On the anxiogenic influence of serotonin

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Jakob Näslund

Fakultetsopponent: Prof. Rainer Landgraf
Max-Plack-Institut für Psychiatrie, München, Tyskland

Avhandlingen baseras på följande delarbeten:

I. **Jakob Näslund**, Erik Studer, Robert Petterson, Melker Hagsäter, Staffan Nilsson, Hans Nissbrandt, Elias Eriksson. 2015. Differences in anxiety-like behaviour within a batch of Wistar rats are associated with differences in serotonergic transmission, enhanced by acute SRI administration and abolished by serotonin depletion. *Int J Neuropsychopharmacol*, Advance online publication, doi: 10.1093/ijnp/pyv018

II. **Jakob Näslund**, Erik Studer, Elin Johansson, Fredrik Stenfors, Jaroslav Eriksson, Elias Eriksson. 2015. The anxiety-enhancing effect of acute SSRI administration is antagonized by a 5-HT6 receptor antagonist. *Submitted.*

III. **Jakob Näslund**, Erik Studer, Karin Nilsson, Lars Westberg, Elias Eriksson. 2013. Serotonin depletion counteracts sex differences in anxiety-related behaviour in rat. *Psychopharmacology*, 230(1):29-35

IV. **Jakob Näslund**, Erik Studer, Elias Eriksson. 2015. Effects of gonadectomy and serotonin depletion on inter-individual differences in anxiety-like behaviour in male Wistar rats. *Submitted.*

V. **Jakob Näslund**, Erik Studer, Staffan Nilsson, Elias Eriksson. 2015. Expression of 22 serotonin-related genes in rat brain after subacute SSRI treatment or serotonin depletion. *Submitted.*

VI. **Jakob Näslund**, Johan Fredrik Emilsson, Staffan Nilsson, Fredrik Hieronymus, Elias Eriksson. 2015. Do SSRIs cause an initial increase in suicidal ideation and anxiety in depressed patients participating in placebo-controlled trials? *Manuscript.*

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UNIVERSITY OF GOTHENBURG

On the anxiogenic influence of serotonin

Jakob Näslund

Department of Pharmacology, Institute of Neuroscience and Physiology,
Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden

ABSTRACT

Despite over half a century of research on the role of serotonin in modulating anxiety, no consensus exists as to if serotonin should be regarded as acting mainly anxiety-dampening or anxiety-enhancing. This question is the focus of this thesis, with special emphasis on the role of serotonin in upholding differences in anxiety between and within sexes, and on the issue why some but not others report enhanced anxiety when exposed to selective serotonin reuptake inhibitors (SSRIs).

In paper I, we investigate the impact of serotonin elevation and depletion on inter-individual differences in anxiety-like behaviour of male Wistar rats as measured using an animal model of anxiety, the elevated plus maze (EPM). We also investigate biochemical correlates of temperament, mainly through gene expression analyses using real-time quantitative PCR (rt-qPCR). Briefly, these experiments indicate that more "anxious" rats display a gene expression profile suggesting a higher capacity for serotonin production, and are more prone to display enhanced such behaviour when acutely exposed to an SSRI and also that differences in baseline temperament are abolished by serotonin depletion.

In paper II, we investigate the possible role of three serotonin receptor subtypes in mediating the anxiogenic effect of acute SSRI administration (as studied in paper I) and find evidence for SSRI-induced acute anxiogenesis being dependent on 5-HT6 signalling.

In paper III, we show that the oft-reported difference in anxiety-like behaviour between the sexes is serotonin-dependent. Further underlining the importance of sex steroid vs serotonin interactions for EPM behaviour, the results in paper IV suggest that castration of male rats abolishes inter-individual differences in EPM behaviour and that the anxiogenic effect of this treatment in non-anxious rats is reversed by serotonin depletion.

In paper V, we employ rt-qPCR to explore the effects of short-term administration of a serotonin synthesis inhibitor and an SSRI, respectively, on the expression of serotonin-related genes in six brain areas, the aim being to shed light on to what extent a measurable change in gene expression is a common adaptive response to changes in extracellular serotonin levels. While many genes were unaffected, some were markedly influenced.

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In paper VI, we perform a post hoc analysis of patient level-data from a large number of placebo-controlled depression trials, the aim being to investigate the prevalence of enhanced anxiety following initiation of treatment (as commonly seen in patients with panic disorder). We note such reactions to be rare in this patient population, and also find no support for a suicide-provoking effect of these substances, but, in contrast, reduced rating of suicidal ideation in SSRI-treated subjects already after one week of treatment.

In summary, our studies suggest that i) SSRI-induced enhanced anxiety, in both animals and humans, is confined to subjects with high baseline anxiety, ii) that enhanced anxiety in animals is associated with indices of enhanced serotonergic activity, and iii) that inter-individual differences in anxiety are abolished by serotonin depletion. The importance of interactions between sex steroids and serotonin in this context gained support by the observation that sex differences in EPM behaviour were abolished by serotonin depletion, and that castration-induced anxiety in non-anxious males (unlike the effects on aggression and sexual behaviour of such treatment) could be reversed by serotonin depletion.

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