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Understanding the Cellular Mechanisms of Opioid -Mediated Respiratory Suppression

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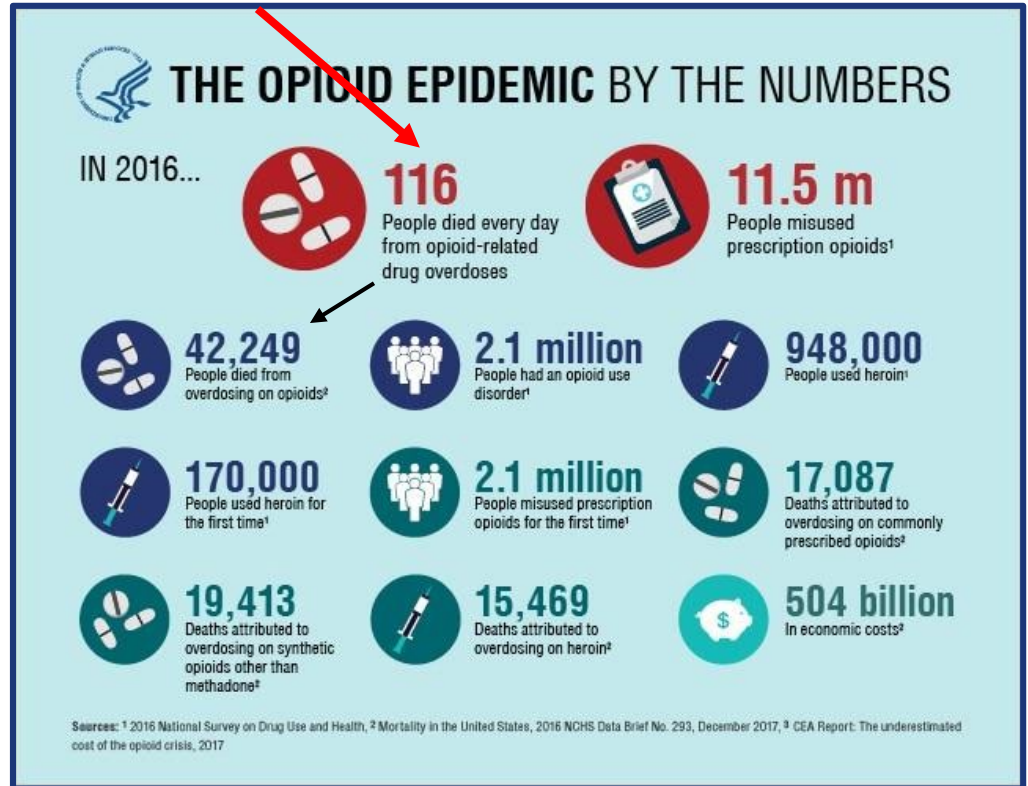
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UW Neurological Surgery Summer Student Program

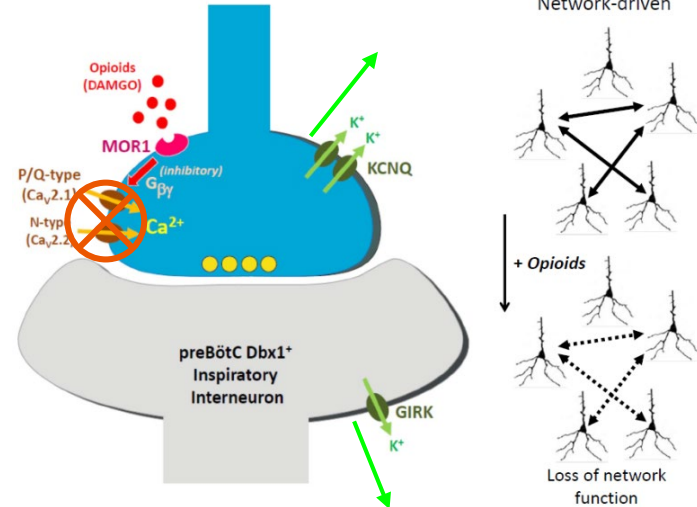
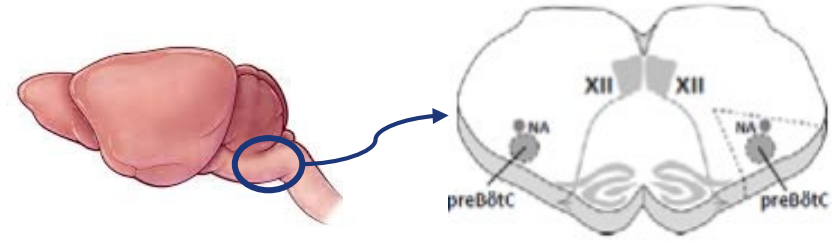
An Epidemic

- Large increase in prescription and non prescription opioid use starting in the late 1990's
- Nationwide public health emergency declared by Pres. Trump in Oct. 2017
- Opioid-mediated respiratory suppression (ORS) is the major cause of death associated with opioid abuse



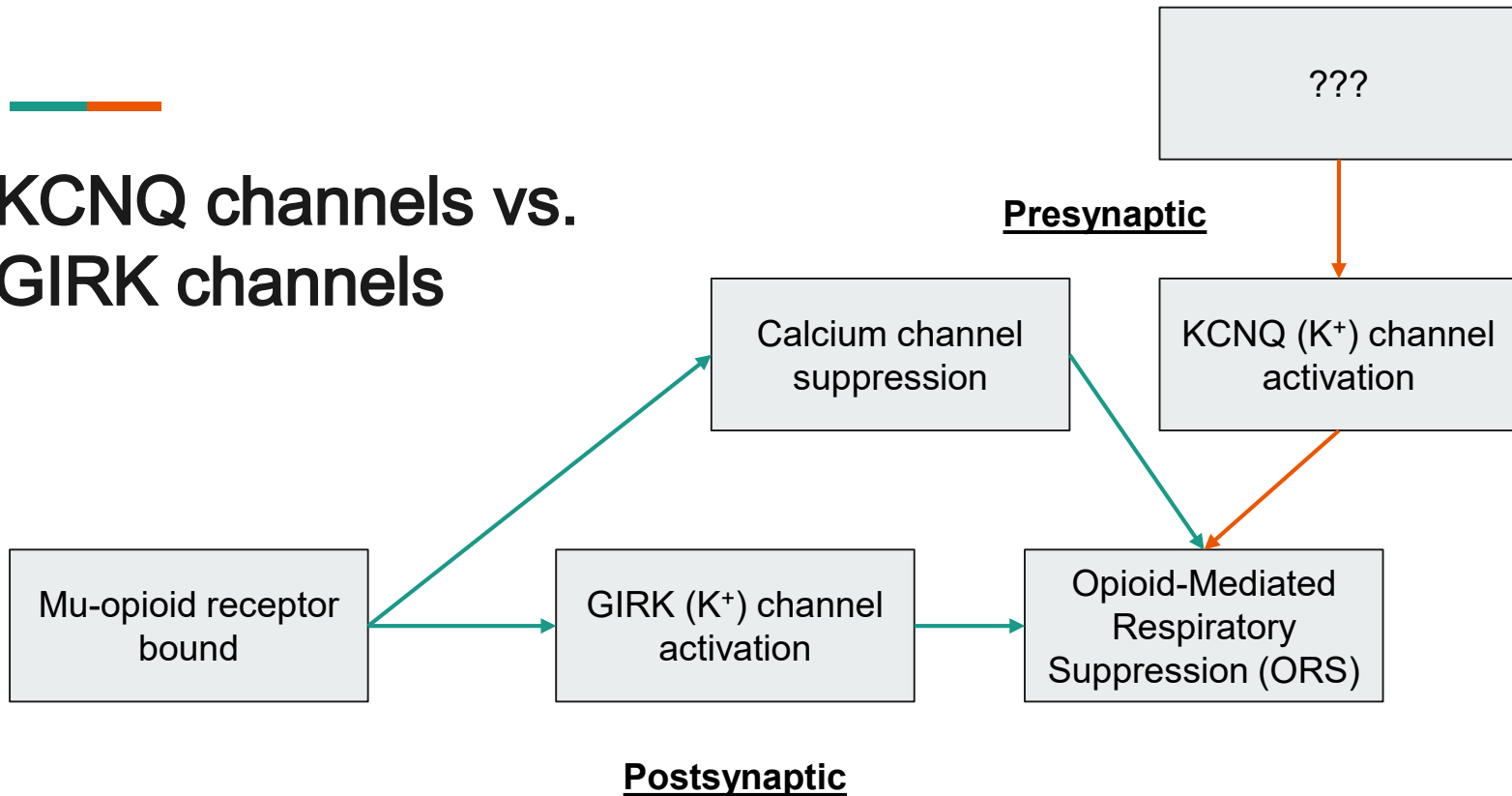
The preBötzing Complex

- PreBötzing Complex (preBötC) is instrumental in breathing and inspiratory rhythm generation
- What happens when opioids bind to opioid receptor?
 - K^+ channel **activation** and Ca^{2+} channel **suppression** inhibits excitability and neurotransmission





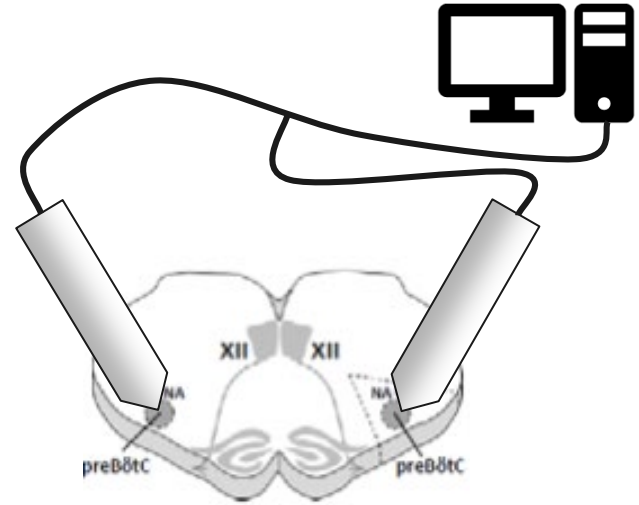
KCNQ channels vs. GIRK channels





Suppressing and restoring inspiratory rhythm

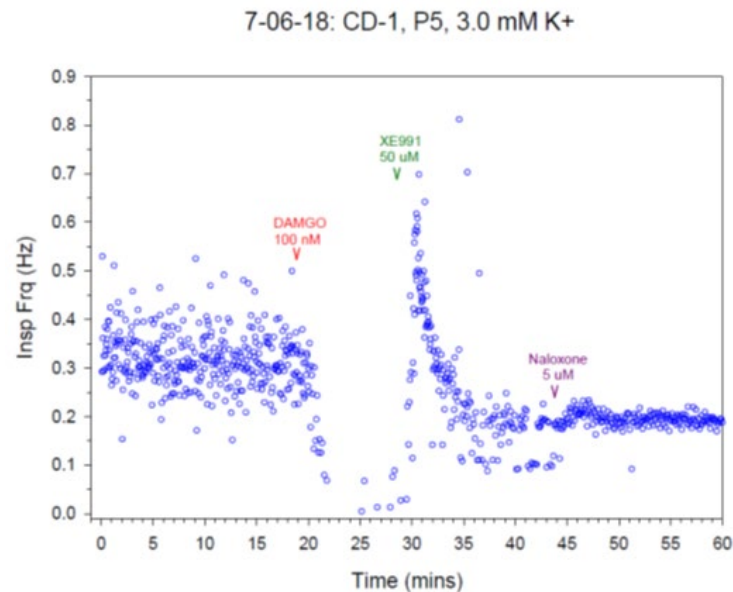
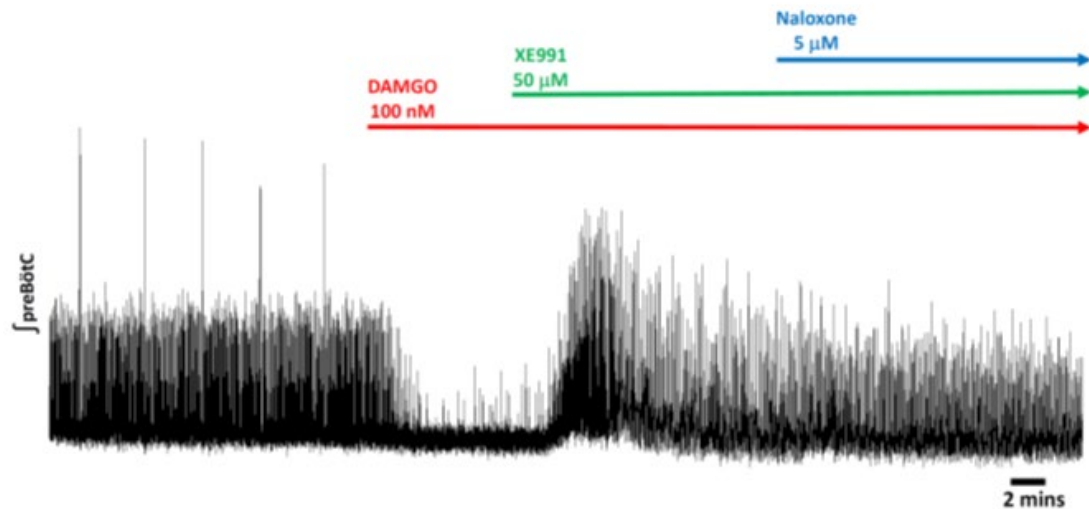
- Brain slice from P2-P11 CD1 mouse
- Integrated extracellular electrical signal shows preBötC inspiratory rhythm
- Application of:
 - DAMGO- a protein that binds to opioid receptor
 - XE991- KCNQ channel blocker
 - Naloxone- antagonistic opioid used to reverse ORS
 - Barium (Ba^{2+})- GIRK channel blockers



Inspiratory Bursts



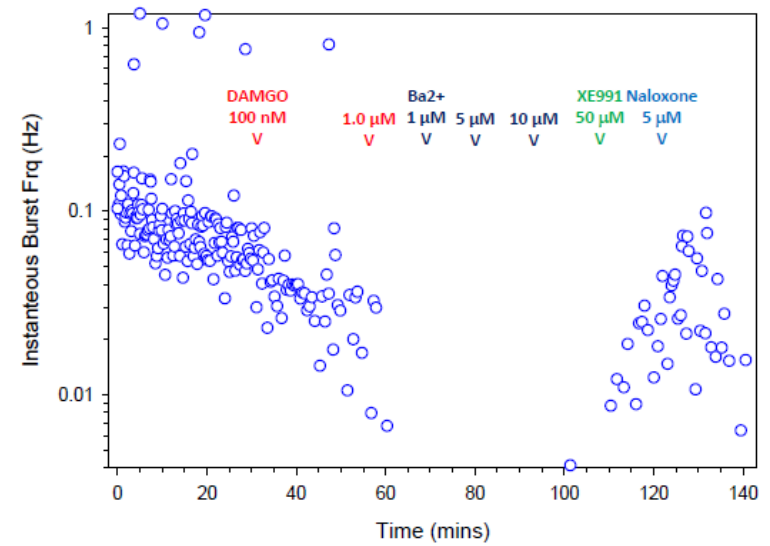
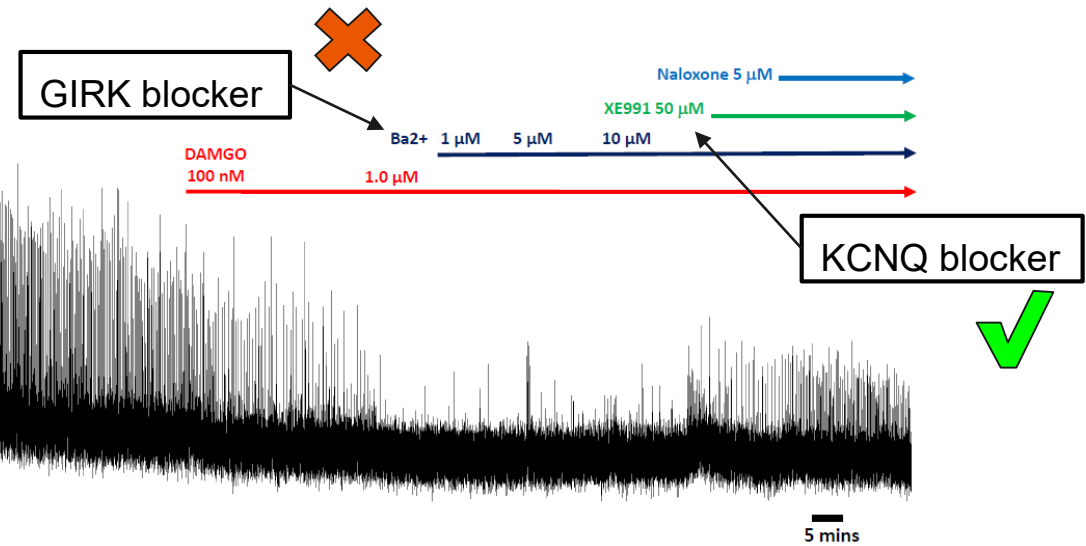
Example of CD -1 preBötC Recording





Using a GIRK channel blocker has no restoring effect

- Review: Potassium channel blockers show which channels suppress inspiratory rhythm.
- GIRK channel blocker, Ba²⁺, has very little restorative effect, if any.
- KCNQ channel blocker, XE991, is able to rescue the rhythm
 - Shows that KCNQ activation contributes more to ORS



Conclusion & Implications

DEATH PAINKILLERS PTSD
TRAUMA CHILD ABUSE MENTAL HEALTH DEPENDENCE DRUG ADDICT ILLEGAL
IMPULSIVE BEHAVIOR OPIOID EPIDEMIC OPIOID CRISIS
PAIN RELIEF ADDICTIVE OVERDOSE BIG PHARMA OPIOID ADDICTION
ADDICT PAIN PILLS EMOTIONAL ABUSE OPIOID ABUSERS PHARMACEUTICALS PRESCRIPTION
TOLERANCE DRUG ADDICTION

- Opioids suppress respiratory drive resulting in thousands of deaths every year due to misuse.
- KCNQ channels more involved in modulating ORS than GIRK channels and act through a mechanism independent of opioid receptor intracellular signalling
- Focused research and studies on ways to exploit KCNQ channel mechanism as an avenue of treatment of ORS in individuals who have overdosed in addition to patients medicated with opioids.



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