

Title: Mechanisms of ORL1 regulation and cross talk

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Abstract

The need for effective analgesic agents with minimal respiratory depressant effects and low addiction potential is profound. Approximately 34 million Americans suffer from chronic pain; 40% of those pain patients have found their treatment to be inadequate. Many cannot tolerate morphine, or the escalated doses of other mu agonists required to maintain a pain-free state over time. This problem is even more pronounced in neuropathic pain patients that require much higher doses of mu opioid agonists. By understanding the mechanisms of action of the endogenous neurotransmitters that modulate nociceptive sensitivity, we can develop more effective analgesic agents for the treatment of pain. Orphanin FQ/nociceptin (OFQ/N) is an endogenous neurotransmitter that produces both anti-analgesic and analgesic effects and has no addiction potential. OFQ/N is also anti-allodynic - making the receptor for OFQ/N, ORL1, a therapeutic target for treatment of neuropathic pain. OFQ/N is implicated in the development of morphine tolerance as chronic morphine treatment increases levels of OFQ/N and ORL1. Moreover, blockade of OFQ/N binding to ORL1 attenuates the development of morphine tolerance. ORL1 receptors are co-localized with mu receptors on many cell populations in the descending analgesic pathway, and cross talk between ORL1 and mu opioid receptors would explain many of the anti-analgesic actions of OFQ/N. Unfortunately, understanding of the cellular regulation of the ORL1 receptor is very limited. Our studies indicate that ORL1 desensitization requires activation of PKC and G protein-coupled receptor kinase (GRK). We hypothesize that ORL1 desensitization is dependent on ORL1 phosphorylation, and that this phosphorylation induces ORL1 internalization. We will determine the role, mechanism and site of phosphorylation responsible for ORL1 desensitization (aim 1) and internalization (aim 2). OFQ/N desensitization of mu receptor responses in neuronal cell lines, natively expressing both ORL1 and mu opioid receptors, involves PKC and GRK, while mu agonist-mediated desensitization of ORL1 requires only GRK. Therefore, this proposal will also study the mechanism(s) by which OFQ/N desensitizes the mu opioid receptor (aim 3), and by which mu agonists desensitize ORL1 (aim 4). By providing new information on the actions and interactions of OFQ/N and the mu opioid system, we can develop new drugs for the treatment of pain and improve the lives of millions.