

α 7 nicotinic acetylcholine receptors and memory processes: mechanistic and behavioral studies

Citation for published version (APA):

van Goethem, N. (2015). α 7 nicotinic acetylcholine receptors and memory processes: mechanistic and behavioral studies. [Doctoral Thesis, Maastricht University]. Maastricht University. <https://doi.org/10.26481/dis.20150625ng>

Document status and date:

Published: 01/01/2015

DOI:

[10.26481/dis.20150625ng](https://doi.org/10.26481/dis.20150625ng)

Document Version:

Publisher's PDF, also known as Version of record

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

Valorisation Addendum

Relevance & Audiences

Cognitive dysfunction is a feature often encountered in a broad spectrum of neurological and psychiatric conditions. These cognitive deficits are most commonly found in patients suffering from Alzheimer's disease (AD), dementia, schizophrenia, stroke, attention deficit hyperactivity disorder (ADHD) and aging. Ameliorating these dysfunctions can dramatically improve the quality of life of patients. Hence, developing treatments, or 'cognition enhancers' (nootropics), is imperative in this respect. The studies described in this dissertation have mainly focused on cognitive impairments as encountered in AD and schizophrenia. The best known example is probably AD, in which memory problems are the major hallmark which place a tremendous burden on the quality of life of patients.

AD is the most common form of elderly dementia. In 2010, the World Health Organization estimated that 35.6 million people worldwide suffered from dementia. Mainly due to the increasing aging of the world population, over 115 million people will be suffering from this disease by the year 2050. A substantial majority of these cases will be due to Alzheimer's pathology. 40% of AD patients will require intensive nursing home care, which will lead to a massive economic burden on social health care resources. There are five approved cognition enhancers for AD on the market which either modulate the cholinergic system by inhibition of acetylcholinesterase (AChE) or presumably reduce glutamate

neurotoxicity via NMDA antagonism. However, all have limited efficacy and severe side-effects. The etiology of AD is not well understood and current treatment for AD is ineffective both in combating cognitive deficiencies as well as in stopping disease progression. Thus, AD represents one of the major unmet medical needs for our lifetime.

The economic burden of AD patient care is enormous. In 2014, the direct costs to the American society of caring for those with AD will total an estimated \$214 billion, including \$150 billion in costs of medical care. This is expected to increase to over \$1 trillion by 2050 in the US alone. Extension of institutionalization of only one year will already greatly reduce these future costs. Cognition enhancers can contribute to this extension of institutionalization by restoring cognitive functioning and hence independent living.

Schizophrenia is a disabling psychiatric disorder that affects about 1% of the population worldwide. It has a major negative influence on the quality of life of patients. The disease is associated with a significant and long-lasting health, social and financial burden, not only for the patients (60% is unemployed), but also for families, other caregivers and the wider society. The extent of cognitive deficiencies is the best predictor of functional outcome when compared to the positive and negative symptomatology. At the same time, the cognitive demands of today's society increase due to the increased flow of information via internet, television and cell phones in daily life as well as at work. However, the current available antipsychotic drugs are not effective in treating cognitive symptoms. Development of treatment for cognitive impairments will have a substantially beneficial effect on the functional outcome of patients, making it possible again to read a book or have a (telephone) conversation. Such a treatment will considerably improve the quality of life of the patient and will additionally have a significant social and economic impact, if the patients can return to work. In addition to the social and economic benefits, the effect of this return to independence would considerably improve the patient's self-esteem. If such a cognition enhancer is available, it could be a major breakthrough.

In addition, most neurodegenerative and psychiatric disorders have cognitive impairments for which no treatment exists. This explains the need and still ongoing search for better cognition enhancers. $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$ nAChRs) ligands are relatively new drugs in this respect.

In this dissertation I showed that the cognitive performance of rodents can be improved by utilizing the $\alpha 7$ nAChR system.

In summary, I showed:

1. that $\alpha 7$ nAChR partial and full agonists have an acute positive effect on learning and memory;
2. that continuous exposure to an $\alpha 7$ nAChR partial agonist did not lead to behavioral tolerance for at least up to 6 days of treatment;
3. that combined treatment with suboptimal doses of an $\alpha 7$ nAChR partial agonist and an AChE inhibitor, which showed no effect when administered separately, led to improved cognitive performance;
4. that low dose administration of $\alpha 7$ nAChR antagonists led to improved memory formation, hippocampal glutamate efflux and cognitive performance.

It has been shown that $\alpha 7$ nAChRs are largely unaffected in the AD brain. Hence, different $\alpha 7$ nAChR agonists have been investigated for their potential to improve memory and attention disorders encountered in AD. A major drawback of $\alpha 7$ nAChRs is that they show rapid desensitization following repeated exposure to full agonists, thereby quickly inducing tolerance in patients taking medicines that agonistically target the $\alpha 7$ nAChRs. The studies in this dissertation indicated that using partial agonists, combinations of suboptimal doses of partial agonists and AChE inhibitors, and even antagonists might prove to be beneficial in AD. It is unlikely that these strategies will lead to the development of tolerance to the drugs.

It has been hypothesized that amyloid plaques in AD brains are actually the lysis remnants of degenerated, beta amyloid peptide 42 (A β 42)-overburdened neurons. The most vulnerable neurons for Alzheimer pathology, in particular the toxic plaque formation, appear to be those that abundantly express the $\alpha 7$ nAChR, and internalization of A β 42 appears to be facilitated by the high-affinity binding of A β 42 to the $\alpha 7$ nAChRs on neuronal cell surfaces. This is followed by endocytosis of the resulting complex and its accumulation within the lysosomal compartment thus results in amyloid plaque formation eventually. Elaborating on this, treatment with $\alpha 7$ nAChR ligands might reduce the disease progression via occupying these receptors and hence prevent A β 42 from binding to the receptor. Therefore, these drugs may make the brain more resistant against the destructive effects of A β depositions. To summarize, $\alpha 7$ nAChR ligands might both directly improve learning and memory, while they also slow down actual disease progression.

Unravelling the working mechanisms of the $\alpha 7$ nAChRs will not only benefit AD. $\alpha 7$ nAChRs have been shown to be involved in other psychiatric conditions like schizophrenia and ADHD. For example in schizophrenia, preclinical and clinical studies have shown that $\alpha 7$ nAChR ligands were able to normalize the auditory gating deficit in both rodent models and in schizophrenic patients. In addition, when considering the cognitive symptoms of schizophrenia and the well-established pro-cognitive effect $\alpha 7$ nAChR ligands have on cognition, it is likely that $\alpha 7$ nAChR ligands are beneficial as an add-on therapy in the treatment of schizophrenic patients. Also in ADHD, it is assumed $\alpha 7$ nAChR ligands can improve the symptoms of this disorder via stimulating working memory and attention processes. Therefore, $\alpha 7$ nAChR ligands can be expected to also be beneficial in these disorders. Until an actual cure is found for these disorders, symptomatic treatment will stay the most desirable solution for these patients. Relieving the symptoms of these disorders will already greatly improve the quality of life of patients.

Furthermore, similar ion channels like GABA_A, glycine and 5-HT₃ would most likely function via a similar mechanism. This opens up a brand new view on these receptor subtypes to develop better treatments for a plethora of different neurological and psychiatric conditions.

Clearly, the results from these studies are of interest for the pharmaceutical industry. Developing new (symptomatic) treatments for AD, schizophrenia or other neurological or psychiatric disorders in which cognition is impaired, is commercially interesting for industry. Actually industry is the stakeholder having the financial resources and infrastructure organization to bring a new drug to the market. Of note, part of research related to the drug EVP-6124 as described in this dissertation is a collaboration with its owner FORUM Pharmaceuticals (Boston, USA). In addition, research on the $\alpha 7$ nAChR antagonist Compound 7i is a collaboration with Intra-Cellular Therapies, Inc. (New York, USA). EVP-6214 (or: Encenicline) is currently in clinical phase III trials for AD and schizophrenia.

In summary, the results of the studies described in this dissertation are of importance to patients, their family and caretakers, governments (reduction in medical costs) and pharmaceutical industries.

Activities/Products & Innovation

Actual products which can be derived from the studies in this dissertation are improved pharmacological treatments for AD and schizophrenia patients. A big advantage of treatment with $\alpha 7$ nAChR partial agonists and antagonists is that desensitization of the receptors, and therefore tolerance to the drugs, does not develop. The development of tolerance is a known phenomenon for selective full agonists, and this resulted in the termination of most $\alpha 7$ nAChR programs in different pharmaceutical companies. Since $\alpha 7$ nAChRs are still abundantly present in the brains of AD patients, the target still seems promising. Partial agonists and antagonists of the $\alpha 7$ nAChR could therefore prove to be very beneficial in the functional outcome of AD patients.

Furthermore, parallel studies with 'follow-up' compounds could be patented for new indications, like for example schizophrenia and ADHD. This opens up new possibilities for specific blocking/mild activation of $\alpha 7$ nAChRs.

In conclusion, the findings of $\alpha 7$ nAChR partial agonists and antagonists to enhance $\alpha 7$ nAChR functioning and therefore learning and memory shed a new light on the $\alpha 7$ nAChR as a target for cognition enhancement and even neurodegenerative pathology reduction.