BACKGROUND AND RATIONALE

Many aspects of our health are determined by what we inherit from our parents. For example, the risk to develop obesity, or certain physical ailments like diabetes, or even predisposition to mental health disturbances like depression can run in families. It is believed that these familial patterns of disease transmission are related to the genes we inherit. However, it has been recently proposed that our health may also be determined by the experiences of our parents, for example, their diet or their mental well-being especially early in life. This concept is called 'epigenetic inheritance' and is largely based on studies from rodents. We have previously shown that adverse conditions early in life of mice can cause depressive behaviors and changes in body fats of adult mice. Importantly, some of these effects are even transmitted to their next generation. Our previous researches also showed that such transmission largely depends on changes in the blood and germ cells of the mice. However, how these changes are caused in the blood by early life trauma and how they reach the germ cells is still unclear.

Fats present in the blood appear as important factors that can carry the abnormalities caused by trauma via the blood to the germ cells. They could be relevant because it is already known that the composition of fats is altered in the blood of animals who had adverse conditions early in life. Interestingly, these fats can carry tiny molecules called microRNAs, which can modify the germ cells. When these germ cells give rise to the next generation of animals, such changes may persist and result in specific abnormalities in the children.

SPECIFIC AIMS

The current project will capitalize on our previous findings and will involve an in-depth assessment of how fats in the blood and fat deposits are altered by early life trauma in mice and if these are accompanied by changes in the microRNAs they carry. It will also test if other life-style factors, such as eating foods high in fat content or alternately, exercise that decreases fats, are able to shape how trauma effects are passed from traumatized mice to their children. Finally, it will be tested if the transmission of trauma effects could be reversed by modifying the fat deposits in the body or by blocking their uptake by the germ cells.

RESEARCH PLAN

Early life trauma will be studied in mice in the form of separation of newly born male pups from their mothers on a daily basis for two weeks. Parallel to that, the mothers will be exposed to stressful conditions. This is done to simulate many cases of childhood trauma in humans, where mothers are not able to provide optimal care to their children due to stressful conditions. Then, these mice will be evaluated for any physical or mental health problems during their adulthood. The mice with early life trauma will be mated with females without a traumatized childhood to produce pups who will undergo similar evaluations when adults. Importantly, fats will be collected from the blood of mice and it will be checked if there are changes in the microRNAs carried by these fats and whether similar changes are present in sperm of these mice.

Furthermore, to show that it is the fat-associated factors that are critical to such transmission, we will collect the fats from the blood of mice with trauma and inject it into mice without trauma and then evaluate them, as well as, their children. We will also test if fats taken from blood of mice who exercise on a running wheel will reverse the harmful effects of trauma or if fats taken from mice that are fed diet enriched in fats will increase the harmful effects.

Finally, we will generate special mice that either do not release microRNAs from their fat deposits or have modified sperm that does not receive the fats carrying microRNAs from the blood. These special mice will be exposed to trauma and evaluated for physical and mental perturbations caused by early life trauma, along with their children.

EXPECTED RESULTS

Based on our previous work, we anticipate that early life trauma will cause changes in fat deposits and fats present in the blood. This will also change the microRNAs that are carried by fat-associated factors to the germ cells and hence the next generation will have abnormalities. As high-fat diet will increase the harmful fats in the body, the effects of early life trauma will even be more pronounced in such mice. On the contrary, exercise will reduce the harmful fats and increase beneficial fats, and will reverse the transmission of harmful effects to the next generation. The injections of fats extracted from traumatized mice into non-traumatized mice will verify these results, whereas, similar injections from mice who were exposed to high-fat diet and exercise to traumatized mice will verify a potential role for life-style factors to modify this association. Finally, we expect that mice that do not release microRNAs from their fatty tissue and mice that have modified sperm that does not uptake fats carrying microRNAs, will not fully transmit the effects of trauma to their children.

IMPACT

This project will help in our understanding of conditions where trauma seems to cause 'trickle-down' effects in generations, for example in Holocaust victims. It will also provide us potential strategies to prevent transmission of harmful effects to children of individuals who suffer from obesity or stressful conditions.