Ketamine is a Potent Antidepressant in Two Rodent Models of Depression

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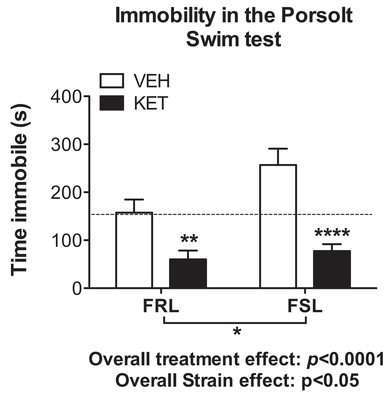
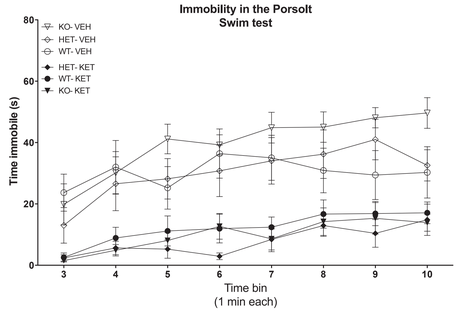
BACKGROUND

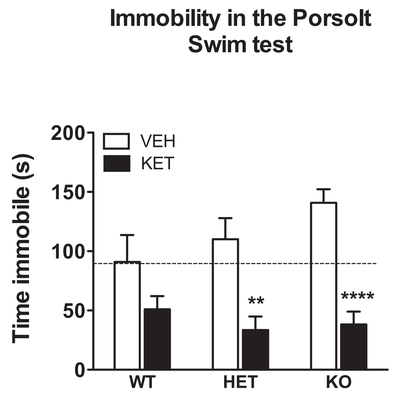
Mood disorders are the major cause of "Years of life lived with disability" and of "Years of life lost because of premature death". Methods to prevent the onset of disease have not been developed and the problem is growing due to the increased life-span and higher depression frequency with increasing age. Using currently available drugs, mostly targeting the monoaminergic systems, 30-40% of patients are only partial- or non-responders and additional compounds based on same mechanisms will not solve the problem. Thus there exists a major unmet medical need to develop treatments based on different modes of action. Changes in the monoaminergic systems may be sufficient but not necessary etiologic/pathophysiological factors leading to depression and converging evidence indicates that other systems, such as the glutamatergic and peptidergic are of paramount importance. Since intravenously infused ketamine alleviates depression in treatment resistant patients, we decided to explore behavioral and molecular effects of ketamine in two different rat models of depression with the aim to, at least in part, elucidate its mechanisms of action.

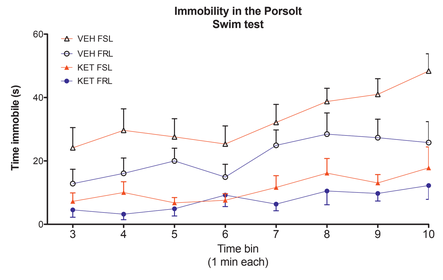
METHODS

All experiments were approved by the Karolinska Institutet´s Committee for Animal Protection. Two rat models, bred at the Karolinska Institutet, i. the Flinders Sensitive Line (FSL) and their controls, the Flinders Resistant Line (FRL), and ii. the SERT KO (homozygous, heterozygous, and the wild type) were used. Male animals were injected 10mg ketamine/kg body weight or vehicle and the Open Field Test (OF) and Porsolt Forced Swim Test (FST) carried out 30 respectively 40 min later. The tests were recorded and subsequently scored blindly using the NOLDUS system. One hour after the injection the animals were euthanized, the brains harvested, immediately deep-frozen, and stored for future analyses. Brains were dissected into frontal cortex, hippocampus and striatum and rtPCR and Western blot used for analyses of NMDA, AMPA, and mGlu2/3 receptors, neuropeptide Y and NPY-Y1 receptor, BDNF and mTor. 2-way ANOVA and Bonferroni post-hoc test were used for statistical analysis.









RESULTS

Behavioral results are presented in this poster.

FSL and FRL

(1) Open Field:

i. FSL moved significantly faster (cm/sec) and covered larger distance (distance/cm) than FRL in the test (p´s< .01).

ii. Ketamine had no significant effect on locomotion.

(2) Forced Swim Test:

i. In line with previous experiments, FSL showed greater baseline immobility compared with FRL (p<.05).

ii. In both strains, ketamine markedly reduced immobility time, both the total time and when assessed minute by minute (p<.0001). Effect of ketamine was more pronounced in the FSL.

SERT KO

(1) Open Field:

i. Although the SERT KO homozygous rats moved faster and covered larger distance than the heterozygous and the wild type, the differences did not reach the conventional statistical levels.

ii. Ketamine had no significant effect on locomotion.

(2) Forced Swim Test:

i. Homozygous rats had larger mean immobility time, though not reaching the statistical level of significance, compared with the heterozygous and the wild type rats p<.001).

ii. Ketamine markedly reduced the immobility time, both the total time and when assessed minute by minute, in both the homozygous and heterozygous animals (p<.001). Ketamine also reduced, though not reaching the statistical level of significance, the immobility time in the wild type rats

COMMENT

This first study of ketamine effects in two rodent models of depression shows that a single injection of the compound has marked behavioral effects in the forced swim test, generally accepted as a tool to assess antidepressant action of putative antidepressants. The results are consistent with the effects of single ketamine injection in treatment resistant depressed patients. Of note, since the FSL and SERT KO models are phenotypically similar but represent clearly distinct brain pathologies, analysis of ketamine effects on brain molecular and cellular levels will likely contribute to identification of the pathways necessary for antidepressant effects, independent of the underlying pathologies.

FINANCIAL DISCLOSURE:

All authors reported no financial interest or potential conflict of interest

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