

6 Qin, Y. *et al.* (1994) Inhibitory effect of bombesin receptor antagonist RC-3095 on the growth of human pancreatic cancer cells *in vivo* and *in vitro*. *Cancer Res.* 54, 1035–1041

7 Roesler, R. *et al.* (2003) Intrahippocampal infusion of the bombesin/gastrin-releasing peptide antagonist RC-3095 impairs inhibitory avoidance retention. *Peptides* 24, 1069–1074

8 Roesler, R. *et al.* (2004) Bombesin/gastrin-releasing peptide receptors in the basolateral amygdala regulate memory consolidation. *Eur. J. Neurosci.* 19, 1041–1045

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Letter Response

Response to Roesler *et al.*: Neuropeptides and stress-related disorders – multiple targets and converging concepts

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Research on improved therapeutic interventions for stress-related disorders such as depression and anxiety continues to evolve and focuses on, among other systems, neuropeptides. In our recent *TiPS* review [1] we discussed five neuropeptides that have received strong interest in the field (the tachykinin substance P, corticotropin-releasing factor, vasopressin, neuropeptide Y and galanin), and evaluated the behavioral effects of manipulating these systems in rodents either by treatment with receptor-specific ligands or by targeted gene mutations.

The list of other neuropeptides that have been implicated in the modulation of stress responses and proposed as potential novel therapeutic targets for stress-related disorders continues to increase in conjunction with an evolving knowledge of the mechanisms that govern stress-related behavior and a better understanding of the neurobiology of affective disorders [2,3]. In this issue of *TiPS*, Roesler and colleagues [4] note that bombesin receptors are localized in limbic areas of the brain and, together with bombesin-like peptides, have been associated with fear-related behaviors in rodent models. In addition to bombesin, recent research has implicated various other neuropeptides in the mediation of stress and emotional behaviors, suggesting that new target systems will continue to be identified in this rapidly advancing field. Of note are the hypothalamic peptides melanocortin and prolactin-releasing peptide, the opioid peptides endorphins and dynorphins, and a plethora of neuropeptides whose function is less well studied, including atrial natriuretic peptide, cocaine and amphetamine-related transcript (CART) peptide, calcitonin gene-related peptide, cholecystokinin, ghrelin, glucagon-like peptide 1, melanin-concentrating hormone, motilin, neuromedin U, neuropeptide FF, neuropeptide W, neurotensin and nociceptin/orphanin FQ. The fact that this list is far from exhaustive illustrates the great

potential for identifying innovative neuropeptide-based approaches to treat stress-related disorders.

Since the publication of our *TiPS* review [1], Merck (<http://www.merck.com/>) have announced the discontinuation of the Phase III clinical development of the tachykinin NK₁ receptor antagonist aprepitant (MK0869) as a result of a lack of demonstrable efficacy in the treatment of depression. Although these results are disappointing, it would be premature to judge them as being indicative of the poor therapeutic value of targeting neuropeptide systems in general. Indeed, Sanofi-Synthelabo (<http://www.sanofi-synthelabo.com/>) has recently reported promising results of their tachykinin NK₂ receptor antagonist sareudant (SR48968) in a Phase IIb study in depression. There is, however, a remaining need to improve both preclinical and clinical development of novel antidepressants and anxiolytics that act on neuropeptide systems. Preclinical research on neuropeptides has shown that therapeutic value is not always readily detected in traditional animal models that are validated for their sensitivity to monoamine-mediated and GABA-mediated effects. Therefore, advances in this field will be facilitated by the development of animal models with improved predictive validity for neuropeptide-targeting compounds. Moreover, the discontinuation of the development of aprepitant as an antidepressant relatively late in the development process emphasizes the need to develop alternative measures for clinical proof of concept, not only for compounds acting on neuropeptide systems, but for anxiolytics and antidepressants in general. Future clinical trials will provide information that is crucial to our understanding of the potential utility of neuropeptide-based therapeutics for a variety of stress-related indications – be it as monotherapy or as adjunct medication to already established anxiolytic and/or antidepressant drugs.

The search for novel treatment strategies for stress-related disorders is driven by the growing medical need to enhance the response rate, efficacy and side-effect profile of

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existing antidepressant drugs. Given the wealth of animal and human data supporting the role for neuropeptides in mediating emotion and stress, targeting these systems remains a highly promising avenue for the development of novel clinical entities in stress-related disorders.

References

- 1 Holmes, A. *et al.* (2003) Neuropeptide systems as novel therapeutic targets for depression and anxiety disorders. *Trends Pharmacol. Sci.* 24, 580–588
- 2 Griebel, G. (1999) Is there a future for neuropeptide receptor ligands in the treatment of anxiety disorders? *Pharmacol. Ther.* 82, 1–61
- 3 Steckler, T. (2001) The molecular neurobiology of stress – evidence from genetic and epigenetic models. *Behav. Pharmacol.* 12, 381–427
- 4 Roesler, R. (2004) Neuropeptides and anxiety disorders: bombesin receptors as novel therapeutic targets. *Trends Pharmacol. Sci.* 25 (xref: doi:10.16/j.tips.2004.03.004, this issue)

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