Oral creatine supplementation depresses ATP in healthy human brain

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Introduction: There have been relatively few studies of creatine supplementation in human brain. Given the known ability of creatine to increase muscle power it may be hypothesized that creatine supplementation would also be beneficial for brain function. Cognitive testing studies have shown that several days of creatine supplementation can improve mental performance, e.g., Watanabe et al (1) found creatine supplementation reduced mental fatigue induced with a sustained arithmetic test. Lyoo (2) used 31P spectroscopy to evaluate creatine's effects in human brain, however this single slab study did not permit regional measurements. In this study we acquired high resolution 31P spectroscopic imaging in human brain before and after 7 days of oral creatine supplementation in n=7 healthy human subjects.

Methods: All studies were performed with a Varian Inova 4T whole body imaging spectrometer with double tuned 1H-31P TEM volume head coil. Off-midline sagittal images were acquired with an IRGE, TE 16msec, to allow prescription of a triply obliqued hippocampal slice along the planum temporale. Whole brain shimming was performed manually, achieving an average whole brain linewidth of ~21Hz. 31P spectroscopic imaging data were acquired using the hippocampal angulation using a pulse acquire acquisition utilizing a three-dimensional spherical sampling scheme (13x13x13, FOV = 24x24x24cm). To provide tissue content quantification, quantitative T1 imaging was also acquired (3). Including scout imaging and calibrations, the typical duration of the study was 75min. The data were reconstructed using image guided single voxel reconstruction. 31P data were fit in the spectral domain with the linewidths for PCr, Pi and ATP assumed to be identical. Concentrations were determined via referencing to the resonance area measured from a standard solution of 50mM sodium phosphate. The corrections include relaxation effects using T1 values measured at 4T (4), coil loading and tissue volumes (determined from the quantitative T1 images using semi-automated image segmentation).

The 31P data were analyzed regionally in three groups, neocortical, subcortical and hippocampal. Neocortical regions included the occipital (left, right) and medial cingulum. Subcortical regions included the thalamus and basal ganglia (caudate and putamen, left and right). Significance was determined using paired t-tests. N=7 healthy adult volunteers were studied at day 0 and day 7, all studies performed in the morning after an overnight fast. The oral creatine supplement was performed using Neotine sachets (Avicena Inc.), 20g/day for 7 days in all volunteers.

Results: At baseline the ratio of PCr/ATP in the hippocampal and subcortical regions was 0.81±0.08 and 0.78±0.11 respectively. After 7 days of creatine supplementation, the hippocampal ratio had significantly increased to 0.88±0.09 ($p<0.05$), the subcortical ratio to 0.83±0.12 ($p<0.025$). The majority of the change was in ATP. Subcortically, ATP declined significantly from 2.32±0.44 to 2.11±0.46 (see Table) while the drop was borderline significant in the hippocampus ($p=0.06$). Figure 1 shows spectra from the thalamus at day 0 and day 7.

		Subcortical mean	Subcortical SD	Hippo Mean	Hippo SD	Neocortical mean	Neocortical SD
PCr/ATP	day 0	0.78	0.11	0.81	0.08	0.78	0.12
	day 7	0.83	0.12	0.88	0.09	0.83	0.13
PCr	day 0	2.77	0.54	3.45	0.51	3.13	0.47
	day 7	2.64	0.53	3.47	0.47	3.18	0.52
ATP	day 0	2.32	0.42	2.81	0.47	2.60	0.38
	day 7	2.10	0.45	2.58	0.34	2.54	0.36

Pairs of shaded boxes were significantly different between each other, between day 0 and day 7.

Discussion: Creatine supplementation causes an increase in PCr/ATP particularly in subcortical and hippocampal regions. Assuming no major changes in relaxation values, the change in the ratio is most likely due to a decline in ATP concentrations seen subcortically and suggested in the hippocampus. Given the size of ATP changes of approximately 0.2 to 0.4mM without much PCr change, with the relatively larger total creatine increases reported in the literature (0.4 to 1mM), consideration of the creatine kinase equilibrium implies that concentrations of ADP would be increasing as well. As a key regulator of intermediary metabolism, creatine may achieve some of its effect through increased ADP levels which may in turn, increase mitochondrial oxidative metabolism.

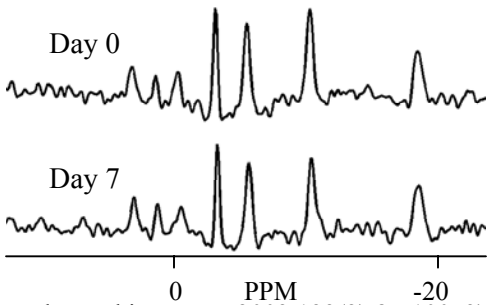

Figure 1. Thalamic spectra from the same volunteer on day 0 and day 7 showing the relative changes in ATP

References: 1) Watanabe, Kato, Kato. Neuroscience Research 2002 42:279-85 2) Lyoo et al. Psychiatry Res. 2003 123(2):87-100. 3) Hetherington et al MRM 1994 32(5): 565-71. 4) Chu WJ et al. Proc Soc Magn Res 5th Ann Mtg, Vancouver Canada 1997; p1407.