Progress in Neurobiology 155 (2017) 2–20

Contents lists available at ScienceDirect

Progress in Neurobiology

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

Review article

Models of progressive neurological dysfunction originating early in life

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ARTICLE INFO

Article history:
Received 17 February 2015
Received in revised form 11 September 2015
Accepted 11 October 2015
Available online 17 October 2015

Keywords:
Perinatal asphyxia
Neonatal hypoxia–ischemia
Epileptogenesis
Schizophrenia
Neonatal
Rodents

ABSTRACT

It is now well established that many of society's most devastating and costly neurological diseases and disorders arise from trauma at, or shortly after birth. In some cases deficits are seen in childhood and in others they are substantially delayed; arising in adolescence or young adulthood. In either case the initial insult initiates a metabolic and/or neurodegenerative cascade that proceeds, often undetected, for a considerable period of time before diagnosable symptoms appear. This affords a potential for detecting and slowing or arresting degenerative and/or malfunctioning processes prior to the appearance of symptoms, but requires an understanding of the mechanisms involved in the progressive dysfunction that characterizes the disease progression process. While numerous preclinical models of end-stage symptoms of neurological disease are established, animal models of progressive neurological dysfunction have received comparatively less attention. This review attempts to introduce the concept of modelling progressive dysfunction in animals and provides descriptions of the current status of several representative examples of models that have been developed and partially characterized for understanding diseases of the brain that arise either at or near the time of birth in rodents. It is our belief that such models are essential to understanding the underlying mechanisms responsible for progressive neurological dysfunction and hold the potential for identifying targets for early detection and presymptomatic therapy of these conditions.

Contents

Abbreviations: AS, asphyxia-exposed, saline-treated; BDNF, brain-derived neurotrophic factor; CS, caesarean-delivered saline-treated controls; DOM, domoic acid; G, gestational day; GAD 65/67, glutamic acid decarboxylase protein 65/67; HI, hypoxia–ischemia; HIF-1α, hypoxia-inducible factor 1α; HPA, hypothalamic adrenal axis; IL, interleukin; LI, latent inhibition; LPS, lipopolysaccharide; LTP, long-term potentiation; MCTs, proton coupled monocarboxylic acid transporter proteins; MEK, mitogen-activated protein kinase kinase; MFS, mossy fibre sprouting; PARP-1, poly(ADP-ribose) polymerase-1; PFC, prefrontal cortex; PKA, cAMP-dependent protein kinase A; PND, postnatal day; PPI, prepulse inhibition; TLE, temporal lobe epilepsy; TLR, Toll-like receptor; trkB, tyrosine protein kinase B; WHO, World Health Organization.

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http://dx.doi.org/10.1016/j.pneurobio.2015.10.001
0301-0082/

1. Introduction

Mental and neurological disorders are increasingly prevalent and constitute a major societal and economic burden worldwide. According to the World Health Organization mental and neurological disorders are responsible for almost 14% of the global disease burden (WHO, 2015). Further, due to increased life expectancy and the ageing of general populations in both developed and developing countries this number is expected to rise (WHO, 2015). Many of the most socially and economically devastating neurological diseases and disorders are characterized by progressive neurodegeneration. The prevalence of some of the most common of these diseases in the United States is depicted in Fig. 1. By extrapolation the prevalence worldwide is probably about 20× that of the USA.

Symptoms of many forms of progressive mental and/or neurological disease often appear in late adolescence or early adulthood and become increasingly severe with increasing age. It is now widely accepted, however, that the disease process often begins long before the onset of the symptoms that lead to a clinical diagnosis. One of the best documented examples of this is Parkinson's disease, where it is estimated that up to 60% of the dopaminergic neurons in the substantia nigra need to be lost before the first clinical signs appear (Schulz and Falkenburger, 2004). Further, many of these progressive neurodegenerative diseases and disorders are now linked to a precipitating event (or events) occurring early in life, often around the time of birth or in early childhood. This concept is depicted in Fig. 2.

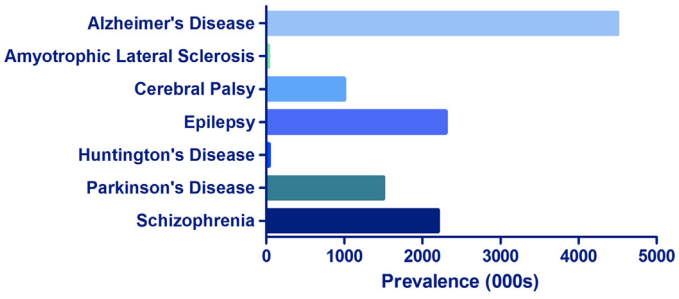

Fig. 1. Prevalence in the USA of several important neurological diseases characterized by progressive neurodegeneration. Numbers are expressed in thousands (000s) of persons affected. Data derived from (OHSU Brain Institute, 2010).

Whether neurodevelopmental or beginning in adulthood, the slowly progressing nature of these conditions constitutes a challenge for early detection but also represents a largely unexplored opportunity for therapeutic intervention. By detecting the disease process earlier, and initiating appropriate therapy to arrest the neurodegenerative process prior to the onset of symptoms, the disease process could be slowed or even stopped long before the patient becomes debilitated by both the primary disease process and secondary complications.

1.1. The concept of modelling progressive disease

Understanding the aetiology and initiation of disease often relies on animal models, as does the development of new therapeutic strategies. But while there are many pre-clinical models available for almost all neurological conditions, most of these models have been created with the aim of identifying new

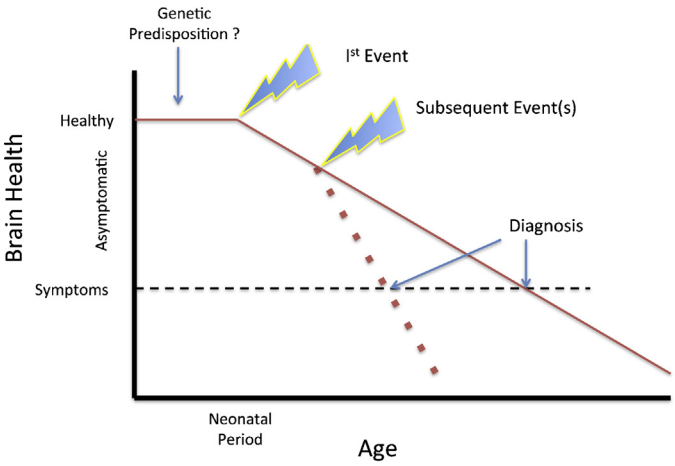

Fig. 2. Graphical depiction of the concept of presymptomatic neurodegeneration originating early in life. Either alone or assisted by a genetic predisposition an event or events, often of unknown origin, initiates a progressive decline in brain health that results in diagnosable clinical signs later in life. In some cases the rate of decline may be accelerated by a subsequent event(s).