Chad Groer
PhD Candidate

“Agonist-Selective Regulation of the Mu Opioid Receptor by βarrestins”

Friday September 10th, 2010
1185 Graves Hall
1-2pm
VITA

March 28, 1982 . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . . .
RECENT PUBLICATIONS

Groer, CE and Bohn, LM. Differential regulation of the mu opioid receptor by βarrestin1 and βarrestin2. (preparing submission).


ABSTRACT

Morphine and other opiates mediate their effects through activation of the mu opioid receptor (MOR). Activation of the MOR results in recruitment of regulatory proteins, βarrestins, that can regulate how this receptor signals. In vivo studies suggest that disruption of βarrestin-mediated MOR regulation may enhance opiate-induced antinociception and reduce tolerance and certain unwanted side effects. Therefore, by understanding the cellular mechanisms by which this receptor is regulated, the development of analgesics which preserve the beneficial effects of opiates while eliminating unwanted side effects may be possible. In this dissertation we test the hypothesis that MOR agonists can bias MOR-βarrestin interactions, and that βarrestin recruitment profiles, in turn, may determine cellular responses evoked by these agonists.

In the first data portion of this dissertation, we characterize several novel MOR agonists that are unable to promote βarrestin recruitment. Herkinorin is a moderately selective agonist at the MOR, based on the structure of a natural product, Salvinorin A. We find that herkinorin promotes very little MOR phosphorylation, does not recruit βarrestins, and does not induce receptor internalization in transfected cells. Herkinorin, is unable to induce βarrestin recruitment or MOR internalization under conditions that facilitate receptor phosphorylation and subsequent βarrestin recruitment with other agonists. We also evaluated several derivatives of herkinorin with similar βarrestin recruitment and MOR internalization profiles. Therefore, herkinorin and its derivatives may be a promising step toward recapitulating morphine’s effects in βarr2-KO mice, which have been used to demonstrate that MOR activation without recruiting βarrestin2
may be therapeutically useful, by producing analgesia with reduced side effects.

In the second data portion of this dissertation, we evaluate the interaction and functional consequences of MOR regulation by βarrestin1 and βarrestin2, in response to the classical agonists, DAMGO and morphine. Using both qualitative (microscopy) and quantitative (cell surface biotinylation and BRET) approaches, we have confirmed that DAMGO can induce robust interactions between the MOR and both βarrestins. Morphine, however, selectively promotes interactions with βarrestin2. Additionally, the agonist specific βarrestin interactions are required for internalization of the MOR. Finally, we show that βarrestin1 is required for agonist-induced MOR ubiquitination, such that only DAMGO, and not morphine, is able to promote MOR ubiquitination.

Taken together, these data suggest that MOR regulation is highly dependent on the complement of proteins available to interact with the MOR, and that the nature of the ligand can determine how the MOR is regulated by the available proteins. Therefore, the development of biased ligands for the MOR should focus activation of the MOR, but circumventing βarrestin-mediated regulation. These concepts may be critical to consider in the development of opiate compounds designed to retain analgesic efficacy, while reducing the occurrence of unwanted side effects.

**RECENT ORAL PRESENTATION**


**RECENT POSTER PRESENTATIONS**

Chad Groer and Laura M. Bohn. *Agonist-selective Regulation of the Mu Opioid Receptor by βarrestins.* Research Fest 2010, The Scripps Research Institute, Jupiter, FL, April 20, 2010

C.E. Groer, L.M. Bohn. *Mu opioid receptor regulation and signaling in the absence of beta-arrestins.* International Narcotics Research Conference, Charleston, SC, July 2008 (This was also presented at the OSU Research Day)
