

Targeting phosphodiesterase type 4 for improving cognitive fronto-striatal functioning

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Valorization addendum

Relevance for society and Target groups

The dopaminergic fronto-striatal circuits constitute the neurobiological basis of several neuropsychiatric disorders, including neurodegenerative disorders like Parkinson's disease and Huntington's disease, psychiatric illnesses such as schizophrenia and obsessive-compulsive disorder (OCD), and pervasive developmental disorders like attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (Alexander et al. 1986; Haber and Rauch 2010; Gunaydin and Kreitzer 2015). Dysfunction of these circuits produces the wide range of motor, cognitive and affective symptoms observed in related neuropsychiatric disorders (Chudasama and Robbins 2006).

The burden that cognitive impairments impose on the quality of life is enormous. Not only for those who suffer from it but also for their families and caregivers. For instance, as many as one million Americans live with Parkinson's disease, which is more than the combined number of people diagnosed with multiple sclerosis, muscular dystrophy and Lou Gehrig's disease. Approximately 60,000 Americans are diagnosed with Parkinson's disease each year, and this number does not reflect the thousands of cases that go undetected. More than 10 million people worldwide are living with Parkinson's disease. Incidence of Parkinson's increases with age, but an estimated four percent of people with Parkinson's disease are diagnosed before the age of 50.

Schizophrenia is another devastating disorder of the fronto-striatal circuits for most people who are afflicted, and very costly for families and society. The overall U.S. 2002 cost of schizophrenia was estimated to be \$62.7 billion, with \$22.7 billion excess direct health care cost (\$7.0 billion outpatient, \$5.0 billion drugs, \$2.8 billion inpatient, \$8.0 billion long-term care). The Prevalence Rate for schizophrenia is approximately 1.1% of the population over the age of 18 or, in other words, at any one time as many as 51 million people worldwide suffer from schizophrenia, including 2.2 million people in the United States (US), 285,000 people in Australia, over 280,000 people in Canada and over 250,000 diagnosed cases in the United Kingdom (UK).

5.1 million Children in the US (8.8% or 1 in 11 of the age group 4-17 years) have a current diagnosis of ADHD: 6.8% of children ages 4-10 (1 in 15); 11.4% of children ages 11-14 (1 in 9); 10.2% of children ages 15-17 (1 in 10). Additionally, 6.4 million children (11% of the age group 4-17 years) have ever been diagnosed with ADHD, and rates of ever-diagnosed ADHD increased an average of approximately 5% per year from 2003 to 2011. Estimated cost to US society entails \$42.5 billion dollar annually.

Without going into the statistics of the other disorders, it becomes clear from the numbers provided for the three examples above, that the need to increase our understanding of the physiology and pathophysiology of the fronto-striatal circuits is of utmost importance. Increasing our understanding of fronto-striatal circuits' biology will not only aid in better understanding the many different disorders related to the circuits, but it will also create new targets for pharmacological treatment and generate possible biomarkers as is further explained below.

Besides cognitive behavioral therapy, there is currently hardly any pharmacological treatment for disorders related to dysfunctional fronto-striatal circuits. Presently available dopaminergic treatments for ADHD, Parkinson's disease and schizophrenia are very nonspecific and induce many side effects (cardiac arrhythmias, addiction, growth inhibition, dyskinesias, dopamine dysregulation syndrome, etc.). This results in low-compliance and high relapse rates, again stressing the need for more basic knowledge regarding the role of dopamine in the physiology of the fronto-striatal circuits and the possible impact of the current dissertation. By modulating the same intracellular machinery via phosphodiesterase type 4 (PDE4) inhibitors as would dopamine itself via the extracellular receptor, we tried to regulate the dopaminergic modulation of the fronto-striatal circuitry. Thereby, we reverse the decrease in intracellular signaling due to the loss in dopamine. Main benefit of PDE4 inhibitors compared to dopaminergic medication includes increased efficacy and improved side-effect profile. From the results of the current dissertation it seems that especially disorders characterized by hypodopaminergia, including ADHD and Parkinson's disease, will benefit from PDE4 inhibition.

Cognitive symptoms observed in ADHD, including sensory gating and attention deficits, as well as impulsivity and hyperactivity seem to be beneficially affected by PDE4 inhibition. Roflumilast is currently the only clinically approved PDE4 inhibitor available for oral administration with a unique side effect profile compared to both, for PDE4 inhibitors typically observed, emetic effects and psychostimulant-induced side effects.

Effectiveness and feasibility for use of knowledge to meet the needs of others

Through publications and presentations at conferences I will inform the scientific community in the field of our results and outcomes of translational research. In the case of positive results, I will also explore the possibilities of patenting new treatments of ADHD based on the newly generated targets using our Technology Transfer Office. On the one hand for monotherapy but also for combination therapy with existing dopaminergic drugs (e.g. Ritalin) to reduce their side effects. This would greatly help my research to bring in extra funding. Further, I will contact relevant patient organizations (like

the foundation Attention Deficit Disorders (ADD)) as well as the Trimbos. Patient organizations would like to learn more about the latest treatment options and the Trimbos focuses on improving health care through sharing knowledge. This way, we will also reach health care professionals to share our knowledge and possibly recruit volunteers for future studies.

Activity/Products and Innovation

Our unique from “bench to bed and back again” approach has the potential to result in the generation of new targets to develop improved treatments for patients with ADHD. PDE4 seems to be a very promising target based on results of the current dissertation. Next to the generation of new treatments, the current project also has the potential to generate new biomarkers including electroencephalogram (EEG) and event-related potential (ERP) correlates. The latter will lead to better and faster diagnosis improving prognosis. Improved prognosis will lead to reduced cost for society and increased quality of life for patients and family.

Additionally, results of the current dissertation further add to the evidence that cognitive projections, or at least those originating in the infralimbic cortex, can induce a tri-phasic response in the SNr. As a result, it also implies the existence of a division within the basal ganglia into a hyper, direct and indirect pathway, in the cognitive fronto-striatal circuit originating in the infralimbic cortex. Thus, this also confirms the hypothesis of the existence of the three pathways in the cognitive fronto-striatal circuits as they do in the motor circuits (e.g. Maurice et al. 1999; Beyeler et al. 2010).

Finally, we have implemented and verified a new model for motor impulsivity as seen in ADHD. Currently, there is no good model for ADHD available in animals except for the Spontaneously Hypertensive Rat. This model shows high face validity but moderate construct validity (Sagvolden et al. 2005) and induces confounding results due to inattentiveness and hyperactivity. In our experiments we wanted to focus purely on motor impulsivity. Therefore, we induced hypodopaminergia via a 6-hydroxy dopamine (6-OHDA) lesion in the medial prefrontal cortex to target the cognitive circuits of the fronto-striatal circuitry. Since the levels of dopamine seem to follow a U-shaped dose-response curve, this model is suited to be used in future studies unraveling the pathophysiology of ADHD-related motor impulsivity and testing promising treatments (Arnsten 2009; Arnsten and Pliszka 2011).

References

- Alexander GE, DeLong MR, Strick PL (1986) Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci* 9 (1):357-381
- Arnsten AF (2009) Toward a new understanding of attention-deficit hyperactivity disorder pathophysiology: an important role for prefrontal cortex dysfunction. *CNS Drugs* 23 Suppl 1:33-41. doi:10.2165/00023210-200923000-00005
- Arnsten AF, Pliszka SR (2011) Catecholamine influences on prefrontal cortical function: relevance to treatment of attention deficit/hyperactivity disorder and related disorders. *Pharmacol Biochem Behav* 99 (2):211-216. doi:10.1016/j.pbb.2011.01.020
- Beyeler A, Kadiri N, Navailles S, Boujema MB, Gonon F, Moine CL, Gross C, De Deurwaerdere P (2010) Stimulation of serotonin2C receptors elicits abnormal oral movements by acting on pathways other than the sensorimotor one in the rat basal ganglia. *Neuroscience* 169 (1):158-170. doi:10.1016/j.neuroscience.2010.04.061
- Chudasama Y, Robbins TW (2006) Functions of frontostriatal systems in cognition: comparative neuropsychopharmacological studies in rats, monkeys and humans. *Biol Psychol* 73 (1):19-38. doi:10.1016/j.biopsycho.2006.01.005
- Gunaydin LA, Kreitzer AC (2015) Cortico-Basal Ganglia Circuit Function in Psychiatric Disease. *Annu Rev Physiol*. doi:10.1146/annurev-physiol-021115-105355
- Haber SN, Rauch SL (2010) Neurocircuitry: a window into the networks underlying neuropsychiatric disease. *Neuropsychopharmacology* 35 (1):1-3. doi:10.1038/npp.2009.146
- Maurice N, Deniau JM, Glowinski J, Thierry AM (1999) Relationships between the prefrontal cortex and the basal ganglia in the rat: physiology of the cortico-nigral circuits. *J Neurosci* 19 (11):4674-4681
- Sagvolden T, Russell VA, Aase H, Johansen EB, Farshbaf M (2005) Rodent models of attention-deficit/hyperactivity disorder. *Biol Psychiatry* 57 (11):1239-1247. doi:10.1016/j.biopsych.2005.02.002