Child Health Research Institute
University of Nebraska Medical Center
Children's Hospital & Medical Center

Therapeutic Potential of Suvorexant on Intergenerational Maternal Oxycodone Exposure

Jina Yi, University of Nebraska - Medical Center

Sneh Koul, University of Nebraska - Medical Center

Gurudutt Pendyala, University of Nebraska - Medical Center

Sowmya V. Yelamanchili, University of Nebraska - Medical Center

The opioid epidemic has led to an increase in maternal prescription opioid abuse. Our lab previously found that the detrimental impacts of in-utero oxycodone exposure (IUO) persist to the F2 generation**.** The overall goal of this project is to test the therapeutic potential of suvorexant (suvo), a dual hypocretin receptor antagonist that is FDA-approved for the treatment of insomnia, to attenuate the impacts of IUO. Previous findings from our laboratory showed that *Hcrtr1,* a key regulator in the hypocretin pathway, is upregulated in both F1 and F2 IUO offspring. The hypocretin system is involved in the regulation of the sleep/wake cycle, feeding behavior, and notably, addiction. It is estimated that the cost of hospital admissions for infants suffering from Neonatal Abstinence Syndrome (NAS) was $316 million in 2012 and still rising. This figure does not take into account long-term costs, nor does it consider the lasting effects on the F2 generation. Thus, it is critical to find a way to mitigate the negative impacts of IUO. Administering a hypocretin receptor antagonist on F1 IUO animals may be able to mitigate the developmental effects of IUO on the F2 generation. To test our hypothesis, nulliparous female F0 rats were orally gavaged with 15mg/kg oxycodone from mating until weaning of the F1 generation. F1 pups were treated with suvorexant or corresponding amounts of the DMSO vehicle through subcutaneous injection (3mg/kg P3-P6, 10mg/kg P7-P10, 30mg/kg P11-P21). 2 females from each condition were mated with naïve males to generate the F2. Phenotype and behavior data were collected from the F2 animals before they were sacrificed for tissue collection. Our data showed that F2 IUO pups whose mothers were treated with suvo (IUO+suvo) exhibited significant differences in body weight, body length, and head circumference at P7 and P14 compared to the control. In addition, at P28 and P45, social novelty and social preference tests showed that IUO+suvo animals showed significant improvements in their social interactions when compared to the DMSO treated animals. Furthermore, our preliminary analysis on oxycodone self-administration experiments conducted between ages P60-P100 revealed that IUO+suvo pups administered less oxycodone, suggesting that suvo treatment can reduce drug seeking behavior. In conclusion, our study reveals that suvo could potentially rescue developmental deficits and reduce drug craving in IUO pups, thereby preventing the long-lasting effects of opioid misuse.