In contrast to the adult, the third-trimester foetus experiences one of the most intense periods of growth and maturation of its lifetime. Early development is characterized by the existence of critical periods when environmental factors effectively produce long-lasting changes. An example is that of the antiangiogenetic substance thalidomide, which during a very limited time period in early pregnancy causes gross malformations. Angiogenesis is important for the alveolarization of the lungs, which in humans mainly takes place after birth in infants born at term (1), and in newborn and infant rats, thalidomide (2) as well as a VEGF-receptor inhibitor (3) reduced lung vascular density and alveolarization. In the central nervous system, maturational processes occur at different times in different brain regions and neural circuits, and therefore, critical periods may be specific for each brain region or neurotransmitter system (4).

The very preterm infant has lost nutrients and other factors supplied by the mother and is exposed to poor nutrition, hyperoxia/hypoxia, infections and other stresses resulting in impaired growth and development. In the eye, reduced physiologic angiogenesis may lead to hypoxia followed by uncontrolled vessel growth. This pathologic angiogenesis is the target for two new treatment modalities for retinopathy of prematurity (ROP), which are being evaluated in ongoing or planned studies. We would like to express our concern about possible adverse effects of these medications on the developing preterm infant.

In the Pan-VEGF Blockade for the Treatment of Retinopathy of Prematurity (BLOCK-ROP) study (ClinicalTrials.gov Identifier: NCT01232777), intravitreal injection of 0.625 or 0.75 bevacizumab (Avastin®, Genentech Inc., South San Francisco, CA) will be compared with standard of care laser for type 1 prethreshold ROP diagnosed at 30–36 postmenstrual weeks. In the Safety and Efficacy of propranolol in newborns with retinopathy of prematurity (PROP-ROP) study (ClinicalTrials.gov Identifier: NCT01079715) (5), preterm infants with stage 2 ROP in zone II or III without plus-disease will receive systemic propranolol, a nonselective beta blocker, up to 90 days in addition to standard care in comparison with standard treatment only.
**AVASTIN FOR ROP**

VEGF promotes both normal and pathologic angiogenesis, and it is a neuronal survival factor. The blockade of VEGF with Avastin® may thus influence other processes than pathologic angiogenesis in the eye. Bevacizumab is a large molecule, and an advantage put forward is its inability to escape the eye unless in very small amounts (6). However, one intravitreal injection of 1.25 mg/50 μL in three adult cynomolgus macaques weighing 3.9–5.5 kg resulted in a maximum serum concentration of 1430 ± 186 ng/mL 1 week after injection and concentration declined more slowly than in the eye, with little change after 4 weeks, and was 67 ± 24.3 ng/mL after 8 weeks (7).

In a recent study (BEAT-ROP, ClinicalTrials.gov Identifier: NCT01232777) (n = 150), infants with stage 3+ ROP were given bilateral intravitreal injections of 0.625 mg of Avastin® bilaterally (6) resulting in a dose equal to that given to the adult macaques. As the blood retinal barrier is compromised in eyes with pathologic neovascularization, one may fear higher serum concentrations in these infants than in the monkeys. Regarding safety, the authors of this study concluded that 2800 infants were needed to assess mortality and an even larger sample for local or systemic toxicity and that the study was too small to address the question of whether intravitreal bevacizumab is safe. Thus, no attempts to monitor adverse effects were made, and serum concentrations of bevacizumab were not reported.

**PROPRANOLOL FOR ROP**

Propranolol has been found to be efficient in reducing the growth of infantile hemangiomas in a number of patients (8,9), although no controlled trials of safety and efficacy have been reported yet. In a mouse model of ROP, propranolol was protective against retinal angiogenesis and ameliorated blood–retina barrier dysfunction in oxygen-induced retinopathy (OIR) (10).

The hypothesis of the PROP-ROP study is that in preterm infants with ROP, VEGF overexpression could be induced by beta2-adrenoreceptor stimulation and that propranolol, administered when ROP stage 2 is detected in zone II or III, could reduce the progression of the disease. As mentioned by the authors, most cases of ROP stage 2 regress spontaneously, which means that most of the infants treated with propranolol never risked blindness anyway.

Propranolol is reported to be well tolerated in most cases. However, hemodynamic effects such as bradycardia and hypotension as well as metabolic effects such as hypoglycemia may be serious (11–13). In addition, beta blockers may cause masking of hypoglycemia, insulin resistance and dyslipidemia (14). It is well known that very preterm infants already have an increased risk of hypotension (15) and deranged glucose metabolism including insulin resistance (16).

Less is known about the roles of the adrenergic system and the beta-adrenergic receptors on the development of the premature infant’s brain. In rats, OIR is induced by exposure to increased oxygen concentrations from birth to postnatal day 11 followed by room air for 7 days after which proliferative retinopathy, similar to human stage 3 ROP, is found (17). In the rat brain, the timing of noradrenergic cortical innervations coincides with neurogenesis, neuronal migration, sprouting of cellular processes and the formation of synaptic contacts and occurs mainly during the first 3 weeks of postnatal life (18), just like the development of OIR and the transition to proliferative disease. Noradrenaline is a neurotransmitter that is essential for the modulation of memory (19) and for the plasticity of visual (20,21) and olfactory systems (19). Propranolol passes the blood–brain barrier and causes memory loss in chicks (19) and blocks early olfactory learning in rats (22).

It is likely that during the period when pathologic angiogenesis is a threat to the eye, windows of susceptibility occur in other parts of the central nervous system, where adequate angiogenesis and development of neural and other tissues are essential for later normal function. Administering potent blockers of VEGF and of the adrenergic system during these periods may be deleterious. As long as we lack methods to explore how the growth and modulation of neuronal networks are orchestrated, medications that possibly alter these processes for the rest of life should be avoided. In preterm infants prone to abnormal brain development, it will be impossible to sort out adverse effects of these drugs. Laser ablation of the retina is not ideal, but its effects are restricted to the eye and it usually works well. Antiangiogenic treatment might be indicated in serious cases when laser treatment has failed, but that is different from it being an alternative to laser. There might be a place for propranolol for pathologic vessels just like for severe hemangiomas, but its use as prophylaxis to prevent proliferative ROP during stage 2 like in the PROP-ROP study should be questioned. If Avastin® is further used in infants, monitoring of serum bevacizumab and exploration of its pharmacokinetics and effects on premature babies are needed.

References

1. Stenmark KR, Abman SH. Lung vascular development: implications for the pathogenesis of bronchopulmonary dysplasia. *Annu Rev Physiol* 2005; 67: 623–61.
2. Jakkula M, et al. Inhibition of angiogenesis decreases alveolarization in the developing rat lung. *Am J Physiol Lung Cell Mol Physiol* 2000; 279: 600–7.
3. Le Cras TD, et al. Treatment of newborn rats with a VEGF receptor inhibitor causes pulmonary hypertension and abnormal lung structure. *Am J Physiol Lung Cell Mol Physiol* 2002; 283: 555–62.
4. Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect* 2000; 108 Suppl 3: 511–33.
5. Filippi L, et al. Study protocol: safety and efficacy of propranolol in newborns with Retinopathy of Prematurity (PROP-ROP): ISRCTN18523491. *BMC Pediatr* 2010; 10: 83.
6. Mintz-Hittner HA, Kennedy IA, Chuang AZ. Efficacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *N Engl J Med* 2011; 364: 603–15.
7. Miyake T, et al. Pharmacokinetics of bevacizumab and its effect on vascular endothelial growth factor after intravitreal injection of bevacizumab in macaque eyes. Invest Ophthalmol Vis Sci 2010; 51: 1606–8.
8. Leaute-Labreze C, et al. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008; 358: 2649–51.
9. Manunza F, et al. Propranolol for complicated infantile hemangiomas: a case series of 30 infants. Br J Dermatol 2010; 162: 466–8.
10. Ristori C, et al. Role of the adrenergic system in a mouse model of oxygen-induced retinopathy: antiangiogenic effects of beta-adrenoreceptor blockade. Invest Ophthalmol Vis Sci 2011; 52: 155–70.
11. Lawley LP, Siegfried E, Todd JL. Propranolol treatment for hemangioma of infancy: risks and recommendations. Pediatr Dermatol 2009; 26: 610–4.
12. Breur JM, et al. Hypoglycemia as a result of propranolol during treatment of infantile hemangioma: a case report. Pediatr Dermatol 2010; 28: 169–71.
13. Bonifazi E, et al. Severe hypoglycemia during successful treatment of diffuse hemangiomatosis with propranolol. Pediatr Dermatol 2010; 27: 195–6.
14. Fonseca VA. Effects of beta-blockers on glucose and lipid metabolism. Curr Med Res Opin 2010; 26: 615–29.
15. Dempsey EM, Barrington KJ. Evaluation and treatment of hypotension in the preterm infant. Clin Perinatol 2009; 36: 75–85.
16. Mitanchez-Mokhtari D, et al. Both relative insulin resistance and defective islet beta-cell processing of proinsulin are responsible for transient hyperglycemia in extremely preterm infants. Pediatrics 2004; 113: 537–41.
17. Sarlos S, et al. Retinal angiogenesis is mediated by an interaction between the angiotensin type 2 receptor, VEGF, and angio-poietin. Am J Pathol 2003; 163: 879–87.
18. Murrin LC, Sanders JD, Bylund DB. Comparison of the maturation of the adrenergic and serotonergic neurotransmitter systems in the brain: implications for differential drug effects on juveniles and adults. Biochem Pharmacol 2007; 73: 1225–36.
19. Gibbs ME, Hutchinson DS, Summers RJ. Noradrenaline release in the locus coeruleus modulates memory formation and consolidation: roles for alpha- and beta-adrenergic receptors. Neuroscience 2010; 170: 1209–22.
20. Inaba M, et al. Facilitation of low-frequency stimulation-induced long-term potentiation by endogenous noradrenaline and serotonin in developing rat visual cortex. Neurosci Res 2009; 64: 191–8.
21. Kasamatsu T, Shirokawa T. Involvement of beta-adrenoreceptors in the shift of ocular dominance after monocular deprivation. Exp Brain Res 1985; 59: 507–14.
22. Wilson DA, Sullivan RM. Olfactory associative conditioning in infant rats with brain stimulation as reward: II. Norepinephrine mediates a specific component of the bulb response to reward. Behav Neurosci 1991; 105: 843–9.