COMMENTARY

Neuronal Atrophy, Not Cell Death, Is the Main Hallmark of Alzheimer's Disease

D. F. SWAAB,* M. A. HOFMAN,* P. J. LUCASSEN,* A. SALEHI*† AND H. B. M. UYLINGS*

**Graduate School Neurosciences Amsterdam, Netherlands Institute for Brain Research, Meibergdreef 33, 1105 AZ Amsterdam, The Netherlands*

†Department of Physiology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

THE EXCITING data of Regeur et al. (23) that global neocortical cell loss does not take place in the brains of Alzheimer patients makes it clear that neuronal shrinkage rather than cell death is the major phenomenon involved (not only in normal aging but also in Alzheimer's disease; AD). The data immediately trigger a number of questions.

First, the finding that the occipital lobe shows the largest reduction in size was unexpected. Atrophy in AD is generally found macroscopically temporoparietally and, although less consistently, in the frontal lobe but not in the occipital lobe. The latter has also the least neuropathological changes (e.g., 3).

Second, comparison of Regeur et al.'s 1993 data with their own earlier studies reveals notable differences with respect to the total neuron numbers.

Pakkenberg et al. (21) reported a decline in total number of neurons with age and a trend of higher neuron numbers in male than in female neocortex. The Regeur et al. 1993 data of 18.1×10^9 neurons in the 10 female neocortices agree with these numbers. However, when we consider the data of Braendgaard et al. (6) on the number of neurons in 5 male neocortical hemispheres, aged between 77 and 82 years, we would expect higher numbers in these 5 male neocortices, but 28% lower numbers are reported instead. Does this difference reflect the presence of extremely large inter-individual differences that may impede future studies or is the height of the optical disector critical for determination of the final numbers? Regeur et al. (23) and Pakkenberg et al. (21) use a height of 15 μm , whereas in Braendgaard et al. (6) a height of 2 μm or 10 μm has been used (five 2 μm steps).

Third, we wonder whether the pathologic diagnosis of AD can be based only on the abundant presence of neuritic plaques in the neocortex. Did the authors not examine the presence of dystrophic neurites (= neuropil threads) in both the hippocampus and neocortex?

Finally, it may also be important, in view of the possible presence of asymmetry, that the authors specify which hemisphere has been studied and that they give the estimates of total neuron number for the different lobes of each case.

Although the data of Regeur et al. (23) on cell shrinkage instead of cell death are intriguing, they may not hold for all brain regions. In the locus coeruleus, we recently found not only an 82% decrease of large pigmented neurons but also a 39% decrease of small unpigmented ones. This observation excludes neuronal

shrinkage, so that cell death has to be a major phenomenon in the locus coeruleus of Alzheimer patients (W. Hoogendijk et al., unpublished observations). The hippocampus may also still be a candidate for cell loss. On the other hand, various claims in the literature of massive cell loss in AD are probably based on (a) inadequate morphometry (7,30) and/or (b) a loss of a marker rather than a loss of neurons. A good example of the latter situation is the nucleus basalis of Meynert (NBM), which is clearly affected in AD (31). Originally it was claimed that a massive loss of large cholinergic neurons took place in the NBM of Alzheimer patients (2,32,35), but later studies revealed that at the same time the number of small neurons increased proportionally (1;24;34). Consequently, neuronal atrophy rather than neuronal loss seems to be a major phenomenon in the NBM of Alzheimer patients, going together with a loss of cholinergic markers. This loss, together with neuronal shrinkage, must be the explanation for the earlier findings claiming cell death. Our recent finding that NBM neuronal metabolism is strongly decreased in AD—judged by the clearly diminished size of the Golgi apparatus of these neurons—reinforces this idea (25).

Our data on the changes in the clock of the hypothalamus, the suprachiasmatic nucleus (SCN), may be explained in a similar way. The SCN showed a 50% loss of vasopressin-expressing neurons in the oldest age group (i.e., 80–100 years), and a 75% loss of vasopressin-expressing neurons in Alzheimer patients (27). This loss could also be the result of cellular atrophy and a subsequent loss of the peptidergic marker, rather than of neuronal loss. The strong circadian (14) and circannual changes in the number of vasopressin-expressing neurons (12,13) in the human SCN are indicative of strong changes in the degree of vasopressin expression, rather than of cell death followed by cell proliferation.

It is noticeable that Regeur et al. (23) at the end of their article, do not hesitate to put "synaptic loss" forward as being the major phenomenon in AD, although synapses are also defined on the basis of activity dependent parameters such as synaptic vesicles (9,10) and synaptophysin (33). It therefore seems conceivable that we will have to conclude later on that rather than being lost synapses merely become inactive as well.

For patients currently suffering from AD it does not seem to make much difference whether neurons are present but inactive, or whether these neurons are lost altogether. It does, however, make a huge difference as far as the search for etiological factors and

therapeutic strategies is concerned, as many etiological theories are based on cell death, e.g., due to accumulation of DNA damage (19), to the loss of receptors for trophic factors (22), to free radicals (26) or to overstimulation by excitatory amino acids (29). It seems we ought to focus, instead, on the reason why a reduction of cerebral metabolic rate of glucose, in particular, in the temporal lobe, is one of the predominant abnormalities as well as one of the abnormalities that occur early on in AD (14a,15,17). The observation that an uncoupler of oxidative phosphorylation induced cytoskeletal abnormalities as found in Alzheimer brains in cultured fibroblasts (5) is also very interesting in this respect. The conclusion to all this is that reactivation of the atrophic neuronal systems should be the aim of therapeutic strategies and not just prevention of cell death. Stimulation of the SCN in Alzheimer patients using light therapy indicates that such an approach is quite promising. The diminished SCN activity, as appears from, e.g., the decreased number of neurons expressing vasopressin in this cell group in Alzheimer patients (27), goes together with disturbed circadian rhythms, sleep disorders, wandering, nightly restlessness, agitation, sundowning, and even delirium. These behavioral disorders almost disappear—and the sleep-wake rhythms improve—when the SCN is stimulated by means of the administration of extra amounts of daylight (20,25a). Phototherapy is effective because the SCN is directly and indirectly innervated by the optic nerve (18). The observation that the degree of education is negatively correlated to cognitive decline and dementia, as is shown in various studies (4,8,36) may be interpreted as a positive effect on

neuronal activity by a more global stimulation of the brain. Earlier, we obtained data suggesting that neurons that are stimulated remain active and are better able to withstand the process of aging and AD (11) (P. F. Van der Woude et al., unpublished research) (28). This concept, namely, that activation of neuronal systems might prevent their degeneration and restore their function during aging and in AD has been paraphrased as “use it or lose it” (28). This concept may have more general applicability in neurodegenerative diseases; it could explain, e.g., the specific pattern of degeneration of the dopamine neurons in Parkinson’s disease. The level of dopamine metabolism in various regions of the brains of young individuals was found to be inversely correlated to the degree of dopamine loss suffered by individuals in the older age group (16). This observation that the most active dopaminergic neurons are the best protected ones, agrees with our “use it or lose it” concept (28) and is contrary to the oxidative stress theory of Parkinson’s disease, which predicts that the most active neurons are also the ones that are most affected (16).

Following the paper of Regeur et al. (23), the key question for Alzheimer research thus seems to be “what is the cause of the metabolic decline of the neurons in neurodegenerative diseases and how can we reactivate these neurons?”

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