



# Role of Phosphorylation in Acute Desensitization and Tolerance of the $\mu$ -Opioid Receptor

Emily R. Leff, Seksiri Arttamangkul, John T. Williams

Vollum Institute, Oregon Health & Science University, Portland, OR

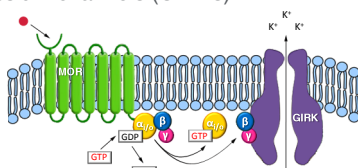


## Background

- There is increasing evidence that  $\mu$ -opioid receptor (MOR) acute desensitization, or the rapid loss of MOR-effector coupling during sustained agonist exposure, is a critical step leading to long-term tolerance to opioids.
- Agonist-induced activation of MOR leads to phosphorylation of the intracellular region by G protein-coupled receptor kinases (GRKs) and phosphorylation of the C-terminal tail of MOR is a necessary step in acute desensitization.
- Acute desensitization is nearly abolished and cellular tolerance induced by chronic morphine treatment is reduced for phosphorylation-deficient mutant MORs in the LC of the rat.
- In this study, we will investigate what kinases are involved in MOR acute desensitization as well as whether or not more desensitization develops following longer applications of opioids.

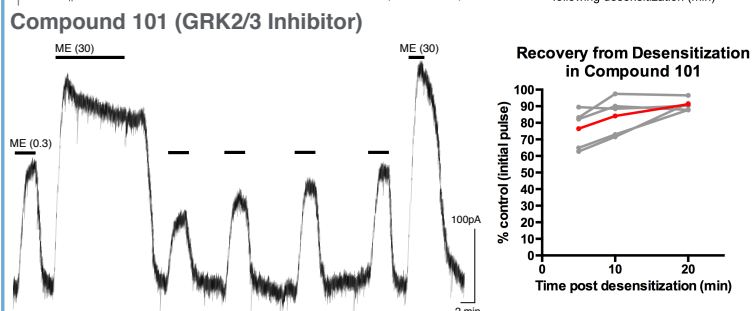
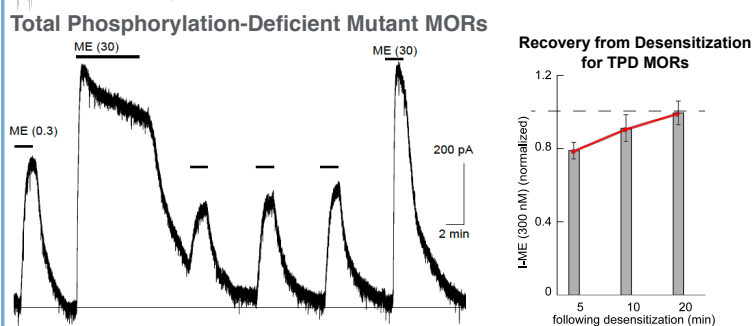
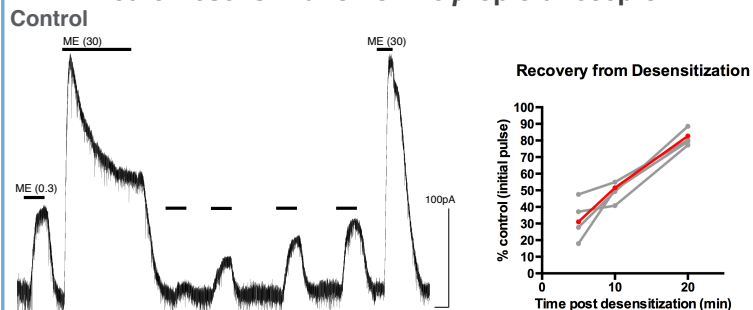
## Methods

- Used whole-cell voltage-clamp recordings from Locus Coeruleus (LC) neurons in acute brain slices from Sprague-Dawley rats
- LC neurons express  $\mu$ -opioid receptors (MORs) that are coupled to G-coupled inwardly rectifying potassium channels (GIRKs)



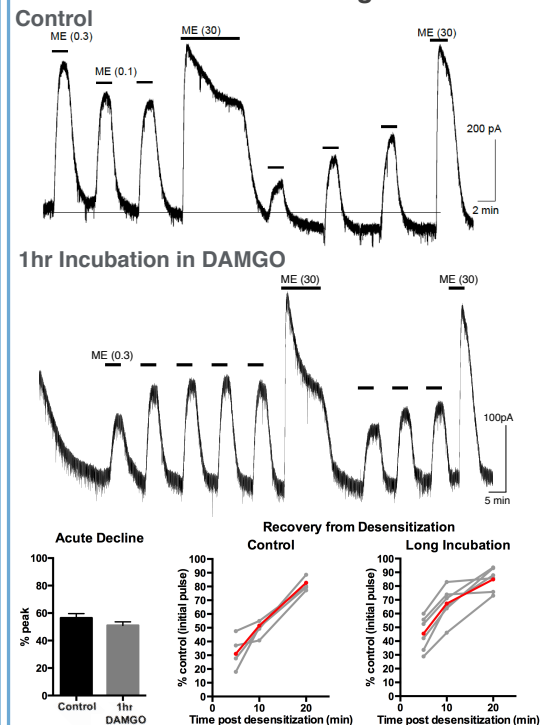
- Degree of acute desensitization was determined using an EC<sub>50</sub> concentration of MOR agonist following treatment with a saturating concentration of agonist for different periods

## Acute Desensitization of the $\mu$ -opioid receptor



- There are similar amounts of desensitization when phosphorylation is blocked with a GRK2/3 inhibitor and when it is blocked with the total phosphorylation-deficient mutant MORs

## Desensitization after Long Incubation



- There is no additional desensitization after a longer incubation in an opioid agonist

## Future Directions

- Treat animals for 2 weeks with morphine and see if there is more cellular tolerance
- Investigate the role of PKC using PKC inhibitors

## Acknowledgments

- Training grant T32DA007262
- ARCS Foundation
- Arttamangkul et al (2018) eLife