

Roberts, Paul A.; Gaffney, Eamonn A.; Luthert, Philip J.; Foss, Alexander J. E.; Byrne, Helen M.

Retinal oxygen distribution and the role of neuroglobin. (English) Zbl 1343.92114
J. Math. Biol. 73, No. 1, 1-38 (2016).

Summary: The retina is the tissue layer at the back of the eye that is responsible for light detection. Whilst equipped with a rich supply of oxygen, it has one of the highest oxygen demands of any tissue in the body and, as such, supply and demand are finely balanced. It has been suggested that the protein neuroglobin (Ngb), which is found in high concentrations within the retina, may help to maintain an adequate supply of oxygen via the processes of transport and storage. We construct mathematical models, formulated as systems of reaction-diffusion equations in one-dimension, to test this hypothesis. Numerical simulations show that Ngb may play an important role in oxygen transport, but not in storage. Our models predict that the retina is most susceptible to hypoxia in the regions of the photoreceptor inner segment and inner plexiform layers, where Ngb has the potential to prevent hypoxia and increase oxygen uptake by 30–40%. Analysis of a simplified model confirms the utility of Ngb in transport and shows that its oxygen affinity (P_{50} value) is near optimal for this process. Lastly, asymptotic analysis enables us to identify conditions under which the piecewise linear and quadratic approximations to the retinal oxygen profile, used in the literature, are valid.

MSC:

92C35 Physiological flow
92C30 Physiology (general)
35K57 Reaction-diffusion equations

Cited in 2 Documents

Keywords:

asymptotics; facilitated diffusion; hypoxia; oxygen transport; reaction-diffusion equations

Full Text: [DOI](#)

References:

- [1] Alder, VA; Cringle, SJ; Constable, IJ, The retinal oxygen profile in cats, *Invest Ophthalmol Vis Sci*, 24, 30-36, (1983)
- [2] Anderson, B, Ocular effects of changes in oxygen and carbon dioxide tension, *Trans Am Ophthalmol Soc*, 66, 423-474, (1968)
- [3] Anderson, B; Saltzman, HA, Retinal oxygen utilization measured by hyperbaric blackout, *Arch Ophthalmol*, 72, 792-795, (1964) · doi:10.1001/archophth.1964.00970020794009
- [4] Bender CM, Orszag SA (1999) *Advanced mathematical methods for scientists and engineers I: asymptotic methods and perturbation theory*. Springer, Berlin · Zbl 0938.34001 · doi:10.1007/978-1-4757-3069-2
- [5] Bentmann, A; Schmidt, M; Reuss, S; Wolfrum, U; Hankeln, T; Burmester, T, Divergent distribution in vascular and avascular Mammalian retinae links neuroglobin to cellular respiration, *J Biol Chem*, 280, 20660-20665, (2005) · doi:10.1074/jbc.M501338200
- [6] Birol, G; Wang, S; Budzynski, E; Wangsa-Wirawan, ND; Linsenmeier, RA, Oxygen distribution and consumption in the macaque retina, *Am J Physiol Heart Circ Physiol*, 293, h1696-h1704, (2007) · doi:10.1152/ajpheart.00221.2007
- [7] Braun, RD; Linsenmeier, RA; Goldstick, TK, Oxygen consumption in the inner and outer retina of the cat, *Invest Ophthalmol Vis Sci*, 36, 542-554, (1995)
- [8] Burmester, T; Hankeln, T, Neuroglobin: a respiratory protein of the nervous system, *News Physiol Sci*, 19, 110-113, (2004)
- [9] Burmester, T; Hankeln, T, What is the function of neuroglobin?, *J Exp Biol*, 212, 1423-1428, (2009) · doi:10.1242/jeb.000729
- [10] Burmester, T; Weich, B; Reinhardt, S; Hankeln, T, A vertebrate globin expressed in the brain, *Nature*, 407, 520-523, (2000) · doi:10.1038/35035093
- [11] Burmester, T; Ebner, B; Weich, B; Hankeln, T, Cytoglobin: a novel globin type ubiquitously expressed in vertebrate tissues, *Mol Biol Evol*, 19, 416-421, (2002) · doi:10.1093/oxfordjournals.molbev.a004096
- [12] Chan, G; Balaratnasingam, C; Yu, PK; Morgan, WH; McAllister, IL; Cringle, SJ; Yu, DY, Quantitative morphometry of perifoveal capillary networks in the human retina, *Invest Ophthalmol Vis Sci*, 53, 5502-5514, (2012) · doi:10.1167/iovs.12-10265
- [13] Costa, LE; Mendez, G; Boveris, A, Oxygen dependence of mitochondrial function measured by high-resolution respirometry in long-term hypoxic rats, *Am J Physiol*, 273, c852-c858, (1997)
- [14] Cringle, SJ; Yu, DY, A multi-layer model of retinal oxygen supply and consumption helps explain the muted rise in inner retinal PO₂ during systemic hyperoxia, *Comp Biochem Physiol*, 132, 61-66, (2002) · doi:10.1016/S1095-6433(01)00530-X

- [15] Dollery, CT; Bulpitt, CJ; Kohner, EM, Oxygen supply to the retina from the retinal and choroidal circulations at normal and increased arterial oxygen tensions, *Invest Ophthalmol Vis Sci*, 8, 588-594, (1969)
- [16] Fago, A; Hundahl, C; Malte, H; Weber, RE, Functional properties of neuroglobin and cytoglobin. insights into the ancestral physiological roles of globins, *IUBMB Life*, 56, 689-696, (2004)· doi:10.1080/15216540500037299
- [17] Gillies, MC; Su, T; Naidoo, D, Electrical resistance and macromolecular permeability of retinal capillary endothelial cells in vitro, *Curr Eye Res*, 14, 435-442, (1995)· doi:10.3109/02713689509003753
- [18] Goldman, D, Theoretical models of microvascular oxygen transport to tissue, *Microcirculation*, 15, 795-811, (2008)· doi:10.1080/10739680801938289
- [19] Hamdane, D; Kiger, L; Dewilde, S; Green, BN; Pesce, A; Uzan, J; Burmester, T; Hankeln, T; Bolognesi, M; Moens, L; Marden, MC, The redox state of the cell regulates the ligand binding affinity of human neuroglobin and cytoglobin, *J Biol Chem*, 278, 51713-51721, (2003)· doi:10.1074/jbc.M309396200
- [20] Hardarson, SH; Stefánsson, E, Oxygen saturation in central retinal vein occlusion, *Am J Ophthalmol*, 150, 871-875, (2010)· doi:10.1016/j.ajo.2010.06.020
- [21] Hardarson, SH; Basit, S; Jonsdottir, TE; Eysteinnsson, T; Halldorsson, GH; Karlsson, RA; Beach, JM; Benediktsson, JA; Stefánsson, E, Oxygen saturation in human retinal vessels is higher in dark than in light, *Invest Ophthalmol Vis Sci*, 50, 2308-2311, (2009)· doi:10.1167/iovs.08-2576
- [22] Haugh, L; Linsenmeier, R; Goldstick, T, Mathematical models of the spatial distribution of retinal oxygen tension and consumption, including changes upon illumination, *Ann Biomed Eng*, 18, 19-36, (1990)· doi:10.1007/BF02368415
- [23] Jürgens, KD; Peters, T; Gros, G, Diffusivity of myoglobin in intact skeletal muscle cells, *Proc Natl Acad Sci*, 91, 3829-3833, (1994)· doi:10.1073/pnas.91.9.3829
- [24] Keener J, Sneyd J (1998) *Mathematical physiology*. Springer, Berlin · Zbl 0913.92009
- [25] Kiger, L; Uzan, J; Dewilde, S; Burmester, T; Hankeln, T; Moens, L; Hamdane, D; Baudin-Creuz, V; Marden, MC, Neuroglobin ligand binding kinetics, *IUBMB Life*, 56, 709-719, (2004)· doi:10.1080/15216540500037711
- [26] Kohen, R; Nyska, A, Invited review: oxidation of biological systems: oxidative stress phenomena, antioxidants, redox reactions, and methods for their quantification, *Toxicol Pathol*, 30, 620-650, (2002)· doi:10.1080/01926230290166724
- [27] Kur, J; Newman, EA; Chan-Ling, T, Cellular and physiological mechanisms underlying blood flow regulation in the retina and choroid in health and disease, *Prog Retin Eye Res*, 31, 377-406, (2012)· doi:10.1016/j.preteyeres.2012.04.004
- [28] Linsenmeier, RA, Effects of light and darkness on oxygen distribution and consumption in the cat retina, *J Gen Physiol*, 88, 521-542, (1986)· doi:10.1085/jgp.88.4.521
- [29] Linsenmeier, RA; Braun, RD, Oxygen distribution and consumption in the cat retina during normoxia and hypoxemia, *J Gen Physiol*, 99, 177-197, (1992)· doi:10.1085/jgp.99.2.177
- [30] Linsenmeier, RA; Padnick-Silver, L, Metabolic dependence of photoreceptors on the choroid in the normal and detached retina, *Invest Ophthalmol Vis Sci*, 41, 3117-3123, (2000)
- [31] Linsenmeier, RA; Yancey, CM, Effects of hyperoxia on the oxygen distribution in the intact cat retina, *Invest Ophthalmol Vis Sci*, 30, 612-618, (1989)
- [32] McGuire, BJ; Secomb, TW, A theoretical model for oxygen transport in skeletal muscle under conditions of high oxygen demand, *J Appl Physiol*, 91, 2255-2265, (2001)
- [33] Ockendon J, Howison S, Lacey A, Movchan A (2003) *Applied partial differential equations*, revised edn. Oxford University Press, Oxford · Zbl 1059.35001
- [34] Ostojić, J; Sakaguchi, DS; Lathouder, Y; Hargrove, MS; Trent, JT; Kwon, YH; Kardon, RH; Kuehn, MH; Betts, DM; Grozdanić, S, Neuroglobin and cytoglobin: oxygen-binding proteins in retinal neurons, *Invest Ophthalmol Vis Sci*, 47, 1016-1023, (2006)· doi:10.1167/iovs.05-0465
- [35] Ostojić, J; Grozdanić, SD; Syed, NA; Hargrove, MS; Trent, JT; Kuehn, MH; Kwon, YH; Kardon, RH; Sakaguchi, DS, Patterns of distribution of oxygen-binding globins, neuroglobin and cytoglobin in human retina, *Arch Ophthalmol*, 126, 1530-1536, (2008)· doi:10.1001/archophth.126.11.1530
- [36] Oyster CW (1999) *The human eye: structure and function*. Sinauer Associates Inc, Sunderland
- [37] Padnick-Silver, L; Linsenmeier, RA, Effect of acute hyperglycemia on oxygen and oxidative metabolism in the intact cat retina, *Invest Ophthalmol Vis Sci*, 44, 745-750, (2003)· doi:10.1167/iovs.02-0432
- [38] Pournaras, CJ; Rungger-Brändle, E; Riva, CE; Hardarson, SH; Stefánsson, E, Regulation of retinal blood flow in health and disease, *Prog Retin Eye Res*, 27, 284-330, (2008)· doi:10.1016/j.preteyeres.2008.02.002
- [39] Rajendram, R; Rao, NA, Neuroglobin in normal retina and retina from eyes with advanced glaucoma, *Br J Ophthalmol*, 91, 663-666, (2007)· doi:10.1136/bjo.2006.093930
- [40] Richmond, KN; Shonat, RD; Lynch, RM; Johnson, PC, Critical PO(2) of skeletal muscle in vivo, *Am J Physiol Heart Circ Physiol*, 277, h1831-h1840, (1999)
- [41] Roh, HD; Goldstick, TK; Linsenmeier, RA, Spatial variation of the local tissue oxygen diffusion coefficient measured in situ in the cat retina and cornea, *Adv Exp Med Biol*, 277, 127-136, (1990)· doi:10.1007/978-1-4684-8181-5_7
- [42] Schmidt, M; Giessl, A; Laufs, T; Hankeln, T; Wolfrum, U; Burmester, T, How does the eye breathe?, *J Biol Chem*, 278, 1932-1935, (2003)· doi:10.1074/jbc.M209909200
- [43] Schmidt, M; Laufs, T; Reuss, S; Hankeln, T; Burmester, T, Divergent distribution of cytoglobin and neuroglobin in the murine eye, *Neurosci Lett*, 374, 207-211, (2005)· doi:10.1016/j.neulet.2004.10.071
- [44] Stefánsson, E, Retinal oxygen tension is higher in light than dark, *Pediatr Res*, 23, 5-8, (1988)· doi:10.1203/00006450-

- [45] Swaroop, A; Kim, D; Forrest, D, Transcriptional regulation of photoreceptor development and homeostasis in the Mammalian retina, *Nat Rev Neurosci*, 11, 563-576, (2010)· doi:10.1038/nrn2880
- [46] Tan, PEZ; Yu, PK; Balaratnasingam, C; Cringle, SJ; Morgan, WH; McAllister, IL; Yu, DY, Quantitative confocal imaging of the retinal microvasculature in the human retina, *Invest Ophthalmol Vis Sci*, 53, 5728-5736, (2012)· doi:10.1167/iovs.12-10017
- [47] Törnquist, P; Alm, A; Bill, A, Permeability of ocular vessels and transport across the blood-retinal-barrier, *Eye*, 4, 303-309, (1990)· doi:10.1038/eye.1990.41
- [48] Trent, JT; Hargrove, MS, A ubiquitously expressed human hexacoordinate hemoglobin, *J Biol Chem*, 277, 19538-19545, (2002)· doi:10.1074/jbc.M201934200
- [49] Wangsa-Wirawan, ND; Linsenmeier, RA, Retinal oxygen: fundamental and clinical aspects, *Arch Ophthalmol*, 121, 547-557, (2003)· doi:10.1001/archophth.121.4.547
- [50] Wilson, DF; Rumsey, WL; Green, TJ; Vanderkooi, JM, The oxygen dependence of mitochondrial oxidative phosphorylation measured by a new optical method for measuring oxygen concentration, *J Biol Chem*, 263, 2712-2718, (1988)
- [51] Yu, DY; Cringle, SJ, Oxygen distribution and consumption within the retina in vascularised and avascular retinas and in animal models of retinal disease, *Prog Retin Eye Res*, 20, 175-208, (2001)· doi:10.1016/S1350-9462(00)00027-6
- [52] Yu, DY; Cringle, SJ, Outer retinal anoxia during dark adaptation is not a general property of Mammalian retinas, *Comp Biochem Physiol*, 132, 47-52, (2002)· doi:10.1016/S1095-6433(01)00528-1
- [53] Yu, DY; Cringle, SJ, Retinal degeneration and local oxygen metabolism, *Exp Eye Res*, 80, 745-751, (2005)· doi:10.1016/j.exer.2005.01.018
- [54] Yu, DY; Cringle, SJ; Alder, VA; Su, EN, Intraretinal oxygen distribution in rats as a function of systemic blood pressure, *Am J Physiol Heart Circ Physiol*, 267, h2498-h2507, (1994)
- [55] Yu, DY; Cringle, SJ; Alder, V; Su, EN, Intraretinal oxygen distribution in the rat with graded systemic hyperoxia and hypercapnia, *Invest Ophthalmol Vis Sci*, 40, 2082-2087, (1999)
- [56] Yu, DY; Cringle, SJ; Su, EN; Yu, PK, Intraretinal oxygen levels before and after photoreceptor loss in the RCS rat, *Invest Ophthalmol Vis Sci*, 41, 3999-4006, (2000)
- [57] Yu, DY; Cringle, S; Valter, K; Walsh, N; Lee, D; Stone, J, Photoreceptor death, trophic factor expression, retinal oxygen status, and photoreceptor function in the P23H rat, *Invest Ophthalmol Vis Sci*, 45, 2013-2019, (2004)· doi:10.1167/iovs.03-0845
- [58] Yu, DY; Cringle, SJ; Su, EN, Intraretinal oxygen distribution in the monkey retina and the response to systemic hyperoxia, *Invest Ophthalmol Vis Sci*, 46, 4728-4733, (2005)· doi:10.1167/iovs.05-0694

This reference list is based on information provided by the publisher or from digital mathematics libraries. Its items are heuristically matched to zbMATH identifiers and may contain data conversion errors. It attempts to reflect the references listed in the original paper as accurately as possible without claiming the completeness or perfect precision of the matching.