Fellows Column: Caloric Restricted Diets Anxiolytic Effect on Progeny

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Anxiety disorders are the most common mental disorder in the United States. More than $42 billion is spent by the United States every year on anxiety disorders (1). With such extensive resources devoted to anxiety disorders each year, research is vital to find a cost-effective, successful form of treatment. Although the use of antianxiety medications has proven to help combat the effects of an anxiety disorder, there may be a more straightforward, cost-effective way to ameliorate anxiety. Environmental factors such as dieting may be the answer to a multibillion-dollar problem. A review of several studies shows the effects of caloric restriction on increasing anxiolytic behavior and that paternal caloric restriction has been shown to ameliorate anxiety in their progeny. DNA methylation may be the reason for the increase in anxiolytic behavior, but further research is needed to establish the mechanism for why caloric restriction ameliorates anxiety.

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In order to determine if the caloric restriction is indeed lowering anxiety, it is vital to understand the neurocircuitry of anxiety. The neurocircuitry of anxiety has been well diagrammed and has shown a few brain regions that play a significant role in the anxiety response. The hypothalamic–pituitary–adrenal axis has been shown to have a significant role in the anxiety neurocircuitry (2). The hormones involved in anxiety are a key component of assessing the effectiveness of treatment options for anxiety. The corticotropin-releasing factor is a peptide hormone heavily involved in the stress response (3). Its principal function is the stimulus of the pituitary to induce the production of Adrenocorticotropic hormone. Corticotropin-releasing factor is released from the hypothalamus and sent to the pituitary. Upon stimulation, the pituitary releases Adrenocorticotropic hormone into the bloodstream, which then travels to the adrenal gland to stimulate the release of cortisol. Cortisol is released to respond to stress and facilitates increased blood glucose levels to provide more energy for the body's consumption. This mechanism that the body uses is well understood as the hypothalamic-pituitary-adrenal axis (HPA-axis) (4-6). With an emphasis on the HPA-axis, we can now discuss the experiments performed showing amelioration in the anxiety response.

The role of dieting in increasing quality of life has been demonstrated. Two studies focused on the physiological changes that intermittent fasting and caloric restriction have on the body. Intermittent fasting has been shown to decrease anxiety through anti-inflammatory pathways (7). Calorie restriction (CR), as previously stated, has been seen to ameliorate numerous diseases outcomes as well as the overall standard of living. Calorie Restriction is defined as lowering the average food intake by a percentage. Many of the studies cut the caloric intake of the experimental group by 25% and 50%. One study reported that when placed on a calorie restriction diet, adolescent mice demonstrated an increase in cerebral blood flow and blood-brain barrier function compared to the controls (3). With age, calorie-restrictive diets were shown to decelerate the steady decline of the cerebral blood flow typically seen in adult mice. Age has been shown to result in a decline in many homeostatic functions. The continued cerebral blood flow allowed for the continued normal function of the hippocampus and frontal cortex. With the normal function of the hippocampus and frontal cortex, the rats demonstrated preserved memory and learning and reduced anxiety. They reported that correlations between vascular integrity, cognitive functions, and mental health induced by calorie restriction in aging mice were significant and that calorie-restrictive diets demonstrated an increase in all of the previously mentioned parameters (8). Further research has demonstrated that caloric restriction delays age-related methylation drift (9). This study and others show that calorie restriction can increase lifespan and ameliorate disease outcomes (10).

Understanding the potential that caloric restriction has for increasing the quality of life leads to learning its effects, specifically anxiety. Its effects on anxiolytic-like effects have been observed. One study subjected rats to 1 of 4 dietary regimens: control, 25% of the controls food amount (CR25%), 50% of the controls food amount (CR50%), and an acute episode of calorie restriction, which was an experimental group given the same size meal as the control, once every three days. They then tested them in the anxiety test known as the open field test. In the open field test, the CR25% and CR50% groups made more central zone entries than the control and Acute groups, demonstrating a distinct increase in anxiolytic behavior.

"One epigenetic factor is DNA methylation. DNA methylation is a unique tool used by our body to affect the expression of DNA. Methylation can change the activity of a DNA segment without changing the sequence. DNA methylation occurs on the cytosine of a guanine-cytosine dinucleotide (12). These methylation results are permanent and can be passed on from one DNA strand to each of its daughter strands."

Moreover, both calorie-restricted groups explored the central zone more than the control group in the initial 5 min of the test (11. Calorie-restricted mice consistently demonstrated a significant decrease in anxiety behavior compared to the controls. They reported that calorie-restricted diets did increase anxiolytic behavior; however, the mechanism of how it works to do so is still unknown. This research is evidence for a calorie-restricted diet's ability to decrease anxiety in mice and shows promise for further investigation into the mechanism of how such behavior changes occur.

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"If differences in DNA methylation sites are shown in those that display the anxiety disorder phenotype instead of those that do not, then there is potential for that being the mechanism of how anxiety can be ameliorated. Researchers have seen that even minimal traumatic brain injury has shown a decrease in DNA methylation and an increase in the anxiety phenotype (13)."

If differences in DNA methylation sites are shown in those that display the anxiety disorder phenotype instead of those that do not, then there is potential for that being the mechanism of how anxiety can be ameliorated. Researchers have seen that even minimal traumatic brain injury has shown a decrease in DNA methylation and an increase in the anxiety phenotype (13). One study examined the amygdala, a fundamental brain structure in the fear response (14), of mice that demonstrated a low behavioral response to novel situations and displayed high fearfulness, anxiety, and diminished sociability and sexual motivation. They compared the methylation of these mice to high novelty responders. In comparison with the high novelty responders, they found that the DNA methyltransferase protein levels were similar, but 793 differentially methylated genomic sites. They then decided to test the hypothesis that increasing the methylation of the low responding mice would decrease the anxiety phenotype. After changing the food of the low responders to an increased dietary methyl donor content diet, they saw a significant decrease in the anxiety phenotype of the mice (15).

Another study showed that prenatal caloric restriction enhances DNA methylation in the offspring. Specific nuclear protein DNA complex formation was associated with prenatal calorie restriction-induced reduction of placental glut3 expression and thereby transplacental glucose transport. This research provided therapeutic interventions for reversing fetal growth restriction (16) and demonstrated that paternal caloric restriction was able to increase DNA methylation in the progeny. Although they were not looking specifically at anxiety and the changes in DNA methylation, we were able to connect the two studies to see that there could be a potential for DNA methylation, given that caloric restriction decreases anxiety behaviors in mice.

The potential mechanisms by which anxiety exists and can be ameliorated are complex. These anxiolytic phenotypes may be passed on to the next generation. There is some evidence that shows that maternal diets can affect the behavior of the offspring. One study showed that sleep homeostasis was affected by the maternal diet (17). Prenatal calorie restriction has been shown to have a wide range of effects on progeny. A recent study done by Dr. Nowacka-Woszuks group showed that paternal caloric restriction could alter the lipid metabolism in their progeny (18). Because of this evidence, Further research into the potential for paternal caloric restriction to eliminate the anxiety phenotype merits attention. This concept is illustrated by the research done by Govic et al. His group showed that Paternal Caloric restriction prior to conception had altered anxiety-like behavior in adult progeny. Adult male rats were exposed to 25% calorie restriction or glucocorticoid elevation for six weeks prior to breeding. Elevated plus maze, open field, and predator odor were assessed in the adult male offspring. Plasma concentrations of corticotrophin-releasing hormone, adrenocorticotropic hormone, and serum leptin were measured in both parents and offspring. Only the calorie restriction induced anxiolytic behavior in the elevated plus-maze.

Moreover, calorie-restricted offspring demonstrated an anxiolytic-like profile in the elevated plus-maze and open field, but no alteration to predator odor induced defensiveness compared to control. This study showed that calorie restriction in paternal mice increases anxiolytic behavior in their adult male offspring. The mechanism as to how this increase in anxiolytic behavior occurred is unknown, but they concluded that there might be some support of an epigenetic factor leading to the decrease in progeny anxiety behavior (19)

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In conclusion, Caloric restriction may be a simple solution to a huge problem in the United States. Compelling research provides evidence that caloric restriction decreases anxiety. The brains of those with anxiety disorders have been shown to display differences in DNA methylation. Caloric restriction has been shown to alter DNA methylation, and although this has not yet been shown to be the mechanism of how caloric restriction works in ameliorating anxiety, there is enough evidence to merit research as a potential mechanism. Another potential area for research is how paternal caloric restriction decreases the anxiety phenotype in their progeny. These studies and subsequent investigations may help us develop novel therapeutic techniques for the many who suffer from anxiety disorders and may be the solution to the multi-billion-dollar problem we face today.

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