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Bladder hyperreflexia induced in marmosets by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

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In marmosets, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes degeneration of the cell bodies of the substantia nigra and the animals subsequently develop parkinsonian symptoms. Cystometrograms obtained from such animals while under pentobarbitone anaesthesia, showed their bladders to be hyperreflexic when compared to those of normal animals of the same age (less than 2 years). Bladder hyperreflexia is present in many parkinsonian patients and is difficult to treat, partly because it is made worse by dopaminergic agents. This is the first demonstration of an effect of MPTP on this type of peripheral function. It suggests the suitability of MPTP-treated marmosets for studying the mechanisms by which a loss of nigrostriatal dopamine leads to bladder hyperreflexia and for devising pharmacological strategies which may be of therapeutic value in the clinic.

Parkinson's disease is a neurodegenerative disorder characterized primarily by slowed voluntary movements, tremor and rigidity. Another symptom of the disease is hyperreflexia of the bladder. This symptom, although less publicized than the motor disturbances, is present in many parkinsonian patients and results in urgency and frequency of micturition [1, 6]. The hyperreflexia cannot be attributed entirely to impaired activity of the striated external urethral sphincter or, in male patients, to prostatic obstruction [1]. A likely causal mechanism is therefore loss of an inhibitory influence of the basal ganglia over the excitatory parasympathetic input to the bladder which originates in the pontine region of the brainstem. In patients, destruction of the outflow pathways from the basal ganglia by thalamotomy or pallidotomy increased the severity of the hyperreflexia [5, 7]. Electrical stimulation of the globus pallidus in immobilized cats, strongly suppressed spontaneous bladder activity, an

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effect obtained more powerfully from mesencephalic structures functionally related to the extrapyramidal system, e.g. areas in and around nucleus ruber, subthalamus and substantia nigra [4].

In primates, systemic administration of the neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) causes a selective loss of dopaminergic neurones in the substantia nigra [3]. This neuronal loss is accompanied by the classical motor features of Parkinson's disease, akinesia, rigidity and postural abnormalities. The purpose of this study was to see whether MPTP administered to a non-human primate, the common marmoset, produced bladder hyperreflexia and if so, whether this could be used as a model of the condition in order to devise means of controlling the bladder dysfunction in parkinsonian patients.

Adult common marmosets (*Callithrix jacchus*) of either sex and less than 2 years old (300–450 g) were given MPTP, 1–4 mg/kg i.p. daily for up to 5 days. When the experiments were performed approximately 3 months later, the severity of the induced symptoms had lessened but the animal movements were obviously parkinsonian. Bladder function was assessed under sodium pentobarbitone anaesthesia (36 mg/kg i.m.) and the results compared with those obtained in 3 age-matched control marmosets. The bladder was first exposed via a midline abdominal incision and the urethra ligated. A catheter (0.6 mm i.d.) was introduced into the dome of the bladder and secured with a purse-string suture. Bladder cystometrograms were then obtained by infusing 0.9% saline into the emptied bladder at a rate of approximately 0.1 ml/min to a maximum volume of between 1.5 and 2 ml. Intravesical pressure changes were recorded with a transducer connected to the catheter via a T-piece. Consecutive cystometrograms were made at intervals of not less than 30 min. At the end of each experiment, the marmoset was killed by an anaesthetic overdose and the brain removed for histological examination.

When empty, the bladders of the control marmosets showed no spontaneous activity as evidenced by an absence of intravesical pressure changes (Fig. 1). Upon infusing saline into the bladder, intravesical pressure rose slowly and after an interval, small spontaneous rises in pressure appeared. The amplitude and frequency of these contractions increased slightly as filling proceeded. In contrast, the bladders of the MPTP-treated marmosets exhibited spontaneous contractions when empty or immediately after commencing bladder filling (Fig. 2). Thereafter, the contractions were continually present and these were typically of greater amplitude than those seen in the control animals. Their frequency was approximately 2–4 contractions/min on which were superimposed smaller and more rapid contractions. At no time, did infusion of saline into the bladder elicit contractions which would have been sufficiently powerful and sustained to cause bladder emptying; in two experiments in which the urethra was not ligated (not shown), saline began to dribble from the urethra before the infusion was complete.

The results demonstrate that bladders of anaesthetized marmosets in which degeneration of the dopaminergic nigrostriatal pathway had been produced by administration of MPTP were hyperreflexic, when compared to bladders from control animals of the same age. Because the excitatory input to the bladder is mediated by the para-

sympathetic nervous system, the onset of hyperreflexia may be explained by the lesion disrupting an inhibitory influence of the basal ganglia on the parasympathetic outflow to the bladder. Experiments are now in progress to determine whether the hyperreflexia is maintained by a continuation of this parasympathetic drive or whether the raised parasympathetic tone gradually induces changes in the state of the bladder wall which alone, eventually become sufficient to maintain the hyperreflexia. MPTP has also been reported to deplete noradrenaline from peripheral sympathetically innervated structures of rats and mice [2]. This is unlikely to be responsible for the hyperreflexia seen in MPTP-treated marmosets because depletion of peripheral noradrenaline stores was temporary, recovery occurring within one week [2], and the inhibitory sympathetic input to the bladder, via the hypogastric nerves, is

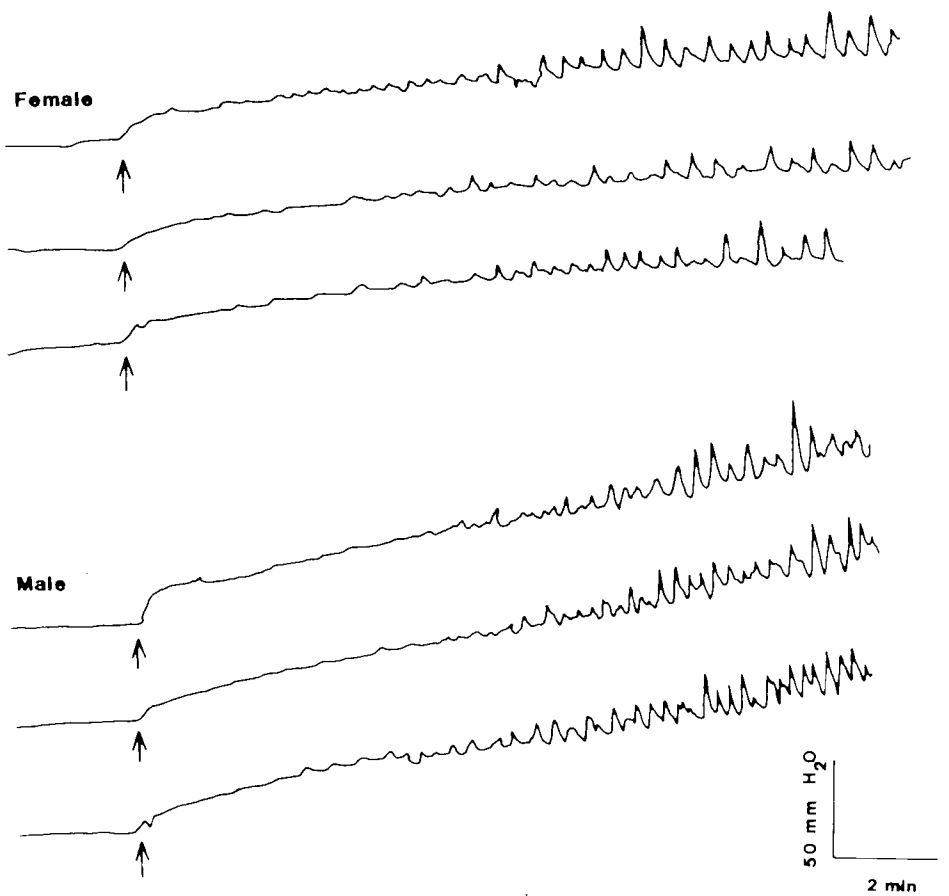

Fig. 1. Intravesical pressure responses of anaesthetized male and female marmosets during constant infusion of saline into the bladder. Bladder filling (0.1 ml/min) commenced at the arrow and continued for the duration of the trace. Three consecutive cystometrograms are shown for each animal. The empty bladder was quiescent and rises in bladder contractions did not occur until after the bladder was partly filled.

thought to be relatively unimportant (see ref. 8 for discussion). This is the first occasion that an autonomically innervated structure has been shown to be affected by an MPTP-induced nigrostriatal lesion and it remains possible that other organs and glands with a parasympathetic innervation may also be affected.

Although the results were obtained in anaesthetized animals after acute surgical intervention, they support the suggestion of Fitzmaurice at al. [1] that bladder hyperreflexia in parkinsonian patients is caused by loss of dopaminergic inhibitory activity from the nigrostriatal system. The MPTP-treated marmoset would therefore appear to provide a model of the clinical condition. This will be of considerable value because hyperreflexia is difficult to treat in patients with Parkinson's disease partly because unlike the motor and postural abnormalities, it is worsened by L-DOPA therapy. We have preliminary evidence that MPTP-induced hyperreflexia is also aggravated by dopaminergic agonists.

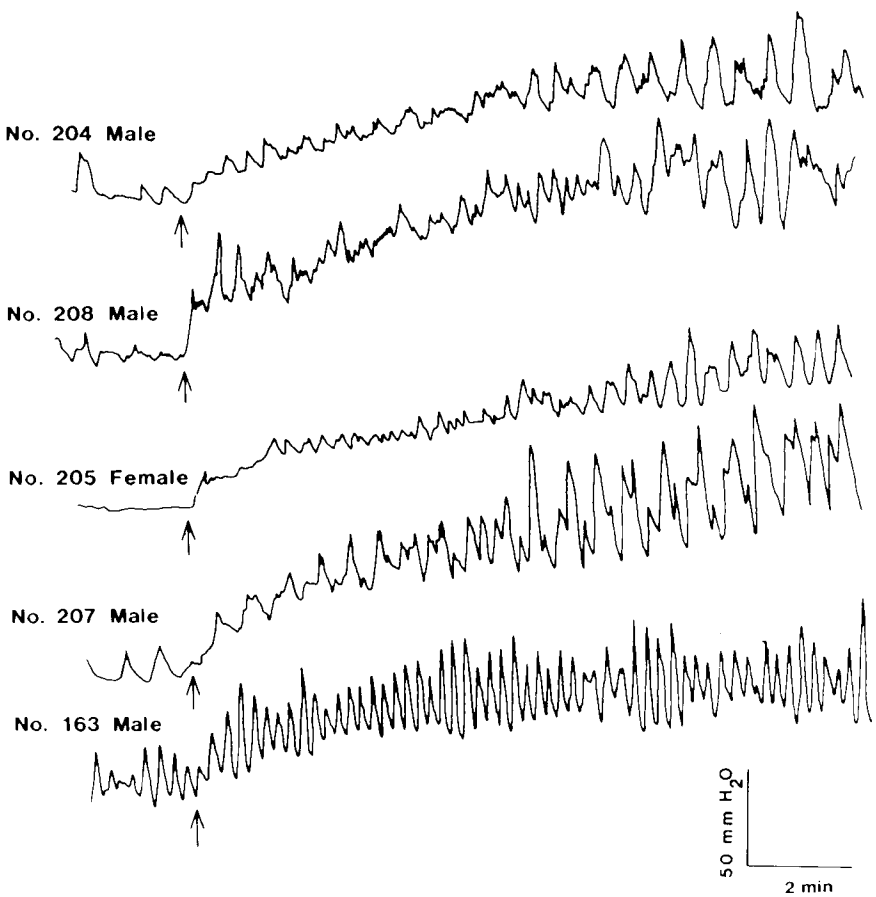

Fig. 2. Cystometrograms from 5 marmosets treated approximately 3 months previously with MPTP. Note the presence of spontaneous rises in intravesical pressure in the empty bladder and throughout filling.

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