J. Anat. (2000) **196**, pp. 587–596, with 6 figures Printed in the United Kingdom

Review

Dopamine and synaptic plasticity in the neostriatum

G. W. ARBUTHNOTT,[1] C. A. INGHAM,[1] J. R. WICKENS[2]

[1] *Centre for Neuroscience and Department of Preclinical Veterinary Sciences, University of Edinburgh, UK and*
[2] *Department of Anatomy and Structural Biology, University of Otago Medical School, Dunedin, New Zealand*

(*Accepted 10 September 1999*)

ABSTRACT

After the unilateral destruction of the dopamine input to the neostriatum there are enduring changes in rat behaviour. These have been ascribed to the loss of dopamine and the animals are often referred to as 'hemiparkinsonian'. In the denervated neostriatum, we have shown that not only are the tyrosine hydroxylase positive boutons missing, but also the medium sized densely spiny output cells have fewer spines. Spines usually have asymmetric synapses on their heads. In a recent stereological study we were able to show that there is a loss of approximately 20% of asymmetric synapses in the lesioned neostriatum by 1 mo after the lesion. Current experiments are trying to establish the specificity of this loss. So far we have evidence suggesting that there is no obvious preferential loss of synapses from either D1 or D2 receptor immunostained dendrites in the neostriatum with damaged dopamine innervation. These experiments suggest that dopamine is somehow necessary for the maintenance of corticostriatal synapses in the neostriatum. In a different series of experiments slices of cortex and neostriatum were maintained in vitro in such a way as to preserve at least some of the corticostriatal connections. In this preparation we have been able to show that cortical stimulation results in robust excitatory postsynaptic potentials (EPSPs) recorded from inside striatal neurons. Using stimulation protocols derived from the experiments on hippocampal synaptic plasticity we have shown that the usual consequence of trains of high frequency stimulation of the cortex is the depression of the size of EPSPs in the striatal cell. In agreement with similar experiments by others, the effect seems to be influenced by NMDA receptors since the unblocking of these receptors with low Mg^{++} concentrations in the perfusate uncovers a potentiation of the EPSPs after trains of stimulation. Dopamine applied in the perfusion fluid round the slices has no effect but pulsatile application of dopamine, close to the striatal cell being recorded from, and in temporal association with the cortical trains, leads to a similar LTP like effect. The reduction of K^+ channel conductance in the bath with TEA also has the effect of making cortical trains induce potentiation of corticostriatal transmission. TEA applied only to the cell being recorded from has no similar effect; the cortical stimulation again depresses the EPSP amplitude, so the site of action of TEA may well be presynaptic to the striatal cell. The morphological and physiological experiments may not necessarily be related but it is tempting to suggest that dopamine protects some corticostriatal synapses by potentiating them but that in the absence of dopamine others simply disconnect and are no longer detectable on electron microscopy.

Key words: Corticostriatal pathways; long-term synaptic potentiation.

WHY IS PLASTICITY IMPORTANT?

Plasticity is the ability of a structure to change its shape and/or function in response to changing circumstances, such as growth and development, or disease or trauma. For the neostriatum there is intense interest in understanding and manipulating plasticity in the treatment of Parkinson's disease. Several groups have been able to implant fetal dopamine-containing cells into striatal sites and to show that the dopamine

Correspondence to Dr Gordon Arbuthnott, University of Edinburgh, Department of Preclinical Veterinary Sciences, R(D)SVS, Summerhall, Edinburgh, EH1 1QH, UK. Tel: +44 (0) 131 650 6177; fax: +44 (0) 131 650 6177; email G.Arbuthnott@ed.ac.uk

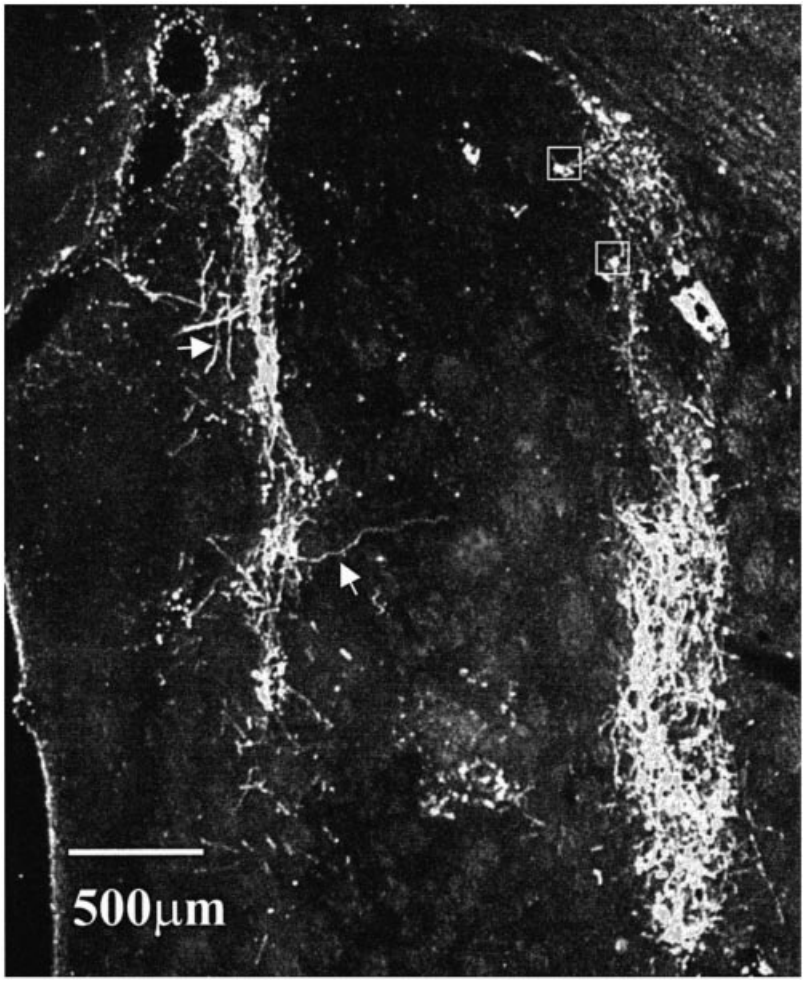

Fig. 1. Dark field photomicrograph from a rat with a 6-hydroxydopamine lesion that removed the dopamine input to the neostriatum. Two columns of embryonic dopamine neurons, which are stained by an antibody to tyrosine hydroxylase, were implanted into the damaged neostriatum (Dr Steve Dunnett). Fibres (white arrows) and cells (within the squares) are visible and the fibre network has grown into the surrounding neostriatum.

neurons grow into the neostriatum when it has been deprived of dopamine (Fig. 1). At least some of that work has promise as a treatment strategy for the replacement of the dopamine fibres which degenerate in Parkinson's disease although it is a long way before it can be seen as the strategy of choice (Dunnett & Björklund, 1999). The work has also revealed a remarkable plasticity both in striatal cells and their cortical input in experiments that more directly model Huntington's disease (Kendall et al. 1998). These experiments suggest that fetal striatal cells may grow and be reconnected to the relevant output nuclei and receive appropriate inputs in a way that may yet provide some hope of symptomatic relief in this devastating hereditary neurological condition.

A second reason for studying plasticity in the neostriatum concerns the possible action of dopamine as a motivator of action. This idea has a long history and owes at least some of its appeal to the writings of C. J. Herrick in the early part of this century (see Herrick, 1948). It may be that the dopamine has evolved from the ancient brain systems involved in assessing the value of smells as cues for movement of the organism towards stimuli in the environment that are associated with food or sex or other major biological drives. Herrick suggested that the 'peri-peduncular field' in the brain of the tiger salamander linked olfactory cues to the motor system. The field lay exactly in the area that is homologous with the mammalian ventral tegmentum. That such a link must be 'trainable' seems obvious and indeed led Crow & Arbuthnott (1972) to speculate that dopamine may have be involved in the expression of behaviour acquired by operant conditioning. This implies a role for dopamine in the modification of synaptic activity. That dopamine has such an action was one of the suggestions from some recent electrophysiological experiments (Wickens et al. 1996).

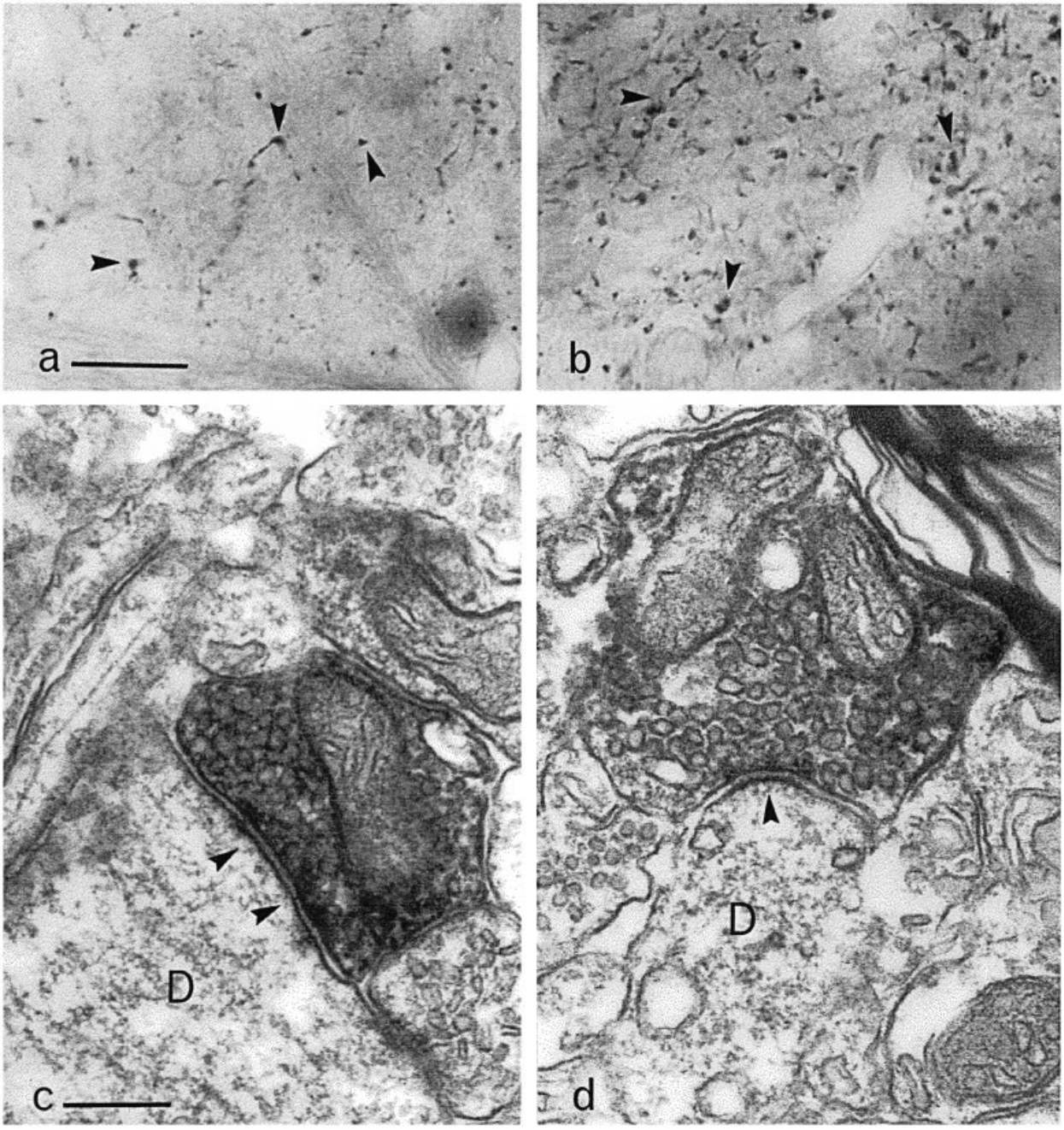

Fig. 2. The reaction of enkephalin-immunoreactive fibres in the neostriatum contralateral (*a*, *c*) and ipsilateral (*b*, *d*) to the loss of dopamine. The light micrographs (*a*, *b*) and electron micrographs (*c*, *d*) are from an animal that had been lesioned 13 mo previously. More immunoreactive fibres and punctate structures are visible and some appear bigger in the light micrograph from the neostriatum ipsilateral to the lesion (*b*). In the electron micrographs, the terminal from the neostriatum ipsilateral to the lesion (*d*) is larger than that from the contralateral side (*c*). The area of immunoreactive boutons was on average 50% larger on the ipsilateral side ($0.30 \pm 0.10\ \mu m^2$ compared with $0.20 \pm 0.04\ \mu m^2$). *a*, *b*, arrowheads mark some of the immunoreactive structures; *c*, *d*, arrowheads mark the symmetric synaptic contacts formed between the densely labelled immunoreactive boutons and postsynaptic dendrites (D). Bars for *a*, *b* shown in *a*, 15 μm; for *c*, *d* shown in *c*, 0.2 μm.

The third reason to explore plasticity in the neostriatum is also one that gave rise to some of our early experiments on the ultrastructure of neostriatum. When Raisman (1969) first showed that the response of the nervous system to damage might be an appropriate reinnervation of denervated synaptic sites, he suggested a principle which might explain the changes in symptoms of Parkinson's disease over time and might even explain the action of 'neuroleptics' (Arbuthnott & Ingham, 1993). Suppose the loss of dopamine led to a replacement of the synaptic sites, vacated by dopamine, by some other nearby nerve

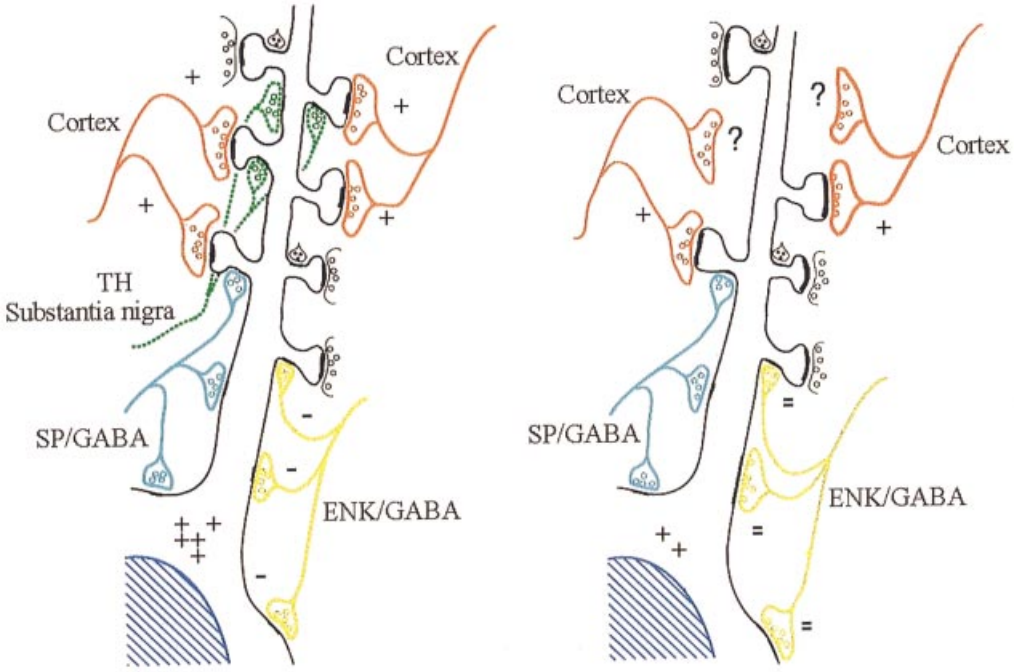

Fig. 3. Diagram based on the work of Bolam et al. indicates the problem that faced us when we tried to interpret the meaning of the loss of spines. If the spines had disappeared there must have been synapses (probably cortical) which had changed their postsynaptic target or perhaps had been totally lost.

terminal? Once we had the information that most dopaminergic synapses were on or near the necks of dendritic spines (Bouyer et al. 1984; Freund et al. 1984) it seemed appropriate to search for the synapses which had replaced them.

Ultrastructural consequences of dopamine damage

The output of the neostriatum is carried by the medium sized densely spiny (MSDS) cells that receive both the cortical input synapses on the head of spines and dopamine on the neck or nearby dendritic shaft (Bouyer et al. 1984; Freund et al. 1984; Groves et al. 1994). Biochemical and histochemical studies with in situ hybridisation localisation of mRNA for prepro-enkephalin both suggested that after destruction of dopamine fibres the synthesis of enkephalin had been increased (Young et al. 1986; Voorn et al. 1987). We examined the rat neostriatum by electron microscopy to investigate whether the increase in enkephalin, which follows dopamine destruction, results from sprouting of enkephalin-containing terminals onto the spine neck sites vacated by dopamine. Enkephalin immunoreactive synaptic boutons were 50% larger after dopamine denervation but they did not contact spines more frequently than in the control neostriatum (Ingham et al. 1991) (Fig. 2). As a parallel study progressed a possible explanation emerged.

Spine density on densely spiny neurons is changed by dopamine loss

The morphology of MSDS cells was compared in the neostriatum ipsilateral and contralateral to the lesion. The study revealed that the density of dendritic spines is reduced on the output cells of the neostriatum, from which the dopamine has been removed by an injection of 6-hydroxydopamine (Ingham et al. 1989). This loss of spines takes place over the first 3 wk after the lesion and the output cells are less spiny even after 1 y (Ingham et al. 1993). Each spine has an asymmetric synapse on its head so these results raised the following questions (see Fig. 3). What happened to these synapses? Did they just move on to the dendritic shaft, or was there also a loss of synapses from the spiny cells after dopamine depletion? It should be pointed out that these asymmetric synapses are likely to be of extrinsic origin, arising from the cortex and thalamus. They are not likely to be those dopamine-containing fibres, which arise from the substantia nigra, because tyrosine hydroxylase immunocyto-chemistry has shown them to make symmetric synapses (Freund et al. 1984; Groves et al. 1994; Bouyer et al. 1984). The dopamine-containing fibres and terminals are of course destroyed in the neo-striatum unilateral to the 6-OHDA lesion as con-firmed by the lack of tyrosine hydroxylase immuno-positive fibres on the lesioned side. In order to assess

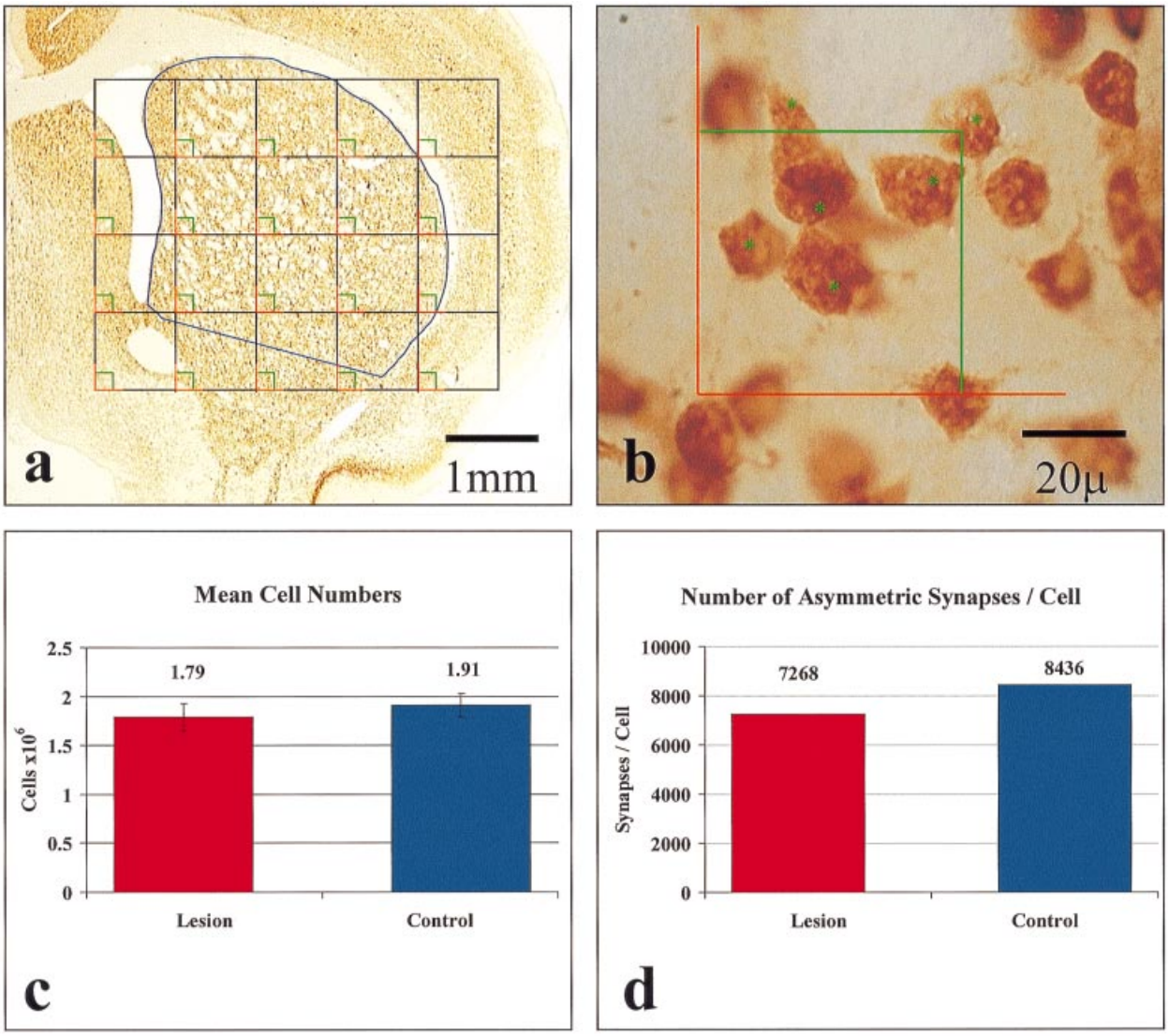

Fig. 4. The low power micrograph (*a*) has a counting grid superimposed upon the neostriatum. The counting frames (red and green squares) which overlie the neostriatum were used to count cells. The area of striatum relevant to the counting is outlined in blue; we used the callosal border, the ventricle border and a straight line from the lowest point of the ventricle to the rhinal fissure. The higher power micrograph (*b*) shows one such frame. Only neurons are stained by the A60 antibody and so the cells marked with the green asterisks would all be counted for that frame. The columns (*c*) show the estimated absolute number of cells, in the area of the striatum that we counted, averaged over 6 animals with 6-hydroxydopamine-induced lesions. The average number of synapses per cell on the 2 sides of the brain (*d*) was assessed by dividing the absolute numbers of synapses (from Ingham et al. 1998) by the number of cells we have obtained in equivalent animals. Even allowing for the small cell loss on the side of the lesion in this way, there is still a 14% loss of synapses/cell in the neostriatum from which dopamine had been removed.

whether or not asymmetric synapses are lost along with spines, we have used 'unbiased' stereological methods to count the number of asymmetric synapses in the neostriatum on the side of a 6-hydroxydopamine lesion compared with the control side. The total number of asymmetric synapses in the neostriatum on the lesioned side is reduced by about 18%, which is similar to the reduction in spine density at equivalent times after the lesion (Ingham et al. 1998). From a recent series of experiments (Wright & Arbuthnott, 1999) it was proposed that the synapse loss is not due to MSDS neuron death in the neostriatum on the side of the lesion (Fig. 4). Cortical terminals are one of the main sources of asymmetric synapses in the neostriatum, and they are particularly associated with dopamine input to the same spines (Smith et al. 1994). Therefore, it seems likely that the reduction in the number of spines is the consequence of the loss of corticostriatal synapses.

Could the lost spines be the ones that originally received dopamine input?

Estimates of the number of spines receiving a dopamine synapse vary in different studies. When all dopaminergic synapses in a small cube of striatal

volume were counted it could be estimated that $< 7\%$ of spines were contacted by this type of terminal (Groves et al. 1994). On the other hand, the estimate derived from studying the dopaminergic synapses onto the dendrite of an identified striatonigral cell showed that $\sim 39\%$ of the spines had a dopaminergic input (Freund et al. 1984). The large range suggests that only some cells have a large percentage of spines innervated by dopamine and our estimate is a global average of neurons with many dopamine synapses on spines and those without.

There were tantalising clues in the literature that led us to predict that the lost spines were only a subset of the dopamine receiving ones. Cortical damage reduces spine density on MSDS in the neostriatum (Kemp & Powell, 1971) and also counteracts the increase in enkephalin, which follows dopamine loss (Campbell & Björklund, 1994). Furthermore, dopamine D2 receptors are upregulated after the lesion, and are mainly expressed by enkephalin-containing cells. The fact that enkephalin production is also upregulated after the lesion and that this is controlled by cortical input suggested that these are not the cells that lose cortical input (or spines).

In a recent series of in vitro electrophysiological studies Wickens et al. (unpublished observations) have been able to show that the long-term potentiation (LTP) which follows cortical stimulation in perfusion fluid containing low Mg^{++} concentrations is sensitive to dopamine depletion. Not only is the LTP abolished by previous depletion of dopamine but the effect is prevented by treatment with a D1 receptor antagonist, but not by a D2 antagonist (Fig. 5). D1 receptors are mainly expressed in neurons that also express substance P. That fact, along with the evidence showing that these cells synthesise less substance P after the lesion, and the interesting delay in the development of this outcome of the lesion (Nisenbaum et al. 1994) suggested that asymmetric synapses (and spines) may be lost specifically from cells expressing D1 receptors. We are presently testing this idea by estimating the numerical density of asymmetric synapses onto the dendritic processes labelled with a D1 receptor protein antibody (Levey et al. 1993). Preliminary counts in 4 animals indicate no difference between the loss of asymmetric synapses on dendrites stained with an antibody to D1 receptors, compared with those lost from unstained (D2 containing) spines. An alternative hypothesis is that asymmetric synapses are lost from specific sites of cortical input, and our preliminary results make that explanation more likely.

Our recent description of 2 corticostriatal pathways from the barrel cortex (Wright et al. 1999), along with similar conclusions from studies mapping the cortical terminals from single cortical neurons (Cowan & Wilson, 1994) suggest that there is a possible differentiation between cortical inputs from different cortical systems. Until the quantitative study is complete we should reserve judgement, but work has started to try to classify the synapses in the neostriatum into one or other of the cortical input classes.

There is evidence from other systems such as the retina (Rogawski, 1987) and from experiments on developing neuronal cells in culture (Meier et al. 1991; Reinoso et al. 1996; Spencer et al. 1996) that dopamine might have a 'morphogenetic' effect. The synapses that disappear after dopamine depletion might be the most vulnerable of a system of corticostriatal synapses 'maintained' somehow by dopamine. Indeed one theory of the 'purpose' of dendritic spines is to limit the toxic consequences of glutamate release to small parts of the cell so that cells lose spines rather than die by excitotoxic action (Segal, 1995).

A continuing conundrum

We still have no clear, system level summary of how dopamine acts in the neostriatum. To shed some light in this difficult area, we have first to abandon some preconceptions. Firstly, it seems that there is no evidence for a 'simple' excitatory or inhibitory action of dopamine. Even the idea that the striatonigral cells are inhibited and the striatopallidal ones are excited by dopamine is not fully substantiated: laboratories that have reported excitatory effects also find inhibitory ones in the same cells, and many laboratories have failed to see either effect. The results of attempts to identify the membrane current in striatal cells that is modified by dopamine application have also been contradictory. Recent work has identified a Ca^{++} current (Bargas et al. 1994, 1999), which may be the target for dopamine action (Surmeier et al. 1995), but it is only likely to change the behaviour of the cells during cortical activation. Similarly, a sodium current that changes the threshold for the generation of action potentials from intracellular current injections (Calabresi et al. 1987; Surmeier et al. 1991) may only be relevant near the threshold for action potential generation in vivo. It has also been shown that dopamine changes the synaptic potentials in spiny neurons but in a way that depends on the glutamate receptor subtype being activated (Cepeda et al. 1993). Similarly, although we could demonstrate an inhibition of the after-hyperpolarisation following trains of action potentials, the effect was only visible in cells

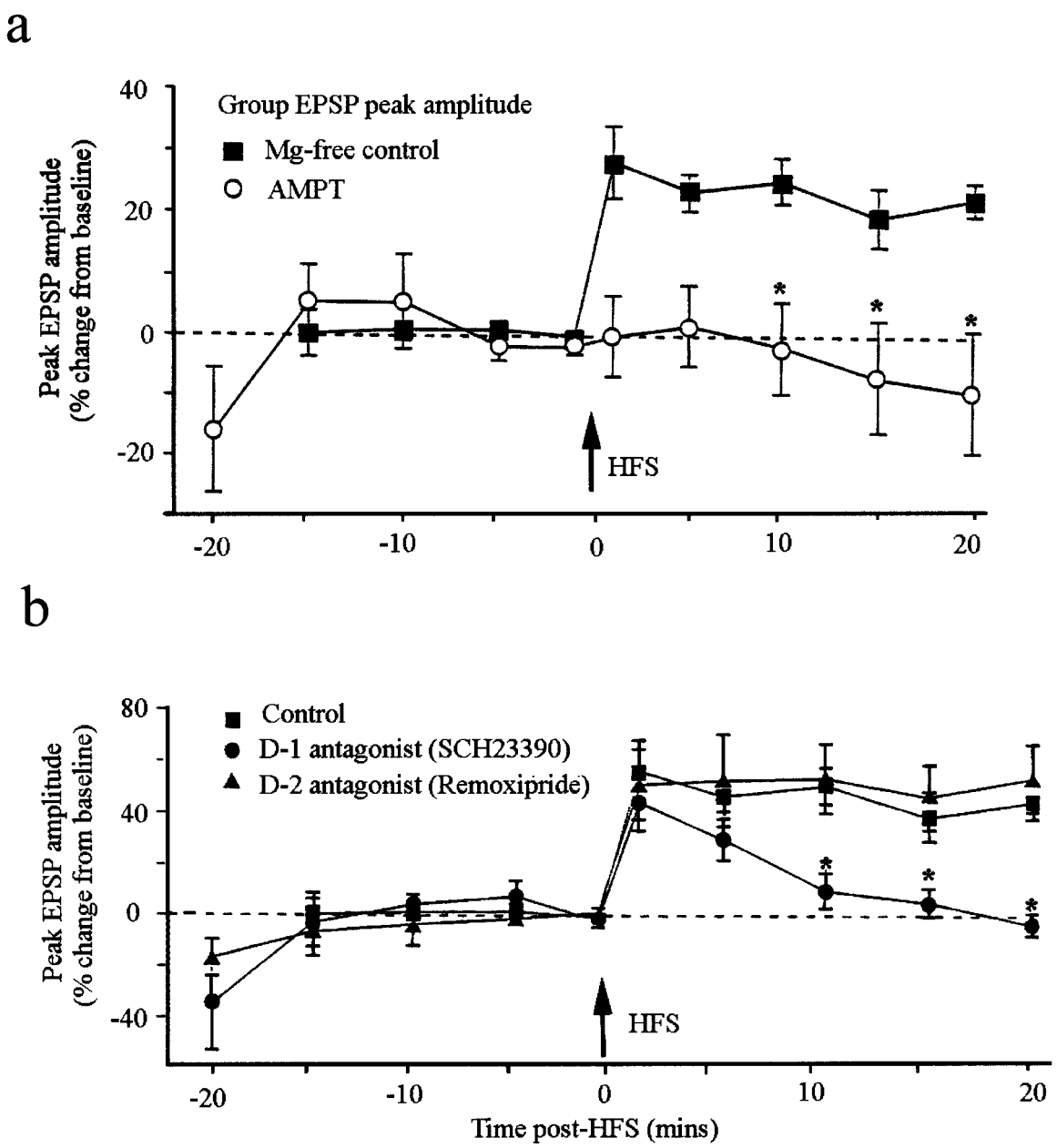

Fig. 5. (*a*) Graph illustrating group mean amplitudes of the EPSP (±S.E.M.) in striatal cells bathed in Mg^{++} free fluid and stimulated with high frequency trains to the cortex at the arrow. Six slices, from animals depleted of dopamine acutely (by pretreatment with α-methyl-para-tyrosine (AMPT)), did not show the usual LTP. (*b*) Results in the same format from slices bathed in dopamine antagonists as well as in Mg^{++} free artificial cerebrospinal fluid. Only the D1 antagonist reduced the long-term effect of the trains suggesting that the long-term potentiation is mediated by the action of dopamine on D1 receptor bearing synapses. There were 6 control slices, 5 with D1 antagonist and 4 with D2 antagonist. (From unpublished observations by J. R. Wickens and J. Kerr).

already depolarised from rest (Rutherford et al. 1988). The effects of dopamine thus seem to depend on the recent history of the membrane potential of the neuron.

A different kind of electrophysiology

Our most recent physiological experiments were an attempt to understand the actions of dopamine at the single cell level in the context of the suggested timing of its release. In the behaving monkey, dopamine cells fire bursts of action potentials as a consequence of stimuli that predict the likelihood of a rewarding event (Schultz, 1998). Schultz and his colleagues suggest that dopamine is released in situations in which unexpected reward arrives (Mirenowicz & Schultz, 1994). During training this release coincides with the solution to a behavioural problem (Ljungberg et al. 1992). The appropriate response is 'do that again'. In order to make use of such an instruction the animals need a record of what has just been done and the arrival of the dopamine must make that sequence

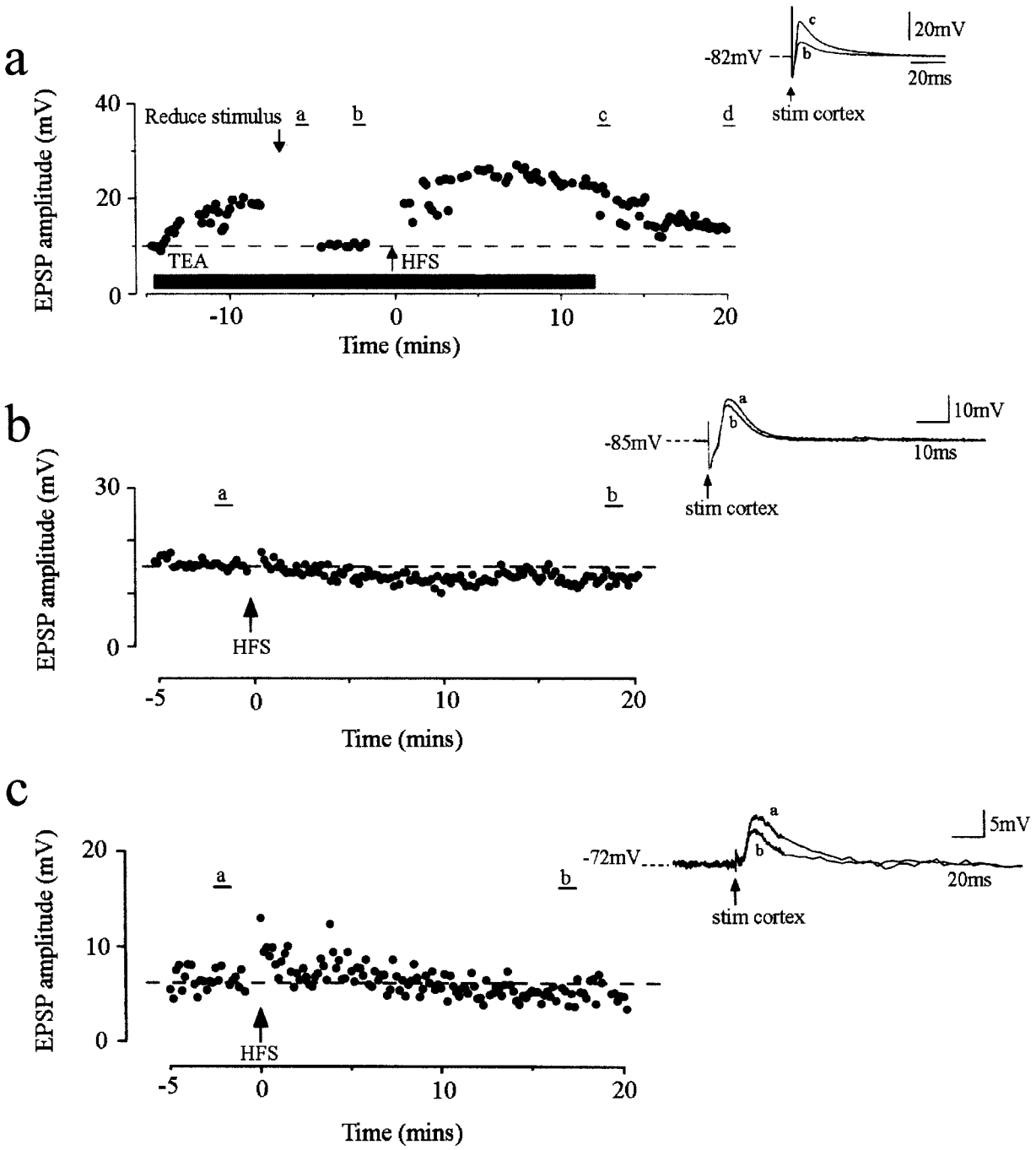

Fig. 6. Results from 3 representative individual cells from slices treated with TEA in the perfusion fluid (*a*), with caesium in the electrode (*b*) and with TEA in the electrode (*c*). The dots correspond to the peak amplitude of EPSPs evoked by stimulation at 0.1 Hz. The small inset traces show example EPSPs (averaged over 3 responses) before and after the tetanic stimulation, at the times indicated over the graphs of EPSP amplitude. In *c* the sampling rate was changed just after the peak of the EPSPs and the traces therefore look smoother beyond that point. (Modified from data published in Wickens et al. 1998).

of events more likely to recur. If we suppose that the dopamine is acting on corticostriatal synapses then the 'trace' of what has just been done would correspond to a set of concomitantly activated cortical cells and their respective striatal partners. The arrival of dopamine must somehow make a 'memory trace' as a more permanent record of this set of connections. Once such a set is 'confirmed' then the activity in a particular set of corticostriatal pairs (and the 'rewarded' actions they represent) becomes more likely to recur in similar circumstances, and continues to do so for some time in the absence of further reward. Thus the changes induced by dopamine must themselves be long-term and outlast the actions of the released dopamine. Synaptic potentiation seemed likely to be a suitable model on which to build this 'conditional' memory system. There were already experiments which suggested that the corticostriatal

terminals were capable of long term changes in their excitability (Garcia-Munoz et al. 1992) and that dopamine played a major role in these changes (Garcia-Munoz et al. 1991). We studied the consequences of trains of stimuli to the corticostriatal system and found (Wickens et al. 1996), like others (Calabresi et al. 1992*a*; Lovinger et al. 1993; Walsh, 1993), that the usual consequence of repetitive trains of stimulation to the cortex is the reduction of the size of the excitatory postsynaptic potential (EPSP) in the striatal cell. Cortical activation—if it is paired with postsynaptic depolarisation in the neostriatum—usually leads to a reduction in the efficacy of the synaptic input to the striatal cell, a kind of long-term depression.

However, if dopamine is applied in a pulsatile manner intended to mimic the release of dopamine thought to follow a train of spikes in a dopamine cell, then the corticostriatal synapses can show LTP (Wickens et al. 1996). LTP is also a consequence of treating slices of the corticostriatal system in ways that enhance the NMDA component of transmission (e.g. with low Mg^{++} solutions; Walsh, 1991; Calabresi et al. 1992*b*) and after blocking potassium channels with TEA (Walsh, 1991). We also looked at the action of TEA in the corticostriatal system and can add (Wickens et al. 1998) that, although TEA certainly changes the action of cortical trains from depression to potentiation, it is only effective when in the perfusion fluid. Potassium channels can be blocked from within the cell being recorded from with caesium, or with a mixture of caesium and TEA, but this does not change the cortical action (Fig. 6). The possibility that the extracellular action is in fact a presynaptic one, which increases dopamine release in the slices, seems plausible in view of the high sensitivity of dopamine cells themselves to extracellular TEA (Harris, 1992). These results suggest that dopamine release has long term consequences for the efficacy of corticostriatal synapses and possibly also for their survival.

A synthesis

Of course this is only a speculation but a mechanism such as LTP, which can change synaptic efficacy for weeks, should have ultrastructural consequences in the neostriatum as has been shown for the hippocampus (Fifkova & Van Harreveld, 1977; Buchs & Muller, 1996). Thus the morphological and physiological experiments, when taken together, suggest that synaptic changes induced by dopamine have morphological consequences. It could be that potentiated synapses survive, and in the absence of dopamine nonpotentiated synapses are eliminated. Testing these ideas will need more detail as to how potentiation occurs and some pharmacological tools with which to interfere with the various stages involved. As the molecular biology of LTP races ahead it seems likely that suitable tools are not so very far away.

REFERENCES

ARBUTHNOTT, GW, INGHAM CA (1993) The thorny problem of what dopamine does in psychiatric disease. In *Chemical Signalling in the Basal Ganglia: Progress in Brain Research 99* (ed. Arbuthnott GW, Emson PC), pp. 341–350. Amsterdam: Elsevier.

BARGAS J, HOW A, EBERWINE J, CAO, Y, SURMEIER DJ. (1994) Cellular and molecular characterization of Ca^{2+} currents in acutely isolated, adult rat neostriatal neurons. *Journal of Neuroscience* **14**, 6667–6686.

BARGAS J, AYALA GX, VILCHIS C, PINEDA JC, GALARRAGA E (1999) Ca^{2+}-activated outward currents in neostriatal neurons. *Neuroscience* **88**, 479–488.

BOUYER JJ, PARK DH, JOH TH, PICKEL VM (1984) Chemical and structural analysis of the relation between cortical inputs and tyrosine hydroxylase-containing terminals in rat neostriatum. *Brain Research* **302**, 267–275.

BUCHS PA, MULLER D (1996) Induction of long-term potentiation is associated with major ultrastructural changes of activated synapses. *Proceedings of the National Academy of Sciences of the USA* **93**, 8040–8045.

CALABRESI P, MERCURI N, STANZIONE P, STEFANI A, BERNARDI G (1987) Intracellular studies on the dopamine-induced firing inhibition of neostriatal neurons in vitro: evidence for D1 receptor involvement. *Neuroscience* **20**, 757–771.

CALABRESI P, MAJ R, PISANI A, MERCURI NB, BERNADI G (1992*a*) Long-term synaptic depression in the striatum: physiological and pharmacological characterization. *Journal of Neuroscience* **12**, 4224–4233.

CALABRESI P, PISANI A, MERCURI NB, BERNARDI G (1992*b*) Long-term potentiation in the striatum is unmasked by removing the voltage-dependent magnesium block of NMDA receptor channels. *European Journal of Neuroscience* **4**, 929–935.

CAMPBELL K, BJÖRKLUND A (1994) Prefronal corticostriatal afferents maintain increased enkephalin gene expression in the dopamine-denervated rat striatum. *European Journal of Neuroscience* **6**, 1371–1383.

CEPEDA C, BUCHWALD NA, LEVINE MS (1993) Neuromodulatory actions of dopamine in the neostriatum are dependent upon the excitatory amino acid receptor subtypes activated. *Proceedings of the National Academy of Sciences of the USA* **90**, 9576–9580.

COWAN RL, WILSON CJ (1994) Spontaneous firing patterns and axonal projections of single coricostriatal neurons in the rat medial agranular cortex. *Journal of Neurophysiology* **71**, 17–32.

CROW TJ, ARBUTHNOTT GW (1972) Function of catecholamine-containing neurones in mammalian central nervous system. *Nature New Biology* **238**, 245–246.

DUNNETT SB, BJÖRKLUND A (1999) Prospects for new restorative and neuroprotective treatments in Parkinson's disease. *Nature* **399**, Supplement, A32–A39.

FIFKOVA E, VAN HARREVELD A. (1977) Long-lasting morphological changes in dendritic spines of dentate granular cells following stimulation of the entorhinal area. *Journal of Neurocytology* **6**, 211–230.

FREUND TF, POWELL JF, SMITH AD (1984) Tyrosine hydroxylase immunoreactive boutons in synaptic contact with

identified striatonigral neurons, with particular reference to dendritic spines. *Neuroscience* **13**, 1189–1215.

GARCIA-MUNOZ M, YOUNG SJ, GROVES PM (1991) Terminal excitability of the corticostriatal pathway. I. Regulation by dopamine receptor stimulation. *Brain Research* **551**, 195–206.

GARCIA-MUNOZ M, YOUNG SJ, GROVES PM (1992) Presynaptic long-term changes in excitability of the corticostriatal pathway. *NeuroReport* **3**, 357–360.

GROVES PM, LINDER JC, YOUNG SJ (1994) 5-hydroxydopamine-labeled dopaminergic axons: three-dimensional reconstructions of axons, synapses and postsynaptic targets in rat neostriatum. *Neuroscience* **58**, 593–604.

HARRIS NC (1992) Sensitivity of transient outward rectification to ion channel blocking agents in guinea-pig substantia nigra pars compacta neurones in vitro. *Brain Research* **596**, 325–329.

HERRICK CJ (1948) *The Brain of the Tiger Salamander*. Chicago: University of Chicago Press.

INGHAM CA, HOOD SH, ARBUTHNOTT GW (1989) Spine density on neostriatal neurons changes with 6-hydroxydopamine lesions and with age. *Brain Research* **503**, 334–338.

INGHAM CA, HOOD SH, ARBUTHNOTT GW (1991) A light and electron microscopical study of enkephalin-immunoreactive structures in the rat neostriatum after removal of the nigrostriatal dopaminergic pathway. *Neuroscience* **42**, 715–730.

INGHAM CA, HOOD SH, TAGGART P, ARBUTHNOTT GW (1998) Plasticity of synapses in the rat neostriatum after unilateral lesion of the nigrostriatal dopaminergic pathway. *Journal of Neuroscience* **18**, 4732–4743.

INGHAM CA, HOOD SH, WEENINK A, VAN MALDEGEM B, ARBUTHNOTT GW (1993) Morphological changes in the rat neostriatum after unilateral 6-hydroxydopamine injections into the nigrostriatal pathway. *Experimental Brain Research* **93**, 17–27.

KEMP JM, POWELL, TPS (1971) The termination of fibres from the cerebral cortex and thalamus upon dendritic spines in the caudate nucleus: a study with the golgi method. *Philosophical Transactions of the Royal Society of London B*. **262**, 429–439.

KENDALL AL, RAYMENT FD, TORRES EM, BAKER HF, RIDLEY RM, DUNNETT SB (1998) Functional integration of striatal allografts in a primate model of Huntington's disease. *Nature Medicine* **4**, 727–729.

LEVEY AI, HERSCH SM, RYE DB, SUNAHARA RK, NIZNIK HB, KITT CA et al. (1993) Localization of D_1 and D_2 dopamine receptors in brain with subtype-specific antibodies. *Proceedings of the National Academy of Sciences of the USA* **90**, 8861–8865.

LJUNGBERG T, APICELLA P, SCHULTZ W (1992) Responses of monkey dopamine neurons during learning of behavioral reactions. *Journal of Neurophysiology* **67**, 145–163.

LOVINGER DM, TYLER EC, MERRITT A (1993) Short- and long-term synaptic depression in rat neostriatum. *Journal of Neurophysiology* **70**, 1937–1949.

MEIER E, HERTZ L, SCHOUSBOE A (1991) Neurotransmitters as developmental signals. *Neurochemistry International* **19**, 1–15.

MIRENOWICZ J, SCHULTZ W (1994) Importance of unpredictability for reward responses in primate dopamine neurons. *Journal of Neurophysiology* **72**, 1024–1027.

NISENBAUM LK, KITAI ST, CROWLEY WR, GERFEN CR (1994) Temporal dissociation between changes in striatal enkephalin and substance P messenger RNAs following striatal dopamine depletion. *Neuroscience* **60**, 927–937.

RAISMAN G (1969) Neuronal plasticity in the septal nuclei of the adult brain. *Brain Research* **14**, 25–48.

REINOSO BS, UNDIE AS, LEVITT P (1996) Dopamine receptors mediate differential morphological effects on cerebral cortical neurons in vitro. *Journal of Neuroscience Research* **43**, 439–453.

ROGAWSKI MA (1987) New directions in neurotransmitter action: dopamine provides some important clues. *Trends in Neurosciences* **10**, 200–204.

RUTHERFORD A, GARCIA-MUNOZ M, ARBUTHNOTT GW (1988) An afterhyperpolarization recorded in striatal cells 'in vitro': effects of dopamine administration. *Experimental Brain Research* **71**, 399–405.

SCHULTZ W (1988) Predictive reward signal of dopamine neurons. *Journal of Neurophysiology* **80**, 1–27.

SEGAL M (1995) Dendritic spines for neuroprotection: a hypothesis. *Trends in Neurosciences* **11**, 468–471.

SMITH Y, BENNETT BD, BOLAM JP, PARENT A, SADIKOT AF (1994) Synaptic relationships between dopaminergic afferents and cortical or thalamic input in the sensorimotor territory of the striatum in monkey. *Journal of Comparative Neurology* **344**, 1–19.

SPENCER GE, LUKOWIAK K, SYED NI (1996) Dopamine regulation of neurite outgrowth from identified *Lymnaea* neurons in culture. *Cellular and Molecular Neurobiology* **16**, 577–589.

SURMEIER DJ, WILSON CJ, STEFANI A, KITAI ST (1991) Dopaminergic modulation of sodium currents in retrogradely-identified rat striatonigral neurons. *Society for Neuroscience Abstracts* **17**, 851–851.

SURMEIER DJ, BARGAS J, HEMMINGS HC JR., NAIRN AC, GREENGARD P. (1995) Modulation of calcium currents by a D_1 dopaminergic protein kinase/phosphatase cascade in rat neostriatal neurons. *Neuron* **14**, 385–397.

VOORN P, ROEST G, GROENEWEGEN HJ (1987) Increase of enkephalin and decrease of substance P immunoreactivity in the dorsal and ventral striatum of the rat after midbrain 6-hydroxydopamine lesions. *Brain Research* **412**, 391–396.

WALSH JP (1991) Long-term potentiation (LTP) of excitatory synaptic input to medium spiny neurons of the rat striatum. *Society for Neuroscience Abstracts* **17**, 852–852.

WALSH JP (1993) Depression of excitatory synaptic input in rat striatal neurons. *Brain Research* **608**, 123–128.

WICKENS JR, BEGG AJ, ARBUTHNOTT GW (1996) Dopamine reverses the depression of rat corticostriatal synapses which normally follows high-frequency stimulation of cortex *in vitro*. *Neuroscience* **70**, 1–6.

WICKENS JR, McKENZIE D, COSTANZO E, ARBUTHNOTT GW (1998) Effects of potassium channel blockers on synaptic plasticity in the corticostriatal pathway. *Neuropharmacology* **37**, 523–533.

WRIGHT AK, NORRIE L, INGHAM CA, HUTTON EAM, ARBUTHNOTT GW (1999) Double anterograde tracing of outputs from adjacent "barrel columns" of rat somatosensory cortex. Neostriatal projection patterns and terminal ultrastructure. *Neuroscience* **88**, 119–133.

YOUNG WSI, BONNER TI, BROWN MR (1986) Mesencephalic dopamine neurons regulate the expression of neuropeptide mRNAs in the rat forebrain. *Proceedings of the National Academy of Science of the USA* **83**, 9827–9831.