REASONS FOR ATTEMPTING A PARTICULAR RESEARCH TOPIC

Semaglutide has garnered significant attention as an efficacious remedy for addressing excessive weight. Manufactured by Novo Nordisk, it is predominantly available in two formulations designed for weekly administration: Ozempic®, employed in diabetes management, and Wegovy®, formulated in higher doses specifically for obese individuals with a BMI $\geq$ 27 to aid in weight reduction. There has been a notable surge in the utilization of semaglutide over the past five years. In 2023 alone, more than 4.3 million Americans were prescribed medications containing this compound, representing a staggering 40-fold increase from previous years. Furthermore, the extensive usage of semaglutide across Europe poses challenges related to its accessibility. Despite its widespread utilization, particularly among women of reproductive age, knowledge concerning the effects of semaglutide on fetal development, specifically on the formation of the nervous system, remains limited. Preclinical studies conducted on various animal models such as mice, rats, rabbits, and monkeys have revealed concerning implications of semaglutide on fetal growth. These studies demonstrated reduced survival rates, compromised normal growth patterns, and abnormalities observed within both skeletal and visceral systems. Particularly alarming was the accumulation of blood in the developing brains of monkeys, raising concerns regarding nervous system development. Significantly, the manufacturer recommends discontinuing semaglutide usage at least two months before attempting conception due to the observed effects on fetal development. However, implementing such guidance might pose challenges, as pregnancies, even in developed nations like the US or European countries, can occur unexpectedly, accounting for approximately 50% of cases. Additionally, many women may remain unaware of their pregnancy until several weeks after conception. The initial trimester of pregnancy, pivotal for fetal development, especially concerning the nervous system, constitutes a critical timeframe.

THE PROJECT GOAL

The primary objective of this project is to undertake a thorough investigation into the potential implications of semaglutide on neurodevelopmental processes, utilizing *in vivo* models. At the core of this project lies the principal hypothesis that exposure to semaglutide during a pivotal stage of pregnancy, specifically the initial trimester, could potentially impact neurodevelopmental processes in offspring. This impact may result in the modification of synaptic plasticity, neuronal connections, and/or cognitive functionalities, stemming from the drug's interaction with neural pathways associated with GLP-1R signaling.

DESCRIPTION OF RESEARCH

The research entails the administration of semaglutide to female mice both preceding and during pregnancy (up to day 14 of gestation). Moreover, it involves exposing male and female mice to semaglutide prior to the reproductive phase and throughout pregnancy (up to day 14). This comprehensive project employs a diverse array of methodologies, encompassing mRNA sequencing, proteomic analysis, and epigenetic profiling, aimed at identifying genetic and epigenetic alterations stemming from semaglutide exposure. Furthermore, the investigation encompasses the scrutiny of processes associated with apoptosis, autophagy, and oxidative stress. The evaluation of the blood-brain barrier's integrity constitutes another crucial facet of the study. Behavioral assessments conducted on offspring are tailored to investigate the correlation between exposure to semaglutide and alterations in behavior, encompassing potential autism spectrum disorders, cognitive impairments, as well as behaviors indicative of anxiety or depression.

SUBSTANTIAL RESULTS EXPECTED

These comprehensive investigations aim to evaluate the potential risks linked to the prenatal exposure of the developing nervous system to semaglutide. Through an extensive array of molecular (including epigenetic) and behavioral assessments encompassing evaluations for autism spectrum disorder, cognitive impairment, as well as anxious and depressive behaviors, this project endeavors to establish a correlation between prenatal exposure to semaglutide and subsequent neurodevelopmental disorders in offspring. This all-encompassing approach strives to elucidate the potential neurological ramifications arising from exposure to semaglutide during fetal development. The findings obtained from this project could be a crucial groundwork for future clinical discussions and treatment considerations. This could help in the development of more effective management approaches against the effects of prenatal exposure to semaglutide.