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BRAIN RESEARCH REVIEWS

Review

A new insight on Al-maltolate-treated aged rabbit as Alzheimer's animal model

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ABSTRACT

Lack of an adequate animal model for Alzheimer's disease (AD) has limited an understanding of the pathogenesis of the disease and the development of therapeutic agents targeting key pathophysiological processes. There are undoubtedly few satisfactory animal models for exploring therapies targeting at amyloid beta (Aβ) secretion, deposition, aggregation, and probably the inflammatory response. However, an understanding of the complex events – tau, Aβ, oxidative stress, redox active iron, etc. – involved in the neuronal cell loss is still unclear due to the lack of a suitable animal model system. The use of neurotoxic agents particularly aluminum–organic complexes, especially Al-maltolate, expands the scope of AD research by providing new animal models exhibiting neurodegenerative processes relevant to AD neuropathology. Examination of different species of aged animals including the rapidly advancing transgenic mouse models revealed very limited AD-like pathology. Most other animal models have single event expression such as extracellular Aβ deposition, intraneuronal neurofilamentous aggregation of proteins akin to neurofibrillary tangles, oxidative stress or apoptosis. To date, there are no paradigms of any animal in which all the features of AD were evident. However, the intravenous injection of Al-maltolate into aged New zealand white rabbits results in conditions which mimics a number of neuropathological, biochemical and behavioral changes observed in AD. Such neurodegenerative effects include the formation of intraneuronal neurofilamentous aggregates that are tau positive, immunopositivity of Aβ, presence of redox active iron, oxidative stress and apoptosis, adds credence to the value of this animal model system. The use of this animal model should not be confused with the ongoing controversy regarding the possible role of Al in the neuropathogenesis, a debate which by no means has been concluded. Above all this animal model involving neuropathology induced by Al-maltolate provides a new information in understanding the mechanism of neurodegeneration.

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Contents

1. Introduction

AD is a complex neurodegenerative disorder comprising complex neurobiochemical and neuropathological events, characterized by three typical pathological features, namely the extracellular deposition of Aβ (Selkoe, 1989, 1991; Hardy and Selkoe, 2002; Hardy and Higgins, 1992), the formation of intraneuronal neurofibrillary tangles (NFTs) (Doll, 1993; Perry and Perry, 1985; Perl and Brondy, 1980; Lovell et al., 1993; Wisniewski and Sofer, 1979), and selective neuronal loss. However, it is still unclear which of these pathological features is the primary event in the initiation and progression of this disease. The etiological factors of AD include genetics, head trauma, oxidative stress, infectious agents, and environmental factors including aluminum (Al) toxicity. The pioneering studies on neurotoxicity of Al in experimental animals were first reported in 1897 by Dollken (1897). Many scientific studies have brought to light the potential toxicity of Al in experimental animal models and in humans under different clinical conditions (Spafforth, 1921; McLaughlin et al., 1962). But the usage of Al in experimental animal came to light following the extraordinary discovery of Klatzo et al. (1965) who showed that injections of Al-salts into rabbit brain led to the formation of NFTs which appeared similar to the NFTs of AD (Klatzo et al., 1965; Terry and Peña, 1986). Later, these results were replicated in cats by Crapper et al. (1973). The complex chemistry of Al and the fact that there was no readily available radioisotope for experimental purposes thus hindered the clarification of this element's involvement in the etiology of AD. However, studies by Priest (2004) on humans and animal using the ^{26}Al radioisotope (Yumoto et al., 2001) have demonstrated that Al can indeed enter the central nervous system following systemic administration (Walton et al., 1995). In addition, there is documented evidence that Al is neurotoxic, both in human disease, as well as in experimental animals (Wills and Savory, 1983). Studies by Wen and Wisniewski (1985) histochemically localized Al in rabbit CNS further supported by Uemura (1984) illustrated intranuclear Al accumulation in chronic animals in turn led to neurofibrillary changes. Thereby Al salts administered intracerebrally or peripherally in rabbit (Klatzo et al., 1965), cat (Crapper et al., 1973), monkey (Games et al., 1995), rat (Brining et al., 1996), and dog (Uno et al., 1999) induce the formation of neurofibrillary aggregates (NFAs) which has contributed to the argument that Al is one of the contributing factor to several neurodegenerative disorders, mainly AD. However, this hypothesis remains controversial.

Although understanding of the complex events involved in neuropathogenesis and neurobiochemical events in AD requires the availability of suitable animal model systems. Understanding the neurodegeneration pathways in relationship to Aβ deposition, NFT and neuritic plaque formation using human tissue is limited since only a single time point, an intrinsic limitation resulting from the use of human