Cytophotometric mapping of neuronal changes in senile dementia

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SUMMARY Results of a cytophotometric study have shown a widespread reduction in cytoplasmic RNA of nerve cells. It appears, therefore, that although certain aspects of the symptomatology of senile dementia may be accounted for by lesions in particular anatomical sites, the main part of the neurological disturbance is related to more broadly based changes in nerve cell metabolism affecting much, if not all, of the CNS.

Mental deterioration occurring in old age, usually termed senile dementia, is one of the most common, yet most poorly understood of neurological conditions. A great number of the early and, indeed, the recent studies (Dayan, 1970; Tomlinson et al., 1970; Colon, 1973; Gibson et al., 1976) have attempted to evaluate its pathogenesis and severity in terms of the most obvious neuropathological findings—namely, senile plaques and neurofibrillary tangles—but as yet the relevance of these features to the underlying mechanism remains uncertain.

Other studies have taken a more biochemical viewpoint. Reports by Gottfries and co-workers (1969, 1974), and Fisher (1972), have indicated a generalised disturbance of monoamine metabolism in the brains of patients suffering from senile dementia. Other reports have implied that accumulation within neurones of lipoprotein pigments may play a significant role in the disease process. Gedye et al. (1972) noted that treatment of some patients suffering from organic dementia with meclofenoxate (Lucidril) improved intellectual function; meclofenoxate has been shown (Nandy, 1968; Spoerri and Glees, 1974) to cause a reduction in lipofuscin in cerebral nerve cells in rodents.

Elsewhere, a number of observations have suggested that metallic intoxications may play a part in dementia. Crapper et al. (1973) showed that aluminium levels in brains of patients with Alzheimer's disease were about four times higher than those of normal controls. Moreover, subarachnoid injection of aluminium salts in cats induced a progressive encephalopathy characterised by neurofibrillary degeneration of nerve cells (Klatzo et al., 1965) which showed many of the clinical features of senile dementia (Crapper et al., 1973). Nikaido et al. (1972) measured increased amounts of silicon in senile plaques and tangle-bearing neurones.

Finally, genetic studies of recent years (Larsson et al., 1963) suggest that dementia is genetically determined by a dominant autosomal gene with late phenotypical penetration.

The diversity of these findings emphasises the present lack of knowledge surrounding the pathogenesis of both Alzheimer's disease and senile dementia.

A technique has been developed in this department which we believe allows both major and minor disease in nerve cell groups to be detected. This method involves measurement of a number of nuclear and cytoplasmic features, including nerve cell cytoplasmic RNA content which is an indicator of the capacity of such cells to form the proteins appropriate for neurophysiological function. We report here our findings in the aged, and in cases clinically assessed as suffering from senile dementia.

Patients and methods

Nervous tissue was obtained at necropsy from 10 patients suffering from senile dementia, and from 15 control subjects of a similar age group who were free from overt neurological illness at death.

Paraffin sections of selected blocks of tissue were cut at 16 μm and stained for cell RNA (Shea, 1970). Measurements of nerve cell RNA content were made, as detailed elsewhere (Mann and Yates, 1974; Mann et al., 1976), on various cell types including

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Purkinje cells, cells of the olivary and dentate nuclei, cells of the lateral ventral nucleus of thalamus, cells of the locus caeruleus and substantia nigra, Betz cells of the precentral gyrus, cells of the motor nucleus of III, V, VI, VII, VIII and XII cranial nerves, and pyramidal cells of all areas of the hippocampus. A minimum of 100 cells of each type was measured in every case, and the mean RNA content calculated. From these mean values of RNA, an overall mean and standard deviation were derived for the group of demented patients as a whole and similarly for the controls.

Results

Results of overall mean cell RNA content derived for each neurone group from 10 demented patients and 15 normal control subjects of similar age range are shown in the Table. The difference in overall mean cell RNA content between the demented and the control groups exceeds the 5% level of significance in all groups of neurones studied and the 0.1% level in most cases. These differences are expressed in the Table as mean percentage losses of cell RNA from neurones of the demented group.

As argued earlier (Mann and Yates, 1974), it is appropriate to use the amount of cell RNA as an index of the level of potential for function present in that cell. As shown in the Table, there are losses of cell RNA for every neuronal type measured, ranging from 7–51%, implying a corresponding reduction in their overall capacity for function.

Discussion

Changes in RNA content of nerve cells have been related to various pathological conditions. Firstly, there is transynaptic degeneration in which loss of function in a group of neurones follows destruction of those cells which make synaptic connection with it, or with which it makes such connection. This leads to reduction in cytoplasmic RNA (chromatolysis).

Secondly, there are situations of abnormal hyperactivity, such as prolonged electrical stimulation (Watson, 1968), and physical exhaustion which have been shown to result in increased production of RNA. Thus the basic level of RNA present in nerve cells at any one time may be varied in extreme conditions, according to the metabolic demands imposed by the state of functional activity.

A progressive decline in RNA in nerve cells has been shown (Mann and Yates, 1974; Mann et al. 1976) to be a feature of aging, and this is linked to the accumulation of lipoprotein pigments in the cerebral body.

The widespread loss of RNA from nerve cells, which we have shown to be a feature of senile dementia, therefore, suggests an overall decline in the level of activity of nerve cells throughout the whole of the nervous system. To what might this general decline in activity be attributed?

Gedye et al. (1972) noted that treatment with meclofenoxate of some patients suffering from senile dementia improved intellectual function, and moreover Nandy (1968) demonstrated that this compound could bring about a reduction in lipofuscin in cerebral nerve cells of experimental animals. These studies infer that lipoprotein pigments may play some part in the disease process. It may, therefore, be argued that in senile dementia, the measured RNA losses could come about because of increased levels of pigment formation. However, it has been shown (Mann and Sinclair, 1977) that there is no significant difference in mean pigment levels between a demented and a non-demented control group of patients, of similar age range, for cells of the inferior olivary nucleus and pyramidal cells of the hippocampus. Both groups of patients show pigment accumulation appropriate to their age. Therefore, despite the observations of Nandy (1968), and Spoerri and Glees (1974), that meclofenoxate beneficially reduces lipofuscin levels in nerve cells, it seems unlikely that pigment removal, per se, has any bearing on the im-
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The relationship of these lesions in the hippocampus to dementia is not clear. It is known that patients suffering from senile dementia show severe memory defects, especially for recent events and for the assimilation of fresh information (Kral, 1972; Miller, 1973), while long-term recall is relatively unaffected. Furthermore, non-demented patients who have displayed serious memory disturbances typical of senile dementia have, at necropsy, shown severe loss of pyramidal cells of the hippocampus (Victor et al., 1961). Thus, it is possible that these lesions in the hippocampus may account for the memory defects associated with senile dementia, but the main body of neurological disturbances are probably related to more broadly based changes in nerve cell function.

References


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