



'Anxious' rats exhibit an enhanced anxiogenic response to acute SSRI treatment and indices of heightened serotonergic transmission

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Background

Upon acute administration, selective serotonin reuptake inhibitors (SSRIs) may elicit anxiety. While rarely seen in non-anxious subjects, this effect is common in patients with anxiety disorders or anxiety-related personality traits^{1,2}, suggesting that such subjects may be characterized by an abnormality in their serotonergic transmission.

Supporting this view, serotonin-related genes seem to be associated with anxiety-related personality traits. If the gene variants linked to anxiety lead to enhanced or reduced serotonergic transmission is however difficult to disclose in clinical studies.

Outbred Wistar rats display consistent inter-rat variation in anxiety-related behaviour³. The aim of the present study was to explore if animals displaying higher baseline anxiety i) are more prone to display enhanced anxiety when exposed to acute SSRI administration and ii) differ from less-anxious controls with respect to brain serotonergic transmission.

Methods

Experiment I: 48 male Wistar rats, aged 10 weeks were tested for five minutes on the elevated plus-maze (EPM). Four weeks later, paroxetine (10 mg/kg, i.p.) was administered. The animals were allowed to return to their cages for one hour before being exposed to an open field paradigm for 40 minutes.

Experiment II: 30 male Wistar rats, aged 10 weeks were tested for five minutes on the EPM. Six weeks later, the animals were sacrificed and the brains dissected. A small block of the brain stem, containing the raphe nuclei was homogenized with protein and mRNA extracted. RT-qPCR was performed using Applied Biosystems Custom LDA cards with reactions run in duplicate. Levels of tryptophan hydroxylase 2 (TPH2) were assayed using SDS-PAGE and western blotting, run in duplicate.

'Anxiety' in the open field test

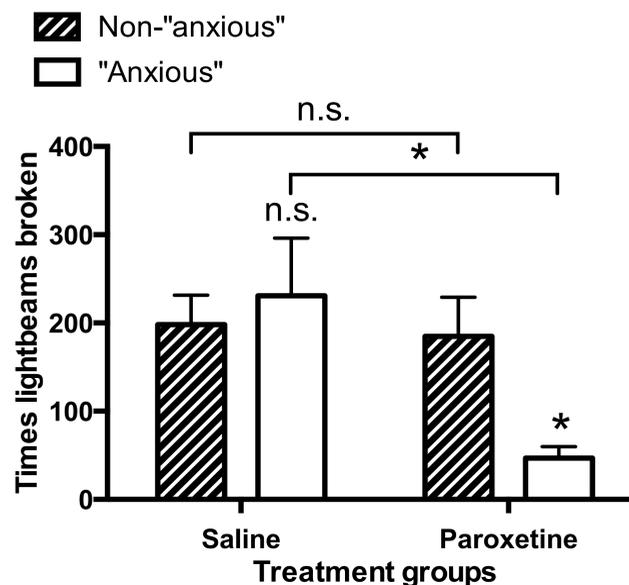


Figure 1: Time spent in centrum of open field (means ± S.E.M.)

Results

Data and analyses here presented pertain to differences between the most "anxious" third of the animals (according to the EPM) as compared to the rest.

Experiment I: "Anxious" animals experienced an anxiogenic-like effect in the open field test, absent in other animals (fig. 1).

Experiment II: "Anxious" animals exhibited higher expression of genes related to serotonergic transmission in the raphe nuclei as well as higher levels of TPH2 as assayed by western blot (figs. 2 & 3).

Raphe gene expression

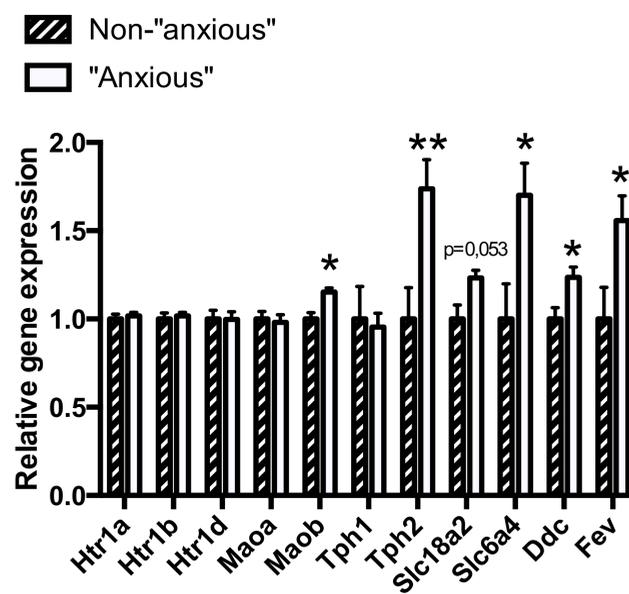


Figure 2: Relative expression of serotonergic genes in the raphe nuclei (means ± S.E.M.)

TPH2 protein levels

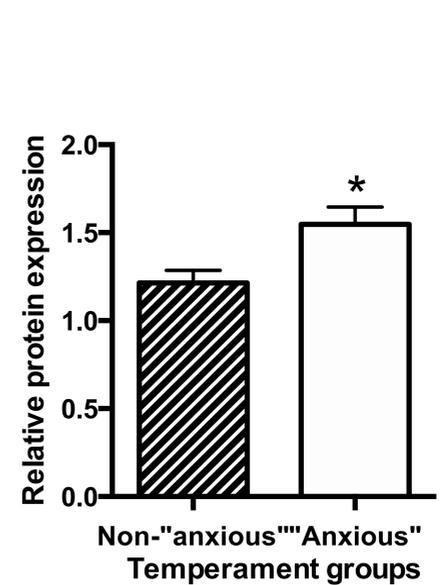


Figure 3: TPH2 protein levels in the raphe nuclei (means ± S.E.M.)

Comment

The data obtained support our hypotheses. Animals displaying a higher baseline anxiety-like behaviour had a strong response to acute SSRI administration while also differing in measures of central serotonergic function in a way that would be consistent with a higher serotonergic activity. This indicates that further investigation of differences in anxiety-like behaviour between rats of the same strain and batch could help shed some light on the relationship between genetic variation in the serotonin system and personality differences in humans, as well as over the mechanisms underlying the acute, anxiogenic effect of SSRIs.

Presented at the 'ECNP Workshop on Neuropsychopharmacology for Young Scientists in Europe' in Nice, March 7-10 2013



Disclosure

The authors report no conflict of interest.

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