Effect of diet and exercise on MR outcomes of a model of vascular dementia in aged rats

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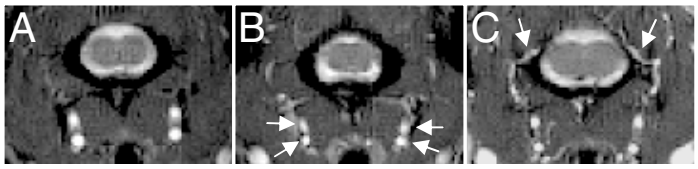
Introduction Chronic hypoperfusion is a prominent risk factor in both vascular dementia [1] and Alzheimer's disease [2]. Other risk factors include a high fat diet as well as a sedentary lifestyle with a lack of physical activity. A model of chronic hypoperfusion in the rat has been developed by de la Torre et al. After completely blocking both common carotid arteries, the forebrain experiences a measurable although surprisingly small decrease in blood flow acutely. This resolves due to enlarging of the vertebral arteries during a period of one or two weeks. Nevertheless aged rats undergoing bilateral common carotid artery occlusion (BCCO) develop measurable neurological deficits 6 months post occlusion [3]. We used this model to study the effect of physical activity and high fat diet on the outcome of this disease. The behaviour data have been presented at SFN Atlanta 2006 [4] while this abstract presents MR imaging data including blood flow (CBF), cerebrovascular reserve (CVR) and relaxation times (T2, T2*).

Methods BCCO or sham surgery was performed on 27 aged rats which were examined at 2 weeks, 1 month and 2 months post surgery and on another 30 aged rats examined at 1 month, 2 months and 6 months post surgery. Rats were divided randomly into 5 groups consisting of high fat, high sugar diet with (HFS) or without BCCO (SHFS), control diet with (CO) or without BCCO (SHCO) and a physical activity group with BCCO (PA) which were allowed free access to running wheels for 3 days per week. Data from the first and second set of rats at the 1 month and 2 months time points were pooled. MR imaging was carried out on a Bruker Biospin/3 7T/21cm system using a 3.2cm ID quadrature volume coil. At all time points, CBF at the level of the hippocampus was measured using a modified arterial spin labeling method [5] before and after i.p. administration of acetazolamide (200 mg/kg) to measure CVR. T2 was measured using a standard CPMG sequence (TE 27ms, NE 8). T2* weighted imaging was carried out with a GE sequence with TE=20ms. Occlusion of the carotid arteries and enlargement of vertebral arteries was demonstrated with TOF angiography acquired at 3, 4 and 5mm posterior to the brain. Post hoc comparisons of CBF were carried out used Tukey-Kramer multiple comparison tests.



Sham operated 2 weeks post BCCO 8 weeks post BCCO

Figure 1: Angiograms demonstrating altered flow in carotids and vertebrals

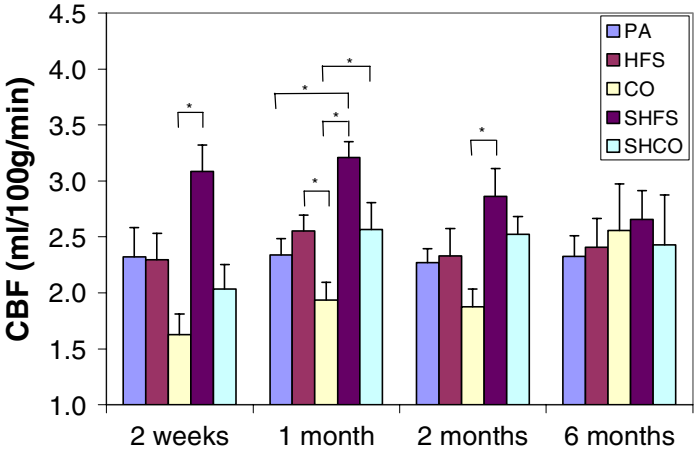


Figure 2: Absolute CBF in occipital cortex at varying times post BCCO grouped by diet, physical activity and surgery type. * p<0.05 (Tukey-Kramer)

Results and Discussion By 6 months post surgery, both BCCO and sham rats on the HFS diet gained 120g more weight than those on control diet while the PA group gained 30g less. Already at 2 weeks post BCCO, substantial blood flow appeared in both internal and external carotid arteries (arrows Fig. 1B) while by 2 months enlargement of the vertebral arteries was also visible (arrows Fig. 1C). The flow that develops in the carotid arteries post BCCO may be attributed to the presence of collateral circulatory pathways and/or autoregulatory mechanisms [6]. These two mechanisms may operate to various degrees. In the latter case, one might expect a reduced CVR due to a decreased capacity for autoregulation. In our rats, the prior mechanism seemed to be dominant as no difference in CVR was found between sham operated and BCCO rats at any time point. A sample of the CVR data is shown in Fig. 3. Also there was a pronounced negative correlation between CVR and pre-acetazolamide CBF. So the CVR in the occipital cortex was negative when the flow was high possibly due to a steal phenomenon. There was a trend towards an increase in hippocampal CBF at 1 month in both the sham and BCCO rats on the HFS diet compared to rats on the control diet. This difference was somewhat more pronounced in the thalamus and was maximal in the occipital cortex (Fig. 2) at the 2 week and 1 month time point while these effects were no longer statistically significant at 6 months. The rats in the physical activity group showed similar CBF to the HFS BCCO group. Differences between sham and BCCO groups also disappeared at the 6 month time point. Absolute T2 values showed no group or time differences. One rat in the second control diet BCCO group showed markedly elevated T2 in the left occipital cortex at all three time points, markedly reduced CBF in that area and a very large CVR of 300% at 2 months. All other rats showed normal T2 scans. The T2* experiment was intended to show imbalances in CBF and CMRO2 which would manifest as changes in deoxyhemoglobin levels. Ratios of intensities between different regions of the brain did not show differences between groups and no effect of acetazolamide could be observed either. This may due to regulation of CMRO2 in response to changes in CBF or a lack of sensitivity to small imbalances between CMRO2 and CBF. Behaviour testing in our previous study [4] was unable to demonstrate a deleterious effect of the HFS diet. This may in part be explained by the elevated CBF due to a coincidental vasodilatary effect of the diet.

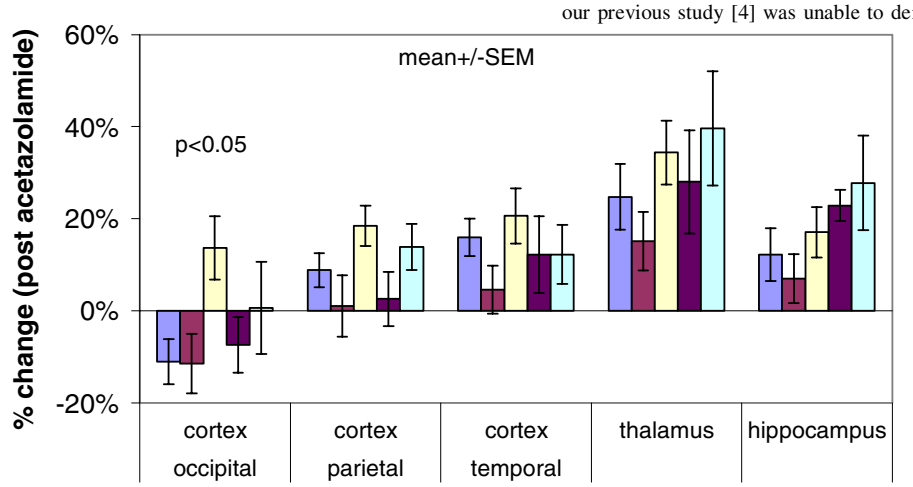


Figure 3: Cerebrovascular reserve at 1 month post BCCO. For legend see Fig. 2. One outlier with very high CVR has been excluded from the CO group. The p-value shown is the ANOVA p-value for group effect in the occipital cortex.

References

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