Epigenetic reversal of maternal deprivation-induced dopamine cell hyperexcitability and synaptic mislocalization of AKAP150 within the VTA

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Child abuse and neglect as early life stressors are shown to increase the risk of developing stress-related disorders and substance abuse. The increased vulnerability seems to be related to brain monoaminergic dysfunction including an altered dopamine (DA) signaling from the ventral tegmental area (VTA). Recently, we demonstrated that a 24h early maternal deprivation (MD, an animal model of child abuse), on postnatal day 9, induces synaptic abnormalities at GABAergic synapses onto VTA DA neurons through disruption of A kinase anchoring protein (AKAP150) signaling in juvenile rats. These synaptic defects were normalized by *in vitro* histone deacetylase (HDAC) inhibition suggesting the potential clinical benefits of targeting the VTA by HDAC inhibitors soon after the insult. Here we further investigated the synaptic localization of AKAP and epigenetic modifications associated with MD in VTA DA neurons and tested the effects of a single in vivo injection of a selective class I HDAC inhibitor (CI-994) on these MD-induced changes within the VTA. We found that MD indeed increased HDAC2 (a class I HDAC) expression specifically in VTA DA neurons resulting in reduction of histone H3 acetylation at lysine 9 (Ac-H3K9). The levels of Ac-H3K9 in VTA of MD rats were restored 3 hours after a single *in vivo* injection of MD animals with CI-994. We also detected that MD induced an increase in AKAP150 localization to VTA synaptosomal membranes and DA cell hyperexcitability, which was also normalized by the in vivo HDAC inhibition. Taken together, our results suggest that a single *in vivo* HDAC inhibition may be sufficient to epigenetically reverse MD-induced changes in AKAP localization, DA cell excitability and synaptic dysfunction within the VTA.
[Supported by 5R01DA039533-02 NIH grant to F.S.N].