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Editorial

Lifestyle Factors and Alzheimer's Disease

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Dedication

This Special issue is dedicated to my PhD mentor and friend Prof. Hanan Frenk. I am forever grateful for his guidance, encouragement and support. He taught me how to ask research questions, design experiments, write papers and how to navigate the world of science. His inspiring personal example and integrity are the bedrock of my scientific pursuits. His jokes and unedited advice ring in my ears even thirty years later:
- If you work only from 9-5 you will never be a scientist.
- If you don't know how to write you will never get a faculty job.
- Life is not fair, just keep your focus.
And: 'Wow, we published your paper [1]. Let me invite you over to our house for dinner to celebrate'.

With the increase in human lifespan, more aging-related cognitive disorders, including Alzheimer's Disease (AD) are being diagnosed. AD is the most common form of dementia and possibly contributes to 60–70% of dementia cases [2]. The impairments associated with this disease are devastating for the patients and their families. According to the World Alzheimer Report 2018, there are about 50 million people worldwide living with dementia and this number may reach 132 million in 2050, accelerating a socio-economic healthcare crisis. The disease results in accumulation of extracellular amyloid plaques and intracellular neurofibrillary tangles, or tau pathology, in the brain. These pathologies are considered to impair neuronal function, especially in the hippocampus and entorhinal cortex, resulting in cognitive deficits and memory loss [3, 4]. Sadly, there are no effective treatment options for AD patients, and recent clinical trials have resulted in failure [5].

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In the absence of medications that can halt or prevent AD, lifestyle interventions that could improve or maintain cognitive function have become increasingly important. This Special Issue of Brain Plasticity includes eight in-depth review articles that focus on the role of lifestyle factors, and the underlying cellular and molecular mechanisms, in the prevention or delay of onset of AD. The Special Issue begins with an article addressing how insulin signaling pathways play an important role in multiple modifiable behaviors such as diet, physical and mental activity, stress exposure and sleep/wake cycles [6]. The authors provide a detailed analysis of the extensive involvement of insulin and insulin-like peptides (IGF-1 and IGF-2) in brain function, including inflammation, oxidative stress, synaptic plasticity, neurogenesis, Aβ clearance, among others. They make a convincing case that disruption of insulinergic function by stress, sedentary behavior and overconsumption can lead reduced levels of these peptides and their cognate receptors in the brain, and so may hasten AD onset.

The following six papers are focused on exercise as a central lifestyle factor and highlight various aspects of the benefits of physical activity on brain function

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and prevention or delay of AD. The role of growth factors is maintaining brain health is highlighted in several of the papers. In particular the upregulation of hippocampal brain-derived neurotrophic factor, IGF-1 and vascular endothelial growth factor (VEGF) by exercise is discussed. The authors concur that elevation of these important factors is not only neuroprotective but also decreases AD pathology [7, 8]. Another highly relevant aspect that is reviewed in the papers by Vecchio et al., (2018) and by Barnes and Corkery (2018) is the role of the vasculature. With aging or disease the blood brain barrier (BBB) deteriorates and may facilitate entry of toxic and inflammatory molecules into the brain. Exercise can protect the BBB by regulation of tight junction proteins [7] and thereby reduce AD risk. The importance of intact vasculature is further supported by research showing that adults with cardiovascular disease or risk factors such as hypertension, diabetes and obesity have a greater incidence of cognitive impairment in old age. Indeed, the authors describe how vascular health is associated with brain structure and function, and is probably a critical link between aerobic exercise and cognitive function [9]. Interestingly, the review article by Barha and Liu-Ambrose (2018) points out that cardiovascular risk factors may be greater in older females than males. Together with sex differences in markers of inflammation, growth factors and differential responsiveness to exercise protocols, there may be multiple mechanisms underlying increased incidence of AD in women [10].

Several of the articles highlight the importance of inflammation in the etiology of AD [6, 8, 10–12]. The Special issue also includes a detailed review as to how exercise may attenuate neuroinflammatory processes that are likely due to elevated cytokines secreted from reactive astrocytes and microglia in the brain. In particular, studies in animal models are discussed that provide evidence that exercise upregulates anti-inflammatory cytokine interleukin (IL)-10 and attenuates levels of IL-β and tumor necrosis factor alpha (TNFα) in the periphery and brain [11]. Finally, two articles provide a comprehensive overview of the effects of exercise and environmental enrichment in mouse models of AD [12, 13]. While both interventions confer benefits for reversal in deficits in adult neurogenesis, synaptic plasticity and memory function, the timing before or after onset of disease is of particular importance in determining outcomes [12].

In conclusion, the reviews in this Special Issue highlight multiple facets of AD pathogenesis, ranging from deficient growth factor signaling and neuroinflammation to impaired adult hippocampal neurogenesis and vasculature. Together they also provide a comprehensive analysis of the cellular and molecular mechanisms underlying the beneficial effects of lifestyle factors that may prevent or delay AD onset.

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