Neurovascular interactions in diseases of the eye

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Presentation Description: Vascular development of the eye is influenced by several integrated pathways. The hyaloid vessel system - the embryonic vascular network of the retina - has served as a model for understanding pathway integration mechanisms. As exemplified by the hyaloid persistence of the Lrp5 mutant mouse and the human syndrome osteopetrosis pseudoglioma, the Wnt signaling pathway plays an important role in promoting regression of the hyaloid vessels. In this case, resident macrophages produce a ligand, Wnt7b, critical for regression. The Wnt pathway response is integrated closely with the activity of Angiopoietin 2, another signaling molecule that enhances Wnt7b expression and suppresses cell survival, via Tie2 antagonism, as a key step in promoting hyaloid regression. Furthermore, it was recently shown that a melanopsin-dependent fetal light response pathway regulates retinal neuron number and, via the hypoxia response pathway, controls the levels of Vegfa in both the vitreous and retina. Normally, light stimulation results in diminished levels of Vegfa and this permits the endothelial cell death that is promoted by the Wnt and angiopoietin pathways. Thus, regression of the fetal vasculature depends on the integration of at least three signaling pathways. The light response pathway that controls Vegfa levels in the retina can also control retinal angiogenesis and, according to a recent study, influences the risk that a premature infant will contract the vascular overgrowth disease retinopathy of prematurity.

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Neurovascular unit in diabetic retinopathy

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Presentation Description: The neural retina represents a complex system of neuronal, glial and vascular cells that interact to allow normal visual function. In the central nervous system, this interaction is often referred to as the neurovascular unit, implying the requirement for neural and glial derived factors in the control of the blood-neural barrier and subsequent regulation of the neural environment by this barrier. Increased vascular endothelial growth factor alters the barrier properties in diabetic retinopathy leading to pathological vascular permeability and loss of vision and represents a change in the normal neurovascular function. Recent research has identified neural derived factors and signaling pathways that regulate formation of the blood-neural barrier. The relationship of these signaling pathways to the blood-retinal barrier formation and its regulation as well as implications for diabetic retinopathy pathology and treatment options will be discussed.


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Myopia: Muscarinic influences on choroidal thickness and ocular growth

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Presentation Description: Myopia, or near-sightedness, is nearing epidemic proportions in Asia, and pathological myopia is a leading cause of blindness. Despite decades of research, the only drug that inhibits the progression of childhood myopia is the non-selective muscarinic acetylcholine antagonist atropine, which has the deleterious side effects of cycloplegia and photophobia. Pirenzepine, a more selective antagonist, and one with fewer side effects, was withdrawn from clinical trials in 2005. Hence the search for relatively specific anti-cholinergics without the attendant visual problems continues in animal models.

Initially, the effects of atropine were attributed to its preventing the excessive accommodation presumed to accompany intensive study and higher education levels, however, animal models have disproven this hypothesis by showing inhibitory effects of atropine on eye growth in chicks, whose ciliary muscle receptors are nicotinic, not muscarinic, and in mammals lacking accommodation. These findings launched the search for the tissue site of action of muscarinics, with the goal of developing drugs that were not detrimental to visual or retinal function. Initially, it was discovered that some muscarinic antagonists inhibited the synthesis of extracellular matrix in scleral explant cultures, suggesting actions downstream of the retina. Subsequent in vitro studies looking for potential choroidal influences showed that the choroid secreted a molecule that inhibited scleral growth, supporting a secretory role for the choroid. Finally, muscarinic antagonists resulted in choroidal thickening, and agonists in choroidal thinning, both in vivo and in vitro, that occurred concurrent with changes in eye growth. Although these various studies are encouraging in ascertaining site and mode of action, the full story remains unknown.

In this talk I will focus on the choroid as a secretory tissue whose effects on eye growth can be altered by the visual environment, and present evidence that changes in choroidal thickness, mediated by muscarinic agents, alter eye growth. I will present evidence that the choroid is an integral tissue in the signal cascade leading to changes in scleral biosynthesis rates, thereby altering eye size and refraction. I will show data suggesting that parasympathetic inputs to the choroid are involved in the choroidal responses to visual stimuli.

Commercial Relationships: Debora Nickla, None

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Glaucma: Astrocyte-vascular coupling in optic nerve blood flow regulation

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Presentation Description: Blood flow autoregulation dysfunction has been proposed as a cause of blood flow deficiency and glaucomatous optic neuropathy. However, the faulty autoregulation demonstrated in both clinic and experimental glaucoma models exhibits diverse hemodynamic changes, which are beyond or even contrary to an explanation within the classic paradigm of autoregulation and therefore, hampers a precise diagnosis of autoregulation dysfunction. We hypothesize that perivascular astrocytes coordinating with other vascular associated cells modulate perfusion pressure-induced ocular blood flow autoregulation and failure of this mechanism results in hemodynamic imbalance in glaucoma.

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