

Imaging rCBF Changes in Response to Insulin-Induced Hypoglycemia at 3T Using Three-Coil CASL

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Introduction

To prevent hypoglycemia during prolonged periods of fasting or hyperinsulinemia, mammalian organisms have developed an elaborate system of hormonal and neurocognitive counterregulatory responses that are elicited by a fall in blood glucose. While much is known about the hierarchical nature of this response and how it is altered in patients with type 1 diabetes and hypoglycemia unawareness, the cerebral regions involved in the detection and coordination of this response remain uncertain. Previous studies have used ¹⁵O and ¹⁸F PET to map changes in regional cerebral blood flow (rCBF) in response to hypoglycemia (1, 2), but the spatial resolution of PET is typically low (8-10 mm). Higher resolution would be advantageous for localizing smaller structures involved in hypoglycemia detection and counterregulation. Arterial spin labeling is an established MR technique for measuring CBF using arterial blood as an endogenous tracer. Continuous arterial spin labeling (CASL) with separate labeling and imaging coils offers the ability to map CBF over a large number of slices at high resolution with relatively low SAR (3). In this study, three-coil CASL was implemented and utilized on a 3 Tesla clinical scanner to determine if changes in rCBF detected at a resolution of $2 \times 2 \times 3$ mm could be used to identify those regions that are activated in response to hypoglycemia.

Methods

Ten healthy subjects (5 male, 5 female, age 28 ± 10 years) were studied. Before the experiment, one IV line was inserted into an antecubital vein of each subject for infusion of insulin, glucose, and potassium phosphate, and a foot vein was cannulated for blood sampling. Insulin was infused from 0-120 min (2.0 milliunits/kg/min), plasma glucose concentrations were measured every 5 min, and 20% glucose was infused in variable doses to clamp plasma glucose concentrations at four levels over the course of the study: 90 mg/dL (0-30 min), 70 mg/dL (30-60 min), 60 mg/dL (60-90 min), and 50 mg/dL (90-120 min). Plasma glucose concentrations were measured with a glucose analyzer in the indirect mode (Analox, Analox Instruments Ltd.). Samples for subsequent measurement of glucagon, epinephrine, and norepinephrine by standard assays were obtained at baseline and every 10 minutes during the experiment.

MR images were acquired using a 3 Tesla whole-body scanner (Siemens MAGNETOM Trio) outfitted with a body transmit coil and an eight-channel receive-only head coil. CASL labeling was performed using a separate two-channel transmit-only neck coil placed on the carotids, connected to a secondary RF transmitter. The coil configuration is shown in Figure 1. For each subject, a T_1 -weighted 3D volume image (3D FLASH, $T_R/T_E = 20/5$ ms, $\alpha = 30^\circ$, resolution = 1.0 mm^3) was acquired for localization of anatomy and to allow for warping into standard Talairach space. CASL images were acquired using 2D GE-EPI (labeling time = 2500 ms, post-label delay = 1000 ms, $T_E = 24$ ms, resolution = $2 \times 2 \times 3$ mm, 17 slices acquired in H \rightarrow F order, 100 label/control pairs). CASL images were acquired over the last 15 minutes of each clamped glucose level (15-30 min, 45-60 min, 75-90 min, and 105-120 min). Statistical comparisons were made between the 90 mg/dL, 70 mg/dL, and 50 mg/dL levels using the GLM function of Brain Voyager QX 1.6.1, with thresholds set according to a false discovery rate (FDR) of 1%.

Results

All subjects developed hypoglycemia during the study (mean glucose nadir = 52 ± 3 mg/dL) and demonstrated robust counterregulatory responses (mean peak values: glucagon 114 ± 41 pg/mL, epinephrine 568 ± 236 pg/mL, norepinephrine 401 ± 132 pg/mL). Figure 2 shows an example CASL subtraction volume averaged over one 15-minute acquisition. The image quality is quite good over most of the volume, with some signal loss due to T_1 recovery evident in the most inferior slices, which were acquired last.

Statistical maps comparing the baseline condition with the final clamped glucose level (55 ± 3 mg/dL) are presented in Figure 3. Increases in rCBF are notable bilaterally in the medial thalamus, anterior cingulate, and posterior cingulate. No significant differences in rCBF were observed between the baseline condition (88 ± 8 mg/dL) and the second clamped glucose level (68 ± 7 mg/dL) at the same statistical threshold. The third clamped level (target 60 mg/dL) was not analyzed, as few subjects stabilized at this level. Of note, a rise in the concentrations of the counterregulatory hormones was not detected until the lowest step of the clamp study (55 ± 3 mg/dL), and the peak values were all obtained at this level of glycemia.

Discussion

When blood glucose was reduced to 55 ± 3 mg/dL, we found rCBF to significantly increase in the medial thalamus and the anterior and posterior cingulates at the same time as the peak counterregulatory hormone response to hypoglycemia. Similar observations have been made previously with PET (2), but the three-coil CASL MRI at 3 Tesla used here has superior resolution to PET. Additional improvements in resolution, coverage, and sensitivity using this technique can potentially be made by moving to higher field strengths such as 7 Tesla. These observations suggest that these regions are involved in the detection of hypoglycemia and/or the coordination of the counterregulatory response.



Figure 1. 3T CASL coil configuration.

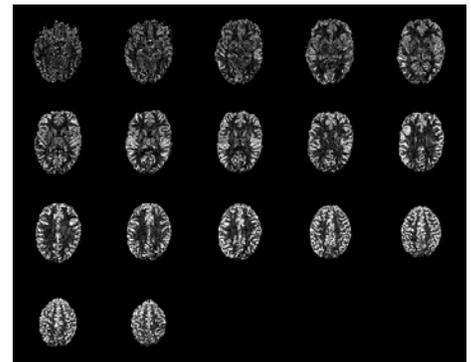


Figure 2. Example CASL subtraction images.

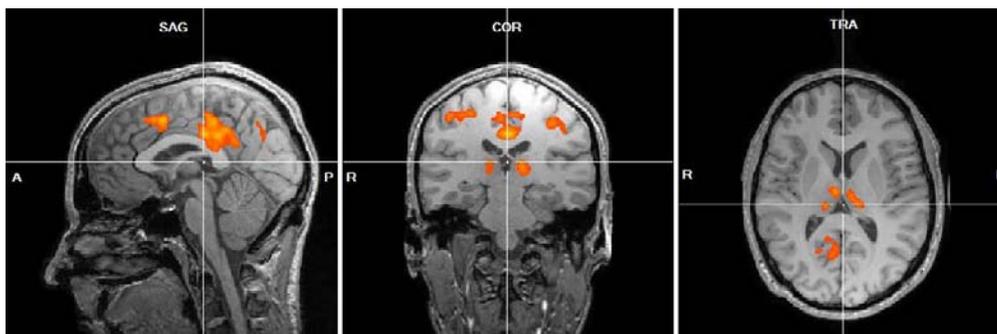


Figure 3. Increases in rCBF observed by CASL: hypoglycemia vs. baseline.

References

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