Mechanisms regulating regional cerebral activation during dynamic handgrip in humans

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Williamson, J. W., D. B. Friedman, J. H. Mitchell, N. H. Secher, and L. Friberg. Mechanisms regulating regional cerebral activation during dynamic handgrip in humans. J. Appl. Physiol. 81(5): 1884–1890, 1996.—Dynamic hand movement increases regional cerebral blood flow (rCBF) of the contralateral motor sensory cortex (MS1). This increase is eliminated by regional anesthesia of the working arm, indicating the importance of afferent neural input. The purpose of this study was to determine the specific type of afferent input required for this cerebral activation. The rCBF was measured at +5.0 and +9.0 cm above the orbitomeatal (OM) plane in 13 subjects during 1) rest; 2) dynamic left-hand contractions; 3) postcontraction ischemia (metaboreceptor afferents); and 4) biceps brachii tendon vibration (muscle spindles). The rCBF increased only during dynamic hand contraction; contralateral MS1 (OM +9) by 15% to 64 ± 8.6 ml·100 g⁻¹·min⁻¹ (P < 0.05); supplementary motor area (OM +9) by 11% to 69 ± 9.8 ml·100 g⁻¹·min⁻¹ (P < 0.05); and there were also bilateral increases at MS2 (OM +9) by 16% to 64 ± 8.6 ml·100 g⁻¹·min⁻¹ (P < 0.05). These findings suggest that the rCBF increase during dynamic hand contraction does not require neural input from muscle spindles or metaboreceptors. The involved fibers, however, may also include mécanoreceptors (group IIb or Ib) that mediate the signal that activates the human cerebral cortex during dynamic handgrip. Thus rCBF was measured during four conditions: 1) rest; 2) unilateral dynamic hand contractions, which presumably activated groups IIb, II, III, and IV afferents; 3) postexercise muscle ischemia, which would primarily stimulate the small groups III and IV metabolically sensitive muscle afferents (12); and 4) vibration of the biceps brachii tendon, which would activate large group Ia primary muscle spindles (6, 19). On the basis of the results from previous blocking studies (9, 26), it was hypothesized that isolation of groups IIb and IV metabolically sensitive muscle afferents during postexercise muscle ischemia would produce significant increases in rCBF.

METHODS

Four female and nine male right-handed volunteers [age = 33 ± 6 (SD) yr, weight = 79 ± 18 kg, and height = 181 ± 10 cm] were studied after giving informed consent for the experiment, which was approved by the Ethics Committee of the University of Copenhagen. With eyes covered, subjects rested horizontally in a dark, quiet room with their head positioned on a pillow to avoid tensing of the neck muscles. The head was placed in a tomograph in such a way that the midslice plane of the recorded two slices was positioned at 5.0 and 9.0 cm above the OM plane (Fig. 1). Each subject was tested four times on the same day in a random order: 1) resting measurements were made with the subjects’ left arm relaxed at their side; 2) dynamic hand contractions consisted of repetitive left-handed squeezing by using a handgrip device at a rate of 60 times/min for 5 min; 3) muscle ischemia of the left arm was induced for 5 min (measurement period) by inflation of a small arm cuff (to 200 mmHg) during the last 15 s of a 2-min bout of left-handed dynamic contractions; and 4) vibration of the left biceps brachii tendon at a frequency of 100 Hz for 5 min was accomplished by using a handheld vibrator (Biothesiometer, Newbury, OH). For all protocols, subjects were given clear instructions not to move or tense muscles other than those directly involved in the hand contractions. Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) data were collected each
minute by using a sphygmomanometer cuff placed on the right arm.

The rCBF was measured by recording the regional distribution of cerebral radioactivity after inhalation of $^{133}$Xe by using a rapidly rotating single-photon tomograph (Tomomatic 232, Medimatic, Denmark) (4, 11, 14). Increases in rCBF lead to a rise in the amount of radioactivity recorded from the respective region (17). One measurement lasted 4.5 min. During the first 90 s, $^{133}$Xe was rebreathed from a closed-airway system with a CO$_2$ absorber and cleared from the brain during the remaining 3 min while the subject breathed normal air. For each measurement, a series of four consecutive samples was recorded at 1.5-, 1.0-, 1.0-, and 1.0-min intervals, respectively. These samples were used to calculate rCBF by deconvolution of the input curve recorded over the apex of the left lung (4, 11). The rCBF of the two slices was displayed on a screen in a 12-step color scale. The Tomomatic 232 has a spatial resolution of 12 mm in the transaxial plane (full width one-half maximum). With a rebreathing volume of 4 liters and a $^{133}$Xe concentration of 740 MBq/l, one study produces an exposure of 0.63 mSv calculated as a whole body dose equivalent (2). The method has an error of $\pm$5%, which is a measure of the overall biological and physical intraindividual and day-to-day variability (28). The cortical areas to be investigated were determined a priori such that each region was located in the same area of the rCBF map during all measurements. Twenty-four regions of interest (ROI) were defined (Fig. 2) as previously utilized by Friedman et al. (9). The size of the ROI map could be proportionally altered to better fit the confines of each individual's brain.

During each measurement of rCBF, end-expiratory PCO$_2$ was measured with an infrared capnograph (CD-101, Datex OY, Helsinki, Finland). On the basis of the baseline value, all rCBF values could be automatically corrected 2% by computer for each milliliter of mercury change in alveolar PCO$_2$ (28). At the end of each activity, the subject was asked to provide a rating of perceived pain (RPP) by using a standard Borg scale (6–20 units) (3). A score of 6 represented no pain, and 20 signified unbearable pain. These ratings were used to describe the sensation involved in the repetitive squeezing and toleration of the muscle ischemia or tendon vibration.
Fig. 3. Flow map data are presented from 1 subject during each of 4 conditions (see text) for OM +9.0 and OM +5.0 planes. Color scale represents flow values in ml·100 g⁻¹·min⁻¹. There is an increased flow to contralateral motor sensory area (MS1) of OM +9.0-cm plane during left handgrip exercise as well as to supplementary motor area when compared with other conditions. In OM +5.0 plane, there is an increased flow bilaterally to motor sensory regions (MS2) during dynamic handgrip compared with other conditions. Corr, corrected; R, right side; L, left side.
An analysis of variance with main effects of condition (rest, exercise, vibration, and ischemia), region of interest (24 ROIs), and side (right, left) was employed to establish areas with a significant increase in cerebral activation as indicated by changes in the rCBF (ml·100 g⁻¹·min⁻¹). When significant F-ratios were present, Tukey’s multiple-range post hoc test was used to determine specific mean differences. A P value < 0.05 was considered to be significant.
RESULTS

Rest. During rCBF measurements at rest, HR was 61 ± 7.4 beats/min, SBP was 123 ± 12.8 mmHg, DBP was 77 ± 6.4 mmHg, and MAP was 92 ± 7.7 mmHg. The rCBF measurements for one individual are shown in Fig. 3, with mean responses of the 13 subjects presented in Table 1. Resting hemispheric CBF was 55 ± 9.1 ml·100 g⁻¹·min⁻¹ bilaterally in the OM +9 and OM +5 brain slices. At the OM +9 level, values for the motor sensory regions (MS1) were 55 ± 7.1 and 54 ± 6.7 ml·100 g⁻¹·min⁻¹ for left and right sides, respectively. The SMA rCBF was 61 ± 8.2 ml·100 g⁻¹·min⁻¹ at rest. The value for motor sensory region MS2, at the OM +5 level, was 57 ± 8 ml·100 g⁻¹·min⁻¹, for both right and left sides. All subjects indicated a baseline RPP at 6 units on a 6–20 scale for the resting condition.

Dynamic hand contractions. Data averaged over the last 2 min of hand contraction for HR (88 ± 12.3 beats/min), SBP (152 ± 15.1 mmHg), DBP (97 ± 7.1 mmHg), and MAP (115 ± 9.1 mmHg) were all significantly elevated from resting values (P < 0.05). The RPP assessed immediately after hand contractions was 16 units (range 12–20 units). The rCBF measurements for one individual are again shown in Fig. 3, with mean responses of the 13 subjects presented in Table 1. During hand contraction, right hemispheric flow increased (64 ± 9.3 ml·100 g⁻¹·min⁻¹; P < 0.05) at the OM +9 level, with no significant increase in left hemispheric flow (60 ± 9.0 ml·100 g⁻¹·min⁻¹). At the same level, rCBF values for both the right MS1 area (64 ± 8.6 ml·100 g⁻¹·min⁻¹; P < 0.05) and the SMA (69 ± 9.8 ml·100 g⁻¹·min⁻¹; P < 0.05) were increased by hand contraction. These increases represented 15 and 11% changes for MS1 and SMA regions, respectively, when corrected for changes in white matter flow. In the OM +5 brain slice, there was activation for both right (68 ± 9.5 ml·100 g⁻¹·min⁻¹; P < 0.05) and left (66 ± 8.9 ml·100 g⁻¹·min⁻¹; P < 0.05) sides were increased by hand contraction. These changes represented 15 and 16% increases in rCBF for right and left sides, respectively, when corrected for white matter flow. There were no significant changes in rCBF to other regions studied during contraction.

Postcontraction muscle ischemia. During the last 2 min of muscle ischemia, HR (75 ± 8.1 beats/min), SBP (153 ± 18.0 mmHg), DBP (94 ± 8.0 mmHg), and MAP (114 ± 10.4 mmHg) were all significantly elevated above resting values. Although HR values were higher during hand contractions (P < 0.05), blood pressure responses were similar between conditions of hand contraction and postcontraction muscle ischemia. The RPP value obtained immediately after deflation of the arm cuff maintaining the ischemia was 16 units (range 10–20 units), and, while higher than rest (P < 0.05), this value did not differ from the rating obtained after hand contraction (P > 0.05). The postexercise muscle ischemia produced no significant changes in rCBF of any region compared with resting values (Fig. 3, Table 1).

Biceps brachii tendon vibration. During biceps tendon vibration, there were no significant changes from rest for HR (61 ± 6.6 beats/min), SBP (123 ± 14 mmHg), DBP (77 ± 7.2 mmHg), MAP (92 ± 8.6 mmHg), or RPP (6 units). Tendon vibration produced no significant changes in rCBF to any region compared with resting values (Fig. 3, Table 1).

DISCUSSION

Consistent with previous findings during hand contraction (8, 9, 26), contralateral increases in rCBF were noted in the OM +9 brain slice in the motor sensory area (15%) and in the SMA (11%) as well as bilateral increases in the motor sensory area at OM +5 (16%). Despite previous findings implicating muscle afferent
given that limb is exercised (10). Also, Jørgensen et al. (10) found no change in MCA flow velocity during postexercise muscle ischemia. In agreement with this finding, postexercise muscle ischemia, which is thought to selectively activate the smaller groups III and IV metabolically sensitive fibers (1, 29), did not result in activation of the motor sensory cortex.

Alternatively, group Ia or thinly myelinated group III muscle afferents serving as mechanosensitive receptors capable of sensing changes in contractile force or intramuscular pressure, respectively (12, 19, 23), were not presently isolated. During hand contractions, reductions in muscle strength (e.g., decreased force and intramuscular pressure) induced by axillary blockade correlate well with the magnitude of decrease in rCBF in motor sensory areas (9), suggesting that a mechanically sensitive receptor could play a role in this response. Although the group III fibers have been implicated in producing reflex increases in blood pressure (22, 30), we are presently unaware of data directly implicating their involvement in rCBF increases. Although this proposed mechanism may be involved in activities producing a moderate muscular contraction, it would appear to have little influence on brain activation during more complex hand activity such as coordinated finger tapping or writing (15).

The changes in rCBF during hand contraction were similar to those reported by Friedman et al. (9) with use of identical methodology, yet the increases in rCBF were smaller in magnitude than those reported for repetitive squeezing of a rubber ball (20) or more complex movement patterns such as finger tapping or writing (15). Similar to methods employed by Friedman et al. (9), specific regions of interest were selected a priori to minimize investigator bias in determining rCBF changes. However, use of these relatively large predefined areas (Fig. 2) can potentially yield smaller changes in rCBF when compared to the relatively small (e.g., 2- × 3-cm) regions where the largest changes in flow occur (20, 21). The smaller rise in flow could potentially be related to cerebral autoregulatory mechanisms evoked in response to the substantial elevations in blood pressure. Of note, the rCBF values obtained under resting conditions were similar to those found by others (8, 9, 15, 27).

In conclusion, rCBF to motor sensory areas investigated was increased during dynamic hand contraction but not by postexercise muscle ischemia of the forearm or biceps brachii tendon vibration. In other words, the isolated afferent stimulation of the large group Ia or the smaller types III and IV (metabolically sensitive) fibers did not result in activation of the motor sensory cortex. However, dynamic hand contraction may have activated group III muscle “mechanoreceptors” to a greater extent than other conditions. Because previous rCBF studies have strongly implicated the involvement of muscle afferent input (5, 8, 9, 25) and have further shown that the increases in rCBF that occur during hand contractions are dependent on afferent input from nerves, it is reasonable to postulate an involvement of group III mechanosensitive fibers or Golgi tendon organs (group Ib) in activation of the motor sensory cortex during dynamic handgrip exercise. Given that the voluntary handgrip exercise will also increase central command, it is possible that some combination of neural input from higher brain centers and muscle afferent input is required for maximal activation of motor sensory regions.

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