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Multiscale modeling and simulation of neurovascular coupling in the retina

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Abstract

The role of nitric oxide (NO), usually considered as a potent vasodilator, in regulating retinal neurovascular coupling is still elusive. Measurements of flicker light-induced functional hyperemia (FH) in humans show that an increase of NO levels reduces vasodilation. This evidence has led to conjecture that such an increase may be responsible for suppressing flicker-evoked vasodilation in diabetic retinopathy. In this paper, we propose a mathematical model to theoretically investigate the effect of an increase in neural NO (nNO) on the vasodilation of retinal arterioles. Simulation results indicate that nNO increase may:

1. significantly affect vasoconstrictive agent production by glial cells; and
2. elicit vasoconstriction rather than vasodilation in retinal arterioles.

Model predictions seem therefore to support the conjecture that NO increase may be responsible for suppressing flicker-evoked vasodilation in diabetic retinopathy.

Keywords: mathematical modeling, retinal dysfunction, retinal regulation, visual neuroscience

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1. Introduction

The multiscale nature of the human body system covers a wide spectrum with respect to both time and space variables. The time scale ranges from nanoseconds to years, whereas the space scale ranges from nanometers to meters. Such hierarchical and complex structure is representative also of the eye as an organ, whose physiology in health and disease is still far from being fully understood.

In this article, we illustrate the simulation results obtained using the multiscale/multiphysics mathematical model proposed in Cardani[1] and presented in Sacco *et al.*,[2] with the goal of exploring the role of nNO, jointly with 20-hydroxyeicosatetraeonic acid (20-HETE) and epoxyeicosatrienoic acid (EET), in the regulation of retinal neurovascular coupling (NVC).

The analysis is motivated by experimental data on flicker light-induced FH in humans, indicating that increased NO levels mediated by 20-HETE reduce vasodilation.[3] The aim of our investigation is to employ the computational tool to provide quantitative predictions of the effect of an increase of nNO on the vasodilation of retinal arterioles in order to assess the validity of the conjecture that increased NO levels may be responsible for suppressing flicker-evoked vasodilation in diabetic retinopathy.[4]

2. Methods

The concept of multiscale modeling proposed to represent retinal microcirculation and regulation mechanisms is illustrated in Figure 1. Retinal vasculature is described by the equivalent electrical circuit illustrated in Figure 2. NVC is described by the interaction between vasoactive agents synthesized by active neurons, and astrocytes and smooth muscle cell (SMC) contraction/dilation. Model inputs are blood pressure at the central retinal artery and vein, intraocular pressure, nNO, and glutamate (GLU) postsynaptic levels. Kirchhoff current law is solved at each node of the circuit to determine the time evolution of nodal blood pressures and compartment diameters.

Model inputs are:

1. P_{in}, P_{out}: inlet/outlet retinal vasculature pressures. Baseline: P_{in} = 30 mmHg; P_{out} = 15 mmHg.
2. GLU: glutamate synthesized by post-synaptic terminal. Baseline: GLU = 0 μM.
3. nNO: NO synthesized by a nearby neuron. The amounts δ*nNO and (1 - δ)*nNO are delivered to astrocytes and SMCs, respectively. Baseline: nNO = 1 μM; δ = 0.99.

The neurochemical model block has been validated against results reported in Hadfield *et al.*,[5] whereas the model biomechanical block has been validated against results reported in Kudryashov and Chernyasvskii.[6]

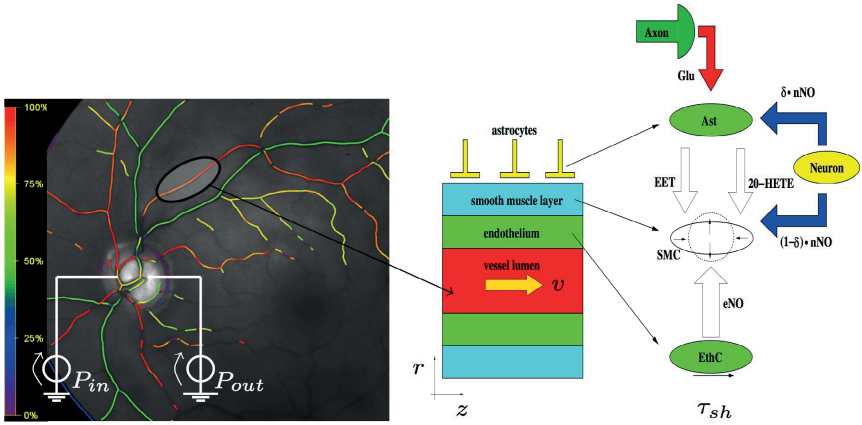

Fig.1. Multiscale model of retinal circulation utilized to assess the contributions of blood flow shear stress (τsh), nNO, 20-HETE, and EET on retinal NVC. Also shown: astrocytes (Ast); smooth muscle cell (SMC); endothelial cell (EthC). Microscale biochemistry adapted from Attwell *et al.*[7]

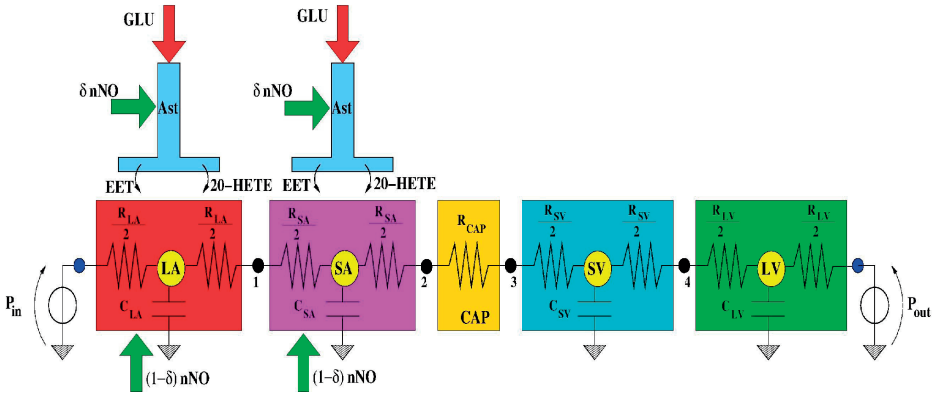

Fig.2. Equivalent electrical circuit for the simulation of retinal NVC. Among the five vascular compartments — large arterioles (LA), small arterioles (SA), capillaries (CAP), small venules (SV), and large venules (LV) — only LA and SA are active.

3. Results

We consider the experimental data set of Newman[3] on the response to flicker-light stimulation in humans. We use the model to investigate the conjecture of Metea and Newman[4] that NO increase may be responsible for suppressing flicker-evoked vasodilation in diabetic retinopathy.

3.1. Clinical data

FH in the retina of five healthy subjects was studied via arterial diameter response to flicker-light stimulation (signal frequency: 12.5 Hz; wavelength: 530–600 nm; duration: 20 s).[4] Maximum dilation was approximately 8%, whereas maximum constriction was approximately 4% (Figs. 4 and 5, black circles correspond to the clinical data). A conjecture was then proposed on how NO modulates NVC *in vivo*, particularly that NO increase may be responsible for suppressing flicker-evoked vasodilation in diabetic retinopathy.

3.2. Comparison between clinical data with model predictions

Figure 3 illustrates how flicker-light application is modeled by a triangular GLU stimulus of 0.07 μM for 20 s. Simulations were performed for the two different reported nNO levels (Fig. 3, black and red curves, bottom panel). Figure 4 shows a comparison of % LA mean diameter change between clinical data[3] (Fig. 4, black circles) and model simulations obtained when two different segments are vasoactive. Model predictions match data only if both LA and SA are vasoactive. Figure 5 shows a comparison of % LA mean diameter change between clinical data[3] (Fig. 5; black circles) and model simulations obtained for different nNO levels. Results show that elevated nNO may reduce vasodilation by a factor of 4.

4. Conclusion

Multiscale simulations of NVC in the retina indicate that:

1. NVC has a noticeable impact on functional hyperemia in the human retina, showing that only if both LA and SA are vasoactive, clinical data on flicker-light stimulation[3] can be correctly reproduced; and
2. nNO increase above baseline significantly affects EET production by glial cells (even by a factor of 4), contributing to elicit vasoconstriction rather than vasodilation, in agreement with data reported in Metea and Newman.[4]

Model predictions seem therefore to support the conjecture that increased NO levels may be responsible for suppressing flicker-evoked vasodilation in diabetic retinopathy.[4]

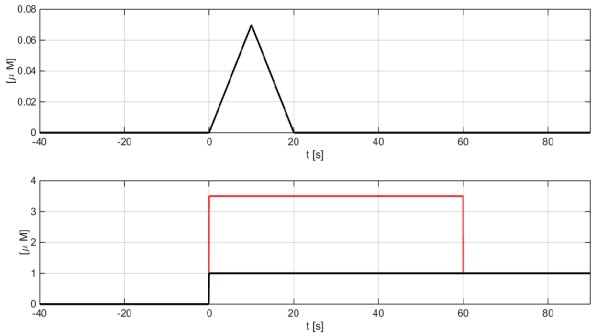

Fig. 3. Time evolution of GLU and nNO input signals.

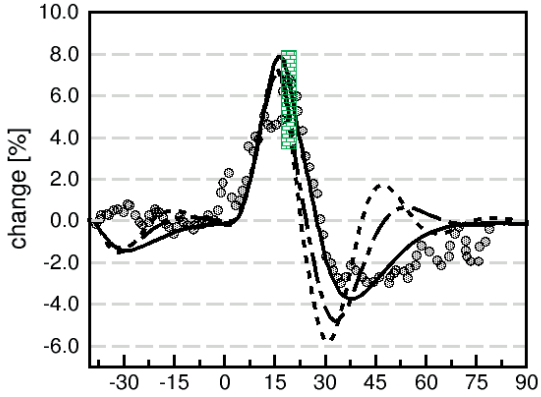

Fig. 4. Simulated effect of vasoactive segments on FH.

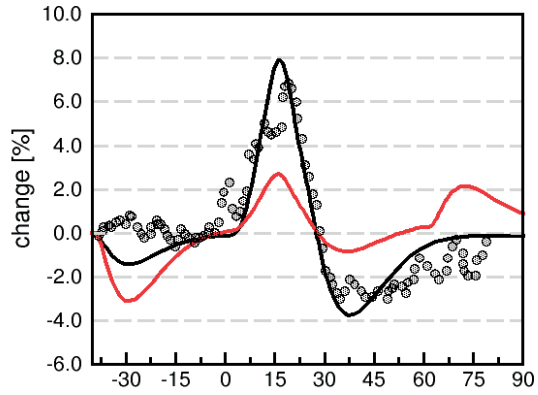

Fig. 5. Simulated effect of nNO level on FH.

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