Nicotinic acetylcholine receptor modulation of attention behavior and prefrontal cortical circuits

At every moment in time, our brain receives numerous sensory information about the environment. This makes attention, the process by which we select currently relevant stimuli for processing and ignore irrelevant input, a fundamentally important brain function. By sustaining your attention you can structure your behavior in time to attain a fututre goal. The prefrontal cortex ia a central structure in the brain involved in regulating attention. In humans we test attention in the 'Continous performance task'. This task has also been adapted for rodents, the 5-choice serial reaction time task, and allows us to study the molecular and cellular mechanisms underlying attention. In these tasks humans and rodents need to report, over a longer period of time, the appearance of rare stimuli. By studying how well they do this, we can assess attention. This thesis tries to contribute to the understanding of the cellular mechanisms through which nicotinic acetylcholine receptors modulate attention.

Acetylcholine is a neurotransmitter that translates a chemical signal in an electrical signal and thereby changes the computational properties of neurons. There is a lot of evidence for the rol of acetylcholine in attention. The dynamics of acetylcholine differ per brain area. During attention there is a special dynamics in the prefrontal cortex and many experiments show that acetylcholine exerts its main effect here. The fast dynamics of cholinergic signals suggest that the nicotininc acetylcholine receptor, a fast ionotropic receptor, could play an important role.

This thesis answers a couple of questions regarding the function of nicotinic receptors in attention and the regulation of the underlying neuronal networks. Firstly, there are several types of nicotinic receptors, are these all important? We show that nicotinic receptors containing 'β2 subunits' play a main role in orchestrating attention. In addtion, we show that the neurons to which this receptor transmits its signal are located in the prelimbic area of the prefrontal cortex.

To understand how this nicotinic receptor influences cortical computation we looked at where these receptors are located in the network. The cortex is build up of different layers. Al these layers have their own specific connections with other brain areas. This thesis answers the question whether these layers are differentially regulated by nicotinic receptors. The answer is yes and the main reason is that pyramidal neurons, neurons that send glutamatergic signals to other brain areas, are differentially regulated by nicotinic receptors in the different layers. In superfical layers they are not regulated by nicotinic receptors, midle layer pyramidal neurons contain α7 receptors and deep layers contain β2 receptors. In addition, activity of pyramidal neurons is fine-tuned by interneurons. We found that interneurons throughout all layers are regulated by nicotinic receptors. Hence they play an important role in regulating

neuronal activity in the prefrontal cortex.

Nicotinic receptors are not only senstive to endogenous chemicals from the body but also for substances that appear elsewhere in nature, like nicotine. Nicotine is a psychoactive substance that activates our reward centre in the brain en that makes it addictive. Nicotine also has an effect on cognitive functions like attention. In certain patient populations nicotine can improve attention. Networks of cells can change the strength of connections between neurons. This makes it possible to assign new functions to networks, for example to remember new things. This so called plasticity is also important during attention. If an input is integrated by a neuron and followed by neuronal output (an action potential), synapses can change strength. We describe that nicotine influences this process by increasing inhibition in the prefrontal cortex. As a consequence, calcium signals in the dendrite are lower and synapses can not become potentiated. This could be a mechanism through which the prefrontal cortex increases its signal-to-noise ratio and consequently not every input leads to a change in synaptic strength in the network.

If the brain is exposed to nicotine over longer periods, in particular during adolescence, this can lead to a decrement in attention performance. A couple of adaptations have been described that change the prefrontal cortical network. These include an increase in the number of nicotinic receptors and a change in metabotropic glutamate receptors. The initial mechanisms that lead to these adaptations remained unknown. In this thesis I show that nicotine strongly interferes with cholinergic signaling in the PFC. It does this mainly by making β2 receptors less sensitive for acetylcholine. This effect is not everywhere the same and some cell types suffer more from this then others. Mainly interneurons show diminshed cholinergic responsiveness. This finding leads to the hypothesis that during nicotine exposure the prefrontal cortex is hyperexcited. This could in turn lead to a compensatory mechanisms increasing nicotinic receptors and increasing the levels of metabotropic glutamate receptors.

These findings contribute to the question how acetylcholine orchestrates attention behavior and prefrontal cortical circuitries. In addition, they show how nicotine can alters these circuits on the short- and long-term. A better understanding of the cellular mechanisms of nicotinic receptor modulation of attention behavior can ultimately lead to better targeted treatment of attention disorders and in particular Alzheimer's disease, in which the cholinergic system is malfunctioning.