Are nicotinic acetylcholine receptors a relevant target for novel antidepressants?

Jesper Tobias Andreasen, MSc

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Official opponents: Mark Tricklebank, UK, Mohammed Shoaib, UK, and Kimmo Jensen.

Tutors: Ove Wiborg and Naheed Mirza.

Correspondence: Jesper Tobias Andreasen, Agerlandsvej 9, 2300 Copenhagen S, Denmark.

Email: repseja@hotmail.com

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ABSTRACT

The present PhD project was carried out at NeuroSearch A/S and Center for Psychiatric Research, Aarhus University. The aim was to examine nicotinic acetylcholine receptors (nAChRs) as a potentially relevant target for novel antidepressants. This was approached with rodent behavioural assays predictive of antidepressant activity, namely the mouse forced swim test (mFST), the mouse tail suspension test (mTST), and the rat chronic mild stress (CMS) model of depression.

In the mFST and the mTST, both agonists and antagonists at nAChRs induced antidepressant-like effects, depending on the mouse strain tested. Further, the results indicated that both high-affinity $\alpha4\beta2$ and low-affinity $\alpha7$ nAChRs – the two predominant nAChRs in the mammalian brain – are involved in the effects observed. It is suggested that stimulation and inhibition of nAChR induces antidepressant-like effects via partially different mechanisms.

In addition to investigating effects of nAChRs ligands per se, the potential interaction between nAChR modulation and effects of antidepressant drugs were studied in female NMRI mice in the mFST and mTST. Acute administration with nicotine facilitated the activity of two antidepressant drugs acting via distinct mechanisms, namely citalopram and reboxetine, reuptake inhibitors selective for serotonin or noradrenaline, respectively. A subsequent study revealed that the activity of citalopram and reboxetine in the mFST was enhanced by selective activation of either $\alpha4\beta2$ or $\alpha7$ nAChRs, suggesting that both receptor subtypes may be involved in nicotine-enhanced action of antidepressants in this test. Enhancement of the effects of antidepressant drugs was also observed after chronic nicotine treatment.

In the rat CMS model of depression exposure to CMS induces decreased voluntary intake of a sucrose solution. This is thought to mimic anhedonia in clinical depression. Depression is also associated with deficits of several cognitive domains, including working memory and attention. Likewise, CMS exposure was found to disrupt performance in the spontaneous alternation behaviour (SAB) test, a test for working memory and/or attention. Interestingly, nicotine alleviated CMS-induced decrease in sucrose intake and completely blocked CMS-induced disruption of the performance in the SAB test.

Based on the data from this project it is suggested that nAChRs may be a relevant target for novel antidepressants treatment strategies.