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RESEARCH ARTICLE

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The role of the pedunculopontine region in basal-ganglia mechanisms of akinesia

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Abstract The akinesia of Parkinsonism is relieved by pallidotomy and subthalamic nucleotomy, but not by thalamotomy. Therefore, this disabling symptom probably depends upon connections other than the pallidal-thalamocortical tracts, possibly efferents of the medial pallidum descending to the upper brainstem. We have previously demonstrated akinesia in the normal monkey following radiofrequency lesioning in the region of the pedunculopontine nucleus (PPN), one of the primary targets for descending pallidal outflow. Here, we confirm that selectively destroying neurones in the PPN area, whilst sparing fibres of passage, results in an akinetic state in normal macaques.

Key words Parkinson's Disease (PD) · Pedunculopontine nucleus (PPN) · Akinesia · Kainic acid (KA)

Introduction

Due largely to work carried out in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), we have over the last ten years seen an exponential rise in our understanding of the neural mechanisms underlying the cardinal symptoms of Parkinson's disease. Loss of the nigro-striatal dopaminergic projection has been shown to result in overactivity of the medial pallidal (GPm) and substantia nigra pars reticulata (SNr) inhibitory output, which in turn depresses the motor activity of the thalamic and brainstem structures to which they have been shown to project (Fig. la and b), leading to the clinical manifestations of akinesia (Sambrook et al. 1989).

lt has long been assumed that the increased inhibitory output of the GPm acts mainly via the thalamocortical feedback route to produce akinesia through its actions upon cortical regions such as the supplementary motor area. However, this view fails to explain the clinical and experimental observation that thalamotomy, despite relieving Parkinsonian tremor, rarely improves akinesia and may even result in a worsening of this symptom (Laitenen and Vikki 1973). Conversely, medial pallidotomy may alleviate akinesia, but has a lesser effect upon tremor (Baron et al. 1996), whereas high frequency stimulation or lesioning the subthalamic nucleus improves both symptoms (Aziz et al. 1992; Limousin et al. 1995; Benazzouz et al. 1996). As thalamic lesioning does not affect the descending outputs of the basal ganglia, whereas pallidotomy and subthalamic nucleotomy both do, a logical conclusion would be that overactivity of descending projections to the pedunculopontine area in the upper brainstem (Jackson and Crossman 1983; Aziz et al. 1992), rather than overinhibition of the thalamic motor nuclei, is responsible for the akinesia of Parkinson's Disease. In support of this hypothesis, the optimal target for the relief of akinesia by pallidotomy is the postero-ventral third of the GPm, the region which has been demonstrated to project mainly to the PPN (Takada 1995). Also, post mortem studies have revealed that, in Parkinson's disease, there is a depletion of neurones in the PPN region (Zweig et al. 1989). One possible explanation for this loss would be that it is secondary to the excessive inhibition of this cell group by the overactivity of the descending pallidal projections.

The PPN is composed of two populations of neurones in the pontomesencephalic tegmentum: firstly, a group of large cholinergic neurones, whose complex and widely distributed efferents allow for it's participation in a variety of functions; secondly, a group of glutamatergic neurones that project caudally to the pontine and medullary

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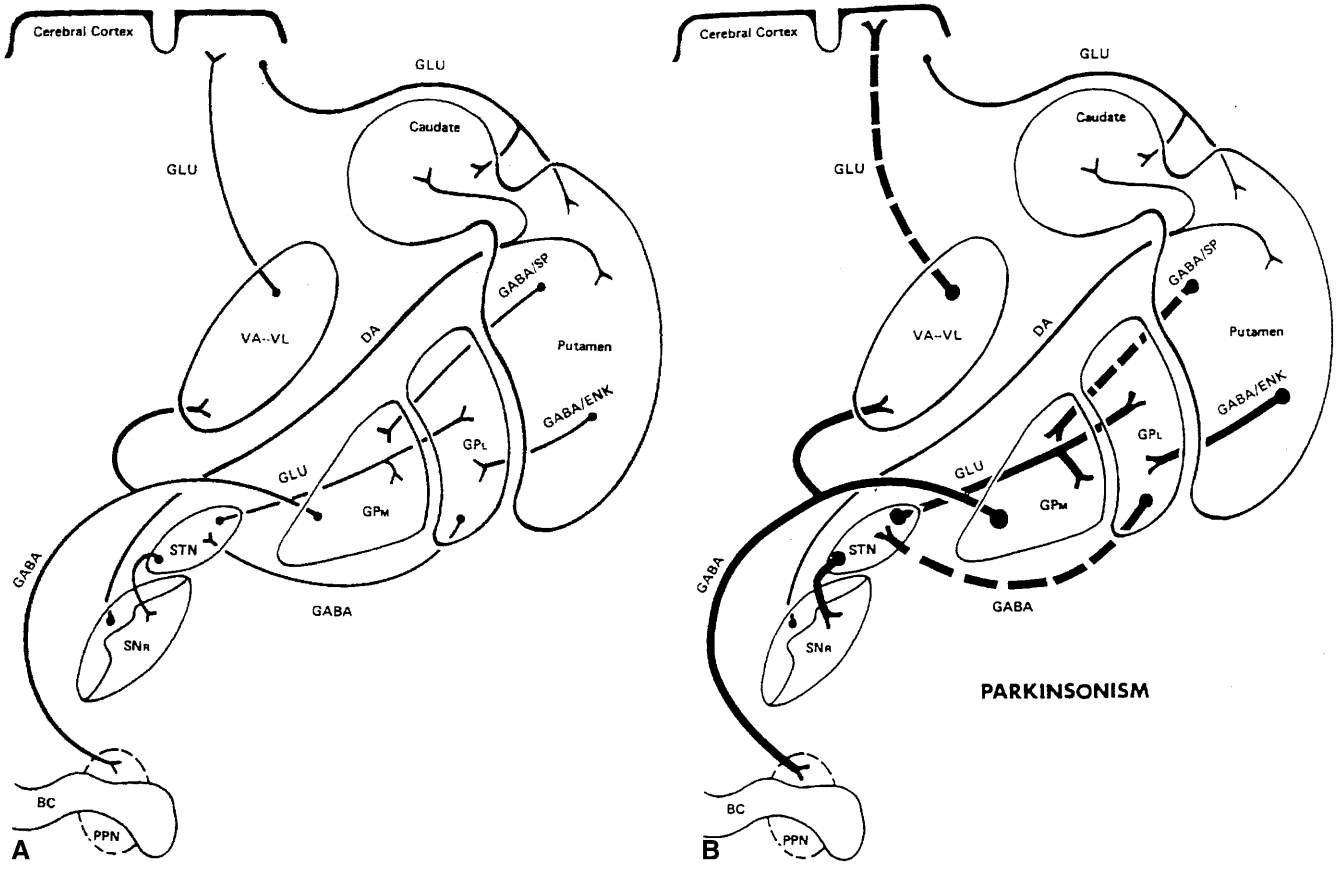

Fig. 1 **A** A simplified diagram of normal basal-ganglia function in the control of movement, in which the *GLU arrows* are excitatory and glutamatergic, the *GABA arrows* are inhibitory and GABAergic, and the *DA arrow* indicates the probably largely inhibitory nature of the dopamenergic nigrostriatal projections. (Taken from Aziz et al. 1992). *BC* Brachium conjunctivum, *ENK* enkephalin, GP_L lateral pallidum, GP_M medial pallidum, *PPN* pedunculopontine nucleus, *SP* substance P, *STN* subthalamic nucleus, SN_R substantia nigra pars reticulata. **B** In the Parkinsonian state, decreased activity in the inhibitory dopamenergic projections leads to a selectively increased activity in the putaminolateral projection, as indicated by the *heavier arrow*. This leads to disinhibition of the STN, which then exerts an excessive excitatory drive to the GP_M with excessive thalamic and PPN inhibition. (Taken from Aziz et al. 1992). *Dashed lines* Underactive, *solid lines* overactive

reticulospinal systems responsible for locomotion and whole-limb movements (Steriade et al. 1988; Garcia-Rill 1991; Scarnati and Floria 1997). Indeed, in rats, electrical or pharmacological stimulation of the PPN has been shown to increase, whereas PPN inhibition decreases the animals' activity (Brudzynski et al. 1986; Milner and Mogenson 1988; Garcia-Rill et al. 1987; Mogenson and Wu 1988). That the PPN region plays a crucial role in the control of proximal limb movement would, therefore, seem a reasonable supposition; and further elucidation of this role, and the part it may play in the development of akinetic syndromes, would improve our understanding of such states and our attempts at effective therapy.

We have previously demonstrated that radiofrequency lesioning of the PPN region in the normal macaque monkey results in an akinetic state (Aziz et al. 1998). However, it could be argued that the lesions generated by this technique may have damaged fibres of passage from the cerebellum, although histology confirmed that the fibres of the superior cerebellar peduncle remained intact and, clinically, there was an absence of any cerebellar signs in these animals. We have, therefore, sought to confirm our earlier findings by studying the effect of lesions of the region, including the PPN, in the normal macaque using a neurone-specific excitotoxic agent, kainic acid.

Materials and methods

Seven macaque monkeys were used in this study (four female *Macaca mulatta*, three male *Macaca fascicularis*), their mean age was 7 years (range 4–17 years) and mean weight was 5.6 kg (range 3–8.4 kg). They were housed in accordance with the Home Office code of practice for the housing and care of animals used in scientific procedures, with all animals housed in a cage of dimensions suitable for those in the 6–9 kg category, i.e. minimum floor space was 14,000 cm^2 with a minimum height of 150 cm. A fixed 12-hour light/dark cycle (07:30–19:30 lights on, 19:30–07:30 lights off) was adhered to throughout, and ad lib food and drink provided at all times, except on the morning prior to surgery.

Mounted above the home cage was a Doppler activity meter that covered a conical field encompassing the cage area. The meter's sensitivity was set so as to require whole-limb or whole-body movements to register a single count, the objective being to record the overall activity of the animal during each 24-h period. The gain of the activity meter was checked and adjusted for each monkey to account for the variation in physical size between animals. Counts were taken at a set daily time, thus representing total

Table 1 The clinical rating scale used to assess Parkinsonism in primates (Clarke and Sambrook 1987)

Item	Score	Definition
Activity	–2	Severe hyperactivity
	–1	Moderate hyperactivity
	0	Normal
	1	Moderate hypokinesia
	2	Severe hypokinesia
Bradykinesia	0	Normal
	1	Moderate bradykinesia
	2	Severe bradykinesia
Freezing	0	None
	1	Some episodes
	2	Many episodes
Balance	0	Normal
	1	Moderately impaired
	2	Severely impaired
Posture	0	Normal erect
	1	Some stooping
	2	Severe Stooping
Tremor	0	None
	1	Moderate tremor
	2	Severe tremor
Feeding	–1	Hyperphagia
	0	Normal intake
	1	Reduced intake
	2	No intake
Vocalisation	–1	Hyperphonia
	0	Normal
	1	Reduced
	2	Markedly reduced
Chorea	0	None
	–1	Moderate
	–2	Severe
Stereotypy	0	None
	–1	Moderate
	–2	Severe
Total	–4 to 16	

counts at 24-h intervals. Activity monitoring by this method was performed for a minimum period of 7 days prior to surgery in order to provide a baseline 24-h activity count for each animal. In addition to the recording of daily activity counts, all animals were scored on the clinical rating scale to assess Parkinsonism in the primate (Table 1) (Clarke and Sambrook 1987), wherein a score greater than zero represents the presence of Parkinsonism. Also, video recordings of both provoked and unobserved activity were performed to provide a record of speed and nature of movements, facial expression and responsiveness to changes in the surrounding environment. All methods of assessment described were performed in an identical manner both pre- and postoperatively.

On the day of surgery, animals were initially sedated with a single dose of intramuscular ketamine (l0 mg/kg body weight). Thereafter, anaesthesia was maintained by means of a continuous intravenous infusion of althesin titrated according to the animals' weight (6 mg/kg/h) and administered via an infusion pump. When anaesthetised, the animals were placed in a stereotactic head frame and surgery performed under sterile conditions. All animals received the intramuscular antibiotic prophylaxis (Synulox 0.06 m1/kg) on the day prior to surgery, on induction of anaesthesia and for two days postoperatively.

Following contrast ventriculography (using 0.5 – 1.0 ml Omnipaque) and proportional correction for size with reference to a standard atlas (Shanta and Manocha 1968), a lesion was placed in the PPN, 2.0 mm lateral to the midline and 6.0 mm below the posterior commissure. In three animals, a unilateral lesion was first made, with a second contralateral lesion being made one week later. In a further three animals, bilateral lesions were made during a single operation, and in one animal a unilateral lesion only was made. Lesions were made by pressure injection of 1–3 µl of a 0.1% solution of kainic acid, dissolved in physiological saline, via a 0.5-mm diameter needle attached to a 1- or 5-µl Hamilton syringe, the needle tip being sited at the targeted PPN as confirmed on X-ray. Injection was made over a period of 5–10 min with gradual withdrawal of the injecting syringe over a further 5 min in order to minimise deposition of kainate within the needle tract secondary to any vacuum effect on withdrawal. An intramuscular dose of buprenorphine (0.06 ml/kg body weight) was administered at the end of each procedure to allow for postoperative analgesia. All animals were maintained on an intravenous hydration regime (80ml/kg/24 h normal saline) until they were able to take fluids orally.

No "sham" injections were performed in the course of this study due to Home Office restrictions on the use of primates, although we acknowledge that this would have been a control group for non-specific effects of the surgery. Permission was declined for the use of primates for sham injections followed by sacrifice for histological analysis and also for the reuse of such animals following sham procedures. The performance of an equal number of sham/actual procedures would, therefore, have doubled experimental costs and resulted in a group of animals post-sham procedure which were exempt from further usage. However, we can report that we have performed acute electrode placements and neural recordings at this site in other macaques without any of the akinetic effects described above occurring post-operatively (unpublished observations).

The animals were allowed to recover in their home cage and their activity was monitored in the same manner as pre-operatively for a period of 7 days. After this period, the animals were killed by means of an intravenous overdose of sodium pentobarbital (60 mg/kg body weight) and perfused transcardially with physiological saline followed by 1.0% formalin in a 0. 1 M phosphate buffer. The heads were then remounted in the stereotactic frame and the region of interest removed en bloc and placed in the same buffered formalin solution containing 30% sucrose. After a period of 7-days fixation in the sucrose/formalin solution, the tissues were cut serially into 50-µm sections on a freezing microtome. Alternate sections were then mounted and stained with cresyl violet to assess lesion placement and size.

Results

Complete recovery from althesin anaesthesia in the primate takes 1–2 h. However, after both the unilateral and bilateral lesions, the animals were completely akinetic for the 24 h following surgery. All animals were "alert" within 1 h post-operation, i.e. their eyes were open with conjugate gaze and visual tracking, but they made minimal spontaneous movements and exhibited increased tone in all limbs. Nevertheless, withdrawal from a noxious stimulus remained brisk during this period.

Complications arising in two cases resulted in complete data being available for three staged and two simultaneous PPN lesioning procedures only. In the animal receiving a single unilateral PPN lesion, a dense, unresolving right hemiparesis with hypertonia and hyperreflexia was observed post-operatively, necessitating euthanasia at 6 days post-operation. Histology in this case revealed a well sited lesion of the left PPN with no associated abnormalities. However, a haemorrhage into the left corpus callosum and adjacent motor cortex was evident and appeared to be secondary to the needle tract utilised for the operative ventriculogram. In a second instance, aspira-

Table 2 Activity counts (24 h) following unilateral pedunculopontine nucleus (PPN) lesions in monkeys A, B and C

	Volume of lesioning kainate	Mean 24-h activity count pre-operative (±SE)	Mean 24-h activity count post-operative (±SE)	Post-operative day						
				1	2	3	4	5	6	7
Monkey A	1 µl	1859 (±73)	926* (±237)	0	120	1025	1224	1119	1322	1672
% reduction				100	93	45	34	29	29	10
Monkey B	1 µl	3340 (±201)	1596* (±386)	3	386	1767	2016	1915	2269	2815
% reduction				100	88	47	40	43	32	16
Monkey C	3 µl	4239 (±313)	773* (±270)	0	3	364	856	1087	1108	1996
% reduction				100	100	91	80	74	74	53

*t=3.8–8.4, P<0.007–0.001 on t-testing (comparing 7 days pre-operative with 7 days post-operative)

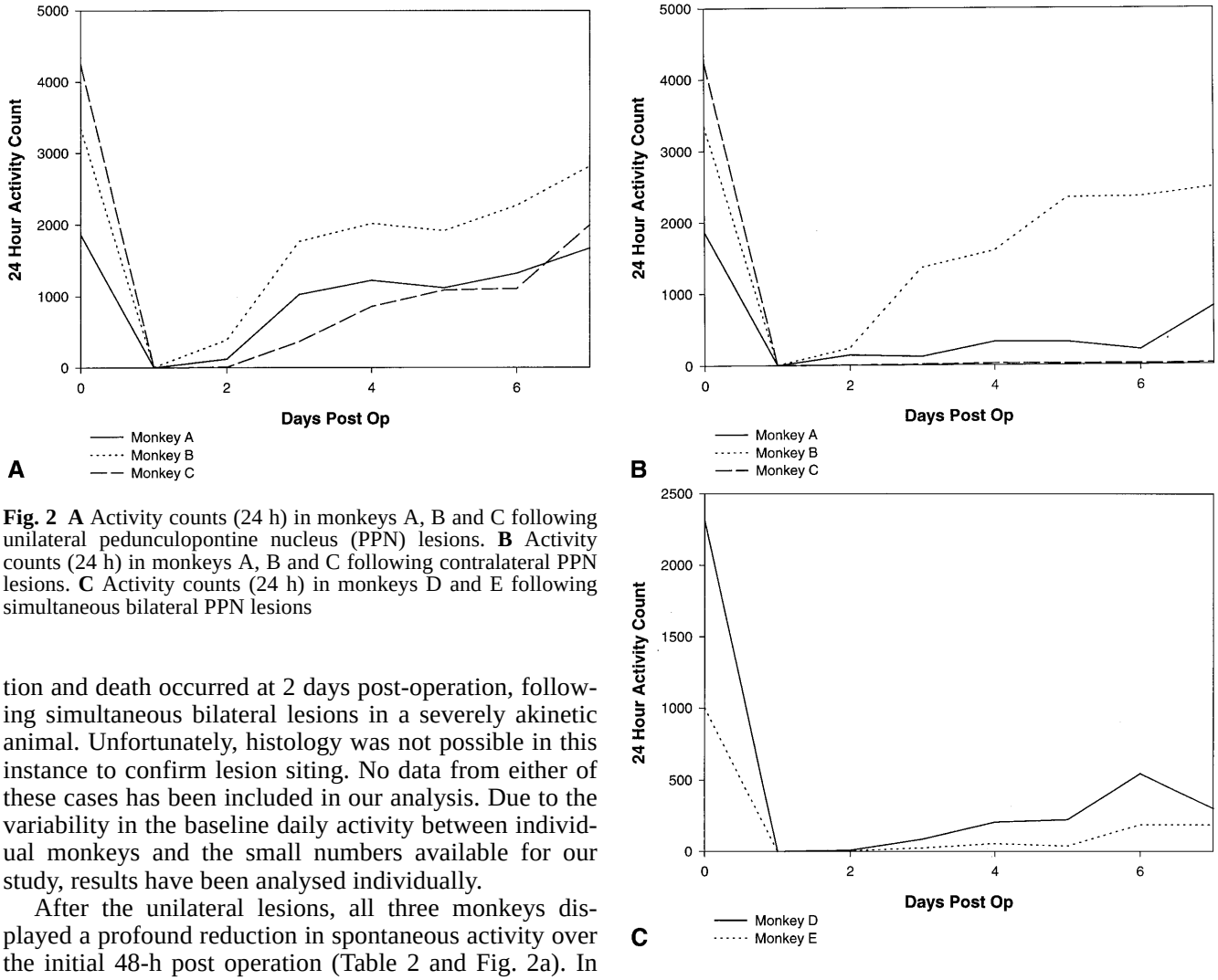

Fig. 2 **A** Activity counts (24 h) in monkeys A, B and C following unilateral pedunculopontine nucleus (PPN) lesions. **B** Activity counts (24 h) in monkeys A, B and C following contralateral PPN lesions. **C** Activity counts (24 h) in monkeys D and E following simultaneous bilateral PPN lesions

tion and death occurred at 2 days post-operation, following simultaneous bilateral lesions in a severely akinetic animal. Unfortunately, histology was not possible in this instance to confirm lesion siting. No data from either of these cases has been included in our analysis. Due to the variability in the baseline daily activity between individual monkeys and the small numbers available for our study, results have been analysed individually.

After the unilateral lesions, all three monkeys displayed a profound reduction in spontaneous activity over the initial 48-h post operation (Table 2 and Fig. 2a). In the subsequent five days, an increase in spontaneous activity was seen, although at 7 days post operation, there remained a reduction in spontaneous activity from that recorded pre-operatively in all cases. In monkeys A and B, where the volume of 0.1% kainic acid used to create the lesion was 1 µl, activity levels were reduced by 10 and 16%, respectively, by 7 days post-operation. Comparing the animals activity averaged over the 7 days after surgery with that before, the reduction was statisti-

Table 3 Clarke rating scores pre- and post-operative

	Pre-operative	Post unilateral lesion	Post bilateral lesion
Monkey A	0	2	6
Monkey B	0	1	3
Monkey C	0	5	10
Monkey D	0		2
Monkey E	0		5

Table 4 Activity counts (24 h) following contralateral pedunculopontine nucleus (PPN) lesions in monkeys A,B and C

	Volume of lesioning kainate	Mean 24-h activity count pre-operative (±SE)	Mean 24-h activity count post-operative (±SE)	Post-operative day						
				1	2	3	4	5	6	7
Monkey A	1 µl	1859	276* (±100)	0	143	120	323	319	211	814
% reduction				100	92	93	83	83	89	56
Monkey B	1 µl	3340	1484* (±389)	2	240	1361	1599	2342	2355	2487
% reduction				100	93	59	52	30	29	26
Monkey C	3 µl	4239	13* (±3)	0	3	10	24	18	16	21
% reduction				100	100	100	100	99.5	99.5	99.5

*t=4.2–13.6, P<0.001–0.0001 on t-testing (comparing 7 days pre-operative with 7 days post operative)

Table 5 Activity counts (24 h) following simultaneous bilateral pedunculopontine nucleus (PPN) lesions in monkeys D and E

	Volume of lesioning kainate	Mean 24-h activity count pre-operative (±SE)	Mean 24-h activity count post-operative (±SE)	Post-operative day						
				1	2	3	4	5	6	7
Monkey D	1 µl	2314	191 (±72)	0	8	86	205	222	544	300
Reduction in activity			100	100	96		91	90		76
Monkey E	1 µl	1001	70* (±31)	0	3	24	54	37	186	185
Reduction in activity			100		100	98	95	96	91	

*t=10.9–18.7, P<0.000 on t-testing (comparing 7 days pre-operative with 7 days post-operative)

cally highly significant in both animals (t=3.8 and 4.0, respectively). In the case of monkey C, where the volume of 0.1% kainic acid used to create a lesion was 3 µl, the reduction in recorded activity remained reduced by 53% at 7 days post-operation. This too represented a highly significant reduction in activity over the week following surgery (t=8.4, P<0.000). At all times, movements remained well co-ordinated, though bradykinetic as compared with observed speed of movement pre-operatively, with no signs of cerebellar ataxia or intention tremor, and reflex movements, such as withdrawal from a noxious stimulus, remained brisk and seemingly unaffected. On assessment on the Clarke Parkinsonism scale for primates, all animals displayed an increase in their scores from their pre-operative "normal" scores of zero (Table 3).

After a further contralateral lesion was performed in monkeys A, B and C, there was a further decrease in the level of spontaneous activity, as recorded by the Doppler meter (Table 4 and Fig. 2b). Once again, this decrease was most marked in monkey C (99.5% reduction in activity at 7 days postoperation), in which a 3-µl volume of kainate was injected. As was the case following unilateral lesions, co-ordination of movements and speed of withdrawal reflexes remained intact. Also, no clinical evidence of cerebellar dysfunction was observed in these animals at this time. A further increase in their Clarke's rating was seen in all monkeys (Table 3).

In monkeys D and E, simultaneous bilateral lesions were performed using l µl of 0.1% kainic acid to form each lesion. In both cases, a marked reduction in spontaneous activity was observed, which persisted at an extremely high level of impairment over the course of the postoperative week. Monkey D showed an 87% reduction in spontaneous activity at 7 days post-operation, whilst in monkey E activity was reduced by 91% at the same post-operative time (Table 5 and Fig. 2c). These results were also highly statistically significant (t=10.9 and 18.7, P<0.0001, respectively). Once again, these animals exhibited no incoordination, tremor or lack of arousal, and they also showed an increase in the Clarke rating (Table 3).

A further observation made post operatively, and confirmed on review of the videotapes of all animals, was a reduction in facial expressiveness following bilateral lesions, with an absence of "threat" behaviour, such as teeth baring with head propulsion, as seen frequently in the normal primate.

Histology was performed on monkeys A,B,C,D and E, as described above. In all five cases, small well-sited areas of focal necrosis were revealed in or around the region of the PPN at the lower margin of a fine needle tract demonstrated with cresyl-violet staining (Fig. 3). These lesions almost certainly represent the ablation of an area including a proportion of the PPN neuronal population, having a volume of approximately 1–3 mm^3, the larger volume lesion being associated with the larger injection

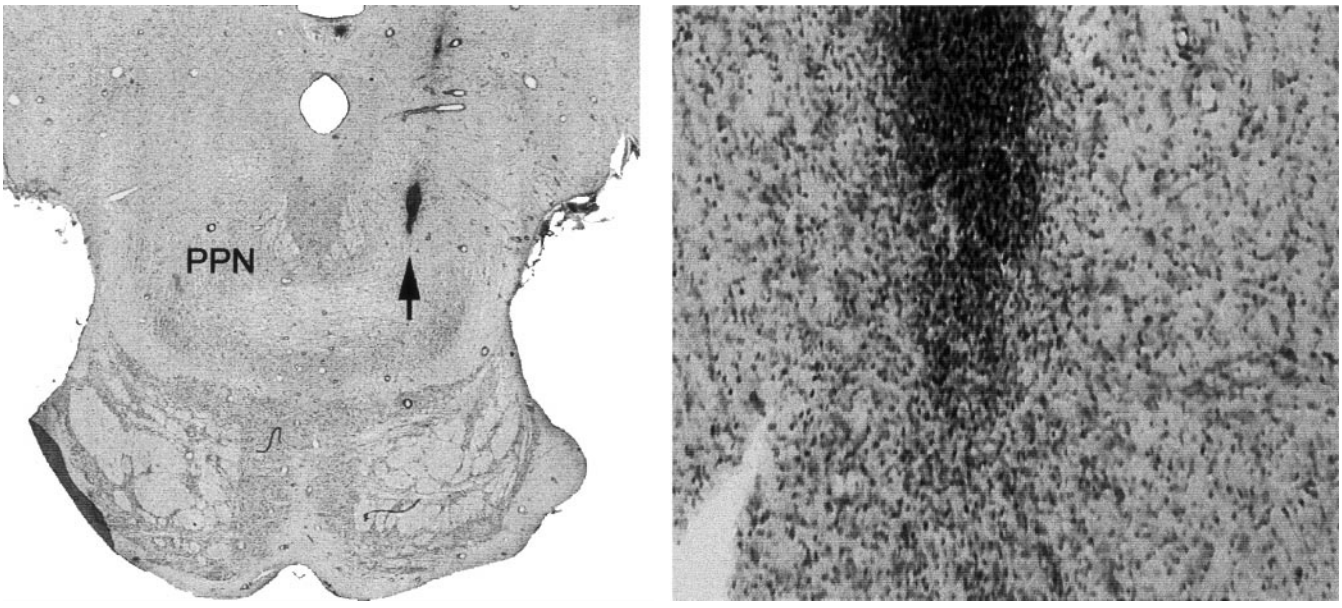

Fig. 3 Histological section illustrating a lesion in the left pedunculopontine nucleus (PPN) region. The *arrow* indicates the lesioned area of gliosis at the distal end of the visible needle tract. Adjacent photomicrograph of gliosis (×135). Right PPN region as labelled

volume in monkey C. The red nucleus, surrounding the mesencephalic locomotor region and fibres of the superior cerebellar peduncle, remained intact in all cases.

Discussion

Interest in the role of the PPN in the circuitry of movement control, and hence in akinetic states, has been fuelled by a number of findings over recent years:

1. The PPN receives dense projections from GPm and, in turn, projects to the pontine and medullary reticulospinal systems (Jackson and Crossman 1983), in addition to its abundant ascending projections.
2. In rats, PPN stimulation produces locomotor activity, whilst inactivation by GABA agonists decreases activity (Brudzynski et al. 1986; Garcia-Rill et al. 1987; Milner and Mogenson 1988; Mogenson and Wu 1988).
3. There is regeneration of the PPN in Parkinson's disease and in the akinetic syndrome of supranuclear palsy (Zweig et al. 1985; Hirsch et al. 1987; Jellinger 1988; Zweig et al. 1989; Malessa et al. 1991).
4. The administration of MPTP in primates has been shown to result in the accumulation of radiolabelled 2-deoxyglucose in the PPN, possibly as a result of increased pallidal outflow in the absence of dopamine inhibition of the striatum (Mitchell et al. 1989).
5. Unilateral radiofrequency lesions of the PPN in normal primates cause temporary akinesia, whereas bilateral radiofrequency lesions of the PPN cause a sustained akinesia (Aziz and Stein 1997).
6. Unilateral excitotoxic lesions of the PPN produce contralateral bradykinesia (Kojima et al. 1997).

These findings led us to perform bilateral excitotoxic lesions of the PPN region in order to confirm that selectively destroying neurones there, rather than axons of passage, causes akinesia. Also, the work of Kojima et al. (1997), although describing a contralateral effect with large unilateral lesions of PPN, had not examined the effects of bilateral lesions within this region.

It is clear that our lesions resulted in a reduction in both the speed and quantity of the animal's spontaneous movements. In the case of 1 µl unilateral lesions, however, recovery to within 10–16% of normal activity was seen over the course of 7 days. Even with a larger 3 µl unilateral lesion, recovery occurred to almost 50% of normal within 1 week. This is most likely because the ascending and descending projections from each PPN to the basal ganglia and pontomedullary reticulospinal systems are bilateral. Hence, the intact side could take over during the recovery period. In the case of bilateral lesions, the animals' activity remained significantly depressed at the end of 1 week post-operation, with activity levels remaining most markedly reduced following simultaneous, smaller lesions or staged larger lesions. This recovery after bilateral lesions, though prolonged, may well have resulted from the fact that the lesions were extremely small, even in relation to the structure targeted, thus allowing undamaged neurones to take over on both sides after a sufficient recovery period. This hypothesis is supported by our finding that the most marked effect of all was seen subsequent to staged larger lesions and that permanent contralateral effects have been demonstrated in unilaterally lesioned animals where the lesions made were five times greater than those in our series (Kojima et al. 1997). The reductions in activity we have demonstrated, therefore, support the hypothesis that Parkinson's bradykinesia results from over-inhibition of the PPN by an overactive GPm.

Further elucidation of the mechanisms underlying akinesia has clinical implications beyond the therapy of

Parkinson's Disease alone, as does a fuller understanding of the widely ramifying efferent connections of the PPN. Also, our proposed role for the PPN in movement control would provide a possible explanation for the variation seen in clinical outcome following pallidotomy in Parkinsonian patients. The patients who demonstrate a lesser improvement in their symptoms (bradykinesia, dyskinesia, tremor) after medial pallidotomy may have a more severe degree of regeneration of the PPN and, therefore, less ability to recover following the release from over-inhibition of this structure that is afforded by medial pallidotomy. Should it be definitively shown that these brainstem mechanism are central to the generation of akinesia, then the therapeutic possibilities of brainstem stimulators or cellular implantation in these regions should also be considered.

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