Neuregulin-1: A Potential Endogenous Protector in Perinatal Brain White Matter Damage

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Key Words

Infant, premature • Brain • White matter damage • Cerebral palsy • Inflammation • Neuregulin • Pathogenesis

Abstract

Brain white matter damage, an important antecedent of long-term disabilities among preterm infants, has both endogenous and exogenous components. One of the endogenous components is the paucity of developmentally regulated protectors. Here we expand on this component, discussing the potential roles of one putative protector, neuregulin (NRG)-1, in brain development and damage. We outline how NRG-1 might be involved in perinatal brain damage pathomechanisms and suggest that NRG-1 might be one target for intervention.

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Introduction

Infants born at or before 28 weeks gestation appear to be at highest risk of brain white matter damage (WMD, 18–36%) [1, 2], which in turn is associated with

an elevated risk of later neurologic and cognitive limitations [3]. An improved understanding of this maturity-related risk is of major importance for those who wish to prevent it and its long-term adverse developmental consequences.

One traditional explanation is that preterm infants are (endogenously) more vulnerable to exogenous insults. Therefore, one extreme view is that improved neonatal care should lead to reduced WMD risk and improved outcome. Recent observational studies tend not to support this claim [4–7].

Another explanation is that preterm infants are more likely than their term peers to experience exogenous insults [8]. For example, intrauterine infection is both a risk factor for perinatal brain damage [9] and occurs more frequently at younger than at older gestational ages [10]. Thus, the increased WMD risk of preterm infants might reflect their higher likelihood of being exposed to adversity.

Third, low gestational age is a surrogate not only for increased vulnerability and adverse exposures, but also for many other endogenous and exogenous factors [11]. Among these are substances we have previously called 'endogenous protectors' [12]. Substances that qualify as

endogenous protectors (a) are endogenously available to the organism, (b) are protective in experimental models of disease, (c) offer biologically plausible interactions with presumed pathways of damage, and (d) are associated with a decreased risk for perinatal brain damage in humans. According to this definition, glucocorticoid and thyroid hormones [13–15] are examples for endogenous protectors.

In this article, we focus on one such potential endogenous protector, neuregulin (NRG)-1. Recent reviews of the molecular characteristics and functions of neuregulin in general [16] and in the brain [17, 18] are available elsewhere, as are reviews of the ErbB family of receptors necessary to signal the effects of NRG [19, 20]. Our goal is to offer the ‘big picture’ that might help decide whether NRG-1 might be a candidate for perinatal neuroprotection. Our hypothesis is supported by the roles of NRG-1 in neuronal development, in potentially damaging mechanisms (hypoxia-ischemia, excitotoxicity, and inflammation), and in neuropsychiatric disorders.

Neuregulin-1

NRG-1 is the first of a family of polypeptide growth factors encoded by four distinct genes, i.e., NRG-1 [21], NRG-2 [22, 23], NRG-3 [24], and NRG-4 [25]. Our focus is on NRG-1, which has been identified in parallel by multiple groups interested in potential ligands for the ErbB2 receptor (which also goes under the names HER2 and neu), in Schwann cell development, and in a growth factor that stimulates acetylcholine receptor expression [for an overview, see 16]. Each of these groups gave the same gene a different name, i.e., heregulin [21], neu differentiation factor [26], glial growth factor [27, 28], acetylcholine receptor-inducing activity [29, 30], and sensory and motor neuron-derived factor [31]. In the present article, we use the name NRG-1 for all of the above, mainly for consistency.

All 16 known isoforms of NRG-1 are encoded by the same gene and result from alternative splicing and usage of different promoters [16]. A classification system (type I–III) is based on the type of epidermal growth factor (EGF)-like domain, N-terminal sequence, and initial synthesis as transmembrane or non-membrane protein [16]. Three additional types (IV–VI) are theoretically possible [32].

ErbB Receptors

The ErbB receptors are a family of four transmembrane receptors, that bind multiple growth factors, including EGF, transforming growth factor- α , and NRG-1–4, among others [19, 20]. ErbB1, also known as the EGF receptor, does not bind NRG-1, while ErbB3 and 4 do serve as its receptors [33].

Historically, interest in ErbB receptors is rooted in their role as part of the erythroblastosis virus oncogene (v-Erb), which bears two domains in chickens, v-ErbA and v-ErbB [34]. One line of interest in NRGs and ErbB receptors is in the fields of cancer biology [35] and therapy [36]. Endogenous negative regulation of ErbB-receptor signaling might be of benefit in cancer therapy [37]. Might a ‘bad’ signal in tumorigenesis be ‘good’ in development?

Neuregulins and ErbB Receptors in the Development of Myelinating Cells

An increasing body of evidence indicates that NRG-1 and its ErbB receptors influence the growth and maturation of immature oligodendrocytes, and that maturation is disordered when a full complement of protein and receptor are not available [38–44]. Since damage to (or aberrant maturation of) developing oligodendrocytes is a likely pathogenetic factor in diffuse perinatal WMD [45], the effects of NRG-1 on developing oligodendrocytes deserve the attention of those who want to prevent WMD and its consequences.

NRG in Multiple Scenarios of Perinatal Brain Damage

Among the multiple experimental approaches to perinatal brain damage are exposure to infection/inflammation, hypoxia-ischemia, and excitotoxicity [46, 47]. In the following sections, we briefly discuss the potential roles for NRG in these three scenarios, as well as in traumatic injury.

Perinatal brain injury, especially in the preterm newborn, is likely to have multiple causes [48]. One important possibility is that antenatal infection elicits maternal/fetal inflammatory responses [49, 50], which either directly damage the developing brain (e.g., via cytokine-induced damage [12, 51, 52]) and/or lead to damage by sensitizing the developing brain to subsequent hits [47, 53] (e.g., a

second inflammatory challenge, hypoxia-ischemia [54, 55], or free radical attack [56]). In what follows, we have listed in due brevity the potential points of intersection of NRG-1 signaling with perinatal brain damage etiology.

NRG-1 and Inflammation

An increasing body of evidence suggests that the NRG-ErbB-signaling system intersects with inflammatory mechanisms [57–64]. Moreover, our own unpublished observations suggest differential ErbB-heterodimerization patterns in lung type-II cells in pro- versus anti-inflammatory contexts.

In the brain, the neuroprotective effect of NRG-1 exposure prior to middle cerebral artery occlusion (v.i.) is accompanied by a prominent reduction in microglia activation and interleukin-1 mRNA expression in the penumbra, indicating a downregulation of peri-infarct inflammation by NRG-1 [65]. The hypothesis that NRG might have anti-inflammatory and anti-oxidative properties in the brain is further supported by the finding that recombinant human NRG attenuates the production of superoxide and nitrite by stimulated N9 microglial cells [66].

Nuclear factor κ B (NF- κ B) is a nuclear component of the cell's inflammatory response [67]. NF- κ B-inducing kinase (NIK) appears to be one component of the signaling cascade initiated by proinflammatory cytokines such as tumor necrosis factor- α , lymphotoxin- β , and interleukin-1 [68], but appears to be required only for lymphotoxin- β signaling [69]. Within our present context, NIK appears to be recruited to all four ErbB-receptors and can activate NF- κ B in wild-type, but not in NIK-deficient cells [70]. On the other hand, recent studies find that NF- κ B is not the predominant signal in white matter inflammation induced by lipopolysaccharide [71, 72].

NRG-1 and Ischemic Brain Injury

Three days after permanent middle cerebral artery occlusion (MCAO), neuregulin was prominently expressed in neurons of the penumbra [73]. In adult rat brain, ErbB-4 (but not ErbB-2 and ErbB-3) protein was upregulated in neurons and macrophages/microglia in ischemic areas after MCAO [74]. From the same group comes the most interesting finding that 'a single intravascular injection of NRG-1 β (approximately 2.5 ng/kg) reduced cortical infarct volume by >98% when given immediately before MCAO' [65]. Based on their observations, these authors speculate that 'the induction of ErbB receptors ... is an adaptive response ... to prevent neuronal injury' [74]. We are not aware of comparable studies in the developing brain.

NRG and Excitotoxicity

Some perinatal brain damage is attributed to excitotoxicity [75]. In models of excitotoxic brain damage [76], ibotenate injection leads to neuronal loss and porencephalic cysts by acting as a glutamate analogue on the NMDA receptor [77, 78]. In cerebellar granule cells from 9-day-old mice, NRG upregulates the expression of the NR2C-subunit of NMDA receptors [79], which appears to be associated with an increased resistance of neurons to the adverse effects of neurotoxicity [for a brief overview, see 80].

At least part of NRG's purported role in the etiology of schizophrenia [81] might be due to a link between NRG/ErbB and glutamate/NMDA signaling [82]. In addition, NRG-1 β appears to play a glutamate-dependent role in memory. Rats exposed to 5 weeks of learning to navigate a maze had increased brain expression of NRG-1 β , but not if they also received the glutamate blocker MK-801 [83].

NRG Might Qualify as a Target for Neuroprotective Intervention

Indirect involvement of the NRG/ErbB signaling in established protective pathways might be one avenue for the development of improved protection strategies. For example, antenatal glucocorticoid administration reduces the incidence of neonatal brain damage [84], although the long-term safety of this potentially adverse exposure has not yet been established. Might some of these effects be due to the stabilization of ErbB-receptor expression after exposure to dexamethasone and hydrocortisone [85, 86]?

Direct NRG-1 administration might be feasible for animal studies designed to protect the animal's brain in the context of perinatal inflammatory, hypoxic-ischemic, and/or excitotoxic insults. The proof of principle has recently been published: NRG-1 can enter the brain after intravenous [87] and intra-arterial [65] administration. In experimental autoimmune encephalitis (one laboratory model for multiple sclerosis), systemic treatment with NRG-1 reduces demyelination and enhances remyelination [88]. This effect might not be due to NRG acting directly on oligodendroglia, but via induction of 'an environment more favorable to remyelination, possibly through modulation of the immune response' [89]. Perhaps, this is just the environment the perinatal brain needs to survive preterm birth without sustaining long-term damage.

Conclusion

The roles discussed above for NRG-1 and its receptors in brain development and damage support our conclusion that the NRG/ErbB system might be what we have previously called an 'endogenous protector' [12]. Our own findings of enhanced late fetal lung surfactant synthesis by NRG-1 β [90] and that all 4 ErbB receptors are present at the fetal endothelial level as early as 24 weeks gestation [91] further underscore its potential importance in the perinatal setting. Thus, NRG might be an endogenous protector in both the perinatal brain and lung. Although we are far from suggesting that NRG-1 administration might be the 'magic silver bullet' in peri-

natal medicine, NRG-1 might still qualify as a potential target for exogenous indirect or even direct neuroprotective intervention.

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