MINI REVIEW

Endothelin: a new vasoactive ocular peptide

**The retinal vasculature and autoregulation**
The tone of most blood vessels in the body is regulated by means of the autonomic nervous system. The vasculature of the human retina, however, lacks extrinsic innervation even though autonomic receptors are present in the walls. Vessel calibre and local blood flow are normally regulated by non-nervous mechanisms intrinsic to the retina. This autoregulatory process helps preserve a uniform retinal blood flow in the presence of a variable perfusion pressure and matches it to tissue oxygen and metabolic requirements. The failure of autoregulation is an important and often early feature of retinal vascular disease and can be influenced in some instances by laser photoagulation, for example diabetic retinopathy.

**Retinal pericytes**
The effector cells in autoregulation are the vascular smooth muscle (VSM) cells, and their tone and active contraction control vessel diameter, blood flow, and tissue oxygen levels. In most mammalian circulations the precapillary arteriolar sphincters play a pivotal role in the control of blood flow to the capillary bed. However these strategic collars of smooth muscle cells are not a feature of the retinal circulation in the primate eye. There is now a considerable body of evidence to suggest that retinal pericytes, which are the microvascular correlates of VSM cells, are responsible for changes in retinal capillary tone and local blood flow. Pericytes have been shown to contain the smooth muscle isoforms of both actin and myosin and cGMP dependent protein kinase, thus providing further documentation of morphological and biochemical similarities to smooth muscle and for a contractile role. Pericytes have also been shown to deform substrata in vitro demonstrating that these cells have the potential to contract and exert significant amounts of traction in vivo.

**Endothelin 1: an endothelium-derived vasoactive agent**
It is now known that vascular endothelium can influence vascular tone and blood flow by the production of potent vasodilators and vasoconstrictors which affect the underlying smooth muscle. In 1988 Yanagisawa et al isolated and characterised an endothelium-derived 21 amino acid vasoconstrictor polypeptide which they termed endothelin. Endothelin is a member of a family of peptides arising from three preproendothelin species which, after proteolysis, yield three isoforms termed endothelin 1, 2, and 3 (ET1, ET2, and ET3). ET1 is the most potent constrictor known of large and small vessels particularly those of the kidney and has major biological effects on VSM cells and the renal mesangial cell which is a pericyte. The mechanism of action of ET1, which has been extensively studied in the renal mesangial cell, suggests that ET1 induced contraction occurs as a result of pharmacomechanical coupling to ET1 receptors with activation of the phosphoinositide cascade involving phospholipase A2 to produce prostaglandins E2, F2α and thromboxane A2. ET1 immunoreactivity has been demonstrated in the vasculature of a wide variety of tissues including brain indicating widespread presence of the peptide. The identification of ET1 mRNA in the neurons of the hypothalamus has suggested a neuromodulatory function for this peptide and stimulated interest in its potential role in ocular tissues.

**ET1 and ocular tissues**
ET1 binding sites have been demonstrated in the ciliary body and the peptide, when injected intracameral, has been shown to increase outflow facility suggesting that it may be involved in the physiological control of ciliary body function and aqueous outflow. Recent studies have shown that ET1 stimulates the release of arachidonic acid and prostaglandins in rabbit iris smooth muscle with activation of phospholipase A2. The capacity of ET1 to increase eicosanoid production by uveal tissue is an indicator of its potential as a mediator of vascular responses in inflammation.

**ET1 and retinal vascular autoregulation**
It is known that ET1 can augment the production of endothelin derived nitric oxide and prostacyclin both of which are potent vasodilators, allowing vascular endothelium to exercise molecular control over vessel tone and diameter, thereby regulating local blood flow. It has recently been shown that cultured retinal capillary endothelial cells secrete ET1 and corresponding pericytes bear receptors for this peptide, suggesting the presence of a specific interactive system for the regulation of retinal capillary blood flow in a circulation which shows no evidence of extrinsic innervation. ET1 exerts its maximal effect at the abluminal aspect of the endothelium/smooth muscle/pericyte interface and, accordingly, intravenously administered ET1 does not cause an increase in cerebrovascular resistance owing to the presence of the blood brain barrier. A similar effect would be expected in the retinal circulation and indeed it has been shown that isolated preparations of retinal branches of bovine short posterior ciliary arteries exhibit rapid, reversible, and repeatable contractions in response to abuminally applied ET1. In contrast ET1 induced contractions in vascular preparations of human isolated resistance vessels and cat middle cerebral arteries are long-lived, relaxation is slow, and the vessels are refractory to further ET1 stimulation. The reasons for this disparity are unclear as vascular smooth muscle cells, renal mesangial pericytes, and bovine retinal capillary pericytes (BRCP) respond in vitro to ET1 stimulation by prolonged contraction which is maintained for periods of up to 2 hours after removal of agonist. Moreover ET1 binding studies on BRCP have revealed that the binding sites are of high affinity with equilibrium dissociation constants in the nanomolar range. The binding is therefore not easily reversible so accounting for the prolongation of the observed contractile response. The easily reversible contraction seen in posterior ciliary vessels in response to ET1 in the above mentioned study suggests the presence of a subtype of receptor rather than the receptor to ET1. The significance of such findings is open to speculation and indicates a differential responsiveness of the various circulatory beds to ET1.
ET1 and hyperglycaemia

Recent studies have shown that vascular endothelium maintained in vitro under conditions of hyperglycaemia simulating diabetes releases less ET1 than under normoglycaemic conditions,28 and pericytes cultured in high levels of glucose exhibit reduced contractility to ET1 stimulation.28 These observations suggest that ET1 production by vascular endothelium and the contractile response of the underlying effector cells may be flawed in diabetes and possibly implicated in the pathogenesis of diabetic microangiopathy.

ET1 and retinal vascular endothelial-cell-pericyte responses

Endothelial cell-pericyte interactions are now considered at least in part to be responsible for the biological control of endothelial cell proliferation as shown by electron microscopic studies of growing blood vessels in healing wounds,2,29 and in experimental choroidal neovascularisation.39 There is a growing body of evidence that endothelial cells and pericytes influence each other’s replicative and biosynthetic behaviour,29 and co-culture of these cells results in activation of transforming growth factor β (TGFβ) which in turn inhibits endothelial cell proliferation.30 TGFβ itself can cause increased transcription of ET1 mRNA showing that biofeedback mechanisms exist allowing these growth factors to influence each other’s production and participate in cellular interactions.31 As ET1 is known to have mitogenic effects on retinal pericytes,32 it is interesting to speculate that activation of TGFβ in vivo can in turn increase the expression of ET1 mRNA thereby influencing pericyte replication, maintenance, and health. The complexity of such interactions involving growth factors such as ET1 and TGFβ has major implications in the pathophysiology of diseases such as diabetes and hypertension where there may be a derangement in endothelial cell-pericyte interactions with consequent effects on the function of the microcirculation. The study of retinal vasculature and retina derived growth factors should improve our understanding of disease pathogenesis and pave the way for the development of better therapeutic modalities.

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