5-5-2022

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, Omaha

Sowmya V. Yelamanchili
University of Nebraska Medical Center

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, Sneh Koul, Gurudutt Pendyala, and Sowmya V. Yelamanchili*

Department of Anesthesiology, University of Nebraska – Medical Center, Omaha, Nebraska

Background:
Maternal opioid misuse is a rising public health concern. Our lab previously published findings that in-utero oxycodone exposure (IUO) has detrimental impacts that persist to the F2 generation, including abnormal genetic expression, increased anxiety, and a difference in phenotypic measurements. The estimated cost of hospital admissions for infants suffering from Neonatal Abstinence Syndrome was $316 million in 2012 and is still rising. This figure does not take into account long-term costs, nor does it consider lasting effects on the F2 generation. Thus, it is critical to find a way to mitigate the negative impacts of IUO.

Suvorexant (suvo) is a dual hypocretin receptor antagonist that is FDA-approved for the treatment of insomnia. The hypocretin system is involved in the regulation of the sleep/wake cycle, feeding behavior, and notably, addiction. Our previous findings showed that *Hcrtr1* is upregulated in both F1 and F2 IUO offspring. This project will test the therapeutic potential of suvorexant to attenuate the impacts of IUO.

Hypothesis:
The administration of suvorexant on F1 animals that have been subjected to IUO will result in the alleviation of developmental impairments in the F2 generation.

Methods:
Female Sprague Dawley rats in the F0 generation were orally gavaged with 15mg/kg oxycodone or equal volumes of saline. Dosing was maintained from mating until weaning at post-natal day 21 (P21). F1 animals were given ascending doses of suvorexant (3mg/kg P3-P6, 10mg/kg P7-P10, 30mg/kg P11-P21) or an equal volume of DMSO through subcutaneous injection. At P60, 2 females from each condition were mated with naïve breeders. Phenotypic measurements of the F2 generation including weight, head size circumference, and body length were taken at P3 and P14. At P21, 6-8 animals were sacrificed, and organs were collected. Social preference/novelty tests were conducted at P28 and P45. The next phase of this study will consist of molecular assays, imaging, and further behavior testing including an oxycodone self-administration study.

Results:
Our preliminary results showed that F2 IUO-Suvo animals exhibited significant differences in body weight, body length, and head size circumference at P7 and P14 compared to the control. Furthermore, in the social preference test, the IUO-Suvo animals had significantly more entries into both the toy and naïve chambers at P45, as well as significantly more contacts with both the toy and naïve animal at P28.

Conclusions:
Administering suvorexant in the F1 generation may mitigate physical and behavioral deficits in the F2 generation caused by intergenerational IUO.