Pathogenesis of Alzheimer's disease – beyond the cholinergic hypothesis: discussion paper

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Introduction

If the importance of a disease is in any way related to the product of its mortality, morbidity and prevalence, then by any standards Alzheimer's disease (AD) is high on the list of priorities for research into its pathogenesis, for it is only in this way that effective therapy is likely to evolve. At present it is common, untreatable, and usually fatal within a few years[1], the intervening period having been one of devastating deterioration in mental function, resulting in emotional and practical pressures for the sufferer's family, and increasing financial ones for the health services[2].

It is appropriate, therefore, that in the past decade much basic research has been devoted to AD, and that major advances have been made in elucidating the nature of the underlying structural and functional disorder. Indeed, in many ways AD now stands at the forefront of attempts to understand disorders of higher neurological function, and as a paradigm for this area of research.

As a result of such research, there have been many papers, symposia and reviews, and it is not my intention to paraphrase these here (see, for example, Wurtman[3]). There are a number of aspects of AD that will not be discussed: for example, the search for a transmissible agent or toxin[4,5]; the role of genetic[3], metabolic and immune[6] factors; or the detailed characterization of the pathological features of the disease and their relation to the clinical picture of AD[7]. Instead, I wish to focus critically on the area that has generated most interest – the cholinergic hypothesis – whereby the loss of cholinergic input to the cortex is seen as the major determinant of the pathogenic process. The hypothesis has become well established in the past decade – almost to the point of dogma – and to the exclusion of other possible factors. I hope to point out the shortcomings of this view, and the way in which it demonstrates the pitfalls of evidence interpretation in this field. An alternative interpretation of the evidence is then put forward, which whilst not excluding elements of the hypothesis, attempts to set it in a wider context, and one which takes into account evidence for other components of the pathogenesis of AD.

The term 'Alzheimer's disease' is used here to encompass both Alzheimer's presenile dementia and senile dementia of the Alzheimer type; this is in line with current practice[8], although discussion continues as to whether this definition includes more than one disease process, which might vary in their pathogenesis[9].

The cholinergic hypothesis

In the mid-1970s, three independent groups reported a significant and selective loss of choline acetyltransferase (CAT) activity in the cortex and hippocampus of AD brains[10–12]. CAT synthesizes acetylcholine from its precursors (acetyl coenzyme A and choline), and is used as a specific marker for cholinergic neurons. It was already known that there is a direct ascending cholinergic input to the cortex from the basal forebrain; this had been shown using both acetylcholinesterase[13] and horseradish peroxidase labelling[14,15]; moreover, electrotoxic lesions there result in a fall in cortical CAT[16]. A previously obscure area of the ventral pallidum, the nucleus basalis of Meynert (NBM), came to prominence when it was identified as the source of this cortical input (Figure 1).

These findings were complemented by the report of Whitehouse *et al.* in 1982 that cells in the NBM selectively degenerated in AD, thus explaining the reduction in cortical and hippocampal CAT[17]; it has since been confirmed using a monoclonal antibody to CAT that the degenerating NBM cells are indeed cholinergic[18].

Interest in the relevance of this cholinergic loss to AD was stimulated by the finding that the degree of loss was related to the severity of the dementia, as well as to the density of the neurofibrillary tangles (NFT) and neuritic plaques – two of the cardinal histological features of AD[10,19]; furthermore, evidence implicated cholinergic terminals in plaque formation[20].

Several other parameters of cholinergic function have been shown to be deranged in AD. High-affinity choline uptake[21], acetylcholine release and synthesis[22], and cortical acetylcholine levels[23] are all reduced. The demonstration that such processes are also affected is important corroborative evidence for

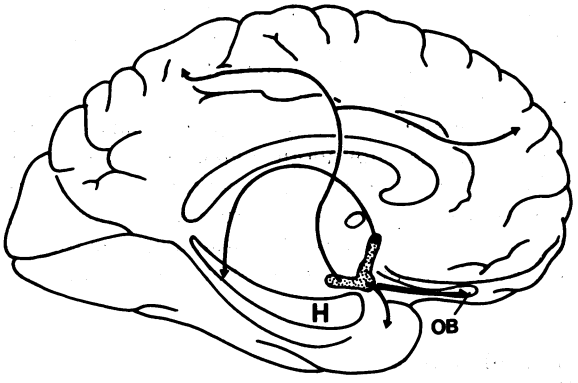

Figure 1. Ascending cholinergic projections from the nucleus basalis of Meynert (stippled). Anteriorly, the medial septal nucleus projects via the fornix to the hippocampus (H)*; inferiorly, the horizontal nucleus of the diagonal band of Broca projects to the olfactory bulb* (OB) *and olfactory cortex; posteriorly, the basal nucleus of Meynert sends cholinergic fibres to the whole neocortex*

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the cholinergic hypothesis, since CAT activity is not rate-limiting for acetylcholine synthesis[24], and the significance of the CAT work had been questioned[25].

Added support for the role of cholinergic dysfunction in the clinical picture of AD comes from separate psychopharmacological work in both animals and man implicating central cholinergic neurons in learning and memory processes[26]. For example, muscarinic antagonists interfere with learning and recall tasks, whereas cholinomimetics or cholinesterase inhibitors enhance such abilities[27].

These various strands of evidence ensured that the cholinergic hypothesis attracted much interest and support, for it represented a major advance in this field of research, and was the first real clue to the aetiology of AD. The hypothesis suggested that the central pathogenic process involves the loss of one transmitter-specific cell population – the ascending cholinergic projection from the NBM – thus inviting a parallel with Parkinson's disease, in which nigrostriatal dopaminergic neurons selectively degenerate. The analogy led Rossor[28] to propose that AD and Parkinson's disease are examples of disorders of the 'isodendritic core', a diffuse but morphologically similar group of cells in the brainstem which are particularly vulnerable to degenerative change. This concept also had the advantage of leading directly to a therapeutic prediction: that cholinergic replacement might be as effective in AD as levodopa had been in Parkinson's disease. No doubt the funding of research programmes – especially in the USA – was facilitated by the mention of a 'possible cure for AD' in researchers' grant applications. Despite this optimism, a large number of clinical trials using a variety of cholinergic agents have so far been generally unsuccessful in producing a significant improvement in AD[26,29].

This failure may be due to a number of reasons. First, the spatial and temporal arrangement of the cholinergic system may render it unsuitable for replacement therapy. If a projection is spatially specific or phasically active (as opposed to divergent or tonically active), simple pharmacological treatment is unlikely to be effective; the degree of divergence and firing patterns of the cholinergic pathways are at present unknown[28,30]. Alternatively, failure may be the result of pharmacological problems, e.g., not using the right agent, or an inability to reach the target site in the right concentration. A third, more pertinent possibility is that the cholinergic changes are but one, not necessarily primary, feature of AD, and that effective therapy will require more than just this approach to treatment.

Consideration of this latter point leads on to a critique of the cholinergic hypothesis, and on to a discussion of other experimental work and its interpretation, in an attempt to explain more fully the pathogenesis of AD. This would appear to be a prerequisite to the development of effective therapy.

Cortical factors

There have been a number of recent reports, both neuroanatomical and biochemical, which suggest that attention should be turned upwards and away from the NBM and the cholinergic system to consider intrinsic cortical factors in AD. AD has always been thought of clinically as a 'cortical dementia', in contrast to the 'subcortical dementias' such as Huntington's chorea or supranuclear palsy[31], and its pathognomonic histological features are also primarily cortical. It seems appropriate, therefore, that the cortex should again become of interest in the pathogenesis of this condition.

Anatomical studies: Despite the description of AD as a global dementia, it is known that it does not affect the cortex uniformly, but involves predominantly the temporal, frontal and parietal association areas, leaving primary visual, somatosensory and motor areas almost untouched[7,32]; the hippocampus and amygdala are also severely affected[33–35].

Pearson *et al.*[36] have investigated the predilection of AD for these sites and provided an explanation for the patchy distribution of pathology. They found that not only were NFT and plaques restricted to these homotypical cortical areas, but that within each focus they were arranged in discrete clusters which were confined largely to laminae III and V and, moreover, that the NFT were in register between these laminae. Lamina III is the site of origin of most corticocortical fibres, both ipsilateral and commissural, and it is thought that such fibres are indeed arranged in discrete bundles[37]. Furthermore, there is a heavy corticocortical projection from primary sensory cortex to parietotemporal association areas, frontal lobes, cingulate gyrus and hippocampus[38].

Thus there is evidence, both from the areas involved, the laminae, and the clustering, that corticocortical connections are selectively affected in AD, with the end of the above pathway being maximally involved (Figure 2). The disease process may thus be proposed to start in the temporal lobe or hippocampus and to spread retrogradely to other association areas along the pathway mentioned[38]; there is also a separate projection from hippocampus and entorhinal cortex back to the association cortex which might be involved in an orthograde fashion[39]. Moreover, the NFT in lamina V might explain the plaques and degeneration seen in subcortical structures, since cell bodies in this lamina project mainly to the striatum[37,40], amygdala, and brainstem, as well as to other ipsilateral cortical areas[33,37,39,40] (Figure 3).

Pearson *et al.*[36] also suggest that the severe and constant involvement of the olfactory system in AD – in contrast to other sensory areas – may represent the first site of disease involvement, progression then spreading from olfactory bulb, via uncus and amygdala, to the entorhinal cortex and thence along the association fibres described above. Whether this olfactory origin might tie in with the putative transmission of AD by slow virus entering through the nose is intriguing but totally speculative at present[41].

Support for the correlation of anatomical connections with the pathology of AD comes from Pick's disease, a rarer dementia which affects the frontal and temporal poles, plus the basolateral amygdala, cingulate and entorhinal areas, all of which are heavily interconnected[33,38,42]. Interestingly, there is no evidence of selective cholinergic loss in this condition.

In summary, recent evidence suggests that corticocortical and corticofugal pathways are selectively involved in AD, and that the disease process extends in a stepwise manner along these connections.

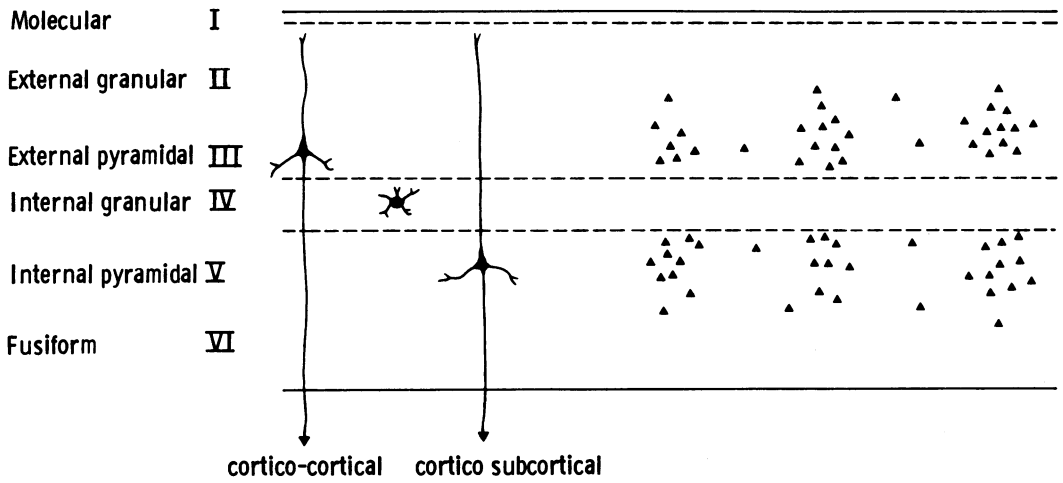

Figure 2. Laminar origin of cortical efferent connections. On the left, pyramidal cells of lamina III send fibres to other cortical areas, whereas those in lamina V project mainly to subcortical sites. On the right, the clustered nature of cortical pyramidal cells projecting to a single site is shown diagrammatically

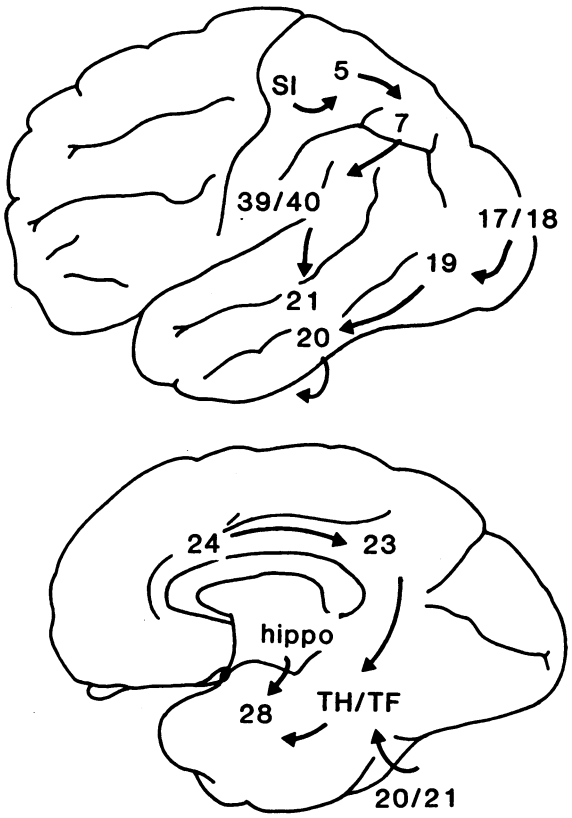

*Figure 3. Corticocortical connections in Alzheimer's disease. The numbers refer to cytoarchitectonic areas of Brodman; TH/TF refers to the cytoarchitectonic classification of Bailey and von Bonn. (*SI = *primary sensory;* hippo = *hippocampal formation)*

Clinical correlations and predictions: Such a progression of the disease process correlates well with the clinical sequence of AD: memory loss is the first reliable feature[31], and this is accounted for by the early and severe involvement of the medial temporal lobe and hippocampus; only later do personality changes, dysphasia and more global deficits arise as the temporal, parietal and frontal association areas become affected. Motor signs are rare and of very late onset in the disease, as the motor cortex is one of the final destinations of the corticocortical progression discussed.

The 'cortical hypothesis' also allows certain predictions to be generated. First, the olfactory bulb may be the first structure to be involved, and thus signs of olfactory dysfunction should be present early in the disease – and, indeed, might occur years before the onset of detectable dementia. In support of this, olfactory impairment in early senile dementia has been described[43,44]; moreover, CAT activity in the olfactory tubercle has recently been found to be markedly reduced[45]. As the olfactory structures are intimately connected with hypothalamic nuclei, disorders of hypothalamic function such as changes in eating patterns or thermoregulation might also be an early feature of the disease.

Such predictions will not be easy to test, ideally requiring the study of 'pre-dementia' patients, who cannot yet be identified as such. Investigation of olfactory and endocrine function in early established cases would still, however, allow useful evidence to be collected. As well as supporting the above theory, were any such parameters shown to be a reliable marker of early or impending dementia, they might have a use as an indicator of later dementia, with both therapeutic and prognostic possibilities.

A third prediction of the cortical hypothesis is that brains from AD patients dying at different stages of the disease should show differing extents of involvement of the pathway. There should always be one area, representing the final area affected before death, that demonstrates an intermediate severity of involvement. The extent of spread along the projection should also correlate with the major clinical features mentioned above. Furthermore, it should never be possible to find involvement of a cortical area within the sequence without severe involvement of the preceding areas; for example, parietal changes must always be accompanied by temporal and hippocampal involvement, whereas the latter may be affected in the absence of any parietal degeneration.

Thus the neuroanatomical work discussed above leads directly to specific pathological and clinical predictions which require detailed study in order to be verified or refuted. In the process, concepts of pathogenesis may well need to be revised or even replaced.

Biochemical studies: Recent independent neurochemical research has also implicated cortical

neurons as having a primary pathogenic role, although it is not yet clear how far it can be integrated with the anatomical work discussed above.

Somatostatin reactivity has been known for some time to be decreased in AD[46], but interest has been kindled by findings connecting it with both NFT[47] and plaques[48]. Roberts *et al.*[47] found that a population of somatostatin-staining cortical neurons showed both degeneration and contained NFT; moreover, these were mainly in laminae II/III and V/VI, where the corticocortical and corticofugal connections originate (Figure 2). The highest density of staining was found in the temporal and entorhinal cortex, hippocampus and amygdala, again correlating with the anatomical work. Morrison *et al.*[48] identified somatostatin staining in neuritic plaques, predominantly in the amygdala, temporal and frontal cortex; furthermore, the density was greatest in laminae III and V. It is tempting to propose that the same neuronal population is being identified by these three approaches, but there is as yet no firm evidence for this; all that can be said is that evidence is accumulating, both anatomical and pharmacological, which suggests that intrinsic cortical cells are involved in a major way in the pathogenesis of AD. It will be important to establish the role of somatostatin, and whether neurons that contain it represent a distinct population, as well as to identify their distribution and connections.

Given that somatostatin and cholinergic elements have both been reported in plaques[30], it will also be necessary to determine whether they coexist in the same neurons and plaques[49], or whether there are different types of plaque, which might suggest they are merely a nonspecific consequence of degenerative processes[47]. Such a role would fit in with the finding that dementia scores correlate more closely with NFT density than with plaque density[50], and that plaques may be a concomitant of the ageing process[7].

Glutamate has also been investigated recently. Research has been hampered by problems of identification and post-mortem changes[12]; however, recent reports have demonstrated a fall in glutamatergic activity in AD[50,51], as well as involvement of the corticostriatal tract, which is thought to be glutamatergic[50]. Moreover, degeneration in the striatum is limited to those areas that receive from heavily affected areas of the cortex[50]. Increased glutamate binding in the caudate has also been reported, which might be due to hypersensitivity following loss of corticostriatal input, given that the same effect is seen after hemi-decortication[51].

Better characterization of glutamatergic pathways will be needed to clarify their role in AD pathogenesis; a more reliable and robust marker would help in this respect.

Cholinergic changes as secondary phenomena

The cholinergic work also allows a tie-in with the cholinergic hypothesis. Kainic acid, which is thought to destroy glutamatergic cells, when applied to the cortical surface results in severe shrinkage of NBM neurons[52]; thus the precedent is there for changes seen in the NBM to be due to transsynaptic neuronal degeneration; this would turn such changes – which form the basis of the cholinergic hypothesis – into secondary phenomena. This is supported by the finding that lesions in the NBM do not cause a fall in cortical somatostatin[49], whereas intrinsic cortical lesions can explain both the NBM changes and the somatostatin loss[45].

A primary cortical pathology can also account for the striking, though variable, reductions in monoamine levels which are seen in AD brains[53,54], and the degeneration of their nuclei of origin[55]. It might be postulated that these afferents end on the same postsynaptic cortical cells as the cholinergic input, and that degeneration of that cortical population causes retrograde degeneration of both forms of input. Conversely, it is not obvious how a primary NBM lesion could explain both the cortical and the monoaminergic changes, especially as there are no connections known from the NBM to the relevant nuclei. Undercutting of the cortex also results in NBM cell shrinkage[56], thus complementing the evidence that degeneration there is a consequence not a cause of cortical changes. Alternatively, atrophy in the NBM could be due to a loss of afferent connections from the temporal cortex or hippocampus[57].

Another problem with the cholinergic hypothesis regards the nature of the primary lesion. It is clearly not a primary biochemical deficit, for example an inherited enzyme deficiency, since other cholinergic neurons, both centrally and peripherally, are unaffected[7]. Moreover, as mentioned, the cortical changes in CAT activity are regional, not global, yet the NBM projects as heavily to primary sensory and motor cortex as it does to association areas[13,15]. It would be necessary to postulate a complex aetiology to explain this selective and regional loss if the NBM lesion were a primary event in AD.

Further important evidence that the cholinergic loss may not have the crucial significance vested in it by some workers is that dementia can occur without such loss[58], and that NBM degeneration is even more marked in Parkinson's disease[59] where dementia occurs in only 20–30% of cases[60,61], and where NBM loss may occur without cortical plaques[62], decreased CAT activity[60], or dementia[62]. Perhaps in both these conditions the NBM cell atrophy is consequent upon loss of presynaptic neuronal populations, whether corticocortical or nigrostriatal, which result in retrograde degeneration; this may prove to be a stronger linking factor between the two disorders than Rossor's concept that they are diseases of the isodendritic core[28]. Furthermore, the NBM has also been reported to degenerate in schizophrenia, in which dementia is not a feature[63]. It seems unlikely that NBM atrophy can be a primary event in AD if similar changes occur in other conditions without producing dementia.

Conclusions

The study of AD exemplifies the way in which basic research paves the way for the understanding of clinical conditions and thence the development of rational therapeutic approaches based on this knowledge.

However, it also demonstrates the complexity of neurological disease processes, and the problems that can occur *en route* to a clear and full understanding of their pathogenesis. The great specialization required to investigate one particular part of the overall picture may sometimes lead to a loss of

perspective and an inability to put research findings into their true context[3]. The interest in cholinergic factors in AD may reflect more the ease of their identification – acetylcholinesterase and CAT are well-established and reliable markers – and thus that changes were discovered there first, rather than any particular significance *per se*. Alterations in somatostatin, glutamate, and other as yet unidentified transmitters and neuronal populations may prove to be equally important in the disease process. The criticism of the cholinergic hypothesis should not, however, detract from the advance it has represented in the understanding of AD, and the way it has stimulated further research; it has been of considerable heuristic value, and, for example, the current work on cortical factors is unlikely to have been undertaken without it.

It is unfortunate that the cortical hypothesis does not lead to any therapeutic optimism of the kind engendered by the cholinergic hypothesis. If AD is indeed a progression along discrete pathways, interfering with a number of transmitter and neuronal populations on the way, replacement therapy is unlikely to be of benefit. Treatment would then be restricted to techniques slowing the spread of the disease, or preventing its onset.

Further research will require better anatomical and chemical characterization of the areas discussed here, and in particular their sequential involvement in AD. This will require brains from AD patients dying at different stages of the disease, in order to allow better understanding of the progression of the condition and separation of primary events from their sequelae.

Integration of this research with the study of other aspects of AD, such as genetic, metabolic and environmental influences, is the approach most likely to produce advances in understanding sufficient to permit effective therapy to be designed. Such understanding would also have significant consequences for the study of other neuropathological conditions which at present are poorly understood and often untreatable.

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