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Minireview

Animal models of dementia and cognitive dysfunction

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ABSTRACT

Recent advances in the understanding of the pathophysiological mechanisms underlying Alzheimer's disease and other cognitive deficits have pointed to novel strategies for drug development. Animal models have contributed noticeably to these advances and are an indispensible part in the evaluation of therapeutics. This review is an exhaustive study of animal models of dementia and cognitive dysfunction. A thorough and critical evaluation of current rodent models of dementia, and discussion about their role in drug discovery and development have been carried out. Since dementia has multiple pathophysiological mechanisms, we have tried to provide a detailed description of various types of animal models which would depict different pathophysiological stages and causes of dementia. This review aims to better understand the prognosis, biochemical, and behavioral alterations that occur during dementia and hence facilitate drug discovery and development.

Contents

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Introduction

Dementia is defined as cognitive impairment in more than one cognitive area characterized by loss of intellectual ability of sufficient severity to interfere either with occupational functioning, usual social activities or relationship of a person in the absence of gross clouding of consciousness or with motor involvement (Sharma and Singh, 2010). A report from aging demographics and memory study, ADAMS (Plassman Langa et al., 2007), estimated that in America the number of people with dementia was 4.5 million and by 2050 it may rise to 16 million (Tayeb et al., 2012). Cognitive areas involved in dementia includes: language (aphasia), motor (apraxia), agnosia (failure in recognition) & executive functions (abstract reasoning, judgment and planning) (Kidd, 2008). There are many types of dementias (Husband and Worsley, 2006; Sodhi et al., 2011) including dementia of Alzheimer's disease, vascular dementia, dementia with Lewy body, frontotemporal dementia, dementia associated with Parkinson's disease, dementia associated with Huntington's disease, Wernicke Korsakoff syndrome, and Creutzfeldt–Jakob disease. Our aging society is confronted with a remarkable increase in incidence of age-related neurodegenerative diseases (Raslan and Kee, 2013). Stress has been reported to have significant contribution towards many cognitive and physiological deficiencies. Chronic stress has been reported to induce atrophy and functional impairments in several brain areas such as the frontal cortex and hippocampus that play an important role in the generation and progression of AD (Wang et al., 2014). Stress affects cognition in a number of ways, acting rapidly via catecholamines and more slowly via glucocorticoids by activating locus coeruleus–norepinephrine–sympathetic nervous system and the hypothalamic–pituitary–adrenal axis respectively (Oken et al., 2011). Suitable animal models of neurodegenerative conditions are valuable to understand the pathophysiology of dementia and development of new therapeutics (Balducci and Forloni, 2010; Laurijssens et al., 2013). Here, we review animal models of Alzheimer's disease which will enable researchers to compare different animal models targeting disease-associated molecules by genomic engineering and to facilitate the development of novel animal models depending on the ultimate research goals (Gotz and Ittner, 2008). High research priority to develop animal model of dementia is due to disease prevalence and poor prognosis of the disease (Elder et al., 2010). Development of animal models is challenging as there is no single animal model that can explain all the cognitive, behavioral, biochemical and histopathological abnormalities (Tayebati, 2006). An ideal animal model should mimic the human disease and reproduce complexities of human behavior in rodents. So far various animals like rodents, monkeys, aged rhesus, worms and flies have been used to develop animal models of dementia. Rodent models play a major role as mice cannot develop plaques and tangles normally; mice can be induced to develop plaques and tangles in specific brain regions (Agca et al., 2008). Monkeys take longer time and are expensive to maintain. Fly and worm brains are vastly different from human brains and it is difficult to develop dementia (Elder et al., 2010). Various chemicals (streptozotocin, scopolamine, colchicines, heavy metals etc.) have also been used to develop animal models of dementia, however the major disadvantage of these models is that no disease progression occur with single administration, some of them are time consuming, have high mortality rate and are invasive in nature (Dam and Deyn, 2006). However the advantage of these animal models is that they have been explored to study many therapeutic agents clinically in use for various types of dementia and cognitive dysfunctions, hence enabling them to closely co-relate with the pathophysiology similar to humans. A number of transgenic animal models (PDAPP mouse, Tg2576 mouse model, App23 mouse, JNLP3 mouse, ApoE mouse models etc.) have been developed for dementia as it has well recognized pathology of senile plaques and neurofibrillary tangles in case of dementia of AD. Accordingly transgenic models of dementia of other than AD have also been developed like animal models for dementia associated with Parkinson's disease (Harvey et al., 2008; Skaper and Giusti, 2010) and Huntington's disease (Hohn et al., 2011). However, transgenic models have a number of disadvantages of being expensive to develop, no disease progression occur and cause neuronal cell death (Pype et al., 2003). So studies are underway in order to develop an ideal animal model that is inexpensive, non-invasive and mimics the pathogenesis of the disease.

Animal models to evaluate dementia and cognitive deficits

Various animal models of dementia (Alzheimer's disease in particular) and cognitive decline have been developed and these may be broadly classified based on diverse pathophysiological basis (Table 1, Fig. 1).

Spontaneous models

Memory loss is a primary characteristic feature of old age therefore aged animals can serve as natural model of memory deficits and dementia. The spontaneous models have been further classified into aging induced dementia and senescence accelerated mouse (SAM) models which are as follows.

Aged induced dementia

Aging animals are used routinely in drug development due to age related cognitive decline and behavioral alterations which mimic not only the neurochemical and morphological alterations (Erickson and Barnes, 2003; Gupta et al., 2013) but also the cholinergic hypofunction (Sherman and Friedman, 1990; de Souza Silva et al., 2013) that is similar to pathophysiology of Alzheimer's disease. Reports indicate that dopaminergic and glutamatergic dysfunctions may also contribute to age related dementia (Collier et al., 1988). The advantage of this model is that it is non-invasive, natural and

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