



# Expression of glucose metabolism genes in a psychosis model: a molecular link between NMDA receptor hypofunction and metabolism disorders?

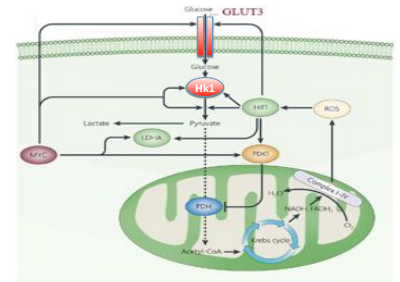
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## Introduction

Ketamine, a non-competitive NMDA receptor (NMDA-R) antagonist, has been used to model psychosis in humans. NMDA-R antagonist administration in rat may cause excessive glutamate release on non-NMDA-Rs, thereby inducing neurotoxic damage in cerebral areas involved in the pathophysiology of psychotic symptoms, and possibly providing a preclinical model of psychosis. Subanaesthetic doses of ketamine are known to affect the cerebral glucose metabolism in several cortical and hippocampal areas. Molecules involved in glucose metabolism, such as Hexokinase I (Hk1) and Glucose Transporter 3 (GLUT3) (Fig.1), may play a role in the pathophysiology of psychosis. Evidence exists that these proteins may be involved in homeostatic response to neurotoxic damage<sup>[1]</sup> and to excessive glutamate release<sup>[2]</sup>. The aim of this study was to verify whether ketamine at subanaesthetic (12mg/kg) and subanaesthetic neurotoxic (50 mg/kg) doses might alter the expression of *Hk1* and *GLUT3* genes.



Modified from Dang et al., 2008

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Figure 1. Hk1 and GLUT3

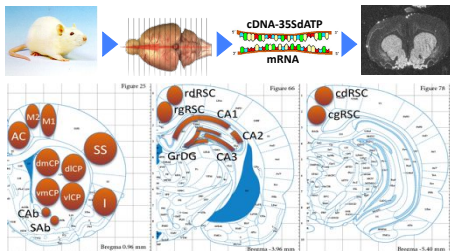


Figure 2. Materials and methods

## Materials and methods

We investigated, by radioactive in situ hybridization, gene expression of *Hk1* and *GLUT3* in the brain of male Sprague-Dawley rats after an acute treatment by: ketamine 12mg/kg; ketamine 50mg/kg; vehicle (VEH). Coronal sections were obtained, *in situ* hybridization was performed and the quantitation of the autoradiographic signal was obtained by an image analysis system in functionally correlated cortical and subcortical Regions Of Interest (ROIs) (Fig.2).

The data were analyzed by a one-way analysis of variance (ANOVA). Student-Newman-Keuls post hoc test was used to assess significant differences between groups.

## Results

*Hk1* gene expression was increased by ketamine 50mg/kg in the motor cortex (M1), in the dorsomedial (dmCP), dorsolateral (dlCP), ventrolateral (vlCP) and ventromedial (vmCP) regions of the caudate-putamen, in the core (CAB) and shell (SAB) of the nucleus accumbens and in the caudal granular (cgRSC), caudal dysgranular (cdRSC) and rostral granular (rgRSC) regions of the retrosplenial cortex (Fig.3). *Hk1* gene expression was increased by ketamine 12mg/kg and ketamine 50mg/kg in CA2, CA3 and dentate gyrus of hippocampus (Fig.3). No significant changes in *GLUT3* gene expression were detected in the ROIs explored (Fig.4).

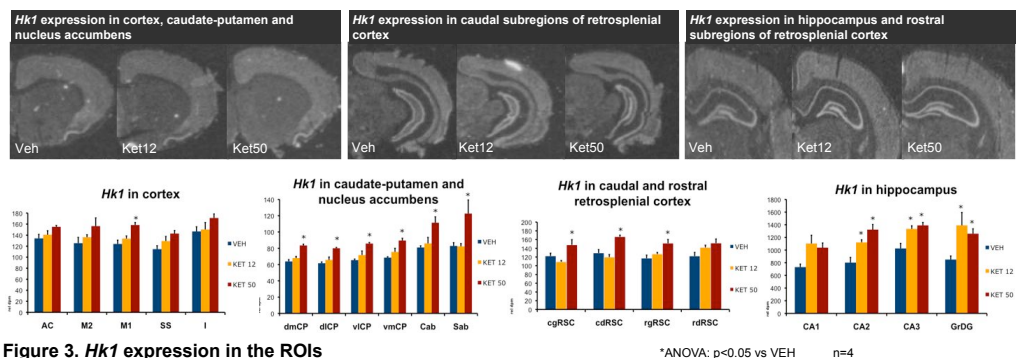


Figure 3. *Hk1* expression in the ROIs

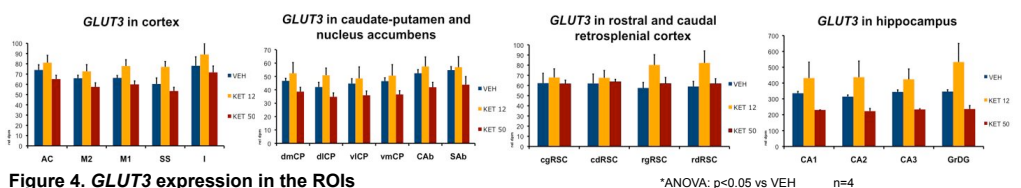


Figure 4. *GLUT3* expression in the ROIs

ROIs: AC, anterior cingulate cortex; M2, medial agranular cortex; M1, motor cortex; SS, somatosensory cortex; I, insular cortex; cgRSC, cdRSC, rgRSC, rdRSC, caudal granular, caudal dysgranular, rostral granular and rostral dysgranular retrosplenial cortex, respectively; dmCP, dlCP, vlCP, vmCP, dorsomedial, dorsolateral, ventrolateral and ventromedial region of the caudate-putamen, respectively; CAB and SAB, core and shell of the nucleus accumbens; GrDG, granular layer of the dentate gyrus of hippocampus.

## Discussion

The distribution of *Hk1* expression increase is partially consistent with previously described distribution of glucose uptake by ketamine. Recent evidence suggests Hk1 may have an antiapoptotic role. The preferential increase in *Hk1* expression at ketamine neurotoxic doses only may be a direct consequence of neurotoxic action of ketamine.

Moreover, our data may suggest that hippocampal areas are sensitive at both neurotoxic and non-neurotoxic doses of ketamine. Our data confirm previous *in vitro* observations of non-increased *GLUT3* expression after transient glutamate excitation.

Other molecules involved in glucose metabolism (such as Akt and GSK3) are thought to be involved in the pathogenesis of psychosis and are known as signaling pathways representing a potential target for novel pharmacological intervention (Fig.5). Our results suggest a possible link between NMDA-R hypofunction and alterations of glucose metabolism in an experimental model of psychosis.

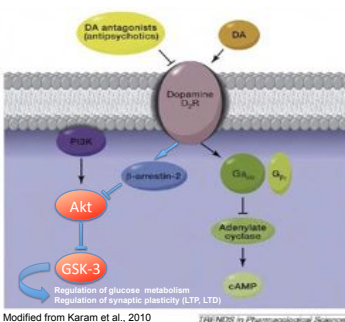


Figure 5. Akt/GSK-3 mediated signaling

## References:

- [1] Pastorino J.G., Hoek J.B., 2008 Regulation of Hexokinase binding to VDAC. J Bioenerg Biomembr 40(3), 171-182.
- [2] Weissová P., Concannon C.G., Devocelle M., Pohn J.H., Ward M.V., 2009 Regulation of glucose transporter 3 surface expression by the AMP-activated protein kinase mediates tolerance to glutamate excitation in neurons. J Neurosci. Mar 4, 29(9):2997-3008