Physiological Properties of Gastrin Releasing Peptide Receptor in Native Dorsal Horn Neurons

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Compared to somatic sensations such as pain, temperature perception, and proprioception, the sensation of itch has long been understudied and poorly understood despite being a prevalent side effect of post-operative morphine pain treatment. Molecular studies reveal that the primary transmitter for itch at the first sensory synapse of the dorsal horn is gastrin releasing peptide (GRP), which targets gastrin releasing peptide receptor (GRPR). Since the physiological properties of GRPR signaling in the dorsal horn have not been previously investigated, we aimed to characterize it using Ca2+ imaging technique on mouse dorsal horn neuron cultures. Additionally, we evaluated the use of a transgenic line of fluorescently tagged GRPR (GRPR-eGFP) for specifically studying dorsal horn neurons that express GRPR.

Since GRPR is a Gq linked G-protein couple receptor (GPCR), it is associated with phospholipase C activation and liberation of inositol triphosphate (IP3) and diacylglycerol, which leads to intracellular Ca2+ release. I observed GRP induced Ca2+ transients in approximately 10% of dissociated dorsal horn neurons. The Ca2+ transient was decreased by an inhibitor of phospholipase C signaling, U73122. Removal of extracellular Ca2+ did not prevent GRP induced Ca2+ transients, suggesting the source is intracellular. This was confirmed when we found that depletion of intracellular Ca2+ with a SERCA pump inhibitor, thapsigargin, prevented GRP induced Ca2+ transients. Furthermore, 2-APB, an inhibitor of the IP3 receptor, abolished GRP induced Ca2+ transients. Finally, confirmed that GRP induced Ca2+ transients occurred in cells expressing GRPR by using a FITC filter to illuminate GRPR-eGFP expressing cells to determine overlap with cells responding to GRP with a Ca2+ signal.

In summary, we have characterized the mechanism of GRP induced Ca2+ signals using a native system of dissociated dorsal horn neurons, and we are verifying the specificity of the GRP signal using a genetic model of fluorescently tagged GRPR.