Neonatal Hypoxia Ischaemia: Mechanisms, Models, and Therapeutic Challenges

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Neonatal hypoxia-ischaemia (HI) is the most common cause of death and disability in human neonates, and is often associated with persistent motor, sensory, and cognitive impairment. Improved intensive care technology has increased survival without preventing neurological disorder, increasing morbidity throughout the adult population. Early preventative or neuroprotective interventions have the potential to rescue brain development in neonates, yet only one therapeutic intervention is currently licensed for use in developed countries. Recent investigations of the transient cortical layer known as subplate, especially regarding subplate's secretory role, opens up a novel set of potential molecular modulators of neonatal HI injury. This review examines the biological mechanisms of human neonatal HI, discusses evidence for the relevance of subplate-secreted molecules to this condition, and evaluates available animal models. Neuroserpin, a neuronally released neuroprotective factor, is discussed as a case study for developing new potential pharmacological interventions for use post-ischaemic injury.

Keywords: neonatal, hypoxia-ischemia, encephalopathy, subplate, neurodevelopment, neuroserpin, neuroprotection

INTRODUCTION: GLOBAL CLINICAL IMPACT OF NEONATAL HYPOXIA ISCHAEMIA

The clinical definition of neonatal HI injury is "asphyxia of the umbilical blood supply to the human fetus occurring at 36 gestational weeks or later" (Perlman, 1997, 2006; Volpe, 2001, 2012; Shah P.S. et al., 2006). Neonatal HI is synonymous with hypoxic-ischaemic encephalopathy (HIE) occurring in the term infant, where term is defined as 36 gestational weeks or later. This review addresses neonatal HI or HIE, any results concerning perinatal hypoxic-ischaemia injury will be clearly indicated in the text. This disorder encompasses a large range of physiological origins

Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; BBB, blood brain barrier; CPR, cardiopulmonary resuscitation; CNS, central nervous system; CSF, cortico-spinal fluid; CSPG, chondroitin sulfate proteoglycan; CTGF, connective tissue growth factor; E(18), embryonic day (18); EM, electron microscopy; GABA, γ-aminobutyric acid; HI, hypoxia-ischaemia; HIF-1, hypoxia inducible factor 1; IL-1ß, interleukin-1ß; IL-6, interleukin-6; IL-9, interleukin-9; LPS, lipopolysaccharide; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NMDA, N-methyl-D-aspartate; OGD, oxygen glucose deprivation; P(8), postnatal day (8); poly(I:C), polyinosinic-polycytidylic acid; rER, rough endoplasmic reticulum; TNF-α, tumour-necrosis factor-α; tPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor.
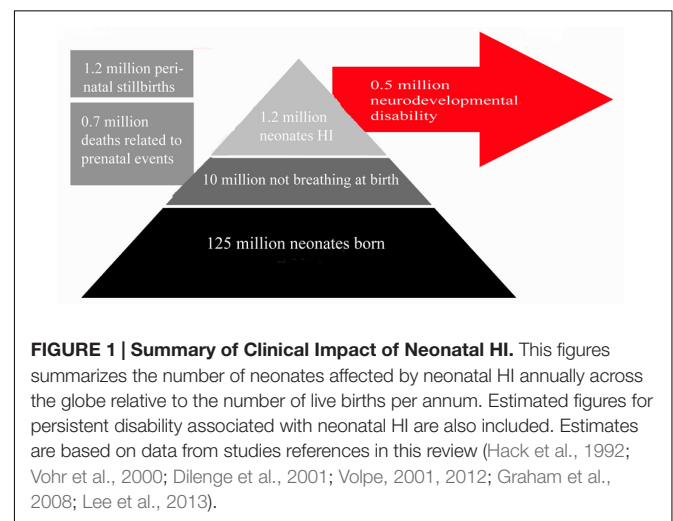
and clinical outcomes (Volpe, 1995). The diagnostic criteria for neonatal HI are based on a set of markers demonstrated to correlate with clinical outcome (Finer et al., 1981; Perlman, 1997; Richer et al., 2001). These include: 5-min Apgar score of less than 5 (Levene et al., 1986; Ruth and Raivio, 1988; Laptook et al., 2009); need for delivery room intubation or CPR (Richardson B.S. et al., 1996; Salhab et al., 2004a; Shalak and Perlman, 2004; Kattwinkel et al., 2010); umbilical cord arterial pH less than 7.00 (Ruth and Raivio, 1988; Perlman and Risser, 1993; Robertson N.J. et al., 2002; Salhab et al., 2004b); and abnormal neurological signs, such as hypotonic muscles or lack of sucking reflex (Levene et al., 1986; Robertson et al., 1989; Richer et al., 2001). Electroencephalography (EEG) has also proved helpful as a predictor of clinical outcome (reviewed in Walsh et al., 2011; van Laerhoven et al., 2013). Amplitude-integrated EEG (aEEG) in particular, a filtered time-compressed continuous one- or two-channel read-out, has been demonstrated a reliable predictor in meta-analyses up to 5 years after birth (al Naqeeb et al., 1999; Sinclair et al., 1999; Toet et al., 1999; Biagioni et al., 2001; Shah D.K. et al., 2006; Nash et al., 2011; Murray et al., 2016; Weeke et al., 2016), however, some report that aEEG remains less reliable than MRI, especially following hypothermia treatment (Doyle et al., 2010; Weeke et al., 2016). The Thompson score, an EEG measure of predictive neurodevelopment, is likely to remain useful to clinicians (Thompson et al., 1997; Horn et al., 2016). This is by no means an exhaustive list of risk factors and signs of clinical concern that can occur during the early postnatal period (Shalak and Perlman, 2004; Hagberg et al., 2015).

Neonatal HI is the most common cause of death and disability in human neonates (Grow and Barks, 2002; Ferriero, 2004; Shalak and Perlman, 2004), accounting for 23% of infant mortality worldwide, and affecting 0.7–1.2 million infants annually (Lawn et al., 2005; see **Figure 1**). In developed countries, incidence of HI injury has not decreased in the past two decades (Himmelmann et al., 2005; Vincer et al., 2006), remaining a significant cause of fatality and disability. The frequency of motor and cognitive disorders linked to perinatal and early postnatal brain injury actually increased during the 1990s, and currently remains stable (Vincer et al., 2006; Robertson and Iwata, 2007; Wilson-Costello et al., 2007). Progress in assisted respiratory and intensive care technology has led to greater than 90% survival of infants born after gestational week 23 (Larroque et al., 2004; Fellman et al., 2010), perhaps accounting for the increased burden of disability within the population as mortality rates have decreased substantially.

Amongst those who survive the initial injury, rates of disability remain high throughout life. Of patients surviving neonatal HI, 5–10% of infants demonstrate persistent motor deficits, and 20–50% display sensory or cognitive abnormalities that persist to adolescence (Hack et al., 1992; Vohr et al., 2000; Volpe, 2001, 2012; Lee et al., 2013). A meta-analysis of seven studies including 386 infant patients investigated the average incidence of mortality and morbidity: 5.9% of all patients across all studies died, 16.3% suffered neonatal seizures, and 17.2% experienced neurological deficits, with 14.2% qualifying for a diagnosis of cerebral palsy (Graham et al., 2008). Long-term outcomes in neonatal asphyxia infants have also been investigated. One meta-analysis found that

1–18% of patients were identified as having severe sensorimotor or learning disorders by the age of 2–5 years, with only 50–60% of patients reported as developmentally normal (Dilenge et al., 2001). This study covered a wide range of injury severities and follow-up ages. Disorders included seizures, hearing and vision loss (Robertson and Finer, 1985), language disorders, microcephaly, and muscle spasticity (Shankaran et al., 1991, 2012). Studies also report more severe neurological signs in patients suffering severe HI compared to those with milder HI injury (Robertson and Finer, 1985). Yet, many individuals who showed abnormal neurological signs at birth were normal at 2-year follow-up (De Souza and Richards, 1978). Clinical features and outcomes of neonatal HI are summarized in **Figure 1**.

Despite the high disability burden associated with surviving neonatal HI patients, there are very few preventative or protective treatments available for infants suspected to have suffered an HI event. The only licensed treatment currently available is hypothermia. This treatment involves subjecting either the infant's whole body or head-only to temperatures of around 33°C (Choi et al., 2012; Tagin et al., 2012). Hypothermia was first demonstrated to improve survival in cases of cardiac arrest (Bernard et al., 2002; Nikolov and Cunningham, 2003), and has since been applied as a neuroprotective treatment in acute neonatal HI injury patients (Gunn et al., 1997, 2005; Gunn and Gunn, 1998; Shankaran et al., 2002, 2005; Eicher et al., 2005; Gluckman et al., 2005; Jacobs et al., 2005, 2013; Shah et al., 2007; Azzopardi et al., 2009; Shah, 2010). A recent meta-analysis found that hypothermia carried out in over 1,200 infants reduced the rate of death and neurological handicaps at 18 months follow-up across all severity categories of neonatal HI injury (Tagin et al., 2012). However, hypothermia alone is not sufficient to prevent all brain injury or neurological symptoms, highlighting the need for additional therapies to use in conjunction. Xenon gas administration is currently being trialed as an additive therapy alongside hypothermia (Hobbs et al., 2008; Thoresen et al., 2009; Johnston et al., 2011). There are currently no other licensed treatments available for neonatal HI.

FIGURE 1 | **Summary of Clinical Impact of Neonatal HI.** This figures summarizes the number of neonates affected by neonatal HI annually across the globe relative to the number of live births per annum. Estimated figures for persistent disability associated with neonatal HI are also included. Estimates are based on data from studies references in this review (Hack et al., 1992; Vohr et al., 2000; Dilenge et al., 2001; Volpe, 2001, 2012; Graham et al., 2008; Lee et al., 2013).

Despite the efficiency of hypothermia (Tagin et al., 2012; Jacobs et al., 2013; Pauliah et al., 2013; Srinivasakumar et al., 2013; Kracer et al., 2014; Kali et al., 2015), death and disability remain a common feature of neonatal HI prognosis. Observations concerning global prevalence and poor long-term outcome reiterate the urgency of finding novel neuroprotective treatments for use during and directly following HI injury. This review examines the neuropathology resulting from neonatal HI injury in humans. The review then examines currently available animal models of neonatal HI and summarizes the strengths and weakness of such models for research into this complex human condition. Finally, the review will detail a potential approach toward identifying new pharmacological targets for neonatal HI therapies, focusing on the protein neuroserpin.

NEUROBIOLOGY OF NEONATAL HYPOXIA ISCHAEMIA IN HUMANS

There is ample evidence that brain damage occurs in human neonatal HI patients with poor clinical outcomes, documented in both imaging and histopathological studies (Mortola, 1999; Volpe, 2008, 2012; Northington et al., 2011). Neuropathology has been characterized in human post-mortem studies, concluding that most areas of the brain are vulnerable to some extent to neonatal HI injury (Miller et al., 2005; Triulzi et al., 2006; Billiards et al., 2008; Cohen and Scheimberg, 2008; de Vries and Groenendaal, 2010; Volpe, 2012). Gray and white matter lesions have been described at term after HI (Eken et al., 1994; Marin-Padilla, 1996, 1997, 1999). Localization and extent of neuropathology has been shown to be associated with neurodevelopmental symptoms, giving insights into the nature of disability the patients may present with.
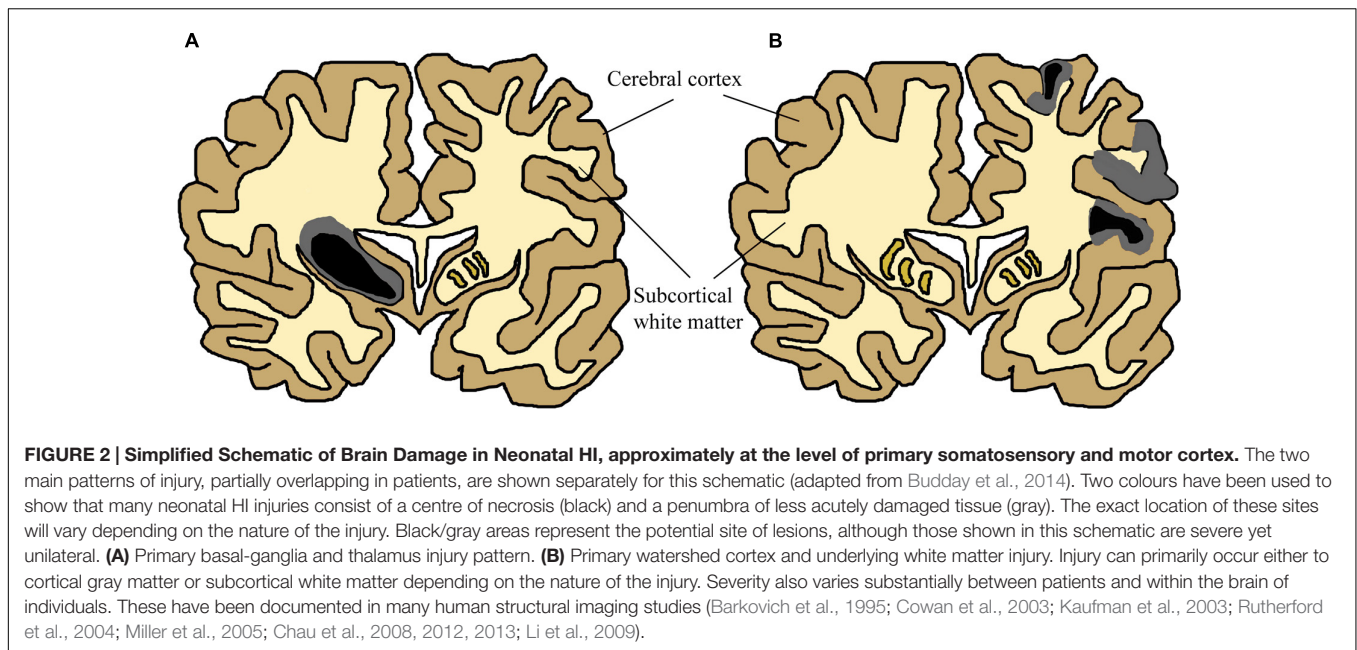
Neuroanatomy: Structural Imaging

Infants who survive the initial HI insult display cerebral damage visible with structural imaging. Magnetic resonance imagining (MRI) studies of term infants with neurological signs and combinations of fetal distress, cord acidemia, and depressed Apgar scores have been carried out in over 1,000 infants (reviewed in Volpe, 2012). These studies report great variation in the anatomical areas involved between individual patients, yet most samples described either patients demonstrating predominant or substantial injury to cerebral cortex (Barkovich et al., 1995; Rutherford et al., 2004; Miller et al., 2005; Chau et al., 2008, 2012, 2013; Li et al., 2009), or basal ganglia and thalamus (Barkovich et al., 1995; Rutherford et al., 1998, 2004; Cowan et al., 2003; Kaufman et al., 2003; Miller et al., 2005; Chau et al., 2008) in partially overlapping subpopulations. These two patterns of injury are shown in **Figure 2**. Cerebral white matter has been described as selectively sensitive to term HI injury (Inder et al., 1999; Craig et al., 2003). Although less common, severe selective involvement of subcortical white matter has been documented (Neil et al., 2002; Vermeulen et al., 2003). One review described the literature concerning structural MRI scans in the acute phase (within 2 weeks after birth): approximately 15–30% of scans were

normal, lesions in basal ganglia and thalamus are present in 40–80% of cases, with abnormalities of watershed white matter and cortex present in 40–60% of patients (Volpe, 2012). MRI anatomy has been shown to agree well with post-mortem studies (Cowan et al., 2003). Therefore, no single area of the brain is specifically damaged following neonatal HI. Any future treatments should take this diversity into account and provide neuroprotection to neurons throughout the brain.

The MRI scan is currently the method of choice for investigation of neonatal anatomy in both clinical and experimental circumstances (Perrin et al., 1997; Ment et al., 2002; Li et al., 2009). Diffusion-weighted MRI imaging has greatly improved identification of the time of onset of brain lesions (L'Abee et al., 2005; Chau et al., 2009). A reduced diffusion coefficient can be calculated, showing restricted diffusion during the first few days after the insult, with pseudonormalization by the end of the first week (McKinstry et al., 2002; Malik et al., 2006; Liauw et al., 2009). Sequential imaging has shown that lesions in the basal ganglia may increase in size during the first week after birth (Soul et al., 2001; Barkovich et al., 2006), and asymmetric diffusion within white matter has been correlated with clinical severity of hemiparesis (Glenn et al., 2007). Cranial ultrasound also remains a valuable clinical tool (Daneman et al., 2006). Another technique promising to add to understanding of neonatal HI is magnetic resonance spectroscopy (MRS), which allows brain metabolism to be imaged in real time (Kemp and Radda, 1994; Soares and Law, 2009). Full-term neonates with perinatal asphyxia have been studied, indicating that brain metabolism becomes abnormal after 6 to 12 h only to decrease even further after 24 h (Wyatt et al., 1989; Moorcraft et al., 1991; Roth et al., 1992). This coincided with clinical deterioration such as development of seizures. The concept of a delayed metabolic abnormality or 'secondary energy failure' has been elaborated in animal models (Lorek et al., 1994; Penrice et al., 1997; Groenendaal et al., 2006). Using MRS in these animal models, neuroprotective strategies could be tested. By using MRS data as real-time measurements of decreased brain metabolism in brain injury. ^{1}H-MRS and ^{31}P-MRS studied have demonstrated metabolic abnormalities following HI insult, which may persist for weeks (Groenendaal et al., 1994; Robertson et al., 1999). Unfortunately, with the magnetic field strength of current clinical systems, only large brain areas can be examined, limiting the use of this technique. Infants who have suffered neonatal HI often exhibit abnormal EEG activity (reviewed in Walsh et al., 2011; van Laerhoven et al., 2013). A range of abnormalities have been described, including: low voltage in isoelectric EEG (Finer et al., 1983; Legido et al., 1991), mild voltage depression (Watanabe et al., 1980; Toet et al., 2002; Murray et al., 2010), and asymmetry of trace (Aso et al., 1989; Zeinstra et al., 2001; Murray et al., 2009), although all of these criteria have been differently defined by different analysts (Rennie et al., 2004; Shellhaas et al., 2007). However, imaging techniques are constantly improving.

Lesions occur in many clinical patients, yet the effect on cognitive function is as diverse as the neuroanatomy. The area of cortex and basal ganglia damaged during the initial HI injury is directly predictive of language and motor outcome in childhood (Steinman et al., 2009; Martinez-Biarge et al., 2011). Examination

FIGURE 2 | Simplified Schematic of Brain Damage in Neonatal HI, approximately at the level of primary somatosensory and motor cortex. The two main patterns of injury, partially overlapping in patients, are shown separately for this schematic (adapted from Budday et al., 2014). Two colours have been used to show that many neonatal HI injuries consist of a centre of necrosis (black) and a penumbra of less acutely damaged tissue (gray). The exact location of these sites will vary depending on the nature of the injury. Black/gray areas represent the potential site of lesions, although those shown in this schematic are severe yet unilateral. **(A)** Primary basal-ganglia and thalamus injury pattern. **(B)** Primary watershed cortex and underlying white matter injury. Injury can primarily occur either to cortical gray matter or subcortical white matter depending on the nature of the injury. Severity also varies substantially between patients and within the brain of individuals. These have been documented in many human structural imaging studies (Barkovich et al., 1995; Cowan et al., 2003; Kaufman et al., 2003; Rutherford et al., 2004; Miller et al., 2005; Chau et al., 2008, 2012, 2013; Li et al., 2009).

of diffusion-tensor imaging of neonates was predictive of survival and motor outcome (Hunt et al., 2004; Ward et al., 2006). Children with basal-ganglia-thalamus pattern of injury tend to be severely disabled due to dyskinetic cerebral palsy and epilepsy (Himmelmann et al., 2007). Infants with predominant watershed white matter and cortex lesions have more prominent cognitive than motor deficits (Miller et al., 2005; Gonzalez and Miller, 2006; Steinman et al., 2009). Severe motor impairment is uncommon, and this group is often considered to have a normal outcome when seen at 12–18 months, although suboptimal head growth, behavioral problems, epilepsy, and a delay in language emerge during late childhood (Mercuri et al., 2000; Miller et al., 2002; Oguni et al., 2008; Sato et al., 2008; Steinman et al., 2009). Therefore, cortical damage appears to be relevant to functional outcome in surviving neonatal HI patients. This information could be used to predict future susceptibility to disability before it manifests, allowing social and educational supports to be put in place early.

Molecular Mechanisms of Cell Death

Anatomical studies describe loss of brain volume following moderate and severe neonatal HI. However, the underlying molecular mechanisms responsible for cell death are debated (McLean and Ferriero, 2004; Fatemi et al., 2009; Northington et al., 2011; Baburamani et al., 2012). Many pathways have been implicated in HI injury in the term brain, primarily: excitotoxicity, oxidative stress, and inflammation. Molecular studies have drawn attention to a fact essential for the development of successful new therapies that the neonatal brain and its injury is fundamentally different from that seen in adult HI stroke injury (McLean and Ferriero, 2004; Johnston et al., 2011; Baburamani et al., 2012; Semple et al., 2013).

There are many important differences between neonatal HI and adult ischaemic stroke. For example, severe HI events in

the infant brain can lead to liquifactive disintegration, not seen after adult stroke (Larroche, 1977; Rorke, 1992). Newly formed blood vessels are fragile and prone to rupture (Trommer et al., 1987; Volpe, 1989; Ment et al., 1991; Jones et al., 2002), and surrounded by fewer astrocyte end-feet (El-Khoury et al., 2006). Another key site of difference is the BBB. Studies in rodents indicate that the BBB is compromised as a result of neonatal HI (Muramatsu et al., 1997; Svedin et al., 2007; Ferrari et al., 2010; Tu et al., 2011; Yang et al., 2012). Yet the common belief that the neonate BBB is less effective has recently come under revision (Saunders et al., 1999, 2012, 2014; McLean and Ferriero, 2004; Baburamani et al., 2012; Stolp et al., 2016). Tight junctions, the occlusive element of the BBB, are present as soon as embryonic vessels invade the brain (Schulze and Firth, 1992; Bauer et al., 1993; Stewart and Hayakawa, 1994; Kniesel et al., 1996), and are functional (Ek et al., 2003, 2006; Daneman et al., 2010). In a model of hypoxia in newborn piglet, BBB integrity was maintained (Stonestreet et al., 1992), yet other experiments have demonstrated damage to the BBB following neonatal HI (Alvarez-Diaz et al., 2007; Leonardo and Pennypacker, 2009).

Cerebrovascular autoregulation is another factor which must be considered in neonates. The concept that preterm infants have a 'pressure passive' cerebral circulation is widely accepted. However, sick term infants demonstrate impaired autoregulation (Pryds et al., 1990; Hardy et al., 1999; Boylan et al., 2000) and the range of blood pressure over which cerebrovascular autoregulation functions expands with maturity (Tuor and Grewal, 1994; Verma et al., 2000). Also, the concentrations and actions of various signaling molecules is different in the developing brain including; caspase-3 (Cheng et al., 1998), VEGF (Carmeliet and Storkebaum, 2002), and HIF-1 (Iyer et al., 1998), among others (reviewed in Baburamani et al., 2012).

One surprising difference is sexual dimorphism in response to neonatal HI. Male babies are at higher risk of cerebral

palsy than females (Jarvis et al., 2005). Cognitive and motor outcomes are worse in male than in female low birth weight infants (Johnston and Hagberg, 2007). Quantitative imaging shows that male premature infants are more vulnerable to white matter injury, whereas females are more vulnerable to gray matter injury (Thompson et al., 2007). This sex difference has also been replicated in rodent *in vitro* models of hypoxic cell death (Zhu et al., 2006; Nijboer et al., 2007; Du et al., 2009). Although many molecular mechanisms are currently under investigation, this sexual dimorphism remains largely unexplained (Hill and Fitch, 2012; Chavez-Valdez et al., 2014; Demarest et al., 2016a,b; Waddell et al., 2016). Therefore, the unique state of the developmental brain should always be at the forefront of the researcher's minds.
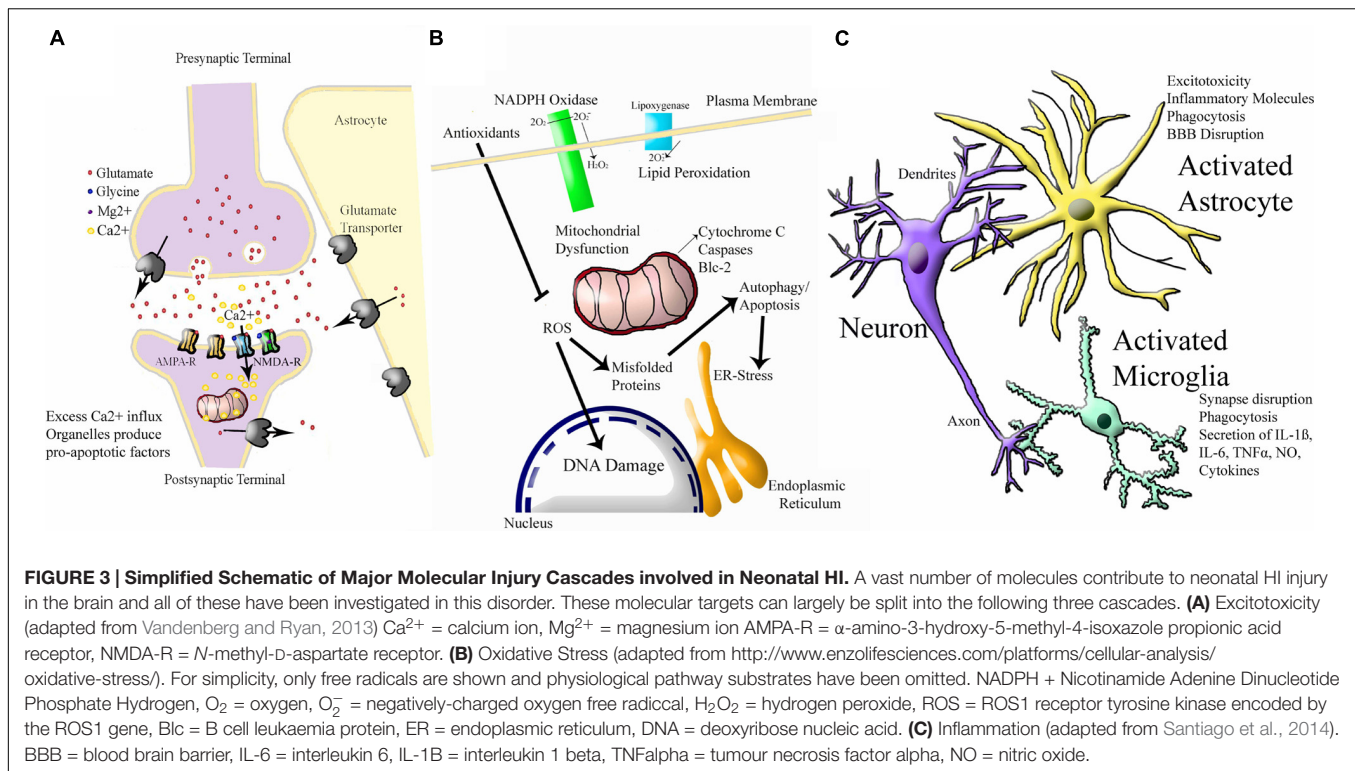
Neonatal HI injury evolves over time (McLean and Ferriero, 2004). Injuries seen with MRI scans within the first few hours after asphyxia are subtle, restricted diffusion typically starting as small lesions in the putamen and thalami, progressing over the next 3 to 4 days to involve more extensive areas of the brain (Takeoka et al., 2002). Within the first few hours, regionally specific fluctuations in blood flow trigger excitotoxicity, free radical generation, and edema (Wigglesworth and Pape, 1978; Bennet et al., 1998; Jensen et al., 1999; Shalak and Perlman, 2004; Ferrari et al., 2010). A secondary phase of injury occurs during the following hours and days, resulting in neuroinflammation, mitochondrial permeabilization, and loss of cerebral autoregulation (Inder and Volpe, 2000; Hamrick and Ferriero, 2003; Scheepens et al., 2003; Hagberg et al., 2009; Leonardo and Pennypacker, 2009). A tertiary phase of brain injury has been proposed, which may exacerbate injury through persistent inflammation (Fleiss and Gressens, 2012).

The balance between molecular cell-death processes which cause this damage in neonatal HI remains debated. Early evidence indicates that the majority of cell death in neonatal HI is necrotic, however, all regions also undergo increased apoptotic death (Edwards and Mehmet, 1996; Edwards et al., 1997; Northington et al., 2001). Some studies suggest a more prominent role for apoptosis (Hill et al., 1995; Sidhu et al., 1997; Pulera et al., 1998; Hu et al., 2000; McLean and Ferriero, 2004). Immature neurons *in vitro* are more susceptible to apoptotic death than mature neurons (McDonald et al., 1997). Others report that necrosis is the major cellular pathology in humans and animals (Adamsons and Myers, 1973; Myers, 1975; Towfighi et al., 1995; Northington et al., 2001, 2005, 2011; Folkerth, 2005; Carloni et al., 2007; Stridh et al., 2013). Yet others recognize that both occur. Some report that necrosis predominates in severe cases, whereas apoptosis occurs in milder injury (Stroemer and Rothwell, 1998; Daval and Vert, 2004; Fatemi et al., 2009). Neurons often display morphologic features along an apoptosis-necrosis continuum (Portera-Cailliau et al., 1997a,b; Nakajima et al., 2000; Northington et al., 2007, 2011). In addition to apoptosis and necrosis, some neurons in the neonatal HI brain undergo autophagy (reviewed in Klionsky and Emr, 2000; Northington et al., 2011; Balduini et al., 2012). Neuronal autophagy occurs in rodent neonatal HI models (Lockshin and Zakeri, 1994; Carloni et al., 2008; Ginet et al., 2009). However, there is conflicting evidence as to whether the occurrence of autophagy augments brain damage (Koike et al., 2008; Puyal et al., 2009), or prevents the spread of necrotic cell death (Carloni et al., 2008). Artificially exclusive classification of cell death may hinder research and therapy development.

To add to this complexity, neonatal HI injury appears to activate several interacting molecular cascades. A simple schematic of the three major cascades is shown in **Figure 3**. The first is excitotoxicity, through which physiological glutamate neurotransmission leads to overactivation of postsynaptic receptors and cell death (reviewed in Hagberg et al., 1987; Choi, 1988, 1992; Hattori and Wasterlain, 1990; Danbolt, 2001). The N-methyl-D-aspartate (NMDA) receptor is relatively over-expressed in the developing brain (McDonald et al., 1989a; Represa et al., 1989; Fox et al., 1996). In P6 rats, the NMDA receptor is expressed at 150–200% of adult levels (Tremblay et al., 1988). The predominating combination of NMDA receptor subunits in the perinatal period seems to favor prolonged calcium influx for a given excitation (Danysz and Parsons, 1998). The same NMDA receptor that promotes plasticity can lead to massive Na^+ and water influx, cellular swelling, pathologically elevated intracellular calcium, and energy failure, leading to a 'spiral of death' (Choi, 1988). Oxygen glucose deprivation (OGD) in rat hippocampal neurons leads to a marked reduction in glutamate removal from the synapse (Jabaudon et al., 2000; Tao et al., 2001). Injection of NMDA into rat brain produces more extensive cell death in the neonate than in the adult (McDonald et al., 1988). Elevated glutamate has been documented in the cerebrospinal fluid (CSF) of infants who have suffered severe HI injury (Riikonen et al., 1992; Hagberg et al., 1993; Pu et al., 2008). The neonatal brain is much more prone to seizure activity than the mature brain (Holmes, 1991; Holmes and Ben-Ari, 2001), suggesting a prominent role for neuronal hyperexcitability and excitotoxicity although the molecular mechanisms behind this have not been fully elucidated (reviewed in Rakhade and Jensen, 2009). However, seizure activity could also be explained by paradoxical excitatory activity of the neurotransmitter gamma-amino butyric acid (GABA) in the developing brain (Staley et al., 1995). Drugs that block NMDA receptors are protective against HI injury in neonatal rodent models (McDonald et al., 1989a,b, 1990). Activation of AMPA receptors also contribute to injury (McDonald and Johnston, 1992; Deng et al., 2003; Talos et al., 2006), however, AMPA antagonists are not as protective (Ikonomidou et al., 1999; Noh et al., 2006). These findings are yet to be exploited in human clinical trials, as the integral role of glutamate receptors in healthy neuronal plasticity (Ikonomidou et al., 1999; Failor et al., 2010; Rocha-Ferreira and Hristova, 2015) could be damaged by the use of NMDA and AMPA antagonists at such a sensitive developmental stage.

An integrally linked cascade is that of oxidative stress. Excitotoxicity causes energy depletion, mitochondrial dysfunction, and cytosolic calcium accumulation, which in turn leads to generation of free radicals (Ferriero et al., 1996; Ferriero, 2001). Free radicals alter membrane pump function, allowing more glutamate release and NMDA receptor activation, leading to more excitotoxicity (Schanne et al., 1979; Robertson

FIGURE 3 | Simplified Schematic of Major Molecular Injury Cascades involved in Neonatal HI. A vast number of molecules contribute to neonatal HI injury in the brain and all of these have been investigated in this disorder. These molecular targets can largely be split into the following three cascades. **(A)** Excitotoxicity (adapted from Vandenberg and Ryan, 2013) Ca^{2+} = calcium ion, Mg^{2+} = magnesium ion AMPA-R = α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor, NMDA-R = N-methyl-D-aspartate receptor. **(B)** Oxidative Stress (adapted from http://www.enzolifesciences.com/platforms/cellular-analysis/oxidative-stress/). For simplicity, only free radicals are shown and physiological pathway substrates have been omitted. NADPH + Nicotinamide Adenine Dinucleotide Phosphate Hydrogen, O_2 = oxygen, O_2^- = negatively-charged oxygen free radiccal, H_2O_2 = hydrogen peroxide, ROS = ROS1 receptor tyrosine kinase encoded by the ROS1 gene, Blc = B cell leukaemia protein, ER = endoplasmic reticulum, DNA = deoxyribose nucleic acid. **(C)** Inflammation (adapted from Santiago et al., 2014). BBB = blood brain barrier, IL-6 = interleukin 6, IL-1B = interleukin 1 beta, TNFalpha = tumour necrosis factor alpha, NO = nitric oxide.

J.D. et al., 2002; Starkov et al., 2004). Oxidative stress is a general term for the increase in free radical production as a result of oxidative metabolism under pathologic conditions (Inder and Volpe, 2000; Ferriero, 2001). When oxygen floods the microenvironment of cells damaged by hypoxia, mitochondrial oxidative phosphorylation is overwhelmed and reactive oxygen species accumulate (Ferriero, 2001). Fetal life elapses in a low oxygen environment (East et al., 1998). In the first minutes of life, an abrupt increase in O_2 partial pressure occurs, which creates a pro-oxidant condition (Stiller et al., 2002). During birth asphyxia, excess calcium influx and other factors lead to severe oxidative stress (Forder and Tymianski, 2009). There is accumulation of hydrogen peroxide after HI in neonatal mice but not in adults (Lafemina et al., 2006). Because of its high lipid content, the brain is particularly susceptible to free radical attack (O'Brien and Sampson, 1965; Northington et al., 2001). The polyunsaturated fatty acid content of the brain increases during gestation (Crawford and Sinclair, 1971; Mishra and Delivoria-Papadopoulos, 1989). Lipid peroxidation may be a major factor in the white matter damage (Back et al., 1998; Baud et al., 2004). The developing brain's immature antioxidant defense also contributes to sensitivity to oxidative stress (Li et al., 1997; Mishra and Delivoria-Papadopoulos, 1999; Li and Jackson, 2002; Felderhoff-Mueser et al., 2002; Vannucci and Hagberg, 2004; Blomgren and Hagberg, 2006; Ikonomidou and Kaindl, 2011; Miller et al., 2012). Adequate stores of antioxidants are necessary to protect against oxidative injury. Specifically, depletion of neuronal reduced glutathione exacerbates oxidative injury (Chen and Liao, 2003; White and Cappai, 2003; Brongholi et al., 2006).

Finally, inflammation is a major component of neonatal HI injury. Low-dose treatment with intrauterine LPS dramatically increases severity of HI injury in neonatal mice, but protects against HI in adult rodents (Wang et al., 2007b). Intracerebral injection of NMDA receptor agonist produces a pattern of white matter injury, in which pretreatment with systemic IL-1ß, IL-6, IL-9, or TNF-α leads to a significant increase in lesion size (Marret et al., 1995; Dommergues et al., 2000). There is now substantial experimental evidence that intrauterine inflammation can exacerbate neonatal HI (Lehnardt et al., 2003; Eklind et al., 2005; Marini et al., 2007), which some have referred to as the "double-hit hypothesis" (reviewed in Agrawal and Hirsch, 2012; Hagberg et al., 2012; Dammann and Leviton, 2014). Microglia, the resident macrophages of the CNS, are among the first cells to become activated after HI (Fujimoto et al., 1989; Tahraoui et al., 2001; Kaur et al., 2007). Activated microglia migrate to damaged regions (Leonardo and Pennypacker, 2009) and produce inflammatory cytokines, glutamate, nitric oxide, and free radicals (Wood, 1995; Kaur and Ling, 2009). Drugs that block microglial activation protect the neonatal brain (Dommergues et al., 2003). Following hypoxia-ischemia, compromise of the BBB allows the entry of macrophages (Alvarez-Diaz et al., 2007; Leonardo and Pennypacker, 2009). Astrocytes also play a role in inflammation (Wang et al., 2003; Girard et al., 2008, 2009). CSF cytokines are elevated in term infants who later develop cerebral palsy (Savman et al., 1998; Dammann and O'Shea, 2008). The diverse network of interacting mechanisms demonstrate the molecular complexity of neonatal HI injury. Potential protective treatments should strive to tackle common mediators of these cascades relevant

to all three pathways, otherwise full protection will not be achievable.

EVALUATION OF AVAILABLE ANIMAL MODELS OF NEONATAL HYPOXIA ISCHAEMIA

Neonatal hypoxia ischaemia has been modeled extensively in mice and rats (reviewed in Hagberg et al., 2002; van der Worp et al., 2007; Yager and Ashwal, 2009; Dean et al., 2015), with a minority of researchers also studying larger animals such as pigs, sheep (reviewed in Roohey et al., 1997; Dean et al., 2015) or primates (Fahn et al., 1979; Volpe, 2012). Models intending to replicate the clinical symptoms of neonatal human HI can be roughly divided into the four categories discussed below. All models have distinct advantages and disadvantages. A summary of available rodent models is shown in **Figure 4**.

Rice–Vannucci Model of Term Hypoxia Ischaemia

Most published studies modeling neonatal HI in animals have employed the Rice–Vannucci model (Rice et al., 1981). This model comprises unilateral carotid artery ligation, recovery with the dam for approximately 1 h, followed by exposure to 8% oxygen for 1–3 h at 37°C. Although, the model was initially described in rat (Rice et al., 1981), it has been successfully adapted for mouse with similar anatomical and behavioral effects (Ditelberg et al., 1996; Ferriero et al., 1996; Sheldon et al., 1998).

Rice' and Vannucci's model replicates anatomical damage seen in human neonates. Their initial study showed selective gray-matter sensitivity to neuronal necrosis, with gray matter injury observed in cortex, hippocampus, thalamus, and basal ganglia (Rice et al., 1981; Andine et al., 1990; Towfighi et al., 1995; Vannucci et al., 1999), encompassing the sites damaged in human neonatal HI. Histologically, there is a gradation of injury that correlates with the duration or severity of insult (Towfighi et al., 1991, 1995). White matter lesions have also been described in this model (de Torres et al., 1997; Ness et al., 2001; Liu et al., 2002; Drobyshevsky et al., 2005, 2007b), the extent of which correlate with the duration of exposure to hypoxia (Liu et al., 2002). However, bilateral common carotid artery ligation appears a stronger model of white matter damage (Jelinski et al., 1999; Uehara et al., 1999; Cai et al., 2001). Metabolic alterations in the Rice–Vannucci model include decreased cerebral blood flow (Sakurada et al., 1978; Vannucci et al., 1988), brain acidosis (Welsh et al., 1982; Yager et al., 1991), and decreased cerebral glucose uptake (Vannucci et al., 1989; Sokoloff et al., 1977). An inflammatory response has also been demonstrated (Bona et al., 1998).

Another convincing aspect of the Rice–Vannucci model is its ability to predict the therapeutic effect of hypothermia following the neonatal HI event. Mice treated with hypothermia showed smaller lesion volumes, in addition to better performance on the Morris water maze and circling tests (Yager et al., 1993; Lee et al., 2010; Kida et al., 2013; Lin et al., 2014). Many papers have
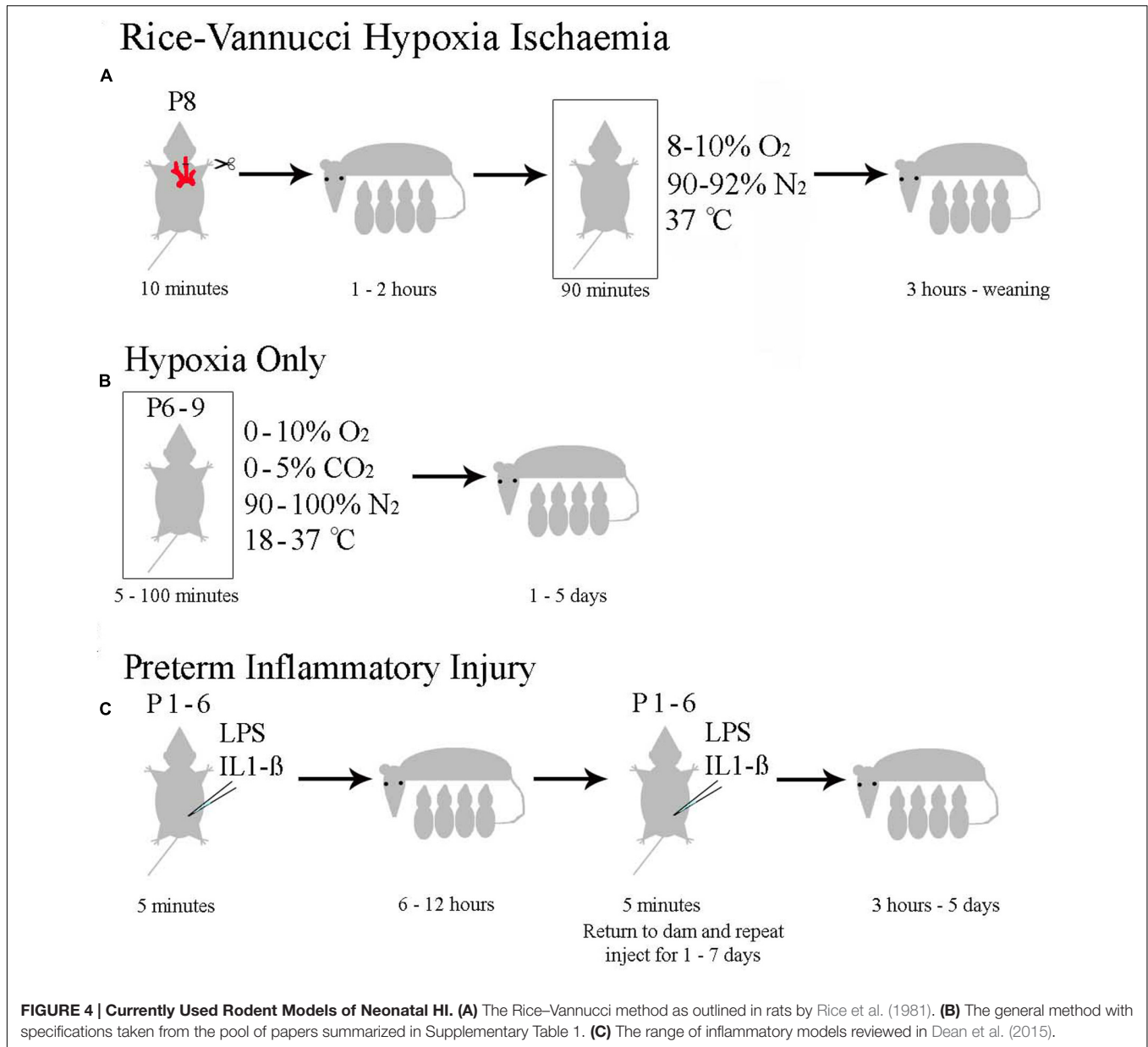
investigated the behavioral outcomes of Rice–Vannucci injury in adult rodents. This model gives rise to well documented behavioral phenotypes including: impaired spatial learning and memory (Balduini et al., 2000, 2001; Ikeda et al., 2001; Wang et al., 2002; Arteni et al., 2003; Pereira et al., 2007; Cai et al., 2009; Greggio et al., 2011; Hill et al., 2012; Zheng and Weiss, 2013; Alexander et al., 2014; Gillani et al., 2015); impaired motor function as assessed by rotarod test, open field and motor reflexes (Barth and Stanfield, 1990; Jansen and Low, 1996a,b; Jansen et al., 1997; Balduini et al., 2000, 2001; Tomimatsu et al., 2002; Ådén et al., 2003; Lubics et al., 2005; Pazaiti et al., 2009; Im et al., 2010; Nijboer et al., 2010; Karalis et al., 2011; Chen et al., 2012; Ruiz et al., 2012; Sanches et al., 2012; Zheng et al., 2012; Xiong et al., 2013; Alexander et al., 2014; Gillani et al., 2014, 2015; Kim et al., 2014; Zhang Q. et al., 2014; Park D. et al., 2015; Park W.S. et al., 2015); sensory processing abnormalities (Alexander et al., 2014); and other cognitive phenotypes, such as reduced attention (Buwalda et al., 1995; Martin et al., 1997; Sanches et al., 2013; Perera et al., 2014; Miguel et al., 2015). Despite this broad range of documented effects, there are some contradictions between individual investigators (reviewed in Lubics et al., 2005), which suggest that different genetic backgrounds, severity, or experimenters can significantly affect the outcome of Rice–Vannucci model.

The Rice–Vannucci model of neonatal hypoxia ischaemia has several advantages. One is its prevalence, allowing direct comparisons with many other published papers (Vannucci et al., 1993, 2005; Yager and Ashwal, 2009; Dean et al., 2015). Another is that the contralateral hemisphere, exposed to hypoxia in the absence of ischemia, appears normal (Yager et al., 1991, 1992, 1996; Vannucci and Yager, 1992), providing a control hemisphere within the experimental brain. Thorough behavioral characterization (Arteni et al., 2003; Lubics et al., 2005) support the long term consequences of this model mimicking neonatal HI. One significant drawback of this model is the high variability in size and severity of infarct between animals, making comparisons between experimenters difficult (Vannucci and Hagberg, 2004; Vannucci and Vannucci, 2005). Additionally, the invasive nature of severing the common carotid artery does not replicate human injury; such severe vascular abnormalities occur rarely, if at all (Ment et al., 1984; Hill, 1991).

Hypoxia-Only Models

Some experimenters induce hypoxia in rodents exclusively using an oxygen deprivation chamber, without a preceding ischaemic procedure. These models are not as widely used as the Rice–Vannucci method, but have the potential to describe milder injuries and avoid the unphysiological occlusion of the common carotid artery. There are currently no published reviews or meta-analyses of hypoxia-only investigations, Supplementary Table 1 contains a brief summary of 122 published papers using hypoxia-only methodology compiled from Pubmed search results.
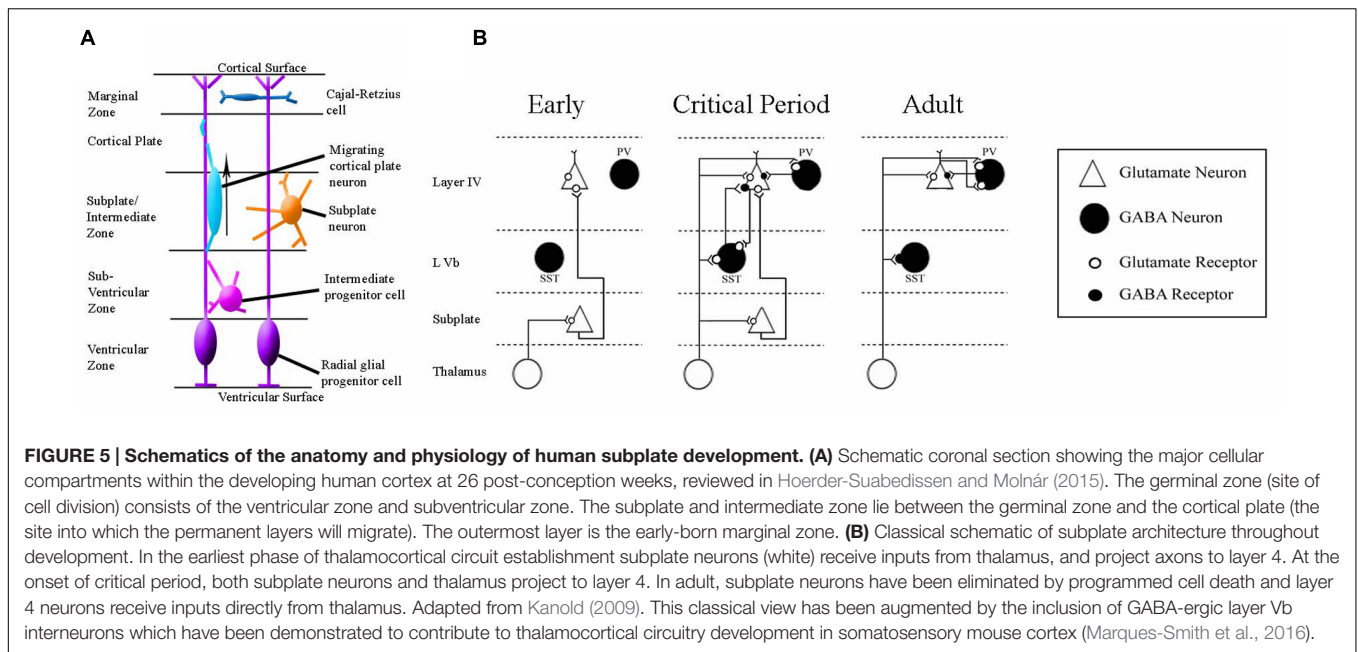
Historically, these methods have been used to investigate hypoxic brain biochemistry. Several studies have documented altered levels of neurotransmitters (Hedner et al., 1980; Kaneko et al., 1985; Yamamoto et al., 1985; Yamamoto and Kato,

FIGURE 4 | Currently Used Rodent Models of Neonatal HI. (A) The Rice–Vannucci method as outlined in rats by Rice et al. (1981). **(B)** The general method with specifications taken from the pool of papers summarized in Supplementary Table 1. **(C)** The range of inflammatory models reviewed in Dean et al. (2015).

1986; Hadjiconstantinou et al., 1990; Seidler and Slotkin, 1990; Dell'Anna et al., 1993; Tanaka et al., 1995; Anju et al., 2010a,b; Anju and Paulose, 2011, 2013). However, there is little consensus over the direction or magnitude of changes (Decker M.J. et al., 2003; Decker et al., 2005). Hypoxia-only models have become an established model used to generate seizures in neonatal rats (Jensen et al., 1995; Applegate et al., 1996; Rodríguez-Alvárez et al., 2015; Sampath et al., 2015). In one such model, P6 rat pups were placed in chambers at 9% O_2 partial pressure and 20% CO_2 partial pressure for 60 min. Some pups were immediately restored to room air, whereas others underwent gradual reduction of CO_2 (Helmy et al., 2011; Tolner et al., 2011). Pups which underwent hypoxia with immediate restoration of CO_2 had a greater mortality rate and higher seizure frequency.

However, subsequent anatomical analysis of these brains at P8 (Boss et al., 2005; Wang et al., unpublished), failed to show any differences in expression of cell death markers or layer-specific markers of healthy cortical neurons. Therefore, the hypoxia-only insult resulting in seizures appears to generate only subtle injury to the brain, far short of that seen in some human patients.

A range of behavioral phenotypes have been reported in hypoxia-only models, including hyperactivity (Shimomura and Ohta, 1988; Dell'Anna et al., 1991; Speiser et al., 1991; Decker et al., 2005); increased aggression (Mikati et al., 2005; Tang et al., 2006), altered ultrasonic vocalization (Venerosi et al., 2006), and disturbed sleep (Decker M.B. et al., 2003). Relatively few investigators have pursued standard tests of spatial memory and

FIGURE 5 | Schematics of the anatomy and physiology of human subplate development. (A) Schematic coronal section showing the major cellular compartments within the developing human cortex at 26 post-conception weeks, reviewed in Hoerder-Suabedissen and Molnár (2015). The germinal zone (site of cell division) consists of the ventricular zone and subventricular zone. The subplate and intermediate zone lie between the germinal zone and the cortical plate (the site into which the permanent layers will migrate). The outermost layer is the early-born marginal zone. **(B)** Classical schematic of subplate architecture throughout development. In the earliest phase of thalamocortical circuit establishment subplate neurons (white) receive inputs from thalamus, and project axons to layer 4. At the onset of critical period, both subplate neurons and thalamus project to layer 4. In adult, subplate neurons have been eliminated by programmed cell death and layer 4 neurons receive inputs directly from thalamus. Adapted from Kanold (2009). This classical view has been augmented by the inclusion of GABA-ergic layer Vb interneurons which have been demonstrated to contribute to thalamocortical circuitry development in somatosensory mouse cortex (Marques-Smith et al., 2016).

locomotor behavior, and have obtained mixed results (Dell'Anna et al., 1991; Speiser et al., 1998; Rotstein et al., 2006; Coq et al., 2008; Raveendran and Skaria, 2013; Wang S. et al., 2015). The majority of hypoxia-only phenotypes are based on custom behavioral tests, making them difficult to compare to other established animal models. Additionally, some studies report no behavioral deficit following neonatal hypoxia alone (Buwalda et al., 1995; Iuvone et al., 1996; Casolini et al., 2005; Blaise et al., 2009; Mikhailenko et al., 2009; Anju et al., 2010c; Wang S. et al., 2015).

Although hypoxia-only models offer the potential to replicate the mechanism of hypoxia without major ischaemia seen in human neonatal HI patients, the models currently available are not ideal. One significant problem is the lack of methodological unity between different experimenters. There is little consensus on age of animal, background strain, oxygen partial pressure, time of exposure to hypoxia, or body temperature (see Supplementary Table 1). One example demonstrating the relevance of close control of these variables is temperature. P0 rat pups exposed to anoxia exhibit behavioral defects when anoxia was conducted at 39°C, yet not at 33 and 36°C (Rogalska et al., 2004, 2009; Caputa et al., 2005; reviewed in Rogalska et al., 2006). Therefore, far more care is needed to justify the design of hypoxia-only experiments before these models can be considered dependable models of human neonatal HI.

Inflammatory Models of Perinatal Brain Injury

Intrauterine infection is strongly associated with preterm birth and brain injury (Stoll et al., 2004; Mitha et al., 2013; Strunk et al., 2014; Dean et al., 2015). Many models have been described which introduce different inflammation-inducing molecules at different ages (Dean et al., 2015), many of which cause

cerebral inflammation and white matter damage seen in human patients.

Administration of live *E. coli* into the uterus of pregnant rats can result in neutrophil infiltration in the fetal brain, increased fetal reabsorption and stillbirth, while surviving pups exhibit increased brain chemokines, cytokines, white matter injury, and behavioral phenotypes (Debillon et al., 2003; Rodts-Palenik et al., 2004; Pang et al., 2005; Yuan et al., 2005; Girard et al., 2009; Bergeron et al., 2013). The effects of bacterial mimetics such as the cell wall component lipopolysaccharide (LPS), have also been investigated. Intracervical injection in embryonic day 15 (E15) mice was associated with mild white matter injury but no behavioral deficits (Bell and Hallenbeck, 2002; Poggi et al., 2005; Wang et al., 2007a), whereas repeated intracervical LPS was associated with delayed neurosensory development (Toso et al., 2005; Rousset et al., 2006, 2013). Other inflammatory models include viral infection simulated by injection of poly(I:C), a synthetic double stranded viral RNA, injection of which is associated with long-term behavioral deficits (Shi et al., 2009; Richetto et al., 2013). Postnatal administration of inflammatory agents is widely used in rodents to model postnatal infection. Subcutaneous injection of live *E. coli* to P3 mouse pups was associated with microgliosis, loss of oligodendrocytes, and impaired motor coordination (Lieblein-Boff et al., 2013). However, most techniques which employ live bacterial injection have very high mortality rates (Rodewald et al., 1992; Tran and Weisman, 2004; Placencia et al., 2009; Loron et al., 2011). Postnatal intraperitoneal injection of LPS can also cause white matter damage and cerebral cytokine response (Brochu et al., 2011; Brehmer et al., 2012; Nobuta et al., 2012; Smith et al., 2014). Repeated daily injection of LPS in mice resulted in elevated serum IL-6, reduced gray matter volume, decreased oligodendrocyte numbers, and decreased myelin staining (Wang et al., 2009; Malaeb et al., 2014). Similarly, repeated IL-1β injection in

P1–P5 mice has been associated with impaired oligodendrocyte progenitor maturation, and severe memory deficits (Favrais et al., 2011).

One of the strengths of the inflammation model is that it reflects the exposure to infectious or inflammatory agents present outside of the highly sterile individually ventilated cages where many academic institutions keep experimental animals. Most of the inflammatory risk factors for increased severity of HI injury in human patients, such as maternal infection (Stoll et al., 2004; Girard et al., 2012; Dean et al., 2015), will result in systemic inflammation in addition to CNS-specific recruitment of microglia. However, there is currently debate concerning the relevance of maternal inflammation to fetal brain damage (Leviton et al., 1999; Redline and O'Riordan, 2000; Neufeld et al., 2005). The debate intensifies when fetal systemic inflammation is contrasted with neuroinflammation. Although the majority of publications cited above administer pro-inflammatory agents by intracerebral injection, some studies have administered LPS by intravenous injection (reviewed in Wang et al., 2006). In fetal sheep, intravenous LPS causes white-matter specific damage (Garnier et al., 2001, 2006; Duncan et al., 2002; Mallard et al., 2003; Peebles et al., 2003; Svedin et al., 2005), suggesting that systemic inflammation may be sufficient to trigger brain injury. However, the results of these experiments could be explained by a secondary neuroinflammatory response to systemic inflammation causing the white matter injury. Separating these parameters in future experiments will prove demanding.

Data suggest that gene expression in mouse models of inflammation closely corresponds to that seen in humans (Takao and Miyakawa, 2015), however, postnatal murine response to inflammation is likely different to that experienced by a human fetus. An important limitation of inflammatory studies is impact on cardiovascular function and the potential for secondary cerebral HI (Eklind et al., 2001; Favrais et al., 2011; Wang C.T. et al., 2015). Another is that varying results have been reported. This may be due to differences in LPS used between groups, purification method (Westphal, 1965; Lam et al., 2014), or dose (Fujihara et al., 2003). Alternatively, there is increasing evidence that the considerable individual variability in response to clinical sepsis between patients is related to host genetics (Christaki and Giamarellos-Bourboulis, 2014). Therefore, although inflammation is doubtless an important factor in neonatal brain injury, the variation between different models makes these methods difficult to evaluate.

Alternative Models

In many ways, non-rodent models are more representative of neonatal HI as it affects human patients. Here follows a brief flavor of techniques. Relatively few studies have investigated neonatal HI in primates. Classical studies asphyxiated term monkey fetuses by covering their heads with a rubber sac and clamping the umbilical cord (Fahn et al., 1979). Fetuses resuscitated after 20 min had extremely high mortality. However, 12 min of asphyxia were required to produce any neuropathologic injury. The fetuses displayed damage predominantly within the brainstem. In a model of partial ischemia (Fahn et al., 1979), pregnant females were rendered hypotensive during the third trimester. When blood oxygen saturation was reduced to 10% for 5 h, fetuses became profoundly acidemic. At birth, these displayed opisthotonus, decerebrate posturing, and convulsions. There is one model of white-matter injury based on baboons delivered prematurely by hysterotomy (Inder et al., 2004, 2005a,b). Premature baboons were treated in an intensive care setting. Approximately half displayed white-matter injury. Analysis of behavior has not been undertaken.

More work has been carried out in fetal sheep. Umbilical cord occlusion and term asphyxia has been carried out (Gunn et al., 1992; Williams et al., 1992; Mallard et al., 1993; Richardson B. et al., 1996; de Haan et al., 1997a,b,c; Richardson and Bocking, 1998; Dalitz et al., 2003), repeated asphyxia at 5-h intervals resulted in injury to the striatum almost exclusively, whereas episodes of asphyxia repeated every 5 min caused diffuse and extensive damage to cortex, thalamus, and cerebellum in 40% of animals, and selective neuronal necrosis in the remainder. White matter injury has also been investigated (Ting et al., 1983), only those fetuses in which the mean arterial blood pressure fell below 30 mmHg exhibit brain damage, irrespective of hypoxia. Neuropathologic injury after carotid artery occlusion for 30 min caused both gray and white matter involvement, with cortical damage and selective neuronal necrosis in thalamus and striatum (Reddy et al., 1998; Petersson et al., 2002). Several laboratories have developed models in sheep after systemic endotoxemia (Duncan et al., 2002; Mallard et al., 2003). Unfortunately, no behavioral outcomes are currently available in sheep.

Finally, other small laboratory animals have been investigated. Preterm rabbit fetuses exposed to sustained placental insufficiency via intrauterine occlusion of the descending aorta displayed significant alterations in motor responses to olfactory stimuli, coordination of suck and swallow, and marked hypertonia, reminiscent of spastic quadriplegia (Yoon et al., 1997; Derrick et al., 2004, 2007; Saadani-Makki et al., 2008). Diffusion-weighted imaging detected a threshold in white matter loss below which all rabbit kits developed hypertonia, (Drobyshevsky et al., 2005, 2007a). Another promising model is that of the spiny mouse, a rodent which shows a similar level of brain development to a human neonate at birth (Brunjes, 1985, 1989, 1990; Gozzo et al., 1985; D'Udine and Alleva, 1988; Brunjes et al., 1989), which also shows varied motor deficits (Ireland et al., 2008, 2009, 2010) and neuroanatomical pathology (Hutton et al., 2009; O'Connell et al., 2013) following neonatal HI.

In brief, large animals can better replicate the conditions of a single human fetus exposed to a non-sterile environment. However, none of these models have access to the same extent of transgenic manipulation or validated behavioral tests that are possible in rodent studies. These models are invaluable for aiding comparison of brain development at birth which occur between species (Clancy et al., 2007), whereas the relative immaturity of mouse and rat brains at birth introduce an unwelcome variable into these experiments. For the foreseeable future, insights from

both rodent work and larger animals will be important for better understanding neonatal HI.

SUBPLATE: A REGION OF HYPER-SENSITIVITY TO NEONATAL HI?

One brain region exemplifying how much remains unknown about the developing brain's response to HI, and the uncertainties involved in interpreting results from animal studies, is subplate. The subplate is an early-born transitory neuronal layer of cerebral cortex which serves an important role in the establishment of thalamocortical connectivity during development (reviewed in Judas et al., 2010; Kanold and Luhmann, 2010; Kostovic and Judas, 2010; Hoerder-Suabedissen and Molnár, 2015) (see **Figure 4**). Thalamocortical axons associate with and grow alongside subplate neurons in the developing cortex (Herrmann et al., 1994; Molnár et al., 1998; Kostovic and Judas, 2006), and selective excitotoxic ablation of subplate disrupts thalamocortical connectivity in animal models (Ghosh et al., 1990; Ghosh and Shatz, 1992; Lein et al., 1999; Kanold et al., 2003; Kanold and Shatz, 2006; Magnani et al., 2013).

Subplate has been identified in a range of mammals by conserved molecular markers (Hoerder-Suabedissen et al., 2009; Hoerder-Suabedissen and Molnár, 2012; Oeschger et al., 2012; Pedraza et al., 2014). Neuronal death occurs in infant subplate during normal development (Chun et al., 1987; Al-Ghoul and Miller, 1989; Hamre et al., 1989; Kostovic and Rakic, 1990; Woo et al., 1991; Price et al., 1997). However, the molecular mechanisms behind this programmed cell-death remain unknown (McQuillen and Ferriero, 2005; Hoerder-Suabedissen and Molnár, 2015). Functional roles for subplate in thalamocortical (Allendoerfer and Shatz, 1994; Kanold and Luhmann, 2010) and corticothalamic (Grant et al., 2016) development have been described, demonstrating lasting significance of this transient population.

The susceptibility of subplate neurons to neonatal HI remains little understood. Early studies claimed subplate is selectively vulnerable. Cultured rat subplate neurons were more vulnerable to OGD compared to mixed cortical neurons (Nguyen and McQuillen, 2010). In rats exposed to systemic HI at E18, a significant decrease in Nurr1-expressing subplate neurons was documented by P2 (Jantzie et al., 2014, 2015a,b,c) and similarly in fetal sheep (Dean et al., 2011). However, Nurr1-expressing Layer VI neurons were also decreased. It is also possible that HI induced differential marker expression in subplate neurons, rather than cell death. *In vitro* electrophysiological recordings in neocortical slices from newborn rats have demonstrated a pronounced functional impairment of subplate neurons following OGD (Albrecht et al., 2005). Another influentiential study that claimed selective vulnerability of subplate to hypoxia used immunohistochemistry to detect cell-death in neurons labeled with BrdU at E10.5 following a modified Rice–Vannucci model in P1 rats (McQuillen et al., 2003; McQuillen and Ferriero, 2004, 2005). However, Layer VI neurons born at this date also expressed cell-death markers, suggesting subplate may not be selectively susceptible to HI injury. Conversely,

a systematic quantification of cell death markers throughout subplate compared with other cortical layers was conducted using immunohistochemistry (Okusa et al., 2014). Three subplate-specific marker positive populations showed little co-staining with caspase-3 in brains with mild to moderate HI lesions. In severely damaged cases, caspase-3 staining was found throughout the cortex. Therefore, layer-specific sensitivity of cortical neurons to HI remains debated. A double birthdating study, targeting subplate and layer V or VI combined with HI could resolve this issue. However, such an experiment has not yet been performed.

Human literature supports the proposition that interstitial white matter, the equivalent of subplate in the postnatal human brain (Clancy et al., 2009; Suarez-Sola et al., 2009; Garcia-Marin et al., 2010; Hoerder-Suabedissen and Molnár, 2015), shows structural damage as a result of neonatal injury. Tissue from preterm human infants with periventricular leukomalacia showed a deficit in the number of MAP-2 expressing neurons throughout the interstitial white matter (Kinney et al., 2012). Scarring has been observed in interstitial white matter, alongside the expression of cell death markers, in brain tissue from human infants (Pogledic et al., 2014). The number of interstitial neurons present in white matter is known to peak at the developmental stage most sensitive to white matter injury (Kostovic et al., 2002; Kostovic and Judas, 2010). Immunohistochemical analysis on neonatal telencephalon samples obtained post-mortem from infants born at 25–32 weeks gestation showed a significant loss of GABA-ergic subplate neurons (Robinson et al., 2006). Many reviews have highlighted the interstitial white matter as a site which should be more thoroughly investigated in neonatal brain injury (Volpe et al., 1996; Leviton and Gressens, 2007; Volpe, 2009; Kostovic et al., 2011). Several of these reviews propose a role for subplate in resultant cognitive and behavioral deficits (Volpe, 2009, 1977; Kostovic et al., 2011), based on the established role of subplate in thalamocortical development. Unfortunately, post-mortem studies are unable to convey whether subplate pathology is responsible for any of the clinical outcomes in patients. The response of both human and rodent subplate to neonatal HI remains unclear, despite assertions of interest from the field. A systematic study of the subplate *in vitro* and *in vivo* following HI injury would provide valuable information. As subplate transiently integrates within the developing cortical circuitry (see **Figure 5**) interactions between subplate neurons and other cortical neurons, such as key interneuron populations, should also be further investigated (Marques-Smith et al., 2016).

There are several reasons for believing that subplate could be critical in neonatal HI. One is the proposed transient secretory function. Subplate is enriched in CSPGs, whereas the adjacent intermediate zone is not (Kostovic et al., 2014). Chondroitin sulfate proteoglycans (CSPGs) are generally secreted from cells, and the subplate transcriptome catalogs a plethora of genes involved in production of extracellular matrix and proteoglycans (Belgard et al., 2011; Hoerder-Suabedissen et al., 2013). Additional genes with subplate-restricted expression in the cortex encode secreted proteins, including neuroserpin (*Serpini1*), neuronal pentraxin 1 (*Nptx1*), and insulin-like

growth factor binding protein 5 (*Igfbp5*) (Hoerder-Suabedissen et al., 2013), several of which have been validated by immunohistochemistry (Kondo et al., 2015). Connective tissue growth factor (CTGF), secreted extracellular matrix-associated protein involved in regulation of cellular adhesion, migration, mitogenesis, differentiation and survival (Brigstock, 1999; Stritt et al., 2009), is also detectable in the subplate at E18, increasing in intensity at P3 and P8 (Hoerder-Suabedissen et al., 2009, 2013). It is unknown whether subplate-secreted proteins serve a protective function in the developing brain or not. Related to this secretory function, subplate neurons express relatively mature rER (Kondo et al., 2015), an organelle essential for production of secreted proteins (reviewed in Novikoff, 1976; Pfeffer and Rothman, 1987; Lodish, 1988; Hurtley and Helenius, 1989; Pelham, 1989). As a result of the cellular pressures of high protein production, cells activate a series of mechanisms referred to as the ER stress response (Schroder and Kaufman, 2005; Wu and Kaufman, 2006; Kondo et al., 2011). Nissl staining demonstrates enriched protein production in subplate at P8 in mouse, although staining is much fainter in adult (Kondo et al., 2015). Morphology of subplate neurons is similar to that of rER-rich plasma cells under EM (Bloom, 1968; Kondo et al., 2015), and immunohistochemistry for ER stress marker binding immunoglobulin protein (BiP) confirmed that ER stress occurs in developing subplate (Okiyoneda et al., 2004; Kondo et al., 2005, 2012, 2015). BiP protein synthesis is up-regulated in whole brain under stress conditions, such as glucose deprivation, hypoxia, or the presence of toxins (Lee, 1987, 2001, 2005). It is not known exactly which proteins are secreted throughout development by the subplate, but this enhanced metabolic stress during hypoxia and the potential for neuroprotective secretion reinforce the value of further study of subplate in neonatal HI models and human patients.

NEUROSERPIN: A CASE FOR A NOVEL NEUROPROTECTIVE TREATMENT

The development of novel treatments to supplement the sole currently licensed therapy, hypothermia (Jacobs et al., 2005, 2013; Shah et al., 2007; Tagin et al., 2012), is imperative. Since the discovery of this groundbreaking treatment, little progress has been made in identifying additive pharmacological therapies. Few potential treatments have translated to human clinical trials. Resuscitation at room temperature (Vento et al., 2001a,b; Rabi et al., 2007) and xenon gas administration alongside hypothermia (Hobbs et al., 2008; Thoresen et al., 2009) are the only therapies shown to have any additive effect. However, more recent publications have questioned the efficacy of xenon as an additive therapy alongside hypothermia. For example, randomized clinical trials have demonstrated that although xenon gas is a safe treatment, there is little or no therapeutic effect of combined hypothermia and xenon gas in moderate and severe cases of neonatal HI at 18 months follow-up (Azzopardi et al., 2013, 2015; Dingley et al., 2014). A similar experiment in rats found that xenon treatment made

no difference to lesion size or neuronal cell numbers in cases of severe HI (Sabir et al., 2016). Barbiturate anticonvulsants have no effect on long-term neurological development when given following neonatal HI (reviewed in Goldberg et al., 1986; Hall et al., 1998; Singh et al., 2004; Vargas-Origel et al., 2004; Evans et al., 2007). Recent clinical studies suggest that high dose erythropoietin (EPo) treatment in term HI neonates reduces disability (Strunk et al., 2008; Zhu et al., 2009; McPherson and Juul, 2010). However, even proponents of this potential treatment advise caution in interpreting these early results, and the therapeutic effect by no means completely prevents disability. Combination therapy of *N*-acetylcysteine, a free radical scavenger, and systemic hypothermia reduces infarct volume after focal HI injury (Jatana et al., 2006). Another free radical scavenger, allopurinol, reduces cerebral edema and neuropathological damage (Palmer et al., 1990). However, these treatments have only been trialed in animals, and the field is still awaiting a candidate neuroprotectice molecule which is both safe and effective in neonatal humans (Lai and Yang, 2011; Pazos et al., 2012).

Another therapeutic approach under development for neonatal HI is stem cell therapy (reviewed in Parolini et al., 2010; Zhang X. et al., 2014; Douglas-Escobar and Weiss, 2015; González-Portillo et al., 2015; Ruiz et al., 2017). These therapies make use of evidence that transplantation of human bone-marrow derived stem cells into the lesion can assist brain plasticity (Bonifacio et al., 2011; Tajiri et al., 2013). Results of this therapy have been promising in animal models (Jendelová et al., 2004; Daadi et al., 2009a,b), however, the technique awaits validation in a clinical setting. Additionally, the use of stem cell therapy for cerebral palsy in human patients has produced mixed results (Li et al., 2012; Liao et al., 2013; Sharma, 2014).

Therefore, new approaches are required to identify potential neuroprotective molecules as treatments for neonatal HI (Tuor et al., 1995; Ferriero, 2004; Fan et al., 2010). Drawing on our detailed yet incomplete knowledge of the physiology of neonatal HI, several factors must be satisfied in a new potential therapy. All potential treatments should be safe for vulnerable neonates and not interfere with essential developmental milestones. This challenges the NMDA-inhibition strategies (Meldrum, 1990; Johnston, 2001, 2005), as the glutamate system is essential for setting up normal synaptic plasticity within the developing brain (Hattori and Wasterlain, 1990; Ikonomidou et al., 1999; Johnston, 2009). Treatments should also be specific, to avoid extreme adverse effects in these vulnerable infants. The ideal treatment would target molecules common to the excitotoxicity, oxidative stress and inflammation pathways (Chaudhari et al., 2014; Fischer and Maier, 2015; Chamorro et al., 2016; Burd et al., 2016). Targeting these common mediators would allow a single therapy to be efficacious against multiple mediators of brain damage, instead of merely eliciting a reshuffle of pathways to favor a different method of cell death. Here follows an outline of one potential therapy under development which may satisfy these theoretical restraints as a model to incite debate concerning how future therapies are identified. Enter: neuroserpin.

Neuroserpin's Molecular Pedigree

Neuroserpin is a neuronally secreted serine-protease inhibitor enzyme with roles in cell death, neural plasticity, and microglial activation. Neuroserpin was first identified in the secreted product of cultured neuronal axons (Osterwalder et al., 1996). Protein expression is primarily localized to neurons (Osterwalder et al., 1996; Hastings et al., 1997; Lee et al., 2015b). The protein neuroserpin is encoded in mouse and human by the gene *Serpini1*. *Serpini1* mRNA expression is specific to the CNS, both in mouse (Krueger et al., 1997) and human (Teesalu et al., 2004). *In situ* hybridization studies have demonstrated expression of *Serpini1* throughout cortex, hippocampus, and olfactory bulbs, with scattered expression in cerebellum, pons, and thalamus from birth until adulthood (Krueger et al., 1997). High *Serpini1* expression has been identified in subplate relative to Layer VI of cortex in P8 mouse brain by microarray (Hoerder-Suabedissen et al., 2009), confirmed by immunohistochemistry (Kondo et al., 2015). Although *Serpini1* expression has been demonstrated in human brain tissue (Teesalu et al., 2004), detailed maps of expression are currently missing. This highly specific localisation suggests that *Serpini1*/neuroserpin modulatory treatments may not create dangerous side effects in other vulnerable organs such as the cardiovascular and pulmonary systems.

Neuroserpin is an inhibitory enzyme. Its primary target is the adult human stroke treatment, tissue plasminogen activator (tPA) (Osterwalder et al., 1996, 1998; Barker-Carlson et al., 2002; Yepes and Lawrence, 2004a; Miranda and Lomas, 2006; Ricagno et al., 2009, 2010). Neuroserpin has also been shown to exhibit weak inhibition of plasmin and urokinase plasminogen activator (Osterwalder et al., 1998). This function is conserved across species (Schrimpf et al., 1997; Hill et al., 2001; Ellisdon et al., 2014). Through inhibition of tPA, neuroserpin has the potential to influence many distinct molecular cascades (Yepes and Lawrence, 2004b,c; Benarroch, 2007; Yepes, 2015). tPA, also secreted by neurons (Krystosek and Seeds, 1981a,b; Lochner et al., 2006), has been shown to interact with a large number of pathways; activating NMDA receptors (Qian et al., 1993; Nicole et al., 2001), activating microglia (Benchenane et al., 2004), and recruitment of cell death related cascades (Yepes and Lawrence, 2004a; Zhao et al., 2007), in addition to its function of cleaving vascular thrombosis (Rijken et al., 1979, 1980). The known components of the neuroserpin/tPA molecular cascade are summarized in **Figure 6**.

Other, tPA-independent enzymatic pathways for neuroserpin have also been described (Ma et al., 2012a). Cell lines over-expressing neuroserpin demonstrate an increase in *N*-cadherin protein expression and related cell adhesion, maintained when the tPA binding site of neuroserpin is mutated (Lee et al., 2008). *In vitro*, neuroserpin has been shown to prevent excitotoxic neuronal death induced by plasmin and kainic acid (Wu et al., 2010), and the 20 methionine residues present within neuroserpin have been claimed to convey protection against oxidative stress (Mohsenifar et al., 2007), and exogenous neuroserpin has been shown to possess anti-inflammatory properties (Munuswamy-Ramanujam et al., 2010). The molecular cascades behind these tPA independent functions are not well understood (Ma et al., 2012a). Therefore,

neuroserpin has the pedigree to target multiple cell death pathways occurring in the brain during neonatal HI.
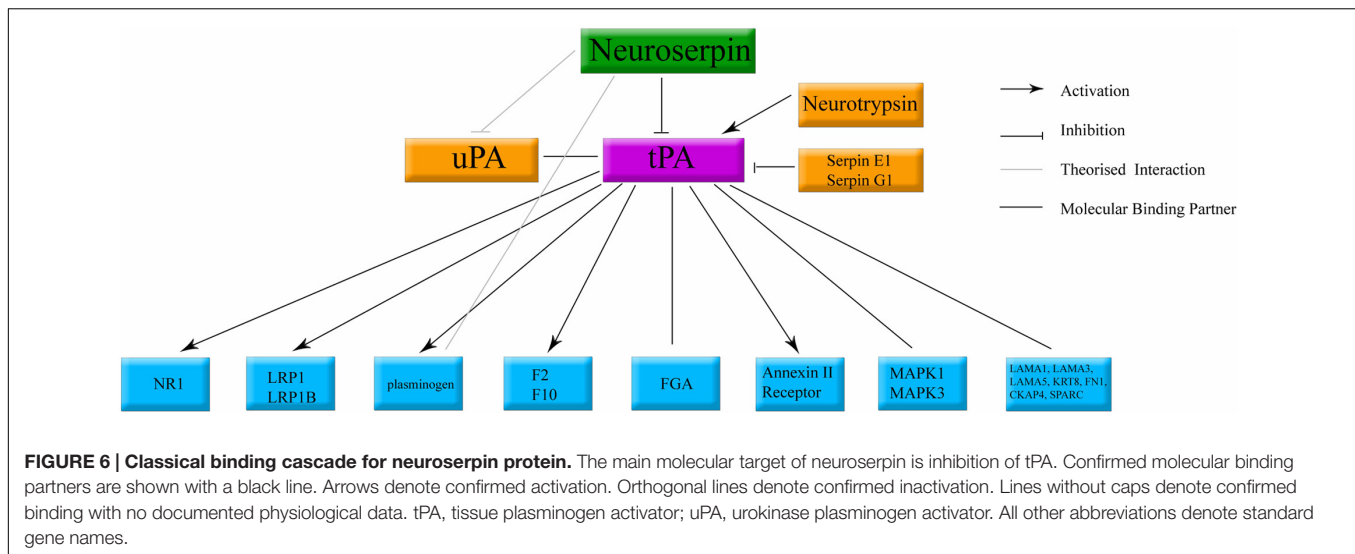
Cell Death, Inflammation, and Plasticity

Neuroserpin's physiological actions can be broadly categorized into three major pathways: cell death, neuronal plasticity, and immune cell activation. These closely follow the major classes of molecular change proposed by pathological theories of neonatal HI, suggesting that neuroserpin offers the potential to target multiple brain-damage pathways.

Neuroserpin has been implicated in protection against neuronal death (Galliciotti and Sonderegger, 2006). Exogenous neuroserpin administration *in vitro* decreases apoptosis caused by tPA, NMDA, kainic acid, and OGD (Lebeurrier et al., 2005a,b; Mohsenifar et al., 2007; Lee et al., 2008; Wu et al., 2010; Rodríguez-González et al., 2011a; Ma et al., 2012b). In addition, aberrant initiation of neuroserpin expression in cancer cells preserves the tumor and has been linked with increased treatment-resistance in prostate cancer (Chang et al., 2000; Hasumi et al., 2005; Valiente et al., 2014). Exogenous neuroserpin reduces spread of kainate-induced seizures in mouse, and decreases the expression of cell death markers (Yepes et al., 2002).

Of the three classes of neuroserpin function, its role in inflammation is the least well understood. When applied to vascular plaques *in vitro*, recombinant neuroserpin reduced T-Cell lymphocyte invasion (Munuswamy-Ramanujam et al., 2010). Administration of intracerebral neuroserpin directly following adult HI stroke in mouse, showed a qualitative decrease in the volume of infarct infiltrated by activated microglia (Yepes et al., 2000), and lower microglial inflammatory marker expression (Gelderblom et al., 2013). In human adult stroke patients, higher levels of neuroserpin in blood samples correlate with lower levels of immune marker proteins (Rodríguez-González et al., 2011c). There is considerable debate whether microglial activation is beneficial or detrimental in neonatal HI (McRae et al., 1995; Mallard et al., 2013; Kaur et al., 2013), so understanding the role of neuroserpin in balancing this cascade could provide important data. The lack of a complete molecular network explaining these anti-inflammatory effects highlights the complexity of the pathways involved in cell death and inflammation. Understanding the underlying explanation for these changes will be an important preliminary to administration in human infants who do not live in the highly sterile environments maintained for experimental animals.

In addition, neuroserpin is involved in neuronal plasticity. This could be problematic in the development of neuroserpin as a neonatal HI treatment for human patients, as the neonatal human brain circuitry is undergoing a great deal of developmental plasticity modifications (reviewed in Aoki and Siekevitz, 1988; Partanen et al., 2013; Simpson et al., 2014). The first evidence that neuroserpin may have a role in neuronal plasticity originated from studies of endocrine cell lines, which grow neurite-like processes when neuroserpin is administered to their media (Hill et al., 2001; Jacovina et al., 2001; Borges et al., 2010). At the molecular level, neuroserpin secretion from dense core vesicles is enhanced by depolarisation in cultured neurons (Berger et al., 1999; Ishigami et al., 2007). Monocular

FIGURE 6 | Classical binding cascade for neuroserpin protein. The main molecular target of neuroserpin is inhibition of tPA. Confirmed molecular binding partners are shown with a black line. Arrows denote confirmed activation. Orthogonal lines denote confirmed inactivation. Lines without caps denote confirmed binding with no documented physiological data. tPA, tissue plasminogen activator; uPA, urokinase plasminogen activator. All other abbreviations denote standard gene names.

enucleation at P11 in mouse led to decreased *Serpini1* mRNA expression in contralateral primary visual cortex compared to the control hemisphere (Wannier-Morino et al., 2003). The relative importance of this molecular cascade for human plasticity is as yet unclear.

Neuroserpin in *In Vitro* and Adult Hypoxia Ischaemia

Neuroserpin has been studied extensively in cell culture models of HI stroke. Administration of neuroserpin protects mouse cortical neurons *in vitro* against NMDA-induced excitotoxicity, but not AMPA-induced excitotoxicity (Lebeurrier et al., 2005a,b; Ma et al., 2012b). Further, neuroserpin is protective in an *in vitro* model of HI, OGD (Wu et al., 2010; Rodríguez-González et al., 2011a; Ma et al., 2012b). Both neurons and astrocytes cultured in OGD undergo less apoptosis and do not exhibit damaged neural processes when exogenous neuroserpin is administered following OGD (Rodríguez-González et al., 2011a; Ma et al., 2012b). Hippocampal neurons from both wild-type and tPA knockout mice were protected from OGD, plasmin-mediated cell death and kainic acid by neuroserpin administration (Wu et al., 2010), demonstrating that neuroserpin's neuroprotective role is not exclusively dependent on tPA inhibition.

Neuroserpin is also neuroprotective *in vivo*. The major model used to simulate hypoxic-ischaemic stroke in adult rodents is analogous to the Rice–Vannucci model described above for neonates (Eklöf and Siesjö, 1973; Rice et al., 1981; Bederson et al., 1986). Adult rats injected with neuroserpin before left common carotid artery ligation followed by acute hypoxia showed a decrease in infarct volume compared to controls, in addition to a decrease in expression of apoptosis markers (Yepes et al., 2000). Neuroserpin knockout mice show increased lesion volumes following adult HI (Cinelli et al., 2001; Gelderblom et al., 2013), whereas transgenic mice expressing six-times normal neuroserpin expression demonstrate smaller infarct volumes (Cinelli et al., 2001). Exogenous neuroserpin injection is also protective against NMDA injection in live adult rat (Lebeurrier

et al., 2005a). Currently, the only evidence for this has come from adults models of HI stroke, far from conclusive evidence of neonatal protection due to the differences in neuroanatomy and neurochemistry between the developing and adult brain. However, this work remains of utility, as at the very least investigating the neuroserpin-tPA system in neonatal models will add to understanding of the differences between neonatal and adult response to HI.

Neuroserpin administration in rats increases the window for effective tPA treatment in a model of adult stroke (Zhang et al., 2002). Increased tPA expression is found in neuroserpin knockout mice undergoing adult HI injury compared to controls (Cinelli et al., 2001; Gelderblom et al., 2013). However, exogenous neuroserpin is neuroprotective in tPA knockout mice (Wu et al., 2010). Ischaemic-reperfusion-induced injury in the retina of tPA knockout mice demonstrated rescued retinal apoptotic marker expression when injected with neuroserpin (Gu et al., 2015). Therefore, the neuroprotective properties of neuroserpin in adult HI appear to involve both neuroserpin's tPA-dependent and tPA-independent molecular cascades.

A role for neuroserpin in human adult HI stroke has also been described. Correlative studies have shown that high concentrations of neuroserpin in blood samples from human patients are associated with better functional outcome (Rodríguez-González et al., 2011b) and reduced inflammation (Rodríguez-González et al., 2011c). However, attempts to find a relationship between neuroserpin polymorphisms in humans and likelihood of stroke have produced little evidence of protective neuroserpin variants (Cole et al., 2007; Tjärnlund-Wolf et al., 2011). Mutations in the neuroserpin gene have been associated with two rare hereditary disorders (Galliciotti and Sonderegger, 2006); individuals present either with epilepsy (Yepes et al., 2002; Coutelier et al., 2008) or dementia with neuroserpin inclusion bodies (Davis et al., 1999a,b, 2002; Yazaki et al., 2001; Ricagno et al., 2010). It is not currently known whether these disorders are caused by novel functions of the mutated protein or by loss of physiological functions (Lee et al., 2015a).

Neuroserpin in Neonatal Hypoxia-Ischaemia

The evidence above from adult models of HI stroke is far from conclusive evidence of neonatal protection due to differences between the developing and adult brain. However, this work remains of utility, as at the very least investigating neuroserpin in neonatal models will add to understanding of the differences between neonatal and adult response to HI.

Evidence for a role of neuroserpin in neonatal HI is not entirely absent. A patent application published online claims that neuroserpin injection 4 h after neonatal HI in rat pups reduced infarct volume, but had no effect on LPS-sensitized HI (Kuan et al., 2010). However, the small number of published rodent microarrays following neonatal HI have failed to detect significant changes in *Serpini1* expression (Carmel et al., 2004; Hedtjarn et al., 2004a,b; Juul et al., 2009; Nagel et al., 2012; Rognlien et al., 2014). This could be explained by the delay between HI injury and sample collection, 6 h to 7 days post injury in this sample, which may be too early or too late to expect to see genomic changes in *Serpini1* expression. Also, microarray studies cannot reveal whether neonatal HI causes differences in neuroserpin translation or secretion, neither of which have yet been studied in neonatal HI.

Despite the lack of evidence for neuroserpin's direct role in neonatal HI, substantially more has been published documenting effects of its primary molecular target, tPA, in neonatal HI. tPA is broadly considered to be deleterious to cerebral recovery from neonatal HI (Adhami et al., 2008; Omouendze et al., 2013). In P7 rats which underwent unilateral common carotid artery ligation, tPA treatment was found to impair blood flow throughout the brain, an effect which was rescued by injection of the tPA inhibitor α2-antiplasmin (Adhami et al., 2008). Release of tPA by the cerebral microvasculature, as seen following neonatal HI, has also been shown to compromise the glucose content of the extracellular medium in neonatal mouse cortical culture (Henry et al., 2013). Administration of tPA inhibitor Plasminogen-activator-inhibitor 1 (PAI1) reduces locomotor disorder and white matter damage in LPS-sensitized neonatal HI rats (Yang et al., 2013a,b; Yang and Kuan, 2015). This pathway is relatively understudied in neonatal HI research, despite the potential to target a multitude of injury-relevant molecules. Drawing attention to molecules like neuroserpin and tPA, potential common moderators of injury pathways, will be essential to the development of new efficacious pharmacological treatments.

CONCLUSION

Neonatal HI remains the most common cause of infant death and disability globally. Reducing the burden of morbidity should be a high priority for biomedical research. A dearth of treatments are currently available postnatally for these vulnerable infants, restricted to only hypothermia, a breakthrough treatment which is not fully effective in all cases, with no currently licensed additive pharmacological treatments. A complex network of interacting molecular cascades, including excitotoxicity, oxidative stress, and inflammation contribute to the gradually developing pattern of neuronal cell death seen in asphyxiated neonates. Targeting common mediators of these pathways with specific targets linked to far-reaching effects offers a potential approach to generating new pharmacological treatments to exact neuroprotection in these neonatal patients.

AUTHOR CONTRIBUTIONS

All authors listed have made substantial, direct, and intellectual contribution to this work, and approved its final version for publication. LM, LS, AH-S, and ZM: conceived the review focus, conducted literature review, evaluated the literature. LM: reviewed literature, wrote first draft, critically revised the first draft, and finalized the manuscript. LS, AH-S, and ZM: gave feedback, and finalized the manuscript. All authors approved final version of manuscript.

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