Impact of High-fat and Western Diets on Anxiety

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Abstract

Prevalence of high-fat and highly palatable foods raises concern about the behavioral and neurochemical consequences of consuming high-fat and western diets. High-fat diets consist of a high caloric content of fat, while the western diet consists of high fat, sugar, and processed food contents. While consumption of these foods often results in obesity and weight gain, previous research has explored the relationship between these diets and emotional states, specifically anxiety. Behavioral studies have found that consumption of a high-fat diet often produces anxiety-like behaviors, with and without the presence of an outside stressor and independent from weight gain. However, short-term consumption of high-fat foods may produce anxiolytic effects. Western diet consumption is also capable of inducing anxiety-like behaviors; however, these behaviors are usually exhibited in response to a stressor. Considering neurochemical changes, high-fat foods modulate behavior by acting on stress responses involving the hypothalamus-pituitary-amygdala axis and acting on the reward circuitry involving the nucleus accumbens. Western diet foods also change the reward circuitry and stress responses in these areas. Removal of both the high-fat diet and the western diet after consumption yields an increased stress response and anxiety symptoms. Overall, consumption of both diets can facilitate development of susceptibility to increased stress responsiveness, a dysregulated reward system, and anxiety, but the exact effects of consumption of these diets are not definitive.
Impact of High-fat and Western Diets on Anxiety

Obesity has commonly been associated with mood disorders, including anxiety. A study in 2008 observed approximately 15.7% of US-dwelling persons had a lifetime diagnosis of anxiety, and these persons were significantly more likely to be a smoker, obese, physically inactive, a binge drinker, and a heavy drinker (Strine et al., 2018). While there seems to be a bidirectional relationship between obesity and anxiety, the concern of the current paper is primarily on the effect of unhealthy diets on anxiety. Due to the prevalence of high levels of fat and sugar in everyday diets and the effect of these diets in promoting obesity, it is important to understand the mechanisms of these diets in potentially producing anxiety-like behaviors. By examining the behavioral, neurochemical, and physiological effects that occur from ingestion of high-fat and “western” or “cafeteria” diets, the understanding of the relationship between obesity, anxiety, and unhealthy behaviors can be culminated.

A high-fat diet (HFD) is characterized by a diet that consists of high ratio of fat-to-calorie content. For example, animal studies implementing a HFD typically use diets containing greater than 30% fat content in calories consumed. The western diet pattern (WD) also contains a high fat content but is accompanied by high sugar content and processed foods, much like ones that would be found in a cafeteria. High palatability and high caloric, fat, and sugar content are typical qualifications for WD foods. Both diets are capable of inducing obesity and have been linked to depressive- and anxiety-like symptoms. The current review will examine the literature linking these diets to change in behavior and with demonstrate the strength of this relationship.

To expand an understanding of the relationship between food and behavior, the connection from the gut to the brain and behavior is relevant to everyday eating habits. Influences on the gut can affect stress-related mood states, including anxiety-related behaviors.
(Foster, Rinaman, & Cryan, 2017). Studies on anxiety and diet typically utilize rat models since rat diets are easily manipulated. To measure anxiety-like behaviors in rats, tests such as the elevated plus maze (EPM), open field test (OF), elevated z-maze (EZM), social interaction test (SI), and light/dark task (LD) are reliable examinations.

The elevated plus maze consists of closed and open arms of a maze. Rats spend significantly greater amount of time in the closed arms, and enter them more frequently than the open arms, where the open arms exhibit greater anxiety-like behavior. Increased exploration of the open arms corresponds to an anxiolytic effect, while a decrease corresponds to anxiogenic effects (Pellow, Chopin, File, & Briley, 1985). The open field test measures anxiety-like behavior on the basis that anxiolytic effects correspond to rats spending more time in the center of the open field, while anxiogenic effects correspond to rats spending less time in the center of the open field (Hall, 1934). Rats showing anxiogenic effects also exhibit less social interaction and exploration than rats showing anxiolytic effects. Moreover, rats emerging to the light in the LD task demonstrate anxiolytic effects, while time spent in the dark demonstrates anxiogenic effects. Studies often use a combination of behavioral measures to assess anxiety-related behaviors in rats.

Behavioral changes observed in these tests are often co-occurring with neurochemical and physiological changes in rats. Commonly observed changes include increase in inflammation, induced obesity and metabolic dysfunction, increases in adipose tissues, and changes in expression of brain-derived neurotropic factor (BDNF), leptin, serotonin (5-HT), insulin, glucose, and corticosterone. These changes often occur in the hypothalamus-pituitary-amygdala axis (HPA axis) due to its regulation of stress behaviors or the hippocampus for its role in cognition and memory. Additionally, changes in the reward circuitry of the brain are evidently
associated with consumption of HFD and WD. For instance, rats exposed to a high-sugar high-fat diet which took larger and less frequent meals in initial exposure gained more weight after maintenance of the diet (Wald & Grill, 2019). Continued eating suggests a lessened reward response to the palatable foods, thus rats experience continued weight gain. Observations such as the previous underline the complex nature of eating, and it is of interest to explore the potential effects of this eating behavior. Surface-level demonstrations of the relationship between HFD and WD consumption and anxiety-like behaviors provide a necessary foundation to explore the underlying mechanisms of the brain in response to consumption of these diets.

Behavioral Studies on High-fat Diet and Anxiety

Behavioral studies concerning high-fat diets and anxiety-like behavior employ many of the same techniques. Methods for examining the effects high-fat diets might have on anxiety include the elevated-plus maze (EPM), light/dark task (LD), elevated z-maze (EZM), open field test (OF), social interaction test (SI), and other stress-inducing tests. Previous research has shown stress-responsiveness in rats exposed to HFD by both the consumption alone of HFD foods and the removal of HFD foods. Responsive behaviors seem dependent upon initial anxiety phenotypes and preferences for HFD as well as time of exposure to HFD. As a whole, findings indicated increased anxiety-like behaviors with exposure to HFD foods and removal of HFD foods, possibly due to physiological changes that result from consumption of HFD foods.

Considering the EPM, decreases in time spent in the open arms of the maze are correlated to anxiety-like behaviors. Studies have utilized this correlation to examine the presence of increased anxiety-like behaviors in rats fed high-fat diets (Kaur & Kaur, 2017; Wang et al., 2018), and increased anxiety-like behaviors as a result of the removal of high-fat diets (Sharma, Fernandes, & Fulton, 2013). A study examined rats’ behaviors in the EPM (Wang et al., 2018).
Rats showed increased anxiety-like behavior indicated by significantly less time spent within the open arms of the maze and a decrease in the number of open arm entries as compared to rats on standard chow diets. Even so, these behaviors were eliminated in the HFD group by treating rats with fibroblast growth factor 21 (rFGF21), a metabolic regulator (Wang et al., 2018). FGF21 is a gene that encodes a member of the fibroblast growth family, which is a secreted endocrine factor that stimulates the uptake of glucose in adipose tissue. FGF21 may have a possible role in reversing HFD-induced metabolic disorders including obesity, impairment in glucose tolerance, insulin resistance, hyperlipidemia, and systemic pro-inflammation. Another study showed rats which exhibited increased anxiety-like behaviors in the EPM in response to the removal of high-fat diets indicate symptoms of withdrawal from HFD (Sharma et al., 2013). This withdrawal also yielded increased physiological measures of stress, including increased corticosterone measures. Thus, withdrawal from a HFD might induce anxiety by promoting a stress response rather than just simply inducing obesity or some other metabolic disorder. Because anxiety-like behaviors accompanied physiological measures of stress, it can be deduced that increases in stress are correlated to increases in anxiety-like behavior; however, differentiating between short-term stress and a state of anxiety is difficult.

Despite anxiety behaviors in HFD rats discussed in previously mentioned studies, studies utilizing the EPM have also shown the preference for HFD corresponds to a less anxious phenotype (Alsiö et al., 2009). Rats which were considered less anxious by showing more open-arm activity in the EPM also showed a preference for HFD, while rats considered more anxious did not show a preference for high-fat diets. It is important to note that the EPM test was conducted prior to the food choice experiment. Therefore, the study considers the bidirectional relationship between anxiety and high-fat food preferences, where an anxious profile is
associated with a decrease in high-fat food preferences. There was a significant correlation of HFD preference and open-arm activity in the EPM, showing less anxiety-like behavior. This gives insight to the importance of the anxious profile of rats prior to high-fat diet consumption, as their anxiety profiles may be as, if not more, important in influencing the results of their anxiety-like behaviors after high-fat diet consumption. For instance, a person with already-established high-anxiety phenotype may prefer HFD, thus consuming a HFD may decrease anxiety. However, for a person with a low-anxiety phenotype and no preference for HFD, HFD feeding may induce anxiety. Thus, preferences and anxiety profiles are influential in determining the effects of HFD on anxiety at the level of the individual.

Another method of studying anxiety-like behaviors is the light-dark task. Rats under HFD conditions showed higher levels of anxiety-like behavior than low-fat diet rats as indicated by more time spent in lighted portions of the LD task (Sivanathan, Tavartnam, Arif, Elegino, & McGowan, 2015). These same rats, however, did not show an effect of the HFD on behaviors in the EPM, suggesting different neural processes associated with the LD task and EPM. This is problematic, since both the EPM and LD tasks are considered reliable tests for anxiety-like behaviors. These rats also showed increases in body weight by week six of exposure to HFD; however, body weight alone was not related to measures of anxiety-like behavior. Supporting this result, another study considered the effect of HFD exposure paired with exercise on anxiety-like behaviors (Kang et al., 2014). It was observed that rats fed HFD showed significantly greater anxiety as measured by percentage of time spent in the light compartment. These results indicated that HFD alone caused a significant increase in body weight of HFD rats compared to control rats, indicating that a change in body weight might be involved in the mechanisms which cause an increase in anxiety-like behaviors. Considering the effect of exercise, it was observed
that exercise was not sufficient to counteract the anxiety induced by weight gain and the HFD. This may be because the exercise was not adequate to reverse the physiological changes occurring with HFD consumption. Despite these results suggesting an increase in anxiety-like behaviors, a study by Prasad and Prasad (1996) showed rats fed a HFD exhibited significantly less time spent in the dark compartment of the LD task compared to control rats, indicating a reduced anxiety response (Prasad & Prasad, 1996).

Anxious behavior is also observed using the open field test. Anxious behavior was exhibited by HFD rats spending less time in the open field as compared to control rats (Almeida-Suhett, Graham, Chen, & Deuster, 2017; Eudave, BeLow, & Flandreau, 2018; Otsuka, Shiuchi, Chikahisa, Shimizu, & Séi, 2019). Increased anxiety behavior based on the open field test has been associated with levels of IL-1beta in the amygdala, a cytokine protein encoded by the IL1B gene, but this relationship needs further exploration (Almeida-Suhett et al., 2017). There has also been an observed interaction between stress and diet on behavior in the OF test. For groups of non-stressed HFD, non-stressed chow diet, stressed HFD, and stressed chow diet, non-stressed chow diet mice spent more time in the center of the OF than any other group, while non-stressed HFD mice spent no more time in the center of the OF than stress-exposed mice (Eudave et al., 2018). Because the non-stressed HFD mice spent the same or less time in the center of the OF compared to the stress-exposed mice, this study suggests HFD may increase anxiety even in the absence of stress. Even so, rats under HFD exposed to stress exhibit anxiety-like behavior in the OF test which was not observed in control rats exposed to stress (Otsuka et al., 2019). Therefore, HFD has been found to increase anxiety-like behaviors in the OF test with and without stress.

Other stress-inducing tests and social interaction tests have been useful in examining the relationship between HFD and anxiety. A stress test was conducted after seven weeks of HFD
exposure and ten weeks of HFD exposure (Kamara, Eskay, & Castonguay, 1998). Rats under HFD exposure showed significantly higher stress-induced corticosterone levels than control rats at the 7th week mark but showed no significant difference in stress responsivity from the control rats at the 10th week mark. This result suggests that short-term exposure to HFD can induce a higher initial stress response, but long-term exposure may show normal stress responsiveness. However, HFD rats did show slower recovery from the stress test at the 10th week mark than control rats. Slower recovery indicates a possible interference with the HPA axis, where HFD interferes with the HPA axis feedback system, in which circulating corticosterone is known to inhibit further HPA axis activation. Considering social interaction, previous studies have linked HFD to significantly less social interaction compared to control rats, which points to anxious behavior, along with significantly less time spent in the central area of the open field (Gancheva, Galunska, & Zhelyazkova-Savova, 2017). In rats exposed to social defeat stress, however, HFD reduced social avoidance for stressed HFD exposed rats compared to stressed control rats, indicating a suppression of social avoidance behavior suggesting decreased anxiety (Otsuka et al., 2019).

In a sample of obese women, surgically-induced weight loss though gastric bypass surgery was associated with significant decreases in neuroticism scores, specifically anxiety (Capuron et al., 2010). While previous studies have gone back and forth as to whether the induction of obesity is necessary to evoke anxiety-like behaviors, this study suggests the weight is the factor that determines anxiety. Despite this finding, eating habits of women post-surgery were not recorded, therefore we cannot consider the effect of HFD on the prevalence of anxiety.

Overall, there are variable results for behavioral markers of the relationship between HFD and anxiety-like behaviors. Many studies resort to observing the stress response, but this
does not necessarily indicate an anxiety state. However, it is reasonable to believe that elevated stress levels in response to HFD feeding may lead to an anxiety state. Even so, the emergence of anxiety-like behaviors with exposure to HFD even in absence of a stressor suggests that this is not simply a stress response. Moreover, the interaction between HFD feeding and anxiety-like behaviors seems to be dependent on whether a physiological change occurs, such as induced obesity or glucose regulation impairment. Without a physiological response to HFD exposure, it is possible that the HFD would not have any effect on anxiety. Even so, previous studies show that rats typically gain weight in response to HFD. Thus, the changes in behavior cannot be attributed to the fat in the diet alone, since other physiological changes may be the culprit. Further, the ineffectiveness of implementing exercise with HFD to decrease anxiety indicates that these physiological responses have a robust effect which may be difficult to eradicate. This might even suggest the alternative, that the actual diet itself is the primary factor into anxiety symptoms, not just weight gain. Undeniably, physiological measures accompanying behavioral responses are necessary to clarify the current understanding of HFD consumption and anxiety.

**Behavioral studies on Western Diet and Anxiety**

Because changes in anxiety-like behavior are likely a response to physiological changes, it is necessary to observe the effects of other diets which may induce these physiological changes. Similar results have been found in behavioral studies concerning the effect of western, or cafeteria diets on anxiety. These studies also utilized measures such as the EPM, OF, emergence test, and social interaction test to determine the presence of anxiety-like behavior. Results indicate a relationship between the WD and the reward circuitry, which may influence anxiety-like behaviors upon withdrawal. Studies have demonstrated an anxiogenic effect of the WD in rats exposed to external stressors as well as in absence of these stressors. Although most
studies induce obesity with consumption of WD foods, it is possible that an obesogenic condition is not necessary to arouse anxiety-like behaviors.

One study using the EPM showed rats exposed to chronic intake of a WD characterized as consisting of 49% fat had increased anxiety like behaviors (André, Dinel, Ferreira, Layé, & Castanon, 2014). This study emphasized that 18 weeks of WD exposure was necessary to increase the anxiety-like behavior, and this resulted in rats becoming 25-30% overweight. This further supports the idea that anxiety-like behaviors occur due to a change in weight. In another study, it was shown that the cafeteria diet was effective in inducing obesity, and obese mice reacted with predictive parameters for anxiety in the EPM (da Costa Estrela et al., 2015). This result, however, was not comparable to the mice behaviors in the OF test, which can be due to the different nature of the tests. This result is problematic, since it challenges the validity of either test in examining anxiety-like behaviors. Since both tests are commonly acceptable measures of anxiety-like behaviors, they should both provide similar results when used to determine these behaviors. Interestingly, the daily caloric intake of the cafeteria diet was higher than the standard diet group, but the stress condition did not influence parameters related to consumption. This suggests that greater caloric intake was not due to stress but to a natural preference for cafeteria foods. Another study opposes the idea that an increase in body weight is necessary for palatable diet-induced anxiety, showing rats exposed to a cafeteria diet consisting of 15% sucrose solution, standard rat chow, chocolate cake, biscuits, dog roll, and 40% high-fat rat chow exhibited cognitive dysfunction and anxiety-like behaviors even without a significant increase in body weights (André et al., 2014). Additionally, the cafeteria diets for these rats was maintained during the behavioral tasks, so the anxiety-like behaviors are not a result of withdrawal from the diet. Since the behavioral changes occurred without a change in weight or
withdrawal, it is possible that there are underlying neural processes which are affected by the intake of cafeteria foods. A study using a high-fat high-sugar diet (43% fat, 17% protein, 40% sucrose), comparable to a cafeteria or western diet, induced stress by limited nesting to assess the effects of cafeteria diet intake and the stress response on anxiety-like behaviors (Maniam, Antoniadis, Le, & Morris, 2016). Limited bedding and nesting was performed by limiting the amount of bedding available to the rats, inducing an early life stress response and affecting HPA axis as well as cognitive and emotional functions. Limited nesting control rats showed increased anxiety-like behavior compared to unstressed control rats, indicating the ability of the limited nesting to invoke a stress response. There was also a main effect of diet on anxiety indicated by more time spent in the open arm of the EPM, which is a decreased anxiety response. This indicates that the stress induced by limited nesting can be ameliorated by a diet rich in fat and sugar. It is possible that since the cafeteria diet foods were presented after the limited nesting stress, the function of these foods was to provide therapeutic value. Results from another study support the anxiolytic effect of palatable diet when employing a diet consisting of chocolate crackers, wafers, marshmallows, mortadella, hot dog sausages, cheese and bacon chips, Doritos® chips, peanut candy, calf’s foot jelly, and soft drinks in male Swiss albino mice (Leffa et al., 2015). Mice submitted to the cafeteria diet spent more time in the open arms of the EPM, showing decreased anxiety behavior. This could be attributed to feelings of satiety and involvement with the dopaminergic system. The diets affect on the dopaminergic system promotes feelings of reward when consuming these foods. However, it is reasonable to speculate that with continual eating and activation of the reward system, the dependence on these palatable foods and dysregulation of the reward circuitry are possible and harmful circumstances. Keeping
this in mind, removal of the diet could evoke feelings associated with withdrawal and an anxiety-like response.

Another study used both the EPM and OF to assess the affect of a cafeteria diet consisting of cake, cookies, chocolate, raisin bread, cooked noodles, sausage, and cheese on anxiety-like behaviors compared to rats on a standard chow diet (Warneke, Klaus, Fink, Langley-Evans, & Voigt, 2014). Both male and female rats were tested to see if the observed effects depend on sex. Only adult male rats showed increased grooming and less entries into the aversive open arms of the EPM, suggesting an anxiogenic effect of the “comfort” food diet specifically in males. The cafeteria diet exhibited an anxiolytic effect in females, expressed by greater time spent on the aversive open arms, less grooming upon an aversive situation, and greater distance travelled in the open field. Both male and female rats showed increases in body weight, although male rats showed anxiogenic effects and female rats showed anxiolytic effects. Sex differences in the current study could be due to interactions of sex hormones with the HPA axis accompanied by interactions of the WD foods with the HPA axis. While these anxiogenic effects were only observed in males, the males are the only group which showed significant impairment of glucose metabolism, pointing to glucose metabolism as the possible contributor to anxiety-like behaviors. Both male and female groups showed increased body weight as a result of WD feeding, but showed opposite behavioral effects. This suggests that the weight gain associated with the diet may not be responsible for changes in behavior. Male rats exposed to a western high-fat diet showed anxiety-like behaviors in the open field test following traumatic stress exposure compared to control rats (Kalyan-Masih et al., 2016). The stress was induced by the presence of a predator odor, and rats consuming the western diet were more susceptible to anxiety following exposure to the stress odor. Anxiety-like behaviors in the open arena were
also exhibited by rats submitted to withdrawal of a cafeteria diet consisting of chow supplemented with pork lard and condensed milk (32% fat, 14% protein, 60% carbohydrate) (Martire et al., 2014). In this study, researchers gave rats the opportunity to choose between cafeteria diet foods and standard chow, finding that rats preferred cafeteria foods. One group of rats consumed the cafeteria diet for a period of either six or fifteen weeks before being switched to standard chow diet, while rats consumed the standard chow diet for a period of either six or fifteen weeks before being switched to cafeteria diet. Further, the composition of foods that were selected was examined. Rats exposed to the cafeteria foods for six weeks ingested more fat and less carbohydrate relative to rats fed cafeteria diet for fifteen weeks, since the six week rats only consumed the foods they preferred which were higher in fat, while rats in the fifteen week group may eat their preferred foods and then eat the standard chow when they ran out of foods higher in fat. This may be due to a change in reward circuitry of the brain, where chronic feeding of the cafeteria diet diminished sensitivity to the reward aspect of palatable foods, so rats in the fifteen weeks continued eating to compensate for the deficits in rewards. Removal of the cafeteria diet was associated with anxiety symptoms demonstrated by a marked decrease in chow intake for rats switching from cafeteria to chow diets and heightened anxiety in the open field. While the food may have become less rewarding, removal still resulted in anxiety behaviors, possibly due to elevated baseline levels of stress as a result of chronic consumption.

Generally, it seems that WD affects behavioral responses comparably to the HFD. There is an important aspect of reward which contributes to these behavioral changes. Anxiolytic effects of comfort foods were observed in multiple studies; although, the change in reward circuitry could decrease sensitivity to reward, overshadowing the therapeutic value of such diets. A repeatedly reported result is increased anxiety responses to withdrawal of WD of HFD foods.
This can aid in explaining the rebound people experience when dieting and abstaining from consuming WD foods and contributes to the anxiolytic effects when eating these foods after depravation. Another result which seems unchallenged thus far is increased responsiveness to stress by rats exposed to WD as compared to control rats. Rats on WD diets seem predisposed to show a greater anxiety response to stress than control rats, indicating a mechanism of the WD that interacts with outside stressors. There is controversy surrounding the notion that obesity must be induced to elicit anxiety-like behaviors. Results showing rats exhibiting anxiety-like behaviors without a change in body weight as compared to control rats conjure concern about the effects of WD beyond obesity. In humans who maintain a WD without increased body weight or obesity, consumption of WD foods may still be a concern when considering anxiety.

**Neurochemical Studies on High-fat diet and Anxiety**

Anxiety-like behaviors have been related to many neurological processes. The hypothalamus-pituitary-amygdala axis (HPA) and the limbic system are of particular interest to researchers studying anxiety. Changes in levels of proteins and neurotransmitters such as brain-derived neurotrophic factor (BDNF), tyrosine, proinflammatory cytokines, leptin, insulin, and corticosterone are indicators of changes in metabolic processes, stress responses, and reward circuitry. Consumption of HFD modulates reward circuitry by decreasing sensitivity to reward, especially the reward aspect of HFD foods, and can increase stress responsiveness. As expected, induced obesity and weight gain are possible factors in increased anxiety-like behavior, as they are also associated with inflammation in the brain, which may change anxiety behaviors. Despite this insight, changes in levels of the previously mentioned proteins and neurotransmitters correlating with increase anxiety levels propose the idea that anxiety-like behaviors can develop independently of weight gain.
One study subjecting male rats to a HFD showed production of a hypo-affective state which included symptoms of anxiety along with increased HPA reactivity (Sharma et al., 2013). Anxiety symptoms were indicated by less time spent in the open arms of the EPM. Increased corticosterone levels upon withdrawal of the HFD, but not with exposure to HFD, also suggest a heightened stress state. Along with these measures, removal of the high-fat food showed reduced tyrosine hydroxylase and pCREB expression in the amygdala, decreased ΔFosB, and increased brain-derived neurotrophic factor (BDNF) protein levels in the nucleus accumbens. Tyrosine hydroxylase is the rate limiting enzyme for dopamine biosynthesis and pCREB is a transcriptional and neurotrophic signal related to reward circuitry. Reductions of both tyrosine hydroxylase and pCREB are correlated to induction of anxiety. The nucleus accumbens importance in reward indicates that the modulation of tyrosine hydroxylase and pCREB from HFD can dysregulate the reward system. ΔFosB is a truncated splice variant of the FosB gene which is related to development of addiction, and decreased ΔFosB could indicate a decrease in feelings of reward. BDNF is a protein encoded by the BDNF gene which promotes the survival of nerve cells important for growth of these cells. Impaired BDNF expression can increase vulnerability to anxiety, and lower BDNF has been linked to individuals with anxiety. Additionally, HFD reduced protein levels for dopamine biosynthesis, which may reduce reward sensitivity and promote compensatory eating of palatable foods. Reduced dopamine biosynthesis in the amygdala may have a role in the anxiogenic effects of HFD feeding. An increase in BDNF in the nucleus accumbens as a result of withdrawal from high-fat feeding also provides speculation that neurotrophic signaling in the nucleus accumbens may be a factor in the observed anxiety behaviors. This supports a previous study by Sharma and Fulton (2013) which found that chronic intake of high-fat foods, specifically a 12-week regimen, induced obesity, produced
anxiety symptoms in the OF task, and enhanced HPA stress responsiveness, promoting anxiety-like behavior and increasing BDNF and dopamine D1A receptor levels in the nucleus accumbens. It was also observed that the high-fat diet consumption increased responses to an acute stressor and increased corticosterone levels. This suggests that high-fat diet consumption increases vulnerability to stressors.

Another study observed chronic HFD feeding for 12 or 16 weeks (Zemdegs et al., 2016). The study induced type 2 diabetes mellitus and produced increases in body weight, fasting hyperglycemia, hyperinsulinemia, and glucose intolerance. After 12 weeks, rats consuming the HFD significantly decreased the time spent in the compartment of the OF, while mice fed HFD for 16 weeks showed both decreased number of entries and time spent in the center field. This suggests anxiogenic effects were more prominent the longer rats were exposed to high-fat foods, and the induction of metabolic disorders along with type 2 diabetes mellitus created anxiety-like behaviors in the rats. Researchers attributed this change in behavior to modifications in the serotonin (5-HT) tone of the hippocampus, an area near the limbic system projecting to the amygdala and hypothalamus. Their study showed an inhibition of 5-HT transmission, which caused a significant decrease in basal extracellular 5-HT levels in this area, a possible link to increased anxiety behavior.

Other studies have linked increased anxiety to alterations in tyrosine. One study investigated whether high-fat diet affects the inhibition of protein tyrosine phosphatase 1B (PTP1B) in the amygdala and causes anxiety behavior (Mendes et al., 2017). PTP1B acts by inhibiting insulin receptors, which have an anorexigenic effect, causing decreased feeding. Increased expression of PTP1B diminishes the anorexigenic effect of insulin, increasing feeding. Rats consuming HFD showed enhanced PTP1B expression in the amygdala and a marked
increase in time spent in the open arms of the EPM. Thus, the high-fat diet seems to have had an anxiety-inducing effect. Knocking down PTP1B in the amygdala with oligonucleotide antisense, however, showed an anxiolytic effect for rats consuming high-fat diet. Because the addition of oligonucleotide antisense decreased expression of PTP1B in the amygdala and ameliorated anxiety behaviors, this result suggests an effect of high-fat diet in increasing PTP1B expression and the particular role of PTP1B expression in anxiety. Another study observed a significantly lower content of tyrosine in the frontal cortex in HFD rats compared to the control group and showed anxiety-like behaviors marked by HFD rats spending less time in the light compartment compared to control rats (Souza et al., 2007). This suggests that the decrease in tyrosine is related to increases in anxiety-like behaviors and a role of the frontal cortex in anxiety.

Other studies observing anxiety-like behaviors attribute them to neuroinflammation. Energy-dense food causes inflammation by adipose tissue infiltration of macrophages and lymphocytes, which secrete pro-inflammatory cytokines causing systemic inflammation (Kaur & Kaur, 2017). Cytokines activate the HPA axis and corticotropin-releasing hormone system, altering the metabolism of monoamines related to anxiety (Capuron et al., 2010). One study investigated the effects of a HFD consisting of 45% fat on biomarkers of inflammation in anxiety-related brain areas such as the hypothalamus and amygdala and increases in skin temperature due to stress (Noronha et al., 2019). Rats on the HFD has increased anxiety-like defensive behavioral responses indicated by the OF test and increased proinflammatory cytokine expression in the amygdala and hypothalamus. Further, the study linked increased visceral fat in HFD rats compared to control rats to low-grade systemic inflammation and neuroinflammation, which may disrupt the neuronal balance among brain structures causing behavioral changes. Another study examined inflammatory gene expression in limbic brain areas along with tests of
anxiety-like behavior (Sivanathan et al., 2015). Symptoms of anxiety were shown in rats exposed
to HFD as compared to rats on a low-fat diet regimen. HFD rats spent more time in the lighted
portion of the LD task and had more entries in the center than the edges of the OF. Observed
changes in behavior were accompanied by gene expression analysis showing decreased pro-
inflammatory gene expression in the hippocampus in HFD rats compared to low-fat diet rats.
Additionally, the study linked this gene expression to dysregulation of the HPA axis and
dysregulation of corticosteroid receptors, which occurs as an enhanced response to stress among
rats exposed to HFD. Therefore, the study suggests that HFD affects anxiety behavior by
exaggerating the response to stress, causing a dysregulation of corticosterone and the HPA axis.
A study by Almeida-Suhett, Graham, Chen, and Deuster (2017) came to a similar conclusion
when rats on HFD (60.3% fat) showed specific overexpression of pro-inflammatory cytokine IL-
1β in the hippocampus and amygdala along with anxiety-like behaviors in the OF and elevated
zero maze test. Rats also showed body weight gain and glucose intolerance, a common theme
among rats exposed to high-fat diet. The study provides an overall examination of the
relationship between increased adiposity, expression of IL-1β, and increased anxiety symptoms
in response to HFD (Almeida-Suhett et al., 2017).

Another element was added to this relationship in a study using male rats on control
(11% fat) versus high-fat diets (45%) (De Noronha et al., 2017). Again, the study observed body
weight gain via elevated adiposity index, anxiety-like behavior by increased latency by trial to
leave the enclosed arm of the ETM task and aversity to open space, and activation of pro-
inflammatory processes in the hypothalamus. However, researchers also identified inhibition of
the dorso-medial hypothalamus (DMH) by activation of GABAa receptors as the causal factor of
the anxiety-like behaviors in the HFD rats. Blockade of GABAa receptors caused anxiety-like
behaviors in lean animals, but this was ineffective in obese rats. HFD rats showed an intense learning capacity to avoid the open arm because of susceptibility to develop anxiety-like behaviors, possibly due to increased fear and modulation of emotion. Muscimol, a GABAa agonist and anxiolytic drug, was ineffective in controlling the anxiety-like condition in HFD rats. Diet-induced obesity may build a pharmacological resistance to muscimol or activation of GABAa in obese rats may produce an anxiogenic effect. It was inferred, then, that the activation of neuroinflammation by obesity caused an imbalance of GABA neurotransmission which is associated with changes in anxiety-like behaviors, but the role of GABA neurotransmission as a mechanism for HFD-induced anxiety is still unclear.

Other studies linking anxiety-like behavior to pro-inflammatory processes have explored the effect of HFD supplemented with mediators of inflammation. One study tested the effect of recombinant human fibroblast growth factor 21 (rFGF21) administration on anxiety-like behaviors in obesity-induced rats (Wang et al., 2018). Rats with HFD-induced obesity showed anxiety-like behavior by less time spent within the open arms of the EPM test compared to standard-diet rats, but increased anxiety-like behavior was eliminated in rFGF21-treated mice. rFGF21 is a metabolic regulator capable of reversing disorders such as obesity, impaired glucose tolerance, insulin resistance, and systemic pro-inflammation, which have all been found to be involved in anxious behaviors. Researchers observed elevated pro-inflammatory cytokine expression in the hippocampus of HFD-mice, which was able to be reversed by rFGF21 treatment. Thus, reversal of anxious behaviors and decreased neuroinflammation in rats treated with rFGF21 demonstrates a strong connection between inflammation and anxious behavior. Another study investigated the effect of a root extract *Withania somnifera* on neuroinflammation and anxiety resulting from diet-induced obesity (Kaur & Kaur, 2017). Researchers induced
obesity with a 30% fat HFD and looked at inflammation in the hippocampus, piriform cortex, and hypothalamus. Anxiety-like behaviors were observed in HFD rats based on the EPM, and serum samples showed upregulated expression of pro-inflammatory cytokines for the HFD group. However, supplementing with *W. somnifera* ameliorated these behaviors. It was observed that *W. somnifera* reduced the serum level of pro-inflammatory cytokines along with reducing anxious behaviors, which further supports the idea that inflammation is a pertinent factor to the anxious behavior caused by HFD-induced obesity.

A human study looked at the relationship between adiposity, low-grade inflammation, eating behavior, and emotional status in obese women (Capuron et al., 2010). A questionnaire measuring neuroticism, extraversion, openness, agreeableness, and conscientiousness was examined and plasma glucose and insulin were measured. Neuroticism included facets of anxiety, hostility, depression, self-consciousness, impulsiveness, and vulnerability. The study observed strong associations between adiposity, glucose homeostasis, inflammatory processes, and psychological characteristics in morbidly obese women. Concerning neuroticism, anxiety was associated with higher levels of inflammatory markers. Weight loss was associated with both decreased neuroticism scores, including anxiety, and significant decreases in inflammation. However, inflammatory factors were related to neuroticism independently of BMI, suggesting that inflammation may influence vulnerability to emotional distress which leads to neuroticism. Because neuroticism scored decreased along with inflammation post-surgery, this suggests a role of inflammation in contributing to psychological and emotional changes such as anxiety and depression.

While previously mentioned studies primarily link HFD to an increase in anxious behaviors, some studies link decreased anxious behavior to consumption of high-fat foods.
McNeilly, Stewart, Sutherland, and Balfour (2015) observed the effects of 12 weeks high-fat feeding (45% fat) on activity in the EPM, 5-HT in the brain, and plasma corticosterone levels. HFD rats exhibited an increase in total activity in the EPM, indicating anxiolytic-like behavior. This behavior did not correlate with the weight of animals or glucose or insulin plasma concentrations. This challenges the idea that changes in adiposity, glucose concentrations, or insulin concentrations impact behavioral responses of rats in the EPM. Basal plasma corticosterone levels were significantly higher in HFD animals compared to standard diet animals. Increased circulating corticosterone levels could be responsible for the anxiolytic effects of the high-fat diet, as repeated daily exposure to an unavoidable stressor has been shown to induce anxiolytic-like behavior in the EPM; however, this speculation requires further inquiry (McNeilly et al., 2015). Another study that observed decreased anxiety-like behaviors in HFD rats by increased time in the center of the OF, decreased time in the closed arms of the EPM, and increased light box entries in the LD task also observed a decrease in SIRT1 in the medial prefrontal cortex and amygdala after only four weeks of high-fat feeding (Xu et al., 2018). This anxiolytic effect, however, did not continue happening for 12 weeks of high-fat feeding. Based on previous literature, it is reasonable to hypothesize that further exposure to high-fat feeding beyond 12 weeks could promote anxiogenic effects. Upon further exploration, the study observed that an SIRT1 inhibitor did not show anxiolytic effects in HFD-fed mice, despite a decrease in SIRT1 expression being linked to anxiolytic effects. This reveals the complex interaction of high-fat diet and anxiety, especially as it relates to regulation of specific genes and neurotransmitters. The relationship between preferences for high-fat foods and anxiety was evaluated and related to gene expression in a study with thirty-six male rats (Alsiö et al., 2009). Preference for HFD was positively correlated with open-arm frequency and time in the EPM,
which is inversely related to anxiety-like effects. The EPM was conducted prior to food choice, showing that an anxious phenotype predicts preference for high-fat foods. There was also a positive correlation between EPM behavior and corticotropin-releasing factor receptor 2 (CRF2) expression in the HPA axis, where low levels of anxiety behavior were associated with increased expression of CRF2. CRF2 is a receptor for corticotropin-releasing hormone, which regulates the HPA axis responses to stress. Deficiency of CRF2 is linked to increased levels of anxiety and hypersensitivity to stress. This supports the idea that HFD acts on the HPA axis to modulate stress responses.

Repeated studies show increased circulating leptin as a result of HFD consumption (Capuron et al., 2010; Alsiö et al., 2009, Kalyan-Masih et al., 2016). Leptin is the hormone in adipose cells which inhibits hunger. One study observed a decrease in BMI and weight were significantly associated with decreases in concentrations of leptin, while also observing that greater leptin levels corresponded to lower activity scores in obese women (Capuron et al., 2010). Additionally, a study found that knocking down PTP1B in mice decreased adiposity, leptin levels, food intake, and anxiety-like behaviors. This improvement in leptin signaling did not keep female mice from gaining weight, however, as they observed decreased energy expenditure (Mendes et al., 2017). Increases in circulating leptin paired with increases in body weight and anxiety-like behaviors support the mechanism of HFD inducing anxiety and insensitivity to leptin.

As previously mentioned, knocking down PTP1B neurons in the hypothalamus improved insulin signaling with a decrease in anxiety-like behaviors, despite an observed weight gain (Mendes et al., 2017). In another study, an increase in IL-6 cytokines correlated with decreased insulin sensitivity and higher BMI in rats exposed to HFD (Capuron et al., 2010). Relationships
between insulin resistance, IL-6 levels, and BMI suggest a role of HFD in changes in insulin sensitivity. Further supporting this role is a study which showed HFD induced hyperinsulinemia in rats with anxiogenic symptoms, along with glucose intolerance and impaired glucose homeostasis (Zemdegs et al., 2016). Specifically, one study demonstrated an increase in insulin in the hippocampus after 16 weeks of HFD exposure (Dutheil, Ota, Wohleb, Rassmusen, & Duman, 2016). Since rats required nine weeks of HFD exposure to cause a significant weight gain, the effects of the diet on insulin observed at 16 weeks could result from a compensatory mechanism to reduce insulin insensitivity in rats. Another study observed insulin sensitivity after 33 weeks of HFD feeding, finding that HFD mice were 58.9% heavier than standard diet mice and experienced hyperinsulinemia (Wang et al., 2018). Therefore, chronic consumption of HFD seems to cause impairment in insulin sensitivity which can reach the extent of hyperinsulinemia.

While insulin and leptin resistance may change without the presence of a stressor, it seems that HFD consumption can cause animals to be more vulnerable to stress, as is indicated by corticosterone levels. After a 30 minute restraint test, HFD rats had higher corticosterone levels as compared to standard diet rats (Kamara et al., 1998). This result suggests interference of HFD consumption with the HPA axis feedback system, where circulating corticosterone may inhibit activation. In another study, HFD rats showed increased serum corticosterone after 16 weeks of HFD exposure, along with behavioral effects of HFD on anxiety (Dutheil et al., 2016). An increase in corticosterone and anxiety-like behaviors proposes the possibility that corticosterone synthesis in the brain with elevated HPA activity can affect anxiety. Exposure to the EPM in another study increased plasma corticosterone levels in both control and HFD rats, while the concentration in HFD animals was higher (McNeilly et al., 2015). This suggests a higher baseline level of corticosterone in rats exposed to HFD. Even so, anxiolytic responses in
HFD rats suggest that an elevated baseline of corticosterone may not affect anxiety-like behaviors as expected. Moreover, one study suggests that it is not the HFD which affects corticosterone levels, but withdrawal from HFD increases corticosterone levels relative to those in low-fat diet mice (Sharma et al., 2013). Elevated corticosterone levels in HFD mice only following restraint stress manipulation highlights the effects of HFD withdrawal on stress. While it is commonly observed that HFD yields elevated corticosterone levels, the interpretation of these levels requires further research.

From this research, a final determination is that the various contributions of actors on the brain create a complex view of the interaction between HFD consumption and anxiety. These results also illuminate the interaction between the reward circuitry of the brain and stress responses, where it is possible that the removal of reward increases stress and increased stress influences reward-seeking behavior. This cycle seems imperative to unhealthy eating habits, as eating palatable, high-fat foods could increase baseline levels of stress, which may cause further feeding of these foods, often considered stress-eating. Inflammation occurring with obesity and decreased anxiety in women who lost weight both indicate a role of obesity and weight gain in anxiety, where weight positively correlates with anxiety symptoms. However, it is difficult to differentiate whether neurological changes which could be factors of increased anxiety behavior are due to obesity or the HFD itself.

**Neurochemical Studies on Western Diet and Anxiety**

The western diet has been evaluated in multiple studies by its effect on behavior and neurochemical processes corresponding to behavioral changes. Neurochemical processes that may occur as a result of WD intake include changes in inflammation and adipose tissues and expression of leptin, insulin, and corticosterone in the brain. Changes that occur in the HPA-axis
are of particular interest in studying anxiety, as it involves responses to stress. Responses of inflammation which correlate with weight gain demonstrate the strength of the role of diet-induced obesity in altering anxiety behaviors. As previously mentioned, palatable WD foods also affect the reward system by causing desensitization to rewarding foods, thus potentiating a stress response upon removal of WD foods.

To test stress responses that might relate to anxiety, one study observed the effect of consuming WD during adolescence and vulnerability to traumatic stress in rats using the acoustic startle test (ASR) (Kalyan-Masih et al., 2016). Rats on the western diet exhibited anxiety-like behaviors in the OF test only following traumatic exposure. This suggest that the WD alone did not cause stress, but it made rats more vulnerable to anxiety when presented a stressor. Further, this study reported reduced ventral hippocampal volumes in WD rats. Studies have demonstrated a role of the hippocampus in anxiety and fear, especially concerning aspects of memory. The reduced hippocampal volume, then, is another insight to the possible harmful effects of WD consumption and the path to anxiety.

Concerning inflammation, a study by André, Dinel, Ferreira, Layé, and Castanon (2014) sought to investigate the emotional, cognitive, and inflammatory impact of chronic consumption of WD, which they defined as consisting of palatable energy-dense food (André et al., 2014). They observed chronic WD intake lasting for 18 weeks enhanced anxiety-like behavior and activated brain cytokine production in response to a systemic immune challenge. Increases in inflammation with chronic WD intake and an anxious behavioral response suggests inflammation is an intermediate step from WD intake to anxiety-like behavior. These results also suggest that 18 weeks of WD consumption is necessary to increase anxiety-like behaviors, as only spatial recognition was dysregulated at nine weeks, which parallels studies on HFD.
suggesting an anxiolytic effect in early stages of consumption and anxiogenic effect in chronic consumption. Another study observed different effects when it examined the impact of four different diets with distinct macronutrient profiles on neuroinflammation related genes and cognitive function in rats (Beilharz, Kaakoush, Maniam, & Morris, 2016). One of these diets is reminiscent of the cafeteria diet, with 36.5% carbs, 16% protein, and 47.5% fat. Hippocampal and hypothalamic markers were not affected by the diets and there was no change in BDNF, contrasting results which indicated the diet’s affect on inflammation. However, the study was only concerned with short-term diet exposure, about two weeks. With this in mind, the study does not show a lack of an effect of the western diet as much as it shows the importance of indicating a time-related threshold for exposure to the western diet to show neurochemical and behavioral responses.

Another study aimed to analyze the relation between altered behavior in response to a cafeteria diet and neurogenesis in the dentate gyrus (André et al., 2014). The study used doublecortin (DCX), a marker for neuroproliferation to estimate the number of DCX-immunoreactive cells. It was again observed that the cafeteria diet impaired spatial learning, along with increased anxiety in cafeteria diet rats compared to standard diet rats. Concerning DCX-immunoreactive cells, there was a decrease in neurogenesis in the dentate gyrus specifically in rats fed CAF diet, so it is reasonable to attribute changes in anxious behavior to neurogenesis. In another study, rats exposed to a high-fat high-sugar diet had decreased PV-immunoreactivity in the medial prefrontal cortex (Baker & Reichelt, 2016). Decreases in PV neurons may affect behavior and has been associated with increased anxiety-like behavior in rats exposed to early-life stress, and the study shows that the PV neurons may be influenced by western diet.
A change that has been repeatedly observed with the influence of cafeteria diets is in adipose tissue. One study observed rats exposed to cafeteria diet foods had observed increases in brown adipose tissue (BAT) and white adipose tissue (WAT) compared to chow fed rats (Martire et al., 2014). The study also showed behavioral changes marked by anxiety in the OF test. Another study also observed increased WAT fat pads in rats fed a high-sugar, high-fat diet as compared to rats fed standard chow (Baker & Reichelt, 2016). These rats also showed anxiety-like behavior on several measures. Analyses showed a significant correlation between WAT and IBA-1, which supports a connection between WAT and immune activity, possibly indicating the presence of neuroinflammation. Thus, WAT can be connected to inflammatory processes involved in anxiety-like behaviors in rats fed high-fat or western diets. In another study, cafeteria-fed rats showed increased social behavior, more time in the center of the OF, and increased percentage of time and entries into the open arms of the EPM, along with the presence of increased WAT (Lalanza et al., 2014). This signifies anxiolytic behaviors with increased WAT. It is possible that this effect is due to the lack of stressors, so there is no reason for the presentation of anxious symptoms. Anxious behaviors exhibited by rats with consumption of WD and increases in adipose tissue suggest that it may be necessary to induce obesity for the WD to yield anxiogenic effects.

As in the HFD studies, changes in BDNF in rats that consume western diets has a potential role in linking the diet to anxious behaviors. In one study, rats consuming cafeteria diet for six weeks showed a reduction of hippocampal BDNF expression, which has been linked to diet and stress (Martire et al., 2014). Decreased BDNF has also been associated with elevated baseline and stress-induced corticosterone levels, although this study did not find increases in corticosterone. This result was not observed in rats exposed to the diet for 15 weeks, which is
unusual considering chronic consumption has typically been more effective in inducing anxious behaviors. Another study showed anxiolytic effects with consumption of a palatable diet for 13 weeks along with increases in hippocampal BDNF (Leffa et al., 2015). It is possible that the consumption of the palatable foods increasing BDNF causes activation of the brain reward system, which induces anxiolytic effects. Anxiolytic effects in this study challenge previous results showing consumption of cafeteria diet for longer periods of time induce anxiogenic effects. Despite the divided results, it is reasonable to believe that removal of the palatable foods in the diet would remove activation of the brain reward circuitry, decreasing anxiolytic effects. Dependence on a diet which is rewarding, then, may still be harmful if its access is decreased or denied after repeated consumption.

Circulating leptin levels are relevant to the effects of cafeteria and WD exposure, as increased leptin levels have been associated with consumption of these diets (André et al., 2014). Elevated leptin was observed in rats exposed to the cafeteria diet compared to rats on standard chow diets (Martire et al., 2014). Moreover, cafeteria diet rats continued to overeat despite elevated leptin levels, promoting the association of obesity and leptin resistance. Another study showed WD consumption yielded an increase in adipose tissue along with increases in leptin levels in both adipose tissue and plasma (André et al., 2014). Even so, systemic immune challenge induced body weight loss in WD animals, which does not confirm the effects of leptin resistance on body weight.

Insulin resistance is another possible effect of western diet consumption. Rats exposed to a high-fat high-sugar diet exhibited elevated serum insulin along with increased visceral adiposity and levels of anxiety, according to the OF and SI tests (Gancheva et al., 2017). Increased body fat composition was also observed in rats submitted to a highly palatable diet
enriched with sucrose (Souza et al., 2007). These rats had increased insulin resistance along with impaired glucose tolerance. Elevated insulin levels (Martire et al., 2014) and insulin resistance (Lalanza et al., 2014) were also demonstrated by rats consuming cafeteria diets. While cafeteria diet rats developed insulin resistance, withdrawal during the 8th week of diet consumption allowed the rats to recover insulin sensitivity. This provides evidence of insulin recovery from the effects of cafeteria diet at early stages of consumption.

The relationship between cafeteria diet consumption and anxiety is further explored through corticosterone levels. One study showed presentation of systemic immune challenge to rats fed WD increased corticosterone levels significantly more than standard diet rats (André et al., 2014). An increased stress response in WD rats compared to standard diet rats suggests vulnerability to stressors caused by consumption of WD foods. Another study showed higher corticosterone levels in rats that consumed the WD, affecting HPA axis activation (Vega-Torres et al., 2018). While corticosterone levels alone may be unaffected by the WD, the diet can predispose a susceptibility to elevated levels of corticosterone in the presence of a stressor, which may lead to anxiety-like behaviors.

In general, previous studies indicate various affects of WD exposure on anxiety-like behaviors as well as weight gain. As in HFD studies, WD may elevate baseline levels of stress to increase susceptibility to anxiety-like behaviors in the presence of a stressor. Inflammatory responses in the brain upon exposure to WD show that inflammation may be a pathway from the WD to anxiety behaviors. Merging the idea or inflammatory effects and the effect of weight gain and diet-induced obesity on anxiety-like behaviors, studies showed a positive correlation between increased adipose tissues and immune activity with anxiety behavior. Changes in leptin
and insulin resistance further solidify the continual eating of palatable foods which modulates reward circuitry, potentially resulting in a stress response with removal of these foods.

Discussion

From the accumulation of past research, it is undeniable that the relationship between diet and anxiety is complex and requires further exploration. While research on this relationship has been primarily performed on rats, it is implicated to human feeding behaviors and consequential anxiety. With the prevalence of anxiety as well as WD and HFD food options, it is natural to speculate a relationship between what humans eat and resulting behavior. Developing an understanding of this relationship can help humans pursue both physically and psychologically healthier lifestyles.

In exploring this relationship, general conclusions can be made regarding the effects of HFD on anxiety-like behaviors. Behavioral studies have contributed a basic indication of the relationship between diet and anxiety, where HFD seems to have anxiolytic effects with short-term exposure, anxiogenic effects with chronic exposure, and increased susceptibility to stress. Previous studies found anxiety-like behaviors in rats exposed to HFD by decreased time in the open arms of the EPM, decreased time in the center of the OF, and increased time spent in the lighted portion of the LD task as compared to rats exposed to a regular chow or standard diet. Remarkably, rats exposed to HFD exhibited anxiety-like behaviors in the OF test even in the absence of stress (Eudave et al., 2018), suggesting HFD alone is capable of increasing anxiety. Regardless of this results, other studies indicate a contribution of HFD consumption to increase the stress response of HFD rats compared to standard diet rats when a stressor is used. HFD also increased anxiety behaviors in rats as indicated by the LD task but not the EPM in one study (Sivanathan et al., 2015). This indicates that the design differences between the LD task and the
EPM can confound the ability to determine anxiety symptoms and challenges the internal validity of each of the tasks. Because of this, more measures should be taken to clarify the nature of the behavioral response. Another behavioral study indicated exercise was not adequate to ameliorate the anxiety induced by HFD consumption. For humans, this result might indicate a necessary effort to abstain from HFD and exercise in order to maintain a healthier lifestyle. Results from these behavioral studies have sparked interest in the brain mechanisms involved in this interaction, but exposure to HFD seems to be undecided between producing anxiogenic or anxiolytic effects.

Considering behavioral studies concerning WD consumption and anxiety, findings indicate that chronic consumption of WD inducing obesity yields anxiogenic effects. However, WD in particular seems to be capable of producing an anxiolytic effect, especially if consumption happens after a stressful experience. Stress induced by limiting bedding and nesting for rats was ameliorated by a diet rich in fat and sugar. The anxiolytic effects may be due to the rewarding aspect of palatable foods, which, in turn, leads to anxiety-like behaviors upon removal. Stress induced by removal of the palatable foods can then lead to increased consumption of these foods in an attempt to seek reward. The therapeutic value of foods with high fat and sugar contents is important in humans and reveals an interesting cycle of consumption that involves reward circuitry. For humans consuming WD foods, it is difficult to remove these foods, because repeated consumption has caused a dependence on the rewarding aspects of these foods. This explains human’s tendencies to rebound into old eating behaviors when attempting to entirely remove these palatable foods. Therefore, the relationship between anxiety and WD consumption seems to be biconditional, as one can affect the other. These results indicated by behavioral studies have peaked interest in understanding underlying
mechanisms of this interaction, but it is difficult to pinpoint specific neurochemical changes which might indicate an anxiogenic or anxiolytic effect caused by exposure to WD.

Considering the neurochemical processes examined with changes in behavior, increases in inflammation in the brain, often co-occurring with weight gain or diet-induced obesity due to exposure of WD or HFD, have been consistently positively correlated with anxiety-like behaviors (Wang et al., 2018; Kaur & Kaur, 2017; Noronha et al., 2019; Sivanathan et al., 2015; De Noronha et al., 2017; Capuron et al., 2010; André et al., 2014; Beilharz et al., 2016). Also correlated with anxiety behaviors is increased corticosterone levels with exposure to WD or HFD (Kamara et al., 1998; Sharma et al., 2013; Sharma and Fulton, 2013; Sivanathan et al., 2015; Dutheil et al., 2016; Vega-Torres et al., 2018). These levels may predispose those consuming HFD or WD to have greater stress responses when presented with a stressor, which could eventually lead to anxiety. Changes in corticosterone indicate an effect of WD and HFD consumption on the HPA axis, a regulator of stress responses. Modulation of the HPA axis is rationale for increased stress responses to removal of HFD or WD foods, and it explains increased stress responses due to outside stressors such as the ASR or limited bedding. Feeding behavior is altered by repeated ingestion of high-fat and western diet foods, indicated by insulin and leptin resistance in rats fed HFD and WD. Not only do anxiety-like behaviors occur with these diets, but insulin and leptin resistance encourages continued eating, which contributes to the obesity associated with anxiety-like behaviors and possible dependence on these foods. Additionally, reduced tyrosine hydroxylase and pCREB expression in the amygdala, decreased ΔFosB, and increased brain-derived neurotrophic factor (BDNF) protein levels in the nucleus accumbens indicate a strong relationship between HFD consumption and the reward system. Involvement of the amygdala implies an emotional aspect of consuming HFD foods, what might
be considered comfort foods, which explains the anxiolytic effect with consumption and anxiogenic effect with removal. Additionally, the role of the nucleus accumbens in reward circuitry indicates a robust effect of HFD consumption on the reward system. While neurotransmitter and protein expression in specific brain areas helps clarify the direct effects of HFD and WD on the brain, there is still speculation surrounding the corresponding behaviors.

One of the more prominent questions concerning past research is whether obesity or weight gain must be induced to see effects of WD or HFD on anxiety. While many studies indicated weight gain as a result of these diets along with increased anxiety behavior, it is not definite whether these behaviors would exist without the obesity. However, it is reasonable to believe that this question would not matter, as any diet with sufficient fat and/or sugar content to induce anxiety-like behaviors would inevitably cause an increase in body weight. While weight gain seems to be an important aspect of increased anxiety symptoms, this should not insist that the consumption of WD or HFD without gaining body weight will not yield the same effects on anxiety.

Although general conclusions such as the ones above can be applied to both HFD and WD research, there are some distinctions between WD and HFD that are worth noting. For instance, consumption of WD seems to be more interactive with reward circuitry as compared to HFD. The high fat and sugar contents in WD comfort foods are potentially more rewarding, leading to desensitization to healthier, less palatable foods. This observation is interesting, because it indicates that cravings and signals from the body about what to eat cannot always be trusted, as a dysregulation in reward circuitry can influence cravings so that foods are craved which are not needed. Additionally, compared to HFD, WD seems to require more outside stress to induce an anxiety-like state, especially due to the anxiolytic effects of comfort foods. While
studies on both HFD and WD showed the affect of diet on elevated baseline levels of stress, which yielded greater stress responses to stressors, WD often elicited an anxiolytic effect until actively inducing a stress response. Contrarily, HFD studies showed that anxiogenic effects could occur in absence of a stressor. These differences show that the reward circuitry may interact with the stress response, where change in reward circuitry, such as from WD consumption, may be harmless until exposure to a stressor. Also due to the perceived anxiolytic effects of the WD, it seems that the WD must induce obesity in order to yield anxiety-like behaviors, while HFD does not necessarily need to induce obesity to affect anxiety.

Regardless of whether WD or HFD need to induce obesity, it might be more important to consider the duration of feeding of these diets rather than associated weight gain. There is much disagreement in the psychology community on how long exposure to WD or HFD is necessary in order to show increases in anxiety, as some studies show symptoms as early as two weeks (Beilharz et al., 2016). Another factor that may contribute to the short duration of feeding, however, is the macronutrient composition of the diet, another aspect of controversy across studies. It is difficult to compare multiple studies on WD or HFD because of the variability in dietary composition. A study that observes anxiety-like behaviors after short-term exposure to a HFD may utilize a diet that contains high caloric fat content. It is difficult to compare this to a study utilizing a diet lower in fat content which might yield anxiety-like behaviors after a different duration of consumption. The variability in caloric fat content and duration of feeding blurs the understanding of the interaction between HFD and anxiety.

Variability in human diets and foods also makes it difficult to apply previous research to humans. While studies show obesity as a contributor to anxiety-like symptoms, it is difficult to know how HFD or WD influences anxiety-symptoms independent from obesity in humans. Also,
rat studies utilize a consistent HFD or WD, where the rats are eating the same foods every day. Humans rarely eat the same foods or the same macronutrient content every day, thus the effects observed in rats eating the same foods everyday cannot be directly applied to humans. It is possible that the timeline of occurrence of anxiety-like behaviors as a result of HFD or WD consumption may be different than the timeline of humans. The reward system may not be impacted to the same extent in humans, as the daily variation in foods might defend against dependence on certain foods. Additionally, human reward systems are dependent on outside factors besides food, whereas rats have less influences on reward circuitry.

Ultimately, further research on the topic of diet and anxiety is needed, especially in order to be useful to humans. While previous research has set the tone for an intricate relationship between consumption of high-fat and western diet foods, further studies could look at specific foods that could induce anxiety. Moreover, studies on anti-inflammatory foods could be used to expand knowledge of the effects of food on anxiety, as inflammation has been an observable change in consumption of HFD and WD. While it is difficult to assign these diets to humans to determine their effects, researchers could utilize human participants who already have HFD or WD eating habits. Previous studies using obese participants show effects on anxiety which are related to weight gain, but this leaves the effect of HFD or WD on humans independent from obesity questionable. Also, this suggests a need to understand the relationship between caloric intake and anxiety, as anxiety symptoms could be due to high caloric intake, not just the fat and sugar contents of calories consumed. Future research can provide a better framework for the way diet and anxiety influence each other so that healthier living can be achieved.
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