Published in final edited form as:

Early Hum Dev. 2016 November ; 102: 13–19. doi:10.1016/j.earlhumdev.2016.09.008.

IGF-1 in retinopathy of prematurity, a CNS neurovascular disease

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Abstract

The retina is part of the central nervous system and both the retina as well as the brain can suffer from severe damage after very preterm birth. Retinopathy of prematurity is one of the major causes of blindness in these children and brain neuronal impairments including cognitive defects, cerebral palsy and intraventricular hemorrhage (IVH) are also complications of very preterm birth.

Insulin-like growth factor 1 (IGF-1) acts to promote proliferation, maturation, growth and survival of neural cells. Low levels of circulating IGF-1 are associated with ROP and defects in the IGF-1 gene are associated with CNS disorders including learning deficits and brain growth restriction. Treatment of preterm infants with recombinant IGF-1 may potentially prevent ROP and CNS disorders. This review compares the role of IGF-1 in ROP and CNS disorders. A recent phase 2 study showed a positive effect of IGF-1 on the severity of IVH but no effect on ROP. A phase 3 trial is planned

Introduction

Very preterm birth occurs in almost 2% of all live births in developed countries including the US[1] and is associated with complications during delivery, within the first few weeks after delivery and many years later[2]. Retinopathy of prematurity (ROP), a major complication of preterm birth is a neurovascular disease of the retina, which is part of the central nervous system. ROP is associated with other cerebral lesions and other morbidities in preterm infants, perhaps indicating similar etiologies. Neurodevelopmental disorders occur in 50–70% of very preterm born infants (<32 weeks gestational age).[3] Up to 40% of this cohort are affected by brain neuronal impairment such as cognitive defects[4, 5], developmental

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Financial Disclosure: Raffael Liegl, Chatarina Löfqvist: None; Ann Hellström and Lois E.H. Smith consult for Shire Pharmaceuticals. AH, CL own shares in a company with financial interest in Shire.

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coordination disorders[6] or language problems[7]. In addition, neurosensory impairments occur in approximately 10% of these preterm infants[8] and include cerebral palsy[9–11], deafness and particularly blindness due to ROP and to cortical visual impairment[12, 13]. Two-thirds of these children require educational support during their school years[14–16].

Although ROP is potentially preventable to some extent, almost 20,000 infants each year worldwide become severely visually impaired or blind from ROP. In birthing facilities with experienced neonatal intensive care, ROP mainly affects those preterm infants that are born before 28 gestational weeks. In contrast, lack of sufficient perinatal care in nurseries results in considerably more ROP, even in more mature infants[17]. Careful control of oxygen supplementation to reduce excessive levels as well as fluctuations in oxygen can reduce severe ROP[18]. However, it is surprisingly difficult to provide optimal oxygenation in the nurseries. In the 1940s, supplementation with 100% oxygen in closed incubators significantly reduced the number of infant deaths, but precipitated the first epidemic of ROP. Oxygen supplementation was then limited, even in respiratory distressed preterm infants, resulting in lower incidents of ROP[19]. However, the downside of this “improvement” was an increase in the mortality rate.[20]. Seventy years later, there is still no definitive understanding as to the right amount of oxygen at each developmental time point that will minimize ROP pathogenesis and optimize survival and brain function of these infants [21, 22].

Levels of important key regulators of growth and development such as insulin-like growth factor 1 (IGF-1) deviate markedly postnatally from the in utero environment. The loss of these factors has been found to have a crucial role in growth retardation and impaired development in very preterm infants[23, 24]. IGF-1 is an anabolic hormone with mitogenic, differentiating, anti-apoptotic and metabolic effects[25]. In infants born preterm there is a strong association between low levels of circulating IGF-1 and ROP development[26] as well as with lower brain volume at post menstrual age 40 weeks[27] and with general head growth[28].

In this review, we will summarize current knowledge on the role of IGF-1 in the development of the retina and the brain and its potential use in the prevention of ROP and possibly other neuronal impairments as a consequence of very preterm birth.

Retinal structure and function in preterm infants

We have more information concerning the development of ROP as routine imaging of the retina is advanced compared to imaging of the brain because of both direct visual access and because of technologies such as optical coherence tomography (OCT), not applicable to brain studies. ROP is diagnosed clinically by directly visualizing the retinal surface with ophthalmoscopy through the pupil. With the advent in ophthalmology of OCT which the equivalent of non-invasive histological sections of the retina and optic nerve, the evaluation of retinal structures has become significantly easier. This technology can be used in even very preterm infants. OCT features of proliferative retinopathy have already been well established in other eye diseases such as diabetic retinopathy and neovascular age related macular degeneration[29, 30]. ROP has some similar and some different aspects as retinal

morphology is affected by interruption of normal uterine fetal development in the third trimester.

Based on the visually observed appearance with ophthalmoscopy (or fundus photography), ROP has been classified into 5 stages depending on the severity. Although OCT has added to the knowledge of retinal alterations in ROP, the accepted classification does not yet consider retinal thickness per se. OCT findings are likely to be incorporated into this classification system in the future. Studies using OCT in neonates undergoing ROP screening, detect preretinal vascular tissue (popcorn retinopathy), epiretinal membranes, cystoid macular changes, retinal layer schisis not visible with photographs or ophthalmoscopy and changes in macular structure and thickness. This allows more precise localization of retinal and vascular changes representative of plus disease, and cellular and subcellular changes related to ROP[31]. These findings have been particularly revealing in patients with aggressive posterior ROP[32, 33].

OCT studies have also shown cystic macular edema (CME) in up to 50% of infants screened for ROP. A positive correlation between ROP severity and extent of CME was found in some[34, 35], although not in all studies[36, 37]. An association with poorer language development and motor skills at 18–24 months corrected for age was also found in a recent study[38] [39].

The overall appearance of the retina in preterm babies suffering from ROP is characterized by the pathological persistence of inner retinal layers in the central fovea and increased foveal thickness. However these findings correlate better with gestational age than with ROP severity[35, 40, 41], which may partially explain why ROP, as currently classified visually, does not necessarily correlate with visual acuity outcomes later [40, 42].

Visual function is currently assessed by visual acuity, contrast sensitivity, visual fields and color vision, which are not very sensitive measures. Although children born preterm with or without ROP may have reduced visual function later[43, 44], there is not a close relationship between the degree of altered retinal structure as is seen with visual assessment and later functional outcome in ROP. This may be explained by cerebral visual defects that decrease vision as the brain is part of the visual system. The large *Early Treatment for Retinopathy of Prematurity Study* (ETROP), which comprised more than 600 patients, reported that 92 eyes (15.2%) had discordant outcomes: 86 eyes (14.3%) had an overall favorable retinal structural outcome but an unfavorable functional outcome as opposed to 6 eyes (1%) that had an unfavorable retinal structural outcome but rather good visual acuity[45]. Further studies will be needed to understand to what degree the eye itself contributes to this reduction in visual function and what discordance is explained by general brain damage, which affects visual function[46, 47].

Further evidence of ROP being a part of general neurovascular disease comes from studies using electroretinography (ERG). ERG allows the study of photoreceptor function even in infants. Photoreceptors are functionally impaired in children with previous ROP compared to matched infants without a history of ROP[48, 49]. There is general evidence that rods are

more affected by ROP than cones[50] and thus only subtle changes in central visual function are often observed even in individuals with a history of ROP[51].

Insulin-like growth factor-1 (IGF-1)

IGF-1 is structurally similar to (pro-) insulin but has its own distinctive receptor (IGF-1R) that shares a homology of about 60% to the insulin receptor[52]. The affinity of IGF-1R for IGF-1 is around 1000x higher than IGF-1R for insulin, while the insulin receptor (IR) has a 100x higher affinity for insulin compared to IGF-1 for IR[53]. Aside from IGF-1 and growth hormone, the IGF system also includes IGF-2, two receptors, types 1 and 2, and six major IGF binding proteins (IGFBP) and IGFBP proteases.[53] Almost 98% of circulating IGF-1 is bound to IGFBP3 (and ALS)[54]. IGFBP-3 is the most abundant IGFBP[55, 56]. IGFBP-3 is crucial in regulating the action of IGF-1 as it can prolong the half-life of IGF-1[57] due to a stronger affinity to IGF-1 than IGF-1 has to IGF-1R. The effect of IGF-1 will be augmented when released in proximity to the IGF-1R and attenuated when IGF-1 stays bound to IGFBP-3. IGF-1 mechanism of action is at least partly mediated through MAPK and AKT signaling pathways, which stimulate cell growth and proliferation. IGF-1R also signals through other pathways. One key pathway is regulated by phosphatidylinositol-3 kinase (PI3K) and its downstream partner, the mammalian target of rapamycin (mTOR), responsible for upregulating Akt, and thereby driving growth. In addition IGF-1 is also a potent inhibitor of programmed cell death[58, 59].

Insulin is the major regulator of metabolic processes under normal physiologic conditions particularly in fat, muscle and liver cells. However, IGF-1 can also influence glucose metabolism and homeostasis[60] as well as influence growth and anabolism. Laboratory studies confirm that IGF-1 promotes glucose uptake in peripheral tissues[61, 62]. The metabolic consequences of IGF-1 deficiency have been studied in a liver specific IGF-1 deficient mouse, which has a 75% reduction in circulating IGF-1, and in insulin insensitivity in muscle. Treatment with IGF-1 reduces serum insulin concentrations and improves insulin sensitivity, providing evidence for IGF-1 as an important component of overall insulin action in peripheral tissues[63].

IGF-1 also acts to promote proliferation, maturation, growth and survival of neural and neural stem cells (NSC). The action of IGF-1 triggered mainly through its interaction with IGF-1R, may vary by cell type and stage of development[23]. Most of our knowledge about IGF-1 in the context of development has come from experimental in vivo studies in mice[64–67].

IGF-1 and the central nervous system (CNS)

In rats, IGF-1 is expressed throughout all parts of the visual pathway including brain and the retina as part of the central nervous system. Retinal IGF-1 is highly regulated developmentally and mainly localized in the ganglion cell layer during the first weeks after birth when retinal vascularization takes place after which the levels of IGF-1 rapidly decrease [68, 69]. In neonatal mice, IGF-1 is found in all retinal layers while the IGF-1 receptor is expressed predominantly in photoreceptors and blood vessels. IGFBP-3

expression is 5-fold greater in neovascular tufts than in normal vessels in oxygen-induced retinopathy during hypoxia-driven neovascularization[70].

The evidence of IGF-1 as a neuronal growth factor comes from *in vitro* studies showing that IGF-1 increases proliferation in neural cells[71–73] as well as reduces apoptosis[74–76]. Many animal studies in knockout (KO) or transgenic (TG) mice have helped our understanding of the action of IGF-1. Overexpressing IGF-1 increases the total number of neurons in many areas of the brain while *Igf-1KO* mice have fewer CNS neurons[77–82].

Less is known about IGF-1 in human neural development although there are a few case reports of patients with known mutations in the IGF-1 gene or its receptor. The findings from these few studies are consistent with the results in the rodent studies using mutant mice[23]. All patients that were reported to have a homozygous IGF-1 gene mutation were characterized by intrauterine growth retardation with a birth weight ranging from 1400 to 2350g and microcephaly with a head circumference of 27 to 32cm. All had persistent growth and mental retardation as well as severe deafness postnatally[83–86]. Reports on individuals with a mutation in the IGF-1R gene support the idea of the IGF-1 signaling pathway having a key role in the developing CNS in humans as most of these patients also exhibited pre- and postnatal growth deficits, microcephaly and other cognitive impairment including learning disorder and mild mental retardation[87–89]. Eye findings were not discussed.

ROP pathogenesis, oxygen and IGF-1

Retinal blood vessels begin to develop during the 4th month of gestation in the human fetus and are fully developed by the end of a full-term pregnancy.[90] In contrast a preterm infant has an incompletely vascularized retina after birth, and has low IGF-I serum concentrations and low vascular endothelial growth factor (VEGF) retinal concentrations compared to those *in utero*. After preterm birth, IGF-1 serum concentrations fall rapidly to around 10 ng/mL as opposed to > 50 ng/mL in utero at PMA 23–30 weeks[91]. Persistent low serum IGF-1 levels are not only associated with ROP but also with other neonatal morbidities such as intraventricular hemorrhage (IVH)[92]. The partial pressure of oxygen (PaO₂) *in utero* is around 50mmHg by the end of pregnancy, compared with around 160mmHg PaO₂ found in ambient room air.[93] Preterm infants that are exposed postnatally to very high oxygen concentrations in closed incubators have a particularly high risk of developing ROP because of a large increase over the partial oxygen pressure *in utero*. The retinal vasculature develops in the beginning of the fourth month of gestation, and grows radially from the optic nerve towards the ora serrata[94]. Vascular development is completed shortly before full-term birth[95] so in infants born preterm the vasculature is not fully developed and postnatal growth is often restricted. Elevated oxygen pressure, (perhaps even in ambient room air), causes attenuation of normal vessel growth and a constriction or loss of already developed vessels[96, 97] resulting in avascularized areas in the retina particularly in the periphery.[98] The area of the initial avascular zone is dependent on the gestational age at birth of the preterm infant. If phase I of ROP with impaired vessel growth could be prevented with control of oxygen but also with restoration of factors that promote postnatal growth that are missing in the preterm infant, then the resulting neovascular phase (see below) would not occur. Hence, restoring normal vascularization that would occur in utero might prevent ROP.

At about 30–32 weeks post menstrual age, the increasing metabolism of the growing preterm infant's incompletely vascularized retina leads to a rising demand for oxygen and nutrients and a subsequent upregulation of angiogenic growth factors such as VEGF.[99, 100] This second phase of the disease, driven by VEGF among other growth factors, is clinically characterized by the outgrowth of new but pathological vessels into the vitreous. As the retina develops further, these pathological vessels may regress. However, fibrous scar tissue can cause traction on the retina, and can lead to retinal detachment and blindness.[101]

The transition of phase 1 to 2 usually occurs weeks to months after birth and the onset as well as the severity of the neovascular phase can be variable[102, 103] Even mild ROP in more mature infants can disturb proper central retinal development.[104] ROP related visual impairment, both in the central part of the retina[105, 106] as well as in the periphery,[105, 107] may remain many years after the initial onset of the disease. The areas of undeveloped retina at birth as reflected in low gestational age as well as the lack of general postnatal growth are strong determinants of proliferative ROP.

Current treatment of ROP

The treatment options that are available today do not aim at preventing ROP but aim to suppress the second proliferative phase or neovascularization. The most common treatment approach for many decades has been retinal ablation therapy, initially using cryocoagulation[108, 109], and now laser photocoagulation.[110] The therapeutic principle is the same. Destroying avascular retina reduces the production of VEGF and other hypoxia-driven growth factors. When applied properly, this procedure is fairly safe and prevents most infants from developing retinal detachment (ROP stages 4 and 5). Intervention to abort neovascularization is important, as repairing late stage (4 and 5) ROP after retinal detachment is generally associated with poor clinical outcomes. [111]

Anti-VEGF therapy was first shown to be effective at inhibiting neovascularization in proliferative eye diseases in adults and is today the most important therapy for neovascular age related macular degeneration. It is now also used off label to treat phase 2 neovascular ROP. However, treating preterm infants is challenging because the drugs leak into the systemic circulation and can potentially suppress the development of other organ systems. The right dose or right drug as well as long-term safety has yet to be determined.

Clinical perspective of the role of IGF-1 in retinopathy

Indirect evidence of a role for IGF-1 in phase 2 retinopathy came from a report of a patient with proliferative diabetic retinopathy who suffered a pituitary infarction. The retinal neovascularization then vanished.[112] Since there were no other treatments available for proliferative retinopathy many patients with proliferative diabetic retinopathy were treated with pituitary ablation. Although the mechanism behind this response was not established at the time, it was thought to be related to the loss of growth hormone from the pituitary.[113, 114]. Growth hormone effects are mediated through IGF-1. Later a link between the GH-IGF-1-SS axis in proliferative retinopathy was found to be mediated through IGF-1. It was concluded that systemic inhibition of GH or IGF-1 might prevent proliferative retinopathy in

the late phase of the disease and that low IGF-1 might also be involved in vessel loss in the early phase of retinopathy.[114–116]

ROP first starts with a phase of impaired retinal vessel growth. Preterm infants were found to have low circulating IGF-1 levels after birth, and an inverse correlation between the level of postnatal serum IGF-1 and ROP severity was observed. Early intervention with replacement of IGF-1 to in utero levels was therefore thought to potentially be a way to prevent ROP.[117, 118]

Most information on the mechanism of action of IGF-1 on retinopathy comes from animal models, particularly the oxygen induced retinopathy (OIR) model in which 7 day old mice pups are placed into an oxygen chamber with an oxygen concentration of 75% for 5 days which causes suppression of retinal vascular growth (similar to phase I of ROP) before they return to room air when the now avascular areas of ischemic retina produce growth factors causing proliferative retinopathy (similar to phase II ROP).[119] On day 17 almost all mice display neovascularization. With exogenous IGF-1 supplementation in OIR mice pups to treat the first phase, there is an increased growth rate, higher endogenous IGF-1 levels, better maturation and less phase 2 proliferative retinopathy compared to the control group.[120]

Role of IGF-1 in ROP treatment

The first studies to determine the pharmacokinetics of IGF-1 treatment in preterm infants were undertaken by administering a product used frequently in this population with minimal complications, fresh frozen plasma that contains measurable quantities of IGF-1. Serum concentrations of IGF-1 and IGFBP-3 were increased with plasma treatment but the half-life of IGF-1 in serum was only ~3 hours compared to ~17 hours when IGF-I was administered sc in adults[121, 122].

Since IGF-1 is bound primarily to IGFBP-3 and ALS as a ternary complex in serum and IGFBP-3 serum levels are also low after preterm birth, a drug, mecasermin rinfabate, was developed which consists of an equimolar preparation of IGF-1 and IGFBP-3. The IGF-1/IGFBP-3 half-life is even shorter (around 1 hour) requiring a continuous intravenous infusion rather than intermittent injections.[123]

Following the first pharmacokinetics studies, an equimolar preparation of rhIGF-1/rh IGFBP-3 in doses between 21 and 111 µg/kg/24h during the first week of life was studied. With continuous infusion, IGF-1 concentrations increased to the lower normal range levels with no evidence of significant adverse effects[124].

Initial results from a multicenter phase 2 study in which 61 infants with a GA 23 to 27 weeks + 6 days were treated with mecasermin rinfabate and 60 untreated controls up to a post-menstrual age of 30 weeks (ClinicalTrials.gov Identifier: NCT01096784) showed no effect on ROP prevention. However only 24/61 treated patients had IGF-1 levels within the intended range. Another possible reason for lack of reduction of ROP with IGF-1 treatment is that higher oxygen saturation ranges of 91–95% were instituted at the start of the study, which are likely to be associated with more severe ROP. The actual level may have exceeded the target ranges as it is difficult to monitor[125–131]. A phase 3 trial is planned.

IGF-1 impact on brain function

Studies of IGF in brain show results similar to retina, which is also part of the CNS. A polymorphism in the IGF-1 promotor region, which regulates serum IGF-1 levels, slows cranial growth from birth through the fifth year of life[132]. Clinical studies also show that IGF-1 levels correlate with brain volumes while no association with cerebral spinal fluid volume was observed. Others found an association of IGF-1 levels with white matter organization and that low birth weight infants had smaller brain volume in general[133]. Higher systemic IGF-1 levels are related to better outcome in terms of neurodevelopment at age 2[134].

It is reasonable to assume that the vascular changes seen in ROP may also impact other vascularized regions in the brain. Experimental studies investigating a relationship between IGF-1 and hypoxic-ischemic brain damage and inflammation show that higher IGF-1 levels may be associated with improved outcome[135, 136]. Furthermore in a rat periventricular leukomalacia model exogenous IGF-1 prevented low dose lipopolysaccharide-induced damage, but was counterproductive at higher lipopolysaccharide doses[137].

Although in the study that investigated the effect of mecasemin rinfabate treatment on complications of preterm infants, there was no clear effect on ROP outcome, there was however a 44% reduction in the incidence of severe intraventricular hemorrhage (IVH; grade III and IV) in all treated patients and a 64% reduction in severe IVH in those with serum IGF-1 levels within the target range.

Conclusion

Preterm and particularly very preterm infants often have severe and long lasting neurodevelopmental and retinal vascular disorders. Both, brain damage as well as retinal damage (ROP) have been linked to low circulating systemic IGF-1 levels compared to the equivalent in utero levels. Clear evidence from experimental studies as well as from initial clinical trials indicate potential benefit with IGF-1 supplementation in preterm babies that are at risk.

However, while it is promising that IGF-1 may reduce the incidence of IVH there is no clinical evidence yet that it prevents ROP in very preterm infants.

Further studies must be undertaken to investigate the role of IGF-1 supplementation in preterm infants.

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