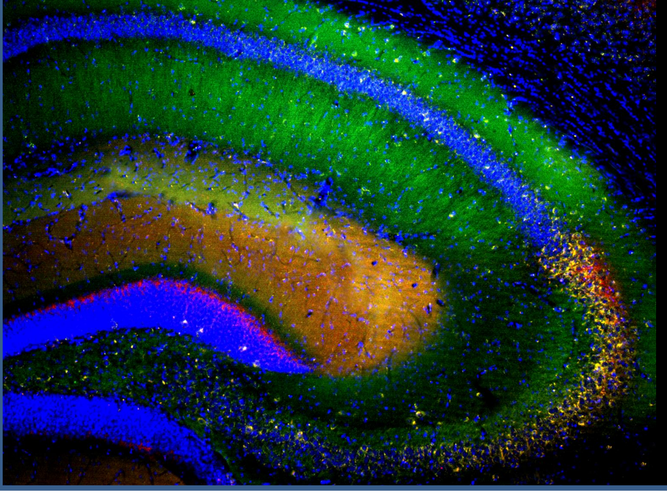
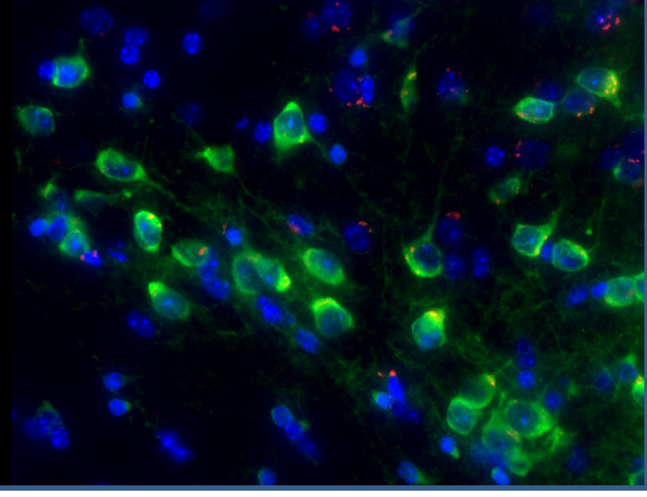


BobeckLab

The Neurobiology of Pain, Tolerance, and Addiction



WHO WE ARE

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DEPARTMENT OF BIOLOGY

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Max McDermott
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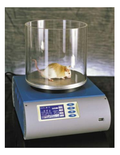
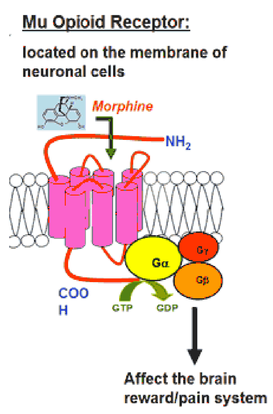
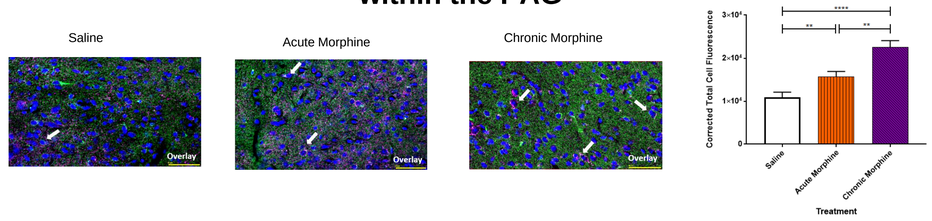
Differential Mechanisms of Opioid Tolerance

One area of focus in the lab is to determine the signaling mechanisms which leads to the development of tolerance to these drugs. When a person becomes tolerant to a drug, the dose must be increased in order to achieve the same level of pain relief, and that will lead to an increase in side effects. If we can determine what cellular changes cause tolerance, we can develop novel drugs that target these specific signaling pathways to better treat pain. Our previous studies reveled that commonly used opioids, such as morphine and fentanyl, produce analgesia and tolerance using different signaling mechanisms. Ongoing studies in the lab have found that blocking different intracellular molecules (PKC) during long-term treatment can decrease tolerance to morphine.

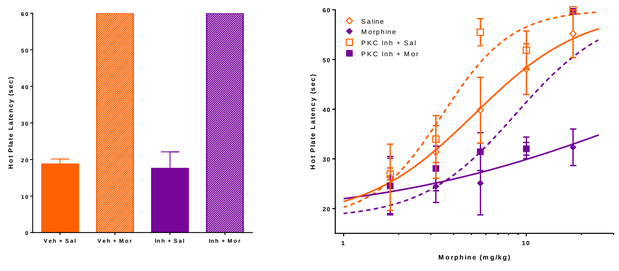




Chronic morphine treatment increases Protein Kinase C activation within the PAG

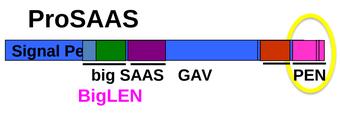


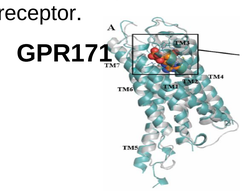
PKC inhibition in PAG decreases morphine tolerance



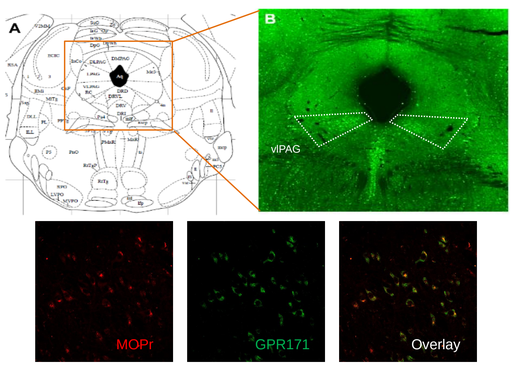
BigLEN-GPR171 Modulates Opioid Analgesia

Chronic pain is a huge problem that affects about one-third of the U.S. population. Despite many years of research for alternatives, opioids remain the most prescribed drugs to treat many types of pain, even though they possess many side effects including addiction. We are exploring the novel neuropeptide-receptor system (BigLEN-GPR171) as a pain therapeutic. To date we find that GPR171 is highly expressed in the periaqueductal gray, a region crucial to the pain-relieving actions of opioids, and is found in cells that co-express mu opioid receptors. We found that in mice a GPR171 antagonist reduces the analgesic effects of morphine, while a GPR171 agonist increases those effects. This leads us to suggest that GPR171 is modulating the effects of morphine, perhaps in the periaqueductal grey, through the actions of the mu opioid receptor.

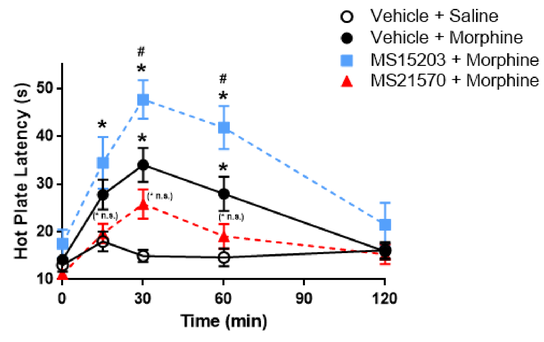




GPR171 is expressed within pain pathway



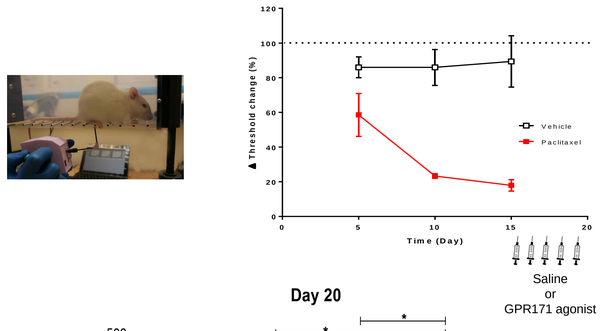
GPR171 modulates morphine analgesia in mice

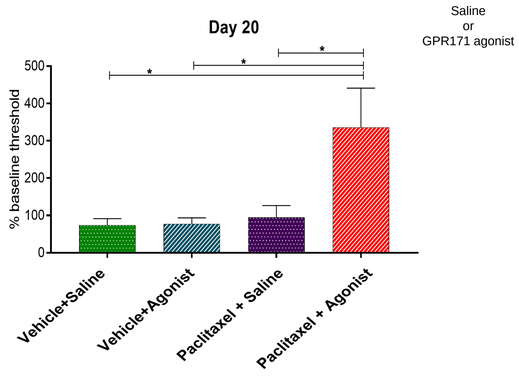


GPR171 Agonist Decreases Chronic Pain

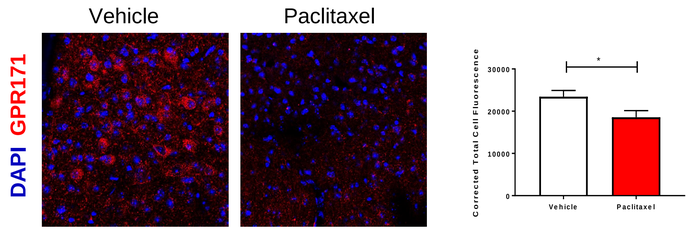
First-line chemotherapies against solid tumors are highly efficacious in reducing the tumor burden, but have many adverse side-effects including nerve damage, leading to chronic pain. Non-addictive, efficacious pain relievers are an area of active interest, and we propose a novel target to address this pressing issue. Mice in chronic pain experience allodynia, in which hypersensitivity to small applications of pressure elicits a pain response. We found that 5 days of GPR171 agonist treatment led to an improvement in their hypersensitivity. While there is a decrease in GPR171 receptors in the PAG of mice that have chronic pain, the agonist can bind to the available receptors to produce pain relief.

GPR171 agonist can relieve touch hypersensitivity caused by neuropathic pain





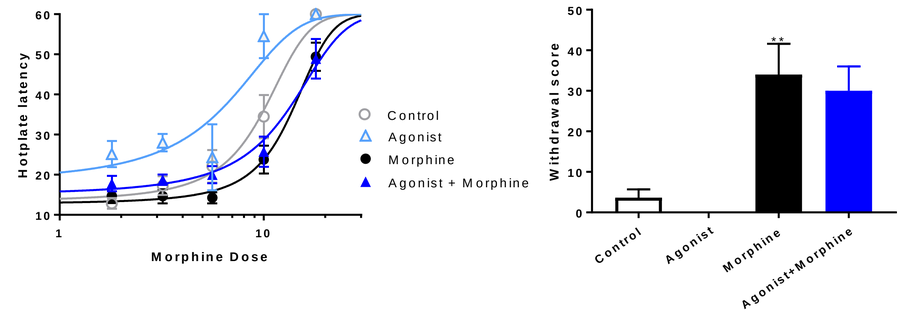
Neuropathic pain decreases GPR171 levels in the PAG



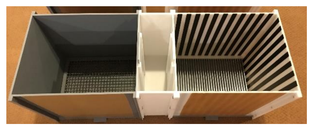
BigLEN-GPR171 in Opioid Tolerance, Withdrawal and Addiction

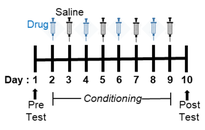
The BigLEN-GPR171 system shows high expression in many brain regions involved in reward, such as basolateral amygdala, hippocampus, and prefrontal cortex, In order for GPR171 compounds to be used as a therapeutic for pain they must show reduced side effects compared to opioids. We find that GPR171 agonist decreases morphine tolerance and has no effect on morphine withdrawal or reward. This suggests that when combined with morphine we can enhance the positive effects (pain relief) but decreases the unwanted adverse effects after long-term administration.

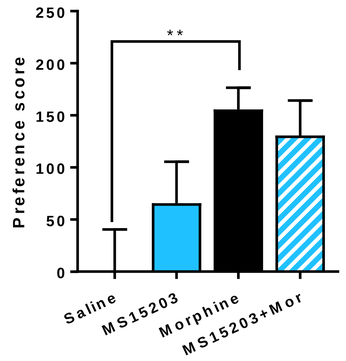
GPR171 agonist decreases morphine tolerance, but no change in withdrawal



GPR171 compounds do not alter morphine reward







RESEARCH SUPPORT

BRAIN & BEHAVIOR RESEARCH FOUNDATION

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