Noradrenaline, adrenaline and tyrosine hydroxylase in adrenal medulla from Parkinsonian patients

Sir: Recent experimental1 2 and clinical3 4 studies have suggested that autografting of tissue from adrenal medulla into the striatum may improve symptoms resulting from nigro-striatal dopamine degeneration. Parkinson's disease is associated with a severe dopaminergic and noradrenergic deficiency in the brain.5 Whether the disease affects central dopamine or noradrenaline levels, or peripheral levels as well, in particular those of the adrenal medulla, has not been reported and is of interest with regard to the usefulness of autografts in patients.3 4

Nine adrenal glands from subjects with no evidence of endocrinological, psychiatric or neurological disease (mean age: 75.3, SEM 1-9 years; post-mortem delay: 18-2, SEM 2.9 hours (range: 6-530)) and 12 adrenal glands from patients with Parkinson's disease (mean age: 73-9, SEM 3 years; post-mortem delay: 20-6, SEM 1-7 hours (range: 10-29)) were examined. The adrenal glands were stored at −70°C until adrenal medulla was dissected free from the cortex at −15°C, under a dissecting microscope. The whole tissue from each adrenal medulla was crushed into powder on dry ice, and biochemical assays were performed on an aliquot of the structure. Noradrenaline, adrenaline and dopamine were assayed by high performance liquid chromatography with electrochemical detection. The dopamine values are not mentioned as they were too low (in the order of 1 ng per mg tissue) and not reproducible. Tyrosine hydroxylase activity was assayed according to Puymirat et al.6 The catecholamine content in adrenals from control subjects was in good agreement with studies in monkey8 (table). Adrenaline concentrations were four times higher than those of noradrenaline. In adrenal glands from patients with Parkinson's disease, the levels of noradrenaline, adrenaline and tyrosine hydroxylase activity were slightly but not significantly decreased compared with control values (table). These observations contrast with the previously reported deficiency in tyrosine-hydroxylase,6 and suggest that the catecholaminergic systems in the adrenal medulla (unlike those in the brain) are not markedly affected in the disease. Thus the histopathological changes observed in adrenals in cases of Parkinson's disease8 may not be associated with a massive catecholaminergic degeneration. In monkey, the Parkinsonian syndrome induced by the administration of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is not associated with a deficiency in adrenal gland catecholamine content6 8 a difference from the central effects of the neurotoxin. Therefore, brain catecholaminergic neurons seem to have a specific vulnerability. The present data: (1) emphasise that adrenal autografts in the striatum of patients have the biochemical capacity to substitute a catecholaminergic activity; (2) suggest that the targets of the pathogenic process in Parkinson's disease are mostly restricted to catecholaminergic neurons in the central nervous system; (3) are compatible with an efficiency of adrenal medulla autografts in patients with Parkinson's disease. The mechanism by which these autografts provide a clinical improvement remains unknown: tyrosine hydroxylase might restore dopamine neurotransmission; implanted cells may reinnervate the host striatum; grafted cells might induce some recovery of dopamine neurons.1 11

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References

Table Noradrenaline, adrenaline and tyrosine hydroxylase levels in adrenal medullas from Parkinsonian patients

<table>
<thead>
<tr>
<th>Control (n = 9)</th>
<th>Parkinson (n = 12)</th>
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<tbody>
<tr>
<td>Noradrenaline</td>
<td>194, 43</td>
</tr>
<tr>
<td>Adrenaline</td>
<td>866, 144</td>
</tr>
<tr>
<td>Tyrosine hydroxylase</td>
<td>71-3, 16-3</td>
</tr>
</tbody>
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Values are expressed in ng/mg tissue for catecholamines and pg/h/mg tissue for tyrosine hydroxylase activity.

n = number of adrenal glands. Data are the mean, SEM.
nerves are usually abnormal by the time spinal cord disease is apparent.\textsuperscript{2,3} However, Victor\textsuperscript{4} stated that the spinal cord initially is affected. A detailed neuropathological study of 41 patients with pernicious anaemia\textsuperscript{1} suggested that the peripheral nerves are rarely involved in early disease and that the earliest neuropathological evidence of Vitamin B12 deficiency is ballooning of large axons in the dorsal columns of the low cervical cord (spongiiform change). At this stage a thin rim of myelin could be seen around the ballooned axons though there soon followed evidence of demyelination.

Neuropsychological evidence, however, has shown that sub-clinical peripheral nerve involvement is common in patients with Vitamin B12 deficiency. Gilliatt \textit{et al}\textsuperscript{5} showed that antidromic lateral popliteal nerve action potentials were reduced at the knee in three out of four patients with pernicious anaemia and Cox-Klazinga and Endtz\textsuperscript{6} showed that distal conduction velocities to extensor digitorum brevis were reduced in 13 out of 20 such patients. Shorvon \textit{et al}\textsuperscript{7} stated that of 50 patients with pernicious anaemia, the eight who had signs or symptoms of spinal cord disease had all abnormal peripheral nerves on electrophysiologic testing. Fine and Hallett\textsuperscript{8} reported the details of peripheral and central nerve conduction in two elderly (age range 73–77 years) and one younger schizophrenic patient with pernicious anaemia; all were seen within 4 months of the onset of their symptoms. The two elderly patients had absent sural nerve action potentials but they were relatively normal in the third. The somatosensory evoked potentials (SSEPs) were delayed in all three patients (N20 latencies, 22–23 ms) and despite poor sural nerve sensory action potentials, two of the cases had normal Erb’s point potentials (N9 latencies, 10–11 ms). They argued that the dorsal columns of the spinal cord were more sensitive to Vitamin B12 deficiency than the peripheral nerves. We present the case of a 72 year old spinstor with pernicious anaemia whose neurological symptoms came on rapidly. Electrophysiologic testing showed normal peripheral nerve conduction but delayed SSEPs. Some improvement was seen after 9 months’ Vitamin B12 therapy.

She presented with a 2 month history of breathlessness and was found to have an abdominal mass and to be anaemic. At laparotomy under halothane/nitrous oxide anaesthesia a leiomyoma of the uterus was removed. Before operation she had a haemoglobin of 7.5 g/dl with an MCV of 125fl, oval macrocytosis and hypersegmented neutrophils. On discharge 3 weeks later she lacked motivation and was unsteady on her feet. Over the course of the next few weeks her unsteadiness increased. She woke one morning 8 weeks after the operation and noticed a tingling/numb sensation, as of sand-paper, in the tips of all the fingers of both hands. This spread to involve the palms over the next few days and was accompanied by waves of tingling spreading up her legs from her feet. Over the course of the ensuing fortnight her hands gradually became weaker, increasingly clumsy and she started to drop things. She was readmitted and examination revealed mild pallor, no glossitis, normal visual acuity, normal optic discs and normal eye movements. She was unable to stand unaided and had finger-nose and heel-shin ataxia. There was a downward drift of the outstretched left arm and athe- toid movements of the fingers of both hands. Voluntary effort was ill-sustained and tone was flaccid. The knee jerks were pathologically increased while tendon reflexes in the arms and at the ankles were present and showed pathological spread. The plantar responses were flexor. Joint position sense was absent at the elbows and ankles but was preserved for gross movements at the knees. Pin-prick sensation was decreased in a glove and stocking distribution. Her haemoglobin was 12.4 g/dl, MCV 112fl and the serum Vitamin B12 33 ng/l with normal whole blood and red cell folate levels. She had intrinsic factor antibody and there was inadequate uptake of orally administered Vitamin B12 during a Schilling test. She was treated with parenteral Vitamin B12 and made a partial recovery over the course of 9 months. During her 2 month stay in hospital she became less lethargic and her dysaesthesiae subsided. Hand function remained impaired and she needed feeding until just prior to discharge. At 4 months she could walk unaided but still required large handled eating utensils. At 9 months she could walk quite well, could manage large buttons and could use normal eating utensils; it was still necessary, however, to cut up her food.

Electrophysiological assessment was performed 6 weeks after the onset of symptoms and after 9 months’ treatment. Peripheral nerve action potentials were normal before and did not change after treatment. Supramaximal square wave pulses of 0.2 ms were delivered to the sural nerves (lower-calf), and the median and ulnar nerves (at the wrist) by a Medelec Myster MS 20. Action potentials were recorded with skin temperatures in the range 30–32°C using surface electrodes over the respective nerves at the ankle and at the elbow. Pretreatment sural
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