Abstract

On the influence of dopamine-related genetic variation on dopamine-related disorders

Olle Bergman

Department of Pharmacology, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Box 431, 40530 Göteborg, Sweden.

Rationale Dopamine synthesizing neurons are involved in a wide variety of functions. The most prominent dopamine pathways originate in the midbrain. The development, function and survival of these dopaminergic neurons are under the influence of numerous transcription and neurotrophic factors. Subtle differences in the genes encoding these factors may be of importance for several psychiatric and neurodegenerative disorders. *LMX1A*, *LMX1B* and *PITX3* are transcription factors that are essential for the development, specification and survival of midbrain dopaminergic neurons. *BDNF* is a neurotrophic factor involved in neurodevelopmental processes including differentiation and survival of dopaminergic neurons. Another protein of importance for dopaminergic neurotransmission is the dopamine transporter (DAT) that mediates reuptake and inactivation of extracellular dopamine and is hence of fundamental importance in regulating dopamine transmission. The specific aim of this thesis was to investigate the possible influence of polymorphisms in these dopamine-related genes on dopamine-related disorders, *i.e.* Parkinson's disease (PD), attention-deficit/hyperactivity disorder (ADHD), social anxiety disorder (SAD) and schizophrenia. **Observations** Three single nucleotide polymorphisms (SNPs) in *LMX1A* and one in *LMX1B* were associated with PD. After splitting for gender, six SNPs were associated with PD in women and four in men (Paper I). Two SNPs in *PITX3* were associated with PD in patients with an early age of onset when compared either to controls or to PD patients with late onset (Paper II). One of the *PITX3* polymorphisms was also associated with schizophrenia, as were two polymorphisms in *LMX1A*, and one SNP in *LMX1B* (Paper III). We assessed longitudinal, quantitative phenotypes of hyperactivity-impulsivity and inattention, and found that the Met allele of the Val66Met polymorphism in the BDNF gene was associated with increased persistent hyperactivity-impulsivity symptoms as well as with increased age-specific inattention symptoms (Paper IV). The amygdala, essential for detection of biologically relevant stimuli and fear generation, is under excitatory influence of dopamine. Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) were used to investigate if a variable number of tandem repeat (VNTR) polymorphism in the DAT gene (*SLC6A3*) influences amygdala function during processing of aversive emotional stimuli in SAD patients and healthy controls, respectively. The 9-repeat allele was associated with significantly increased amygdala activity, as assessed with PET, across tests (*i.e.* public speaking, processing of angry and neutral faces) in SAD patients, but with decreased amygdala activity in controls. Moreover, 9-repeat carriers, regardless of diagnosis, displayed augmented amygdala reactivity, *i.e.* a greater activation, of the left amygdala in response to angry compared to neutral faces. Blood oxygen level-dependent (BOLD) fMRI was used to assess healthy volunteers, and in line with the results from the PET study, 9-repeat carriers displayed higher reactivity of the left amygdala in response to angry faces, compared to neutral geometric shapes (Paper V). **Conclusions** All of the studies were based on *a priori* hypotheses regarding the possible relationship between the genes and the disorders under investigation. Some of the associations reported in this thesis have not been described earlier, others have been confirmed in independent samples, whereas in some cases, earlier studies have been inconclusive. In summary, our results support the notion that variation in dopamine-related genes is of importance for dopamine-related disorders and amygdala function.

Key words: dopamine, neurodevelopment, amygdala, schizophrenia, Parkinson's disease, social anxiety disorder, ADHD, PITX3, LMX1A, LMX1B, DAT, genes, BDNF, genetics

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I. *PITX3* polymorphism is associated with early onset Parkinson's disease. **Olle Bergman**, Anna Håkansson, Lars Westberg, Kajsa Nordenström, Andrea Carmine Belin, Olof Sydow, Lars Olson, Björn Holmberg, Elias Eriksson and Hans Nissbrandt. *Neurobiology of Aging (2008) Apr 16 (Epub. ahead of print).*

II. Do polymorphisms in transcription factors *LMX1A* and *LMX1B* influence the risk for Parkinson's disease? **Olle Bergman**, Anna Håkansson, Lars Westberg, Andrea Carmine Belin, Olof Sydow, Lars Olson, Björn Holmberg, Laura Fratiglioni, Lars Bäckman, Elias Eriksson, Hans Nissbrandt. *Journal of Neural Transmission (2009) 116:333–338.*

III. Polymorphisms in dopamine-related transcription factors *LMX1A*, *LMX1B* and *PITX3* are associated with schizophrenia. **Olle Bergman**, Lars Westberg, Lars-Göran Nilsson, Rolf Adolfsson and Elias Eriksson. Preliminary manuscript.

IV. Association of brain-derived neurotrophic factor polymorphism with the developmental course of attention-deficit/hyperactivity disorder. **Olle Bergman**, Lars Westberg, Paul Lichtenstein, Elias Eriksson and Henrik Larsson. Submitted manuscript.

V. Amygdala function is associated with a dopamine transporter gene polymorphism in patients with social anxiety disorder and healthy controls. **Olle Bergman**, Fredrik Åhs, Tomas Furmark, Lieuwe Appel, Clas Linnman, Vanda Faria, Stephen B. Manuck, Robert E. Ferrell, Ahmad Hariri, Susanne Henningsson, Mats Fredrikson, Elias Eriksson, and Lars Westberg. Submitted manuscript.

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