

On the association between panic disorder and autonomic regulation – With special focus on the roles of respiration and on the catechol-O-methyltransferase gene

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av Kristina Annerbrink.

Fakultetsopponent: Professor Nils Lindefors, Institutionen för Klinisk Neurovetenskap, Karolinska Institutet, Stockholm

The thesis is based on the following papers:

- I. Annerbrink K, Olsson M, Melchior LK, Hedner J, Eriksson E. Serotonin depletion increases respiratory variability in freely moving rats: implications for panic disorder. *International Journal of Neuropsychopharmacology*, Mar;6(1):51-6, 2003.
- II. Olsson M, Annerbrink K, Bengtsson F, Hedner J, Eriksson E. Paroxetine influences respiration in rats: implications for the treatment of panic disorder. *European Neuropsychopharmacology*, Jan;14(1):29-37, 2004.
- III. Annerbrink K, Olsson M, Hedner J, Eriksson E. Acute and chronic treatment with serotonin reuptake inhibitors exert opposite effects on respiration in rat: Implications for panic disorder. *Submitted manuscript*.
- IV. Annerbrink K, Westberg L, Olsson M, Andersch S, Sjödin I, Holm G, Allgulander C, Eriksson E. Panic disorder is associated with the Val308Iso polymorphism in the hypocretin receptor gene. *Submitted manuscript*.
- V. Annerbrink K, Westberg L, Olsson M, Allgulander C, Andersch S, Sjödin I, Holm G, Eriksson E. Association between the catechol-O-methyltransferase Val158Met polymorphism and panic disorder: a replication. *Submitted manuscript*.
- VI. Annerbrink K, Westberg L, Nilsson S, Rosmond R, Holm G, Eriksson E. Catechol O-methyltransferase Val158Met polymorphism is associated with abdominal obesity and blood pressure in men. *Metabolism*, May;57(5):708-11, 2008.

Abstract

On the association between panic disorder and autonomic regulation – With special focus on the roles of respiration and on the catechol-O-methyltransferase gene

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Background and aims: Panic disorder is a psychiatric disorder characterized by sudden attacks of intense anxiety. It displays a lot of features suggesting that it may be associated with an underlying aberration in the autonomic regulation of heart activity and respiration: i) the attacks are often characterized by respiratory symptoms and symptoms from the heart, ii) the attacks can be elicited by respiratory stimulants, iii) between attacks, patients with panic disorder often display enhanced respiratory variability and reduced heart rate variability, and iv) patients with panic disorder display enhanced prevalence of respiratory disorders and enhanced mortality in cardiovascular disease. Addressing the reasons for these physiological aberrations may help in elucidating the pathophysiology underlying panic disorder, and shed light on why this disorder is associated with enhanced mortality in cardiovascular disease. Serotonin is believed to be a neurotransmitter of great importance for panic disorder, as well as for the regulation of respiration: one main purpose of the animal studies presented in this thesis hence was to increase our knowledge regarding the role of serotonin in respiratory regulation, the hypothesis being that aberrations in respiration may cause the anxiety attacks, and that serotonin-modulating drugs may prevent panic attacks partly by stabilizing the regulation of respiration. In the first part of the thesis, data is presented on the effects on respiration in freely moving rats of various serotonergic compounds. The second part of this thesis is focused on genetic variations that may be associated with panic disorder. Orexin is a neuropeptide of suggested importance for both respiratory regulation and arousal. We investigated two polymorphisms in the orexin receptors 1 and 2, HCRTR1 Ile408Val and HCRTR2 Val308Iso, in panic disorder patients and healthy controls. Catechol-O-methyltransferase (COMT) is an enzyme that degrades catecholamines such as dopamine and noradrenaline, and may thus be of importance for both autonomic control and psychiatric symptoms. The functional Val158Met polymorphism in this gene has been associated with panic disorder in several studies; in an attempt to replicate this finding, we genotyped this polymorphism in the same group of panic disorder patients. In a separate cohort, we also explored if the same polymorphism is associated with risk factors for cardiovascular disease. **Observations:** 1) Serotonin depletion with parachlorophenylalanine *decreased* respiratory rate and *increased* respiratory variability. 2) Chronic treatment with serotonin reuptake inhibitors *increased* respiratory rate. 3) Acute treatment with serotonin reuptake inhibitors, as well as the serotonin releasing drugs d-fenfluramine and m-CPP, and the 5-HT_{1A} antagonist WAY-100635, *decreased* respiratory rate. 4) The HCRTR2 Val308Iso polymorphism was significantly associated with panic disorder in women. 5) In line with previous studies in Caucasian samples, the COMT Val158 allele was significantly more frequent in PD patients than controls. 6) Met158 allele carriers displayed significantly higher waist-hip-ratio, sagittal diameter, systolic and diastolic blood pressure, and heart rate, than Val158 allele carriers in a population of healthy men. **Conclusions:** Our results suggest that serotonin exert a modulatory role on respiration, and support the notion that an influence on respiration may contribute both to the anxiogenic and the anti-panic effects of serotonergic drugs. The association between panic disorder and the hypocretin receptor-2 Val308Iso polymorphism is a novel finding in need of replication, whereas the association between panic disorder and the COMT Val158 allele can by now be regarded as confirmed. The association between the COMT Val158Met polymorphism and cardiovascular risk factors is of interest, but does not support the theory that this polymorphism contributes to the enhanced mortality in cardiovascular disease seen in panic disorder patients.

Key words: panic disorder – serotonin – respiration – polymorphism – COMT Val158Met – HCRTR2 G1246A – blood pressure – anthropometry

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