Ageing, metabolic homeostasis, and the brain

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Ageing is the principal risk factor for a large number of diseases posing chronic and substantial dents in the clinical infrastructure. There are many hallmarks and aspects of ageing, and understanding these is expected to offer new insights into the maintenance of health span and/or our understanding of disease progression and susceptibility[1]. The most robust intervention known to modulate the ageing process is dietary restriction, by which different dietary paradigms elongate lifespan and health span[2]. From the observation that Creb-binding protein correlates with lifespan in the hypothalamus, our lab showed that effects of dietary restriction are blocked in *C. elegans*[3]. Here we present an extension of these observations by demonstrating that in adult mice, reducing Creb-binding protein in the nutrient-sensing hypothalamus results in overt obesity and phenotypical metabolic syndrome[4]. Conversely, we also show that dietary restriction in mice prevents neurodegenerative effects in a Huntington's Disease mouse model with concomitant increased expression of Creb-binding protein[5].

Evidence in the ageing field suggests that at least some aspects of ageing can be modulated in a hierarchal manner through such structures as the hypothalamus[6,7]. On the other hand, studies from heterochronic parabiosis support more holistic mechanisms, such as tissue renewal dysfunction[8]. This latter view posits that the status of stem cell niches drive ageing phenotypes as postulated by the Stem Cell Theory of Ageing[9]. We propose an integration of both views and describe future approaches that tests the effects of focal progeroid manipulations in brain structures to delineate both local from peripheral changes in ageing phenotypes. Strategically, these questions will be explored by the StemCARE centre for its unique qualifications to assess such mechanisms.

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