MULTIMODAL PET-MRS INVESTIGATION OF GLUTAMATE-DEPENDENT NEURORECEPTOR PLASTICITY IN THE HEALTHY HUMAN BRAIN

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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, which in turn depends on the receptor plasticity. Thus, the dynamics of synaptic neurotransmitter secretion and reception affect nearly every aspect of brain function and dysfunction. Here, we investigate the functional interplay between the major excitatory neurotransmitter glutamate (Glu) and the density of the metabotropic glutamate receptor subtype 5 (mGluR5) that is predominantly found on postsynaptic membranes (1). For the first time, we evaluate a multimodal PET-MRS imaging approach that allows for the investigation of glutamate-dependent neuroreceptor plasticity in the healthy human brain. To that, we combined J-resolved proton magnetic resonance spectroscopy (^{1}H-MRS) with positron emission tomography (PET) using ^{11}C-ABP688, a ligand that binds to an allosteric site on the mGluR5 with high specificity (2) and thus enables the investigation of e.g. glutamate-dependent receptor internalization after pharmacological challenge. As a tool compound, we used the NMDA-receptor antagonist ketamine that was robustly shown to increase synaptic glutamate release (3-5). By focusing on the interplay between these molecular targets using in vivo molecular imaging techniques, we highlight areas of emerging understanding in the physiology of synaptic transmission and pharmacological action.

MATERIALS & METHODS: 20 sex- and age-matched healthy subjects (mean age: 32 ± 8.2 years) completed two separate imaging sessions (at least 7 days apart to avoid carry-over effects) including ^{11}C-ABP688-PET (2) performed in three-dimensional mode on a DVCT PET/computed tomography scanner (GE Medical Systems, Glattbrugg, Switzerland) followed by a ^{1}H-MRS scan on a Philips Achieva 3T whole-body magnetic resonance unit equipped with a transmit/receive head coil. Single voxel spectra were acquired using a maximum echo–sampled 2-dimensional J-resolved point-resolved spectroscopy (JPRESS) sequence (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 supression from a volume of interest (VOI: 18 x 25 x 20 mm) in the pregenual anterior cingulate cortex (PACC, s. Fig) and quantified using ProFit2 (6). Metabolite levels were normalized to internal water and a segmentation based volume tissue composition correction was applied (7). PET data were analyzed using PMOD according to well established routines (8); averaged mGluR5 densities from the spectroscopy VOI were extracted. Before PET 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.

RESULTS: Although the mean levels of glutamate (^{1}H-MRS) and mGluR5 (^{11}C-ABP688-PET) did not change significantly in the PACC after drug administration compared to placebo, we found a highly significant correlation between post-infusion glutamate levels and mGluR5 densities in the PACC following ketamine challenge (r = -.614, p = .005), that was not apparent under placebo conditions (s. Fig). Additional pairwise comparisons revealed increased total choline (tCho) metabolite levels (p = .056) after ketamine administration (1.181 ± 0.122) compared to placebo (1.134 ± 0.108).

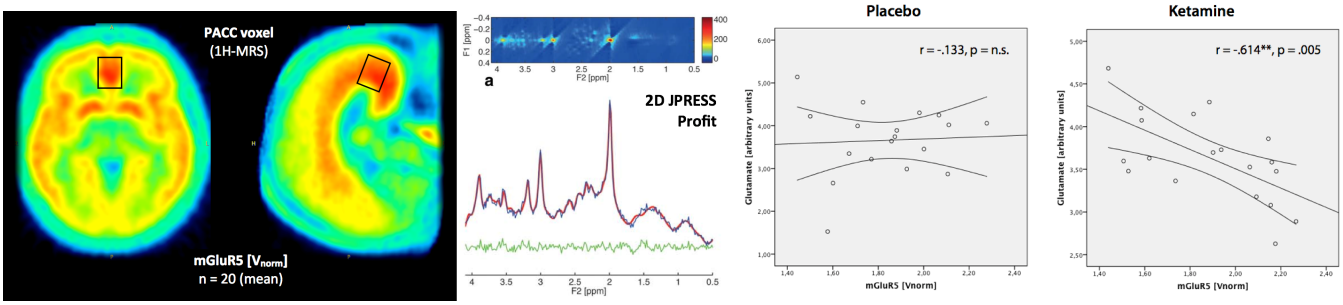

Figure: On the left, the MRS voxel placement (18 x 25 x 20 mm) in the bilateral PACC is shown overlaid on color-coded normalized volumes of distribution (V_{norm}) of 11C-ABP688. In the middle, the measured (blue), fitted (red) and residual (green) signal of a projection of a representative 2D JPRESS spectrum (top) is displayed (6). On the right, correlation plots demonstrate the drug-induced functional coupling (Pearson's r correlation coefficient) between glutamate levels (H_2O-referenced and tissue-corrected arbitrary units) and mGluR5 availability (V_{norm}) in the PACC.

DISCUSSION: To our knowledge, this is the first double-blind, randomized, placebo-controlled PET-MRS study that reports a pharmacological modulation of glutamate-dependent neuroreceptor plasticity in the healthy human brain and thus complements previous reports of increased glutamate release during ketamine challenge (3-5) by providing additional in vivo molecular imaging evidence for drug-induced neurotransmitter-receptor coupling. The increase in total choline levels following ketamine infusion are likely to reflect concurrent changes in molecular dynamics in the synaptic environment due to neuroreceptor trafficking and remodelling of cell membranes. Since the interaction between neurotransmitters and receptors is expected to drive the dynamics of receptor expression (e.g. receptor internalization), a better knowledge of the molecular mechanisms underlying such functional coupling is crucial for the understanding of synaptic plasticity in health and disease. Hence, multimodal and molecular imaging techniques are promising approaches for the in vivo investigation of these processes in humans and animals and offer powerful tools for experimental pharmacology.

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