Abstract
Millions of Americans live with Opioid Use Disorders (OUD). Patients with OUD are at high risk of accidental overdose, which can produce opioid-induced respiratory depression (OIRD) leading to severe injury or death. Opioid-involved overdose deaths have continued to rise over the past decade. Synthetic opioids such as fentanyl are the primary contributing factor to this increase in drug overdose deaths. Fentanyl is more difficult to treat due to its higher potency and increased lipophilicity. In addition, fentanyl produces skeletal muscle rigidity, known as wooden chest syndrome, which is difficult to reverse with naloxone. The rise in opioid-involved overdose deaths and the challenges associated with treating fentanyl-induced respiratory depression and muscle rigidity make it critical to explore new ways to address this issue. While a number of studies have evaluated opioid effects in brainstem respiratory networks, our preliminary data suggest that the cardiorespiratory depression and wooden chest syndrome that is observed following intravenous administration of fentanyl is driven by opioid receptors located outside the central nervous system. Moreover, selective antagonism of peripheral opioid receptors appears to be an effective method of preventing fentanyl-induced respiratory depression and muscle rigidity without any adverse side effects. From a mechanistic standpoint, opioid receptors located on vagal afferent fibers may be a primary contributor to the onset of respiratory depression. The goal of the current application is to 1) dissect the role of MOR-expressing vagal-brainstem pathway in contributing to fentanyl-induced respiratory depression and muscle rigidity and 2) investigate the extent to which systemic peripheral opioid receptor antagonism can reverse cardiorespiratory depression and wooden chest syndrome without causing significant withdrawal. Data generated from these studies will provide valuable insight into the central and peripheral contributions that cause respiratory depression and might lead to the development of novel treatments that can prevent or reverse respiratory depression while sparing the CNS-driven acute opioid withdrawal that occurs with nonselective opioid receptor antagonism.