Alzheimer's Disease

Cellular and Molecular Aspects of Amyloid β

Subcellular Biochemistry
Volume 38

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Preface

To understand Alzheimer's disease (AD) is one of the major thrusts of present-day clinical research, strongly supported by more fundamental cellular, biochemical, immunological and structural studies. It is these latter that receive attention within this book. This compilation of 20 chapters indicates the diversity of work currently in progress and summarizes the current state of knowledge.

Experienced authors who are scientifically active in their fields of study have been selected as contributors to this book, in an attempt to present a reasonably complete survey of the field. Inevitably, some exciting topics for one reason or another have not been included, for which we can only apologize.

Standardization of terminology is often a problem in science, not least in the Alzheimer field; editorial effort has been made to achieve standardization between the Chapters, but some minor yet acceptable personal / author variation is still present, *i.e.* β-amyloid/amyloid-β; Aβ42/Aβ1-42/$A\beta_{1-42}$!

The book commences with a broad survey of the contribution that the range of available microscopical techniques has made to the study of Alzheimer's amyloid plaques and amyloid fibrillogenesis. This chapter also serves as an Introduction to the book, since several of the topics introduced here are expanded upon in later chapters. Also, it is significant to the presence of this chapter that the initial discovery of brain plaques, by Alois Alzheimer, utilized light microscopy, a technique that continues to be extremely valuable in present-day AD research. Then follow 19 further chapters dealing with interesting areas of research that have a bearing upon

Alzheimer's disease. The authors present their own data within the context of a review of related work from others in their field of study.

Transgenic mouse models for AD are increasingly important and widely used, as is the understanding of the enzymology and biochemistry of amyloid β production from the amyloid precursor protein (APP) by the β- and γ-secretases, and the non-amyloidogenic APP cleavage products due to α-secreatases. Similarly, discussion of the enzymes responsible for the natural degradation of amyloid-β is included. Oxidative stress in AD and the possible protective role of vitamin E have emerged as highly significant topics. Likewise, the role of the metals, aluminium copper and zinc in AD is thoroughly addressed, along with the possible value of metal chelation. Current concepts as to the fundamental importance of amyloid-β oligomers *versus* Aβ fibrillar deposits (diffuse and senile plaques) in the pathogenesis of AD is presented, along with the likely role of tissue and cellular cholesterol in the promotion of Aβ fibrillogenesis, and Congo red binding to Aβ fibrils.

Several naturally occurring human proteins have the ability to bind to Aβ and are found in AD diffuse and senile plaques. Apolipoprotein E4, clusterin (ApoJ) and acetylcholinesterase are considered in depth. The direct effects of Aβ on neuronal membranes, in terms of neuronal membrane fluidity changes and calcium ion transport are dealt with, then the role of amyloid inhibitors and β-sheet breaking drugs is included. The likely important beneficial effects of the cholesterol-lowering drugs, the statins, in lowering brain Aβ and consequently the therapeutic prevention of AD by reducing Aβ deposition in plaques is discussed thoroughly. Finally, an exciting new concept is advanced, namely the possible significance of phosphorylated Aβ in Alzheimer's disease. From *in vitro* experiments Aβ phosphorylation appears to increase the proportion of Aβ oligomeric forms, an observation which correlates with the higher cytotoxicity of this species, compared to non-phosphorylated Aβ.

The editors hope that this book will be of interest and value to both medical and scientific research communities working on AD, and to others with a more general interest in the understanding of this devastating neurodegenerative disorder of the elderly.

Prof. J. Robin Harris
Prof. Falk Fahrenholz

University of Mainz
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