of everyone in health and social care to be aware of all the problems and their possible solutions. The medical profession should accept that knowledge of social security benefits is part of their responsibility. (The most important of these and how to claim them are given in table II.)

Department of Health pamphlets on social security benefits should be available in all general practice and hospital waiting rooms and on hospital wards, and copies should be given to all disabled patients or their relatives. Both groups should be told how to apply for benefits by a member of the health care team, whether doctor, ward sister, health visitor, or social worker. It is the doctor's responsibility to ensure that each patient receives the medical services he requires. It should be accepted that this principle is extended to include referral for the appropriate social security allowance.

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Reference

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For Debate . . .

Parkinson's disease and Alzheimer's disease as disorders of the isodendritic core

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Abstract

Parkinson's disease and Alzheimer's disease may represent two parts of a spectrum of disease characterised by a primary loss of cells of the isodendritic core. Secondary cell loss from the striatum and cerebral cortex therefore occurs as a consequence of the loss of ascending projections from the isodendritic cells. The anatomy of this system should provide a unique opportunity for therapeutic intervention. Neurotransmitter replacement treatment may be provided either by enhancing transmitter release by any remaining neurones or by direct agonists. The wide dispersal of the isodendritic projection systems affected in Parkinson's and Alzheimer's diseases and the possibility that they are tonically active create an opportunity for neurotransmitter replacement treatment.

Animal studies should be able to show whether such treatment can delay secondary cell loss, and, together with human postmortem studies, whether the hypothesis that the primary lesion is a loss of isodendritic cells is correct.

Introduction

Biochemical analyses of postmortem brain tissue have yielded valuable information on the pathophysiology of several neurological and psychiatric disorders. In particular, the demonstration of a reduced concentration of dopamine in the corpus striatum of patients dying with Parkinson's disease[1] has led to the development of levodopa treatment. The loss of striatal dopamine is the most prominent biochemical abnormality in Parkinson's disease, but there is also a loss of subcortical noradrenaline.[2] The losses of dopamine and noradrenaline accord well with the histological observations of losses of brainstem pigmented neurones.[3] Areas of loss include not only the substantia nigra (the origin of the dopamine nigrostriatal pathway) but also the locus coeruleus (the origin of the noradrenergic innervation of the forebrain).

Several studies have shown deficits in specific neurotransmitters in Alzheimer's disease. The most prominent abnormality is the reduction in the activity of choline acetyltransferase, the biosynthetic enzyme for acetylcholine, in the cerebral cortex.[4-7] Since the cerebral cortex contains few, if any, intrinsic cholinergic neurones,[8] this loss of choline acetyltransferase activity reflects a loss or dysfunction of ascending cholinergic projections.[7 9] The origin of the hippocampal projection lies in the septum, and the origin of most of the cholinergic projections to the neocortex seems to be within the substantia innominata.[8] As well as the reduction in cortical choline acetyltransferase activity there is also a loss of cortical and subcortical noradrenaline[10] and of cortical dopamine-β-hydroxylase activity.[11] These observations seem to provide the biochemical correlate of the observed loss of cells from the locus coeruleus in Alzheimer's disease.[12-14]

Loss of ascending projections

These biochemical studies point to a similarity between Parkinson's disease and Alzheimer's disease in that they both show a loss of ascending projections. This loss predominantly affects the dopaminergic striatal projection in Parkinson's disease and the cholinergic cortical projection in Alzheimer's disease, but both diseases also show a loss of the noradrenergic projection from the locus coeruleus. This similarity is further

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emphasised by the fact that the cells of the locus coeruleus, substantia nigra, substantia innominata, and septal nuclei all share a non-specialised, isodendritic pattern.[15 16] Golgi staining shows a characteristic generalised dendritic pattern of extensive intermingling with other axons and dendrites, and these cells can be considered as forming a continuous isodendritic core extending from the spinal cord to the basal forebrain.[15] The similarity between the histological appearance of the isodendritic core and the relatively disorganised nervous system of the lower vertebrates has led to the suggestion that the core may represent a phylogenetically ancient pool of relatively undifferentiated cells.[15] The isodendritic core probably subsumes the cells that correspond to the reticular formation.[17]

If Parkinson's and Alzheimer's diseases are seen as disorders of the isodendritic core the primary condition would be a loss or dysfunction of the isodendritic cells. The losses of other cell groups outside the isodendritic core may therefore be secondary phenomena, due to trans-synaptic degeneration after the loss of the ascending inputs. There is evidence that cells are lost within the terminal fields of the projection systems affected in Parkinson's disease and Alzheimer's disease. Thus striatal cells may be lost in Parkinson's disease,[18 19] and this may be an important reason why treatment fails.[20] The claim that generalised neocortical cell counts are reduced in patients with Alzheimer's disease when compared with age-matched controls[21] has not been confirmed in some studies.[22 23] Biochemical studies of intrinsic cortical neuropeptides report normal concentrations of vasoactive intestinal polypeptide[7] and of cholecystokinin,[24] with a reduced concentration of somatostatin.[25 26] Thus any loss of cortical cells in Alzheimer's disease would appear to be selective. Senile plaques and neurofibrillary tangles, characteristic of Alzheimer's disease, are also reported in many cases of Parkinson's disease[27 28]; similarly, Lewy bodies, characteristic of Parkinson's disease, have been reported in Alzheimer's disease.[29] Nevertheless, senile plaques, neurofibrillary tangles, and Lewy bodies may be found in otherwise normal elderly people,[27 30 31] so they may reflect non-specific patterns of response to a variety of insults. The senile plaque and neurofibrillary tangle formation in the cortex in Alzheimer's disease might thus be seen as a secondary response to the loss of ascending inputs.

Clinical consequences of loss of isodendritic cells

Although Parkinson's and Alzheimer's diseases may represent different parts of a spectrum of isodendritic cell loss, in their classic forms this cell loss will predominantly affect either the substantia nigra or the substantia innominata and septal nuclei. Clinically, therefore, they are characterised by dysfunction of the respective terminal fields. But they both share a loss of cells from the locus coeruleus, and as the disease progresses a more extensive loss of isodendritic cells might be expected to occur, leading to an overlap of clinical features. Many patients with Alzheimer's disease show extrapyramidal rigidity and hypokinesia, particularly in the later stages of the disease,[32 33] and reduced concentrations of dopamine in the caudate nucleus have also been reported.[10 34] Several patients with Parkinson's disease also show evidence of cognitive impairment.[35] The cognitive impairment of Parkinson's disease is particularly interesting since it is similar to that seen in progressive supranuclear palsy; its pattern in these two disorders has been termed "subcortical dementia."[36 37] The relative absence of apraxias, agnosias, and dysphasias in subcortical dementia has been contrasted with the cortical dementia of Alzheimer's disease.[37] Nevertheless, since both Parkinson's disease and Alzheimer's disease share a subcortical pathology, this distinction can be seen as reflecting the dysfunction of the different terminal fields affected. In the light of the argument that cortical cell loss or dysfunction in Alzheimer's disease is secondary to the loss of the ascending projections, it is interesting that apraxias, agnosias, and dysphasias often occur later in the course of Alzheimer's disease.[33]

Predictions

The hypothesis that both Parkinson's and Alzheimer's diseases are primarily disorders of the isodendritic core generates several predictions. It implies that isodendritic cells are vulnerable to environmental injury—for example, from toxins and viruses—or have a biochemical predisposition to premature aging. In the early stages of both diseases pathological changes will be most prominent within the isodendritic core, but as the disease progresses they will become more obvious in the terminal fields. Loss of cells should be observed in other areas of the isodendritic system—for example, the reticular formation of the spinal cord, the dorsal vagal nucleus (as occurs in Parkinson's disease[3]), the raphe nuclei, the hypothalamus, and perhaps the intralaminar and reticular nuclei of the thalamus.[16 17] There is evidence that 5-hydroxytryptamine concentrations fall in both Parkinson's disease and Alzheimer's disease, which may reflect loss of raphe cells.[34 38] Recently cell loss has been shown in the medial amygdala in Alzheimer's disease, an area which also contains many isodendritic cells.[39] Postmortem biochemical changes should be confined to the isodendritic core and its projection fields. Lesions of the ascending projections in animals should cause trans-synaptic degeneration of some of the cells in the terminal fields, as occurs in the intrastriatal kainic acid model for Huntington's chorea.[40] Several of these predictions can be directly tested by postmortem and animal studies.

Therapeutic implications

The hypothesis also carries certain therapeutic implications. Attempts at replacing neurotransmitters after neuronal loss may mean either enhancing transmitter release by any remaining neurones or using direct agonists which do not depend on the existence of a residual population of neurones. The efficacy of drugs aimed at enhancing transmitter release or synaptic concentrations of released transmitter will depend on the anatomy of the remaining neurones. For example, if all the neurones projecting to a given area of brain were damaged function could not be restored to that area. Nevertheless, the cholinergic and noradrenergic projections to the cortex and, to a lesser degree, the dopaminergic projection to the striatum show considerable divergence.[41 42] Thus in the extreme example of a disperse projection, in which each neurone projects to all areas of the terminal field, replacement might theoretically be achieved with only one remaining neurone assuming an adequate functional reserve.

With direct agonists the postsynaptic effect is divorced from neuronal activity and the information derived from the spatiotemporal pattern of action potentials is therefore lost. As discussed above, spatial specificity may be less important in divergent systems. Temporal specificity would be expected to be very important in phasic systems, in which direct replacement treatment is unlikely to be beneficial and may block the neuronal transfer of information. With tonic systems, however, it may be possible to mimic to some extent the normal postsynaptic activity. The success of levodopa treatment in Parkinson's disease may, in part, depend on the fact that the dopaminergic nigrostriatal pathway is tonically active.[43 44] Moreover, the locus coeruleus also appears to be tonically active, although the frequency of firing varies throughout the sleep-wake cycle.[45] It is unknown whether tonic activity is a general feature of isodendritic cells. The wide dispersal of the isodendritic projection systems affected in Parkinson's disease and Alzheimer's disease and the possibility that they are tonically active create an opportunity for neurotransmitter replacement therapy which may be denied to disorders in which spatially specific, phasically active cells are lost. Clearly, secondary loss of cells from the terminal fields will militate against effective treatment,[20] and it remains to be seen whether replacement treatment, including any coexistent neurotransmitters, can delay secondary cell loss.

This optimism has yet to be realised, but the hypotheses should be verifiable using animal models.

The validity of this hypothesis depends on its usefulness in generating pathophysiological and therapeutic models. It remains to be seen whether the predictions support the view that the primary lesion can be related to the isodendritic core.

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Is a colour television set a hazard to a toddler who is allowed to play close to it for hours on end?

Colour television sets produce *x* rays, but with proper design there is no problem in reducing the escaping radiation to very low levels. The main source of *x* rays in a modern set is the picture tube, and the maximum accessible dose rate will usually occur at the face of the tube. International and British standards[1] exist which limit the dose rate at 5 cm from the surface of the screen under specified conditions to 0·5 mrem/h (5 μSv/h). A comprehensive survey[2] of dose rates from colour television sets was carried out about 10 years ago by the Radiological Protection Service, which now forms part of the National Radiological Protection Board. This survey showed that dose rates from colour sets that had been adjusted for normal viewing were very much lower than 0·5 mrem/h and were between 0·05 and 10 μrem/h (0·0005 and 0·1 μSv/h) close to the surface of the tube and about 50 times lower than these values at 2·5 metres. More recent measurements by the National Radiological Protection Board on a limited number of British and imported colour television sets have also shown doses to be negligible. There is therefore no radiological hazard to the toddler, who would in any case be receiving (as we all do) some hundreds of μrem (several μSv) a day from natural sources of radiation.—A KNIGHT, National Radiological Protection Board, Didcot.

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