Focal physiological uncoupling of cerebral blood flow and oxidative metabolism during somatosensory stimulation in human subjects

(positron emission tomography)

PETER T. FOX*†‡ AND MARCUS E. RAICHLE*†

*Department of Neurology and Neurosurgical Surgery (Neurology), †Department of Radiology (Radiation Sciences), and The McDonnell Center for Studies of Higher Brain Function, Washington University School of Medicine, St. Louis, MO 63110

Communicated by Oliver H. Lowry, October 7, 1985

ABSTRACT Coupling between cerebral blood flow (CBF) and cerebral metabolic rate of oxygen (CMRO2) was studied using multiple sequential administrations of 15O-labeled radiotracers (half-life, 123 sec) and positron emission tomography. In the resting state an excellent correlation (mean r, 0.87) between CBF and CMRO2 was found when paired measurements of CBF and CMRO2 from multiple (30-48) brain regions were tested in each of 33 normal subjects. Regional uncoupling of CBF and CMRO2 was found, however, during neuronal activation induced by somatosensory stimulation. Stimulus-induced focal augmentation of cerebral blood flow (29% mean) far exceeded the concomitant local increase in tissue metabolic rate (mean, 5%), when resting-state and stimulated-state measurements were obtained in each of 9 subjects. Stimulus duration had no significant effect on response magnitude or on the degree of CBF-CMRO2 uncoupling observed. Dynamic, physiological regulation of CBF by a mechanism (neuronal or biochemical) dependent on neuronal firing per se, but independent of the cerebral metabolic rate of oxygen, is hypothesized.

It has been widely accepted that a close regional coupling between blood flow and tissue metabolic rate is dynamically maintained in normal brain. Local modulations in neuronal electrical activity are thought to induce similar modulations in local metabolism that, in turn, alter local blood flow. Blood flow and metabolism, therefore, have been considered virtually equivalent, indirect indices of brain work (1). Direct evidence, however, that cerebral blood flow (CBF) is dynamically coupled to cerebral metabolic rate is remarkably meager.

Whole brain measurements of CBF and cerebral metabolic rate of oxygen (CMRO2) cannot be construed as establishing a strict coupling between these two variables. Pathological depression of brain function (e.g., hypoglycemic coma or general anesthesia) has consistently depressed oxidative metabolism but variably affected CBF (2, 3). The generalized increase in neuronal activity accompanying rapid eye movement (REM) sleep, however, increases whole brain CBF without affecting CMRO2 (4, 5), clearly showing that CBF and CMRO2 can exhibit dissociated responses to physiological activation.

Excellent regional correlations between CBF and CMRO2 (6, 7) and between CBF and deoxyglucose uptake (7, 8) have been shown by obtaining paired measurements of these variables from multiple brain regions. Such studies have shown that, in resting or anesthetized brain, structures having high blood flow (e.g., grey matter) tend also to have high metabolic rates, while structures having lower blood flow (e.g., white matter) have lower metabolic rates. The existence of a resting-state regional correlation between blood flow and metabolism, however, does not prove that they are dynamically coupled during physiological fluctuations in regional work.

Equivalent increases over resting-state values in regional CMRO2 and regional CBF in sensorimotor cortex during voluntary hand movement were reported by Raichle et al. (6). This was, however, a single observation in a neurologically abnormal subject. We know of no other quantitative simultaneous determination of the effects of physiological activation on brain blood flow and metabolism. Measurements of blood flow, oxygen consumption, and glucose utilization, therefore, have not satisfactorily demonstrated dynamic coupling between blood flow and metabolism, either globally or regionally.

The current study tested the postulate that, in the human brain in vivo, blood flow and oxidative metabolism are coupled both in the resting state and dynamically—i.e., during the focal physiological enhancement of neuronal electrical activity accompanying somatosensory stimulation. Regional CBF, CMRO2, oxygen extraction fraction (OEF), and cerebral blood volume (CBV) were measured by positron emission tomography using a repeated-measures protocol in which each subject provided control (resting state) and activated (somatosensory stimulation) measurements for each variable (Fig. 1).

METHODS

Thirty-three paid normal volunteers were studied with the PETT VI system (9). CBF was measured using a bolus intravenous injection of 15O-labeled water with a 40-sec emission scan initiated as the tracer entered the brain (10, 11). CBV was measured using a brief inhalation of air containing trace amounts of 15O-labeled carbon monoxide with a 180-sec emission scan initiated 120 sec after inhalation (12, 13). OEF was measured using a brief inhalation of 15O-labeled molecular oxygen with a 40-sec emission scan initiated as the tracer entered the brain (13). CMRO2 was calculated pixel-by-pixel as the product of OEF, CBF, and the arterial oxygen content (13). Each set of measurements (CBF, CBV, OEF, and CMRO2) was obtained over 30–40 min, requiring two inhalations and one injection.

All 33 subjects were studied in a resting state, during which no direct stimulation was given and no task was performed. The subjects' eyes were closed and covered. Room sounds were dampened with plastic ear-canal molds.

For 9 of the 33 subjects, measurements were also made during somatosensory stimulation of the finger pads of one hand. The hand and arm were supported and relaxed while

Abbreviations: CBF, cerebral blood flow; CMRO2, cerebral metabolic rate of oxygen; CBV, cerebral blood volume; OEF, oxygen extraction fraction; Pco2 and Po2, carbon dioxide and oxygen pressure, respectively; ANOVA, analysis of variance.

†To whom correspondence should be addressed.
FIG. 1. Physiological uncoupling of brain blood flow and metabolism. (Left) Resting-state measurements. (Right) Stimulated-state measurements (unilateral vibrotactile stimulation of the fingers). All images are from a single subject’s scanning session and pass through the same brain plane. Color scales are linear with the maxima set at a fixed multiple (1.6) of the global average, to facilitate visual comparisons (16). During specific somatosensory stimulation a marked focal increase in CBF (29% of mean, nine subjects, three trials per subject) was produced in the contralateral sensorimotor cortex. The observed increase in the CMR\textsubscript{O\textsubscript{2}} was much smaller (5% of mean, nine subjects, three trials per subject) and failed to attain significance. This physiological uncoupling of CBF and CMR\textsubscript{O\textsubscript{2}} flow produced a highly significant decrease in the local OEF (~19% of mean), indicating that tissue Po\textsubscript{2} (and probably pH) rose during stimulation. Note that, although the data were analyzed as contralateral/ipsilateral ratios (see text and Tables 1–4), the disparity between blood flow and metabolism was evident from the raw data and was not dependent on a particular strategy of analysis.

stimulation was applied. Muscular activity was not affected in finger flexors or extensors by this stimulation modality, as determined by electromyography. No alteration in systemic blood pressure was induced by stimulus onset or offset.
Cutaneous vibration (130 Hz, 2-mm amplitude; Daito model 91, Higashi, Osaka, Japan) was used because it provides a topographically discrete, potent, physiological stimulus that can be applied without discomfort or habituation for prolonged periods of time.

Three sets of stimulated-state measurements and one set of resting-state measurements were acquired for each of the nine subjects undergoing sensory stimulation. The three stimulation trials differed only in stimulus duration. Stimulation began at isotope delivery, 60 sec prior to isotope delivery, or 300 sec prior to isotope delivery. Stimulation was halted at the end of each data acquisition; at least 10 min elapsed before initiation of the next stimulation period. The resting-state measurements were always obtained first, but the stimulated-state measurements were obtained in random order thereafter. The subjects’ heads were rigidly immobilized within the tomograph without interruption until completion of the entire experimental sequence (14).

The regional correlation between CBF and CMRO₂ was tested in the resting state (n = 33) and for each stimulation condition (n = 9). Thirty to 48 (15–24 per hemisphere) nonoverlapping 13.5 × 13.5 mm (5 × 5 pixel) regions of interest were identified within cortex, white matter, and deep nuclei (thalamus and basal ganglia). Region-of-interest localization was standardized with a stereotactic method of anatomical localization developed and validated for use with positron emission tomography (14, 15).

Vibratory stimulation induced an intense focal increase in CBF in the hemisphere ipsilateral to the stimulated hand in every trial of every subject stimulated (n = 9) (see Fig. 1 and below). No appreciable local increase in CBF occurred in the hemisphere ipsilateral to stimulation. The area within the contralateral cerebral hemisphere undergoing the greatest percentage change in CBF (from the resting state) was determined (16). A homologous region of interest was then created in the ipsilateral hemisphere by reflection about the midsagittal plane. The ratios (contralateral/ipsilateral) of measurements from these regions of interest were analyzed statistically. Use of contralateral/ipsilateral ratios provided a simultaneous within-subject control for global measurement fluctuations [e.g., CBF changes due to fluctuations in CO₂ pressure (PCO₂); ref. 16] and for occasional subject movements in the z axis (14). Logarithmic transformation of ratio data was performed to ensure sample normality (17). Each of the four variables (CBF, CBV, CMRO₂, and OEF) was compared across the four test conditions by a repeated-measures analysis of variance (ANOVA). Statistical significance for the F statistic was set at 0.0125: i.e., 0.05 divided by the number of ANOVAs performed (four) (17, 18). When significant variation between test conditions was indicated by ANOVA, post hoc testing (repeated-measures Newman–Keuls) was performed (17).

RESULTS

An excellent regional correlation between flow and metabolism was found in every instance. This was demonstrated both by the uniformity of OEF across all brain regions (Fig. 1) and by multiregional correlational analysis. When paired resting-state measurements of CBF and CMRO₂ from multiple (30 to 48) discrete regions of interest within the cerebral hemispheres were correlated, the results were unequivocally statistically significant (P < 0.0000001) in every instance (n = 33), with a mean r value of 0.87.

Division of each local measurement by the mean value from all brain regions for that subject provided a simple scalar transformation that negated the discrepancy in magnitude between the units of CBF and CMRO₂. Regional variations in CBF and CMRO₂ were of equal relative magnitude, as indicated by a mean scaled slope of 0.97 ± 0.09 SD (not significantly different from unity; n = 33). Equal local changes in CBF and CMRO₂ during functional activation, therefore, would be predicted and hitherto have been assumed based on multiregional correlation analysis.

The excellent correlation between CBF and CMRO₂ was maintained during physiological activation throughout nonactivated brain regions. First, OEF remained uniform across the brain, except within the activated zone (Fig. 1). Second, no differences were found in the CBF/CMRO₂ correlation coefficients among the four test conditions (P < 0.2, ANOVA; regions falling within the zone of task-induced blood flow augmentation in the hemisphere contralateral to the stimulation were excluded from analysis.

An intense, unilateral, unfocal increase in CBF was present in peri-rolandic (sensorimotor) cerebral cortex of the hemisphere contralateral to the stimulated hand during all stimulated-state scans of every subject undergoing stimulation (Fig. 1), with a mean response of 29% (P < 0.0000001, ANOVA; Table 1). An equivalent local increase in CMRO₂ was not present (Fig. 1), with a mean response of only 5% (P = not significant, ANOVA; Table 2). A marked local decrease in OEF was present, −19% of mean (P < 0.0000001, ANOVA; Fig. 1 and Table 3), and served to establish two corollary conclusions. First, blood flow and oxidative metabolism were uncoupled; i.e., the local CBF increase during tactile stimulation significantly exceeded (P < 0.0000001, ANOVA) the small local increases in CMRO₂. Second, local tissue oxygen pressure (PO₂) rose during stimulation, as O₂ delivery (O₂ content × CBF) increased with the increase in flow while the extracted fraction of available oxygen decreased; this agrees with observations from other techniques. Blood volume showed a small (7% mean), statistically significant (P < 0.005, ANOVA; Table 4) increase within the region of interest, as would be anticipated.

Variations in stimulus duration produced no significant variations in response magnitude for any variable (Tables 1–4). The regional uncoupling of CBF and CMRO₂ shown by these data, therefore, was not merely a transient overshoot of CBF or a brief latency in metabolic response. The consistency of the responses over multiple trials (Tables 1–4) also served to confirm the strength of these observations.

DISCUSSION

Equivalent local responses of CBF and CMRO₂ to focal physiological activation (somatosensory stimulation) were not found when these variables were measured during iden-
Neurobiology: Fox and Raichle

Table 2. Regional O2 metabolic rate responses to tactile stimulation (contralateral/ipsilateral ratios)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Resting ratio</th>
<th>S1 Ratio %</th>
<th>S2 Ratio %</th>
<th>S3 Ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.87</td>
<td>0.96</td>
<td>10</td>
<td>0.97</td>
</tr>
<tr>
<td>2</td>
<td>1.14</td>
<td>1.26</td>
<td>10</td>
<td>1.26</td>
</tr>
<tr>
<td>3</td>
<td>1.18</td>
<td>1.22</td>
<td>3</td>
<td>1.23</td>
</tr>
<tr>
<td>4</td>
<td>0.95</td>
<td>0.95</td>
<td>0</td>
<td>1.09</td>
</tr>
<tr>
<td>5</td>
<td>1.03</td>
<td>1.11</td>
<td>8</td>
<td>1.09</td>
</tr>
<tr>
<td>6</td>
<td>1.04</td>
<td>1.11</td>
<td>7</td>
<td>1.14</td>
</tr>
<tr>
<td>7</td>
<td>1.09</td>
<td>1.08</td>
<td>0</td>
<td>1.14</td>
</tr>
<tr>
<td>8</td>
<td>1.02</td>
<td>1.09</td>
<td>7</td>
<td>0.95</td>
</tr>
<tr>
<td>9</td>
<td>1.08</td>
<td>1.03</td>
<td>-4</td>
<td>1.11</td>
</tr>
</tbody>
</table>

Mean 1.04 1.09 5 1.11 6 1.08 3 SD 0.09 0.10 5 0.11 6 0.10 5

ANOVA: F = 3.4, P = 0.03 (not significant). Newman–Keuls test: not performed. Stimulation began at (S1) or 60 sec (S2) or 300 sec (S3) before tracer administration.

The fastigial nucleus of the cerebellum that produce increases in CBF without accompanying increases in metabolic rate has been established by Reis and coworkers (23).

Table 3. Regional OEF responses to tactile stimulation (contralateral/ipsilateral ratios)

<table>
<thead>
<tr>
<th>Subject</th>
<th>Resting ratio</th>
<th>S1 Ratio %</th>
<th>S2 Ratio %</th>
<th>S3 Ratio %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.07</td>
<td>0.84</td>
<td>-22</td>
<td>0.92</td>
</tr>
<tr>
<td>2</td>
<td>1.10</td>
<td>0.87</td>
<td>-21</td>
<td>0.91</td>
</tr>
<tr>
<td>3</td>
<td>1.10</td>
<td>0.83</td>
<td>-25</td>
<td>0.82</td>
</tr>
<tr>
<td>4</td>
<td>1.05</td>
<td>0.88</td>
<td>-16</td>
<td>0.89</td>
</tr>
<tr>
<td>5</td>
<td>1.04</td>
<td>0.89</td>
<td>-15</td>
<td>0.83</td>
</tr>
<tr>
<td>6</td>
<td>1.00</td>
<td>0.89</td>
<td>-11</td>
<td>0.94</td>
</tr>
<tr>
<td>7</td>
<td>1.03</td>
<td>0.82</td>
<td>-20</td>
<td>0.87</td>
</tr>
<tr>
<td>8</td>
<td>1.00</td>
<td>0.82</td>
<td>-18</td>
<td>0.68</td>
</tr>
<tr>
<td>9</td>
<td>1.07</td>
<td>0.80</td>
<td>-25</td>
<td>0.89</td>
</tr>
</tbody>
</table>

Mean 1.05 0.85 -19 0.86 -18 0.83 -21 SD 0.04 0.03 5 0.08 7 0.06 8

ANOVA: F = 33.4, P < 0.000001. Newman–Keuls test: resting > S1 = S2 = S3; inequalities P < 0.001, equalities P > 0.2. Stimulation began at (S1) or 60 sec (S2) or 300 sec (S3) before tracer administration.

The methods used to measure CBF and CMRO2 in this study have been subjected to validation and error analysis (11, 13). The diffusion limitation of water is known to cause a slight systematic underestimation of CBF and also of CMRO2 (as the product of CBF and OEF) at high rates of flow. If this systematic underestimation influences CMRO2 to a greater extent than CBF (which is not the case), an apparent uncoupling of CMRO2 and CBF would be produced. Measurement of OEF, however, is not subject to this error; thus, uncoupling of CBF and CMRO2 is still demonstrated by the marked decrease in local OEF. Moreover, the possibility of a systematic methodological error must be considered extremely unlikely in view of the excellent regional correlation between CBF and CMRO2 across all nonactivated brain regions (thereby including extreme values for both variables) evident statistically and by the uniformity of OEF (Fig. 1). The possibility that this phenomenon (flow–metabolism uncoupling) is idiosyncratic to somatosensory activation was eliminated by a series of experiments (unpublished) in which marked CBF responses without detectable CMRO2 responses were produced in pre-rolandic cortex with a manual motor task and in striate cortex with a visual stimulus paradigm described elsewhere (16).

The magnitude of a local response detected by positron emission tomography will be directly influenced by the size of the responsive area (32). Metabolic responses confined to a much smaller brain region than simultaneously occurring vascular responses (e.g., metabolic responses confined to a single cortical lamina with hemodynamic responses extending across all laminae) could produce a local discrepancy between CBF and CMRO2 such as we have described.
Equivalence in the spatial extent of the electrical, vascular, and metabolic responses evoked by focal enhancement of neuronal activation, however, has been elegantly demonstrated by Hand and Greenberg and co-workers (33, 34).

A local increase in the cerebral metabolic rate of glucose due to physiological stimulation has been inferred from measurements of deoxyglucose uptake (35). The presence of an increase in glucose metabolism does not, of itself, contradict the observations of ourselves and others (4, 5) that blood flow and oxidative metabolism are uncoupled during acute physiological increases in neuronal activity. Quantitative paired determinations of regional CBF and glucose metabolic rate (such as we have described for CBF and CMRO2) are needed for meaningful comparison of the changes in blood flow and glucose utilization occurring during focal physiological enhancement of the brain’s electrical activity. These studies have not yet been performed in humans or animals primarily because of their inherent technical difficulty. A major difference, however, between oxygen utilization and glucose utilization would require an increase in rate of anaerobic glycolysis. This is unlikely because, as discussed above, tissue PO2 rises and tissue pH either rises or remains stable during physiological stimulation. Furthermore, electrical stimulation of superior cervical ganglia in vitro produces no increase in tissue lactate (36).

This work was supported by the McDonnell Center for Studies of Higher Brain Function and by National Institutes of Health Grants NS-06833, HL-13851, NS-14834, NS-07205, and NS-00904 (Teacher Investigator Development Award, to P.T.F.).