Neuroscience and Biobehavioral Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

Environmental factors as modulators of neurodegeneration: Insights from gene–environment interactions in Huntington's disease

Q1 Christina Mo[a,b], Anthony J. Hannan[a,c,*], Thibault Renoir[a]

[a] The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, Australia
[b] Department of Neurobiology, The University of Chicago, Chicago, IL, USA
[c] Department of Anatomy and Neuroscience, The University of Melbourne, Parkville, Australia

ARTICLE INFO

Article history:
Received 7 December 2014
Received in revised form 13 February 2015
Accepted 3 March 2015
Available online xxx

Keywords:
Environmental modifiers
Tandem repeat disorders
Polyglutamine disease
Neurodegenerative disorder
Alzheimer's disease
Parkinson's disease
Lifestyle
Cognitive stimulation
Environmental enrichment
Exercise
Physical activity
Stress
Diet

ABSTRACT

Unlike many other neurodegenerative diseases with established gene–environment interactions, Huntington's disease (HD) is viewed as a disorder governed by genetics. The cause of the disease is a highly penetrant tandem repeat expansion encoding an extended polyglutamine tract in the huntingtin protein. In the year 2000, a pioneering study showed the disease could be delayed in transgenic mice by enriched housing conditions. This review describes subsequent human and preclinical studies identifying environmental modulation of motor, cognitive, affective and other symptoms found in HD. Alongside the behavioral observations we also discuss potential mechanisms and the relevance to other neurodegenerative disorders, including Alzheimer's and Parkinson's disease. In mouse models of HD, increased sensorimotor and cognitive stimulation can delay or ameliorate various endophenotypes. Potential mechanisms include increased trophic support, synaptic plasticity, adult neurogenesis, and other forms of experience-dependent cellular plasticity. Subsequent clinical investigations support a role for lifetime activity levels in modulating the onset and progression of HD. Stress can accelerate memory and olfactory deficits and exacerbate cellular dysfunctions in HD mice. In the absence of effective treatments to slow the course of HD, environmental interventions offer feasible approaches to delay the disease, however further preclinical and human studies are needed in order to generate clinical recommendations. Environmental interventions could be combined with future pharmacological therapies and stimulate the identification of enviromimetics, drugs which mimic or enhance the beneficial effects of cognitive stimulation and physical activity.

Contents

* Corresponding author at: The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Kenneth Myer Building, Melbourne, VIC 3010, Australia. Tel.: +61 3 903 56638.
E-mail address: anthony.hannan@florey.edu.au (A.J. Hannan).

http://dx.doi.org/10.1016/j.neubiorev.2015.03.003
0149-7634/

1. Huntington's disease: a tandem repeat disorder

It is established that environmental factors such as toxins, infections, exercise, and stress contribute to the progression of some neurodegenerative diseases (Brown et al., 2005; Schulte et al., 1996). However, until recently, this was not considered the case for Huntington's disease (HD), a fatal and incurable neurodegenerative disorder that is a model example of genetic determinism. Indeed, HD is caused by a single gene mutation: the CAG trinucleotide tract in the HD gene is a tandem repeat (the repetition of a motif of adjacent DNA base pairs) which is at a pathological length in HD patients. The gene follows autosomal dominant inheritance with 50% chance of transmission to offspring. A mutation of 40 CAG repeats or longer guarantees disease manifestation given a normal lifespan (Bates et al., 2002; Lee et al., 2012) while lengths below 35 repeats are generally considered non-pathological. Mutations of 36–39 repeats show incomplete penetrance. A translated pathological Huntingtin protein (Htt) leads to a plethora of molecular and cellular abnormalities including abnormal gene transcription, protein aggregation, mitochondrial dysfunction, oxidative damage, disrupted intracellular transport, impaired synaptic plasticity and reduced trophic support (Imarisio et al., 2008; Landles and Bates, 2004; Li and Conforti, 2013; Sugars and Rubinsztein, 2003). Such dysfunctions cause the degeneration of cells throughout the brain and body, but most dramatically in the striatum and cerebral cortex (Rosas et al., 2003; Spargo et al., 1993). This widespread pathology progresses to an insidious onset of symptoms of which there is currently no effective treatment.

HD 'gene-positive' individuals harbor the tandem repeat mutation from conception, however the accumulation of functional deficits do not reach clinical threshold for many years. Phenoconversion, or diagnosis, is based on the appearance of motor symptoms, which can manifest between 2 and 80 years of age (Myers, 2004). The majority of cases are diagnosed during the 3rd–4th decade of life, however 5% (with CAG repeats of >60) show juvenile onset (Dijk et al., 1986; Nance and Myers, 2001). Cognitive and psychiatric symptoms, including apathy and depression, are detectable prior to the appearance of motor abnormalities (Lawrence et al., 1998; Pla et al., 2014; van Duijn et al., 2014). There is progressive weight loss and muscle-wasting associated with abnormal energy metabolism (Djoussé et al., 2002; Goodman et al., 2008) as well as circadian, neuroendocrine, peripheral and sexual symptoms (Aziz et al., 2010; Polleri et al., 1980; Sassone et al., 2009; van der Burg et al., 2009; Van Raamsdonk et al., 2007). Typically, there is progressive decline to dementia and dependent care and death follows 15–25 years post-diagnosis from complications such as respiratory or cardiac failure (Anne-Wil and Raymund, 2012; Bates et al., 2002).

Even though the tandem repeat expansion causing HD was discovered over two decades ago, the pathophysiology remains only partly elucidated and the widespread, insidious progression cannot be slowed by any treatment to date. Current efforts to develop disease modifiers focus on pharmacological and genetic strategies but until recently environmental manipulations were not generally considered disease modulators of HD (Blackstone, 2014; Clabough, 2013; Hersch and Rosas, 2008; Zuccato et al., 2010). Lifestyle factors may offer another avenue to delay disease progression, particularly in premanifest HD, a population which can be identified by genetic testing decades before symptom onset.

2. Beyond genetic determinism: potential for environmental contributions to age of HD onset and rate of progression

Prior to the identification of the HD gene (Huntington's Disease Collaborative Research Group, 1993), case studies documented disease onset in monozygotic HD twins to occur within 2–3 years (Bird and Omenn, 1975; Oepen, 1973), even in twins raised apart (Sudarsky et al., 1983). This supports the strong genetic component to HD onset as expected. In contrast, other cases of monozygotic HD twins, showed a large discordance in age of onset (Friedman et al., 2005; Georgiou et al., 1999). Symptomatology also differed between HD twins in some cases (Anca et al., 2004; Georgiou et al., 1999). However, somatic mutation of the CAG repeat in the HD gene could also contribute to discordance of monozygotic twins (Swami et al., 2009). Nevertheless, although interpretations are limited in case studies, they provided early indications that genetic factors different from the expanded CAG repeat length as well as epigenetic (Babenko et al., 2012; Gapp et al., 2014), pre-natal and rearing factors could have a substantial impact on disease development.

The HD gene was the first autosomal disease gene identified using genetic linkage analysis (Huntington's Disease Collaborative Research Group, 1993) and the expanded CAG repeat tract showed a remarkably strong inverse correlation with age of onset or diagnosis. Diagnosis is based on the clinical presence of motor symptoms. A simple exponential regression curve explains ~70% of the variability in age of onset (Andrew et al., 1993; Duyao et al., 1993; Gusella and MacDonald, 1995; Snell et al., 1993; Stine et al., 1993) and other statistical models also demonstrate that repeat length is the major, but not sole predictor of onset (Langbehn et al., 2004). When examining genotype–phenotype correlations in 72 HD patients, a study suggested that the factors that determine the development of psychiatric symptoms in HD patients might not to be limited to a dose-related toxicity of the polyglutamine-expanded huntingtin protein (Vassos et al., 2008). In addition, non-motor deficits such as cognitive and psychiatric performance do not correlate with CAG repeat length (Zappacosta et al., 1996).

The first clinical evidence for environmental factors in HD came from a large study of Venezuelan HD kindreds (Wexler et al., 2004), which followed up work in a mouse model of HD (van Dellen et al., 2000) (see section below). Wexler and a consortium of researchers found that the variability in age of onset unexplained by CAG repeat length could be attributed to other genetic (40%) and environmental factors (60%) (Wexler et al., 2004). Many gene candidates other than the trinucleotide expansion have since been identified, including polymorphisms in genes encoding neurotransmitter receptors, Htt-interacting proteins, stress response, apoptosis, synaptic processes and energy metabolism (reviewed by Arning and Epplen, 2011). The majority of variability in the CAG repeat length – age of onset relationship could be ascribed to unidentified shared and non-shared environmental factors (Wexler et al., 2004). Although these may largely remain unidentified, here we review the emerging preclinical and clinical evidence for physical and cognitive

Please cite this article in press as: Mo, C., et al., Environmental factors as modulators of neurodegeneration: Insights from gene–environment interactions in Huntington's disease. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.03.003