Acta Neuropsychiatrica
An International Journal of Translational Neuropsychiatry

Acta Neuropsychiatrica 2012: 24: 65–66

DOI: 10.1111/j.1601-5215.2012.00660.x

Editorial

Neuropeptide Y: a promising candidate in affective disorders

There is an increasing support for a crucial role of neuropeptides in the pathogenesis of affective disorders transcending the monoaminergic neurotransmitter systems traditionally suspected to constitute the major neurobiological pathomechanism of depression and anxiety. Particular evidence has accumulated for neuropeptide Y (NPY), one of the most abundant peptides in the human brain, to influence the pathogenesis of depression: NPY has been found to be decreased in rodent models of depression and in the cerebrospinal fluid of depressed patients. In turn, NPY administration seems to counteract depression-like behaviour in animals, and antidepressant treatment increases NPY and NPY receptor expression (1). Accordingly, the human gene coding for NPY on chromosome 7p15.1 has attracted much attention in the investigation of the molecular genetic basis of affective disorders.

In this issue of *Acta Neuropsychiatrica*, Koefoed et al. (2) report on a case–control-based association study of the *NPY* Leu7Pro (T20C, formerly T1128C; rs16139) polymorphism in a large Danish sample of 593 patients and 2912 controls. Authors discerned association of the Pro7 allele with depression, while no association was observed in a sample of patients with schizophrenia ($n = 503$) as a psychiatric disease control group. Authors additionally explored potential functional effects of the Pro7 substitution *in vitro* and reported evidence for Pro7 to confer reduced levels of NPY in cell cultures without affecting mRNA levels.

This study provides an additional major piece in the molecular genetic puzzle of affective disorders, strengthening the role of neuropeptides, particularly NPY in the picture. While the observed decrease in NPY levels conferred by the presently associated Pro7 allele is consistent with animal models suggesting a deficit in NPY to increase the risk of depression-related behaviour, the present results are in contrast to previous studies reporting association of the Leu7 allele with depression (3,4). This flip-flop phenomenon of allelic association potentially due to multilocus effects and variation in interlocus correlations is a well-known occurrence in molecular genetic research in complex disorders (5), not necessarily diminishing the generally confirmatory nature of the finding.

The present study by Koefoed et al. (2) did not discern association with anxiety-related traits within the examined sample of patients with depression. However, there is an accumulating evidence from rodent and human studies for NPY to be involved as well as in the pathogenesis of anxiety, partly in interaction with environmental stressors (e.g. panic disorder, generalised anxiety disorder and anxious depression) (1,6–8), suggesting a potential common molecular genetic trunk for affective and anxiety disorders to be mediated, at least in part, by NPY.

Therefore, the NPY system seems to hold great promise for the investigation of the molecular genetic underpinnings of affective and anxiety disorders and thereby to have high potential for the development of innovative therapeutic mechanisms in these disorders (9). Furthermore, pharmacogenetic studies of *NPY* gene variation in affective disorders (7) might contribute to a genotype-based personalised medicine with an individually tailored antidepressive pharmacotherapy according to genotype thus reducing the patients' suffering and lowering healthcare costs at the same time.

Professor Katharina Domschke, MA, MD, PhD
Department of Psychiatry, University of Wuerzburg, Fuechsleinstrasse 15, D-97080 Wuerzburg, Germany

References

1. Wu G, Feder A, Wegener G et al. Central functions of neuropeptide Y in mood and anxiety disorders. Expert Opin Ther Targets 2011;**15**:1317–1331.
2. Koefoed P, Woldbye DPD, Hansen TvO et al. Association of the leucine-7 to proline-7 variation in the signal sequence of neuropeptide Y with major depression. Acta Neuropsychiatr 2011 (this issue).

3. Heilig M, Zachrisson O, Thorsell A et al. Decreased cerebrospinal fluid neuropeptide Y (NPY) in patients with treatment refractory unipolar major depression: preliminary evidence for association with preproNPY gene polymorphism. J Psychiatr Res 2004;**38**:113–121.
4. Sjöholm LK, Melas PA, Forsell Y, Lavebratt C. PreproNPY Pro7 protects against depression despite exposure to environmental risk factors. J Affect Disord 2009;**118**: 124–130.
5. Lin PI, Vance JM, Pericak-Vance MA, Martin ER. No gene is an island: the flip-flop phenomenon. Am J Hum Genet 2007;**80**:531–538.
6. Amstadter AB, Koenen KC, Ruggiero KJ et al. NPY moderates the relation between hurricane exposure and generalized anxiety disorder in an epidemiologic sample of hurricane-exposed adults. Depress Anxiety 2010;**27**: 270–275.
7. Domschke K, Dannlowski U, Hohoff C et al. Neuropeptide Y (NPY) gene: impact on emotional processing and treatment response in anxious depression. Eur Neuropsychopharmacol 2010;**20**:301–309.
8. Domschke K, Hohoff C, Jacob C et al. Chromosome 4q31-34 panic disorder risk locus: association of neuropeptide Y receptor Y5 variants. Am J Med Genet B Neuropsychiatr Genet 2008;**147**:510–516.
9. Crespi F. Influence of neuropeptide Y and antidepressants upon cerebral monoamines involved in depression: an in vivo electrochemical study. Brain Res 2011;**1407**:27–37.

https://doi.org/10.1111/j.1601-5215.2012.00660.x Published online by Cambridge University Press