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Impact of short-term inhibition of PKA in Nucleus Accumbens on voluntary wheel running

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Objective Based upon a Booth lab goal of establishing molecular regulators of physical activity motivation, my current study focuses on the effects of short-term inhibition of protein kinase A (PKA) activity in the nucleus accumbens (NAc). The NAc is a brain region integral to motivated behaviors. Downstream immediate-early gene (IEG) expression from PKA has been shown to exhibit rapid responses to acute stimuli, such as voluntary wheel-running behavior. According to previous work in our lab, long-term NAc overexpression of the endogenous PKA inhibitor, Protein Kinase Inhibitor Alpha (PKIα), increased nightly running distance in rats selectively bred for low voluntary running (LVR) behavior (Mol Neurobiol 2018 Jun 21). However, paradoxically, the same PKIα overexpression failed to increase running distance in wild-type (WT) rats. It is known that chronic manipulation of the NAc PKA pathway produces different molecular (gene expression profiles) and behavioral outcomes from that of acute manipulations. Given the above, the goal of the current work is to determine how short-term inhibition of PKA in the NAc influences its downstream gene networks and the nightly voluntary running behavior in WT rats.
Methods An ex vivo preparation of the NAc was utilized to determine the effects of Rp-cAMPS, a selective protein kinase A inhibitor, upon its stimulation of dopamine D1-like receptor agonist SKF 38393 on downstream gene expression level in sedentary WT female rats. Further, real-time PCR was implemented to analyze the transcriptional expression of IEGs (Homer-1, Arc, Zif268) following Rp-cAMPS administration.
Results Data showed that there were no significant difference of mRNA level for Homer-1, Arc or Zif268 among the vehicle, 50uM, 100uM and 200uM Rp-cAMPS treatment groups upon the stimulation of 10uM SKF 38393.
Conclusions In addition to the PKA, other protein kinases such as Ca++ activated and growth factor activated kinases have both been shown to phosphorylate CREB at Ser^{133}, and thus, lead to activation of gene transcription. Given the above results of the ex vivo experiment, in which NAc slices were treated with multiple dosages of Rp-cAMPS concurrent with the stimulation of SKF 38393, it is possible that other protein kinase pathways could be compensating the effects of short-term inhibition of PKA and, in turn, lead to no difference of IEG expression. Further experiments will need to be performed in order to testify this hypothesis.