Opioid tolerance and pain hypersensitivity associated with mTOR activation

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Currently, opioids are the standard treatment for chronic pain. Patients on opioids for long periods of time become desensitized to these drugs or become paradoxically hypersensitive to pain (hyperalgesia); however, the adaptive mechanisms are not well understood.

In this issue of the *Journal of Clinical Investigation*, Yuan-Xiang Tao and colleagues from the New Jersey Medical School at Rutgers University report that the protein mTOR, which is a global regulator of translation, plays a major role in morphine tolerance. Using animal models of opioid exposure, the authors found that mTOR is highly expressed in neurons of the dorsal horn, which is where opioid desensitization and hyperalgesia are thought to originate. Inhibition of mTOR activity with the drug rapamycin prevented and treated opioid tolerance and hyperalgesia in rats that had been exposed to chronic morphine injections.

Chronic morphine injection increased activity of mTOR and two of its target proteins in the neurons of the dorsal horn. Furthermore, the authors determined that mTOR links a key opioid receptor to downstream proteins that are known to be involved in morphine tolerance and hyperalgesia, and that blocking mTOR reduced the production of these proteins.

This study details a potential mechanism that drives opioid desensitization and hyperalgesia and suggests that targeting the mTOR pathway may improve pain management

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