

Targacept's NNR Drugs Rehabilitate Nicotine

Wendy Wolfson

DOI 10.1016/j.chembiol.2010.01.005

Tobacco has been used for centuries despite its health risks. Cigarettes are hard to quit because they deliver nicotine, a potent and addictive drug, along with "tar." But now nicotine is angling for redemption in the form of a new class of CNS drugs targeting neuronal nicotinic receptors (NNRs) also known as neuronal acetylcholine nicotinic receptors (nAChRs), which modulate the flow of neurotransmitters throughout the brain and nervous system.

Tobacco companies have long capitalized on the addictive properties of nicotine, but the future boom may come from biotechs like Targacept (<http://www.targacept.com>) and their pharmaceutical company partners. Enriched with a dowry of 450 research patents

Jersey-based Memory Pharmaceuticals, which Roche purchased in 2009.

I'll Have My Nicotine Straight Up, Thank You

NNRs are pentameric ligand-gated ion channels composed of five protein subunits containing binding sites for acetylcholine and other neurotransmitters. These receptors are activated by nicotine as well. NNRs are widespread in the central nervous system, autonomic nervous system, and skeletal muscles. Nicotinic receptor research is over a century old, but it is only in the last 20 years that it became evident that these receptors were also abundant in the brain. Researchers started becoming aware of nicotine's positive effects and developing

specific nicotinic acetylcholine receptors in a particular brain site could be used to treat a variety of cognitive deficits in various disorders. This may be possible because the neuronal mechanisms that mediate a cognitive deficit in attention, for example, may be the same.

According to Edward D. Levin, Ph.D. Professor of Psychiatry, Duke University Medical Center, and Targacept collaborator, multiple studies have shown that administering nicotine via skin patches can improve cognitive functions such as attention and memory. "Nicotine can be deadly in promoting tobacco addiction, but there is also a possible benefit," said Levin. "Part of the brakes on the field has been the demonization of nicotine. I think if we can pull the nicotinic treatment away from the tobacco addiction, we can open the way to useful therapeutics."

But patches delivering a low dose of nicotine over a long period of time can profoundly desensitize receptors, according to Marina Picciotto, Ph.D, Professor of Psychiatry, Yale University. According to Picciotto, one of the puzzles of the nicotine literature is determining what effects of nicotine are due to activation and/or inactivation of receptors or a combination thereof.

"Nicotinic receptors are modulators," said Picciotto. "They are not like glutamate receptors or GABA receptors where they turn on or shut down a neuron. What that means is that they are extremely sensitive to the starting conditions of the system." According to Picciotto, introducing nicotine or a nicotinic agonist to highly active neurons will likely decrease their activity through increasing the release of GABA. Conversely, an agonist would accelerate the firing rate of silent neurons both by local depolarization as well as increasing release of more excitatory neurotransmitters. In an aberrant state of circuit level dysregulation, nicotinic receptors are extremely good at getting a system back to the mean. "It is your brain that gives you some of the specificity of the drug, not only the actual subtypes of the

If we can pull the nicotinic treatment away from the tobacco addiction, we can open the way to useful therapeutics.

from tobacco company R.J. Reynolds, Winston-Salem, North Carolina-based Targacept is developing NNR-targeting drugs to treat conditions like major depression, adult attention deficit hyperactivity disorder (ADHD), Parkinson's disease, cognitive dysfunction in schizophrenia, and, of course, smoking cessation. Targacept, now public, was spun off from R.J. Reynolds in 1997.

Targacept has collaborations with AstraZeneca and GlaxoSmithKline, but other large pharmaceutical companies also have NNR discovery programs. Pfizer launched the first NNR drug, varenicline (Chantix), for smoking cessation in 2006. Danish biotech NeuroSearch (<http://www.neurosearch.com>) has codeveloped Abbotts' NNR compounds: ABT-894 for ADHD and ABT-560 for cognitive dysfunction. Roche has a single NNR drug, RG3487 (formerly MEM3454), which is a nicotinic $\alpha 7$ receptor agonist for Alzheimer's/schizophrenia that is currently in phase 2 trials. RG3487 was acquired by Roche from Montvale, New

Jersey-based Memory Pharmaceuticals, which Roche purchased in 2009.

NNR agonists to treat cognitive function in the early 1990s. "There is much comorbidity between tobacco smoking and psychiatry disorders, probably because people attempt to self-medicate symptoms of psychiatric disorders with the nicotine contained in tobacco," said Athina Markou, Ph.D., Professor, Department of Psychiatry, School of Medicine, University of California at San Diego. According to Markou, studies estimate that people with mental illness smoke at a much higher rate than the general population. Almost 90% of schizophrenics smoke and half of the people with depression smoke, compared to between 13% and 22% of the general population.

"Schizophrenia patients have cognitive deficits," said Markou. "The cognitive deficits that you see in Alzheimer's or in dementia or in other disorders may have the same neurobiological substrates as the cognitive deficits that you see in schizophrenia." According to Markou, perhaps a single compound that activates

receptor or even the receptors on the individual neuron.” said Picciotto.

Modulating Mood

In some neuropsychiatric disorders, nicotinic receptor groups are lost or missing, according to Dr. Merouane Bencherif, Vice President, Preclinical Research at Targacept. One theory is that Alzheimer’s patients lose certain NNRs and the neurons that contain them, which is why they slide into dementia. Schizophrenics have genetic abnormalities in receptors that cause difficulty in sensory gating and processing information. In Parkinson’s patients’ brains, certain receptors die, causing motor control problems. Incidentally, epidemiological data shows that smoking strikingly reduces the risk of developing Parkinson’s disease.

According to Bencherif, NNRs normalize the neurotransmitter tone in the brain. There are diverse subtypes of NNRs. “This is very important for our company, because we go and target specific receptors and we don’t interact with the receptors in the heart or ganglia so we don’t have the side effects,” said Bencherif. (That’s why most drug development focuses on eliminating the effects on $\alpha 3/\beta 4$ receptors that are highly expressed in ganglia, to avoid activation of the peripheral nicotinic receptors in end organs and the autonomic nervous system.)

Targacept Pipeline

Targacept’s lead small molecule compound is TC-5214, a drug for major depression that modulates the $\alpha 4/\beta 2$ NNR subtype. TC-5214 is the (S)- (+) enantiomer of mecamylamine hydrochloride, a nicotinic channel blocker. About 14.8 million Americans suffer from major depression (and about 44 million worldwide); the most frequently prescribed drugs, selective serotonin reuptake inhibitors (SSRIs), only work in about 60% of patients.

According to Bencherif, one hypothesis is that depression is due to too much acetylcholine being released in the brain. TC-5214 completed a phase 2b trial this year as adjunctive therapy for nonresponders to SSRI drugs. While the results have not been replicated by other groups, AstraZeneca agreed to take it further in a collaboration worth potentially \$1.34 billion if all scientific and sales milestones are met.

Targacept’s phase 2 compound TC-1734 (now AZD 3483) for adult ADHD is a small molecule agonist for one or more forms of $\alpha 4/\beta 2$ NNR. About 5 to 8 million adults in the U.S. have ADHD as well as over 12 million children. ADHD symptoms are generally treated with stimulants and sometimes antidepressants. But stimulants are addictive, raise blood pressure, and can cause serious cardiovascular problems. In July 2009, AstraZeneca announced continued development in a collaboration worth up to \$100 million, if milestones are met, and made a milestone payment of \$10 million. According to Bencherif, AZD 3483 works upstream from synapses, enhancing activity in certain areas of the brain, and seems to have placebo-like side effects.

Targacept’s phase 1 drug TC-6683 (AZD 3483) for Alzheimer’s disease is an agonist of one or more forms of $\alpha 4/\beta 2$ NNR. “The drug seems to help retain receptor viability,” said Bencherif. “We are counting on this property to try to decrease, inhibit, or stop the neural degeneration seen in Alzheimer’s disease.”

TC-5619 for cognitive impairment in schizophrenia has initiated a phase 2 clinical proof-of-concept trial. TC-5685 in phase 1 for depression and anxiety disorders inhibits activity of one or more forms of the $\alpha 4/\beta 2$ NNR. Targacept also has a global alliance with GlaxoSmithKline for five NNR preclinical compounds.

Getting Booted from the Mile-High Club

In July 2009, the FDA slapped varenicline (Chantix), a partial agonist $\alpha 4/\beta 2$ NNR smoking cessation drug, and bupropion (Zyban), a competing drug, with a black box warning. Both had been banned for use by pilots and air traffic controllers the previous year because, out of 6 million plus prescriptions written, a few hundred people had suicidal thoughts and some acted upon them. The FDA noted that while people with underlying psychiatric conditions should not take these drugs, not all people who experienced symptoms had a psychiatric history. On the other hand, nicotine withdrawal can precipitate depression.

“Existing NNR drugs are not very selective compounds,” commented Daniel Timmermann, Ph.D., Vice President, Director of CNS Pharmacology, NeuroSearch. “What we are trying to do at

NeuroSearch is to create very selective compounds.” NeuroSearch and Abbott’s two NNR compounds for ADHD in phase 2 and for cognitive function in phase 1 stemmed from a 5 year collaboration between the two companies, with Abbott responsible for the clinical development under a license agreement.

NeuroSearch/Abbott’s ADHD compound is a full agonist of $\alpha 4/\beta 2$. “At a very basic level, you can say that what we believe to be the mechanism of action of NNR modulation in ADHD is partly based on the ability of the NNR agonist to enhance dopaminergic and noradrenergic transmissions in the basal forebrain,” said Timmermann.

According to Timmermann, neurotransmission based on these transmitter systems is aberrant in the basal forebrain in ADHD patients. By enhancing these neurotransmitters, NNR selective compounds can correct the imbalance as well as augment cognitive function. “There is a host of clinical studies deriving from many years back that uniformly show agents capable of activating nicotinic receptors, namely the $\alpha 4/\beta 2$ subtype, are good for enhancing attention,” said Timmermann.

Targacept’s ADHD AZD-3480 drug has a mechanism of action comparable to ABT-894, noted Timmermann. NeuroSearch’s NNR compound ABT-560 also targets $\alpha 4/\beta 2$ receptors. The company’s earlier stage NNR drug candidates target $\alpha 7$, the second most common type of NNR receptor found in the mammalian brain, which is also associated with cognitive function.

While patients have been dosed in clinical studies lasting several weeks or months, the effects of long-term use remain unknown. “This has been a conundrum in nicotinic receptor research for many years: how can you activate these receptors permanently with agonists when you know from various cell-based systems that these receptors are prone to become desensitized upon prolonged exposure to agonists,” Timmermann said. “To tell you the truth, there is really not a uniform solution to that problem. However, it does appear to be dose dependent. There has really been a highly competitive race in last 5 years to see who would reach the clinic first with some of these compounds.”

Wendy Wolfson is a science and technology writer based in the Bay Area. wendywolfson@nasw.org