Molecular Neurobiology of Alzheimer Disease and Related Disorders
To Megumi Takeda (September 12, 1957 – February 4, 2002)
Molecular Neurobiology of Alzheimer Disease and Related Disorders

Editors

Masatoshi Takeda Osaka
Toshihisa Tanaka Osaka
Ramón Cacabelos Coruña

140 figures, 72 in color, and 18 tables, 2004
Contents

VIII  Foreword
Nishimura, T. (Osaka)

X  Preface
Takeda, M.; Tanaka, T. (Osaka); Cacabelos, R. (Coruña)

1  Methods of Regulating Alzheimer Pathogenesis: Diet, Oxidative Damage and Inflammation
Cole, G.M.; Morihara, T.; Lim, G.P.; Calon, F.; Teter, B.; Yang, F.; Frautschy, S.A. (Sepulveda, Calif.)

17 The RNA-Binding Protein Causes Aberrant Splicing of Presenilin-2 Pre-mRNA in Sporadic Alzheimer’s Disease

31 Alzheimer’s γ-Secretase Mechanism Produces Amyloid-β-Protein Like Peptides Simultaneously with Release of Intracellular Signaling Fragments

42 Pivotal Role of Neurofibrillary Degeneration in Alzheimer Disease and Therapeutic Targets
52 Tau Pathology of Sporadic Tauopathies

62 Deregulation of GSK-3β and JNK in a Mouse Model of Tauopathy: A Kinase Combination That Induces Alzheimer-Type Tau Hyperphosphorylation

71 Clinical Assessment of the Genetic Risk Functions in Alzheimer’s Disease
Kamino, K.; Kida, T.; Takeda, M. (Osaka)

79 Hydrogen Sulfide Is Severely Decreased in Alzheimer Disease Brains
Kimura, H. (Tokyo)

84 Functional Analysis of the Presenilin Complex and γ-Secretase Activity

94 Pharmacogenomic Studies with a Combination Therapy in Alzheimer’s Disease
Cacabelos, R.; Fernández-Novoa, L.; Pichel, V.; Lombardi, V.; Kubota, Y. (Coruña); Takeda, M. (Osaka)

108 Nicotinic Receptor Stimulation Blocks Neurotoxicity Induced by Amyloid-β via the Phosphatidylinositol-3-Kinase Cascade
Kihara, T.; Shimohama, S. (Kyoto)

123 Involvement of Unfolded Protein Responses in Alzheimer’s Disease
Kudo, T.; Katayama, T. (Osaka); Imaizumi, K. (Takayama); Kanayama, D.; Sowa, M.; Okochi, M.; Tohyama, M.; Takeda, M. (Osaka)

134 Advances in the Development of Biomarkers for Alzheimer’s Disease – From CSF Total Tau and Amyloid-β(1–42) Proteins to Phosphorylated Tau and Amyloid-β-Antibodies

157 Genetic Analysis of Familial Alzheimer’s Disease in a Japanese Population
Foreword

The dawn of psychogeriatrics in Japan was celebrated with the symposium entitled ‘Psychiatry for the Elderly’ in the frame of the annual meeting of the Japanese Society of Psychiatry and Neurology in 1954, on which occasion Professor Ziro Kaneko (Osaka University), Professor Tadashi Inose (Yokohama City University), and Professor Naotake Shinfuku (Tottori University) delivered their lectures on the psychological process of aging, neuropathology of aging and psychopathology of aging, respectively. The proceedings of the symposium entitled The Psychiatric Aspects of Senility (Igagu-shoin, Tokyo, 1956) were published as a monograph in Japanese; this was an epoch-making achievement in Japanese psychiatry because the interest in psychogeriatrics had been so sparse until then.

In the 1960s, dementia in Japanese elderly people was mainly regarded to be cerebrovascular dementia. Most Alzheimer’s disease patients were unrecognized and there were only a few case reports of early-onset Alzheimer’s disease. In those days, basic research in Alzheimer’s disease was confined to neuropathology or histochemistry. Electron microscopy, however, revealed the unique structure of paired helical filaments in Alzheimer brains, which triggered biochemical research aimed at elucidating the mechanism of paired helical filament formation. My colleagues at the Department of Neuropsychiatry, Osaka University and I found that soluble proteins were insolubilized in Alzheimer brains, which was reported at the International Meeting of Neuropathology in Budapest in 1974. This report, which attracted considerable interest and stimulated neurochemical research on the dementia brain in several
leading institutes, implied that neurochemical or biochemical research could be successfully applied to elucidate the pathogenesis of Alzheimer’s disease. I am proud of this contribution of the Department of Neuropsychiatry, Osaka University which I chaired at that time and I am happy to observe the strong trend of psychogeriatric research launched by Professor J. Kaneko, as mentioned above, and pursued under the leadership of the present chairman, Professor M. Takeda.

Most of us would agree with the recognition that research activity in the Department of Neuropsychiatry, Osaka University, has played an important role in Alzheimer research and the Department achieved a solid reputation as one of the leading research institutes in psychogeriatrics.

The success of the 21st Annual Meeting of the Japanese Dementia Study Society and the International Symposium on Neurobiology of Alzheimer’s Disease and Related Disorders in October 2002 appears to be additional evidence for this. The International Symposium, especially, had an impact on Alzheimer research in this country, gathering many scientists from major research institutes in Japan and abroad to exchange their research findings. I would say the program of the symposium was well suited to stimulate young researchers in this field.

This monograph contains selected papers presented at the symposium and, just like the monograph The Psychiatric Aspects of Senility published half a century ago, will certainly contribute to promote scientific research in this field. It is my pleasure to write a foreword to this book and I would like to congratulate this collaborative achievement of Professors Masatoshi Takeda, Toshihisa Tanaka, and Ramón Cacabelos, who dedicated their time to this monograph, cultivating the long tradition of research of the Department of Neuropsychiatry, Osaka University.

Prof. emeritus of Osaka University Tsuyoshi Nishimura, Osaka
The average life expectancy of human beings had remained essentially unchanged since ancient times until the end of the 18th century, and it was only in those two centuries that our life expectancy increased. Since then, from an aging society (the elderly exceeding 7%), our society has become an aged society (the 65-year-olds and over exceeding 14% of the total population). In Japan this has happened in 2000; thus Japan has transited from an aging to an aged society in only 24 years, which is the most rapid transition in the world – almost four times faster than many European countries. The last national census of Japan reported that the average life expectancy of the Japanese was 85.23 years for females and 78.32 years for males in the year 2002. The Japanese now enjoy the longest average life expectancy, whereas in 1947 it was only 53.96 years for females and 50.06 years for males. Due to this rapid extension of life expectancy, Japanese society is now facing strains and problems related to its high proportion of elderly people (17%), and its very high percentage (7%) of very old people (above 75 years old).

In many European countries, the increase in the elderly population has already brought about some changes and modifications in the social life system, but there are still many things to be implemented to build a new society in which people can lead mutually cooperative lives regardless of their biological age. In the 21st century, the elderly population will increase all over the world because developing countries are showing a more rapid increase in the elderly population at the present time. By the year 2025, 70% of the elderly will live in developing countries, and by the year 2050, 80% of the elderly will be found in
present developing countries. These facts indicate that the rapid increase in the elderly population is a global social problem to be solved by taking advantage of information and experience from all countries. In a sense, Japan is the top runner in terms of society aging, and the Japanese experience may serve as an example to younger societies in other countries.

Alzheimer’s disease is the most malignant disease in aged societies. It affects 6–10% of the elderly population, causing impairment in cognitive functions and significant disability in daily living for more than 10 years. In Japan it affects 750,000 individuals, and by the year 2035, this number will have increased to 1.5 million.

Neurofibrillary tangles, amyloid deposits and neuronal loss are the three hallmarks of Alzheimer’s disease. Neurofibrillary tangles and amyloid plaques are insoluble depositions with unique structural characteristics, abundantly observed in Alzheimer brains and to some extent in normal aged brains. Due to the insolubility of these unique structures in Alzheimer brain tissues, they were difficult to study by usual biochemical methods in the past. In 1980s, owing to the use of a solubilization method with formic acid or perchloric acid, the neurobiological study of Alzheimer’s disease made significant progress. The major neurobiological findings include partial identification of the amino acid sequence of amyloid precursor protein (APP) (1984), identification of amyloid precursor protein gene on chromosome 21 (1987), detection of mutations in APP with familial Alzheimer’s disease (1991), identification of apolipoprotein E4 as a significant risk (1993), discovery of presenilin-1 and presenilin-2 (1994). Some neurobiological research outcomes have been applied in the clinical treatment of patients with Alzheimer’s disease. Acetylcholine esterase inhibitors are now widely used to treat Alzheimer patients. Tau and beta-amyloid protein levels can be useful as biological diagnostic markers of Alzheimer’s disease.

Active research is going on, aiming to elucidate the pathogenesis of Alzheimer’s disease. Major topics of neurobiological study of Alzheimer’s disease include the unraveling of the molecular mechanisms of neurofibrillary tangle formation in neuronal and glial cells; the molecular processing of amyloid precursor protein in intracellular organelles and in extracellular space, and the molecular mechanism of neuronal loss. In this book, these major topics are covered by leading scientists in the field of neurobiology of Alzheimer’s disease.

Alzheimer’s disease attracted researchers from diverse academic fields, including clinical, basic and social sciences. It is essential to promote the understanding of this formidable disease and to share new findings among researchers in the field.

Clinical and basic research of Alzheimer’s disease has been the main interest of the Department of Psychiatry and Behavioral Proteomics,
Osaka University Graduate School of Medicine, since the time of Professor Jiro Kaneko and Professor Tsuyoshi Nishimura, and it has been our great pleasure to compile this book as a milestone of the activity in our Department.

In October 2002, the Department of Psychiatry and Behavioral Proteomics, Osaka University Graduate School of Medicine organized the 21st Annual Meeting of the Dementia Study Academy of Japan, in which more than 400 researchers in this field got together to discuss their research progress in clinical and basic fields of dementia study. The three-day meeting program included two official symposia entitled ‘Neurobiology of Amyloid and Presenilins’ and ‘Neurodegeneration Mechanism with Tau, Syneclein and Neurofilaments’, two satellite symposia entitled ‘Early Diagnosis of Alzheimer’s Disease’ and ‘Treatment of Alzheimer’s Disease’, four luncheon seminars of ‘Strategy for BPSD’, ‘Neuroimaging of Dementia’, ‘Normal Pressure Hydrocephalus’, and ‘Treatment of Vascular Dementia’, in addition to 85 general presentations.

In conjunction with the 21st Annual Meeting of the Dementia Study Academy of Japan, we organized an International Symposium on the ‘Molecular Neurobiology of Alzheimer Disease and Related Disorders’. The articles in this book were selected from papers presented at this two-day International Symposium, which was very successful, with the participation of eight leading scientists from the USA, Canada and Europe. They are: Dr. Greg M. Cole (University of California), Dr. Khalid Iqbal (New York State Institute for Basic Research), Dr. Peter St. George-Hyslop (University of Toronto), Dr. Konrad Beyreuther (University of Heidelberg), Dr. Ramon Cacabelos (EuroEspes Biomedical Research Center), Dr. Harold Hampel (University of Munich), Dr. Inge Grundke-Iqbal (New York State Institute for Basic Research), and Dr. Roger M. Nitsch (University of Zurich).

We were very happy to host leading scientists from all over the world and are thankful to the speakers, and especially to the authors of the articles of this book, which, we believe, will be useful not only to basic scientists but also to clinicians interested in Alzheimer’s disease and related disorders.

Masatoshi Takeda, MD, PhD
Toshihisa Tanaka, MD, PhD
Ramón Cacabelos, MD, PhD
October 5, 2002
(First row) from left to right
Ramón Cacabelos, Khalid Iqbal, Roger Nitsch, Inge Grundke-Iqbal, Masatoshi Takeda, Konrad Bayreuther, Greg Cole, Peter St. George-Hyslop, Harald Hampel
(Second row)
Takashi Kudo, Tetsuaki Arai, Katsuya Urakami, Katsuhiko Yanagisawa, Nobuo Yanagusawa, Takeshi Tabira, Hiroshi Mori, Tomohiro Miyasaka, Yoshitaka Tatebayashi, Toshihisa Tanaka
(Third row)
Kouzin Kamino, Masaki Nishimura, Taisuke Tomita, Taiichi Katayama, Kazunori Imaizumi, Hideo Kimura, Shun Shimohama, Hisahi Tanii, Akihiko Nunomura, Masayasu Okochi
October 6, 2002
(First row from left to right)
Ramón Cacabelos, Harald Hampel, Khalid Iqbal, Inge Grundke-Iqbal, Konrad Bayreuther, Yasuo Ihara, Masatoshi Takeda, Roger Nitsch, Greg Cole
(Second row)
Takashi Kudo, Toshihisa Tanaka, Katsuhiko Yanagisawa, Akihiko Takashima, Takeshi Ishihara, Takeshi Tabira, Akihiko Nunomura, Tetsuaki Arai
(Third row)
Yoshitaka Tatebayashi, Taichi Katayama, Hiroshi Mori, Masaki Nishimura, Tomohiro Miyasaka, Taizo Taniguchi, Kazunori Imaizumi, Masayasu Okochi