Where and when ketamine alters the dopamine system: translational implications for drug addiction and psychoses.

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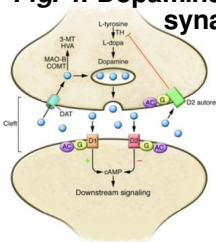
A dysregulated interplay between glutamate and dopamine systems in cortico-subcortical brain regions may be involved in the pathophysiology of psychoses and drug-addiction. Ketamine, a non-competitive antagonist of the N-methyl-D-aspartate receptor (NMDA-R) used in preclinical models of psychosis, affects dopaminergic transmission in both synthesis and release of dopamine, as well as in receptor binding and availability of the dopamine transporter (DAT). Dopamine transporter (DAT), dopamine receptor 1 (D1R) and dopamine receptor 2 (D2R) represent functional markers of the dopamine system and have been proposed as candidate genes in schizophrenia[1] (*Fig.1*).

Fig. 1. **Dopaminergic synapse**



Modified from Blackstone, J *Clin Invest.* 2009

We investigated the spatial and temporal distribution of DAT, D1R and D2R transcripts in the brain of male Sprague-Dawley rats after acute (ketamine 12 mg/kg or 50 mg/kg) and subchronic (7 days, 12 mg/kg) treatment by ketamine. *In situ* hybridization was performed and the autoradiographic signal was analyzed in cortical and subcortical functionally correlated ROIs (*Fig.2*). 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.

Fig. 2. **Experimental design**

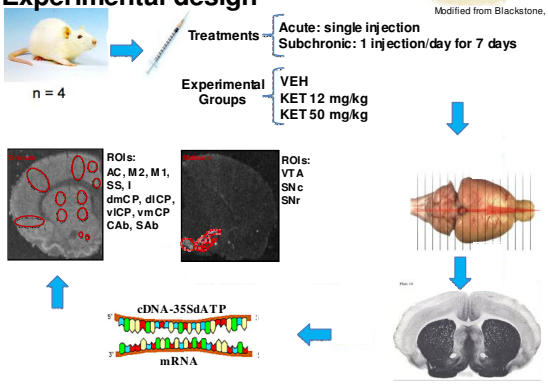
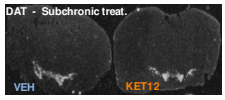
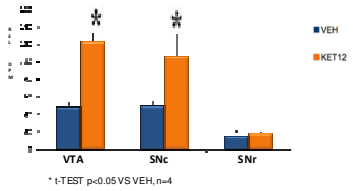


Fig. 3. **DAT in Midbrain – Subchronic treatment**

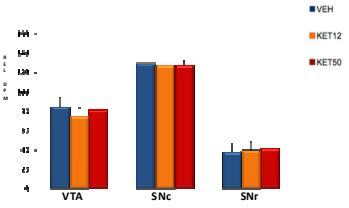




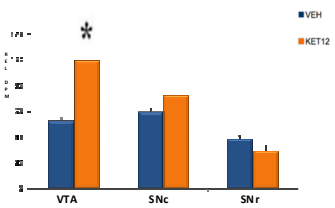
* t-TEST p<0.05 VS VEH, n=4

DAT expression was increased in VTA and SNc after subchronic treatment (*Fig.3*). In a previous work, we showed a significant increase of DAT expression in midbrain after acute treatment by ketamine at 12 mg/kg and 50 mg/kg *(Iasevoli et al., 2007).*

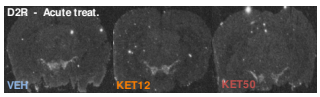
Fig. 4. **D2R in Midbrain – Acute and Subchronic treatment**

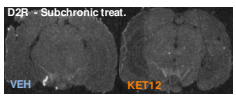


ANOVA p>0.05 VS VEH, n=4



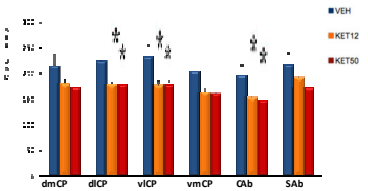
* t-TEST p<0.05 VS VEH, n=4



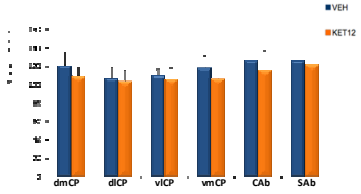


D2R expression was increased in the VTA after subchronic treatment, while it was not affected in the acute paradigm (*Fig.4*). Comparative analysis showed that the relative expression of D2R was increased in the VTA after the subchronic compared to the acute treatment (t-test = 4.16).

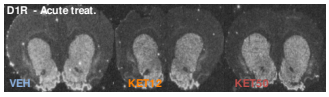
Fig. 5. **D1R in Striatum – Acute and Subchronic treatment**

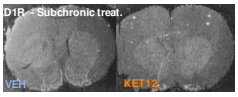


*ANOVA p<0.05 VS VEH, n=4



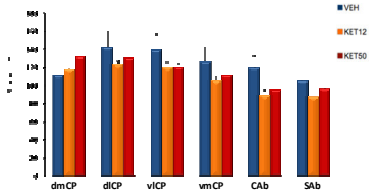
t-TEST p>0.05 VS VEH, n=4



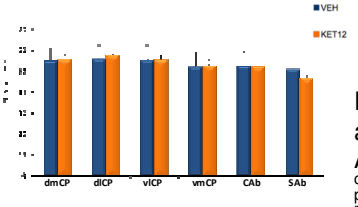


In the acute paradigm, D1R expression was reduced in dlCP, in vlCP and in the Cab by both ketamine doses. In the subchronic paradigm, no significant changes in D1R expression were found (*Fig.5*).

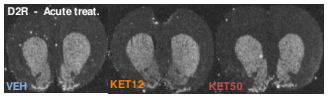
Fig. 6. **D2R in Striatum – Acute and Subchronic treatment**

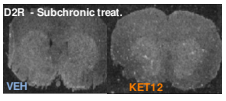


*ANOVA p<0.05 VS VEH, n=4



t-TEST p>0.05 VS VEH, n=4





D2R expression was not significantly affected in striatal regions after both acute and subchronic treatment protocols (*Fig.6*).

Abbreviations: for Midbrain sections: VTA, ventral tegmental area; SNc, substantia nigra pars compacta; SNr, substantia nigra pars reticulata. For Striatum sections: AC, anterior cingulate; M2, premotor cortex; M1, motor cortex; SS, somatosensory cortex; I, insula; dmCP, dlCP, vlCP, vmCP, respectively dorsomedial, dorsolateral, ventrolateral and ventromedial region of caudato-putamen; CAb, SAb, respectively core and shell of nucleus accumbens.

These results may confirm previous evidence of increased dopaminergic output after pharmacological perturbations of the glutamate system. Our data may also suggest that acute and subchronic ketamine cause differential and complex adaptive changes in dopamine neurocircuitry, specially at striatum and midbrain levels.
Trascriptional striatal decrease of D1R may represent a mechanism of receptorial down-regulation possibly induced by the increased dopaminergic output associated with acute ketamine administration. At the midbrain level, the increase in DAT and D2R expression after subchronic ketamine administration could underlie neurochemical sensitization in mesocorticolimbic circuitry. This phenomenon is thought to be involved in the pathophysiology of psychostimulant-induced psychosis and could explain some clinical aspects of relapsing acute psychotic states in schizophrenia[2].

Bibliography
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[2] Yui K., Goto K., Ikemoto S., Ishiguro T., Angrist B., Duncan G.E., Sheitman B.B., Lieberman J.A., Bracha S.H., Ali S.F. 1999 Neurobiological basis of relapse prediction in stimulant-induced psychosis and schizophrenia: the role of sensitization. Mol Psychiatry Nov 4(6), 512-523

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