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Arginase in retinopathy

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ABSTRACT

Ischemic retinopathies, such as diabetic retinopathy (DR), retinopathy of prematurity and retinal vein occlusion are a major cause of blindness in developed nations worldwide. Each of these conditions is associated with early neurovascular dysfunction. However, conventional therapies target clinically significant macula edema or neovascularization, which occur much later. Intra-ocular injections of anti-VEGF show promise in reducing retinal edema, but the effects are usually transient and the need for repeated injections increases the risk of intraocular infection. Laser photocoagulation can control pathological neovascularization, but may impair vision and in some patients the retinopathy continues to progress. Moreover, neither treatment targets early stage disease or promotes repair. This review examines the potential role of the ureahydrolase enzyme arginase as a therapeutic target for the treatment of ischemic retinopathy. Arginase metabolizes L-arginine to form proline, polyamines and glutamate. Excessive arginase activity reduces the L-arginine supply for nitric oxide synthase (NOS), causing it to become uncoupled and produce superoxide and less NO. Superoxide and NO react and form the toxic oxidant peroxynitrite. The catabolic products of polyamine oxidation and glutamate can induce more oxidative stress and DNA damage, both of which can cause cellular injury. Studies indicate that neurovascular injury during retinopathy is associated with increased arginase expression/activity, decreased NO, polyamine oxidation, formation of superoxide and peroxynitrite and dysfunction and injury of both vascular and neural cells. Furthermore, data indicate that the cytosolic isoform arginase I (AI) is involved in hyperglycemia-induced dysfunction and injury of vascular endothelial cells whereas the mitochondrial isoform arginase II (AII) is involved in neurovascular dysfunction and death following hyperoxia exposure. Thus, we postulate that activation of the arginase pathway causes neurovascular injury by uncoupling NOS and inducing polyamine oxidation and glutamate formation, thereby reducing NO and increasing oxidative stress, all of which contribute to the retinopathic process.

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1. Introduction

1.1. Need for new therapies for ischemic retinopathy

Ischemic retinopathy develops in a variety of retinal disorders, including diabetic retinopathy, retinopathy of prematurity and retinal vein occlusion and is the most frequent cause of vision loss and blindness in the industrialized world. The retina is the most metabolically active tissue in the body and when retinal blood flow is insufficient to match the metabolic demands, retinopathy will occur. At the cellular level, the pathological process represents a destructive cycle involving neuronal depolarization, calcium influx and oxidative stress initiated by energy failure and increased glutamatergic stimulation. Diabetic retinopathy is the most frequent cause of blindness in working age adults in the US and affects over 40% of diabetic patients (NEI, 2008). By 2030, 366 million people are expected to have diabetes and over 146 million will have diabetic retinopathy. Retinal-vein occlusion is the second most common retinal vascular disease (Wong and Scott, 2010), with a prevalence of 1–2% in persons older than 40 years, affecting 16 million persons worldwide (Joussen et al., 2007). Retinopathy of prematurity (ROP) affects ~16,000 US infants yearly; many have

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lifelong vision impairment (Hartnett, 2010). Each of these conditions is associated with neuronal as well as vascular injury (Barber et al., 2011; Fulton et al., 2009; Osborne et al., 2004). So far laser photocoagulation is the only recommended treatment for advanced retinopathy. Laser treatment is usually effective, but can impair vision and in some patients the retinopathy continues to progress. Clinical trials of anti-VEGF intra-ocular injections show promise in reducing diabetic macular edema (Nicholson and Schachat, 2010). However, the beneficial effects are usually transient and the treatment does not promote tissue repair. Therefore, there is great need for new strategies and therapies to prevent retinal injury and enhance repair. The mechanisms underlying early vascular and neural injury during retinopathy are not understood and no treatments are available yet to prevent the damage. Understanding the mechanisms that underlie the initiation of vascular and neural injury in the ischemic retina is a critical step toward developing new therapies to reduce vision loss.

Our studies in models of retinopathy have revealed that the urea cycle enzyme arginase is critically involved in both vascular and neuronal injury. Arginase metabolizes L-arginine to form proline, polyamines and glutamate. Excessive arginase activity reduces the L-arginine supply for nitric oxide synthase (NOS), causing it to become uncoupled and produce superoxide and less nitric oxide (NO). Superoxide and NO react rapidly and form the toxic oxidant peroxynitrite. Glutamate and the catabolic products of polyamine oxidation can induce more oxidative stress and DNA damage, both of which are damaging to retinal cells. Our studies indicate that neurovascular dysfunction and injury during retinopathy are associated with increased arginase expression/activity, decreased NO, increased polyamine oxidation, oxidative stress and death of vascular and neural cells. Thus, we postulate that activation of the arginase/polyamine pathway plays an important role in neurovascular injury during retinopathy (Fig. 1). The scientific literature and experimental data supporting this concept will be developed in the subsequent sections.

1.2. Actions of arginase

Arginase is a member of the ureohydrolase family of enzymes. In the liver, arginase catalyzes the final step in the urea cycle, in which the body disposes of toxic ammonia produced by protein catabolism. Specifically arginase converts L-arginine into urea and L-ornithine (Fig. 2). Arginase processes ammonia and ornithine into L-citrulline by activity of carbamoyl phosphate synthase-1 (CPS-1) and ornithine carbamoyl-transferase (OCT). L-citrulline can be recycled back to L-arginine by argininosuccinate synthase (ASS) and argininosuccinate lyase (ASL) to complete the urea cycle (Osowska et al., 2004). However, most non-hepatic tissues lack OCT or CPS-1 and therefore do not have the complete urea cycle.

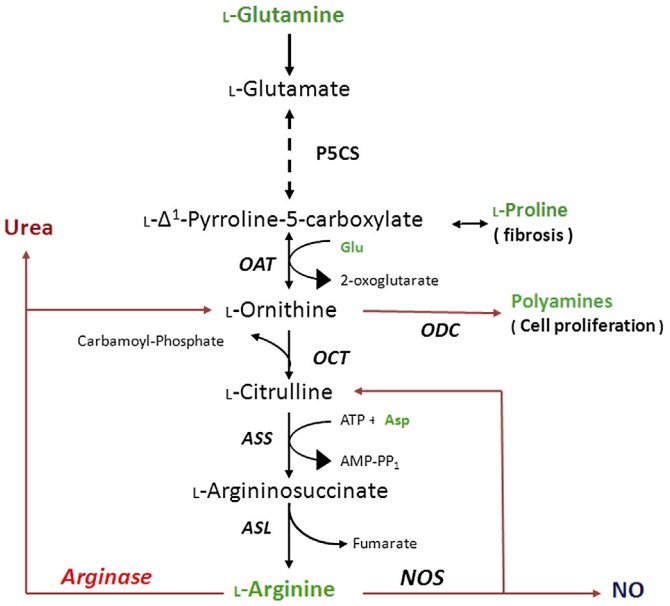

Fig. 2. Scheme for synthesis of L-arginine from L-glutamine. Also shown are catabolism of L-arginine to L-ornithine/urea or L-citrulline/NO, production of polyamines and anabolism and catabolism of proline. Abbreviations: ASL, aminosuccinate lyase; ASS, aminosuccinate synthase; Asp, aspartate; NOS, nitric oxide synthase; OAT; ornithine aminotransferase; ODC, ornithine decarboxylase; OCT, orthinine carbomoyltraferase; P5CS, pyrroline-5-carboxylate synthase.

When arginase activity is elevated it can compete with NOS for their common substrate, L-arginine. L-arginine is a semi-essential amino acid and when the supply needed for NOS activity is insufficient, NOS can become uncoupled (Romero et al., 2008; White et al., 2006). Uncoupled NOS will use more molecular oxygen to form superoxide which will react with any available NO to form peroxynitrite, leading to further decreases in NO (Fig. 3). These effects of arginase become pathologically significant when its activity and expression are elevated in diseases such as diabetes, hypertension and aging. In these conditions endothelial-dependent vasorelaxation is impaired and vascular smooth muscle cell proliferation and vascular and perivascular fibrosis can occur (Yang and Ming, 2006). Arginase activity and expression have been shown to be enhanced by inflammatory processes and reactive oxygen species associated with disease states (Morris, 2009; Munder, 2009).

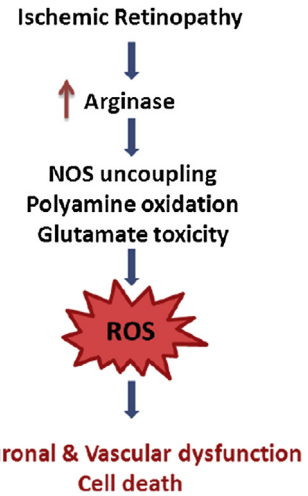

Fig. 1. Working model for suggested mechanisms of arginase-induced retinal neurovascular dysfunction and death.

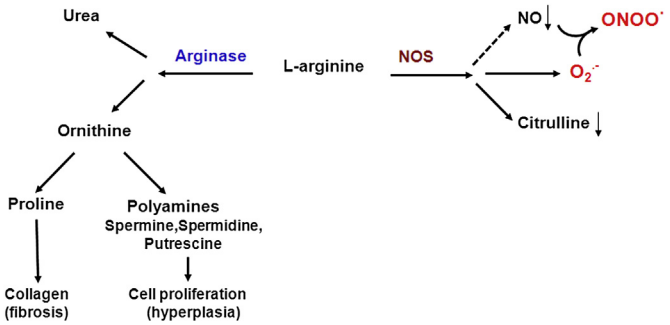

Fig. 3. Impact of the arginase pathway on NOS function and ROS formation.