritic inhibition since PLTS neurons in the striatum target primarily the dendrites of MS cells (Kubota and Kawaguchi, 2000), similar to SOM^+ interneurons in the hippocampus (Katona et al., 1999).

Thus, while neostriatal interneurons are probably functionally heterogeneous, at least 2 classes appear to be specialized for providing powerful feed-forward inhibition onto spiny neurons. Given the effectiveness of the evoked IPSPs at delaying or abolishing spiking in spiny neurons, these feed-forward GABAergic inputs appear to be the principal mediators of the GABAergic modulation of spike timing in the spiny neurons.

3. SPINY NEURON AXON COLLATERALS

Direct demonstration of the spiny neuron axon collateral IPSP was first reported with paired intracellular current clamp recordings in striatal slices (Tunstall et al., 2002).

Evoked action potentials in one spiny neuron produced a small IPSP in a second spiny neuron in 9 of 45 pairs recorded an average of 264 μm apart. The IPSP had a mean of about 277 μV, excluding failures, or only about 1/6 the amplitude of IPSPs generated in spiny cells by interneurons under reasonably similar postsynaptic conditions of membrane potential, input resistance and chloride concentration (Koós and Tepper, 1999). Individual IPSPs could sometimes be seen, but usually required averages of 200 sweeps for reliable detection. The probability of synaptic connection was relatively low, only 9/90 or 10% and there were no reciprocally connected pairs in the sample. In addition, the IPSP exhibited a rather high (38%) mean failure rate. Like the interneuronal IPSP, the collateral IPSP was mediated by $GABA_A$ receptors.

Soon after, the spiny cell collateral IPSP was detected with paired whole cell recordings in cortical-striatal-nigral co-cultures (Czubayko and Plenz, 2002). While many of the characteristics of the IPSP were the same as those reported by Tunstall et al. (2002) in the slice, the amplitude of the IPSP was much larger (~2 mV) in the co-cultures. In addition, the probability of connection also significantly greater (24.6%), and reciprocal connections were observed in 31% (8/26) of the connected pairs, suggesting that a greater connectivity exists among neurons in the co-cultures than in acute slices, where the probability of synaptic connectivity ranged between 10 and 18% (Koós et al., 2002, 2004; Tunstall et al., 2002; Taverna et al., 2004a, b). Nevertheless, if the IPSPs of Czubayko and Plenz (2002) were normalized to those of Tunstall et al., (2002) by correcting for differences in input resistance and membrane potential, the IPSP amplitudes in the two studies were similar (Tepper et al., 2004).

Subsequent reports using voltage clamp in acute slices reported collateral IPSCs in spiny neurons under a variety of different conditions (principally Cs+ substitution for K+ and/or high Cl- in the internal solution) intended to optimize the size of the chloride-mediated synaptic response (Koós et al., 2002; Guzman et al., 2003; Taverna et al., 2004, Venance et al., 2004). When the peak conductance and decay time constants of the IPSCs were used in a single compartment model to simulate the IPSP that would be recorded near the maximal subthreshold up-state membrane potential (-47 mV), the results (–171 to 340 μV; Tepper et al., 2004) were very close to those reported by Tunstall et al., (2002). These data seemed to indicate that the spiny cell axon collateral IPSP was several fold smaller in amplitude than the feedforward IPSP originating from striatal interneurons (Koós and Tepper, 1999), but direct comparison was difficult because of the large number of methodological differences among the different studies. Therefore we compared the characteristics of the feedforward and feedback synaptic responses directly by measuring IPSPCs originating from the axon collaterals and from the GABAergic interneurons with dual whole cell or perforated patch recordings in identical preparations under the same recording conditions.

4. COMPARISON OF AXON COLLATERAL AND INTERNEURONAL INHIBITION

Whole cell recordings were obtained in striatal slices from adult rats from neuron pairs consisting of two spiny neurons or one FS interneuron and one spiny neuron (Koós et al., 2004). The presynaptic neuron was recorded in current clamp using a standard internal solution and the postsynaptic neuron was recorded in voltage clamp

using an internal based on 140 mM CsCl. Under these conditions the FS→spiny cell IPSC was 269±213 pA (n=9). Under identical recording conditions, the spiny→spiny IPSC was 51±39 pA (n=26) or a little less than 1/5 as large. If recorded with the same chloride concentration in the internal but without Cs^+ ions (which block K^+ channels and greatly reduces the effects of electrotonic attenuation), the IPSC was only 18.3±13.8pA (n=3). This suggests that one important factor contributing to the difference is the location of the synapse. Immunocytochemical studies show that PV+ terminals make the majority of their synapses proximally, often forming pericellular baskets around the soma and proximal dendrites of spiny neurons (Kita et al., 1990; Bennett and Bolam, 1994). In contrast, electron microscopy of intracellularly labeled spiny cell axons shows that 88% of the synapses are located in the spiny (i.e., intermediate and distal) regions of the dendrites (Wilson and Groves, 1980). Spines give the dendrites of the spiny cell approximately twice the electrotonic length of a similarly sized, aspiny dendrite (Wilson et al., 1983). This coupled with the strong inward rectification which gives the spiny cell a very low resting input resistance makes location a large factor in synaptic efficacy in these neurons, and is responsible for decreasing the somatic effects of the collateral IPSP by about a factor of 3 (Koós et al., 2004).

In addition to location, the differences in the amplitudes of the spiny→spiny IPSC and the FS→spiny cell IPSC could be due to a variety of presynaptic factors including the probability of release, the quantal size and/or the number of presynaptic release sites (active synapses). To distinguish among these possibilities, the data were subjected to variance-mean analysis (Clements and Silver, 2000) and nonstationary PSC analysis (Scheuss et al., 2002) from which the release probability (p), quantal current (q*) and the number of release sites (N) can be extracted. The results of this analysis are shown in Table 1.

The two IPSCs were quite similar, differing only in amplitude, as expected, and in the number of release sites. The difference in number of release sites is in actuality likely greater than our data suggest. When we searched for pairs of spiny neurons for recording and analysis we biased our sample towards pairs which showed the largest and most robust synaptic connection. This likely resulted in our sample having a larger N than is representative of the entire population. In any even, it is this difference in the number of release sites that accounts for the greatest fraction of the difference in amplitude between the FS→spiny and spiny→spiny synapses (Koós et al., 2004). The difference in N is also responsible for the much greater failure rate of the SP→SP synapse than the FS→SP synapse which fails completely less than 1% of the time (Koós and Tepper, 1999).

Table 1

Group	Peak Current (pA)	Rise Time	Half-width	N release sites	q* (pA)	p_r
spiny→spiny	51+39	1.3+0.6	12.9+3.4	2.9+1.6	43+16	*0.76+0.18*
FS→spiny	*269+213*	*1.6+1.0*	*11.6+3.8*	*6.7+7.8*	*64+17*	*0.57+0.24*

5. FUNCTIONAL IMPLICATIONS

The connectivity of the feed-forward and feedback circuits also exhibits important differences. Using estimates for the interneuron population based on the number of

highly GAD_{67} positive neurons (3-5 %), the convergence of GABAergic interneurons onto spiny neurons is between 4 and 27 (Koós & Tepper, 1999; Kubota and Kawaguchi, 2000). If the calculations are made based on more recent unbiased stereological cell counts of immunolabeled PV, CR and SOM positive neurons (2%, Rymar et al., 2004) the convergence becomes smaller and if only FS interneurons are considered is between 4 and 1 (Tepper et al, 2004). But even a single presynaptic GABAergic interneuron exerts a powerful enough IPSP to block spiking in a spiny neuron (Koós and Tepper, 1999). Thus the feedforward inhibitory system has the appropriate characteristics to precisely and powerfully modify both the overall firing rate and the timing of single action potentials in spiny neurons.

This stands in sharp contrast to the situation with respect to feedback inhibition. The influence of a single projection neuron on the spike timing of its postsynaptic targets can be estimated through a comparison with the same effect of FS interneurons, since the magnitude of the delay of postsynaptic action potentials is approximately linearly related to the somatic amplitude of the IPSP. Thus even in the presence of the relatively high *in vitro* somatic input resistance of spiny neurons, a single 0.05-0.3 mV collateral IPSP (Figure 1 E) would cause a spike delay of only 0.25-1.5 ms if the postsynaptic neurons fire at physiological rates (20-50 Hz). Consequently, the influence of a single collateral input on the firing rate of its targets is largely negligible. Along with the rarity or absence of reciprocal collateral inhibition (Tunstall et al., 2002; Koós et al., 2002, 2004; Taverna et al., 2004), this indicates that the axon collaterals are not well-suited to create the type of winner-take-all lateral inhibition widely proposed to occur in the neostriatum. Rather, since the IPSP generated by single projection neurons is expected to be much stronger at their dendritic site of origin, both unitary connections as well as their

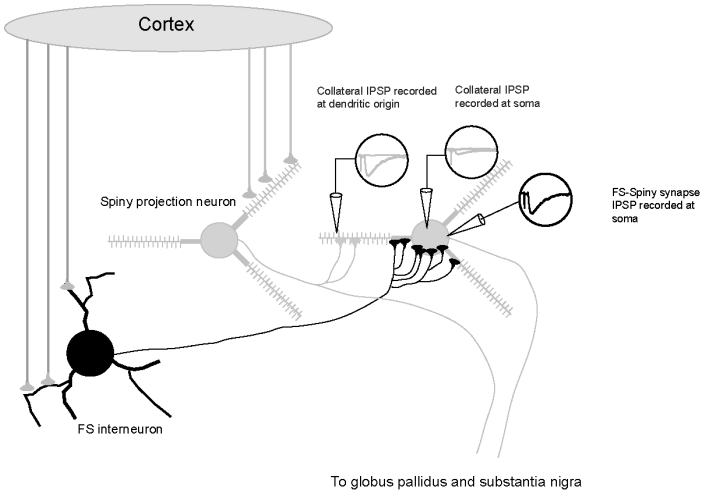

Figure 2. Simplified schematic illustration of the organization of the feedforward and feedback GABAergic pathways in neostriatum and their major differences. The somatic amplitude of the FS→SP IPSC is many times larger than that of the SP→SP IPSC. In addition, the SP→SP IPSC has a high failure rate while the FS→SP IPSC fails > 1% of the time. The difference in failure rate and part of the difference in amplitude is due to the number of synapses each presynaptic neuron makes. Each spiny neuron typically makes 2 or 3 synapses on each postsynaptic spiny neuron while each FS interneuron typically makes 6 or more synapses on each postsynaptic spiny cell. The rest of the amplitude difference is due to the distal location of the SP→SP synapses in contrast to the proximal location of the FS→SP synapses.

populations can be instrumental in and specialized for controlling distal dendritic events perhaps including modulation of synaptic plasticity, spike backpropagation and the integrative properties of the distal dendrites (Kerr and Plenz, 2002, 2004; Vergara et al., 2003; Koós et al., 2004).

At the population level, however, despite the weak effect of unitary collateral inputs, feedback inhibition may contribute significantly to firing rate control due to the convergence of numerous inputs onto single postsynaptic cells. Based on the observed probability of connectivity among spiny neurons in vitro, a convergence of 407-518 presynaptic projection neurons innervating each postsynaptic cell can be estimated, which, depending on the population size and exact convergence of FS and other interneurons (see above), translates into approximately 16 to over 125 times more presynaptic MS neurons than interneurons innervating each projection cell (see also Guzman et. al., 2003; Tepper et al., 2004), and represents a 3-25 times larger net synaptic conductance associated with the feedback circuitry (Koós et al., 2004).

Consequently, it is likely that both the feed-forward and the feedback circuits contribute to the net inhibitory control of the firing rate of neostriatal projection neurons, but through significantly different input circuits and biophysical mechanisms.

Supported by NS34865 (JMT) and NS20743 (CJW).

6. REFERENCES

Bar-Gad, I. ,and Bergman, H., 2001, Stepping out of the box: information processing in the neural networks of the basal ganglia, *Curr. Opin. Neurobiol.* **71**:439-473.

Beiser, D.G. and Houk, J.C., 1998, Model of cortical-basal ganglionic processing: encoding the serial order of sensory events, *J. Neurophysiol.* **79**: 3168.

Bennett, B.D. and Bolam, J.P., 1994, Synaptic input and output of parvalbumin-immunoreactive neurons in the neostriatum of the rat, *Neuroscience* **62**: 707-719.

Bennett, B.D. and Bolam, J.P.,1993, Characterization of calretinin-immunoreactive structures in the striatum of the rat, *Brain Res*. **609**:137-48.

Bishop, G.A., Chang, H.T. and Kitai, S.T., 1982, Morphological and physiological properties of neostriatal neurons: An intracellular horseradish peroxidase study in the rat, *Neuroscience*. **7**: 179-191.

Bolam, J.P., Clarke, D.J., Smith, A.D.and Somogyi, P., 1983, A type of aspiny neuron in the rat neostriatum accumulates [3H]γ-aminobutyric acid: Combination of golgi-staining, autoradiography, and electron microscopy, *J. Comp. Neurol.* **213**: 121-134.

Bracci, E., Centonze, D., Bernardi, G.and Calabresi, P., 2003, Voltage-dependent membrane potential oscillations of rat striatal fast-spiking interneurons. *J. Physiol*. **549**: 121.

Cowan, R.L., Wilson, C.J., Emson, P.C., Heizmann, C.W., 1990, Parvalbumin-containing GABAergic interneurons in the rat neostriatum, *J. Comp. Neurol.* **302**:197-205

Czubayko, U. and Plenz, D., 2002, Fast synaptic transmission between striatal spiny projection neurons, Proc. Natl. Acad. Sci. U.S.A. **99**: 15764.

Clements, J.D. and Silver, R.A., 2000, Unveiling synaptic plasticity: a new graphical and analytical approach, *Trends Neurosci.* **23**:105-113.

Freund, T.F. and Buzsáki, G., 1996, Interneurons of the hippocampus, *Hippocampus* **6**:347-470.

Graveland, G.A. and DiFiglia, M.,1985. The frequency and distribution of medium-sized neurons with indented nuclei in the primate and rodent neostriatum, Br*ain Res.* **327**: 307-311.

Groves, P.M., 1983, A theory of the functional organization of the neostriatum and the neostriatal control of voluntary movement, *Brain Res. Rev.* **5**:109-132.

Guzman, J.N., Hernandez, A., Galarraga, E., Tapia, D.. Laville, A., Vergara, R., Aceves, J., and Bargas, J., 2003, Dopaminergic modulation of axon collaterals interconnecting spiny neurons of the rat striatum, *J. Neurosci.* **23**: 8931-8940.

Jaeger, D., Kita, H. and Wilson, C.J., 1994, Surround inhibition among projection neurons is weak or nonexistent in the rat neostriatum, *J. Neurophysiol.* **72**:1-4.

Katayama, Y., Miyazaki, S. and Tsubokawa, T., 1981, Electrophysiological evidence favoring intracaudate axon collaterals of GABAergic caudate output neurons in the cat, *Brain Res.* **216**:180-186.

Katona, I., Acsády, L. and Freund, T.F., 1999, Postsynaptic targets of somatostatin immunreactive interneurons in the rat hippocampus, *Neuroscience* **88**:37-55

Kawaguchi, Y., 1993, Physiological, morphological and histochemical characterization of three classes of interneurons in rat neostriatum, *J. Neurosci.* **13**:4908-4923.

Kawaguchi, Y., Wilson, C.J., Augood, S.J. and Emson, P.C., 1995, Striatal interneurones: chemical, physiological and morphological characterization, *Trends Neurosci.* **18**:12:527-535.

Kerr, J.N. and Plenz, D., 2002, Dendritic calcium encodes striatal neuron output during up-states, *J. Neurosci.* **22**:1499-1512.

Kerr, J.N. and Plenz, D., 2004, Action potential timing determines dendritic calcium during striatal up-states, *J. Neurosci.* **24**:1877-885.

Kita, H., Kosaka, T. and Heizmann, C.W. (1990) Parvalbumin-immunoreactive neurons in the rat neostriatum: a light and electron microscopic study, *Brain Res.* **536**:1-15.

Koós, T. and Tepper, J.M., 1999, Inhibitory control of neostriatal projection neurons by GABAergic interneurons, *Nat. Neurosci.* **2**:467-472.

Koós, T. & Tepper, J.M., 2002, Dual cholinergic control of fast spiking interneurons in the neostriatum, *J. Neurosci.* **22**:529-535.

Koós, T., Tepper, J.M., Goldman-Rakic, P. & Wilson, C.J., 2002, Electrophysiological properties and dopaminergic modulation of GABAergic inhibition among neostriatal projection neurons, *Soc. Neurosci. Abstr.* **28**:764.17.

Koós, T., Tepper, J.M. and Wilson, C.J.,2004, Comparison of IPSCs evoked by spiny and fast-spiking neurons in the neostriatum, *J. Neurosci.* **24**;7916-7922.

Kubota, Y. and Kawaguchi, Y., 2000, Dependence of GABA ergic synaptic areas on the interneuron type and target size, *J. Neurosci.* **20**: 375-386.

Levine, M.S., Fisher, R.S., Hull, C.D. and Buchwald, N.A., 1982, Development of spontaneous neuronal activity in the caudate nucleus, globus pallidus-entopeduncular nucleus, and substantia nigra of the cat, *Dev. Brain Res.*, **3**: 429-441.

Lighthall, J.W.and Kitai, S.T., 1983, A short duration GABAergic inhibition in identified neostriatal medium spiny neurons: in vitro slice study, *Brain Res.Bull.*, **11**: 103.

Luk, K.C. and Sadikot, A.F., 2001, GABA promotes survival but not proliferation of parvalbumin-immunoreactive interneurons in rodent neostriatum: An in vivo study with stereology, *Neuroscience* **104**:93-103.

Marin, O, Anderson, S.A., Rubenstein, J.L., 2000, Origin and molecular specification of striatal interneurons, *J Neurosci.* **20**:6063-76.

Markram, H. Toledo-Rodriguez, M., Wang, Y., Gupta, A., Silberger, G., Wu, C., 2004, Interneurons of the neocortical inhibitory system, *Nat. Rev. Neurosci*. **5**:793-807.

Monyer, H. and Markram, H., 2004, Interneuron diversity series: Molecular and genetic tools to study GABAergic interneuron diversity and function, *Trends Neurosci.* **27**:90-97

Nisenbaum, E.S. and Berger, T.W., 1992, Functionally distinct subpopulations of striatal neurons are differentially regulated by GABAergic and dopaminergic inputs--I. In vivo analysis,. *Neuroscience* **48**: 561-578.

Park, M.R., Lighthall, J.W. and Kitai, S.T., 1980, Recurrent inhibition in the rat neostriatum, *Brain Res*. **194**:359-369.

Plenz, D., 2003, When inhibition goes incognito: feedback interaction between spiny projection neurons in striatal function. *Trends Neurosci*. **26**:436-443.

Plenz, D.and Aertsen, A., 1996, Neural dynamics in cortex-striatum co-cultures--I. anatomy and electrophysiology of neuronal cell types, *Neuroscience* **70**: 861-891.

Plenz, D.and Kitai, S.T., 1998, Up and down states in striatal medium spiny neurons simultaneously recorded with spontaneous activity in fast-spiking interneurons studied in cortex-striatum-substantia nigra organotypic cultures, *J. Neurosci.*, **18**: 266-283.

Preston, R.J., Bishop, G.A. and Kitai. S.T.,1980. Medium spiny neuron projection from the rat striatum: an intracellular horseradish peroxidase study. *Brain. Res*. **183**:253-263.

Redgrave, P., Prescott, T.J.and Gurney, K., 1999, The basal ganglia: a vertebrate solution to the selection problem?, *Neuroscience*, **89**: 1009.

Richardson, T.L., Miller, J.J and, McLennan, H., 1977. Mechanisms of excitation and inhibition in the nigrostriatal system, *Brain Res*. **127**:219-234.

Rymar, V.V., Sasseville, R, Luk, K.C., Sadikot, A.F., 2004, Neurogenesis and stereological morphometry of calretinin-immunoreactive GABAergic interneurons of the neostriatum. *J. Comp Neurol.* **469**:325-339.

Scheuss, V., Schneggenburger, R. and Neher, E., 2002, Separation of presynaptic and postsynaptic contributions to depression by covariance analysis of successive EPSCs at the calyx of Held synapse, *J. Neurosci.* **22**:728-739.

Somogyi, P., Bolam, J.P. and Smith, A.D., 1981, Monosynaptic cortical input and local axon collaterals of identified striatonigral neurons. A light and electron microscopic study using the Golgi-peroxidase transport-degeneration procedure, *J. Comp. Neurol*. **195**:567-584.

Stern, E.A., Jaeger, D.and Wilson, C.J., 1998, Membrane potential synchrony of simultaneously recorded striatal spiny neurons in vivo, *Nature*, **394**: 475-478.

Takagi H, Somogyi P, Somogyi J, Smith AD. (1983) Fine structural studies on a type of somatostatin-immunoreactive neuron and its synaptic connections in the rat neostriatum: a correlated light and electron microscopic study. *J. Comp. Neurol.* **214**:1-16.

Taverna, S., Canciani, B.and Pennartz, C.M., 2005, Dopamine D1-receptors modulate lateral inhibition between principal cells of the nucleus accumbens, *J Neurophysiol*. **93**:1816-1819.

Taverna, S., van Dongen, Y.C., Groenewegen, H.J.and Pennartz, C.M., 2004, Direct physiological evidence for synaptic connectivity between medium-sized spiny neurons in rat nucleus accumbens in situ, *J. Neurophysiol.*, **91**: 1111-1121.

Tepper, J.M. and Bolam, J.P. ,2004, Functional diversity and specificity of neostriatal interneurons, *Curr. Opin. Neurobiol.* **14**: 685-692.

Tepper, J.M., Koós, T. and Wilson, C.J., 2004, GABAergic microcircuits in the neostriatum, *Trends Neurosci*. **27**:662-669.

Tepper, J.M.and Trent, F., 1993, In vivo studies of the postnatal development of rat neostriatal neurons, in: *Chemical Signalling in the Basal Ganglia* G.W. Arbuthnott, P.C. Emson, eds., Elsevier Science Publishers, Progress in Brain Research Vol. 99, pp. 35-50.

Tunstall, M.J., Oorschot, D.E., Kean, A. and Wickens, J.R., 2002, Inhibitory interactions between spiny projection neurons in the rat neostriatum, *J. Neurophysiol.* **88**:1263-1269.

Venance, L., Glowinski, J.and Giaume, C., 2004, Electrical and chemical transmission between striatal GABAergic output neurones in rat brain slices, *J. Physiol.*, **559**: 215-230.

Vergara, R., Rick, C., Hernandez-Lopez, S., Laville, J.A., Guzman, J.N., Galarraga, E., Surmeier, D.J., and Bargas, J., 2003, Spontaneous voltage oscillations in striatal projection neurons in a rat corticostriatal slice, *J. Physiol., (Lond.)* **553**:169-182,

Wickens, J.R., Kotter, R.and Alexander, M.E., 1995, Effects of local connectivity on striatal function: stimulation and analysis of a model, *Synapse*, **20**: 281-298.

Wickens, J.R. and Oorschot, D.E., 2000, Neural dynamics and surround inhibition in the neostriatum: A possible connection, in Conceptual Advances in Brain Research, Dynamics and the Striatal Complex, R. Miller and J.R. Wickens, eds., Gordon and Breach, Reading, UK, pp. 141-150.

Wilson, C.J., 1979, Light and electron microscopic observations on neurons of the rat caudate-putamen stained by intracellular injection of horseradish peroxidase. *Anat. Rec*. **193**:722-723.

Wilson, C.J., 1995, Dynamic modification of dendritic cable properties and synaptic transmission by voltage-gated potassium channels, *J. Computational Neurosci.* **2**:91-115.

Wilson, C.J., Groves, P.M., Kitai, S.T.and Linder, J.C., 1983, Three-Dimensional Structure of Dendritic Spines in the Rat Neostriatum, *J.Neurosci.*, **3**: 383-398.

Wilson, C.J., Kita, H. and Kawaguchi, Y., 1989, GABAergic interneurons rather than spiny cell axon collaterals are responsible for the IPSP responses to afferent stimulation in neostriatal spiny neurons, *Soc. Neurosci. Abstr.* **15**:907.

Wilson, C.J., Groves, P.M., 1980, Fine structure and synaptic connections of the common spiny neuron of the rat neostriatum: A study employing intracellular injection of horseradish peroxidase. *J. Comp. Neurol*. **194**:599-615.

Wilson, C.J. and Groves, P.M., 1981, Spontaneous firing patterns of identified spiny neurons in the rat neostriatum, *Brain Res.*, **220**: 67-80.

Woodward, D.J., Kirillov, A.B. Myre, C.D. and Sawyer, S.F., 1995, Neostriatal circuitry as a scalar memory: Modeling and ensemble neuron recording. In: *Models of Information Processing in the Basal Ganglia*, edited by J.C Houk, J.L. Davis and D.G. Beiser (MIT Press, Cambridge, 1995), pp.315-336.

Xu, Z.C., Wilson, C.J.and Emson, P.C., 1991, Synaptic potentials evoked in spiny neurons in rat neostriatal grafts by cortical and thalamic stimulation, *J.Neurophysiol.*, **65**: 477-493.