# Background

Delta opioid receptor (δOR) agonists are promising therapies for the treatment of chronic pain, migraine, and depression. However, some δ agonists produce convulsions, which has limited their development for clinical use. The ligand-specific nature of these convulsions suggests that there is a biased activation of certain pro-convulsant signal transduction pathways. Previously, our group has examined the receptor trafficking of two δ agonists with similar analgesic properties but pro-convulsant (SNC80) and non-convulsant (ARM390) effects. We found that the ability to induce δ receptor internalization correlated with pro-convulsant effects. The aim of this study is to further develop tools necessary to screen additional δ compounds, and to characterize the anatomical specificity of δ-mediated convulsions.

## Methods

An in vitro screening assay was developed to examine receptor internalization following agonist exposure. Briefly, HEK-293 cells stably expressing Flag-epitope tagged δORs (F-DOR-HEK293) were treated with SNC80, ARM390 or vehicle, and analyzed by flow cytometry.

In addition, c-fos expression was analyzed in C57Bl6J mice treated with vehicle, SNC80, or ARM390.

## Results

In agreement with our previous results, SNC80 induced δOR internalization more efficiently than ARM390 in F-DOR-HEK-293 cells. Furthermore, we also found that a sub-threshold dose (non-convulsive) of SNC80 produced significantly greater c-fos immunoreactivity in mouse hippocampus, compared to ARM390.

## Conclusions

These results suggest that the internalization of the δ opioid receptor may be key to the pro-convulsant effect of certain δOR agonists, and that these convulsions are mediated through the hippocampus.