RESEARCH COLLECTION ON

INFLAMMATORY DISEASES AND RHEUMATOLOGY

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Research Collection on Inflammatory Diseases and Rheumatology

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Chapters from books edited by: **Mahin Khatami, Jan Tore Gran, Andrew Harrison, Andrew Lemmey, Miroslav Harjacek** and **Hiroaki Matsuno**

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Preface

In recent years it has been realized that some inflammatory and rheumatic diseases are in fact immune disorders, and as a result the fields of immunology and rheumatology are coming to overlap more and more. Many of the conditions discussed in this book are a reflection of this fact: systemic lupus erythematosus, Sjögren's syndrome, sepsis and the debilitating metabolic condition cachexia, which is a consequence of the exaggerated immune response that occurs in many chronic diseases.

A key area of focus for the book is the subject of rheumatoid arthritis, including its etiology, co-morbidities, molecular and pathophysiological mechanisms, and potential new treatments, formulations and targeted delivery systems. Further chapters will discuss acute appendicitis, inflammatory myopathies, the economic impacts of rheumatic diseases, the role of vitamin D deficiency, and experimental modeling of the inflammatory mechanisms involved in the pathogenesis of Alzheimer's disease.

This book is essential reading for practicing clinicians (especially immunologists and rheumatologists), and will also provide valuable insights for those carrying out research in these disciplines.

INFLAMMATORY DISEASES – IMMUNOPATHOLOGY, CLINICAL AND PHARMACOLOGICAL BASES

Edited by **Mahin Khatami**

Dementia – A Complete Literature Review on Various Mechanisms Involves in Pathogenesis and an Intracerebroventricular Streptozotocin Induced Alzheimer's Disease

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1. Introduction

Dementia is a brain disorder characterized by a decline in several higher mental functions (e.g. memory, intellect, personality) that causes significant impairments in daily functioning (Kuljis, 2007). The prevalence of dementia rises with age, doubling every 5 years between the ages of 60 and 90 (Corrada et al., 2008). Based on the epidemiological data, dementia is widely recognized as a major medical, social and economic problem in developed countries where the age over 65 accounts for an increasingly high percentage of the dementic population (Breitner et al., 2009). Unfortunately, dementia is now becoming a major problem in developing countries where it did not exist 50 years ago (Zilkens et al., 2009). More than 50 million people worldwide have dementia and the most common and irreversible cause of this dementia is Alzheimer's disease (AD) (Adlard et al., 2009). AD is a neurodegenerative disorder divided into two forms namely familial (FAD) and sporadic (SAD) cases characterized by cognitive deficits and extensive neuronal loss in the central nervous system (CNS) (Michon et al., 2009; Reed et al., 2009) and at the molecular level by the presence of specific cytoskeletal abnormalities, including intracellular neurofibrillary tangles (NFT) formed by hyperphosphorylated tau protein and the presence of high levels of the 40- and 42-amino acid long amyloid beta (Aβ) (Woodhouse et al., 2009). The early onset form (i.e. FAD) has a strong genetic correlation that exists between characteristic features of AD pathogenesis and mutations in amyloid precursor protein (APP), (Bernardi et al., 2009), presenilin (PS-1) and PS-2 (Huang et al., 2009). Of particular interest, the other form of AD, SAD is a multifactorial disease to which both genetic and epigenetic factors contribute (Zawia et al., 2009). The well confirmed genetic factors for SAD are apolipoprotein E (APOE) epsilon 4 allele (Wharton et al., 2009) and PS-2 promoter polymorphism (Liu et al., 2008). Accumulating data indicates that disturbances of several aspects of cellular metabolism appear pathologically important in SAD. Among these, increased brain insulin resistance (Salkovic-Petrisic, 2008), decreased glucose utilization and energy metabolism are observed in the early stages of the disease (De la Torre, 2008),

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consequently energy deficit, oxidative stress (Droge and Kinscherf, 2008) and inflammation (De la Monte, 2009) in neuronal tissue which further cause neurodegeneration in SAD.
By understanding some of the pathological aspects of SAD in humans currently, intracerebrovetricular (ICV) administration of streptozotocin (STZ) in rats is commonly employed to study experimental dementia. Most importantly, subdiabetogenic doses of ICV -STZ induce alterations of brain insulin receptor (IR) and its signaling and consequently insulin resistant brain state and behavioral, neurochemical, biochemical, morphological, and histological changes similar to aging brain (Salkovic-Petrisic, 2008; Ishrat et al., 2009 a, b). Further, it has been well demonstrated that ICV -STZ rat model is targeting the functioning of brain IR signaling cascade. In brain, decreased levels of glucose/energy metabolism particularly in cerebral cortex and hippocampus regions have been reported starting from 3 weeks following ICV -STZ administration (Pathan et al., 2006) and consequently mitochondrial dysfunction (Agrawal et al., 2009). Additionally, a progressive trend towards oxidative stress has also been found starting as early as 1 week following the ICV -STZ administration (Pathan et al., 2006). In addition to reduced energy metabolism and mitochondrial dysfunction, increased free radical generation and subsequent oxidative and nitrosative stress which are well reported to impair learning and memory leading to cognitive dysfunction (Ishrat et al., 2009 a, b; Tiwari et al., 2009). Furthermore, decreased cholinergic transmission (decreased choline acetyltransferase and increased acetylcholinesterase activity) has started to be persistently found later on in the hippocampus of ICV -STZ treated rats (Blockland and Jolles 1993, Terwel et al., 1995). ICV -STZ administration has also been associated with certain brain morphological changes followed by extensive cell loss and neurodegeneration by induction of specific damage to myelinated tract and astrogliosis found 1 week following the treatment regardless the age of animals (Sonkusare et al., 2005). Further, ICV -STZ induced reduction in energy availability may also results in increase in cytoplasmic calcium (Ca^{2+}) ions (Muller et al., 1998) confirmed by pharmacological use of calcium channel blocker (lercanidipine) that markedly attenuated behavioral and biochemical alterations in ICV -STZ rats (Sonkusare et al., 2005). It is well known that ATP dependent brain functions are markedly affected in energy failure and reduced glucose metabolism states. Relevant to this, all these neurochemical and structural changes have been observed as early as 2 weeks after ICV -STZ administration and reported to still persist 12 weeks accompanied by long term progressive deficits in learning and memory (Lannert and Hoyer, 1998, Grunblatt et al., 2007) and play a major role in the pathogenesis of SAD.

2. Dementia – a background

Dementia is a syndrome that in most cases is caused by an underlying disease of brain disorder characterized by a decline in several mental functions e.g. memory, intellect, personality that significantly impair daily functioning (Ferri et al., 2005). Dementia is a clinical syndrome with multiple etiologies that particularly affects older people (Corrada et al., 2008). Up till now, there is a lack of full understanding of the underlying causes and molecular mechanisms leading to this progressive form of dementia. Given the seriousness of the impact of dementia, the ageing of the world's population, and that the prevalence of dementia increases with age, a lot of attention is understandably now focused on the treatments, care services and support arrangements needed by people with dementia and their families, both today and over the coming decades.