LETTER TO THE EDITOR

It is most stimulating to see an alternative to the idea of a central role of β-amyloid in the pathogenesis of Alzheimer's disease (AD), especially because alternatives give us an opportunity to rethink a hypothesis that many people believe is quite established. In a paper published in JNEN (1), Terry included in his model new parameters including dispersion of the Golgi apparatus (GA) in the pathogenesis of AD. Our studies regarding the change of the GA in AD have shown that a decrease in the size of the GA is most characteristic for AD rather than dispersion, and that GA shows changes in AD not, as indicated in his scheme, as a result of cytoskeletal alterations, but independent of amyloid deposition or cytoskeletal alterations. This conclusion is based upon observations in different brain structures with different patterns of AD changes. The hypothalamic nucleus tuberalis lateralis (NTL) shows strong early cytoskeletal alterations, which appear from the intense staining of NTL neurons by the antibodies Alz-50, tau-1 and 3-39 (2). Interestingly, silver stained neurofibrillary tangles (NFTs) and senile plaques (SPs) are rare in the NTL of AD brains. Our study (2) showed that there is no reduction in the GA size of this area in AD (2), which indicates that strong pretangle cytoskeletal alterations in the NTL are not accompanied by a decrease in GA size. This is not in agreement with Terry's scheme, suggesting that the early stages of cytoskeletal alterations lead to GA dispersion. Furthermore, there appeared to be no difference in the size of the GA between CA1 neurons containing NFTs and those that did not (3). So, although NFT and decreased metabolic activity are present in AD in the same brain area, i.e. CA1, they do not seem to be causally related. This is again not in agreement with Terry's scheme, which suggests that cytoskeletal alterations are directly related to GA dispersion. Since, as Terry points out, evidence of amyloid toxicity has not yet been satisfactorily revealed in vivo, we measured metabolism of neurons in relation to plaque distance. If a plaque contains neurotoxic compounds, one would expect that the closer a neuron is situated to the plaque, the lower its metabolic rate. Our measurements did not support such a mechanism, which indicates that metabolism and SPs are basically independent phenomena.

In the model we propose that amyloid accumulation is not the main cause of AD or of changes of the GA. However, decreased neuronal activity as measured by the size of the GA is proposed to be a major independent characteristic of AD. Many studies support the view that decreased metabolic rate is a major hallmark of AD. It has been reported that the AD brain shows a lower total amount of protein, a clear reduction in total RNA, reduced glucose metabolism, as shown by PET, a smaller size of the neuronal GA (3–5) and a lower cytochrome oxidase level.

Since the reduction in neuronal metabolic activity thus seems to be an important hallmark of AD, one may also assume that restoration of neuronal activity leads to diminishment of cognitive impairment. Although it is not yet clear whether decreased metabolic activity is a primary process in the course of AD, it has been shown that reactivation of neurons may in principle be beneficial for AD patients. Global stimulation by exercise, transcutaneous electric nerve stimulation, tactile nerve stimulation, and a combination of the latter two significantly improves memory and affective behavior of patients with probable AD (6). Fragmentation of sleep-wake patterns occurs in AD (7), which is believed to be due to degenerative changes in the suprachiasmatic nucleus. It has been shown that exposure of AD patients to more intense light improves the sleep-wake rhythms of these patients (8). The best way to prove that decreased metabolic activity indeed plays a major role in the development of dementia is, of course, to show that reversing decreased neuronal activity leads to a considerable improvement of cognitive functions.

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