Editorial: Advances in Alzheimer Therapy: Something Old, Something New, Something Borrowed, Something Blue

The 8th International Montreal/Springfield Symposium on Advances in Alzheimer Therapy was held in Montreal on April 14-17, 2004. Under the skilled organization of Dr. Ezio Giacobini (Department of Geriatrics at the Hôpitaux Universitaires de Genève, Geneva, Switzerland), Dr. Serge Gauthier (McGill Centre for Studies in Aging, Montreal, Canada), and Dr. Jean-Pierre Michel (Department of Geriatrics at the Hôpitaux Universitaires de Genève, Geneva, Switzerland) the symposium brought together some 750 international scientists and health care professionals to provide an update on the most recent advances in the basic and clinical sciences with relevance to elucidating the etiology, pathogenesis, diagnosis and treatment of Alzheimer’s disease (AD). The symposium, occurring every two years, has succeeded in increasing our knowledge of the most recent advances in the therapy of AD - a complex disease that afflicts the elderly without prejudice for gender, race or social strata. As the name indicates, the first symposia in this series was located in Springfield, Illinois, the site of Southern Illinois University School of Medicine (SIU), and was conceived by Drs. Ezio Giacobini and Robert Becker, formerly of the Departments of Pharmacology and of Psychiatry, SIU, respectively. The highlights of prior Springfield symposia have been published in either book or journal form. We are proud to extend this legacy, and selected presentations from the recent 8th International Montreal/Springfield Symposium are published within.

During our initial interactions with the authors that kindly made this issue possible, we emphasized the broad scope that Current Alzheimer Research has provided the scientific community as a conduit and vehicle for thought-provoking primary research papers and hot topic review articles related to AD. Free reign within the scope of the journal and the symposium was granted, and the resulting exemplary, cutting edge contributions are stimulating and provide both intriguing and exhilarating directions for future basic and clinical research with an emphasis on treatment and slowing disease progression. The current issue comprises 11 articles, selected from both oral and poster presentations that run the full gambit of over-arching hypotheses of AD development and treatment.

NOVEL CHOLINESTERASE INHIBITORS: CAN THEY LOWER Aβ?

In line with the title of this preface, the initial article overviews a new agent, phenserine, in the treatment arena that has moved into phase 2 and 3 clinical trials for mild to moderate AD. Based on the backbone, of one of the oldest known anticholinesterases, physostigmine - a natural product derived from the calabar bean of West Africa that proved a powerful tool in elucidating the nature of chemical transmission of nerve action and the cholinergic system (Sir Henry Dale and Professor Otto Loewi, Nobel Prize 1936) – phenserine was developed and incorporates user-friendly features to optimize anticholinesterase actions for AD therapy. On the background of the controversy that recent clinical trials have caused concerning the size and the relevance of improvement in cognitive function of cholinesterase inhibitors in AD [1,2], there has been a focus to design drugs that go beyond symptomatic treatment. Phenserine offers potential along this avenue, and combines the actions of a cholinestrase inhibitor, with a preference for the acetyl enzyme form (AChE), and brain vs. plasma distribution, with non-cholinergically mediated actions to lower β-amyloid peptide (Aβ) levels via actions on its precursor protein (APP). Optimizing the translation of basic science into clinical efficacy is complex and ongoing, and remains key to maximize the utility of this and other new generations of drug candidates for AD.

Extending this theme, the once separate and exclusionary amyloid, tau and cholinergic hypotheses, that a decade ago tended to fractionate scientists, now increasingly overlap [3]. The involvement of common molecular pathways leading to cellular dysfunction and eventual death over-arches numerous neurodegenerative diseases [4] and, thereby, not only broadens the utility of breakthroughs made in a specific disease, such as AD, but also provides an inclusive forum that brings together the research and scientists.

ACETYLCOLINESTERASE: IS IT INVOLVED IN DISEASE PROGRESSION?

The article by Rees and colleagues provides intriguing new findings that support the importance of cholinergic-amyloid interrelationships in the development of AD. Utilizing available transgenic mouse models developed to help understand AD – (i) Tg2576 mice that incorporate the Swedish mutation of human APP to drive expression of Aβ and (ii) FVB/N transgenic mice that express synaptic human (h) AChE in mammalian brain neurons and exhibit a 2-fold increase in total brain AChE activity – the two were crossed to provide new double transgenic mice. Whereas, Tg2576 mice show an age-dependent elevation of insoluble Aβ in brain, FVB/N transgenic mice do not express amyloid plaques but have learning and memory deficits. Interestingly, in doubly transgenic progeny Aβ deposition proceeded faster than in singly transgenic APPswe littermates and Tg2576 mice. The underlying mechanism relating to this and memory affects are discussed by these authors.

Detrimental interactions between AChE and Aβ can occur on numerous levels and an additional one to those described by Rees and colleagues is the focus of the article by Inestrosa and colleagues. A specific region of AChE that is involved in the binding of specific cholinesterase inhibitors, the peripheral anionic site (PAS), appears to be intricately involved in the aggregation of Aβ into Alzheimer’s fibrils. Studies indicate the involvement of AChE as a chaperone to intensify oligomerization and increase Aβ neurotoxicity consequent to AChE-Aβ complex formation. An electrostatic interaction between a positively charged amino acid cluster present in the region corresponding to Aβ residues 12-16 and the PAS domain localized on the surface of AChE may account for this and are described together with alterations in the Wnt signaling pathway.
BUTYRYLCHOLINESTERASE: A TARGET FOR AD THERAPY?

The Cinderella sister of AChE is butyrylcholinesterase (BuChE). The two cholinesterase forms differ genetically, structurally and in their kinetics. Both enzymes cleave acetylcholine (ACh), among numerous other functions [5], but the role of BuChE in brain during health, development, aging and disease has been difficult to interpret. As described in an article by Ballard and colleagues, in human brain, BuChE is found in neurons and glial cells as well as in neurotic plaques and tangles associated with AD. Whereas AChE activity decreases progressively in the brain of AD patients, BuChE activity becomes elevated and in late stage disease likely represents the major cholinesterase form. The survival of mice nullizygote for AChE with normal levels of BuChE, suggests that the latter can replace AChE in hydrolyzing brain ACh. Based on the changes of cholinesterase activity in the brain of AD patients and the co-localization of BuChE with the classical hallmarks of the disease, a rational argument can be made for BuChE as a new target for AD therapy as well as for indications exemplified by dementia with Lewy Bodies.

CLINICAL TRIALS: HAVE WE FORGOTTEN SOMETHING?

The translation of experimental treatment strategies from the laboratory to the bedside is both complex and fraught with uncertainties. Additionally, such studies must adhere to both ethical and regulatory authority guidelines that quantify and balance safety vs. efficacy. As discussed in a thought-provoking article by Becker, clinical trials provide the modern gold standard for determining drug efficacy. Results from numerous clinical trials of different cholinesterase inhibitors, for example, provide consistent proof for the superiority of specific members of this drug class over placebo for periods up to a year. In contrast, in clinical settings many AD specialists convey gloom about the effects expected from such treatment of patients and their reliance [1,2] – something blue. As challenged by Becker, clinical pharmacology has dual research responsibilities to patients: to provide the most effective use of today’s remedies and improvements for tomorrow generated by innovating and testing new therapies. Becker poses the critical question as to whether methodological innovations can be made in clinical trials and clinical practice to optimize AD therapies for each afflicted individual? This is most certainly a valuable goal and worthy of pursuit.

γ-SECRETASE: A VIABLE DRUG TARGET FOR AD?

The central component of the amyloid hypothesis, Aβ, that is proteolytically derived from a large transmembrane protein, APP, which undergoes subsequent cleavages by β- and γ-secretases to liberate the N- and C-terminal moieties of Aβ, respectively [6,3], offers numerous targets for the design of inhibitors. The focus of an article by Checler and colleagues is γ-secretase, a generic term that refers to both presenilin (PS)-dependent and -independent entities. The PS-dependent γ-secretase activity is associated with a multicatalytic complex composed at least, by four distinct proteins; specifically, nicastrin, APH-1, Pen 2 and PS. As described in the article, the exact nature of the biologically active molecular complex is ambiguous as most of these proteins have various isoforms and can functionally interact with one another in numerous ways. Hence, the precise identity of the catalytic core of the PS-dependent γ-secretase complex has still to be definitively identified. In the face of such uncertainty, any rational approach designed to inhibit γ-secretase must overcome numerous potential problems. A key one is whether γ-secretase is specific for APP or is involved in the proteolytic regulation of other substrates of physiological relevance. Checler and colleagues describe a recently designed series of isocoumarin compounds, called JLK inhibitors, that have been shown to inhibit Aβ production without altering Notch cleavage, in vitro [7]. The characteristics and properties of these agents to selectively target Aβ-generating γ-secretase pathways are critically reviewed and, importantly, demonstrate the feasibility of designing agents to lower Aβ by targeting γ-secretase activity.

TAUOPATHIES: TIME FOR A TREATMENT?

A further classical hallmark of AD, as well as related tauopathies, is the characteristic neurofibrillary degeneration. As reviewed in an article by Iqbal and Grundke-Iqbal, the neurofibrillary changes derive from abnormally hyperphosphorylated tau. Contrasting with normal tau that promotes assembly and maintenance of the structure of microtubules, abnormal tau is not only deficient of these functions but, additionally, sequesters normal tau, MAP1 and MAP2, and induces the disassembly of microtubules. This aberrant action associated with abnormal tau appears to be exclusively due to its hyperphosphorylation, since dephosphorylation restores it into a normal-like protein. Such abnormal hyperphosphorylation, furthermore, promotes its self-assembly into paired helical or straight filaments. The state of phosphorylation of a phosphoprotein is a function of the activities of protein kinases and protein phosphatases that regulate the level of phosphorylation. As described in the article, a cause of the abnormal hyperphosphorylation in AD brain is a fall in the activity of protein phosphatase (PP)-2A, a key regulator of the phosphorylation of tau. A reduction in PP-2A activity causes abnormal hyperphosphorylation of tau by both lowering tau dephosphorylation and by stimulating the activities of tau kinases – thereby providing two strategic routes to limit/inhibit tau hyperphosphorylation: by lowering tau protein kinase activity or by restoring tau protein phosphatase activity. The development of drugs to inhibit neurofibrillary degeneration via these approaches is explored.

LOWERING CHOLESTEROL: WILL IT REDUCE AD?

The recent finding that cholesterol can modulate the yield of Aβ has boosted research on its role in AD [for review 8]. Consequently, several cholesterol-reducing drugs are currently being evaluated for the treatment of AD. An article by Sparks and colleagues describes the clinical benefit in the use of Atorvastatin treatment of AD. Atorvastatin is a synthetic lipid-lowering agent that inhibits 3 hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to me-
valonate, which represents an early and rate-limiting step in cholesterol biosynthesis. As described within the article, the principle that lowering circulating cholesterol levels would have a positive impact on cognitive and non-cognitive deterioration in mild-to-moderate AD was tested. In an investigator-initiated clinical evaluation, Sparks and colleagues describe a proof-of-concept trial evaluating Atorvastatin calcium for clinical benefit employing a randomized, double-blind, placebo controlled design. The trial, of one-year duration, utilized widely accepted clinical instruments that were administered quarterly. Primary and secondary outcome measures are described and support an exciting avenue for further research – where drugs “borrowed” from another disease may prove valuable in AD.

INFLAMMATION: STILL AN IMPORTANT MECHANISM IN AD ETIOLOGY?

Inflammation is common feature of a broad spectrum of neurodegenerative diseases, including AD, Parkinson’s (PD) and Huntington’s diseases, amytrophic lateral sclerosis, all tauopathies and multiple sclerosis – supporting a “neuroinflammatory hypothesis” of neurodegenerative diseases. It is, additionally, a common characteristic of numerous systemic diseases, exemplified by rheumatoid arthritis. Albeit that inflammation represents a first line of defense against injury and infection, a disproportionate inflammatory response can initiate additional injury, particularly to neural cells. In this regard, many neurodegenerative disorders are associated with the accumulation of abnormal protein assemblies, exemplified by Aβ in AD and α-synuclein in PD. Such assemblies can instigate cellular stress and neuroinflammation, to which neurons have a relatively low tolerance, and thus instigate a self-propagating cycle of auto-destructive immune and inflammatory processes that hamper the recovery or intensify neuronal injury. As reviewed in an article by Klegeris and McGeer, epidemiological evidence indicates that anti-inflammatory agents, such as non-steroidal anti-inflammatory drugs (NSAIDs), have a sparing effect on AD and PD. NSAIDs are protective in transgenic animal models of AD, providing further support of the aberrant effects of inflammation during disease progression. The protective effects of NSAIDs are described in an in vitro model with specific focus on underlying mechanisms and concentration-dependence. Such studies have previously proved priceless for many drug classes to optimize an agent in clinical trials. Classical NSAIDs as well as other anti-inflammatory agents may still represent a valuable strategy to slow the progression or delay the onset of AD and other neurodegenerative diseases, despite the failure of past clinical trials.

STEM CELLS THERAPY: A FUTURE TREATMENT OPTION?

The latest developments in stem cell technology have broadened our horizons as to what is possible in science by expanding our ability to replace many types of tissue throughout the body, previously thought to be irreplaceable. In the past, cognitive impairment caused by degeneration of neuronal cells had been considered incurable once the pathway of dysfunction had moved to cell death, as it was believed that neurons could not regenerate during adulthood. However, as described in an article by Sugaya, there is provocative new evidence that neurons do, indeed, have the potential to be renewed after maturation. The discovery of multipotent neural stem cells (NSCs) in the adult brain has instigated revolutionary changes in the theory of neurogenesis, which now establishes that regeneration of neurons can occur throughout life, thereby opening a new door for the development of novel therapies to treat neurodegenerative diseases, including AD, by neuronal regeneration using stem cell technologies. The bright future of stem cell technology is balanced by the complexities that have yet to be overcome, with specific focus on AD and APP/Aβ synthesis and metabolism.

SIMULATING CELL SURVIVAL AND INHIBITING CELL DEATH, A WAY AHEAD?

Finally, an article by Perry and Greig reviews the potential benefits of stimulating biochemical pathways that favour cell survival over apoptosis as an approach to treat neurodegenerative diseases. The strategy they focus upon is initiated by stimulation of the glucagon-like peptide-1 receptor (GLP-1R) in brain. This is something new and is borrowed from a different disease. GLP-1 is an endogenous insulinotrophic peptide that is secreted from the gastrointestinal tract in response to food. It induces glucose-dependent insulin secretion, and lowers blood glucose and food intake in patients with type 2 diabetes mellitus. It additionally enhances pancreatic β-cell proliferation. GLP-1 receptors, are coupled to the cyclic AMP second messenger pathway, and in addition to the pancreas, are expressed throughout the brain of rodents and humans. Long-acting peptide analogues have been developed as experimental therapeutics for type 2 diabetes, and GLP-1 and specific analogues appear to be transported at the blood-brain barrier. It is the CNS action of these GLP-1R agonists, which promote neuronal survival and differentiation in both classical cellular and in vivo models, that is the focus of the article. The elevated risk of a variety of neurodegenerative diseases with type 2 diabetes, including AD [9], peripheral neuropathy and stroke, coupled with the rising incidence of type 2 diabetes in the US population may lead to the assessment of GLP-1R agonists as a strategy to off-set neurodegenerative diseases.

Clearly, it would be idyllic to provide an article on each presentation from the Montreal/ Springfield Symposium, but including these within a single issue of a peer-reviewed journal would be problematical. This issue hence captures a snapshot of a truly electrifying meeting that would serve as a nucleus to further enhance new ideas, hypotheses and testing models for future basic and clinical research with an emphasis on drug development and treatment strategies for this devastating disease. In closure, we wish to thank the publisher and staff of Current Alzheimer Research for their cooperation and efforts in promoting and distributing this important volume (http://www.bentham.org/car/).

REFERENCES


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