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Editorial

Therapeutic impacts of environmental enrichment: Neurobiological mechanisms informing molecular targets for enviromimetics

Genomics is transforming our understanding of biology and medicine. In contrast, our knowledge of 'enviromics' (an individual's entire environmental exposures across a lifespan; McOmish et al., 2014) remains relatively rudimentary. Therefore, in order to elucidate how genetic and environmental factors affect health and disease across the lifespan, much more research into the effects of environmental stimuli and experimental environmental interventions is required. In the preclinical literature over the past half century, some of the most striking effects of environmental interventions in animal models have utilized environmental enrichment to induce therapeutic effects. Environmental enrichment (EE) involves increased novelty and complexity of housing conditions, so as to enhance cognitive stimulation and physical activity (Nithianantharajah and Hannan, 2006). In this Special Issue, a series of articles addresses the neurobiology of EE, its effects on both the healthy and diseased brain, and the molecular and cellular mechanisms which may inform the development of new therapeutic approaches. Some of the articles focus on the therapeutic effects of EE in preclinical models of specific neurological and psychiatric disorders. Others address the impacts of EE on the normal, healthy mammalian brain, but may also be relevant to the development of new therapeutic approaches.

This Special Issue begins with a series of reviews addressing key issues in the EE field. Ohline and Abraham (2019) review the literature on the neurophysiological effects of EE, with a focus on the hippocampus, one of the key brain areas shown to exhibit some of the most extensive experience-dependent plasticity following such environmental interventions. Whilst some of the synaptic and cellular effects of EE are understandably broad, considering the diverse forms of cognitive stimulation and physical activity that are induced, EE can also have specific impacts on the structure and function of neurons, and synapses in particular. A series of other reviews then address the impacts of EE in traumatic brain injury (de la Tremblaye et al., 2019), alcohol use disorders (Pang et al., 2019) and preclinical models of various brain disorders, including cognitive and affective disorders (Rogers et al., 2019).

The remaining contributions to this Special Issue are research articles, showcasing the wide range of impacts that EE has on the healthy and dysfunctional nervous system, and their implications for the development of novel therapeutic approaches. EE and exercise interventions can be applied at various critical periods across the lifespan. O'Leary et al. (2019) compared the effects of exercise in rats initiated at either adolescence or adulthood. The exercise intervention initiated in adulthood was found to enhance both contextual and cued fear conditioning, whereas exercise initiated in adolescence had no effect on these hippocampal and amygdala-dependent behaviours. The authors also found differential effects of these two temporally distinct exercise interventions on gene expression in the hippocampus, and the gene ontologies were related to experience-dependent plasticity in this key brain structure.

The article by Birch and Kelly (2019) addresses the key issue of how EE might slow brain aging and thus protect against age-related cognitive decline. In particular, they provide evidence that an EE intervention not involving running wheels (and thus not specifically inducing aerobic physical exercise) is still beneficial, reinforcing the importance of cognitive stimulation as a key component of such beneficial effects of EE. Another article, investigating the effects of EE preclinically, involved a model of experimental autoimmune encephalomyelitis (EAE) which is relevant to multiple sclerosis (Bonfiglio et al., 2019), while a study reporting therapeutic effects of EE in a model of optic neuritis (Aranda et al., 2019) emphasizes the impact of EE across a range of central and peripheral systems.

Thus far, we have only discussed the effects of EE within individual organisms of a single generation. However, a relatively new and intriguing field of research has revealed that EE, through both the maternal and paternal line, can have intergenerational effects on offspring and transgenerational effects on subsequent generations, via epigenetic mechanisms (Yeshurun and Hannan, 2018). An article in this Special Issue provides new insights into the intergenerational effects of EE, demonstrating that pre-reproductive EE of female rats led to altered behavior, as well as specific changes in the oxytocin system, in their offspring (Cutuli et al., 2019).

The molecular and cellular mediators of therapeutic effects induced by EE have been widely pursued, although there is clearly a great need for more extensive and systematic investigations. This kind of research promises to deliver novel therapeutic approaches for a wide range of nervous system disorders. Much more preclinical and clinical progress is needed to understand the mechanisms whereby EE induces therapeutic effects, its relevance to cognitive stimulation and physical activity interventions in humans, and the implementation of this knowledge to inform the development of new therapies. Understanding the therapeutic effects of environmental enrichment will guide the development of enviromimetics, novel therapeutics which mimic or enhance the beneficial effects of cognitive stimulation and physical activity (McOmish and Hannan, 2007). One signaling system that has been closely scrutinized involves neurotrophins, and brain-derived neurotrophic factor (BDNF) in particular. In this context, an article in this Special Issue involves intranasal administration of BDNF (Sansevero et al., 2019). It could be speculated that drugs which mimic or enhance the actions of BDNF could constitute one class of enviromimetics.

'Exercise mimetics' (reviewed by Guerrieri et al., 2017) constitute a subclass of enviromimetics. Another research article in this Special Issue, by Moon et al. (2019), provides new leads with respect to the

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identification and development of such enviromimetics. One candidate exercise mimetic is AMP-kinase agonist 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR). Moon et al. (2019) exposed skeletal muscle cells to AICAR in vitro, collected the supernatant and administered this to adult neural precursor cells (aNPCs). It was found that this treatment of aNPCs increased neuronal differentiation, and a specific active component of this AICAR-induced conditioned media was found to be glycolytic enzyme glucose-6 phosphateisomerase (GPI). These findings may facilitate the generation of new exercise mimetics, with potential therapeutic efficacy across a wide range of diseases.

In conclusion, experimental approaches to EE and exercise interventions may lead to the development of enviromimetics, including the specific subclass of exercise mimetics. These, and other, novel therapeutic approaches are urgently needed for the many devastating disorders of brain development and function, which constitute the largest burden of disease, and unmet need, in the 21st century.

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Áine Kelly

Department of Physiology, School of Medicine & Trinity College Institute of Neuroscience & Trinity Biomedical Sciences Institute, University of Dublin, Trinity College Dublin, Dublin 2, Ireland

Anthony J. Hannan*

Florey Institute of Neuroscience and Mental Health, Melbourne Brain Centre, University of Melbourne, Parkville, Victoria, Australia

Department of Anatomy and Neuroscience, University of Melbourne, Parkville, Victoria, Australia

E-mail address: anthony.hannan@florey.edu.au.

* Corresponding author.