Targeting the Alpha7 Nicotinic Receptor Subtype to Restore Working Memory Deficits in Rats Following Sub-chronic Ketamine Exposure

Introduction

- Schizophrenia is a debilitating disorder affecting ~1% of the population.
- Cognitive deficits are one of the core disabling features of the disease, yet remain inadequately treated by any pharmacological or behavioural therapy currently available.
- Clozapine is currently the most clinically-effective antipsychotic for treating cognitive deficits.
- Nicotine can improve cognitive performance in animal models and may be used as a form of self medication in schizophrenic patients since around 80% of this group are regular smokers.

Aims

- To assess the effects of sub-chronic ketamine exposure on non-spatial working memory using the Odorant Span Task (OST).
- To validate the significance of ketamine-induced deficits in the OST as a model of impaired cognition using the clinically-effective clozapine and U404039, a novel generation antipsychotic.
- To assess the ability of nicotine, nicotine agonists and nicotinic positive allosteric modulators (PAMs) to restore OST performance in rats treated with sub-chronic ketamine exposure.
- To assess the contribution of the α7 receptor to this restoration by antagonising the α7 nAChR with methyllycaconitine (MLA).

Nicotine

- Nicotine reversed ketamine-induced deficits in a dose-dependent manner.
- Nicotine also improved span length in control animals.

α7 Agonists

- Both PAM’s significantly improved OST performance; this effect was blocked by α7 antagonist MLA which also impaired performance in control subjects.

Methods

- Male hooded Lister rats weighing 200-300g were given an intraperitoneal injection of ketamine (100mg/kg) and xylazine (10mg/kg) followed anesthetised with intratracheal intubation.
- Once performance was stable, animals were treated with nicotine, PNA543612, clozepine or U404039 to assess their ability to restore ketamine-induced deficits in OST performance to pre-ketamine baseline.

Stability of Ketamine Deficits

- Ketamine produced significant deficits, persistent over 21 days.
- Once performance was stable, animals were treated with nicotine, PNA543612, clozepine or U404039 to assess their ability to restore ketamine-induced deficits in OST performance to pre-ketamine baseline.

γ-Frequency Network Oscillations

- In the prelimbic region of the PFC, the α7 nAChR agonist compound ‘X’ increased γ-frequency network oscillations in the prefrontal cortex (7).
- Knockout targeting α7 nAChR’s can enhance γ-frequency network oscillations in these regions is still unknown.

Conclusions

- Ketamine induces significant long lasting and stable deficits in OST performance.
- This deficit was fully reversed with acute nicotine administration and also improved performance in the control subjects.
- The α7 and α4β2 nicotinic agonists improved performance in ketamine-treated animals but had differing effect in controls; PHA543613 impaired performance in control animals, both dietary choline and 5IA had no effect on control animals where as nicotine-supplemented diet.
- Both α7’s significantly improved OST performance; this effect was blocked by α7 antagonist MLA which also impaired performance in control subjects.

These data suggest that the both the α7 and α4β2 nAChR subtypes may have a role in modulating improvements in OST task performance.
- Both application of nicotine increases γ-frequency network oscillations in the prelimbic region of the PFC in normal animals.
- This effect is blocked by broad spectrum nAChR antagonist mecamylamine.

These data support the use of nicotine in the OST to model cognitive deficits in schizophrenia and indicates nicotine and nicotinic agonists as viable targets for the treatment of neurocognitive disorders.

References

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