Alzheimer’s Disease Is Still a Mystery

Alzheimer’s disease (AD) is the most common cause of dementia. It is characterized by progressive cognitive decline and by the loss of ability to form and recall short-term memories (Nelson et al., 2009). The cellular hallmarks of AD include the appearance of amyloid-β plaques and neurofibrillary tangles in the hippocampus; i.e. in the structure responsible for memory formation and learning. Current treatments can alleviate some symptoms of AD, but there is no way to prevent or delay disease onset, to stimulate brain repair, or to replace diseased or dead neurons (Giacobini and Gold, 2013). Much of our knowledge of the AD-associated brain changes originates from looking at the brain post-mortem; i.e., at the very last stage of the disease. For this reason, the earliest pathological signs and the putative protective response of the brain that would precede the clinical symptoms are, for the most part, still a mystery. Identification of the early signs of AD is an important focus for future research because it would facilitate finding early treatment strategies.

Neurogenesis and Alzheimer’s Disease Are Interrelated

The first clinical symptoms of AD include impaired formation of new memories (due to hippocampal lesions) and problems with smell-related memories (due to degeneration of the olfactory bulb and its connections; Attems and Jellinger, 2006). Neurogenesis is a process by which new neurons are produced in active proliferation pools. Newly formed neurons then migrate to brain regions where they are needed. Adult neurogenesis occurs during the entire lifetime, predominantly in two specific brain regions (see review in Abrous et al., 2005); namely in the subventricular zone (SVZ, a region near the lateral ventricles) and the subgranular zone (SGZ, in the dentate gyrus of the hippocampal region; Ming and Song, 2011). The anatomical colocalisation of AD-specific lesions and neurogenesis has prompted the hypothesis that the initial effect of AD is impaired neurogenesis in these regions. If this hypothesis is true, enhancing neurogenesis could be a viable treatment strategy to make early interventions in AD.

If AD Is Diagnosed Early, the Reversal of Cell Death Is Feasible

In recent years, medical research has turned its focus toward the detection of preclinical neuropathological changes as well as to the introduction of preventive and early therapeutic interventions. Great advancements have been made in our understanding of mild-cognitive impairment, and there has been success in the development of screening tools such as brain scans that detect amyloid-β plaques (PiB scans) and blood biomarkers. Lending weight to the importance of neurogenesis research in this endeavour, is our research team’s observation that
neurogenesis becomes defective long before either the onset of clinical symptoms or the appearance of amyloid-β plaques in a mutant mouse model of AD (Kim et al., 2013; Fu et al., 2014). To identify the early morphological signs of AD, we examined six major stages across the lifespan of an established mouse model of AD, and measured changes in the neuronal cell numbers and neurogenic activity. Our data show that neurogenesis is decreased at the age of 7 weeks in AD mice; well before cognitive symptoms start to appear (at about 5 months of age). Research into neurogenesis, therefore, may open up the opportunity to identify novel disease-associated biomarkers. Thorough investigation of the anatomical features involved in neurogenesis and its impairment in AD, including cell surface markers or the level of neurotropic factors, may reveal biochemical markers characteristic of the earliest disease processes in either the blood or cerebrospinal fluid. Reliable identification of appropriate biomarkers may make an impact on the early diagnosis and clinical care for AD patients.

**Lifestyle Factors Can Modify Neurogenesis**

Several non-invasive enrichment strategies have been demonstrated to potentiate neurogenesis in mice. One of these is “Environmental enrichment”, which is the provision of running wheels, spacious housing, regular challenges to balance and memory, varied textures and bedding, climbing toys, and tunnel mazes for voluntary use. Environmental enrichment increases neuron survival and improves spatial memory; the latter is being one of the early targets of AD (van Praag et al., 2005; Hu et al., 2010). In addition, our trial study showed that pleasant odours increase the number of neurons in the mouse olfactory bulb. In contrast, it has been described that stress reduces cell proliferation and spatial memory through cortisol-induced hippocampal glutamatergic activity (Abrous et al., 2005). These observations suggest that positive stimuli are important for neurogenesis.

The reported numbers of newly produced cells in the hippocampal dentate gyrus are highly variable across several studies (ranging from 3000 to 9000 cells/day), purportedly due to differences in the age of the mice (Cameron and McKay, 2001; Rao and Shetty, 2004). Indeed, there is an age-related decrease in neurogenesis, which seems to be due to changes in the cellular environment (Wagers, 2012). It was demonstrated, for example, that introducing a blood borne factor present in old mice into the blood of young mice suppress neurogenesis (Villeda et al., 2011). In contrast, several research groups have found that specific changes in the diet and environment of the experimental animals have a positive impact on the aged brain, and they may counterbalance the deteriorating effects of ageing (Stangl and Thuret, 2009; Lledo et al., 2012).

Intervention during the pre-symptomatic stage of AD may be effective in preventing or retarding neurodegeneration, but the potential adverse effects of prophylactic pharmacological treatments in individuals who may never become symptomatic has an inherent risk. Non-invasive and non-toxic stimuli, such as environmental enrichment and exposure to novel odours, were shown to affect hippocampal and olfactory bulb cell proliferation and neurogenesis, respectively (van Praag et al., 1999; Lucassen et al., 2010; Hawley et al., 2012; Huang et al., 2012; Speisman et al., 2013). This suggests that these interventions can delay the onset of symptoms with no or minimal adverse effects. The significance of the present proposal is that it investigates whether and how enriched lifestyle may facilitate self-repair or delay the progression of AD. The information yielded from the successful completion of the proposed work contributes our understanding of the anatomy and biochemistry of neurogenesis in health and disease.
References:


