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Understanding the Role of Insulin Signaling in the Prefrontal Cortex (PFC) of Opioid Overdose Cases

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Opioid overdose (OD), the most severe outcome of Opioid Use Disorder, is the leading cause of accidental deaths in the US. Genetic and epigenetic studies of OD have nominated key loci that provide insights into disrupted molecular mechanisms through the course of this disorder. However, limited functional understanding of these genes in human cells has hindered understanding of underlying pathophysiology. Hence, we sought to generate iPSC derived forebrain neurons (iFB) and model the epigenetic variation identified in postmortem PFC tissues of OD cases. In our previous study, we show that OD case specific hypoacetylation regions called variant enhancer loci are associated with five genes in the PFC– ASTN2, DUSP4, ENOX1, GABBR2 and KCNMA1. We knocked-down each gene and identified 120-2000 differentially expressed genes (DEGs). Surprisingly, while downregulation of these five genes altered different gene sets, insulin signaling was identified as likely upstream regulator of the DEGs in 3/5 knockdowns indicating a potential overlap in their functional effect. Insulin signaling is known to regulate cellular polarity, modify axonal length and neuronal secretions. Through immunohistochemistry analysis, we observed significant reduction in axonal length (25%) with downregulation of ASTN2, DUSP4 and ENOX1. This phenotype was reversed when insulin signaling was rescued in ASTN2, DUSP4 and ENOX1 downregulated samples. Furthermore, fentanyl exposure to iFB downregulated ASTN2, DUSP4 and ENOX1, and reduced expression of insulin signaling receptors. Overall, our results suggest that genes downregulated in OD lead to aberrant insulin signaling and suggest a potential avenue for rescuing the impact of OD on neuron pathophysiology.