

Title: Orphanin FQ/Nociceptin (OFQ/N) mediation of morphine tolerance

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Abstract

Opioid analgesics are critical for treating severe chronic pain and maintaining quality of life for millions of Americans. However, tolerance develops to the analgesic effects of these drugs and dosages must be increased to maintain sufficient pain relief. Higher doses of drug predispose patients to increased incidence of side effects, and many physicians are simply unwilling to increase the doses of morphine and other narcotics to levels high enough to adequately treat severe pain. Untreated pain costs taxpayers billions of dollars in lost wages and time. Our proposed project fulfills three purposes by examining the cause of analgesic tolerance to morphine in order to prevent this from occurring, by contributing new knowledge to allow physicians to understand the basis for increased drug dosing requirements, and by providing sufficient evidence to drive the development of new formulations of morphine and related analgesics to block the development of morphine tolerance.

Specifically we propose to test the hypothesis that the analgesic tolerance to morphine treatment following prolonged morphine administration results from μ opioid receptor desensitization that is mediated by release of the endogenous neuropeptide, OFQ/N, in pain processing centers of the brain and spinal cord. We propose that this desensitization involves OFQ/N-induced μ opioid receptor phosphorylation, internalization and down-regulation.