Aging of the Brain

Editors

Willem Hendrik Gispen and Jörg Traber

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AGING OF THE BRAIN

Proceedings of the First International Tropon Symposium on Brain Aging, held in Cologne, Federal Republic of Germany, on November 16-18, 1982

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PREFACE

As an ever-increasing proportion of the population is made up of elderly people, society is becoming more concerned about the malfunctions that parallel the aging of the human being. In particular, there is an increased awareness of the disorders that signify loss of brain function. Although the fact that otherwise healthy aged people complain of cognitive disfunctions has long been recognized, little is known about the brain mechanisms that are affected by aging.

There is hardly a more rapidly growing field of interest in the neurosciences than that of the aging of the central nervous system. Interest in this topic is apparent in nearly all disciplines. Thus it is not surprising that recent results arising from quite diverse research approaches have yielded new clues to further our understanding of the aging of nervous tissue. The symposium "Aging of the brain" at Cologne in November 1982, was organized to facilitate the exchange of information between representatives of leading groups in the field of aging and to stimulate discussions of various aspects of the mechanisms of brain aging.

The symposium covered morphological and neurochemical correlates of aging. plasticity and regeneration, circulation and metabolic correlates in brain function, behavioral correlates in animal and man and diseases of the aged.

The quality of the presentations was outstanding and provoked lively and thorough discussions. An informal round table discussion dealt with future directions for human health applications. Originally, publication of the proceedings of this symposium was not planned. However, in view of the unique gathering from eminent groups in the brain aging field, it was decided to invite the various speakers to prepare a manuscript that more or less covered the facts presented in their oral communication.

We are grateful to the authors and Elsevier Biomedical Press for their efforts to make these proceedings a success. In addition we are grateful to Dr. M.A. Davies, Mrs. A. Barz, Mr. G. Bertram, Mr. H. Demmer and Mr. W. Dreher for their help in organizing the meeting. Some chapters are short, but give a concise description of the state of the art, others are longer, detailed papers presenting original data. As a whole, the proceedings give a balanced view of what is known about the mechanisms of brain aging, new information and

ideas placed in context with established facts.

We thank TROPON GmbH for making it possible to have this symposium. Furthermore, we expect that the proceedings of this symposium may serve as a comprehensive treatise on brain aging research today. Most of all, we hope that the reader be it a graduate student or a senior scientist will find this volume stimulating in furthering insight into brain ageing and in providing new ideas for further research.

August, 1983. Utrecht, Willem Hendrik Gispen

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INTRODUCTION

Among Grimm's fairy tales is one very short, poignant story, which is not actually a fairy tale with magicians, witches and princes. It is a very realistic story which can be easily transposed in our times. It is called: "The grandfather and the grandson", and goes as follows:

"Once upon a time there was a very old man, whose eyes were clouded, whose ears were deaf and who could not think clearly any more. When he sat at the table and could hardly hold his spoon, he spilt soup on the table cloth and some dribbled out of his mouth. His son and daughter-in-law were repulsed by him and therefore he finally had to sit behind the stove in the corner, and had to eat from a small bowl. Once, his trembling hands could not hold the bowl, and it fell and broke. The young wife bought him a wooden bowl for a few pence, and now he had to eat from this.

As they were sitting together, the small four-year-old grandson carried in some small boards. "What are you doing?", asked the father. "I am making a little bowl", replied the child, "so that father and mother can eat out of it, when I am grown up"."

I can remember that as a child, this story made a strong impression on me, and I swore not to behave towards my parents as the ones in the story. At the time I had no idea that it might be possible to alter these symptoms of aging, and accepted them as inevitable.

As with most fairy tales, this one also has a happy ending. The parents are ashamed of their behavior and think of their own possible future and invite the old grandfather back to the table. Expressing this in a modern way, we would say that the solution to the problem was sought in this case by integration in the family group and resocialisation.

WHAT ELSE DO WE HAVE TO OFFER NOWADAYS?

From the earliest history of mankind, aging and its associated loss of function have been considered a highly deplorable state. One should not, however, deny that philosophers and writers have tried to attribute more positive qualities to old age. As La Rochfoucaulde said: "As we grow older we become both sillier and wiser". The German poet Marie Ebner von Eschenbach put it the following way: "Age petrifies or clarifies".

The theme of the present volume is certainly not philosophy. It is concerned with a very practical question: "What can we do to slow down or prevent the various symptoms which are caused by vascular lesions or degenerative foci in the aging brain?".

I feel that everyone, and not only the older of us, will agree that the time is more than ripe to make the causes and therapy of the chronic brain syndrome one of our major research themes. I would even go so far as to say that this problem is, or will become, one of the greatest challenges to present-day medicine and physiology.

Research as we understand it today cannot be carried out in an attic. The complex interactions with which we are concerned today, require the cooperative effort of many disciplines in order to reach a common goal. This cooperation is particularly necessary for such a subject which is only beginning to be discovered, or better, uncovered. Therefore, this book "Aging of the Brain", discusses both clinical and experimental aspects of aging and is an attempt to define the status quo of present knowledge.

I feel that research in the field of brain aging has been neglected too long and considered uninteresting, unfruitful or even perhaps unscientific. I am sure that the reader of this book will be convinced that this is not the case, but that indeed we stand at the brink of a new stage of CNS pharmacology and that possibilities will be opened up to influence the course and consequences of the aging process.

These proceedings emphasize the importance of the exchange of ideas between industry and university researchers in the task of unravelling the physiological and pathological mechanisms underlying normal and abnormal brain aging. The success of this endeavour depends on close cooperation to achieve the common goal.

Cologne, August 1983
Harald Horstmann

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MORPHOLOGICAL AND NEUROCHEMICAL CORRELATES

Aging of the Brain, W.H. Gispen and J. Traber eds.

DENDRITIC GROWTH IN AGING BRAIN?

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During the past half dozen years a body of evidence has accumulated which indicates that the aging nervous system retains considerable potential for growth of neuronal processes. The dendrites of single neurons provide an important focus of attention in studies of growth and regression in the aging brain. Since dendrites represent as much as 95% of the receptive surface that a neuron offers for contact with other neurons (1), their extent is an important determiner of the functional capacity of neuronal networks. Also since dendrites may expand and contract even in the mature nervous system (2) in response to influences impinging on them they offer a sensitive means of examining the way(s) in which the brain may age.

The first evidence of dendritic growth in the aging brain was provided by the excellent stereological light and electron microscopic study of Hinds and McNelly (3). Their study of the rat olfactory bulb demonstrated an increase in the volume of dendrite per mitral cell from 24 to 27 months of age. This increase of dendritic volume per cell paralleled a fallout of mitral cells with the net result being maintenance of the volume fraction of mitral cell dendrites. After 27 months of age the rate of fallout of mitral cells increased, dendritic growth per cell decreased and the volume fraction of dendrites fell markedly. Hinds and McNelly (3) suggested that the dendritic growth per cell that they observed between 24 and 27 months was a compensatory response to the loss of neighboring neurons.

The finding of dendritic growth was extended to the aging human brain by the quantitative Golgi-Cox studies of Buell and Coleman (4,5). They described age related increased dendritic extent of layer II pyramidal neurons in the cerebral cortex of the parahippocampal gyrus of humans over an age range from 44 to 92 years. These studies showed that the increased dendritic extent was to be found largely in the terminal branches of the dendritic tree, suggesting that the expansion of the dendritic tree during aging was taking place by growth at the tips of the dendritic tree, just as it does during early development (eg. 6). Regression analysis of these data over the age range studied gave (for the apical portion of the dendritic tree) a correlation of +.57 ($p < .05$) between age, in years, and average length of a terminal dendritic segment per cell. The corresponding correlation for the basilar portion of the dendritic tree was +.53. The regression equation describing the growth of the average terminal segment of the apical dendritic tree was $y = 0.21 x +$

22.64 where y = average length of an apical terminal segment and x = age in years. See Figure 1 for a plot of this regression line. Thus, an average apical terminal segment grows in the aging human brain at the rate of 0.21 um per year. Multiplying this by 9.5, the average number of terminal segments found per apical tree, gives a growth of 1.99 um per year in the apical dendritic tree of each cell. Similar data for the basilar dendritic tree indicate dendritic growth of 2.78 um/yr/cell. Although no comparable quantitative data exist for the period of early development it is to be taken for granted that this rate of growth is considerably less than that seen during early development. Nevertheless, the growth found in aging brain can be substantial in terms of the total dendritic growth in the cerebral cortex.

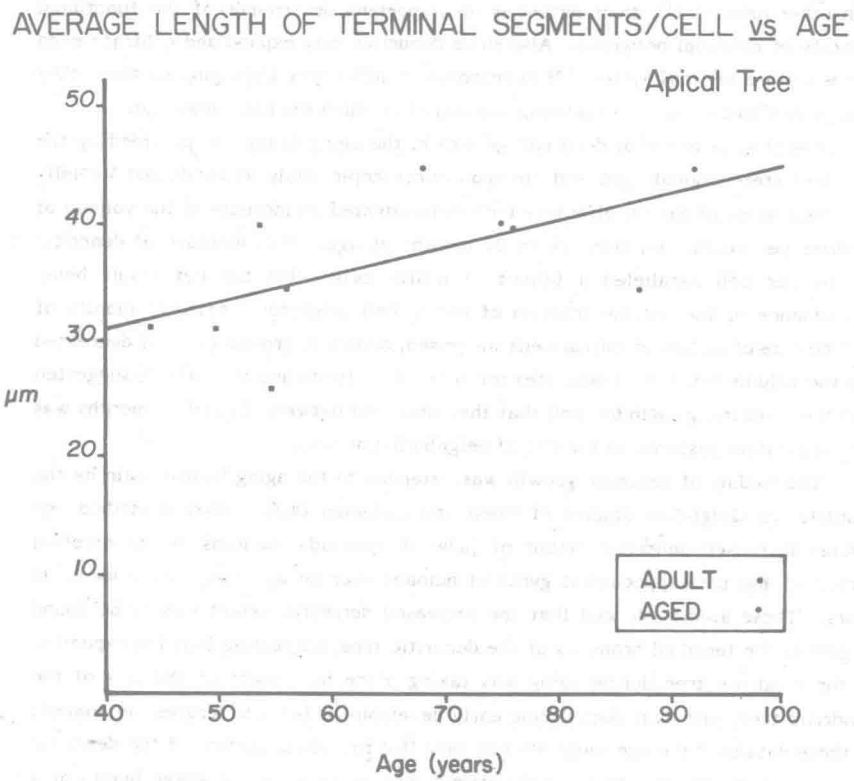

Figure 1. Best fit least squares regression of average length of terminal dendritic segments (apical dendritic tree) as a function of age. Points are average values for each of ten cases. The correlation between these two variables is +0.57 (p .05). The regression equation is y = 0.21 + 22.64. Data are from layer II pyramidal neurons of human parahippocampal gyrus.

Multiplying the annual dendritic growth per neuron of 1.99 + 2.78 = 4.77 um by the estimated ten billion neurons in the human cerebral cortex (7) gives an estimated dendritic growth of 4.77×10^7 mm per year. This impressive figure is, of course, offset by the apparently generalized age-related loss of neurons in the human cerebral cortex (see 8 for a recent review). The death of only one cortical neuron with its thousands of microns of total dendritic extent clearly will cancel the contribution of many surviving, growing neurons to the dendritic extent to be found in the total cortical neuropil. The net effect on the cortical neuropil of these two opposing factors of death of neurons and growth of surviving neurons is currently unknown.

The impending death of some cortical neurons was indicated to us in our Golgi-Cox stained material by the appearnace of neurons with grossly atrophic dendritic trees, similar to those described by Scheibel et al. (9) in their qualitative rapid Golgi studies of aging human cerebral cortex. Contrary to the Scheibels, however, our data clearly showed such cells to be in the minority and to show no increase in numbers with increasing age. We believe this discrepancy in results may derive from a sensitivity of the rapid Golgi method to post-mortem delay in fixation (10). The finding of dendritic growth in aging brain has more recently been further supported by data from aging primate (11) and rodent (12,13) models as well as from additional regions of human brain (14).

The available data have led us to suggest (4,5), in agreement with Hinds and McNelly (3) that dendritic growth in aging brains is a compensatory response to loss of neurons. More recent evidence suggests that in the absence of neuronal loss (15) there is no age-related cortical dendritic growth (16). Furthermore, we suggest that in the aging brain there exist two populations of neurons; one is regressing and dying while the other is growing and surviving. Since our samples of neurons were drawn randomly and included cells from both populations we must conclude that in normal aging the growing and surviving population must predominate until some as yet unspecified age. With the passage of time there must be some shift of neurons from the growing, surviving population to the regressing and dying population. These concepts are illustrated in Figure 2.

The development of a convincing rodent model of the phenomenon of dendritic growth in aging human brain has, thus far, been hampered by clear species differences in cortical aging in which aging is defined in terms of survival curves for each species. Intensive study of layer II pyramidal neurons in entorhinal cortex of F344 rat has failed to provide evidence of age-related dendritic growth at either the electron microscopic (17) or light microscopic (18) levels to 30 months of age. Golgi-Cox studies of dendritic extent in the posteromedial barrel subfield of somatosensory cortex of aging C57Bl/6 mouse has also failed to reveal evidence of dendritic growth to 30 months (16). Thus, although there have been reports of