Sensory Neuron Hyperexcitability is Prevented by Group 2 Metabotropic Glutamate Receptors in Mouse and Human

Steve Davidson¹, Judith P. Golden¹, Guy Page², Jingming Zhang², Andrea Ghetti², and Robert W. Gereau IV¹
1. Pain Center and Department of Anesthesiology, Washington University School of Medicine, St. Louis, MO. 2. Anabios Corporation, San Diego, CA.

Background and Significance

1. mGlu2/3
2. Peripheral injection of mGluR2/3 agonist during inflammation hastens recovery from hyperalgesia
3. Peripheral injection of mGluR2/3 antagonist delays recovery from hyperalgesia
4. Two ways to address the "translation problem" 1) Non-reflexive tests of ongoing pain, 2) Preclinical studies in human tissues

Results

mGlu2 potentiation blocked formalin place aversion

A Test 1 Preconditioning
- Time in chamber (s)
- Condition
Formalin Saline
Formalin + Vehicle + ENA

B Test 2 Preconditioning
- Time in chamber (s)
- Condition
Formalin Saline
Formalin + Vehicle + ENA

mGlu2 expression in mouse DRG

CGRP mGlu2 IB4 mGlu2

8% 26% 2% 100%
(n=367)

100% 24% 33%
(n=389)

mGlu2 expression in human DRG

mGlu2 expression in mouse spinal cord and skin

CGRP mGlu2 IB4 mGlu2

mGlu2 expression in human DRG and human DRG under patch-clamp conditions

APDC blocks PGE2-induced hyperexcitability (human)

Ramp Amplitude
- Current (mA)

APDC blocks PGE2-induced hyperexcitability (mouse)

Rheobase
- AP Threshold (mv)
- Spike Latency (ms)

Conclusions

- mGlu2 activation or potentiation of endogenous activity prevents and reverses indicators of pain.
- mGlu2 immunoreactivity is present in medium sized DRG neurons, peripheral terminals in the epidermis and nucleus propius of the spinal cord dorsal horn
- mGlu2 activation blocks PGE2-induced hyperexcitability in mouse and human DRG neurons.
- Non-reflexive assays of ongoing pain and preclinical human physiology are useful tools to enhance translational efficacy of potential analgesics.

Acknowledgements

NIH Grants: R01DA025493, R01DA026379; American Pain Society, Future Leaders Grant

Pain Center