# Rostral ventromedial medulla

The rostral ventromedial medulla (RVM) exerts bi-directional descending modulation of pain, attributable to the activity of electrophysiologically-identified pro-nociceptive ON and anti-nociceptive OFF neurons. Jiao et al. reported that GABAergic ON neurons specifically express G protein-coupled estrogen receptors (GPER). GPER+ neurons exhibited characteristic ON-like responses upon peripheral nociceptive stimulation. Optogenetic activation of GPER+ neurons facilitated, whilst their ablation abrogated pain. Furthermore, activation of GPER caused depolarization of ON cells, potentiated pain, and ameliorated morphine analgesia through desensitizing μ-type opioid receptor (MOR)-mediated activation of potassium currents. In contrast, genetic ablation or pharmacological blockade of GPER attenuated pain, enhanced morphine analgesia, and delayed the development of morphine tolerance in diverse preclinical pain models. These data strongly support GPER as a marker for GABAergic ON cells and also illuminate the mechanisms underlying hormonal regulation of pain and analgesia, highlighting GPER as a promising target for the pain treatment and opioid tolerance [1)]

[1)]

Jiao Y, Gao P, Dong L, Ding X, Meng Y, Qian J, Gao T, Wang R, Jiang T, Zhang Y, Kong D, Wu Y, Chen S, Xu S, Tang D, Luo P, Wu M, Meng L, Wen D, Wu C, Zhang G, Shi X, Yu W, Rong W. Molecular identification of bulbospinal ON neurons by GPER which drives pain and morphine tolerance. J Clin Invest. 2022 Nov 8:e154588. doi: 10.1172/JCI154588. Epub ahead of print. PMID: 36346677.