Public Abstract
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Physical inactivity, a primary contributor to numerous diseases including obesity, type 2 diabetes, depression, and dementia, has reached pandemic levels worldwide. Alarmingly, the percentage of individuals engaging in physical activity is low and decreasing. Accelerometry data shows that > 90% of adults fail to meet the U.S. Physical Activity Guidelines despite the excess of knowledge suggesting exercise improves health. Therefore, beginning to understand the molecular mechanisms which influence physical activity levels is imperative for the development of therapies to reduce sedentary behavior. The work presented in this dissertation made use of three independent experimental paradigms in rats to test the hypothesis that differences in the mesolimbic dopamine system associate with/cause changes in voluntary physical activity. In the first study, rats selectively bred for high (HVR) or low (LVR) voluntary wheel running distance were used to assess inherent differences in opioidergic signaling between HVR and LVR, as well as the influence of dopamine on opioid-induced changes in voluntary wheel running. Mu-opioid receptor expression and function was increased in the nucleus accumbens (NAc) of HVR compared to LVR. Likewise, naltrexone injection decreased dopamine-related mRNA expression in mesolimbic brain regions and reduced wheel running in HVR, but not LVR. Finally, lesion of dopaminergic neurons in the NAc prevented the decrease in running following naltrexone administration in HVR, suggesting opioidergic signaling requires downstream dopaminergic activity to influence voluntary running. In the second study, the transgenerational effect of maternal Western diet (WD) on offspring voluntary wheel running was assessed. Wheel running was increased in female WD offspring from 4-7 weeks of age, but decreased running from 16-19 weeks of age, compared to offspring from chow fed dams. These age-specific changes in wheel running are associated with the up- and down-regulation of dopamine receptor 1 in the NAc at 6 and 18 weeks of age, respectively, in WD female offspring, which in turn was negatively associated with leptin receptor mRNA in the ventral tegmental area. In the third study, age-related influences on wheel running were assessed in 8 and 14 week-old rats. In addition to a ~60% reduction in running, RNA-sequencing revealed down-regulations in networks related to cAMP-mediated signaling and synaptic plasticity in the NAc from 8 to 14 weeks-old. The down-regulations of these networks was mirrored by reductions in dendritic spine density in the NAc from 8 to 14 weeks-old. Additionally, intra-NAc injection of the Cdk5 inhibitor roscovitine, a known modulator of dendritic density and dopamine signaling, dose-dependently decreased wheel running. Despite the varying experimental models used in this dissertation, these findings collectively suggest that alterations in dopaminergic signaling in the NAc associate with, and influence, voluntary physical activity.