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 (1H-MRS) with positron emission tomography (PET) using 11C-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 11C-ABP688-PET (2) performed in three-dimensional mode on a DvCT PET/computed tomography scanner (GE Medical Systems, Glattbrugg, Switzerland) followed by a 1H-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 suppression 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 (1H-MRS) and mGluR5 (11C-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).

REFERENCES