EFFECTS OF AN ANTIDEPRESSANT DOSE OF KETAMINE ON PREFRONTAL ASPARTATE, GLUTAMINE AND GABA LEVELS IN HEALTHY SUBJECTS: ASSESSING THE POST-INFUSION INTERVAL WITH 1H-MRS

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INTRODUCTION: Recently, the discovery of the antidepressant effect of NMDA-receptor antagonism stimulated a novel research interest in antidepressant drugs targeting the glutamatergic system [1]. Especially ketamine, which has been mostly used for anaesthetic and analgesic purposes, has emerged as an easily accessible and safe research compound for the evaluation of NMDA-receptor antagonism as a potential biomechanism for rapid antidepressant intervention [2]. Increasing evidence points to a glutamatergic deficit and impaired neuron-glia interaction that is most consistently found in the anterior cingulate cortex (ACC) and that correlates with the clinical severity, the current state, and the duration of major depressive disorder (MDD) [3-5]. In preclinical studies, a short term increase in glutamate release has been reported 30-180 minutes after ketamine administration [6-7] that is associated with the stimulation of neurotrophic and synaptic signalling pathways as putative mediators of the antidepressant response [8]. Proton magnetic resonance spectroscopy (1H-MRS) in healthy human subjects confirmed this finding, as an increase in glutamate and glutamine concentrations has been found during ketamine challenge [9,10]. Interestingly, a reduced Glx/glutamate ratio as a putative surrogate marker of glutamine was associated to greater improvement in response to ketamine treatment in MDD patients, suggesting that a disturbed neuroglial homeostasis may represent a relevant neuropathological target in a subgroup of MDD patients [11]. Hence, to further elucidate the biomechanism of ketamine’s antidepressant action, we aimed at investigating the neurometabolic changes in the 3-4 hour post-infusion interval when the antidepressant effect usually starts to build up [2]. To that we acquired 1H-MRS data from the pregenual anterior cingulate cortex (PACC) in healthy subjects approximately 210 minutes after the double-blind, randomized, intravenous administration of either placebo or an antidepressant dose of ketamine.

MATERIALS & METHODS: A total of 13 healthy subjects (7 women, 6 men; mean age: 30.7, SD 8.9) with no history of neurological or psychiatric illness were recruited for this study. All subjects completed two separate MRS sessions following the double-blind, randomized administration of either ketamine or placebo on a Philips Achieva 3T whole-body magnetic resonance unit equipped with a transmit/receive head coil. Approximately 210 minutes prior to the MRS session, S-ketamine was administered as an intravenous bolus of 0.12 mg/kg, followed by a continuous infusion of 0.25 mg/kg/h over 40 minutes. Single voxel 1H MRS data were acquired from a volume of interest (VOI: 18 x 25 x 20 mm) in the pregenual anterior cingulate cortex (PACC, Fig. 1), a brain region implicated in mood regulation and the pathophysiology of MDD. To enable unambiguous and simultaneous in vivo quantification of glutamate, glutamine and GABA concentrations along with concentrations of metabolites involved in energy metabolism MRS data were acquired using a maximum echo–sampled 2-dimensional J-resolved point-resolved spectroscopy (JPRESS) sequence including outer volume suppression (OVS) and quantified using ProFit 2.0 (for details cf. [12]). 2 subjects had to be excluded from pairwise statistical comparisons due to poor spectral quality in one of the imaging sessions.

RESULTS: First, we report a significant increase in glutamine (paired t-test, n=11, p=0.039) as well as a significant decrease in aspartate concentrations (p=0.023) in the 3-4 hour post-infusion interval after ketamine administration compared to placebo (Fig. 2). Second, we report a trend-level increase in the glutamine to glutamate ratio (p=0.062) as well as a trend-level decrease in GABA concentrations (p=0.099) in the ketamine compared to the placebo condition (Fig. 2 and 3). The concentrations of other metabolites such as N-acetylaspartate (NAA), glutamate (Glu), glucose (Glc), myo-inositol (mI), or choline (Cho) did not change significantly between the experimental conditions. However, anterior cingulate glutamate following ketamine administration was significantly related to psychotomimetic side effects during ketamine infusion assessed by the Altered States of Consciousness rating scale ‘5D-ASC’ [13] with increasing levels of glutamate indicating higher scores on the ,anxious ego dissolution’ (r=.600, p=0.026) and ,negative derealisation’ (r=.642, p=0.017) subscale as well as a higher overall sum score in items corresponding to the PANSS positive syndrome rating scale (r=.547, p=0.041).

DISCUSSION: To our knowledge, this is the first double-blind, randomized, placebo-controlled MRS study that reports a pharmacological modulation of metabolite concentrations in the 3-4 hour post-infusion interval following ketamine administration in healthy subjects. Thus, this study complements previous reports of increased glutamate and glutamate concentrations during ketamine challenge [9,10] by expanding the temporal window of observation. An increase in glutamate relative to glutamine concentrations has been proposed to mirror an increase in synaptic glutamate release and overall neuroglial glutamate-glutamine-cycling [3]. The post-infusion changes in metabolite concentrations could be interpreted as a shift in the excitatory (glutamine-to-glutamate ratio) to inhibitory (GABA) balance, in terms of an increased glutamatergic and a decreased GABAergic signalling in the anterior cingulate cortex following NMDA-receptor antagonism. Interestingly, increased levels of glutamate post-infusion were associated with increased levels of psychotomimetic side effects during the infusion. In line with Mangia et al. [14] the decrease in aspartate might indicate an elevated level of oxidative energy metabolism following elevated neurotransmitter signalling. Most notably, reduced glutamine levels were found in MDD patients with high levels of anhedonia [4], thus the increase in glutamine concentrations that we observe in healthy subjects during the 3-4 hour post-infusion interval when the antidepressant effect usually starts to build up may play an important role in restoring parts of the disrupted neurometabolic homeostasis in MDD patients. However, due to the restriction to healthy subjects and the small sample size, these findings have to be considered as preliminary and need further replication in a clinical population.

REFERENCES