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Invited review

Enhancement of cognitive function in models of brain disease through environmental enrichment and physical activity

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ABSTRACT

This review will provide an overview of the non-drug based approaches that have been demonstrated to enhance cognitive function of the compromised brain, primarily focussed on the two most widely adopted paradigms of environmental enrichment and enhanced physical exercise. Environmental enrichment involves the generation of novelty and complexity in animal housing conditions which facilitates enhanced sensory and cognitive stimulation as well as physical activity. In a wide variety of animal models of brain disorders, environmental enrichment and exercise have been found to have beneficial effects, including cognitive enhancement, delayed disease onset, enhanced cellular plasticity and associated molecular processes. Potential cellular and molecular mechanisms will also be discussed, which have relevance for the future development of 'enviromimetics', drugs which could mimic or enhance the beneficial effects of environmental stimulation.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

The controversy and continual debate over the ethical implications of the use, and possible misuse, of cognitive enhancing drugs (such as methylphenidate) by healthy individuals appears to have overshadowed another group of potential beneficiaries. Those afflicted with pathological conditions that result in a compromise of cognitive ability, such as executive decision making and memory formation or recall, are clearly the key target population for such cognition enhancing drugs as a means of improving their quality of life. There is good evidence to support potential efficacy, with several drugs already in late-phase clinical trials as a means to delay or avert cognitive decline. However, these clinical assessments are more recent, with much of the current evidence of drug effects coming from animal studies. In comparison, non-drug interventions that improve cognitive ability in a healthy organism and also as a means of delaying cognitive decline and rescuing memory-related deficits in animal models of neurological conditions have been well-established to have significant beneficial effects.

Environmental factors which have been shown to enhance cognition in animal models include environmental enrichment, physical exercise and diet. Prior to discussion of environmental stimulation approaches in further detail, we will briefly outline the abundant evidence that a change in dietary environmental factors, namely nutritional intake and dietary supplementation of specific compounds, can have a significant impact on cognitive ability (see review by Gomez-Pinilla, 2008). A comprehensive discussion of diet-mediated enhancement of cognitive function warrants its own review and we recommend the expert review (XXXXX) in this issue for further reading. However, it is necessary to make mention of some of the dietary evidence in order to establish the most relevant

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comparative behavioural and molecular indicators of enhanced cognitive function in rodent models.

It is well-established that omega-3 fatty acids are essential for brain function, with rodent studies reporting increased expression of a key neurotrophic factor, brain-derived neurotrophic factor (BDNF) in the cortex and hippocampus of rats provided dietary supplementation of omega-3 fatty acids (Vines et al., 2012). In contrast, a diet deficient in omega-3 fatty acids, especially during brain development, is associated with diminished capacity for neuronal plasticity and an emergence of anxiety-related behavioural changes (Bhatia et al., 2011). It might even result in greater susceptibility for addiction-related behaviours by causing an imbalance in key neurochemical signalling systems (McNamara et al., 2008).

Docosahexaenoic acid (DHA) is an omega-3 fatty acid crucial for the integrity of synaptic membranes. It has been shown to be involved in neuronal development and synaptic function (Cao et al., 2009), partly via its direct modulation of the voltage-gated Kv1.5 potassium channel (Koshida et al., 2009) for the maintenance of cell membrane potential. It is also involved in facilitating the movement of proteins crucial for vesicular release (Mazelova et al., 2009), and DHA-induced enhancement of neurotransmitter release (Mathieu et al., 2010) is one possible mechanism for its effect on synaptic signalling. DHA administration has been shown to effectively slow the development of memory deficits in the 3xTg-AD mouse model of Alzheimer's disease (AD) associated with minimising the loss of membrane area of neurons in the entorhinal cortex (Arsenault et al., 2011). In an alternative animal model of AD, Tg2576 transgenic mice, DHA supplementation improved learning and memory on the Morris water maze while preventing the loss of postsynaptic proteins (Calon et al., 2004). In a rat model of AD which develops learning deficits following infusion with beta-amyloid (1-40), pre-treatment with DHA improved avoidance learning in association with greater fluidity of synaptosomal plasma membrane (Hashimoto et al., 2006).

Given the importance of omega-3 fatty acids for a healthy structural composition of the cell membrane, there appears to be great potential for further investigation into the effectiveness of this combinatorial approach as a therapeutic option for neurological conditions that feature both neuronal loss and cognitive impairment. Other food-derived compounds have also been demonstrated to have cognitive enhancing effects. However, it has also been shown that inappropriate consumption of dietary supplements might have deleterious effects on cognitive function (Sumien et al., 2009). Due to space limitations, we refer the reader to other articles for a more in-depth discussion of this matter (Ramassamy, 2006, Kim et al., 2010, Howes and Perry, 2011).

Conversely, being overweight and obese associated with poor food consumption habits (and inadequate physical activity levels) are risk factors for lower cognitive performance, cognitive decline and dementia. There is an emerging field of clinical research to study the relationship between weight and cognitive functioning (see reviews by Burkhalter and Hillman, 2011, Elias et al., 2011, Siervo et al., 2011). The benefits of caloric restriction have been linked to a neuroendocrine response to low energy availability originating in the hypothalamus (Minor et al., 2009) and caloric restriction has also been demonstrated to counteract age-related hippocampal alterations in key synaptic proteins involved in neuronal signalling (Eckles-Smith et al., 2000, Fontan-Lozano et al., 2007, Shi et al., 2007) as well as DNA processing (Chouliaras et al., 2011). Caloric restriction has also been reported to up-regulate neurogenesis-related genes (the birth of new neurons is proposed to contribute to the encoding of new memories) in the hippocampus of a conditional double mutant mouse model of AD correlating with an improvement in novel object recognition performance and contextual fear conditioning memory (Wu et al., 2008b). The effects of caloric restriction extends beyond rodent models with a study of non-human primates demonstrating improved spatial working memory performances of grey mouse lemurs in a spontaneous alternation task and circular platform task (Dal-Pan et al., 2011), therefore the potential for clinical application certainly warrants further investigation. One aspect of caloric restriction is that it induces enhanced physical activity via weight loss and increased food-seeking behaviours, and the mechanisms involved may overlap with those of physical activity interventions, as discussed below.

2. Running has beneficial effects on cognitive performance

As the age-old adage goes 'Mens sana in corpore sano'. This quotation can be traced back to pre-Socratic times, and can be translated simply to mean 'A sound mind in a sound body'. While one might postulate that the beneficial effects of sound physical well-being were clearly exhibited during that period, the early philosophers could not have imagined that physical activity might be associated with improved cognitive function through its consequential effects on neural processes such as hippocampal neurogenesis (van Praag, 2008), brain angiogenesis (Kerr et al., 2010a) and increased expression of neurotrophic factors (Lista and Sorrentino, 2010). The effectiveness of physical activity to modulate cognitive function is well-described in the current scientific literature (Nithianantharajah and Hannan, 2009). In fact, the evidence supporting the cognitive benefits of exercise is so convincing that the collective findings from preclinical studies are being examined to identify potential molecular targets (some of which will be discussed below) for novel pharmacological interventions termed 'pharmacomimetics of exercise' (see review by Stranahan et al., 2009), which can be considered a subclass of 'enviromimetics' (see review by McOmish and Hannan, 2007).

2.1. Running delays cognitive decline associated with aging

The natural aging process is marked by impaired memory function and this is well accepted to be linked with a decline in hippocampal neurogenesis, although causal evidence of this relationship has yet to be uncovered. Also, while the age-related reduction of adult hippocampal neurogenesis is observed across several species (Gould et al., 1999, Amrein et al., 2011), it has yet to be definitively demonstrated in *Homo sapiens*. This was partly addressed by a study of the expression patterns of cell markers of neurogenesis that are routinely reported in rodent studies (Knoth et al., 2010). Despite the major caveat of assuming that humans and rodents share an expression profile of neurogenic markers, the study by Knoth et al. found similar quantitative age-related changes to markers of hippocampal neurogenesis in murine and human samples. MR imaging provides an alternative assessment of this process by demonstrating age-related volumetric reductions of the hippocampal formation (Apostolova et al., 2012) and in a randomised controlled trial of older adults, it was found that aerobic exercise training reversed age-related decline in hippocampal volumes and improved spatial memory (Erickson et al., 2011). This followed on from a previous randomised trial showing beneficial effects in older adults at risk of AD (Lautenschlager et al., 2008).

In rodents, functional neurogenesis in the hippocampus is well-established (van Praag et al., 2002), however the extent of age-related changes is also highly dependent on species and strain (Kuhn et al., 1996, Jucker et al., 2000, Lichtenwalner et al., 2001, Bondolfi et al., 2004, Epp et al., 2009). In mice, the expression profile of genes within the hippocampus changes with age but can be reversed by engagement in voluntary running (Kohman et al.,