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Akademisk avhandling

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On the anxiogenic influence of serotonin

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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.

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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