Propagation of Vasoconstrictive Responses In A Mathematical Model of the Rat Afferent Arteriole

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Abstract

We have formulated a mathematical model for the rat afferent arteriole (AA). Our model consists of a series of arteriolar smooth muscle cells, each of which represents ion transport, cell membrane potential, cellular contraction, gap junction coupling, and wall mechanics. Blood flow through the AA lumen is described by Poiseille flow. Model results suggest that interacting calcium and potassium fluxes, mediated by voltage-gated and voltage-calcium-gated channels, respectively, give rise to periodic oscillations in cytoplasmic calcium concentration, myosin light chain phosphorylation, and crossbridge formation with attending muscle stress mediating vasomotion. The AA model's representation of the myogenic response is based on the hypothesis that the voltage dependence of calcium channel openings responds to transmural pressure so that vessel diameter decreases with increasing pressure. With this configuration, the results of the AA model simulations agree well with findings in the experimental literature, notably those of Steinhausen et al. (J Physiol 505:493, 1997), which indicated that propagated vasoconstrictive response induced by local electrical stimulation decayed more rapidly in the upstream than in the downstream flow direction. The model can be incorporated into models of integrated renal hemodynamic regulation. This research was supported in part by NIH grants DK-42091 and DK-89066, and by NSF grant DMS-0715021.

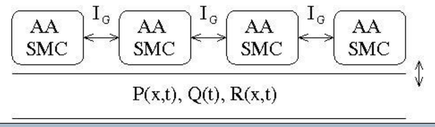
Introduction

Propagated vasomotor responses are believed to be of importance in the coordination of the microsovascular tone. Steinhausen et al. (1997) analyzed propagation of vasomotor responses, induced by local electrical stimulation, in split hydronephrotic rat kidneys. Their results indicate that the responses decay with increasing distance from the stimulation site, and that the decay is significantly faster upstream than downstream. The reason for the asymmetric decay rates remains to be elucidated.

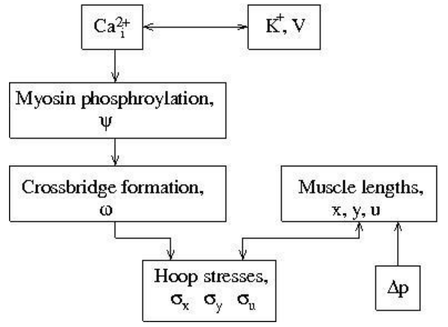
This study presents a detailed mathematical model of the myogenic response of an AA . In the model, the myogenic mechanism includes a rate-dependent component that generates responses to changes in both mean and systolic blood pressure. The model is used to study the AA's response local electrical stimulation.

Mathematical Model: AA Smooth Muscle Cells and Vessel

The model consists of a series of 100 AA smooth muscle cells (SMCs), whose membrane potentials are coupled via their gap junctions.
P, pressure;
Q, flow;
R, radius.



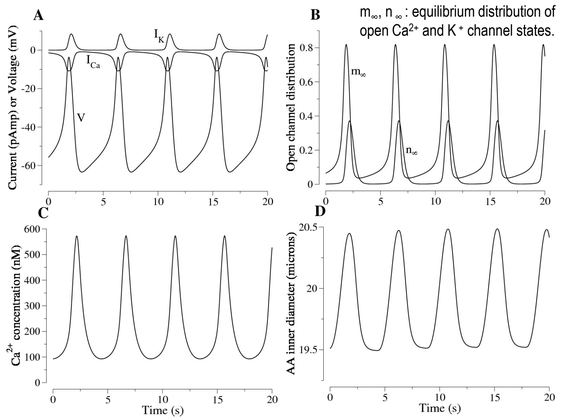
The AA cell model (Chen et al. 2011) simulates the interactions among voltage-sensitive Ca^{2+} channels, Ca^{2+}- and voltage-sensitive K^+ channels, and the membrane potential. The oscillations in free cytosolic Ca^{2+} concentration vary the phosphorylation of the 20-kDa myosin light chains, which are involved in the formation of cross-bridges and smooth muscle contraction.



Fluid flow through the AA lumen is represented by Poiseuille flow.

Spontaneous Vasomotion in an AA Smooth Muscle Cell

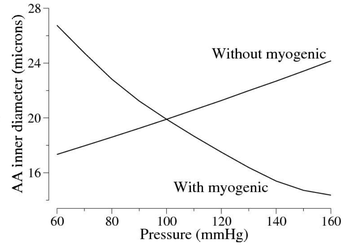
The model predicts that the asynchrony between the Ca^{2+} and K^+ currents gives rise to oscillations in the SMC membrane potential, ionic currents, and the vessel's diameter. The frequency of the oscillations is ~175 mHz, and the amplitude of the vessel diameter oscillations is ~1 micron.



Mathematical Model: Myogenic Response

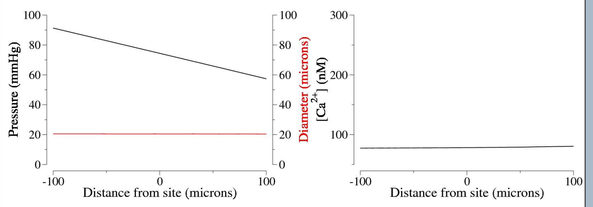
Our model of the AA myogenic response is based on the hypothesis that the dependence of Ca^{2+} channel openings on voltage is shifted by changes in transmural pressure P. Thus, we assume that v_1, the voltage associated with the opening of half of the Ca^{2+} channels, is a decreasing function of P.

FIGURE. Average vessel diameter as a function of steady-state transmural pressure, with or without myogenic response.

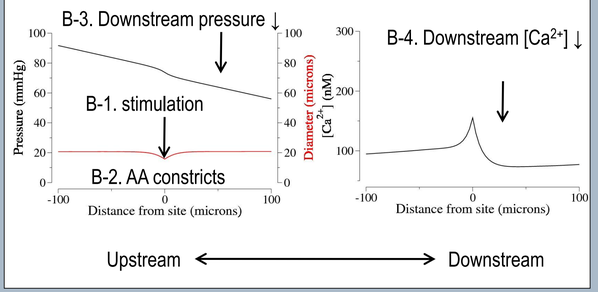


Propagation of Vasoconstrictive Responses

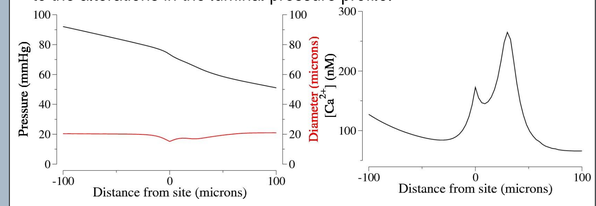
A. time = 0 s. Before electrical stimulation: ~ linear drop in pressure, vascular diameter and intracellular $[Ca^{2+}]$ oscillating around constant means.

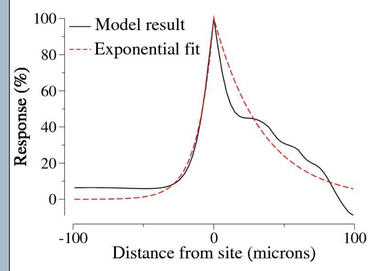


B. time = 25 s.
B-1. Local electrical stimulation applied;
B-2: AA constricts locally;
B-3: Downstream pressure decreases;
B-4: Myogenic response induces a decrease in downstream intracellular $[Ca^{2+}]$.



C. time = 50 s. Vasomotor response propagates via electrotonic conduction. Asymmetry arises from amplification of membrane potential and cytosolic $[Ca^{2+}]$ changes, induced by the local myogenic responses to the alterations in the luminal pressure profile.





The model predicts that vasomotor responses decay more rapidly upstream. The upstream and downstream decays are approximated by exponential functions with length constants of 751 and 288 μm. Steinhausen et al. (1997) measured slower decay constants of 420 and 150 μm, using a stronger stimulus in a vascular tree that comprised mostly of cortical radial artery. Nonetheless, our model predicts a length-scale ratio (2.61) similar to Steinhausen et al. (2.80).

Summary

1. We have developed a multi-cell model for a rat renal afferent arteriole (AA) and a model for the AA's myogenic response.
2. The model myogenic response is based on the hypothesis that the voltage associated with the opening of half of the calcium channels is a decreasing function of transmural pressure.
3. Vasomotor responses, induced by local electrical stimulation, propagate via electrotonic conduction.
4. Vasomotor responses decay with increasing distance from the stimulation site, more rapidly in the upstream flow direction than downstream. That asymmetry arises from amplification of membrane potential and cytosolic $[Ca^{2+}]$ changes, induced by local myogenic responses to the alterations in luminal pressure.

References

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