Volume 13
Washington University Undergraduate Research Digest

Spring 2018

Amplification of Motivated Behaviors Through Mu-Opiod Signaling in the Nucleus Accumbens

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Motivation, or the desire to obtain rewarding stimuli, is an integral part of human psychology, and appears to be mediated by complex interactions in the mesocorticolimbic pathway in the brain. The mu-opioid receptor system plays a role in modulating motivated behaviors. Here, we genetically and pharmacologically manipulated mu receptors to test whether they are involved in baseline or hyper-motivated behaviors using food intake and social interaction behavioral paradigms. Under baseline conditions, global knockout mice (KO) and wildtype mice consumed the same amount of food and socialized to the same degree. After 24 hours of food deprivation or one week of social isolation, wildtype mice increased their intake by 300% and interactions by 150%. By contrast, KOs didn't show any increase in motivated behaviors. The nucleus accumbens (NAc), located on the ventral forebrain, is involved in generating intense motivation. The two major types of neurons in the NAc that contain mu-receptors are enkephalin releasing and dynorphin releasing neurons. Mice that were bred to delete mu-receptors on all enkephalin neurons (*Oprm1*$^{fl/fl}$ x enkephalin-cre) showed a decrease in food deprived intake and social interactions after isolation by 50% compared to wildtype mice. By contrast, mice bred to delete mu-receptors on all dynorphin neurons (*Oprm1*$^{fl/fl}$ x dynorphin-cre) showed an increase in motivated behavior similar to that seen in wildtype. Concurrently, a separate group of *Oprm1*$^{fl/fl}$ mice received local viral infusions of a cre containing virus to selectively delete mu from accumbens neurons. Surprisingly, we didn't see the same blunting of motivated behaviors observed in *Oprm1*$^{fl/fl}$ x enkephalin-cre mice. In contrast, deleting mu receptors off of incoming neurons that project to NAc blunted motivated behaviors. Finally, we injected a fluorescently tagged retrograde virus into the NAc of Enkephalin-cre mice and found that the paraventricular nucleus of the thalamus (PVT) most robustly projects into the NAc.