Ketamine Improves Astroglial Metabolic Activity and Neurotransmission in Social Defeat Model of Depression: A ^{1}H-[^{13}C]-NMR Study

Pravin Kumar Mishra[1] and Anant Bahadur Patel[1]
[1]*Centre for Cellular and Molecular Biology, Hyderabad, India*

TARGET AUDIENCE: Clinicians and researchers interested in brain energy metabolism and intervention in depression.

INTRODUCTION: Depression is a complex neuropsychiatric disorder with high morbidity rates and increased mortality[1]. Recent studies have indicated perturbations in glutamatergic and GABAergic neuronal metabolic activity in depression[2]. Although astroglia play a major role in recycling and metabolism of neurotransmitters across synapse[3], their functional characteristics are not very clear under depression. Recently, it has been shown that single dose of ketamine (an NMDA receptor antagonist) produces rapid and long lasting antidepressant effect[4]. Furthermore, sub-anesthetic dose of ketamine restored the neuronal metabolic activity in social defeat (SD) model of depression[5].

PURPOSE: To understand astroglial metabolic activity in the SD model of depression, and evaluate the effects of ketamine on the astroglial metabolic pathway and neurotransmitter cycling.

MATERIALS AND METHODS: All animal experiments were performed under approved protocols by the Institutional Animal Ethics Committee. Two month old male C57BL6 mice were used for the study. Mice were divided into four groups: Group (i) Control+normal saline (NS, n=6), Group (ii) Control+Ketamine (n=8), Group (iii) SD+NS (n=7) and Group (iv) SD+Ketamine (n=8). Group (iii) and (iv) mice were subjected to social defeat for 10 days[6]. Ketamine (10 mg/kg, i.p.) was administered in Group (ii) and (iv) mice on 12th day, while, the rest of mice were given NS. Depression like phenotype was assessed using sucrose preference and social interaction test[6]. For metabolic measurements, urethane (1.5 g/kg, i.p.) anesthetized mice were infused with [2-^{13}C]acetate for 15 min[7]. Mice head was frozen in-situ in *liq.* N_2, and metabolites were extracted from frozen prefrontal cortex (PFC)[8]. The concentration and ^{13}C labeling of metabolites were measured by ^{1}H-{^{13}C}-NMR spectrum of PFC extracts[9].

RESULTS AND DISCUSSION: Mice subjected to social defeat exhibited significant ($p<0.01$) reduction in sucrose preference (SD 62±2%; Control 86±3%), social interaction (SD 57±6%; Control 139±6%), and increased immobility time in forced swim test (SD 71±7; Control 15±3 s) as compared to control (Fig. 1). Acute ketamine treatment in SD mice was able to restore sucrose preference (85±2%), social interaction (133±18%) and immobility time (16±5 s) to the control level. The analysis of NMR spectrum (Fig. 2A) suggested that homeostasis of neurometabolites remains unperturbed in SD mice. The ^{13}C labeling of Gln_{C4} (SD 0.38±0.05; Control 0.50±0.04 μmol/g, p=0.006), Glu_{C4} (SD 0.39±0.07; Control 0.52±0.06 μmol/g, p=0.0005) and $GABA_{C2}$ (SD 0.06±0.01; Control 0.07±0.01 μmol/g, p=0.14) was found to be decreased significantly in the PFC of SD mice (Fig. 2B). The cerebral metabolic rate of acetate oxidation ($CMR_{Ac(ox)}$), estimated by incorporation of ^{13}C label into brain Gln_{C4}, Glu_{C4}, and $GABA_{C2}$, was found to be decreased significantly (p=0.0017) in SD mice (0.056±0.08 μmol/g/min) as compared to controls (0.072±0.06 μmol/g/min, Fig. 3). Acute administration of ketamine restored the ^{13}C labeling of Gln_{C4} (0.47±0.05 μmol/g), Glu_{C4} (0.56±0.07 μmol/g), $GABA_{C2}$ (0.08±0.01 μmol/g) and $CMR_{Ac(ox)}$ (0.073±0.008 μmol/g/min) to control values. Acetate is exclusively oxidized in the astrocytes. Hence, $CMR_{Ac(ox)}$ reflects the metabolic activity of astrocytes. The finding of decreased $CMR_{Ac(ox)}$ suggests towards reduced metabolic activity of astrocytes in SD mice. Moreover, reduction in ^{13}C labeling of Glu_{C4} points towards decreased glutamate-glutamine cycling under depression. Most importantly, the findings of increased $CMR_{Ac(Ox)}$ and Glu_{C4} labeling in ketamine treated mice suggests improved astroglial metabolic activity and glutamate-glutamine cycling with acute ketamine intervention.

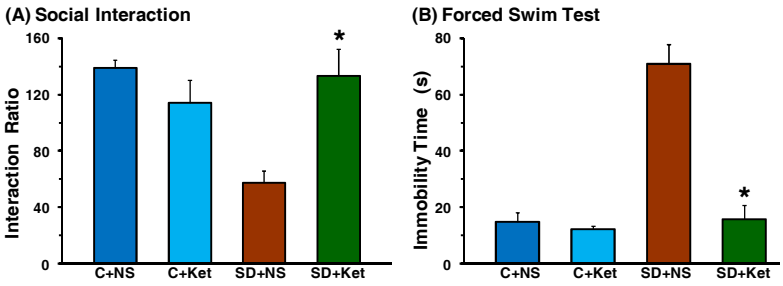

Fig. 1 (A) Social interaction and (B) Forced swim test in ketamine treated mice

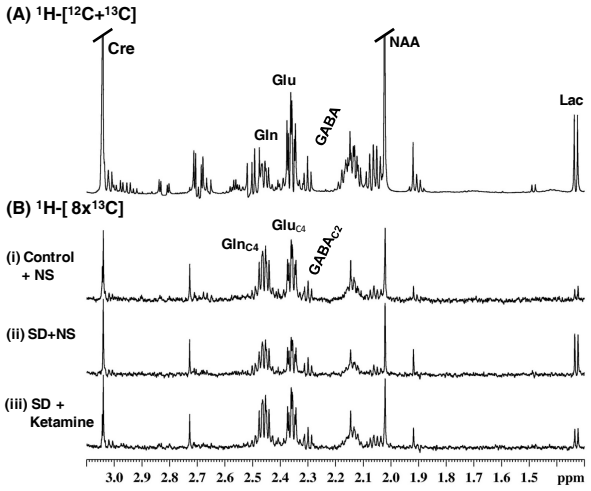

Fig. 2 ^{1}H-[^{13}C]-NMR spectra of extract depicting **(A)** Concentration and **(B)** ^{13}C Labeling of metabolites in PFC

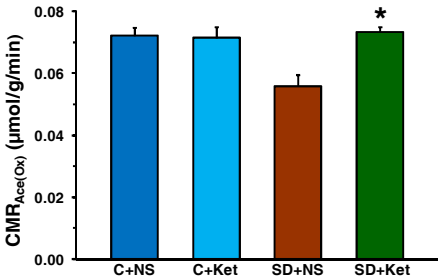

Fig. 3 Cerebral metabolic rate of acetate oxidation under Ketamine exposure

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