Evidence that Neuronal Signaling and not Energy Consumption Controls the Hemodynamic Response

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ABSTRACT

We examined bilateral neuronal and hemodynamic changes, and observed evidence of spatiotemporal brain imaging in response to unilateral somatosensory stimuli in the primary somatosensory cortex (SI). In contrast to the contralateral forepaw area where neuronal activity, blood oxygenation/flow and deoxyglucose uptake increase in unison, we observed bilateral oxygenation/flow decrease and arterial vasodilatation in response to increased deoxyglucose uptake in the ipsilateral hemisphere. Oxygen-sensitive dye measurements revealed a bilateral decrease in deoxyglucose uptake and hyperpolarization bilaterally. Relative to the initial deolpolarization hyperpolarization was stronger on the ipsilateral side, suggesting stronger recruitment of inhibitory interneurons in ensemble response.

Laminar electrophysiologic recordings revealed an increase in ipsilateral spiking consistent with the observed increase in deoxyglucose uptake. The vasocostriction and decrease in blood flow in response to an increase in both neuronal spiking and deoxyglucose uptake in ipsilateral SI argues against feedback signaling by energy metabolites. Rather, our results are consistent with feed forward neuronal control of vasodilatation and vasocostriction.

Decreases in blood oxygenation and flow are observed in ipsilateral SI.

RESULTS

Figure 1. Bilateral hemodynamic optical imaging reveals a decrease in ipsilateral blood oxygenation and flow

(A) HbO, Hb, and speckle contrast images following stimulus onset (red). The color scale is expressed as percent signal change relative to pre-stimulus baseline (left). The baseline concentrations of 60 μM and 40 μM for HbO and Hb, respectively. An image of raw vasculature corresponding to the time frame is shown in upper left corner. (B) Bilateral hemodynamic optical imaging reveals a decrease in ipsilateral blood oxygenation and flow (red) and a relative increase in contralateral blood oxygenation and flow (blue) (12). The top panel shows the spatial extent and time course of the hemodynamic optical imaging responses. (C) The baseline is defined as the average signal intensity for the entire image at the baseline. Each trace represents a recording from one single electrode in the array. The traces are overlaid on 2-photon image of vasculature within the exposure. The image of raw vasculature is shown in upper left corner. (D) The traces are overlaid on 2-photon image of vasculature within the exposure. The image of raw vasculature is shown in upper left corner.

Figure 2. Bilateral VSD imaging shows stronger relative hyperpolarization in ipsilateral hemisphere

(A) Consecutive VSD images following stimulus onset (left). The color scale is expressed as percent signal change relative to the baseline (right). The baseline concentration of 60 μM for HbO is shown. (B) Bilateral VSD imaging reveals a decrease in deoxyglucose uptake and hyperpolarization bilaterally. The relative to the initial depolarization hyperpolarization was stronger on the ipsilateral side, suggesting stronger recruitment of inhibitory interneurons in ensemble response. (C) The baseline is defined as the average signal intensity for the entire image at the baseline. Each trace represents a recording from one single electrode in the array. The traces are overlaid on 2-photon image of vasculature within the exposure. The image of raw vasculature is shown in upper left corner. (D) The traces are overlaid on 2-photon image of vasculature within the exposure. The image of raw vasculature is shown in upper left corner.

Figure 3. Laminar recordings of multiunit activity measure an increase in ipsilateral spiking

(A) Laminar profile of MUA response in contralateral (left panel) and ipsilateral (right panel) hemispheres. Each trace represents a recording from one single electrode in the array. Corresponding cortical depth is indicated on the left. 500 stimulus trials were averaged. (B) MUA from supragranular, granular and infragranular layers. The responding layer was estimated using the earliest response time. Each trace is overlaid on a 2-photon image of vasculature within the exposure. The image of raw vasculature is shown in upper left corner. (C) The traces are overlaid on 2-photon image of vasculature within the exposure. The image of raw vasculature is shown in upper left corner. (D) The traces are overlaid on 2-photon image of vasculature within the exposure. The image of raw vasculature is shown in upper left corner.

Figure 4. 2DG-autoradiography in response to a unilateral stimulus

(A) Sector map used for quantitative analysis is overlaid on a coronal brain section. The color scale is expressed in units of local cerebral metabolic rate of glucose, LCMRglu (μmol/100g/min). (B) Cortical glucose utilization profile as a function of sector number. The direction is from close to the medial ridge (sector 1) to the most lateral part of the hemisphere (sector 20). Profiles from contralateral (blue) and ipsilateral (red) hemisphere, posterior to the active area (green), and control subjects (no stimulus, black) are superimposed. The profiles were extracted from each sector and normalized to the mean sector intensity before averaging. Y-axis is expressed as % change relative to mean sector intensity. Data points statistically significant from the control (p<0.05) are indicated by stars. (C) Raw (not normalized) profiles extracted from contralateral hemisphere (blue), ipsilateral hemisphere (red), posterior to the active area (green), and control subjects (no stimulus, black). Each line represents one hemisphere. Subject data are superimposed on each plot.

These results indicate that ipsilateral increase in spiking is accompanied by small but significant increase in glucose consumption. The finding of the increased ipsilateral glucose consumption is significant in light of the decrease in blood flow and oxygenation, and challenges the classical view of tightly coupling between blood flow and glucose metabolism.

Figure 5. Arterial diameter change in response to contra- and ipsilateral stimulus

White traces show percent diameter change relative to the baseline (red) at different locations indicated by arrows. At every location the upper and lower trace in a pair represents the response to the contra- and ipsilateral stimulus respectively. Dilation is plotted upward, constriction downward. The center of the neuronal response was superimposed on each plot. The traces are overlaid on 2-photon image of vasculature within the exposure. The image was calculated as a maximum intensity projection of an image stack of 0-300 μm in depth. Individual images were acquired every 10 μm. The horizontal dimension is 3.2 mm.

Figure 6. Comparison of arteriole dilatation and constriction in response to contra- and ipsilateral stimulus

(A) An average of arteriolar diameter changes (ΔD) in response to contralateral stimulus (blue) and ipsilateral stimulus (red). All measured vessels from 3 subjects are superimposed. (B) Peak dilation (crosses) and peak constriction (circles) as a function of distance (in mm from the center of evoked neuronal response) in response to contra- and ipsilateral stimulus (top panel) and ipsilateral stimulus (bottom panel). Each dot represents a measurement from a single arteriole. Data from 7 subjects are superimposed.

Figure 7. Comparison of surface and diving arterioles

(A) Diameter changes (ΔD) in response to contralateral stimulus (blue) and ipsilateral stimulus (red) at 6 locations were measured in one subject. At every location the measurement was made from a parent surface arteriole (top pair of traces) and a penetrating (diving) arteriole (bottom pair of traces). Dilation and constriction are plotted upward and downward, respectively. Black arrows indicate stimulus onset. Red arrows point to specific surface arterioles from which the measurements were made. Red circle shows the center of neuronal response. Depth (in μm) is indicated next to each penetrating arteriole. The image of the vasculature was calculated as a maximum intensity projection of an image stack of 300-300 μm in depth. Individual images were acquired every 10 μm. The horizontal dimension is 3.2 mm.