Altering Potassium Channel Activity to Investigate Morphine Tolerance and Opiate Induced Hypersensitivity

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Opiates are effective analgesics for chronic pain, currently one of the barriers to effective opioid treatment is due to drug tolerance and withdrawal after stopping medication. Tolerance is mainly due to receptor desensitization caused by a functional uncoupling of mu opiate receptors from their effector systems. Potassium channels, such as ATP sensitive potassium channels (K_{ATP} channels) are expressed peripheral nociceptors and contribute to the analgesic properties of opiates as downstream effectors (Cunha et al., 2010). We sought to characterize the effects of K_{ATP} channel deletion in the spinal cord and dorsal root ganglia on the behavioral onset of tolerance.

Methods: Mice were given intrathecal injection of associated adenovirus (AAV) particles designed to decrease activity of SUR1-subtype K_{ATP} channels in mice. One method, C57Bl6 mice were inoculated with short hairpin (sh) RNA designed to decrease production of the SUR1-subtype of K_{ATP} channels (AAV9-GFP-U6-m-Abcc9-shRNA, i.t., 10uL). Another method using SUR1 conditional knock-out mice (Nakamura and Bryan, 2014), we intrathecally injected AAV constructs containing a Cre-recombinase to delete K_{ATP} channel expression in the spinal cord and dorsal root ganglia (AAV9-hSyn-GFP-Cre, i.t., 10uL). By using either shRNA or flox-Cre recombinase strategies *in vivo* to delete K_{ATP} channels over a time-course of six weeks, we found a decrease in mechanical thresholds (e.g. hypersensitivity), a decrease in morphine efficacy, and a potentiation in morphine tolerance in mice compared to their genetic controls.

Results: K_{ATP} channel downregulation in the lumbar spinal cord and dorsal root ganglia potentiates the development of hyperalgesia and morphine tolerance seen behaviorally in mice.

Discussion: These studies have also shown light as to the potential ability of K_{ATP} channels to alter opioid tolerance and potentially withdrawal in rodents. Further pharmacology and genetic studies will highlight the possible clinical utilization of KATP targeting pharmaceuticals in the future.

References: Cunha, Thiago M., et al. "Morphine peripheral analgesia depends on activation of the PI3Kγ/AKT/nNOS/NO/KATP signaling pathway." *Proceedings of the National Academy of Sciences* 107.9 (2010): 4442-4447.

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