Choline – a differential marker of glutamatergic neurotransmission ?

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Introduction:

Information processing in the brain relies on the release and diffusion of neurotransmitter molecules across the synaptic cleft and on functional coupling to postsynaptic receptors. Thus, the dynamics of synaptic neurotransmitter secretion and reception affect nearly every aspect of brain function and dysfunction and represent highly relevant molecular imaging targets. Proton magnetic resonance spectroscopy allows for the detection of the major neurotransmitters glutamate (Glu) and gamma-amino-butyric acid (GABA) and quantification of their global mean tissue concentrations [1]. However, information about changes in neurotransmitter secretion was so far inaccessible by this method. Another readily detectable spectroscopic marker is free choline (Cho), which contributes to composing cell membranes. The concentration of Cho is very low in most tissue types across the human body and usually only detectable if elevated in disorders such as tumors. In contrast the Cho concentration in the healthy human brain is relatively high making the Cho peak one of the highest resonance lines in a brain spectrum [1]. It remains to be answered why this is the case.

In this work, we demonstrate that the cerebral Cho concentration is related to adaptive changes in neurotransmitter and more specifically glutamate secretion. To this we used the NMDA-receptor antagonist ketamine as a tool compound, which was previously shown by invasive methods to largely increase synaptic glutamate release [2-4].

Methods:

Three independent cohorts of sex- and age-matched healthy subjects (mean age: 32 ± 8.2 years) completed two separate magnetic resonance spectroscopy scans on a Philips Achieva 3T whole-body magnetic resonance unit equipped with a transmit/receive head coil. The first cohort (n=18) underwent a scan session under baseline condition versus a scan session 20 min after onset of an acute infusion of S-ketamine (i.v. bolus of 0.12 mg/kg, infusion of 0.25 mg/kg/h over 40 min) that was continued until the end of the scan. For the second (n=20) and third cohort (n=16) 3-4h or 24h before MR scanning, either placebo or S-ketamine (i.v. bolus of 0.12 mg/kg, infusion of 0.25 mg/kg/h over 40 min) was administered in a cross-over, double-blind, and randomized study design.

Single voxel spectra were acquired using a maximum echo–sampled 2-dimensional J-resolved point-resolved spectroscopy (JPRESS) sequence (6) (TR of 1600 ms, TE ranging from 26 to 224 ms with step size of 2 ms, 100 encoding steps, 8 averages per step) with VAPOR water and interleaved inner volume suppression from a volume of interest (VOI: 18 x 25 x 20 mm) in the pregenual anterior cingulate cortex (PACC) and quantified using ProFit2 (5). Metabolite levels were normalized to either internal water or internal creatine and a segmentation based volume tissue composition correction was applied (7). Pearson correlation analyses between glutamate and choline concentrations were performed for all conditions.

Results:

In all three volunteer cohorts scanned during acute infusion, 3-4 h post infusion or 24 h post infusion choline and glutamate showed a statistically significant correlation exclusively in the Ketamine condition. Neither at baseline nor under placebo infusion choline and glutamate was correlated nor was a correlation between GABA and choline detected under any condition. Neither Cho nor Glu correlated across conditions i.e. baseline versus acute Ketamine infusion in cohort one and Placebo versus Ketamine in cohorts two and three.

Discussion and Conclusion:

A correlation analysis between Cho and neurotransmitter concentrations enables the detection of adaptive changes in neurotransmitter secretion such as increased Glu secretion induced by Ketamine infusion. Cho concentrations are higher in the brain than in other organs of the body due to neurotransmission related membrane restructure processes in the context of neurotransmitter vesicle fusion and possibly also neurotransmitter receptor trafficking.

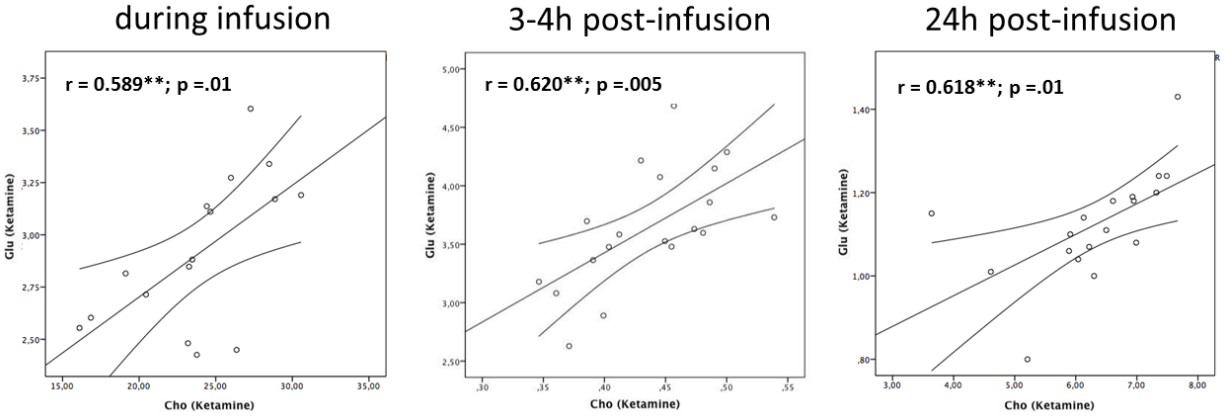

Fig 1: *Correlations between Glu and Cho have been consistently found during, 3-4h post and 24h post Ketamine infusion. In contrast neither at baseline condition nor under placebo infusion Glu and Cho correlate in any of the three sub-cohorts.*

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