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FESTIVAL OF NEUROSCIENCE

23 - 26 April 2023 | Brighton, UK

Book of abstracts

Mental Health & Neuropsychiatric Disorders

Poster number: M_PZ2_033 (TP)

Sub-Theme: Dopamine, Nicotinic Receptors, and Neuromodulation: Exploring Therapeutic Strategies for Schizophrenia and Parkinson's Disease

Effect of alpha-4 beta-2 nicotinic acetylcholine receptors on L-DOPA-induced dyskinesia in 6OHDA rat model of Parkinson's Disease

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Introduction: Accumulating evidence suggests that CNS α4β2 nicotinic acetylcholine receptors (nAChRs) are important targets for the development of therapeutic approaches for Parkinson's disease (PD). L-DOPA is the gold standard treatment for PD but within a few years, dyskinesia presenting as abnormal involuntary movements (AIMs) becomes a debilitating side effect of treatment. Extensive pre-clinical work using a wide variety of rodent and primate models shows that nicotine not only protects against damage to nigrostriatal and other neuronal cells, but is also antidyskinetic. This suggests that nicotine or sub-unit selective nAChR agonists may be disease modifying and antidyskinetic. Studies in several parkinsonian animal models including hemi-parkinsonian rats show that nicotine reduces L-DOPA-induced AIMs but the role of α4β2 nAChRs has not been previously investigated in dyskinesia. The aim of this study therefore, is to investigate whether α4β2 nAChRs possess therapeutic antidyskinetic potential .

Method: This study evaluated the role of A85380, an α4β2 agonist and dihydro-β-erythroidine hydrobromide (DHβE), an α4β2 competitive antagonist in a hemi-parkinsonian rat model. Rats were unilaterally lesioned with 8µg 6-hydroxydopamine then primed with 8mg/kg L-DOPA plus 15 mg/kg benserazide given orally once daily for 33 days until stable AIMs developed. The effect of A85380 at doses 0.001- 0.01mg/kg and DHβE at doses 1-10mg/kg were examined on AIMs induced by L-DOPA/benserazide treatment by blinded observers in a latin-square design.

Approaches for statistical analysis: The AIMs scores for each experiment were analysed using a two-way ANOVA (time x concentration) and $p \leq 0.05$ was considered statistically significant.

Results and conclusion: Treatment with 0.003 and 0.01mg/kg A85380 significantly reduces total ALO (axial, limb and orolingual) AIMs (n=12; *$p \leq 0.05$) but has no significant effect on locomotive AIMs. In addition, treatment with DHβE did not significantly affect L-DOPA induced ALO AIMs or locomotive AIMs. Therefore, the α4β2 agonist, A85380 was extremely potent in reducing AIMs in the rat hemiparkinsonian model suggesting that α4β2 nAChR drugs may be useful in reduction of established dyskinesia in man.