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# OPIOIDERGIC SYSTEM AND N-METHYL D-ASPARTATE RECEPTOR (NMDA-R) HYPOFUNCTION: TRANSLATIONAL IMPLICATIONS FOR THE PATHOPHYSIOLOGY OF PSYCHOSIS AND DRUG ADDICTION

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Enkephalin is an opioidergic neuromodulator that has been implicated in long-term behavioural sensitization after administration of drugs of abuse. Enkephalin is also a molecular marker of GABAergic neurons in the striato-pallidal pathway that is involved in sensory-motor gating and has been considered dysfunctional in the pathophysiology of psychosis.

In this study we investigated in male Sprague Dawley rats putative changes in Enkephalin transcripts by in situ hybridization after acute or subchronic administration of ketamine in either high or low subanaesthetic doses (50 mg/kg and 12 mg/kg respectively). Ketamine is a non-competitive NMDA-R antagonist that perturbs glutamate neurotransmission and provides a preclinical model of psychosis-like behaviour in rats.

In the acute paradigm the expression of Enkephalin was reduced in the motor, premotor, somatosensory cortices as well as in anterior cingulate. In the subchronic paradigm Enkephalin expression was reduced in the premotor cortex, in the ventromedial caudate-putamen and in the shell of nucleus accumbens. Comparative analysis showed that the relative decrement in gene expression was not significantly different between the acute and subchronic paradigm for each region of interest.

Changes in distribution of Enkephalin expression and correlation analysis of functionally related brain regions suggest that Enkephalin transcripts reduction may be implicated in the motivational aspects of drug addiction and may help explaining some aspects of the pathophysiology in ketamine-induced psychosis.

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