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Review article

Models of progressive neurological dysfunction originating early in life

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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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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.

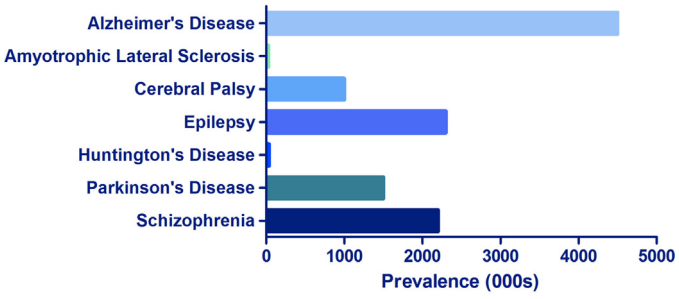

Fig. 1. Prevalence in the USA of several important neurological diseases characterized by progressive neurodegeneration. Numbers are expressed in thousands (000s) of persons affected. Data derived from (OHSU Brain Institute, 2010).

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

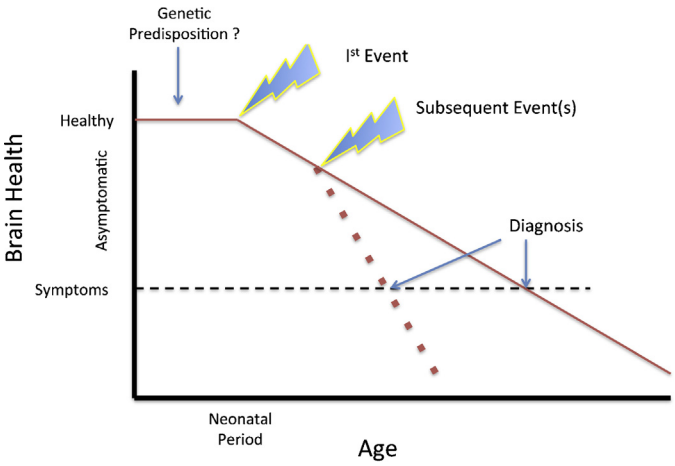

Fig. 2. Graphical depiction of the concept of presymptomatic neurodegeneration originating early in life. Either alone or assisted by a genetic predisposition an event or events, often of unknown origin, initiates a progressive decline in brain health that results in diagnosable clinical signs later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

therapeutants to alleviate end-stage symptoms, and hence do not allow study of the development of disease. Understanding disease development is the key to identifying early intervention strategies. There exists, therefore, a largely unmet need to develop and exploit animal models designed to understand the origins and progression of neurological disease. This review will introduce several examples of animal models of progressive neurodegenerative disease. Because many diseases are neurodevelopmental in origin, the current review will deal with some of the models that involve altering brain development at or shortly after the time of birth in experimental animals. Preclinical models that involve manipulations *in utero* will not be discussed but are clearly highly relevant to a comprehensive review of the field. Further, the descriptions below are not intended to be all-encompassing or even to be an exhaustive review of all such models or of the existing models of all important neurological diseases. They are intended, rather, simply as examples to illustrate the concept of modelling disease progression as a means to lay a foundation for mechanistic studies and to identify predictive and/or preventative therapeutic strategies.

1.2. Critical periods of CNS development

The mammalian brain acquires its complex structure and exquisite organization along prenatal and postnatal periods, when multiple processes occur in a precise time, involving specific regions (Molofsky et al., 2012), thus forming critical periods for short and long term functioning of the central nervous system (CNS). Damage occurring during the perinatal period would produce severe impairment in CNS functioning, leading to a plethora of deleterious effects, depending upon the degree of damage and the region mainly affected (Herrera-Marschitz et al., 2014). Accordingly, pre-clinical developmental models of disease rely on this concept of critical periods in brain development, and target interventions during species-specific "windows" of vulnerability.

1.2.1. Prenatal-postnatal development of the brain

Neuronal and glial growth is predominantly a postnatal event in the mammalian CNS (Altman, 1967), although the CNS *primordium* is already established when the neural tube is closed, in humans around the third-fourth weeks of gestation (G), to rapidly develop up to the time of delivery, when the main compartments of the CNS are already established and generally organized. In the rat, gestation lasts three weeks, and sufficient brain development has to occur during this time to meet the demands occurring during birth, to allow the newborn to initiate pulmonary ventilation and to sense the environment and produce coordinated motor behaviour and reflexes required for proper nurturing by the dam.

Development, including neurogenesis, synaptogenesis and the formation of neural circuits continues throughout life and is dependent upon a complex multi-step process that includes cell fate specification, differentiation and migration, followed by neurite growth, guidance, synapse formation and pruning, with a specific timing for different neurochemical systems and different brain regions (Segalowitz and Davies, 2004; Sowell et al., 1999). This carefully orchestrated sequence can be illustrated by formation of the dopaminergic system. Tyrosine hydroxylase (TH) positive cells can already be identified in the mesencephalon of rat foetuses at G15 (also in mice, see Riddle and Pollock, 2003), suggesting the presence of dopamine synthesizing neurons, and at G19 the distribution of TH positive cells in the substantia nigra and ventral tegmental area is very similar to that observed at term (Foster, 1998a,b; Park et al., 2000) and at postnatal day 1 (PND 1). Dopamine fibres start to invade the neostriatum before birth (Seiger and Olson, 1973) and peak at the fourth postnatal week, although mature targeting is fully achieved later, when patches are replaced by a diffuse innervation pattern (Antonopoulos et al., 2002; Loizou, 1972; Olson and Seiger, 1972; Seiger and Olson, 1973; Voorn et al., 1988). Dopaminergic axons continue to grow at a slow rate during adulthood (Loizou, 1972; Voorn et al., 1988) in concert with naturally occurring waves of dopamine cell death (Antonopoulos et al., 2002; Oo and Burke, 1997). Dopamine pathways have an earlier and faster development than noradrenaline- and 5-hydroxytryptamine pathways (Loizou, 1972). The functional development of telencephalic neurocircuitries depends upon mesencephalic, but also upon neocortical inputs, which mature at various postnatal stages (see Herrera-Marschitz et al., 2010). In the rat, neocortical pyramidal projections are physiologically viable only one week after birth (Li and Martin, 2000; Meng et al., 2004; Meng and Martin, 2003).

This heterogeneity in the developmental timing of the CNS provides a regionally variable vulnerability to systemic metabolic insults occurring at strategic periods, including the perinatal period and the period from PND 7–21 in the rat (see Section 1.2.2). Immaturity of a particular brain region plays a role, because the insult affects the initial plastic changes required for establishing neural circuits and synaptogenesis, and the energy demands of re-establishing homeostasis competes with that required for consolidating neural circuits.

1.2.2. The brain growth spurt

The brain growth spurt is a period of time in mammalian development when the brain undergoes a particularly rapid and sigmoidal increase in weight (Dobbing and Smart, 1974). During this time of rapid brain growth and change a number of critical processes are occurring including axonogenesis, dendritic arboration, development of neurotransmitter systems, developmental cell death, synaptogenesis, myelination, and pruning of synapses to form functional circuitry (McDonald and Johnston, 1990). Even small alterations that occur during this time can have significant and long lasting effects, both structurally and functionally. While some species progress through this growth spurt before they are born, others do not experience it until after birth. Dobbing and Sands (1979) suggest that different species can be categorized as prenatal, perinatal or postnatal brain developers, based on the point in development when their brains undergo the growth spurt, although the range of developmental time periods follows a continuum more so than it is restricted to those three particular points in time. In rats, the brain growth spurt begins on the day of birth and continues until the third week of life (Dobbing and Smart, 1974) and is generally considered comparable to that of a third trimester in humans (Dobbing and Sands, 1979). For the purposes of the current review we will consider two of the three major windows of neonatal brain development in the rat. The first week of life (i.e. PND days 0–7) and the period from PND 8–21. This distinction is somewhat arbitrary although many of the primary neurotransmitter systems come "on line" during the first week but are subject to post-transcriptional and post-translational modifications, many of which are activity dependent, during the second phase. Perhaps more relevant, however, is that models involving manipulation in the first postnatal week are intended to simulate trauma at the time of birth (e.g. asphyxia and hypoxia) whereas those in weeks 2 and 3 do not simulate birth trauma but do model trauma at an approximately equivalent developmental stage to that of human birth.

2. Models of birth trauma

Pregnancy culminates at the time when labour begins, implying a complex interchange of molecules generated by uterine and extrauterine tissue, leading to increased myometrial contractility, cervical dilatation, decidual/membrane activation, and rupture of

chorioamniotic membranes (Romero et al., 2006). The switch of the myometrium from a quiescent to a contractile state is accompanied by a shift from anti-inflammatory to proinflammatory signalling chemokines and cytokines, as well as contraction-associated proteins, warrantying a successful delivery (Romero et al., 2014). Delivery, however, can be a risky episode, whenever the onset of pulmonary respiration is delayed, leading to perinatal asphyxia if oxygenation is not promptly re-established. Delay in the onset of pulmonary ventilation at birth implies a decrease of oxygen saturation in blood and its supply to the brain, which depends on aerobic metabolism for maintaining the respiratory chain and mitochondrial ATPase activity. Whenever hypoxia is sustained, there is a switch to glycolysis, a poor metabolic alternative, because of low stores of glucose in brain tissue and deficient ATP output by the glycolysis pathway. This results in lactate accumulation and acidosis. Newborn rodents and humans cerebral energy metabolism utilizes ketone bodies β-hydroxybutyrate and acetoacetate rather than glucose to satisfy energy requirements (see Nehlig and Pereira de Vasconcelos, 1993), but it is not yet established how ketone bodies are available before lactation begins, although the proton-coupled monocarboxylic acid transporter proteins have been reported to be very high in the blood–brain barrier as well as neurons and glia in the PND 1–14 rat brain (Vannucci and Simpson, 2003).

Oxidative stress is inherent to re-oxygenation, resulting in over activation and inactivation of buffering enzymes (see Gitto et al., 2002). In the clinical scenario, resuscitation implies increased PaO_2, free radical production and oxidative stress, worsening brain injury (Davis et al., 2004; Kapadia et al., 2013; Solberg et al., 2007). Thus, perinatal asphyxia is a highly relevant clinical issue, with a reported incidence of 1–6/1000 term birth (de Haan et al., 2006; Kurinczuk et al., 2010), with few relevant therapeutic alternatives for reducing the risk of death and long-term disabilities (Edwards et al., 2010; Lawn et al., 2010).

2.1. An experimental model of perinatal asphyxia

The short-and long-term clinical outcome of perinatal asphyxia in patients is well documented (Odd et al., 2009; van Handel et al., 2007). However, pre-clinical research is still exploratory, mainly because of a lack of consensus on reliable and predictable experimental models. A model for investigating the issue was proposed at the beginning of the nineties (Andersson et al., 1992; Bjelke et al., 1991; Herrera-Marschitz et al., 1993), although its validity is still marshalled, because the model works with on term pups and not with neonates at PND 7. The main argument is that the brain of a neonatal rat is premature compared to the neonatal human brain, a statement mainly referring to the neocortex (see Romijn et al., 1991), but also to the pattern of oligodendrocyte lineage progression required for cerebral myelination (Craig et al., 2003). The degree of maturity depends upon the tissue examined and the functions selected for the comparison, and vulnerability to injury may be related to both the timing and the location of the insult (Craig et al., 2003; de Louw et al., 2002). Indeed, it has been reported that susceptibility to hypoxia–ischemia induced by common carotid artery ligation and hypoxemia is greater when performed at P7 rather than at earlier postnatal periods (Towfighi et al., 1997).

In the model described below the authors have chosen a pragmatic approach, inducing asphyxia at the time when rats are delivered. Several features support the usefulness of the proposed model: (i) it mimics well some relevant aspects of human delivery; (ii) it is largely non-invasive; (iii) it allows studying short- and long-term consequences of the insult in the same preparation, and (iv) it is highly reproducible among laboratories. The model is suitable for studying the early phases of perinatal asphyxia, as observed in the clinical setup, performed on term, during delivery, at the time when labour has started, together with a cascade of pro-inflammatory pathways, including chemokines (interleukine-8; IL-8) and cytokines (IL-1, IL-6) and contraction associated proteins (oxytocin receptor, connexin-43, prostaglandin receptors) (see Romero et al., 2014). Furthermore, the model implies membrane rupture, playing a role in the initiation and contractions required for the labour process (Moore et al., 2006). Thus, there are a number of biochemical and physiological events occurring at the time of delivery, all of which have to be considered when proposing suitable experimental models of perinatal asphyxia.

The proposed model starts by an evaluation of the oestral cycle of young female Wistar rats (~2 months of age), in order to plan for a programmed mating. A vaginal frotis is taken for exposing the female to a male at the time of the pro-oestrous for one night, evaluating thereafter the presence of a vaginal clot. Thus, the gestation time is calculated, predicting the exact time of delivery (21 days, after a vaginal clot has been recorded). At the time of delivery, a first spontaneous birth can be observed before the dam is anaesthetised, neck dislocated, and subjected to hysterectomy (Fig. 1). The uterine horns containing the foetuses are immediately immersed into a water bath at 37 °C for various periods of time (0–22 min). Following asphyxia, the pups are removed from the uterine horns and resuscitated by cleaning the nose and mouth from fluid and amniotic tissue. Pulmonary breathing is stimulated by touching the surface of the nose and mouth, as well as by pressing the thorax. Pups exposed to caesarean-delivery only (CS, 0 asphyxia), or to mild asphyxia (2–10 min) are rapidly resuscitated, without requiring anything else but removing fluid and amniotic tissue from the head. Pups exposed to zero or mild asphyxia start breathing with a gluttonous gasp, which is rapidly replaced by regular and synchronised breathing. For pups exposed to longer than 19–21 min of asphyxia resuscitation implies expert and skilful handling, taking a long time (4–6 min) for stimulating a first gasping, and even longer time for establishing a more or less regular breathing, always supported by gasping. After 80 min of care taking, the pups are given to surrogate dams for nursing, pending further experiments (Dell'Anna et al., 1995; see Herrera-Marschitz et al., 2011) (Fig. 3).

Apart from the effects produced by perinatal asphyxia on the survival rate, the model allows to describe early molecular, metabolic and physiological effects observed minutes after recovering from a caesarean delivery, without any asphyxia, or from mild to severe insults. Behavioural scales are applied 60–80 min after delivery, avoiding competing with the resuscitation and nursing manoeuvres. Tissue sampling can be started soon after delivery.

Asphyxia-exposed and the corresponding control pups can be used for preparing organotypic cultures (Morales et al., 2003, 2005; Klawitter et al., 2007). Organotypic cultures offer the opportunity to study neurocircuitry formation, since the procedure moves back development to an earlier stage. The model, originally developed by Gähwiler (1981), provides a complexity between cell lines and primary cultures, allowing to study *in vitro* neural connections development and neurochemical phenotype, reproducing many of the physiological features observed *in vivo*, enlightening neuronal targeting and reciprocal modulatory interactions (Plenz and Kitai, 1996a,b; Gomez-Urquijo et al., 1999), evaluating the effect of pharmacological treatments applied directly into the culture tube (Plenz and Kitai, 1998), or in vivo, before the pups are used for culturing (Klawitter et al., 2007). Experiments with organotypic cultures demonstrated the regional and neurochemical vulnerability elicited by perinatal asphyxia, affecting the number and the branching of TH-positive neurons in mesencephalon, but increasing the number and neurite tree of nitric oxidase synthase (nNOS)-positive neurons in the same region, decreased, however, in

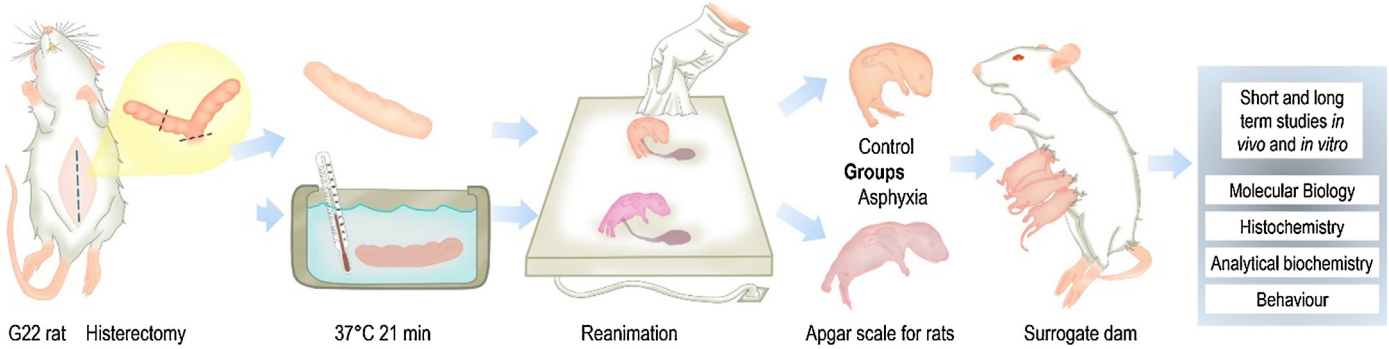

Fig. 3. The Swedish model of perinatal asphyxia. Pregnant Wistar rats (gestation day 22) are anaesthetized, euthanized by neck dislocation and hysterectomized. Two or three pups are removed immediately, corresponding to caesarean-delivered controls (CS), and remaining foetuses are immersed in a water bath at 37 °C for 21 min (AS). Following asphyxia, pups are removed from the uterine horns, stimulated to breathe and after 60 min evaluated by an Apgar scale adapted for rats, thereafter, the neonates are given to surrogate dams, pending further experimental procedures.

neostriatum, without any effect on neocortical nNOS positive neurons (Klawitter et al., 2007).

2.1.1. Short- and long-term effects

Perinatal asphyxia implies a primary insult, depending upon the duration of the period lacking oxygenation, leading to death if re-oxygenation is not re-established, and a secondary insult produced by re-oxygenation, worsening the oxidative stress status (Herrera-Marschitz et al., 2014). Perinatal asphyxia affects different regions of the brain, increasing pro-inflammatory signalling (NF-κB) (Neira-Peña et al., 2015), hypoxia cell response (hypoxia inducible factor-1α, HIF-1α) (Rojas-Mancilla et al., in preparation), DNA sensing (PARP-1) (Allende-Castro et al., 2012; Bustamante et al., 2003; Neira-Peña et al., 2015), and astrocyte reactivity (Rojas-Mancilla et al., in preparation). Further asphyxia affects neuronal branching (Klawitter et al., 2007; Morales et al., 2003) and synaptogenesis, leading to apoptotic-like cell death (Dell'Anna et al., 1997; Morales et al., 2010; Neira-Peña et al., 2015).

A particularly interesting observation is that perinatal asphyxia induces a decrease in neurite branching of dopamine neurons (Klawitter et al., 2007; Morales et al., 2003), supporting the idea that dopamine neurons are particularly vulnerable to hypoxic insults (Chen et al., 1995, 1997; Andersson et al., 1995; Bustamante et al., 2003, 2007; see Herrera-Marschitz et al., 2011). Consistent with these results, neurite length and branching in primary hippocampal neurons from asphyxia-exposed rats are also decreased and at a synaptic level, an increase in synaptophysin and PSD-95 levels (pre- and post-synaptic proteins, respectively) was observed in perinatal asphyxia-exposed rats at PND 7, without any change in the number of synaptic contacts (Rojas-Mancilla et al., in preparation). This latter change was followed by a decrease of pre-synaptic puncta in the hippocampus at PND 22–24 (Fig. 4). These changes suggest that the ultrastructure of synapses was altered by the insult, implying synapsis degradation by microglia and astrocytes, shown to be implicated in synapse pruning during mammalian brain development under both normal and pathological conditions (Chung et al., 2013; Kettenmann et al., 2013; Schafer et al., 2012). The precise mechanisms causing these alterations in synapsis structure has not yet been elucidated, but it is proposed that down regulation of growth factors, such as brain-derived neurotrophic factor (BDNF) plays a role in the observed dendritic atrophy. In fact, it has been reported that hypoxia–ischemia encephalopathy is associated with low levels of BDNF, increasing the risk for developing mental disorders (Zornberg et al., 2000).

Astrocytes constitute the most abundant cell type in the mammalian brain, in charge of multiple metabolic functions important for maintaining neuronal homeostasis (Allaman et al., 2011; Barres, 2008; Parpura et al., 2012; see Hamilton and Attwell, 2010; Perea et al., 2014) but astrocytes in the neocortex and hippocampus of control rats have reduced number of branches and long projections when assayed at birth, suggesting an immature stage. Following asphyxia, morphological changes in astrocytes have been observed both in vitro and *in vivo* (Rojas-Mancilla et al.,in preparation), indicating astrocyte reactivity. Astrocyte reactivity has been previously described under pathological brain conditions (e.g. traumatic brain injury, inflammation, hyperthermia) (Middeldorp and Hol, 2011), appearing to be a heterogeneous process, depending upon the type and severity of the insult. Indeed, differential gene expression has been reported to be elicited in astrocytes following traumatic brain injury and/or inflammation (Zamanian et al., 2012). Astrocytes also play important roles in synapsis formation, and plasticity (Clarke and Barres, 2013; Eroglu and Barres, 2010; Papa et al., 2014; Sloan and Barres, 2014), modulating extracellular excitatory neurotransmitter levels (Bergles and Jahr, 1997; Carmignoto, 2000; Domingues et al., 2010; Halassa and Haydon, 2010; Hamilton and Attwell, 2010), preventing stimulation of extrasynaptic *N*-methyl-D-aspartate (NMDA) receptors, a mechanism triggering excitotoxic cascades (Kretschmer et al., 2002; Olney et al., 1971), and neurodegeneration (Bustos, 2012). Thus, the functioning of astrocytes is critical for overall brain physiology (Parpura et al.,

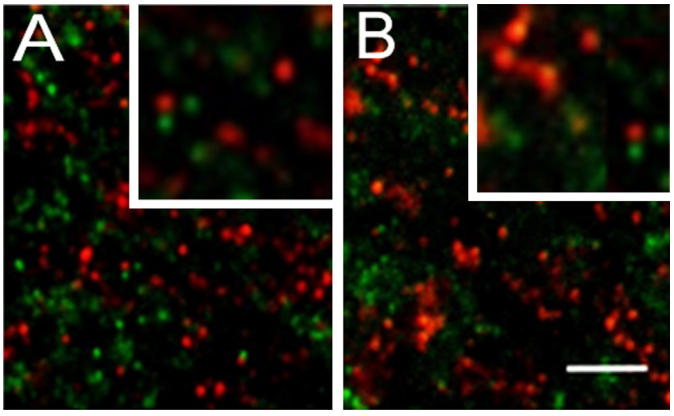

Fig. 4. Perinatal asphyxia induces a decreased number of synaptic contacts, and increased size of pre- and postsynaptic dots in stratum radiatum CA3 of hippocampus at postnatal day 22. Representative microphotograph of synaptophysin (green) and PSD95 (red) labelling in stratum radiatum of CA3 from control (A) and asphyxia-exposed (B) rats. Scale bar: 3 μm. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2012; Vangeison and Rempe, 2009), and the effect of perinatal asphyxia on astrocytes further compounds the negative effects on neurons, affecting or even interrupting neurodevelopment (Fig. 5).

2.1.2. Functional studies in perinatal asphyxia

Long-term potentiation (LTP) in the CA1 region of the hippocampus is a classical and exhaustive model for studying activity-dependent synaptic plasticity associated to learning and memory (Bliss and Lomo, 1973; Lomo, 2003; Whitlock et al., 2006), where glutamate plays a central neurotransmitter role. Perinatal asphyxia has been found to be associated with a decrease in LTP in hippocampi at PND 22–24, thus suggesting an impairment of synaptic plasticity. In agreement with this observation, behavioural changes have been observed at adulthood wherein asphyxia-exposed rats exhibited impairments in non-spatial memory as assayed by the novel object recognition paradigm (Simola et al., 2008), as well as spatial memory in an Oasis maze test (Rojas-Mancilla et al., in preparation) and performance alteration in Y and Barnes mazes (Simola et al., 2008) indicating a special susceptibility of hippocampus to hypoxic–ischemic injuries (Morales et al., 2007).

2.2. Neonatal hypoxia–ischemia

Based on the original work of J.E. Levine (1960), a widely used experimental model inducing hypoxic–ischemic (HI) brain lesions by unilateral common carotid artery ligation followed by 8% hypoxia for 3.5 h at PND 7 is well described (Rice et al., 1981). The lesion produces moderate to severe ischemic neuronal changes in the ipsilateral cerebral cortex, striatum and hippocampus, including neocortex, and surviving pups exhibit permanent neurological and behavioural deficits (see Vannucci and Vannucci, 1997, 2005; Vannucci and Hagberg, 2004). The model has been useful for characterising the effect of hypoxia/ischemia on cerebral blood flow and metabolic correlates, as well as molecular alterations in immature and genetically modified animals and has led to physiological and pharmacological interventions leading to neuroprotective strategies (Vannucci and Vannucci, 2005). The authors have stressed the feature that the model is performed in immature rodents, at a time when histological development is similar to that of a 32–34 week gestation human foetus or newborn infants, when neuronal neocortical layering is complete, the germinal matrix is involuting, and myelination is still in progress. The strength of the model has been widely promoted (Patel et al., 2014), although the model has also been criticized because the physiological transition from intra to extra-uterine life is missed (see Tyzio et al., 2006).

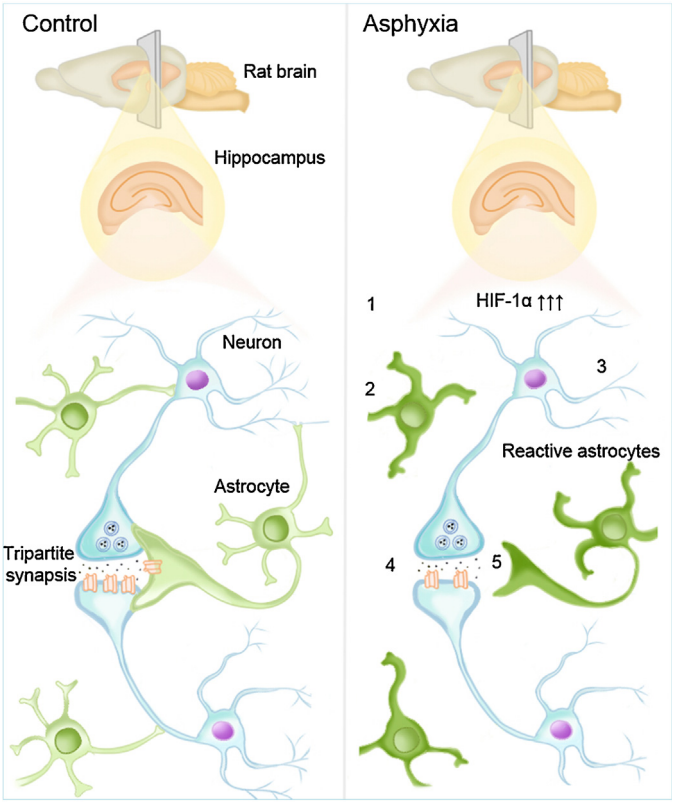

Fig. 5. Perinatal asphyxia impairs both neurons and astrocytes, altering hippocampal functioning. Branching and synaptogenesis are early postnatal events in the hippocampus of the newborn rat. Glutamate synapses imply astrocytes, conforming what is called a tripartite synapse (Perea et al., 2014), where the astrocytes efficiently remove glutamate from the synaptic and extrasynaptic space, maintaining the homeostasis. Following asphyxia: (1) HIF-1a is increased, leading to (2) astrocyte reactivity, (3) reduction in branching and (4) synaptogenesis, resulting in loss of synaptic contacts and structure, possibly affecting long-term potentiation (LTP) in the young rats. (5) Impairment of astrocyte functioning also implies reduction in glutamate buffering.

One of many interesting features of the neonatal HI model, however is that sex also comprises an important interdependent risk factor for ischemic brain injury and is a significant predictor of outcome. This mirrors observations in newborns where recent clinical studies reported an increased incidence of arterial ischemic stroke (Lenicek-Krleza et al., 2009; Lynch et al., 2002; Fullerton et al., 2001) and cerebral sinus venous thrombosis in male children (Lenicek-Krleza et al., 2009). Male "sensitivity" to ischemic injury is also reported in experimental studies where neonatal male mice with HI injury show increased brain volume loss compared to females (Mayoral et al., 2009) and in a recent preliminary report sex differences in long-term functional outcome were also reported in HI injured rats (Askalan et al., 2014).

The mechanisms of these sex-related differences of neonatal HI injury are poorly understood. Oestrogen is unlikely to account for the observed protection in females because circulating oestrogen is minimal in neonatal females (Carrel and Willard, 1999). Early hormonal factors, therefore, cannot fully explain sex-differences in the outcome of HI injury. Neuronal cultures (absence of circulating hormones) subjected to cytotoxicity have shown differences in pathways of cell death; male (XY) neurons predominately die by activating caspase-independent AIF-mediated apoptosis whereas female (XX) neurons die by utilizing the caspase-dependent pathway (Carrel and Willard, 2005). Brain sexual differentiation may also contribute to the responses to pathological stimuli such as HI insult. In this regard, PND 2 female rats have higher levels of NF-κB in the anteroventral periventricular nucleus whereas NF-κB signalling is suppressed in male neonates (Zhao and Eghabali-Webb, 2002). These results, taken together, suggest that male and female neurons utilize different pathways of cell death that may explain sex-differences in outcome of neonatal HI injury.

2.2.1. Functional studies

While the neonatal HI model has been used for a very long time and generated a great deal of important information, it has proven extremely challenging to reliably detect long-term functional deficits in this model. There are probably three major contributors to this "failure": (i) the protocols employed by different laboratories demonstrate a wide range of experimental conditions including the location of the occlusion (common carotid versus internal carotid) and the duration of the occlusion and the duration and oxygen content of the hypoxia as well as the temperature maintained, (ii) the extreme variability commonly observed in the size of the resulting infarct, and (iii) the remarkable ability of the neonatal brain to manifest plasticity thereby limiting (or masking) the resulting deficits. Despite these limitations long-term functional deficits have

been reported in rats and mice following neonatal HI. Several groups have reported on significant sensorimotor deficits weeks after rats underwent HI (Felt et al., 2002; Pazaiti et al., 2009; Lubics et al., 2005) also reported changes in neurological reflexes, motor function and open field behaviour during the first month following HI. But in general long-term deficits in complex behaviours such as learning and memory have been hard to detect although quite recently Smith et al. (2014) reported on lasting deficits in working memory using a more challenging version of the radial arm maze task, so it may be that more complex paradigms are able to reveal deficits that are not detectable in more simple tasks.

3. Models originating during the second and third postnatal week

In contrast to models originating at the time of birth there are a number of well-established and well-validated animal models that involve manipulation of brain development during the second and third postnatal week. There are probably two main reasons for this: (1) in both rats and mice the period from PND 6/7 until weaning is the time of the brain growth spurt in which rapid development with accompanying plasticity of the CNS is occurring (see Section 1.2.2), and (2) this time point corresponds roughly to the period shortly before birth in humans, allowing for investigations of human perinatal trauma in a rodent model that is experimentally easier to deal with than *in utero* or PND 0 manipulations. Because of the multiplicity of such models we provide herein a comparatively brief overview of the models and consequences in text, and have included additional experimental detail with appropriate citations in the form of two comprehensive tables (see Tables 1 and 2).

3.1. Models of epileptogenesis

Epilepsy is a complex, symptomatically-defined cluster of disorders that affects 1–1.5% of the population worldwide (Murray and Lopez, 1994). Characterized by recurrent seizures manifesting either as motor convulsions or abnormalities in electroencephalographic (EEG) recordings, epilepsy can be either generalized (affecting the whole brain) or partial (affecting discrete brain regions such as the temporal lobe). Partial epilepsy may or may not progress to generalized seizures (Engel and Schwartzkroin, 2006). Epilepsy is also frequently neurodevelopmental in origin, whereby a strong correlation exists between early-life CNS trauma (e.g. hypoxia, closed head trauma, febrile seizures) and the subsequent development of seizure disorders such as temporal lobe epilepsy (Jefferys, 2003). While childhood epilepsy is not uncommon, early trauma is often followed by a latent, or "silent", period ranging from years to decades before the onset of epileptic seizures. This delayed onset is a time when the brain is undergoing progressive changes in structure and function that ultimately culminate in seizures, and is referred to as "epileptogenesis" (i.e. the process of becoming epileptic) (Engel and Schwartzkroin, 2006).

The process of epileptogenesis is poorly understood, but because it is presymptomatic, the epileptogenic period represents a window in which therapeutic intervention could slow or even stop the development of epilepsy. Understanding the molecular changes occurring during epileptogenesis and identification of potential biomarkers for presymptomatic intervention (see Section 4.4), however, requires the development of appropriate animal models. There are a number of well-established and extensively documented epilepsy models that involve chemical or electrical induction of spontaneous recurrent seizures in adult animals (for review see Jefferys, 2003). Modelling epilepsy as a disease, and particularly epileptogenesis, in neonatal animals has proven more difficult. This is due, in part, to what appears to be a paradox. It is well established that the immature brain is more prone than the adult brain to seizures arising from chemical or environmental intervention (Cavalheiro et al., 1987; Stafstrom et al., 1992; Stafstrom et al., 1993; Doucette et al., 2000), probably because of a difference in the developmental maturation of excitatory and inhibitory systems (Ben-Ari et al., 1997). Despite this increased susceptibility to seizure genesis, however, the neonatal brain has generally been regarded as largely resistant to the development of long-term consequences consistent with epilepsy (e.g. spontaneous recurrent seizures, mossy fibre sprouting, hippocampal cell loss) (Nitecka et al., 1984; Sperber et al., 1991; Haas et al., 2001), although others have reported long-lasting consequences of neonatal seizures particularly when multiple convulsants are administered during early development (Holmes et al., 1999; Liu et al., 1999).

Of particular relevance to understanding the neurodevelopmental origins of epilepsy and epileptogenesis, however, are two recently described rodent models of epilepsy that produce slowly-developing, or delayed onset, changes in epilepsy-relevant morphology, neurochemistry and behaviour. These are the neonatal inflammation model and the neonatal domoic acid model; each of which is described in more detail below.

3.1.1. Neonatal inflammation

Several years ago an interesting model linking neonatal inflammation and seizure susceptibility was described (Galic et al., 2008, 2009; Riazi et al., 2010). Sprague-Dawley rat pups injected intraperitoneally with the bacterial endotoxin lipopolysaccharide (LPS) on PND 14 manifested enhanced susceptibility to seizures induced by lithium–pilocarpine, kainic acid or the GABA antagonist pentylenetetrazol when challenged at 6–8 weeks of age. The effect was antagonized by concurrent administration of an antibody to tumour necrosis factor α (TNFα). The authors also investigated whether the same result was obtained following LPS injection at other stages of development, and reported that injections on PND 7 also reduced seizure threshold, but that LPS injections on PND 1 or PND 20 did not; strongly implicating the second postnatal week of life as a "critical window" for the lasting effects (see Section 1.2.2). A follow-up paper by the same group described how direct (i.c.v.) injections of the viral mimetic polyinosinic:polycytidylic acid into PND 14 rat pups produces central inflammation and also results in a reduced seizure threshold when tested at 7–8 weeks of age (Galic et al., 2009). Thus both peripheral and central inflammation during the second postnatal week of development in the rat appears to initiate a chronic neurodegenerative condition that culminates in reduced seizure threshold.

3.1.2. Neonatal domoic acid

The other neurodevelopmental model of epileptogenesis that has been described is the neonatal domoic acid model. Domoic acid (DOM) is a naturally occurring excitotoxin that is structurally similar to kainic acid and an analogue of glutamate. Domoic acid is recognized as a selective, but not specific, agonist at the kainate subclass of non-NMDA glutamate receptors (Verdoorn et al., 1994; Tasker et al., 1996). In the late 1980s DOM was identified as the causative agent in an outbreak of human toxicity in which patients experienced dose-dependent neurotoxicity culminating in seizures and death (Perl et al., 1990; Teitelbaum et al., 1990). One of the patients who survived subsequently went on to develop temporal lobe epilepsy (Cendes et al., 1995). Building on this background of clinical data, Doucette and co-workers investigated the response of neonatal rats to very low doses of domoic acid (Doucette et al., 2000, 2003) and in 2004 they described a unique low-grade seizure response that occurred in aged adult rats exposed to novel and/or stressful environments even though the only drug treatment had been as neonates (Doucette et al., 2004).

Table 1
Behavioural deficits observed in several developmentally based models for schizophrenia research.

Model name	Gating	Cognitive behaviour	Social behaviour	Response to antipsychotic drugs	References
Neonatal domoic acid	Disrupted PPI	Disrupted LI; alterations to memory and emotionality; altered response to novelty and reward	Social withdrawal	Unknown	Adams et al. (2009, 2008), Burt et al. (2008a, 2008b) , Doucette et al. (2007), Marriott et al. (2014, 2012), Robbins et al. (2013) and Ryan et al. (2011)
Neonatal quinpirole model	Unknown	Impairments in the MWM Increased quinpirole-induced yawning response	Unknown	Olanzapine alleviated cognitive impairment on the MWM place version and increases in yawning	Brown et al. (2008, 2004, 2002), Kostrzewa and Brus (1991) and Thacker et al. (2006)
Maternal separation	Disrupted PPI	Enhanced LI; improved avoidance learning; disrupted LI; increased anxiety-like behaviour and decreased memory performance	Social withdrawal	PPI deficit reversed by haloperidol and quetiapine	Bouet et al. (2011), Ellenbroek et al. (2004, 1998), Ellenbroek and Cools (1995a,b), Lehmann and Feldon (2000), Lehmann et al. (1998) and Weiss et al. (2001)
Social isolation rearing	Strain dependent disrupted PPI	Reduced LI (may be age/strain dependent); impaired avoidance learning; hyperactivity in a novel environment; impaired novel object recognition and impaired attentional set-shifting; increased anxiety and decreased performance in the MWM; spatial working memory impairments; modified response to reward	Increased social interaction and aggression and impaired social recognition	PPI deficits reversed by Raclopride; seroquel and olanzapine; risperidone and haloperidol	Bakshi et al. (1998), Domeney and Feldon (1998), Einon (1980), Ferdman et al. (2007), Gentsch et al. (1988), Geyer et al. (1993), Han et al. (2012), Hellemans et al. (2004), Marriott et al. (2014); McLean et al. (2010), Shao et al. (2009), Stevens et al. (1997), Varty and Geyer (1998), Varty and Higgins (1995), Weiss et al. (2001, 2000), Wilkinson et al. (1994) and Wongwitdecha and Marsden (1995)
Neonatal DOM + social isolation rearing	DOM treatment made animals refractory to the social isolation induced deficit in PPI amplitude; additive decrease in PPI latency	Abolished LI and abnormal presence of LI depending on sex and timing of testing	Unknown	Unknown	Marriott et al. (2014)
Maternal separation + social isolation rearing	No additive or interacting effects on PPI	No additive or interacting effects on LI	Unknown	Unknown	Weiss et al. (2001)

Adapted from Animal Models for Schizophrenia Research, www.schizophreniaresearchforum.org.

Table 2
Summary of molecular and morphological changes observed in developmentally based models for schizophrenia research.

TeModel name	Region	Molecular/morphological	References
Neonatal domoic acid	Hippocampus	↑ BDNF mRNA ↓ Cell counts ↑ Mossy fibre sprouting ↑ trkB receptor expression ↓ GAD65/67 immunostaining ↓ Number of parvalbumin containing neurons	Bernard et al. (2007), Doucette et al. (2004), Gill et al. (2010) and Robbins et al. (2013)
	PFC	• Altered tyrosine hydroxylase immunoreactivity	
	NAc	• Altered tyrosine hydroxylase immunoreactivity	
Neonatal quinpirole model	Hippocampus	↓ In nerve growth factor (NGF) ↓ BDNF ↓ Acetyltransferase	Brown et al. (2008, 2006), Kostrzewa (1995), Kostrzewa et al. (2004), Maple et al. (2007) and Thacker et al. (2006)
	PFC	↓ In nerve growth factor (NGF) ↓ BDNF ↓ Acetyltransferase	
	NAc	↓ Regulator of G-protein signaling 9	
	Striatum	↓ Regulator of G-protein signaling 9	
	Other	↑ Dopamine D2 receptor sensitivity but no change in the number of DA receptors	
Maternal separation	Hippocampus	• Neuronal degeneration ↑ Astrocytes in hippocampus, • Altered cannabinoid receptor expression ↑ Levels of 5-HT	Llorente et al. (2010, 2009, 2008)
	PFC	↑ Levels of 5-HT ↑ Levels of DA	
	Striatum	↑ levels of 5-HT ↑ Levels of DA	
	Other	• Neuronal degeneration ↑ GFAP+cells in cerebellum ↑ Plasma glucocorticoid levels	
Social isolation rearing	Hippocampus	↓ Number of parvalbumin and calbindin positive GABAergic interneurons	Bloomfield et al. (2008), Day-Wilson et al. (2006), Harte et al. (2007), Heidbreder et al. (2000) and Roncada et al. (2009)
	PFC	↓ Volume (neuron # unchanged) ↓ Reduced GAT-1 expression	
	NAc	• Altered protein expression (some correlated with PPI deficits) ↑ Basal DA level ↓ Basal 5-HT turnover	
Neonatal DOM + social isolation rearing	Unknown	Unknown	
Maternal separation + social isolation rearing	Unknown	Unknown	

Adapted from Animal Models for Schizophrenia Research, www.schizophreniaresearchforum.org.

In addition to manifesting seizures in adulthood, post-mortem analysis of these animals at 15 months of age revealed many hallmark features of clinical temporal lobe epilepsy (TLE) including hippocampal cell loss, mossy fibre sprouting (MFS) in the dentate gyrus and area CA3 (see Fig. 6), and regionally-selective elevation of the neurotrophin BDNF (Doucette et al., 2004). Of particular interest in the context of the current review, however, is that these changes did not occur at the time of drug administration (unpublished) but were progressive in nature with changes occurring over time. Adolescent rats (PND 29) showed no hippocampal pathology with the exception of a mild astrogliosis (unpublished) whereas younger mature animals (PND 75) displayed less severe MFS than aged rats and no loss of hippocampal cells (Bernard et al., 2007). Further, confirming the relevance of this model to understanding epilepsy and epileptogenesis are two reports by Gill et al. (2009, 2010) demonstrating alterations in electroencephalographically recorded sleep patterns and reductions in seizure threshold that accompany selective loss of inhibitory neurons in the hippocampus.

The same research group has subsequently attempted to better understand the molecular basis of these changes through the use of organotypic hippocampal slice cultures. Transient (24 h) exposure of cultures to a low concentration (2 μM) of domoic acid was shown to produce a mild regionally-specific toxicity in hippocampal subfield CA1 that stimulated neurogenesis in the dentate gyrus (Perez-Gomez and Tasker, 2012) that was subsequently shown to be dependent on both mitogen-activated protein kinase kinase (MEK) and cAMP-dependent protein kinase A (PKA) intracellular signalling pathways (Perez-Gomez and Tasker, 2013). And consistent with what was observed *in vivo* (see Fig. 6) slice cultures also demonstrated mossy fibre sprouting and increased synaptogenesis in response to domoic acid (Perez-Gomez and Tasker, 2014a). The neonatal domoate model of epileptogenesis represents, therefore, an interesting example of "reverse translation" in that the model began with a clinical case that was subsequently replicated in vivo in the rat and now in vitro using hippocampal slice cultures.

3.2. Models of schizophrenia and related disorders

Schizophrenia is a complex and debilitating mental disorder characterized by impairments in the perception of reality. It is found in approximately 1% of the general population and results in great emotional cost to those directly affected, as well as large financial cost to the economy worldwide (Knapp et al., 2004; Rössler et al., 2005).

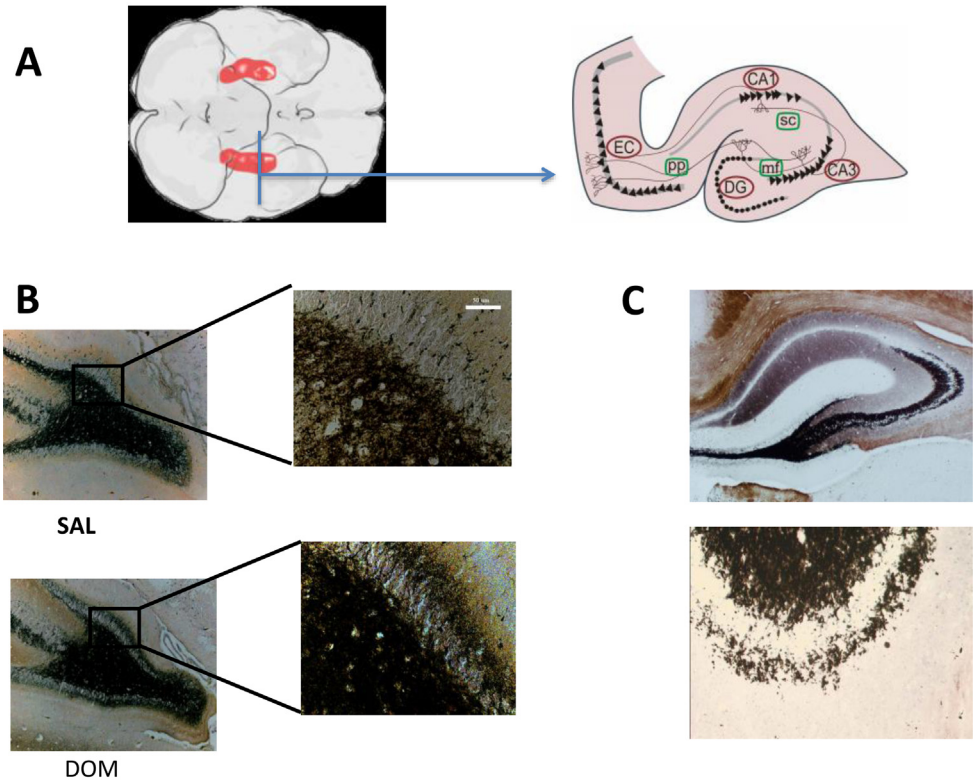

Fig. 6. Mossy fibre sprouting in the neonatal domoic acid model of epileptogenesis. The orientation of the hippocampus is depicted in A. Photomicrographs illustrating Timm's stain labeled fibre's sprouting in Dentate Gyrus (B) and *stratum oriens* of the CA3 region (C) of hippocampus of control and Domoic acid (DOM) treatment are shown. Sprouting of abnormal dentate granule cell axons is first seen in the dentate gyrus (B) and at a later age in hippocampal area CA3 (C). Scale bar 50 μm.

Believed to arise due to a combination of genetic susceptibility and environmental influence (Rapoport et al., 2005), schizophrenia manifests great variability in symptom profiles, developmental time course and response to treatment (Tamminga and Holcomb, 2005). It has been suggested that events occurring long before the formal onset of the illness (potentially during gestation and/or early life), disrupt the normal development of the CNS leading to significant and long-lasting changes in CNS functioning (Rapoport et al., 2005). While genetic factors likely contribute to the development of schizophrenia by causing an individual to be more vulnerable to the illness, a variety of early life events have been implicated in a higher than average risk of developing schizophrenia (as illustrated in Fig. 2). These events include maternal illness during gestation (Mednick et al., 1988), prenatal stress (reviewed by Baier et al., 2012), obstetric complications (Cannon et al., 2002; Geddes et al., 1999) and toxin exposure (Fiore et al., 2004). Such events can lead to subtle alterations in the functioning of the CNS which may result in an increased vulnerability to environmental triggers later in life (Lieberman et al., 2001).

Of relevance to the current review, there are a number of developmentally based animal models of schizophrenia and related disorders that seek to study the effect of various developmental insults during the postnatal period and the effects that such events may have in adulthood. This is a logical approach, for although schizophrenia generally arises in adolescence or early adulthood, it is increasingly regarded as being neurodevelopmental in origin. It is believed that subtle perturbations in the developing brain result in a permanent change in brain development, increasing the risk of developing schizophrenia later in life. The approach to using environmentally adverse events to model schizophrenia in animals has come about due to epidemiological studies showing that a variety of early life events can increase a person's likelihood of developing schizophrenia including childhood trauma, abuse, illness, infection, famine, etc. (Brown, 2011). Some of the major features of the models described below are summarized in Tables 1 and 2.

3.2.1. Neonatal quinpirole

Repeated administration early in development of the dopamine D2/D3 receptor agonist quinpirole results in a long term increase in D2 receptor sensitivity (Kostrzewa et al., 1990). As a result of this treatment during the neonatal period, rats display a variety of behavioural and neurological changes in adulthood consistent with schizophrenia and potentially, with other disorders that implicate DA dysfunction (Brown et al., 2004a, 2004b; Kostrzewa and Brus, 1991; Kostrzewa, 1995).

The neonatal quinpirole model consists of a single daily i.p. injection of quinpirole (usually 50 μg/kg/day) for some period of time following birth. Following treatment, both male and female Sprague-Dawley rats display increased behavioural sensitization illustrated by hyperlocomotion, increased vertical jumping and enhanced quinpirole-induced yawning, an effect which persists into adulthood (Kostrzewa and Brus, 1991; Kostrzewa, 1995; Kostrzewa et al., 1990, 1993a, 1993b). Other behavioural effects observed in adulthood include deficits in the Morris water maze, hyperlocomotion and enhanced skilled reaching (Brown et al., 2002, 2004a, 2004b, 2005; Thacker et al., 2006) (see Table 1). Neonatal quinpirole treatment produces a significant decrease in nerve growth factor in the hippocampus and prefrontal cortex (PFC), as well as decreases in BDNF and acetyltransferase in the hippocampus and PFC (Brown et al., 2006; Thacker et al., 2006) (Table 2). Furthermore, some of the reported behavioural and neurochemical alterations have been found to be partially or totally blocked by the administration of the antipsychotic olanzapine (Brown et al., 2008; Thacker et al., 2006) as well as

by the administration of nicotine (Brown et al., 2004a, 2004b, 2006; Tizabi et al., 1999) (Table 1).

3.2.2. Maternal separation

A stressful environment can cause maladaptive brain development and functioning from the period of prenatal development until adulthood. These effects can be modelled in animals in a variety of ways. Some stress paradigms such as mild chronic stress (Hill et al., 2012) and social defeat (Kudryavtseva et al., 1991; Venzala et al., 2012) are used most often to model depression in animals, while neonatal maternal separation (Schmidt et al., 2011) and social isolation rearing are used to model schizophrenia and related disorders (Weiss et al., 2001).

The maternal separation model consists of separating mice or rat pups from their mothers for a period of 1–24 h, with some set frequency, thereby limiting the maternal care that they are able to receive. The methodologies used are highly variable with common differences being the age of the animals at which the separation occurs, the length of the separation, as well as if the separation is repeated and how often (Bouet et al., 2011; Lehmann and Feldon, 2000; Schmidt et al., 2011). The degree of social separation is also a factor with some protocols calling for rat pups to be isolated when they are separated (McIntosh et al., 1999; Zimmerberg and Shartrand, 1992) while others consist of removing the litter as a whole from the mother (Lehmann et al., 2000b) or removing only the mother from the homecage (Bouet et al., 2011; Lehmann et al., 2000a). Related to this, the temperature at which the pups are kept during the separation appears to be important, with colder temperatures leading to greater deficits (Zimmerberg and Shartrand, 1992).

Maternally separated animals show a variety of behavioural alterations including altered spontaneous locomotor activity in an open field, (Lehmann et al., 1999a, 1999b; Zimmerberg and Shartrand, 1992), social withdrawal and an increase in anxiety-like behaviour (Bouet et al., 2011) (see Table 1). Studies have also found that these animals display reduced sensitivity to d-amphetamine (Matthews et al., 1996; Zimmerberg and Shartrand, 1992), increased sensitivity to apomorphine (Ellenbroek and Cools, 1995b; Rots et al., 1996) as well as alterations to hypothalamic-pituitary (HPA) axis functioning and corticosterone responsiveness to stressors (Ladd et al., 1996; Meaney et al., 1996; Plotsky and Meaney, 1993; Stanton et al., 1988). The effects of maternal separation on measures of attention and information processing have often produced conflicting results. Some groups have shown that maternal separation leads to reduced pre-pulse inhibition (PPI) (Ellenbroek et al., 2004) while others have found no change (Weiss et al., 2001). Likewise, studies have shown that maternal separation can lead to both enhanced latent inhibition (LI) (Lehmann and Feldon, 2000; Lehmann et al., 1998; Weiss et al., 2001) and disrupted LI (Ellenbroek and Cools, 1995a). There are a number of other inconsistencies in the literature regarding the behavioural outcomes of maternal separation, some examples being anhedonia-like behaviour, sucrose consumption and sucrose preference (Schmidt et al., 2011). While some of this variability may be attributed to strain differences and thus a specific genetic vulnerability (Ellenbroek and Cools, 1995b; El Khoury et al., 2006) it is also likely that such inconsistencies can be attributed to the wide variety of experimental paradigms used although they are all collectively referred to as "maternal separation" (Lehmann and Feldon, 2000).

3.2.3. Social isolation rearing

Since Hatch et al. (1963) first reported that housing rats in isolation produced abnormal behavioural reactivity, many studies have shown that rats who experience social isolation (housed one animal per cage for some period of time post-weaning but still in auditory, visual and olfactory contact with other animals) display a variety of profound behavioural, neurobiological and neuroanatomical differences when compared to those rats who are raised in groups (Ferdman et al., 2007; Hall, 1998; Lehmann and Feldon, 2000; Paulus et al., 1998; Weiss et al., 2004).

Examples of behavioural alterations include locomotor hyperactivity (Einon and Morgan, 1978; Gentsch et al., 1988; Heidbreder et al., 2000), spatial working memory impairments (Einon, 1980) increased food hoarding behaviour (Heidbreder et al., 2000), impairments in reversal learning (Jones et al., 1991), a modified response to reward (Wongwitdecha and Marsden, 1995), increases in anxiety-like behaviour (Bouet et al., 2011), increase in social-avoidance (Bouet et al., 2011) and increased sensitivity to amphetamine (Jones et al., 1990) (see Table 1). A number of studies have also demonstrated that social isolation rearing can affect various measures of information and attention processing. Social isolation rearing has been shown to disrupt LI, however, the results indicate that these effects may vary according to the timing of the isolation, the timing of the testing period, the strain of rat used, and the other experiences of the animal (Gentsch et al., 1988; Han et al., 2012; Shao et al., 2009; Weiss et al., 2001; Wilkinson et al., 1994). In contrast, PPI can be reliably disrupted by post-weaning social isolation (Domeney and Feldon, 1998; Geyer et al., 1993; Stevens et al., 1997; Harte et al., 2007). This effect of social isolation on PPI has been shown to be reversible by various antipsychotics (Bakshi et al., 1998; Stevens et al., 1997; Varty and Higgins, 1995) and is routinely used in preclinical drug development (for reviews see Johansson et al., 1995; Swerdlow et al., 2008). It is important, however, to keep in mind that as with other measures, various experimental variables can impact the result of social isolation rearing on PPI such as the length of the isolation period (Varty et al., 1999), exposure to other behavioural tests (Domeney and Feldon, 1998), type of housing (solid bottomed vs wire bottom cages) (Weiss et al., 1999) and the strain of rat used (Varty and Geyer, 1998; Weiss et al., 2000).

3.2.4. Neonatal domoic acid

The neonatal domoate rat model uses repeated s.c. injections of low doses (20 μg/kg) of DOM to stimulate the glutamatergic (presumably non-NMDA) system of rats during the second postnatal week of life, from postnatal days (PND) 8–14. DOM can induce excitotoxicity by acting on both pre and post-synaptic receptors (for review see Perez-Gomez and Tasker, 2014b). As described previously, at low concentrations DOM is selective for kainate receptors, in particular the low-affinity kainate receptors (Verdoorn et al., 1994; Tasker et al., 1996), although at higher concentrations other receptors are also able to be activated (see Perez-Gomez and Tasker, 2014b). While this treatment protocol does not produce overt signs of toxicity in the rat pups (Doucette et al., 2003) once the animals reach adulthood they display a host of behavioural, neuropathological and neurochemical alterations indicating the potential usefulness of this paradigm to model certain aspects of neuropsychiatric illness.

Behavioural changes (summarized in Table 1) include altered responses to novelty and reward (Burt et al., 2008a, 2008b), changes in cognitive functioning (Adams et al., 2009; Doucette et al., 2007; Robbins et al., 2013), altered social interaction (Ryan et al., 2011) and changes in stress response (Gill et al., 2012). Alterations to measures of information and attention processing have also been observed with both LI (Marriott et al., 2012, 2014) and PPI (Adams et al., 2008; Marriott et al., 2012) being affected depending on the sex of the animal and the specific paradigm used. Alterations to brain regions, systems, and specific measures known to be implicated or affected in schizophrenia include increases in hippocampal BDNF mRNA, increases in hippocampal mossy fibre sprouting, decrease in hippocampal cell counts and elevated trkB

receptor expression (Bernard et al., 2007; Doucette et al., 2004). Alterations to dopaminergic and GABAergic system proteins have also been observed. A study by Robbins et al. (2013) found that neonatal DOM treatment leads to significantly less TH immunoreactivity in the right mPFC of male rats, and significantly greater TH immunoreactivity in the left core and right shell of the nucleus accumbens in female rats. Gill et al. (2010) found decreased GAD65/67 combined immunostaining in the ventral dentate gyrus (females) and ventral CA3 area (males) of the hippocampus. It was also found that DOM treated rats displayed a significantly lower number of parvalbumin containing neurons in the dorsal dentate gyrus, the mid dentate gyrus and the mid CA3 subfield with these results often being present in only one sex (Gill et al., 2012). These changes are summarized in Table 2.

3.2.5. Developmentally based postnatal multi-hit models

Historically, efforts to model schizophrenia and similar disorders in animals have concentrated on using only one experimental intervention to produce disease characteristics. More recently (and consistent with the concept depicted in Fig. 2), attention has turned to the possibility of developing animal models that incorporate two or more developmental insults in what has come to be referred to as a "multi-hit" approach. In doing so, models may be created that better mimic the aetiology of the disorders, which are often considered to result from multiple interacting factors (see Fig. 2). In animal models of schizophrenia, these multi-hit models usually involve using some combination (often two) of previously established interventions. The two manipulations may be from different categories of models (e.g. gene-environment models) or may be from the same model category (e.g. two developmentally based interventions). Established models that have been used in combination include maternal infection (Dalton et al., 2012; Deslauriers et al., 2013) and stress paradigms (Deslauriers et al., 2013), as well as a variety of gene-environment models (Cash-Padgett and Jaaro-Peled, 2013; Karl, 2013) and a combination of NMDA receptor antagonism and social isolation rearing (Ashby et al., 2010; Gaskin et al., 2014; Gilabert-Juan et al., 2013; Hawken et al., 2013; Hickey et al., 2012; Lim et al., 2012). While most multi-hit models combine a prenatal and postnatal intervention, there are a small number of developmentally based two-hit models where both manipulations occur during the postnatal period.

3.2.5.1. Neonatal DOM and social isolation. A recently developed two-hit model that combines neonatal DOM treatment and social isolation rearing has demonstrated both singular and additive effects in measures of information and attention processing. In this model, rats are given low doses of DOM as described above (Section 3.2.4). Animals are then weaned on PND 21 and housed alone in cages where they can still see, hear and smell other rats, but cannot interact socially. In this paradigm neonatal treatment with DOM abolished LI behaviour in adult male rats regardless of housing condition when tested 48 h after conditioning (Marriott et al., 2014). When tested again one week later, animals who received both neonatal DOM treatment and isolation rearing displayed significant LI whereas control animals, those that received DOM alone or were isolated alone did not (Marriott et al., 2014). Further, while social isolation alone significantly lowered PPI amplitude in male (but not female) rats in a manner consistent with previous literature using this model (Domeney and Feldon, 1998; Geyer et al., 1993; Stevens et al., 1997), DOM treatment appeared to make animals refractory to this isolation rearing effect. Additionally, combining social isolation and DOM treatment caused an additive decrease in PPI startle latency that was observed in both sexes as described in a preliminary report (Marriott et al., 2013). In conclusion, both neonatal low-dose DOM treatment and social isolation rearing have been shown to affect the development of attentional processing in rats. However, each paradigm may exert these effects through different neuronal signalling systems and these different systems may be responsible for different aspects of the behavioural changes that were observed.

3.2.5.2. Maternal separation and social isolation. Another proposed multi-hit model that focuses solely on postnatal events consists of a combination of pre-weaning maternal separation and post-weaning social isolation. A study by Weiss et al. (2001) made use of this model and found that maternal separation did not affect PPI but resulted in enhanced LI, while social isolation disrupted PPI in male rats when tested 12 weeks after weaning (but not when tested 30 weeks after weaning) but did not affect LI (see Table 1). Additionally they found no additive effects or interaction between the two experimental manipulations with regard to their effect on either PPI or LI by combining maternal separation and social isolation rearing, although both of the effects on PPI and LI that were observed separately were maintained. While additive effects were not observed, this model does produce sustained alterations to both PPI and LI and provides support for the theory that the two behaviours implicate different psychological and neurobiological mechanisms (Ellenbroek et al., 1996; Weiss et al., 2001; Wilkinson et al., 1994).

3.3. Models of disease co-morbidity

Examination of Section 3.1 (epilepsy) and Section 3.2 (schizophrenia) reveals that two of the pre-clinical models described appear in both sections. Both neonatal inflammation and neonatal low dose DOM have been described as models of epilepsy but also as models of schizoaffective disorders. This is because both exhibit behavioural and histopathological changes consistent with both conditions depending on what the authors chose to investigate. In short, if one chooses to measure seizure threshold and finds significant reductions it is concluded that the model is a model of epilepsy. Conversely, if one chose to measure sensory gating using PPI and found deficits the conclusion would be a model of schizophrenia. But in truth are these models of both, or neither? In these particular examples it is tempting to say "both" because seizure disorders are a common comorbidity with schizophrenia with one recent study estimating that 6% of epileptic patients manifest psychosis (Clancy et al., 2014) so logically there must be some overlap of the underlying neuropathology although it must be acknowledged that the opposite was speculated when proposing electroconvulsive shock therapy for treating schizophrenia. But by the same argument it is entirely possible that one or both models also show changes consistent with other diseases or disorders that have simply not been investigated or reported to date.

One way to resolve the paradox described above is to avoid labelling the protocols as "models" that are representative of a single disease (e.g. an "epilepsy" model) and rather to simply view these paradigms as experimental manipulations that result in "progressive neurological dysfunction" in rats. This is a personal opinion of the authors and many would disagree, but if one avoids labels and simply measures progressive alterations in brain structure and function arising from a neonatal challenge it becomes possible to objectively describe changes over time and ultimately, through mechanistic investigations, to determine causality or lack of causality between different types of change. Again, in our opinion this represents an alternate path for studying disease development as opposed to symptom reduction (see Section 1.2).

The argument above is not intended to suggest that models of symptoms do not have value; they do. If a particular new chemical

entity is developed as an anticonvulsant then determining efficacy in a model of chemically-induced acute convulsions is useful. But similarly, most neurological and/or psychiatric patients present with multiple, and often personalised, groups of symptoms, implying that either they have different pathologies or they have differing overt responses to the same underlying pathology. In either case using preclinical models to mechanistically dissect progressive brain dysfunction not exclusive to a single disease seems a viable approach.

4. Potential therapeutic strategies

Clearly the ultimate goal of studying disease and disease models is to identify potential therapeutic strategies. In the case of modelling progressive neurological dysfunction there is the further hope that treatments can be found to slow or arrest the disease process prior to the onset of clinical signs (see Fig. 2). At this time our understanding of the processes involved in presymptomatic neurodegeneration is very limited, and accordingly, treatment options are largely absent. None-the-less a few strategies have been attempted as described below.

4.1. Supportive therapy

Perinatal asphyxia requires neuroprotective treatments for preventing or reducing catastrophic consequences, including mortality and major disabilities. Different approaches have been explored, but the focus has been on the reanimation of the affected baby.

Oxygen therapy was proposed as a universal approach for critical illnesses implying hypoxemia (American Heart Association guidelines, 1992). It is now accepted, however, that high concentration of supplemental oxygen can be harmful to the newborn (see Saugstad et al., 2006) probably by increasing reactive oxygen (ROS) and nitrosylated (RNS) species (Kapadia et al., 2013; Martin and Grocott, 2013; Saugstad et al., 2006; van Zanten et al., 2014), therefore, oxygen therapy is no longer recommended.

Hypothermia has also been proposed as a relevant therapeutic intervention against hypoxic/ischemic insults, aiming to decrease energy expenditure (Ginsberg et al., 1992). It has been shown that hypothermia can be a potent therapeutic intervention for preventing the short-term effects of perinatal asphyxia, even more effective than glutamate antagonism, but suffers from a narrow therapeutic window (Engidawork et al., 2001). Nevertheless, there is now compelling clinical evidence that hypothermia improves the neurodevelopmental outcome following hypoxic–ischemic encephalopathy (Edwards et al., 2010; Guillet et al., 2012; Shankaran et al., 2012; Wu et al., 2014), although the protocols are not yet fully established, and the issue of distinguishing between beneficial or deleterious effects on risk of death and/or severe disability is not fully clarified (see Wassink et al., 2014) and the neuroprotective potential of hypothermia is still being discussed (Bonifacio et al., 2015; Robertson et al., 2012; Jacobs et al., 2013).

4.2. Signalling pathways during asphyxia

It has been proposed that the effects observed long after perinatal asphyxia can be explained by overexpression of sentinel proteins, including PARP-1, competing for NAD^+ during the re-oxygenation period (Klawitter et al., 2006), supporting the idea that PARP-1 overactivation is an early endpoint and hence a possible therapeutic strategy (see Herrera-Marschitz et al., 2014; Kauppinen and Swanson, 2007). Nicotinamide, a PARP-1 inhibitor (Virag and Szabo, 2002), prevents several of the short- and long-term outcomes elicited by perinatal asphyxia (Allende-Castro et al., 2012), evaluated at neurochemical (Bustamante et al., 2003, 2007), cellular (Klawitter et al., 2007) and behavioural (Morales et al., 2010; Simola et al., 2008) levels, and it has recently been reported that the neurodegenerative cascade elicited by perinatal asphyxia involves PARP-1 overactivation, pro-inflammatory signalling and cell death; which can be prevented by systemic neonatal nicotinamide administration (Neira-Peña et al., 2015), further supporting the idea that PARP-1 inhibition represents a suitable therapeutic strategy.

The role of HIF-1α, a cue molecule for oxygen homeostasis (Wang et al., 1995) that is involved in erythropoiesis, angiogenesis, energy metabolism, cell proliferation/survival and apoptosis (Ke and Costa, 2006) has also been investigated. *In vitro*, hypoxia and hypoxia/re-oxygenation was shown to increase levels of HIF-1α together with astrocyte reactivity and these changes were prevented by HIF-1α inhibition (Rojas-Mancilla et al., in preparation). The same authors also observed *in vivo* that HIF-1α protein levels were increased by 60% and translocated to the nucleus of astrocytes and neurons, suggesting increased transcriptional activity. These finding suggested that HIF-1α is a suitable therapeutic target. Indeed, the competitive HIF-1α inhibitor, YC-1 (3-(5′-hydroxymethyl-2′-furyl)-1-benzylindazole), which accelerates HIF-1 elimination, inhibits *de novo* synthesis of HIF-1 through mouse double minute 2 homolog (mdm2) inhibition and stimulates FIH-dependent p300 dissociation from HIF-1α (Cox-Limpens et al., 2014). YC-1 was found to prevent the loss of synaptic contacts induced by perinatal asphyxia in the hippocampus (Rojas-Mancilla et al., in preparation). The effect of YC-1 was also investigated on long-term behavioural outcomes of perinatal asphyxia, finding that it improved spatial and non-spatial memory deficits, in agreement with previous reports (Lopez-Hernandez et al., 2012; Sheldon et al., 2009).

4.3. Inflammatory preconditioning

Based on the frequent observation that subtoxic doses of a stressful stimulus can lead to the generation of a protective state, the possibility of using preconditioning strategies in neonates to confer long-term reductions in the severity of insults has been described in several models.

In the neonatal HI model (see Section 2.2) preconditioning by exposure to low doses of neurotoxins acting as Toll-like receptors (TLRs) agonists such as LPS has been proposed as a therapeutic strategy (Hickey et al., 2011). LPS is a known specific agonist for Toll-like receptor 4 (TLR4), one of the 13 mammalian TLRs that recognize foreign pathogens. LPS mediates ischemic tolerance in the adult brain by stimulation of TLR4 signals either by MyD88 (myeloid differentiation primary response gene 88)-dependent or by MyD88-independent pathways. Activated MyD88 recruits a series of downstream adaptor proteins, which then activate the transcription factor NF-κB, leading to expression of pro-inflammatory cytokines. TLR4 can also activate a series of adaptor proteins independently of MyD88, ultimately inducing type 1 interferon (for review see Marsh et al., 2009). The pathways and potential of LPS preconditioning in the neonatal brain (and corresponding neonatal HI model) is, however, less well described. Several recent papers by the Askalan group, however, have provided compelling evidence that LPS preconditioning is neuroprotective in neonatal HI (Hickey et al., 2011). Interesting these authors have shown that the timing of the preconditioning stimulus is critical and is correlated with the time-dependent expression of different TLRs (Shi et al., 2013), suggesting that new chemical entities with specificity for TLR subtypes could be developed, achieving desired-, without the undesirable-side effects of non-specific inflammation.

4.4. Biomarkers

In most cases presymptomatic intervention will still require some reliable indicator that the disease process is underway. Of late we are seeing that even commonplace preventative strategies such as vaccination are being questioned, so deciding that an infant or child warrants preventive intervention for a neurological condition that has X% of occurring in adolescence or adulthood is a medical dilemma with profound ethical consequences, and accordingly, a need for an extremely reliable indicator, or biomarker, that a disease process is underway. To further confound the issue, most of the relevant changes are likely to be found in the infant brain subsequent to trauma. Biopsy of brain tissue is not a viable option and non-invasive imaging of prospective patients is impractical in terms of both time and expense (although may be warranted if there is a clear indication of risk, for example extreme hypoxia at birth). So ideally either a serum biomarker or a definitive deficit on some early test of cognition, motor function, etc. probably represents the best possibility for early diagnosis. At this time, studies in animal models such as those described above are far from identifying such markers and those changes that are seen quite consistently (e.g. increases in the neurotrophin BDNF have been observed in most of the models described; see above) are relatively non-specific (or presumed to be so at this time). None-the-less the goal of identifying biomarkers of disease progression that can be obtained non-invasively or using minimally-invasive techniques is worthy of considerable effort.

5. Conclusions

In this review we have attempted to briefly summarize the concept of modelling disease progression rather than end-stage symptoms as a valuable means of improving clinical translation of experimental findings. To maintain some focus we have limited our descriptions to models in rodents (almost exclusively rats) and to models that originate in neonatal life. Further, we have not provided a comprehensive overview of all of the models or dealt with most of them in any great detail, but have rather attempted to illustrate both the current status and potential of this approach. The goal of basic biomedical research is to understand normal and abnormal brain function relevant (primarily) to humans and to use that knowledge to reduce the incidence, severity and societal burden of these devastating conditions. It is our belief and hope that the use of animal models is essential to achieving that goal, but that advancement of the field requires a re-thinking of the way we use models in both biomedical investigation and therapeutant development.

Conflict of interest statement

RAT is a co-inventor of the neonatal domoic acid model of epilepsy that is patent protected (US patents 7034201B2, 7521589, 7622101; Canadian patent CA2448647) and licensed for commercial use to Neurodyn Life Sciences Inc.

All other authors declare no conflict of interest.

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