Journal of Neurology, Neurosurgery, and Psychiatry 1982;45:113-119

The noradrenergic system in Alzheimer and multi-infarct dementias

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SUMMARY The number of melanin containing nerve cells of the locus caeruleus and vagus nucleus is reduced in Alzheimer's disease by 60% with decrease of 22% in the protein synthetic capability of remaining cells. These changes are matched by reductions in brain noradrenaline in eight regions, averaging 36%. In multi-infarct dementia, however, all three of these features are unchanged. These findings indicate that degeneration of central noradrenergic nerve cells is a specific aspect of the pathogenic process underlying Alzheimer's disease.

Changes in cholinergic nerve cells were first reported in Alzheimer's disease in 1976,[1] with substantial losses of the enzymes choline acetyl transferase (CAT) and acetyl cholinesterase being observed. Since then, these findings have been amply confirmed in both biopsy[2 3] and necropsy[4-10] brain tissue, and the reduction in CAT activity correlated with degree of histological change and mental status of the patient.[3 11] Although these changes have been widely thought[2 4 9] to represent a selective involvement of cholinergic pathways in Alzheimer's disease, therapeutic trials[12-19] aimed at making good this deficiency have not demonstrated any consistent or long-lasting improvements in mental ability, following such treatments; this suggests that alterations in this kind of nerve cell may only be part of a more widespread degenerative process.

Recent biochemical studies[20-25] have indicated that deficiencies in the noradrenaline containing nerve cells of the CNS may occur also, in Alzheimer's disease but not in that dementia associated with cerebrovascular alterations.[21 22] Therefore, in this report, the involvement (in dementia) of noradrenergic nerve cells is morphometrically investigated, through microscopic counting of cell number, together with histometric evaluation of their capacity to produce the proteins appropriate to physiological function. The nerve cells examined are the melanin pigmented cells of the locus caeruleus and dorsal motor nucleus of the vagus nerve, on which this neurotransmitter system is principally based.

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Received 14 August 1981 and in revised form 25 September 1981
Accepted 8 October 1981

Materials and methods

Brains were obtained at necropsy from 19 patients (table 1) who, in life, showed a profound progressive dementia with no localising neurological signs. Neuropathological examination revealed numerous senile plaques and nerve cells containing neurofibrillary tangles, in cerebral cortex, hippocampus and amygdala, with no significant amount of vascular disease or ischaemic change. A diagnosis of Alzheimer's disease was made. Another eight patients (table 1), whose mental deterioration was clearly related to extensive macro-infarction and micro-infarction of cerebral cortex and basal ganglia, were classed as cases of multi-infarct dementia. Twenty-one patients, none of whom had suffered from overt neurological or psychiatric illness, and in which there were no significant histological findings other than minimal amounts of cerebral softening or Alzheimer type changes, or both, were controls (table 1).

The cause of death was broadly similar in all three groups, being generally associated with a terminal respiratory illness or cardiac insufficiency. There were no

Table 1 *Mean age, post mortem delay time, fresh brain weight and sex distribution of 21 controls, 19 cases of Alzheimer's disease and 8 of multi-infarct dementia*

Case	*n*	*Sex*		*Age (years)*	*PM delay (hours)*	*Brain weight (g)*
		F	*M*			
Control	21	15	6	85·1 ±1·1	37·8 ±4·7	1205·2 ±25·2
Alzheimer's disease	19	12	7	84·7 ±1·1	41·6 ±5·8	1149·6 ±24·7
Multi-infarct dementia	8	4	4	78·2 ±2·7	36·7 ±3·1	1196·3 ±55·4

significant differences within the groups with respect to age and sex distribution, post mortem delay time, or fresh brain weight (table 1).

From the formalin fixed tissue, blocks of brain stem were cut from the central parts of the locus caeruleus and vagus nucleus. Five paraffin sections of 20 μm thickness were prepared at 100 μm intervals and stained for RNA using Azure B.[26] Measurements of nucleolar volume were made on 40 pigmented cells of locus caeruleus and vagus nucleus, and on 40 of the non-pigmented cells of the vagus also, as described elsewhere,[27] from which mean nucleolar volume was derived. These individual values were pooled and overall mean values were calculated for Alzheimer, multi-infarct and control groups, for all three cell types. Such values give estimates of the capacity of such cells to form the proteins necessary for correct physiological function.

The numbers of nucleolated nerve cells were also counted[28] in the five Azure B stained 20 μm sections from which the mean number per 20 μm section was determined for all three cell types. This kind of sampling has been shown[28] to give quantitatively similar findings to those obtained by counting cells in every 10th section throughout the entire length of the locus.[29] In these and in adjacent 5 μm sections stained by conventional neuropathological methods, the general cytological features of the locus caeruleus and vagus nerve nucleus in age and dementia were detailed.

In seven patients (two Alzheimer, three multi-infarct and two controls) the brains were obtained after similar post mortem delay times, but all within 24 hours of death and these, prior to fixation, were sectioned down the mid-line having first removed the brain stem and cerebellum. The right half and brain stem were fixed in formalin and examined histologically whilst from the left side and cerebellum standard samples of frontal, temporal and occipital cortex, caudate nucleus, putamen, hippocampus, hypothalamus and cerebellar cortex were dissected and analysed[21] for noradrenaline concentration which was expressed as μg/gm brain tissue. Residual tissues were then fixed also for histological inspection.

Results

In the control and multi-infarct groups, the pigmented cells of the locus caeruleus were concentrated and evenly distributed (fig 1). Occasional cells showed shrinkage of the cell body with reduction in nuclear and nucleolar sizes. Final heterolysis of contents results in aggregates of the residual melanin being freely deposited in the neuropil or within macrophages (fig 2). A few cells were seen to contain Lewy type inclusion bodies and others with neurofibrillary tangles (fig 3) were noted. Macroscopic examination showed gross underpigmentation of the locus caeruleus in eight of the 19 cases of Alzheimer's disease, while in the others either a slight pallor, or no distinct change was seen. Microscopic observations showed that this pigment loss was due to loss of cells (fig 4) rather than depigmentation without change in cell number. Large amounts of extraneuronal pigment was present in macrophages. Again, occasional nerve cells showed neurofibrillary alterations, though none containing Lewy bodies were noted. There was no generalised gliosis, nor significant vascular disease, in the region of the locus, in any of the cases of Alzheimer's disease. These kinds of changes were also seen in the few remaining pigmented cells of the vagus, but no distinct alterations were observed in the non-pigmented cells of this area, in any case, demented or control.

Mean values of number of nucleolated pigmented

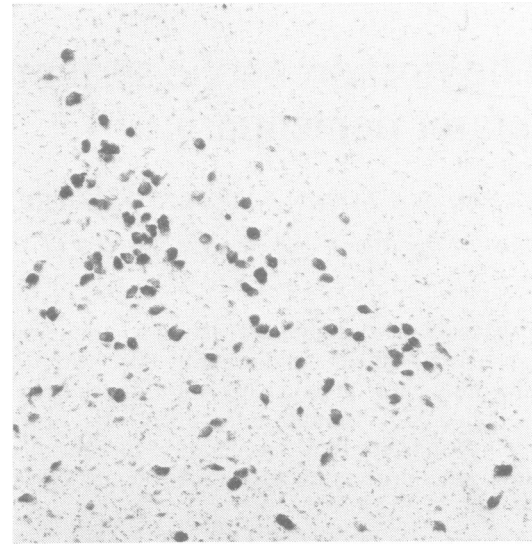

Fig 1 *Locus caeruleus in a non-demented 80-year-old subject. Azure B* $\times 57$.

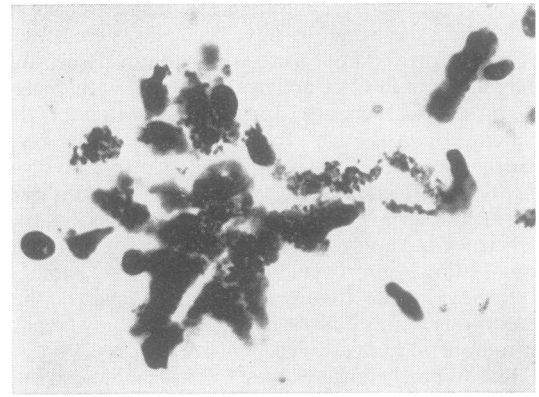

Fig 2 *Locus caeruleus in a non-demented 83-year-old subject showing removal of nerve cell melanin by macrophages. Azure B* $\times 275$.

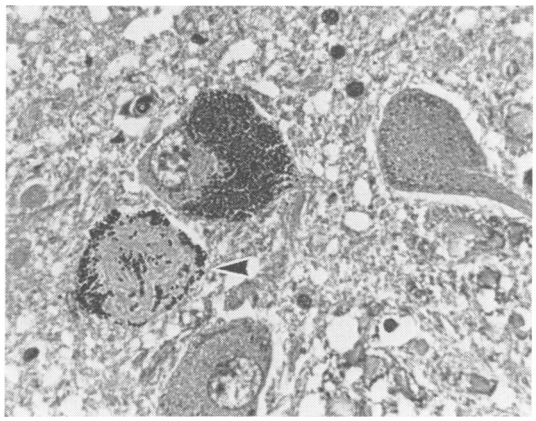

Fig 3 *Nerve cell containing neurofibrillary tangle in the locus caeruleus (arrow head) in a non demented 83-year-old subject. H and E ×310.*

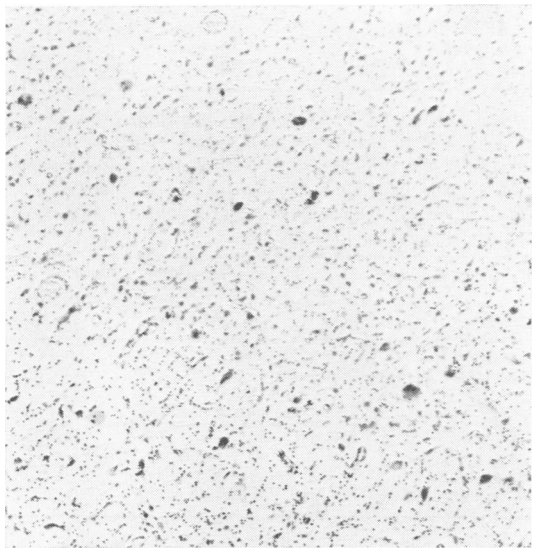

Fig 4 *Locus caeruleus in a 83-year-old subject with Alzheimer's disease showing severe depletion of nerve cells. Azure B ×64.*

nerve cells per 20 μm section in the locus caeruleus and dorsal vagus nucleus, and those of the non-pigmented cells of vagus also, are shown in fig 5, for the 19 cases of Alzheimer's disease and the 21 controls. Corresponding values for nucleolar volume are shown in fig 6. The distributions of values of cell number and nucleolar volume in the multi-infarct group are similar to those in the controls and are therefore not depicted in figs 5 and 6.

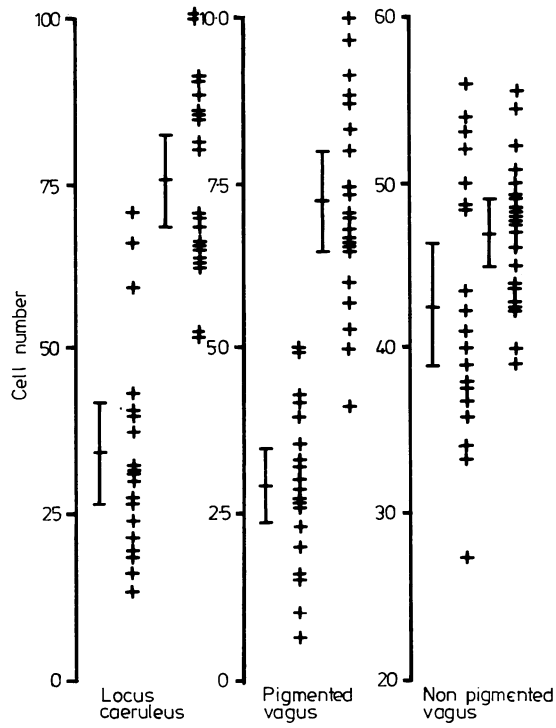

Fig 5 *Number of nucleolated nerve cells per 20 μm section, in locus caeruleus, and in pigmented and non pigmented divisions of dorsal motor nucleus of vagus nerve, in a group of 19 cases with Alzheimer's disease (A, in each instance) and in a control group of 21 subjects (C).*

Overall mean values of cell number and nucleolar volume of neurones of locus caeruleus and vagus nerve nucleus in Alzheimer, multi-infarct and control groups, are shown in table 2. In the Alzheimer's disease group the mean number of pigmented cells of the locus caeruleus is significantly reduced by 55% ($t = 8{\cdot}4$, $p < 0{\cdot}001$) and that of the dorsal motor vagus by 60% ($t = 9{\cdot}6$, $p < 0{\cdot}001$). In remaining cells of these two types, nucleolar volume is significantly reduced by 19% ($t = 6{\cdot}5$, $p < 0{\cdot}001$) and 25% ($t = 8{\cdot}1$, $p < 0{\cdot}001$) respectively. Non-pigmented cells of the vagus are, however, only diminished in number by 10% ($t = 2{\cdot}2$, $p < 0{\cdot}05$) and nucleolar volume of remaining cells, only decreased by about 11% ($t = 5{\cdot}1$, $p < 0{\cdot}001$). In the multi-infarct group neither cell number nor nucleolar volume is altered, for any of the three nerve cell types, when compared with the control group (table 2).

Values of noradrenaline concentration in the

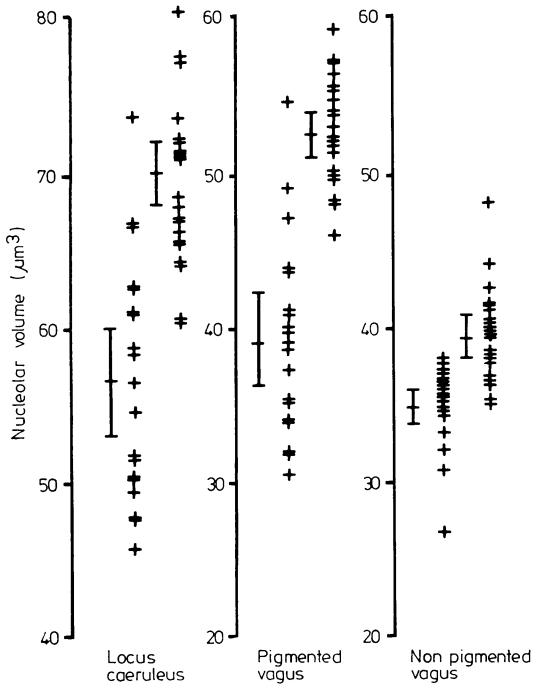

Fig 6 *As for fig 5, but showing nucleolar volume for all 3 nerve cell types in both groups.*

eight brain areas analysed were pooled by group and mean values are shown in table 3. Noradrenaline concentrations in the multi-infarct group are similar in all eight regions to those of the control group; both sets of data are therefore pooled and averaged (table 3). When values of noradrenaline concentration in the Alzheimer's disease group are compared with these overall control values, decreases are noted, in all eight areas, which range in magnitude

Table 2 *Mean (± SE) number of nucleolated neurones per 20 μm section and nucleolar volume of nerve cells of locus caeruleus and vagus nerve nucleus, in 19 cases of Alzheimer's disease, 8 of multi-infarct dementia and 21 controls. Also shown is percentage cell loss and reduction in nucleolar volume in the Alzheimer group, together with level of significance; *, † indicates p < 0·05, < 0·001 respectively*

Cell	*Mean number of nucleolated nerve cells*			*% Loss from Alzheimer group*
	Control (n = 21)	*Multi-infarct (n = 8)*	*Alzheimer (n = 19)*	
Locus caeruleus	75·8 ± 3·2	73·6 ± 5·2	34·3 ± 3·8	54·8†
Vagus (pigmented)	7·2 ± 0·3	7·5 ± 0·6	2·9 ± 0·3	59·5†
Vagus (non pigmented)	47·2 ± 1·0	48·3 ± 1·2	42·6 ± 1·8	9·6*
Cell	*Mean nucleolar volume (μm³)*			*% Loss from Alzheimer group*
	Control (n = 21)	*Multi-infarct (n = 8)*	*Alzheimer (n = 19)*	
Locus caeruleus	69·9 ± 1·0	68·4 ± 1·6	56·6 ± 1·8	19·0†
Vagus (pigmented)	52·6 ± 0·8	50·5 ± 1·7	39·3 ± 1·4	25·2†
Vagus (non pigmented)	39·4 ± 0·6	40·7 ± 2·6	34·9 ± 0·6	11·5†

Table 4 *Mean (± SE) number of nucleolated neurones per 20 μm section and nucleolar volume of pigmented nerve cells of the locus caeruleus and vagus nerve nucleus, in the 2 cases of Alzheimers disease, the 3 of multi-infarct dementia and the 2 controls, on which noradrenaline assays were also performed*

Cell	*Mean number of nucleolated nerve cells*		
	Control (n = 2)	*Multi-infarct (n = 3)*	*Alzheimer (n = 2)*
Locus caeruleus	83·0 ± 2·6	74·4 ± 2·3	34·9 ± 2·7
Vagus (pigmented)	6·6 ± 1·4	7·5 ± 0·5	4·0 ± 1·0
Cell	*Mean nucleolar volume (μm³)*		
	Control (n = 2)	*Multi-infarct (n = 3)*	*Alzheimer (n = 2)*
Locus caeruleus	71·0 ± 0·4	67·6 ± 1·1	57·4 ± 0·9
Vagus (pigmented)	51·6 ± 3·8	52·3 ± 1·3	40·8 ± 3·6

Table 3 *Mean noradrenaline concentration in 8 brain areas, as measured in 3 cases of multi-infarct dementia, 2 controls and 2 cases of Alzheimer's disease. Also shown is the percentage loss in the Alzheimer cases, compared to values of the overall control group*

Brain area	*Noradrenaline concentration (μg/gm)†*				*Percentage loss in Alzheimer group*
	Multi-infarct (n = 3)	*Control (n = 2)*	*Overall control (n = 5)*	*Alzheimer's disease (n = 2)*	
Hypothalamus	1·01 ± 0·21	1·07 ± 0·58	1·03 ± 0·22	0·51 ± 0·18	50·9*
Caudate	0·37 ± 0·14	0·40 ± 0·01	0·38 ± 0·08	0·21 ± 0·02	44·7*
Putamen	0·41 ± 0·13	0·38 ± 0·15	0·40 ± 0·09	0·28 ± 0·08	30·6
Hippocampus	0·14 ± 0·04	0·17 ± 0·05	0·16 ± 0·03	0·11 ± 0·03	29·5
Cerebellum	0·18 ± 0·05	0·16 ± 0·08	0·17 ± 0·04	0·10 ± 0·05	44·1
Frontal cortex	0·13 ± 0·04	0·24 ± 0·12	0·16 ± 0·04	0·10 ± 0·05	39·7
Occipital cortex	0·17 ± 0·04	0·17 ± 0·06	0·17 ± 0·03	0·12 ± 0·04	31·6
Temporal cortex	0·15 ± 0·02	0·16 ± 0·04	0·15 ± 0·01	0·12 ± 0·04	15·5

*Significant, p < 0·05.
†Mean ± SE.

from 15% in temporal cortex to over 50% in hypothalamus. Although only those reductions in hypothalamus and caudate nucleus are significant ($p < 0.05$), the authenticity of the other losses may be judged by reference to the group values of cell number and nucleolar volume measured in the pigmented cells of locus caeruleus and vagus nucleus in these seven cases (table 4), all of which do not differ significantly from corresponding group values obtained from all 48 cases (table 2).

Discussion

Findings presented here demonstrate that in Alzheimer's disease there is severe loss of the noradrenaline containing pigmented neurones of the locus caeruleus and dorsal motor vagus nucleus, together with substantial reductions in the capacity of those cells that remain to form proteins appropriate to a correct level of function. These changes are associated with decreases in noradrenaline concentrations within brain regions innervated by these cells. Our measurements of 55-60% reductions in numbers of cells of these two types closely match those findings recently reported by Bondareff[30] and Tomlinson,[28] where cell number in the locus caeruleus was on average reduced by 52 and 56% respectively, when compared with mentally preserved control groups of similar age. Although direct correlative studies have not been made in every study, it is highly likely that loss and atrophy of the cells of these two areas, are responsible for the deficiencies in brain noradrenaline content,[20-22] dopamine-β-hydroxylase activity[23] and MHPG levels in brain[24] and urine,[25] demonstrated in other cases of Alzheimer's disease. The non-pigmented cells of the vagus nucleus which do not use noradrenaline as neurotransmitter, showed only slight loss of cells and only a modest reduction in protein synthetic capacity; changes which may result as a consequence of alterations in either the pigmented cells, or of changes in other regions of the brain. The lack of alteration in either number or nucleolar volume, of pigmented nerve cells of locus caeruleus and vagus nucleus, in cases of multi-infarct dementia are in keeping with other findings of unchanged brain noradrenaline content[21 22] and dopamine-β-hydroxylase activity.[23] The noradrenaline neurotransmitter system is presumed therefore, to be functionally preserved in this condition, where the clinical symptoms of dementia result from widespread tissue destruction, in key brain areas, rather than selective degenerations of specific nerve cell types.

It is of course possible that alterations in the noradrenaline containing nerve cells on Alzheimer's disease are simply epiphenomena, arising secondarily to changes in other brain regions. However findings of reduced levels of MHPG in urine,[25] and loss of noradrenaline fluorescence in cortical biopsies[31] of mildly demented patients, would argue against a late involvement. Furthermore a greater loss of nerve cells from the locus caeruleus seems to occur in those cases of Alzheimer's disease with high plaque counts,[28] and is related to a greater degree of mental impairment;[30] findings which indicate that early changes in the noradrenaline neurotransmitter system may play a fundamental role in the pathogenesis of Alzheimer's disease.

The pigmented cells of the locus caeruleus and dorsal motor vagus, in conjunction with cells of the paraventricular and supraoptic nuclei of the hypothalamus, form pathways which act to maintain homeostasis within the CNS,[32] by regulating the rate of blood flow in the cerebral microcirculation and its' permeability to water and metabolites through action on the capillary pericyte.[33] Changes in functional integrity of these pathways of the locus caeruleus (see above) and hypothalamus,[34 35] in Alzheimer's disease may be presumed therefore to alter capillary permeability in such a way as to restrict local access of water or other metabolites to the brain, or prevent the removal of metabolic waste products with potential cytotoxic effects.

In such contexts, possible roles of metal ions in the pathogenesis of Alzheimer's disease have been proposed with either deficiencies of zinc[36] or accumulations of aluminium,[37] leading to alterations in the efficiency of those enzymes concerned with DNA synthesis, repair and transcription. Alterations in these cellular mechanisms could lead to a cascade of metabolic changes in nerve cells, but particularly in relation to their ability to form new proteins,[38 39] culminating in their widespread dysfunction and even eventually their death.

Recently, there have been reports[40-42] of trials of levodopa, in patients with Alzheimer's disease but without extrapyramidal signs where significant improvements in mental performance were made during treatment, over periods of 6-9 months which were lost during a drug free period, but subsequently regained on resumption of medication.[40 41] Since the brain's dopamine system is essentially unaltered in Alzheimer's disease,[1 9 20 21 43] it is therefore possible that beneficial effects of L-dopa on mental function may have arisen through preferential modulation (stimulation) of the noradrenaline system.

Further studies are needed to establish the time course of the degeneration of the noradrenaline pathways in Alzheimer's disease, and its relationship to the pattern of alterations in mental function, since it may be that an additional noradrenergic deficit

is one reason as to why patients may not respond to cholinergic treatment alone.

We thank Drs DV Bansal and DJ Marshall at North Manchester General Hospital for their assistance in collection of specimens. We also thank Miss A Hoyle for the preparation of the manuscript.

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