In-vivo fMRI study of hypothalamus activation during thermoregulation in the rat

G. Vanhoutte[1], M. Verhoye[1], E. Raman[2], A. Van der Linden[1]
[1]Bio-Imaging Lab, RUCA, University of Antwerp, Antwerp, Belgium; [2]Visie Lab, RUCA, University of Antwerp, Antwerp, Belgium;

Introduction

The hypothalamus is the major site of thermoregulation(1). Thermal stimulation of hypothalamic areas results in a discrepancy between the posterior hypothalamus which evokes behavioural changes, and the anterior preoptic hypothalamic region which evokes both autonomic and behavioural thermoregulation . Hyperthermia can be fatal and to protect against this, animals developed specialised heat-loss mechanisms, especially in the body appendages. In the rat, heat loss through the naked and highly vascularized tail, is sympathetically mediated through the hypothalamus which results in opening of arteriovenous anastomoses (AVAs)(2) . We studied hypothalamic activation during thermoregulation using functional MRI applying both, blood oxygenation level dependent (BOLD) and cerebral blood flow (CBV) sensitive MRI protocols.

Methods

A fMRI study was performed on 6 (BOLD n=2, CBV n=4) adult male albino Wistar rats (250g). Imaging was done on a 7T SMIS (U.K.) MR-system. Anaesthesia was induced with a mixture of Ketamine/Rompun (7/1, 60mg/kg) and subsequently during the fMRI protocol, alfa-chloralose was administrated i.p. (25mg/kg). The tail vein was catheterised for contrast injection, 20mg/kg NC100150 (ClariscanTM, kindly given by Nycomed Imaging AS, Oslo, Norway before the rats were inserted in the magnet. We used a customised headphone RF transmission antenna and a circular surface receive antenna (f:20mm) positioned on the stereotaxically positioned head of the rat. The rats were positioned on a warm water blanket connected to a circulation system through which body temperature (Tr) could be experimentally modified. To monitor rectal temperature, a thermistor probe was inserted 5cm beyond the anal sphincter. The MRI protocol started with the acquisition of a set of horizontal high resolution images (TE/TR=6/500ms, FOV=20, acquisition matrix 256*128, averages=2). Subsequently fMRI images were acquired during an experimental increase of Tr (from 37°C to 40°C) as a gradual stimulus paradigm (TE/TR=14/150, FOV=20, acquisition matrix 64*128, averages=1).For the CBV and BOLD enhanced experiments, the same parameters were used. Data processing was performed on a PC using home developed programs in IDL (RSI). Mean intensity was calculated from controle images at Tr 37°C and were subtracted from the consecutive data obtained during thermal stimulation. Negative BOLD signal change of 5 à 10% was superponed on the high resolution images.

Results

There is a transient decrease in fMRI BOLD signal intensity in certain brain areas during the rise of Tr from 37°C to 40°C. This fMRI signal change is not seen in brain of rats held at a constant temperature. In figure 1 you can clearly see the white spots in the hypothalamus, insular cortex, jaw muscles and neck blood vessels which represents a 5 à 10% decrease in BOLD signal. To estimate the contribution of CBV changes in the negative BOLD signal, we perfused the brain with NC100150 a USPIO class blood pool agent. Relative intensity measurements in figure 2 show e.g. a 20% decrease in hypothalamic area during brain imaging with BOLD whereas the intensity in the cortex is constant. Injection of contrast results in a small increase of relative intensity, similar for the hypothalamus and the cortex and this is equal for controle rats (not shown)(Fig. 2).

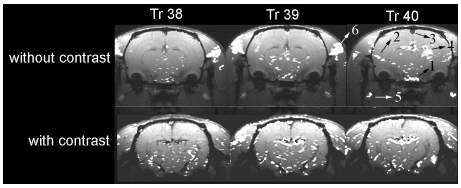

Fig.1: Subtracted images with different Tr, showing negative fMRI signal in white. 1:hypothalamus, 2:insular cortex, 3:sagittal sinus, 4: major draining vessels from hippocamus[3] 5:neck blood vessels, 6:jaw muscles

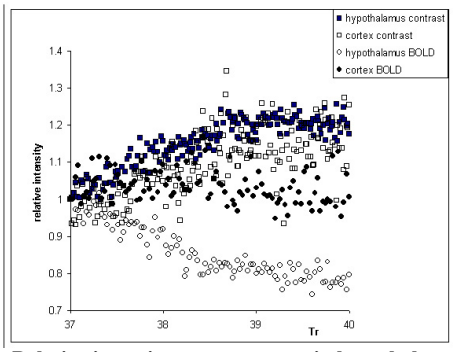

Fig.2: Relative intensity measurements in hypothalamus and cortex as measured in BOLD and CBV sensitive MRI experiments

Discussion

Negative BOLD signal in hypothalamic areas has been reported in other fMRI studies(4,5). The meaning of this decrease in fMRI signal from a functional point of view remains a topic of current investigation, naturally it could be considered to be a sign of hypo-oxygenation. The fMRI signal in BOLD images, harbors information on the CBV and on the blood oxygenation status while MRI plus NC100150 as blood pool agent, provides exclusively CBV information.

The CBV in de hypothalamus stays the same as compared to the cortex (fig.2). As a consequence we can conclude that the negative signal in the hypothalamus of the contrast enhanced images is due to a rise in activation. This could be a possibility if we suggest that the blood vessels around the hypothalamus are always dilated so the negative signal in hypothalamus might be the result of oxygen consumption without blood volume increase. This is a plausible explanation because the regulatory function of the hypothalamus depends on conversion of synaptic information to humoral signals. A high blood volume is necessary in the vicinity of the hypothalamus for release of hormones during activation. Because the physiologic body temperature is 38°C, the hypothalamus regulation starts from this point while the rat remains heat loadet. You can see in figure 2 the initial decrease starts from Tr 38°C.

References

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