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Neurocomputing 70 (2007) 1674–1679
NEUROCOMPUTING
www.elsevier.com/locate/neucom

A computational model relating changes in cerebral blood volume to synaptic activity in neurons

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Available online 10 November 2006

Abstract

Brain imaging methods, and in particular fMRI (functional Magnetic Resonance Imaging), do not detect neural activity directly, but rather changes in blood flow and oxygenation in neighboring blood vessels, this being the BOLD (Blood Oxygenation Level Dependent) effect. We have constructed a model of the steps leading from neural activity to increased blood flow in arterioles, in which astrocytes play a crucial role. Glutamate released from neuronal synapses binds to metabotropic receptors on the astrocyte processes that ensheath these synapses. This initiates a calcium wave that travels along the endfeet of astrocytes that abut the endothelial cells forming the walls of blood capillaries; this calcium wave is propagated by the extracellular diffusion of ATP (adenosine triphosphate) that acts on metabotropic purinergic receptors on the astrocytes. A further second messenger (taken to be nitric oxide) relays this signal to the smooth muscle cells forming the outer walls of arterioles, and the subsequent wave of hyperpolarization reduces calcium influx and allows relaxation of the muscle cells and hence increased blood flow. The model gives results that are in agreement with experimental measurements of blood volume changes in the arterioles in the visual cortex of optically stimulated cats.

Keywords: Blood volume; Astrocytes; Capillaries; Calcium waves

1. Introduction

The assumption that there is a tight coupling between neural activity and blood flow and oxygenation underlies the interpretation of brain images produced by modern non-invasive techniques, particularly fMRI (functional Magnetic Resonance Imaging) [5]. However, this assumption has recently come under critical scrutiny, with some commentators going so far as to compare the brain maps constructed using fMRI to the maps of mental function deduced from the presence of lumps on the skull by nineteenth-century phrenologists [12]. Given that fMRI is increasingly being used as a non-invasive way of visualizing brain function, both in the normal brain in order to gain insight into cognitive function and also in the diseased brain in order to detect changes related to neurodegenerative diseases, a detailed understanding of the neurophysiology underlying the fMRI signal is vital. The wrong interpretation of the resulting scans could lead to misdiagnoses of brain diseases or the incorrect implementation of surgical procedures on the brain. Some questions that need to be addressed concern spatial specificity (the accuracy of maps generated by fMRI compared with the actual sites of neural activity), temporal correlations (the relation between the time course of the fMRI signal and the time course of neural activity), linearity of response (the magnitude of the signal as a function of neural activity) and the very basic problem of the signal being generated mainly by neurons firing action potentials versus a substantial contribution from subthreshold behavior.

A central reason for controversy is that there is only an indirect, and at present incompletely understood, relation between what is seen on the screen and what is happening at the neuronal level. The basic problem is that fMRI detects changes in blood flow and oxygenation in cerebral blood vessels, and not electrical activity in neurons (Fig. 1). If the fMRI signal is indeed a true reflection of neural activity then there must be some mechanism for information to pass from a neuron to the neighboring capillaries

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doi:10.1016/j.neucom.2006.10.071

and arterioles supplying the blood. It is now becoming increasingly clear that a key element in this signalling process is the astrocyte (a type of glial cell that actually outnumbers neurons in the brain). The detailed processes by which astrocytes communicate between neurons and the endothelial cells of blood vessels are being clarified experimentally and there is now enough information for a start to be made on putting together the complete seq uence of steps in a quantitative and comprehensive model.

2. The model

We have constructed a model of process (3) in Fig. 1; that is, of the steps leading from neural activity to increased blood flow. It involves the following steps (Fig. 2): (A) neural activity leads to glutamate release at synapses; (B) this glutamate acts on metabotropic receptors on astrocytes leading to ATP (adenosine triphosphate) release; (C) extracellular diffusion and regeneration of ATP propagates a calcium wave along astrocyte endfeet in contact with a blood capillary; (D) a similar elevation of calcium causes nitric oxide to be released from endothelial cells; (E) nitric oxide diffuses to the arteriole interface and hyperpolarizes smooth muscle cells of the arteriole; (F) a hyperpolarization propagates electrotonically along the smooth muscle cells of the arteriole; (G) this leads to vasodilation and hence increased blood flow.

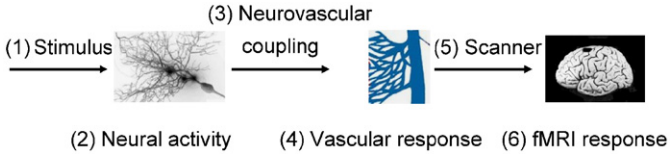

Fig. 1. An external stimulus (1) leads to increased neural activity (2). This is signalled to the vasculature by some pathway (3), leading to a change in blood flow and oxygenation (4) that is detected by an MRI scanner (5). These changes are quantified and shown as a color-coded image superimposed on a brain map (6).

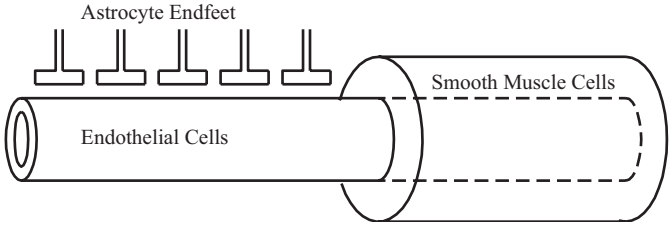

Fig. 2. Schematic diagram of model: astrocyte endfeet abuts the endothelial cells that form the wall of a blood capillary which then joins to an arteriole that has an outer layer of smooth muscle cells.

More detail of these steps: (A) It is assumed that neural activity leads to a step release of glutamate.

(B) The terminals of astrocyte processes form close contact with the synaptic connections between neurons. Hence glutamate, released at synapses, can readily bind to metabotropic receptors on the astrocytes, initiating a G-protein cascade that triggers both the release of Ca^{2+} from internal stores and the also release of ATP from the astrocytes into the extracellular space (Fig. 3(A)). A crucial step in both these processes is the release of IP_3 (inositol trisphosphate) into the cytosol. The steps leading from metabotropic receptor activation to IP_3 release are well known, and we use the theory developed in [11]. The mechanism for the release of ATP, however, is still unknown, but there is evidence that IP_3 rather than Ca^{2+} is the activating agent (see the discussion in [3]). We have therefore assumed that ATP is released from an astrocyte endfoot into the extracellular space at a rate given by [3]

$$V_{\mathrm{ATP}}\chi(t)\frac{[\mathrm{IP_3}]-[\mathrm{IP_3}]_{\min}}{K_{\mathrm{rel}}+[\mathrm{IP_3}]},$$

where V_{ATP} and R_{rel} are constants and $[\mathrm{IP_3}]_{\min}$ is the level of $[\mathrm{IP_3}]$ required before release occurs. The function $\chi(t)$

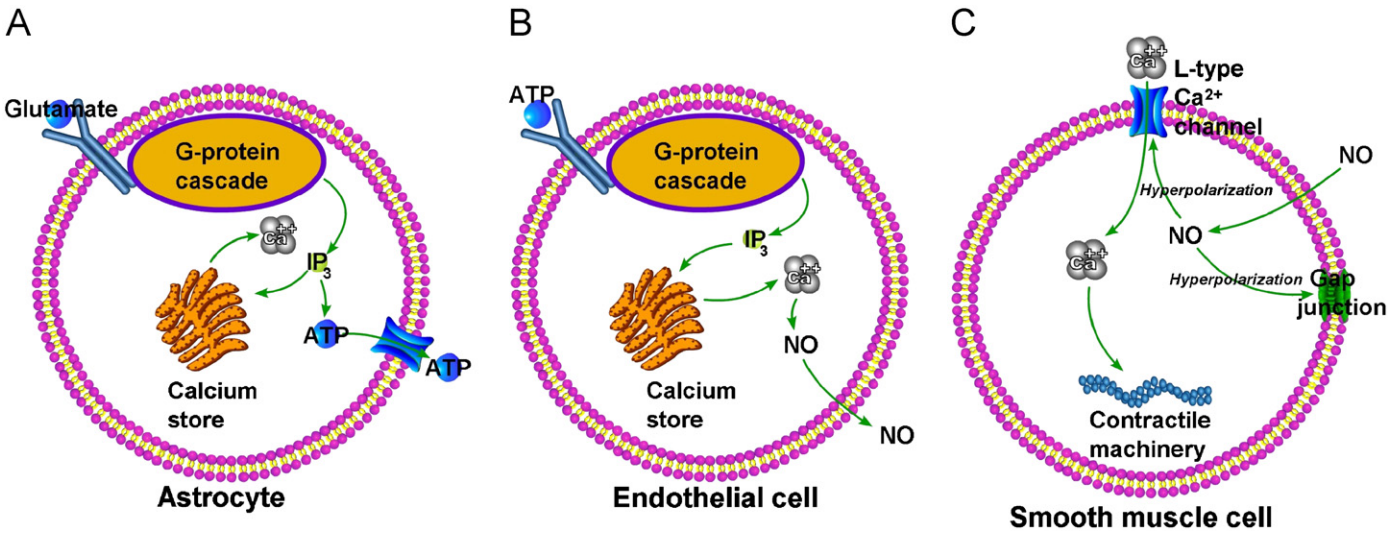

Fig. 3. Schematic diagrams of the cell types used in the modelling.