Association of serotonin-1A and 2A receptor promoter polymorphisms with depression, pain and function in patients 6 months after lumbar disc surgery

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Background/Aims
Several studies have suggested that genetic polymorphisms in 5-HT system components are associated with susceptibility to affective and depressive symptoms (Caspi et al., 2003; Lemond et al., 2003) and pain-related disability is strongly associated with depressive moods (Arpino et al., 2004), but the results have remained somewhat conflicting. A recent meta-analysis of 54 studies investigating the association between a promoter variant (5-HTTLPR) in the 5-HT transporter gene and depression yielded strong evidence that this variation, rather than directly influencing depression risk, instead mediates the relationship between stress and depression, particularly in clinical subgroups demonstrating “childhood maltreatment” and “specific medical conditions” as environmental stressors (Karg et al., 2011).

While there is substantial evidence that the development of depression is affected by a gene environment interaction involving the promoter region of the serotonin transporter gene, little is known about the effects of other genes encoding components of the serotonergic system, including the 5HT1A and 5HT2A receptors.

In the present study, we examined the impact of 5HT1A (rs6295) and 5HT2A (rs6311) promoter variations on depression in a group of patients who were assessed six months after lumbar disc surgery.

We hypothesized that the severity of persisting pain may act as a stressor in a gene x environment model to modulate the effect of 5HT1A and 5HT2A variation on depression levels. We further explored the impact of 5-HT receptor polymorphisms on the degree of related physical function and disability, and all analyses examined potential interactions with gender.

Methods
Sample and research design
- 224 patients (116 female, 108 male) 6 months after first lumbar disc surgery participated in a physical examination and were genotyped for our target SNPs.
- We subdivided all participants according to their pain status (no pain: 16%; mild pain: 52.7%, severe pain: 16.9%), their depression level measured with the BDI (no depression: 69.4%, subclinical depression: 23.1%, moderate to severe depression 7.5%), their physical functioning measured with the FFHQ and their pain-related disability (PDS).
- Genotyping was performed by polymerase chain reaction (PCR).

References

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Results
Depression:
- For 5HT2A we found a significant gene x sex x pain interaction (F = 5.489, p = 0.005), where in case of severe pain (>4 SAS), woman carrying at least one A allele exhibited a higher (p = 0.004) woman who reported no pain a lower (p = 0.051) BDI score. Male only exhibited an effect of pain on depression, which was not influenced by the 5HT2A genotype (Fig. 1).
- For 5HT1A we found a borderline significant main effect for patients homzygous for the G- allele relative to the CG/CC genotype (p = 0.049).

Physical functioning:
- For 5HT1A we found a significant gene x sex interaction (p = 0.040). A subsequent ANCOVA including only female subject harboring the GG- allele revealed a significant main association between genotype and lower physical functioning. Men did not show any differences related to genotype (Fig. 2a).
- For 5HT2A we again found a gene x sex interaction related to women homzygous for the A- allele (p = 0.002) and lower physical functioning. Men did not show any differences related to genotype (Fig. 2b).

Table 1: Means (± standard deviation) of BDI depression scores stratified for 5HT1A and 5HT2A genotypes, levels of pain and sex. Results of analyses of covariance (ANCOVA).

Table 2: Means (± standard deviation) of physical functioning and disability scores stratified for 5HT1A and 5HT2A genotypes and sex. Results of analyses of covariance (ANCOVA).

Conclusion
Our research revealed evidence for an impact of 5HT1A and 5HT2A promoter variation on depression, physical functioning and disability as well as complex interaction effects between environmental stressors and gender in patients 6 months after lumbar disc surgery. According to our data, acute pain can be seen as an environmental condition influencing gene expression.