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Spatiotemporal Control of Opioid Signaling and Behavior

Highlights

- A light-sensitive mu-opioid-like receptor (opto-MOR) was generated and characterized
- Opto-MOR initiates canonical MOPR signaling both in vitro and in neurons
- Photoactivation of opto-MOR in selected GABAergic neurons induces reward or aversion
- Opto-MOR is a novel tool for in vivo optodynamic control of opioid signaling

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In Brief

Siuda et al. develop a photosensitive mu-opioid-like receptor (opto-MOR) that triggers cAMP inhibition and MAP kinase activation, couples to GIRK currents, and internalizes like the mu-opioid receptor. Photostimulation of opto-MOR within discrete GABAergic nuclei induces real-time preference or aversion.

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Spatiotemporal Control of Opioid Signaling and Behavior

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SUMMARY

Optogenetics is now a widely accepted tool for spatiotemporal manipulation of neuronal activity. However, a majority of optogenetic approaches use binary on/off control schemes. Here, we extend the optogenetic toolset by developing a neuromodulatory approach using a rationale-based design to generate a Gi-coupled, optically sensitive, mu-opioid-like receptor, which we term opto-MOR. We demonstrate that opto-MOR engages canonical mu-opioid signaling through inhibition of adenylyl cyclase, activation of MAPK and G protein-gated inward rectifying potassium (GIRK) channels and internalizes with kinetics similar to that of the mu-opioid receptor. To assess in vivo utility, we expressed a Cre-dependent viral opto-MOR in RMTg/VTA GABAergic neurons, which led to a real-time place preference. In contrast, expression of opto-MOR in GABAergic neurons of the ventral pallidum hedonic cold spot led to real-time place aversion. This tool has generalizable application for spatiotemporal control of opioid signaling and, furthermore, can be used broadly for mimicking endogenous neuronal inhibition pathways.

INTRODUCTION

Opioid receptor-targeting drugs have been used as analgesics and recreationally abused for hundreds of years. Due to a lack of effective alternatives, they remain on the front lines for acute pain management, severe anti-tussive treatment, and other indications despite their high abuse potential. Mu (MOPR), kappa (KOPR), delta (DOPR), and nociceptin opioid peptide receptors (NOPR) persist at the forefront of basic science and drug discovery efforts on disorders ranging from gastrointestinal ailments to pain, addiction, and depression (Al-Hasani and Bruchas, 2011). Among these receptor systems, the mu-opioid receptor has been the most intensely studied due to its long-established involvement in analgesia, euphoria, and reward in response to morphine-like analogs. However, despite years of study, opioid research had been limited by a fundamental challenge. Studying the specific effects of opioids with spatial, temporal, and cell-type-specific control is virtually untenable, especially in the context of the CNS. Systemic drugs bind MOPRs on heterogeneous cell populations across multiple brain regions. MOPR expression at both pre- and post-synaptic sites within overlapping discrete regions precludes determination of circuit level contributions. Therefore, approaches to selectively limit engagement of MOPR signaling to restricted cell populations with temporal control that closely mimics endogenous opioid kinetics is a first key step toward unraveling these issues and developing future therapeutic strategies where opioids are the most effective treatment regimen.

Recent developments in optogenetics and molecular biology provide an ideal strategy for addressing these questions. Class A G protein-coupled receptors (GPCRs), including the rat rhodopsin receptor and MOPR, have structural and functional similarities that can be exploited to create hybrid receptors with unique functional properties. More specifically, the light-sensitive external portion of rhodopsin receptors can be combined with internal signal transduction components of other GPCRs to produce so-called opto-XR chimeras capable of initiating and terminating receptor-specific signaling events with temporal precision enabled by pulses of light (Airan et al., 2009; Gunaydin et al., 2014; Kim et al., 2005; Masseck et al., 2014). Furthermore, packaging these receptors into Cre recombinase-dependent viruses using loxP flanked doubled inverted open (DIO or FLEX) reading frames allows for restricted expression in discrete cell types within isolated brain regions yielding spatial control of GPCR signaling in vivo (Atasoy et al., 2008; Zhang et al., 2010).

Here, we present the generation and characterization of a new photosensitive mu-opioid-like chimeric receptor (we term opto-MOR). We show that opto-MOR suppresses cyclic AMP (cAMP) levels, activates MAPK signaling, and internalizes in a similar time course to native MOPR. Furthermore, it functionally couples