Long-term consequences of nicotine exposure during adolescence: synaptic plasticity in rodent and human cortical neuronal networks

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2012

document version
Publisher's PDF, also known as Version of record

Summary

The prefrontal cortex, the area responsible for higher executive functions such as long-term planning, decision-making, attention and cognitive control, is one of the last areas to mature and is still actively developing during adolescence. This places the adolescent brain in a vulnerable state of imbalance, susceptible to the influence of psychoactive substances such as nicotine. In prefrontal networks, nicotine modulates information processing on multiple levels by activating and desensitizing nicotine receptors on different cell types and in this way affects cognition. The prefrontal cortex of adolescents is especially sensitive to the effects of nicotine, possibly due to its immature state. Studies in human subjects indicate that smoking during adolescence increases the risk of developing psychiatric disorders and cognitive impairments in later life. In addition, adolescent smokers often suffer from attention deficits that aggravate with the years of smoking. Based only on human studies, it is difficult to distinguish cause and effect of nicotine exposure and potential lasting effects on cognitive function. The neurobiological mechanisms underlying lasting nicotine effects on the function of prefrontal networks are still unknown. Animal models of nicotine exposure, in contrast, can offer more insight in mechanisms of lasting adaptations caused by nicotine during adolescence.

This thesis addresses the short- and long-term effects of nicotine on the adolescent prefrontal cortical function and cognitive behavior. For this purpose, adolescent smoking was modelled in rat and nicotine injections were used during the developmental period equivalent to adolescence in humans. The short-term effects of nicotine exposure were studied on the first day of the withdrawal while the long-term effects were assessed 5 weeks later in adult animals. The functional adaptations on synaptic level caused by nicotine are central to my work.

In **Chapter 2** I addressed the question whether adolescent nicotine exposure leads to changes in nicotinic receptor expression and synaptic function of interneurons in PFC. Adolescent, but not adult nicotine exposure resulted in transient increases in the expression of high-affinity nicotine receptor of$\alpha 4\beta 2$ subtype on the first day of withdrawal. This receptor is predominantly expressed on cell bodies and dendrites of interneurons in PFC and I showed that their nicotinic modulation is increased. However, this increase in $\alpha 4\beta 2$ nicotine receptors was transient in nature and 5 weeks later returned to normal levels.

In **Chapter 3** the question was addressed which long-term molecular and synaptic adaptations in PFC take place following adolescent nicotine exposure. Based on proteomics screening of all synaptic proteins in prefrontal cortex, lasting molecular adaptations secondary to nicotinic effects could be traced. In particular, the inhibitory mGluR2 autoreceptor was significantly downregulated 5 weeks after nicotine exposure. In chapter 3 I investigated the function of this receptor on principal neurons (pyramidal cells in layer V) in PFC, its location and its modulation of excitatory transmission. I showed that mGluR2-dependent inhibition of principal neuron in PFC together with short-term plasticity was also decreased 5 weeks after adolescent nicotine exposure. In addition, stimulating this receptor by intra-PFC infusion of mGluR2/3 agonist could reverse the nicotine-induced lasting impairment of attention performance. Thus, mGluR2-dependent inhibition is proposed as the synaptic mechanism underlying lasting effects of nicotine exposure during adolescence, leading to reduced synaptic information filtering and attention.

In **Chapter 4** I examined how nicotine during adolescence can have lasting impact on complex information processing in PFC such as spike-timing dependent plasticity. I showed that adult animals show more spike-timing dependent potentiation as a result of nicotine exposure during adolescence. Building on Chapter 3, I propose that reduced mGluR2 signaling disinhibits prefrontal network and is responsible for this effect.

Finally, in **Chapter 5**, I tried to link my findings on synaptic plasticity in rodent cortex to the way human synapses process information, stressing the relevance of animal research for understanding the function of human brain. This is the first attempt in the field to study mechanisms and rules of STDP in human cortical synapses. For this purpose we used healthy neocortical tissue cut from epilepsy patients undergoing deep brain surgery. We found that despite few important differences, the core mechanisms and rules of plasticity are shared by both rat and human.

The results of this work offer an insight in long-term functional adaptations on the level of information processing in prefrontal networks caused by nicotine exposure during adolescence. I conclude my thesis with **Chapter 6** where I argue that these lasting effects of nicotine represent compensatory adaptations in prefrontal network aimed to counteract the initial inhibitory nicotinic effects on adolescent PFC function. The core of these adaptations is the reduction in mGluR2 signalling which has profound functional consequences: it leads to overall disinhibition of the network and in this way changes the way information is processed and, ultimately, leads to deficits in cognitive functions.

Although my research was performed in rodents, these results are highly relevant for the human situation. Despite the smaller volume of the rat brain, the reward circuitry is similar to humans and consists of the same structures, including the PFC and its important connections. As I show in Chapter 5, even on the level of complex information processing rodent synapses follow similar rules and cells show almost identical active and passive properties. Therefore, also for humans, smoking during adolescence may lead to the same adaptations in network function and cause cognitive deficits. Importantly, the damaging consequences of adolescent nicotine exposure seem to be permanent and possibly persist even after quitting smoking.

It is therefore crucial to educate adolescents and children about the life-long consequences of experimenting with cigarettes during this critical developmental period. The best way to avoid nicotine damage to brain function is to avoid smoking completely.