Cloning of the opioid receptor family has added a new dimension to opioid pharmacology. In common with the endogenous μ, δ, κ opioid subtypes, recombiant opioid receptors, when expressed in a variety of cell types, couple to K⁺ channels, Ca²⁺ channels and adenylyl cyclase.¹⁻⁴ The net effect in the CNS is reduction in neuronal firing and excitability. If this occurs in neurones involved in the processing of noxious stimuli then analgesia results. Despite these monumental advances the clinical “holy grail” of analgesia without respiratory depression remains to be realized. In this editorial we summarize briefly a new development in opioid pharmacology— isolation of a novel receptor involved in pain processing and discovery of an endogenous ligand for this receptor. Shortly after the publication of the μ, δ and κ opioid receptor sequences several groups reported the isolation of an atypical “opioid-like” receptor subtype⁵⁻¹¹ with approximately 50% homology to μ, δ and κ opioid receptors. There is general consensus that these different clones represent the same receptor. From sequence and structural analysis the receptor is predicted to be a new member of the G-protein coupled receptor superfamily and is known euphemistically as the orphan opioid receptor (ORL₁). A common characteristic of the orphan receptor was that opioid receptor ligands bound with very low affinity compared with opioid receptors. In the rat, orphan receptors are found “scattered” throughout the CNS with high levels found in the thalamus, hypothalamus, amygdala, cortex (diffuse but layered), hippocampus, periaqueductal gray, dorsal raphe, locus coeruleus and spinal cord.¹²⁻¹⁴ At the time of cloning no endogenous ligand had been isolated. In November 1995, Reinscheid and colleagues¹² and Meunier and colleagues¹³ reported the isolation of a heptadecapeptide (fig. 1) that was named orphanin FQ or nociceptin (throughout the remainder of this editorial orphanin FQ (OFQ) is used and refers to the full 17 amino acid peptide). The heptadecapeptide displayed nanomolar binding affinity for the recombinant ORL₁ receptor in radioligand binding studies. The first amino acid differed in OFQ compared with opioid peptides, but of these peptides its closest match was with dynorphin (fig. 1). When injected intracerebroventricularly (i.c.v.) (i.e. supraspinally) in the mouse, the peptide appeared to be hyperalgesic.¹²⁻¹³ In addition, it has been reported recently that OFQ is antinociceptive at spinal level. These differences at spinal and supraspinal sites clearly need further exploration. Unlike μ receptor activation orphan receptor activation with OFQ (and hence a clinical orphan receptor agonist when available) does not produce dependence and as such has little or no abuse potential.¹⁷ The cellular effects of OFQ have received some attention and have been shown to inhibit cAMP formation.¹²⁻¹³ In addition, OFQ increases inwardly rectifying K⁺ currents¹⁸⁻²⁰ and inhibits voltage-sensitive Ca²⁺ channels.²¹⁻²² Activation of K⁺ channels, closing of voltage-sensitive Ca²⁺ channels and inhibition of adenylyl cyclase are features common to opioid receptors.¹⁴ We have demonstrated recently that OFQ inhibits the release of glutamate from rat cerebrocortical slices in a naloxone-insensitive manner.²³ These data are in agreement with the inhibitory effects of OFQ on glutamatergic transmission in the rat spinal cord.²⁴ If this depression in glutamatergic transmission is mirrored in the hippocampus then this might provide an explanation for the effects of OFQ on spatial learning.²⁵ Similarly, if observed in the cerebellum, this may go some way to explain the effects of OFQ on locomotion.¹²⁻²⁵ In addition to glutamate, OFQ also inhibits the release of tachykinin,²⁶ acetylcholine²⁷⁻²⁸ and dopamine.²⁹ These data suggest the presence of presynaptic ORL₁ receptors involved in neurotransmitter release. Is OFQ released in significant quantities to provide inhibition of release under physiological conditions? This is another important issue that needs to be resolved in the near future. The recent development of a sensitive radioimmunoassay³⁰ should prove useful in this regard.

1. Orphanin FQ/Nociceptin
Amino acid sequence

Single letter code
Orphanin
FQ
FGFTGARKSARKLANQ

2. Dynorphin
Tyγ-Gly-Gly-Phe-Leu-Arg-Ile-Arg-Pro-Lys-Leu-Lys-Trp-Aap-Aasn-Gln

3. Met-enkephalin
Tyγ-Gly-Gly-Phe-Met

4. β-endorphin
Tyγ-Gly-Gly-Phe-Met-Thr-Ser-Glu-Lys-Ser-Gin-Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Ala-Ile-Val-Lys-Ala-Ala-His-Lys-Gly-Gly

Figure 1 Amino acid sequence and single letter code of the heptadecapeptide nociceptin/orphanin FQ. Amino acid sequences of dynorphin met-enkephalin and β-endorphin are included for comparison. Amino acid code: Ala = alanine; Arg = arginine; Asn = asparagine; Asp = aspartate; Cys = cysteine; Gln = glutamine; Glu = glutamate; Gly = glycine; His = histidine; Ile = isoleucine; Leu = leucine; Lys = lysine; Met = methionine; Phe = phenylalanine; Pro = proline; Ser = serine; Thr = threonine; Trp = tryptophan; Tyr = tyrosine; Val = valine.
The clinical significance of OFQ has yet to be fully explored but studies reporting hyperalgesia (though these have been questioned) raise some interesting clinical questions. For example, in pain states will there be increased concentrations of OFQ spinally or supraspinally, or both? Are there any clinical applications for OFQ antagonists? Where should OFQ or an antagonist be administered? Spinally, OFQ may be expected to produce analgesia, but spread to supraspinal sites via spinal or i.v. administration may produce hyperalgesia or even reverse opioid-mediated analgesia. Conversely, administration of antagonist at spinal sites may reduce analgesia whereas access to supraspinal sites in chronic pain states may facilitate the actions of opioids. These suppositions need to be explored in a coordinated manner using the skills of medicinal chemistry to design an OFQ antagonist, basic pharmacology to assess its potential, and clinicians in pain specialties to evaluate its clinical potential.

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References