

A unique role of RGSz1 in behavioral responses to pain killers

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While there is a great amount of information on the cellular mechanism of opiate actions, the brain region-specific signal transduction events triggered by MOR activation are not fully understood. Previous studies from our group investigated the effects of morphine and other opiate analgesics in the MOR signal transduction and desensitization in the mouse brain reward center. Here, we identified the GPCR signal transduction modulator RGSz1 (Regulator of G protein signaling Z1) as a key component of the complexes modulating MOR function in the Periaqueductal Gray, a brain region that controls nociceptive transmission and analgesia. Using constitutive knockout mice lacking the RGSz1 gene (RGSz1KO), we found that prevention of RGSz1 action increases the efficacy of morphine and other opiate analgesics, and delays the development of analgesic tolerance in models of acute and chronic (neuropathic and inflammatory) pain. Notably, this phenotype was observed in both male and female mice. RGSz1 On the other hand, RGSz1KO mice show lower sensitivity to the rewarding effects of morphine in the place preference paradigm and they do not develop locomotor sensitization when treated with standard doses of morphine that promote sensitization to wild type mice. Moreover, RGSz1 does not affect the development of somatic morphine withdrawal. Conditional knockdown of RGSz1 in the PAG (via PAG infection of RGSz1 floxed mice with AAV vectors expressing Cre recombinase) recapitulated the analgesia and tolerance phenotype observed in RGSz1KO mice. Conditional knockdown of RGSz1 in the nucleus accumbens revealed that the reward-related phenotypes were associated with actions of RGSz1 in this brain region. Using co-immunoprecipitation assays we show that acute morphine increases the abundance of MOR/RGSz1 complexes in the PAG, while chronic morphine has the opposite effect. Next generation RNA-Seq studies were also used, to determine the impact of chronic morphine treatment in gene expression adaptations in the PAG, and the influence of the RGSz1 gene in such adaptations. Our data on differential expressed genes and pathway analysis provided important information on the molecules and pathways that can be targeted in order to prevent the development of analgesic tolerance.

Together, our findings point to a novel intracellular regulator of MOR function, that differentially modulates the analgesic versus the addiction-related actions of pain killers. Thus, interventions in RGSz1-regulated pathways may be used for the management of chronic pain without increasing the risk of addiction.