Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 14217–14219, December 1997

Commentary

Orphan anxiety

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The recent discovery of several new endogenous opioid peptides has generated excitement over their potential physiological roles. For example, endomorphins are likely to have well defined functions due to their affinity and selectivity for a class of extensively studied opioid receptors (1). However, nociceptin/orphanin FQ is an endogenous opioid-like peptide with less well defined effects on animal physiology and behavior (47). A study published in this issue by Jenck *et al*. (2) proposes a novel function for this peptide, a potential role in modulating anxiety and/or behavioral responses to stressors. These new findings may change the direction of nociceptin/orphanin FQ research as well as add another candidate for novel anxiety therapies.

The orphan receptor ORL1 (human) or LC132 (rat), hereafter referred to as the orphan opioid receptor, was found by PCR cloning using primers corresponding to conserved regions of members of the G-protein-coupled receptor gene family (3–6). The orphan opioid receptor has high homology to opioid receptors, yet it does not bind known opioid peptides with high affinity (4, 7). Nociceptin/orphanin FQ itself, despite its high homology to opioid peptides, does not bind with high affinity to opioid receptors. However, as in opioid receptor systems, binding of nociceptin/orphanin FQ to the orphan opioid receptor modulates intracellular cAMP levels and cell excitability (5, 6, 8).

Nociceptin/orphanin FQ was named because it was shown to enhance nociception or pain perception, a finding that was later explained as a reversal of stress-induced analgesia (5, 9). Other laboratories quickly found similar results, and excitement was generated over the possibility that this was an endogenous anti-opioid peptide, joining the ranks of other anti-opioid peptides such as neuropeptide FF (10). It was found, however, that nociceptin/orphanin FQ also appears to produce analgesia under certain conditions (11, 12). Once anatomical studies began to show a wide distribution of nociceptin/orphanin FQ and the orphan opioid receptor (4, 7, 13–18), research branched away from analgesia. It was soon found that nociceptin/orphanin FQ had many other physiological effects.

Nociceptin/orphanin FQ not only reverses morphine analgesia (9) but also depresses cardiovascular function (19, 20), enhances penile erectile activity (21), inhibits neurogenic inflammation (22), increases food intake (23, 24), inhibits long-term potentiation (25), increases or decreases locomotor activity (5, 26, 27), impairs spatial learning (28), and produces diuresis and antinatriuresis (29). The fact that an opioid-like peptide has many functions is not surprising, but in many studies physiological effects were seen only with relatively high doses of the peptide and only a single behavioral measure was used, and most studies have been done in only one species. The study by Jenck *et al.* (2) in this issue is significant in that a new role for nociceptin/orphanin FQ, namely an anxiolytic-like effect, is demonstrated, and effects were seen at physiologically relevant doses with multiple behavioral measures in two separate rodent species.

The major finding of the study reported in this issue (2) is that nociceptin/orphanin FQ has anxiolytic-like effects. One potential problem in interpreting any study that shows an anxiolytic-like effect for a novel agent is whether competing behavioral effects oppose each other. Nociceptin/orphanin FQ has been shown to have many different behavioral effects, including interfering with motor performance, stimulating feeding, producing hyperalgesia, reversing stress-induced analgesia, and producing analgesia. These are all effects that might interfere with one behavioral measure used, the conflict paradigm. In this paradigm, food-deprived mice press a lever for food and receive an associated mild electric footshock. However, with the peptide doses used, none of these competing behavioral effects are likely to interfere with the conflict paradigm. First, the authors show that effective anxiolytic doses do not interfere with motor performance. In addition, previous studies showing increased feeding behavior used doses higher than the effective doses in this study (23). Furthermore, if nociceptin/orphanin FQ produced hyperalgesia or reversed stress-induced analgesia in the study of Jenck *et al*. (2), mechanisms working against anxiolytic-like activity would be activated, making the anxiolytic effects more profound. Last, previously reported (12) analgesic effects of intracerebroventricularly delivered nociceptin/orphanin FQ occurred at a dose almost twice as high as that used in this study. Taken together, these results suggest that other reported behavioral effects of nociceptin/orphanin FQ do not compete with detection of its anxiolytic-like actions.

It has been shown recently that nociceptin/orphanin FQ reverses stress-induced analgesia (9). Thus, it appears from the new results that nociceptin/orphanin FQ is reversing the stress component of the stress-induced analgesia and not the analgesic response. It is important to keep in mind that experiments such as those of Jenck *et al.* (2), in which an endogenous peptide is given exogenously, might not reflect what happens in a functioning organism. To determine whether nociceptin/orphanin FQ might act as an endogenous anxiolytic, it will be critical to assess the action of a nociceptin/orphanin FQ antagonist. In addition, it will be important to show that extracellular peptide levels and/or mRNA levels of the nociceptin/orphanin FQ precursor are activated upon exposure to stress. Orphan opioid receptors are found in several brain regions involved in the integration of stressful stimuli, including the locus coeruleus, central gray, raphe nucleus, hypothalamus, and amygdala (4, 13–15, 30), and these regions should be examined for regulation of nociceptin/orphanin FQ peptide levels. Once it is established that nociceptin/orphanin FQ levels are increased by stress and the peptide is released in these regions, it will be important to determine whether nociceptin/orphanin FQ affects other neurotransmitter systems, including γ-aminobutyrate (GABA) and glutamate. Also unknown is whether nociceptin/orphanin FQ acts

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through more than one orphan opioid-like receptor with different anatomical locations and functions (31).

If nociceptin/orphanin FQ functions as an endogenous anxiolytic, it provides an attractive mechanism for the body's response to alleviate stressful and/or painful stimuli. Upon exposure to stress, nociceptin/orphanin FQ may be released to turn off excessive anxiogenic responses. In addition, if painful stimuli are involved, opioid peptides would be released to produce analgesia. Stress and pain, therefore, might be counteracted by peptides with sequence homology but with distinct functions.

A logical extension of the present functional hypothesis is that nociceptin/orphanin FQ may interact with opiate dependence. It would be interesting to determine, for example, whether intracerebroventricular administration of nociceptin/orphanin FQ reduces symptoms of precipitated withdrawal in opioid-dependent rats. Orphan opioid receptor mRNA is rich in the locus coeruleus (LC) and periaqueductal gray, regions thought to be involved in the opioid withdrawal syndrome (32, 33). Morphine and clonidine reduce opioid withdrawal symptoms, and like nociceptin/orphanin FQ, reduce intracellular concentrations of cAMP and modulate potassium channels when applied to the LC (5, 6, 33–35). Given that anxiogenic-like effects are reduced by administration of nociceptin/orphanin FQ, opioid-withdrawal anxiogenic-like responses may also be reduced.

Sedative hypnotics have a variety of medical uses, including anticonvulsant activity. It will be interesting to explore the similarities of nociceptin/orphanin FQ to other sedative hypnotic actions. Nociceptin/orphanin FQ might also lack well known undesirable side effects of anxiolytics and anticonvulsants, namely sedation, tolerance, and dependence (36). Sedation might be avoided, as the anxiolytic-like effects of the peptide were at doses that did not disrupt motor function. Also, orphan opioid receptor agonists used for sedative hypnotic actions might not have abuse liability, as a study in rats has shown a lack of conditioned place preference (or aversion) to nociceptin/orphanin FQ (27). This evidence suggests that orphan opioid receptor agonists may lack rewarding properties and are therefore not likely to be abused.

Nociceptin/orphanin FQ now joins a host of new pharmacological targets that offer promising directions for anxiolytic and/or anti-stress therapy (see Table 1). Among neuropeptides, cholecystokinin (CCK)-B and corticotropin-releasing factor (CRF) receptor antagonists have shown some promise, as well as neuropeptide Y agonists. Preclinical evidence suggests that neurosteroids, as well as 5-HT_3 serotonin receptor and other serotonin receptor antagonists, might also be useful targets for anxiolytic agents (37). Last, studies that determine if multiple orphan opioid receptor subtypes are utilized to produce anxiolytic-like effects of nociceptin/orphanin FQ will aid in the development of nonpeptide agonists, and therefore useful pharmacologic agents, at this receptor.

The evidence for an additional role for nociceptin/orphanin FQ also changes the way this peptide is viewed. Is nociceptin/orphanin FQ an opioid or an anti-opioid? This latest finding suggests an opioid-like role. Future studies defining the role of endogenous nociceptin/orphanin FQ will be critical. Regardless, the nociceptin/orphanin FQ system can now be viewed as a potentially effective target for development of anxiolytic or anti-stress medications.

Table 1. Drug classes with anxiolytic-like activity in animal models of anxiety

Drug class	Activity in animal model		
	Conflict	Light–dark	Plus-maze
5-HT_3 receptor antagonists	− (38)	+ (38)	− (38)
Neuropeptide Y	+ (39)	ND	+ (40, 41)
CCK receptor antagonists	+ (42)	+ (42)	+ (43)
CRF receptor antagonists	+ (44)	+ (45)	+ (46)
Benzodiazepines	+ (38)	+ (38)	+ (38)
Nociceptin/orphanin FQ	+	+	+

Reference numbers are given in parentheses. ND, not done; +, possesses anxiolytic-like activity; and −, lacks anxiolytic-like activity.

This is manuscript number 11264-NP from The Scripps Research Institute.

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