V1b vasopressin receptor accelerates interaction between β-arrestin and μ-type opioid receptor and enhances opioid tolerance and adenylate cyclase sensitization

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Chronic and repeated exposures of morphine accelerate adenylate cyclase (AC) signaling and reduce analgesic efficacy, a condition known as opioid tolerance. Non-opioid neurotransmitters can modulate the development of opioid tolerance, but the mechanism has not been fully clarified. We found that analgesic tolerance to morphine developed with significant delay in mice lacking vasopressin V1b receptors (V1bRs) and in mice administered with a V1bR antagonist, but not in V1a-deficient mice. In rostral ventromedial medulla (RVM), V1bRs and μ-type opioid receptors (MORs) were co-expressed. In HEK cell model, the V1bR was constitutively phosphorylated and associated with β-arrestin 2. Complex formation between V1b-β-arrestin 2 and MOR was necessary for AC sensitization. Genome editing and deletion of the leucine-rich segment in V1bR carboxyl-terminus, which was necessary for β-arrestin 2 binding, increased morphine analgesia. These findings indicated that inhibition of V1bR provides a novel approach to enhance morphine analgesia without accelerating analgesic tolerance.