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# Neuropeptides in anxiety and depression

## *Editorial*

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This issue of *Amino Acids* includes papers based on presentations at the 9th Congress on Amino Acids and Proteins which was held in Vienna in August 2005. The symposium where these presentations were given focused on the role of neuropeptides in anxiety and depression-like behavior.

Anxiety is a protective, if at times uncomfortable, emotion that is fundamental to adaptation and survival. Pathological, i.e. excessive, anxiety can prove disabling and can severely interfere with normal life. The individual level of anxiety is attributed to genetic variation, epigenetic switches and environmental factors that interact to confer vulnerability.

Rodents often exhibit both anxious and depressive behaviors in behavioral tests, thus mirroring clinical comorbidity. The distinction between anxiety and depression, however, is artificial (Spedding et al., 2005); from a neurobiological point of view, both should be considered as phenomena along a continuum (Landgraf and Neumann, 2004; Landgraf and Holsboer, 2005). Accordingly, pathological anxiety evolves from normal anxiety, and some putative antidepressants are equally active in anxiety and depression.

Despite enormous progress in our fundamental knowledge in neuroscience and many decades of study, the pathophysiology of anxiety disorders and depression remains elusive, and no revolutionary therapies in psychiatry have emerged in the past decades. All traditional medications are based on serendipitous discoveries made more than half a century ago. Antidepressants must be given for at least several weeks for their actions to become manifest and, despite many interesting and promising leads, the changes they induce in the brain remain largely unclear. Over the years it became evident that factors beyond (i) monoamine deficiency or imbalance traditionally related to depression and (ii) allosteric modulators of the $GABA_A$ receptor (benzodiazepines, the archetypal anxiolytic drugs; barbiturates; neurosteroids; ethanol) traditionally related to anxiety, must be taken into consideration as molecular reasons for depression- and anxiety-like behavior.

Particularly neuropeptides which play multiple and varying roles in interneuronal signalling (Landgraf and Neumann, 2004), may be considererd as ''rosetta stones'' translating genetic polymorphisms and environmental influences into behavioral regulation at multiple levels of complexity. More than any other class of neurochemicals, neuropeptides as primary products of protein synthesis were and are shaped by evolution in number and diversity to become critically involved in emotional facets. As exemplified by the ''gold standard'' vasopressin, neuropeptides in appropriate animal models are differentially expressed and released depending on the anxious phenotype, reveal physiological involvement in emotional regulation upon their experimental manipulation and show genetic polymorphisms related to the phenotype. Furthermore, patients who lack vasopressin or subjects who were treated with exogenous vasopressin, show corresponding behavioral consequences indicative of a causal neuropeptide involvement in emotionality. Thus, although not being the usual suspects in anxiety-related signalling, neuropeptides and their receptors are hot candidates linking neuroendocrinology to psychopathology.

The role of neuropeptides was elucidated in proper animal models relying on the circuitry-level homology that exists between species. Conceptually straightforward approaches base on the assumption that the brain circuitry underlying anxiety is evolutionary conserved, although inter-species differences do exist. In light of the distinctive emotional and cognitive capacities of humans, it is prudent to wonder whether the neural circuitry and signalling that regulate human behavior perform similar roles in rodents. Although 99% of mouse genes have human counterparts, mice are mice and humans are humans, and diverse social phenomena including embarrassment, suicidal thoughts and charisma may hardly be mirrored in rodents. Conscious emotional experiences, in other words, cannot be proven to occur in rodents. However, many key hypotheses generated from clinical information are simply untestable in humans. Thus, given acceptable face, construct and predictive validity, clinically relevant rodent models may represent the best way forward for anxiety and depression modelling.

Studies using proper animal models suggest that, in addition to transport, targeting and interaction issues, a major problem with neuropeptides is their complex involvement in multiple processes, making it difficult to selectively affect anxiety- and depression-related phenomena. Thus, the evolutionary advantage of neuropeptides raises concerns about possible side effects of agonists or antagonists after their clinical use. Furthermore, they will only become promising medications, if the corresponding neuropeptide system is likely to causally contribute to psychopathology. It will, therefore, be essential to identify reliable biomarkers as tools to characterize the state of an endogenous neuropeptide system, thereby optimizing the individual diagnosis of psychiatric patients. The following articles provide excellent examples of how neurobiological research in close association with clinical issues may pace this development.

Harro (2006) focuses on CCK and NPY systems as targets for anxiolytic treatment. While CCK peptides are thought to be anxiogenic, CCK receptor antagonists failed to induce reliable anxiolytic effects. In many studies, sedation, impairments in attention and memory as well as changes in locomotor activity were reported, often contaminating effects on emotionality. The specific variables determining either anxiety-reducing or -enhancing CCK effects remain to be defined. Similarly, the most abundant neuropeptide in the brain, NPY, may act in either direction, depending on the site of action and the classical neurotransmitter(s) involved. While one role of the Y1 receptor in feeding might be to eliminate the negative influence anxiety may have on consummatory behavior, Y2 antagonists could serve as more selective anti-anxiety agents.

As reviewed by Karlsson and Holmes (2006), there is a potential for developing galanin-targeting anxiolytics and antidepressants. Probably interacting with dopaminergic and serotonergic nuclei, this neuropeptide exerts antidepressant-like effects. However, resembling the situation with NPY and CCK, others report pro-depressive effects, suggesting that the role of the neuropeptide in anxiety and depression might be complicated by differences in its effects across species and animal models, brain areas and behavioral paradigms. Indeed, some data indicate that neither intracerebroventricular galanin nor its transgenic overexpression necessarily alter depression-like behavior. Conceivably, a certain threshold level of emotional provocation, stress or neuropathology may be required to recruit galanin's emotionality-related effects.

As described by Keck (2006), aberrant stress hormone regulation is related to causality of depression. Both CRF and vasopressin are not only principal regulators of HPA axis activity, but also mediate effects on emotional and cognitive behaviors. Importantly, neuropeptide or antagonist effects depend on the animals' stress and trait anxiety levels. Massive efforts to develop CRF1 antagonists as anxiolytic and antidepressant medications are hampered by their inconsistent activity in standard screens. Unfortunately, pharmacokinetic and hepatotoxicity issues have led to the discontinuation of research on numerous *a priori* promising CRF1 antagonists. Compelling evidence suggests anxiogenic and depressant activities of centrally released vasopressin. While targeted gene mutations indicate no critical role of the V1b receptor subtype in emotionality, its antagonist has been shown potential antidepressant effects.

Ebner and Singewald (2006) address the role of neurokinins, particularly the substance P/NK1 system, in stress and psychopathology. They raise a number of interesting methodological issues including in vivo microdialysis and push-pull superfusion to quantify intracerebral release patterns, stimuli and mechanisms of release (vs. measurements of contents), receptor internalization etc. Substance P effects on anxiety remain ambiguous, depending on a variety of variables. Limbic brain areas seem to be involved in anxiolytic and antidepressant effects of NK1 receptor antagonists. Their potential clinical use is a challenging, but promising task. Concomitantly with behavioral regulation, substance P may affect HPA axis activity, both under basal and stimulated conditions, although the pathways involved in this phenomenon remain largely unknown.

In addition to this issue of *Amino Acids*, the reader interested in neuropeptides, animal models and emotion-

ality is further referred to *Stress* 6 (2), 2003 and 8 (4), 2005, *Drug Development Research* 65 (4), 2005 and *CNS & Neurological Disorder-Drug Targets* 5 (2), 2006.

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