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What's wrong with my mouse cage? Methodological considerations for modeling lifestyle factors and gene–environment interactions in mice

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HIGHLIGHTS

- Brain disorders are caused by combinations of genetic and environmental factors.
- Cognitive stimulation, physical activity, stress and other factors modify brain disease.
- Rodent models need to encapsulate both genetic and environmental construct validity.
- Laboratory housing conditions have major impacts on animal models of brain disorders.
- Specific protocols for environmental interventions can be used to model 'enviromes'.

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ABSTRACT

The mechanistic understanding of lifestyle contributions to disease has been largely driven by work in laboratory rodent models using environmental interventions. These interventions show an array of methodologies and sometimes unclear collective conclusions, hampering clinical interpretations. Here we discuss environmental enrichment, exercise and stress interventions to illustrate how different protocols can affect the interpretations of environmental factors in disease. We use Huntington's disease (HD) as an example because its mouse models exhibit excellent validity and HD was the first genetic animal model in which environmental stimulation was found to be beneficial. We make a number of observations and recommendations. Firstly, environmental enrichment and voluntary exercise generally show benefits across laboratories and mouse models. However, the extent to which these environmental interventions have beneficial effects depends on parameters such as the structural complexity of the cage in the case of enrichment, the timing of the intervention and the nature of the control conditions. In particular, clinical interpretations should consider deprived control living conditions and the ethological relevance of the enrichment. Secondly, stress can have negative effects on the phenotype in mouse models of HD and other brain disorders. When modeling stress, the effects of more than one type of experimental stressor should be investigated due to the heterogeneity and complexity of stress responses. With stress in particular, but ideally in all studies, both sexes should be used and the randomized group sizes need to be sufficiently powered to detect any sex effects. Opportunities for clinical translation will be guided by the 'environmental construct validity' of the preclinical data, including the culmination of complementary protocols across multiple animal models. Environmental interventions in mouse models of HD provide illustrative examples of how valid preclinical studies can lead to conclusions relevant to clinical populations.

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Contents

1. Introduction

Neurodegenerative disorders arise from a complex multifactorial interplay between genes and environment. The contribution of genetic factors can be studied using genetic linkage analyses and modeled well in genetically edited animal lines. On the other hand, lifestyle factors such as physical activity, toxins, diet and stress are extremely difficult to manipulate in human populations with the appropriate controls. Laboratory animals are subjects with low genetic variation and offer the ability to control the environment throughout life. From this approach, we have learnt that environmental factors are integral to disease pathology and been able to elucidate potential experience-dependent mechanisms (Nithianantharajah and Hannan, 2006). This raises the tantalizing prospect for changing one's living conditions or lifestyle in order to delay or mitigate disorders for which effective treatments remain elusive. However, this must be directed by reliable and replicable preclinical research. Current work on environmental modulators using mouse models shows widely variable experimental methodologies, sometimes yielding conflicting results and hampering clinical interpretations. In this review, we use examples from environmental studies in Huntington's disease mice to comment on the experimental paradigms of environmental enrichment, exercise and stress. We also make methodological suggestions aimed to improve clinical relevance of such studies.

1.1. Huntington's disease mouse models reveal environmental impacts on disease progression

As the exemplar and apparent epitome of genetic determinism, Huntington's disease (HD) is one of the more remarkable illustrations of environmental contributions to disease. It is a monogenic neurodegenerative disorder caused by an unstable CAG trinucleotide expansion in exon 1 of the HD gene (Huntington's Disease Collaborative Research Group, 1993). The mutation is also almost fully penetrant and its length a strong predictor of age of symptom onset (Andrew et al., 1993; Campodonico et al., 1996). The HD mutation follows autosomal dominant inheritance and translates to a dysfunctional huntingtin protein which accumulates in cells throughout the brain and body. After many years, the cumulative array of molecular and cellular dysfunctions expresses in cognitive, psychiatric and motor symptoms, as well as neuroendocrine, metabolic, peripheral and circadian rhythm abnormalities (reviewed in Bates et al., 2015). Although the presence of the HD mutation remains the main predictor of the disease phenotype, over the last 15 years, there has been mounting evidence for environmental contributions to phenotype onset and progression (reviewed in Mo et al., 2015).

As a brief summary, the idea was first sparked in HD transgenic mice where environmentally enriched housing conditions substantially delayed the onset of the motor phenotype (van Dellen et al., 2000). This idea that cognitive, physical and sensory lifestyle stimulation could impact on HD was subsequently supported in a large population of HD kindreds (Wexler et al., 2004), and translated in a smaller clinical investigation on lifetime activity levels in HD patients (Trembath et al., 2010). Alongside stimulating living conditions, exercise has also been found to have beneficial impacts on HD progression in mouse models (Pang et al., 2006; van Dellen et al., 2008), although translation to patients awaits larger clinical studies (Khalil et al., 2013). Dietary factors have also been reported to improve aspects of the HD phenotype in mouse models, including caloric restriction, antioxidants and caffeine, but this does not appear to be reflected well in patient intervention trials (reviewed in Mo et al., 2015). Finally, stress has only been recently investigated as an environmental modulator of HD with current data showing generally negative effects on a variety of phenotypes in a transgenic mouse model (Mo et al., 2013, 2014a,c,d).

Other factors are yet to be identified and the preclinical and clinical literature for environmental modulators in HD is relatively small compared to work in other diseases such as Alzheimer's disease (Cannon and Greenamyre, 2011; Grant et al., 2002). However, HD transgenic lines closely model the pathologies and symptoms seen in patients (Pouladi et al., 2013) and work on environmental interventions in mice allows us to identify such factors and their underlying mechanisms not otherwise possible in human studies (Box 1).

Taking advantage of valid mouse models, the HD field has made strides in identifying potential lifestyle factors in disease development (Mo et al., 2015). However, some experimental challenges remain for the environmental intervention, including navigating the methodologies available and choosing the type, level and duration of intervention. Results and interpretations of HD mouse studies on enrichment housing, exercise through wheel running and stress will be discussed below, followed by relevant methodological recommendations.

2. Environmental enrichment

A stimulating lifestyle can be modeled in the laboratory by environmental enrichment (EE), a housing condition that enhances sensory, cognitive, motor and social engagements relative to standard housing conditions. EE is generally achieved by the