The Impact of Sugar Consumption on Stress Driven, Emotional and Addictive Behaviors.

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Highlights

- A diet high in sugars has been linked to cognitive impairments, negative neuroplasticity and emotional disorders such as anxiety and depression.
- Sugar consumption increases the impulsivity to feed.
- Sugar overconsumption leads to changes in neurobiological brain function which alter emotional states and subsequent behaviours.
- Addiction, stress, fear, anxiety and depression involve overlapping neural mechanisms.

Abstract: In 2016 the World Health Organization reported 39% of the world’s adult population (over 18 y) was overweight, with western countries such as Australia and the United States of America at 64.5% and 67.9% respectively. Overconsumption of high fat/sugar containing food and beverages contribute to the development of obesity. Neural plasticity that occurs as a result of long term sugar consumption has been shown to reduce impulse control and therefore lower the ability to resist the high fat/sugar foods contributing to the obesity epidemic. There is significant overlap between the neural pathways involved
in emotions that guide behavioural responses to survival situations with those regulating overconsumption of highly palatable food. This suggests that having a clearer understanding of the role of stress and emotions in the development of obesity will lead to the development of novel therapeutic strategies. Sucrose consumption activates the mesocorticolimbic system in a manner synonymous with substances of abuse. There is overwhelming evidence to support the hypothesis that sucrose consumption results in pathophysiological consequences such as morphological neuronal changes, altered emotional processing and modified behaviour in rodent and human models. In this comprehensive review, we examined >300 studies investigating the interaction between sugar consumption, stress and emotions. Preclinical and clinical trials investigating highly palatable foods and stress, anxiety, depression and fear are reviewed. Importantly, the synergy between sugar consumption and neurobiology is addressed. This review summarizes the neurochemical changes and neural adaptations – including changes in the dopaminergic system – that influence emotion and behaviour following sugar consumption.

Keywords: sucrose consumption; stress; anxiety; depression; fear; obesity; addiction; emotion; behaviour

1. Introduction

A sedentary lifestyle combined with a high caloric diet plays a significant role in obesity. In 2016 the World Health Organization reported more than 1.9 billion adults were overweight. World obesity has essentially tripled since 1975. Excessive sugar consumption has been shown to be one of the leading contributors to weight gain. Furthermore, a diet high in sugars has been linked to cognitive impairments, negative neuroplasticity changes such as hippocampal dysfunction and emotional disorders such as anxiety and depression. High
Sugar intake increases the risk of cancer, oxidative stress, inflammation, and obesity, as well as impacting cognitive function and mental health. For example, a diet higher in refined sugar has been shown to predict a worsening of schizophrenic behaviour over a two year period. Despite the many psychological, physical and neurological burdens of sugar overconsumption and consequent obesity, there are no therapies directed at reducing sugar consumption, and few therapies capable of successfully treating obesity (for review see).

Obesity, arising from overconsumption of rewarding foods such as those with a high sugar content, may result in negative consequences, such as a loss of self-control and subsequent poor decision-making. This loss of control poses a significant challenge for overweight individuals attempting to lose weight. The desire to eat is regulated by brain regions known as feeding centers, located in the arcuate nucleus of the hypothalamus. Importantly, these regions are interconnected with the limbic system and cerebral cortex (specifically the hippocampus and amygdala), which are responsible for the modulation of emotions.

Sugar, artificial sweeteners and obesity

Sugar became embedded in the food chain in the late 1960s and replaced fats to mask bitterness and make food more palatable. In the 1970’s a shift toward increased sugar-sweetened beverages became apparent. Our early ancestors obtained sugar from either fruit, limited by seasons, or honey, protected by bees. In the last half century, sugar consumption has tripled worldwide, partially due to the hidden use of added sugars in processed food. The first artificial sweetener (saccharin) was introduced in 1879 with low production costs during wartime, increasing its popularity. In the 1950s as sugar became readily available, the use of sweeteners shifted to so-called ‘diet products’ with low caloric content.
The development of obesity relies on both the hedonic, sweet taste of food in conjunction with the negative emotional properties of food consumption. \(^{22-24}\) Hedonic reactions to a 10% sucrose solution (and as low as 3.4%) were tested and found to be significantly higher in adolescent rats when compared to adult rats. \(^{25}\)

**Sugar and emotions**

Emotional eating has been shown to stem from the desire to mitigate the effects of stress \(^{26}\) and stress is partially regulated by the hypothalamic-pituitary-adrenal (HPA) axis. Interestingly, activity of the HPA axis has been shown to be reduced through the consumption of sugar containing foods. \(^{27}\) Following consumption, hormones are released to reduce the feelings of stress, which also increase the desire for comfort foods, thus perpetuating emotional eating habits. \(^{27,28}\)

The objective of this review is to summarize research that examines how the consumption of sugar leads to changes in neurobiological brain function that alters emotional states and subsequent behaviours. We will examine findings from studies at the intersection between the consumption of sucrose and changes in the performance of tasks with a stressful or emotional component and review neurobiological and neurochemical mechanisms involved in addiction, stress, fear, anxiety and depression to determine whether there are overlapping neural mechanisms. Lastly, we will determine whether there are novel pharmacotherapeutics and/or interventions that target these brain circuits or neurochemical pathways to improve the current approaches for the treatment of obesity.

2. Common neuronal pathways for sucrose consumption, addiction, emotions and obesity

Addiction is characterized by a difficulty to control habitual behaviour even in the face of negative consequences. \(^{29}\) Early addiction research focused on drugs of abuse such as alcohol, morphine and nicotine. This has since been extended to include gambling, eating and
more recently, sugar consumption. Addiction to substances of abuse relies on the drug binding to specific protein targets which elicits certain physiological and behavioural responses unique to that drug. Psychoactive drugs commonly result in rewarding sensations that lead to repeated use and, depending on genetic susceptibility, environmental factors and subsequent addiction. Stress has long been associated with both the motivation to use rewarding substances and the result of not attaining those substances (for review see). The negative symptoms produced through withdrawal are common to all forms of addictive substances including highly palatable food. These include prolonged sensitization to the substance of choice and associative learning where environmental cues become associated with the pleasure derived from the substance. These associative memories, combined with intense cravings, increase the incidence of relapse even after sustained abstinence. These commonalities may be due to substances of addiction utilizing the same circuitry within the brain’s mesocorticolimbic system (Figure 1).

Food consumption is necessary to regulate homeostatic energy balance. However, humans also consume food for pleasure or comfort. The hedonistic desire for palatable food is considered reward-related and may result in maladaptive or negative neuroplasticity that can override homeostatic regulation and result in overeating behaviours. Reward is delivered through stimuli that produce pleasurable or enjoyable experiences, contrasting with addiction, which involves compulsive and sometimes painful behaviour, yet both share similar neuroadaptive responses and overlapping neuronal pathways. The reward or mesocorticolimbic pathway plays an influential role in what we choose to eat as demonstrated by studies where rats appear willing to endure noxious stimuli such as extreme cold, heat and foot-shock to procure highly palatable foods over standard rat chow.

Figure 1 here.
The reward pathway consists of the prefrontal cortex (PFC), amygdala (AMG), ventral-tegmental area (VTA) and nucleus accumbens (NAc) and in accord with drugs of abuse, is thought to be stimulated by the overconsumption of sugar, thus contributing to the development of obesity. The reward pathway is highly associated with the efflux of dopamine which regulates the motivational state of wanting or craving that substance or behaviour. Once overstimulated, the pathway becomes primed to require that particular stimuli when presented with contextual cues or emotional stress. The VTA induces this sensitization while the NAc modulates its expression through dopaminergic control.

Nucleus accumbens

The NAc consists of two sub regions (core and shell), each containing specific neuronal populations fundamental in processes of motivation, aversion, fear related avoidance, reinforcement learning, pleasure seeking, addiction and behavioural sensitization. To examine motivation and the role played by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in the NAc, intra-NAc infusions of AMPAR antagonists were given to obesity prone and obesity resistant male rats. Compared with controls, findings showed the obesity-prone animals exhibited cue-triggered food seeking and the behaviour was mediated by increased surface expression of AMPA receptors in the core of the NAc. This data suggests cue-triggered food seeking may elicit greater motivational feedback in individuals prone to obesity, and thus play a role in driving the compulsive over-consumption of food. Similarly, consumption of a 10% sucrose solution resulted in alterations in synaptic strength via AMPA receptor trafficking, which modulates the compulsive tendencies characteristic of any drug-seeking.

Drug induced neuroplasticity has been observed in the NAc through alterations in dendritic morphology and altered gene expression. Similar to psychoactive
substances, sugar binging has been shown to cause repeated increases in dopamine release and altered expression of NAc Delta FosB as demonstrated in rats with an increase in Delta Fos B expression after consumption of a high sugar diet. Dopamine release increases as a direct effect of chronic drug use and results in postsynaptic changes of Delta FosB and CREB accumulation. The intracellular build-up of Delta FosB can alter the gene production of receptors which may result in reinstatement during withdrawal. This data suggest that neuroadaptations in the brain reward pathway in obese subjects may contribute to the progression of compulsive eating. The NAc is considered to be the main region to undergo neuroadaptation after sugar consumption, but changes have been noted in many brain regions encompassing the mesocorticolimbic system.

**Amygdala**

The AMG plays a key role in negative reinforcement, the progression towards addiction and extensively in the learned associations that lead to relapse. Neuroplastic changes occur in the AMG which facilitate the level of dependence to a substance of abuse to move from impulsivity to compulsion. This was demonstrated by long term sucrose consumption in rats which produced maladaptive alterations in the apical dendritic morphology of AMG principle neurons. Optogenetic stimulation of central AMG neurons was paired with a sucrose reward to test reward incentive in rats. Stimulation increased incentive to choose the sucrose reward over a similar sweet alternative and amplified the degree of effort the rats were willing to exert to obtain the reward. These findings suggest neuroplastic changes in the AMG may occur due to sucrose consumption and increased addictive-like compulsive behaviour. The AMG and PFC share a role in motivation, associative learning (including negative reinforcement), compulsive behaviour and deficits in executive functioning. Relapsing into addictive behaviours is most likely due to dysregulation of motivational...
processes. Negative reinforcement, or substance abuse to alleviate an hedonic, anxious, irritable or dysphoric state, is characteristic of addiction withdrawal.

**Prefrontal cortex**

The orbitofrontal cortex and anterior cingulate are associated with compulsive cravings for drugs of abuse. Interestingly, neurons in the orbitofrontal cortex of rats were shown to encode this same compulsion to seek a sucrose reward solution (15%)\(^1\). The PFC is the brain region responsible for executive functions such as planning and decision making. Addiction and periods of withdrawal from substances of abuse are generally accompanied by a loss of executive function, which is due to dysfunctional neurocircuitry in the medial PFC\(^2\). Sucrose and fructose consumption have also been linked to metabolic and electrophysiological changes in the hippocampus\(^3,\,4\), the thalamus\(^5\) and the hypothalamus\(^24,\,27\); brain regions involved in the associative learning of cues that lead to receiving rewards.

3. **Physiological and neural substrates of sugar consumption**

Feeding centers linked to limbic regions relaying emotional information influence our behaviour towards food\(^12\). The current view of what drives us to eat takes into account the drive to maintain an internal balance between energy expenditure and consumption. However, the influence of external cues that promise immediate reward may negate this balance\(^88,\,89\). Sucrose added to food provides this immediate reward, with the human desire for sucrose or any sweet taste being comparable to the degree of yearning and reward produced by drugs of addiction\(^90\). Sugar or sucrose (table sugar) is a disaccharide composed of the monosaccharides glucose and fructose\(^91,\,92\). Unlike most drugs of addiction (excluding alcohol), sugar does not cross the blood brain barrier to bind to molecular substrates/receptors.
on the cell surface and subsequently alter neural plasticity. Recent research has observed astrocytes, a type of glial cell that helps maintain the blood-brain barrier appear to sense and uptake sugar to regulate neuronal signaling related to appetite\textsuperscript{93}. However, as sugar is a food, ingestion begins in the mouth.

Sugar is initially sensed by heterodimeric G protein-coupled receptors on taste cells located in the mouth and gut\textsuperscript{94}. Once in the small intestine, sucrose is broken down into glucose and fructose; which are metabolized by separate and disparate mechanisms\textsuperscript{92}. Glucose increases the absorption of fructose from the gut, whereas fructose acts as a catalyst for the uptake and storage of glucose by the liver\textsuperscript{95}. Fructose is absorbed into the bloodstream at a slower rate and persists for longer\textsuperscript{96}. As opposed to glucose, fructose is not well absorbed by pancreatic beta cells and therefore stimulates very little insulin secretion\textsuperscript{97}. Insulin increases satiety and subdues the reward value derived from food, suggesting fructose may play a more complex role in the development of obesity than glucose consumption\textsuperscript{98}. In addition to these observed features fructose can increase the rate of carbohydrate oxidation after a meal, also decreasing satiety levels\textsuperscript{95}.

Glucose and fructose have the ability to cross the blood-brain-barrier. However, as the gut and liver rapidly break down fructose, the blood concentration levels are generally low, resulting in only small amounts available to cross the barrier\textsuperscript{99}. Once across the barrier glucose signaling mechanisms are activated. As demonstrated in animal studies\textsuperscript{100, 101}, emerging arguments suggest fructose is produced from glucose in the brain via the polyol pathway (glucose → aldose reductase → sorbitol → sorbitol dehydrogenase → fructose), driven by hyperglycemia\textsuperscript{102}. Glucose consumption increases functional connectivity between the hypothalamus, thalamus and striatum where fructose does not affect striatal connectivity\textsuperscript{103}. Regional cerebral blood flow patterns also differ post ingestion of these monosaccharides, with reduced flow in appetite and reward regions of the brain after glucose
consumption inclusive of the hypothalamus, thalamus, insula, anterior cingulate, and striatum. Alternate to this, fructose reduces flow in the thalamus, hippocampus, posterior cingulate cortex, fusiform, and visual cortex. These differences may assist in clarifying the role of sucrose consumption in obesity and diabetes mellitus. Both human and rat studies have shown that fructose and not glucose consumption results in conditions such as metabolic syndrome and contributes to obesity.

On the neuroanatomical level, regulation of energy homeostasis is dependent on the hypothalamus, however, the NAc, part of the reward-pathway, is pivotal in the pathophysiology of sugar consumption. Table 1 depicts the findings of several studies examining the effect of sugar consumption on brain regions involved in the reward pathway, defining the molecular mechanisms resultant of the neural adaptations and the subsequent behavioural changes demonstrated by the animals.

To determine separation of neural networks engaged in choosing to eat based on palatability or nutritional status, striatal dopamine levels were measured in sugar consuming mice. Only when the sweet solution contained energy was the dorsal striatum, basal ganglia descending pathway recruited. Energy content drives the release of dopamine in the NAc, however, sweetness modulated this efflux, inhibiting dopamine release as palatability decreased. Alternatively, suppression of the sweeteners nutritional value inhibited dopamine release in the dorsal striatum, demonstrating recruitment of different circuitry when separating energy requirements from pleasurable taste.

Table 1 here

3.1 The effect of sugar on the neurobiology of food consumption

The hedonic value of food, the reward associated with its consumption and the learned external cues which trigger the desire to feed are modulated via bidirectional circuitry
between the reward pathway, hippocampus and orexigenic cells (which induce appetite and stimulate food intake) in the lateral hypothalamus \(^{120-122}\) (see Figure 2) and for a comprehensive review see \(^{52}\). Studies activating the lateral hypothalamus show glutamatergic inhibition of feeding \(^{123}\) and GABAergic stimulation of feeding \(^{124}\). Furthermore, a subset of these GABAergic neurons project from the VTA to the hypothalamus and express galanin (a neuropeptide) which enhances motivation for sucrose consumption \(^{125,126}\).

Lateral hypothalamic orexin neurons gain input regarding food intake from the arcuate nucleus of the hypothalamus via endogenous melanocortin receptor antagonists; neuropeptide Y (NPY) and agouti-related peptide-expressing neurons (AgRP). Further, metabolic homeostasis is sensed by the lateral hypothalamus through surrounding glucose, ghrelin and leptin levels, and this drives food seeking behaviours \(^{127}\).

Hypothalamic orexigenic and anorexigenic pathways are regulated by NPY/AgRP and POMC/CART peptides and are affected in different ways by the consumption of sugar \(^{52}\). The orexigenic pathway is influenced by two specific neuronal populations within the arcuate nucleus, the first population expresses NPY and AgRP and stimulates food intake \(^{106,127}\). Variations in both NPY and AgRP were associated with rats consuming more chow after being provided with a 30% sucrose solution \(^{128}\). Reduced expression of these peptides was noticed following sucrose consumption, which then increased thirty to sixty minutes later, prior to feeding \(^{128}\).

Figure 2 here.

The link between p53 (a gene encoding a protein involved in regulating the cell cycle) in AgRP neurons (which regulate ghrelin-induced appetite) and obesity, has been demonstrated in mice, with its overexpression resulting in excessive weight loss \(^{129}\). Under normal
circumstances, a lack of available nutrients drives AgRP neurons to initiate feeding behaviour. In mice, it has been shown that the desire to feed does necessarily involve AgRP neuronal activation when the food has been enriched with sugar and fat. In this case dopamine signaling initiates the desire to eat and feeding behaviour becomes driven by reward, through the neural circuits involved in emotion, as opposed to the orexigenic pathway induced by metabolic need. This appears to be the case when eating for comfort.

Further examinations directly link sucrose consumption with the orexigenic pathway. In two separate studies sucrose intake was found to be increased following NPY infusion into the lateral ventricle or AgRP administration into the NAc shell. The effects of AgRP administration into the NAc shell is, however, halted by pre-treatment of α-flupenthixol, a non-selective dopamine receptor antagonist. Furthermore, chemogenetic and optogenetic manipulation of AgRP neurons activity modulates the emotional valence of feeding. Specifically, arcuate nucleus AgRP neurons were shown to regulate the emotional aspects of feeding involved with anxiety, fear-like behaviour and aggression.

The second, or anorexigenic pathway contains proopiomelanocortin (POMC), a precursor to melanocortin receptor agonist α-MS, and cocaine- and amphetamine-regulated transcript (CART). This pathway is used to inhibit the consumption of food. Disruption of the genes encoding POMC, CART or the melanocortin-4 receptor may lead to obesity. Mice fed a high fat diet and then provided with sucrose-sweetened water showed a down-regulation of POMC mRNA expression in the hypothalamus. Prolonged limited access to sucrose lead to decreased activity of the anorexigenic oxytocin system (associated with satiety and termination of feeding), in the hypothalamus of rats. Together, these findings suggest sugar plays a role in limiting the activation of this pathway, thus increasing the desire to feed.
Neural pathways connecting feeding centres of the brain to the limbic system have been identified through optogenetic activation of melanin-concentrating hormone neurons during the intake of an artificial sweetener (sucralose)\textsuperscript{140}. Sucralose was found to increase striatal dopamine levels which transposed the preference to sugar normally shown by mice into a preference for the sweetener\textsuperscript{140}. Further to this, Domingos and colleagues showed that melanin-concentrating hormone neurons projecting to reward areas are necessary for the rewarding effects of sucrose\textsuperscript{140}.

Furthermore, the serotonergic system is indicated in the regulation of hedonic feeding, with increases of serotonin causing decreased food intake and decreased serotonin increasing motivation to feed\textsuperscript{141}. The suggested mechanism of action for serotonin in feeding behaviour is via AgRP and POMC neurons in the arcuate nucleus\textsuperscript{142}. The serotonin transporter-linked polymorphic region (5-HTTLPR) regulates vulnerability to stress, which is increased in cases of pathological fear, and influences energy intake, suggesting its role on stress related overeating\textsuperscript{143}. Neural adaptations resulting from sugar dependence in rodents include alterations in dopamine and opioid receptor binding in the mesolimbic cortex, changed expression of encephalin mRNA and modified NAc release of dopamine and acetylcholine\textsuperscript{115}.

**Leptin and Ghrelin**

There are several alternate neuronal populations, pathways and brain nuclei which drive overeating behaviour and sucrose consumption. Along with hypothalamic orexin neurons, MCH producing neurons and leptin-receptor cells projecting from the lateral hypothalamus to the VTA also influence hedonic feeding and reward seeking behaviour\textsuperscript{126}. High fructose intake results in lower insulin levels, decreased levels of leptin and increased concentrations of ghrelin when compared to meals high in glucose\textsuperscript{96}. Alteration to levels of these satiety hormones (which result in the feeling of ‘fullness’ following food consumption) may be a precursor to overeating. These results concur with those found after
intracerebroventricular injection of concentrated fructose or glucose into the hypothalamus of rats exposed to 2-deoxy-Dglucose (2DG)\textsuperscript{144}. DG is an analogue of glucose that cannot be metabolized and is known to cause increased food intake in rats by interfering with the process of glycolysis\textsuperscript{145}. Rats provided with fructose injections showed enhanced food intake both in the presence and absence of 2DG, where glucose suppressed 2DG induced food intake suggesting a role for brain glucoreceptors in the control of food consumption\textsuperscript{144}. Glucoreceptors monitor blood glucose levels and are located within the hypothalamus. They have been shown to be stimulated by low blood sugar levels to increase feeding behaviour\textsuperscript{146}.

Dopaminergic neurons projecting from the VTA to the NAc are inhibited by leptin and insulin and stimulated by ghrelin\textsuperscript{147}. Overconsumption of sugar has been shown to increase dopamine D1 receptor binding in the NAc core and shell, decrease dopamine D2 binding in the dorsal striatum and increase binding to dopamine transporters in the midbrain\textsuperscript{148, 149}. Increases in dopamine delays the release of acetylcholine during feeding, which postpones satiety and paves the way for overconsumption\textsuperscript{150}. Alternatively, opioid receptor binding (mu-1) was increased in the NAc shell, hippocampus, locus coeruleus and cingulate cortex after rats were permitted intermittent binging on a 25% glucose solution\textsuperscript{148}. Together these findings suggest the overconsumption of sugar may sensitize dopamine D1 and opioid mu-1 receptors in a similar manner to drugs of dependence. Table 2 depicts studies examining the effect of sugar consumption on brain regions, molecular mechanisms and behavioural changes involved in the orexigenic pathway.

Table 2 here
3.2 Compulsive sucrose seeking

Since the 1980’s it has been known that neurons from the lateral hypothalamus encode reward-associated cues and both feeding and drinking behaviour. In 2015 an attempt was made to define the neural circuits specific to compulsive sucrose seeking. Photoinhibition was employed to show a selective pathway from the lateral hypothalamus to the VTA reduced compulsive sucrose-seeking in mice without affecting normal feeding behaviour. The study found a bidirectional circuit of both inhibitory and excitatory projections from the lateral hypothalamus to dopaminergic and GABAergic neurons in the VTA. It is possible that this circuit increases the focus and intensity of sucrose motivation, highlighting it as a potential therapeutic target for the compulsive overeating of sugar.

As obesity occurs due to excess caloric intake, the incentive value of the food consumed must be considered in parallel to the satiation of hunger. 5-hydroxytryptamine 2C receptors (5-HT2CRs) play a role in incentive motivation via hypothalamic-VTA feeding circuits and have therefore been considered a target for obesity treatments. Lorcaserin, a 5-HT2CR agonist was administered to mice and shown to reduce both standard food intake and the desire for chocolate pellets with a corresponding increase in c-fos expression in VTA 5-HT2CR GABAergic neurons (not dopaminergic neurons), validating their role in the inhibition of motivational behaviour. Similar findings arose from observations of sucrose drinking where leptin administered to the VTA was found to reduce food intake and knockdown of the leptin receptors increased sucrose seeking. Interestingly, mediation of the orexigenic pathway between the VTA and NAc may affect behavioural changes towards reward seeking for drugs of abuse, including withdrawal and relapse behaviour.

Decreased dopamine levels and simultaneous increased acetylcholine levels are associated with behavioural signs of withdrawal from drugs of abuse. Rats provided intermittent sugar access show similar imbalances to initiate withdrawal after provision of the
opioid receptor antagonist naloxone\textsuperscript{164}. An animal will crave a substance of abuse it has been deprived, as shown by elevated operant responding even when unrewarded and increased responding to associated drug cues \textsuperscript{165, 166}. Rats deprived of sugar after glucose overconsumption (i.e. permitted 25\% glucose for 30 min per day for 28 days and glucose access in their home cages for an additional 11.5 h per day) responded significantly more in operant chambers compared to controls suggesting that sensitization of the dopaminergic system and associative learning leads to increased motivation to seek sugar \textsuperscript{167}. The neural adaptations required to cause the behavioural change appear long lasting as sugar consumption ceased 2 weeks prior to testing. Similar results were shown in rat studies of alcohol consumption \textsuperscript{168}.

3.3 Sucrose consumption and the hypothalamic-pituitary-adrenal axis

Long term stress, depending on its severity, appears to correlate with a preference for high sugar foods, suggesting its contribution to the progression of obesity. Chronic stress may develop through an accumulation of physical (traumatic), chemical (dietary), physiologic (painful), psychologic (fear) or social (lifestyle) stressors \textsuperscript{169}. Extended periods of stress result in hyper activation of the hypothalamic-pituitary-adrenal (HPA) axis, a mammalian stress response system involving the endocrine and central nervous systems \textsuperscript{170}. Hyper activation of the HPA axis leads to increased release of corticosteroids (steroid hormones produced in the adrenal cortex) see figure 3 \textsuperscript{170, 171}.

Activation of the HPA axis leads to increased adrenocorticotropic hormone (ACTH) levels and increased glucocorticoids, which affect the utilization of energy stores \textsuperscript{15}. This is of particular importance, as people regularly report choosing to consume sweet tasting food (of higher caloric content) due to its ability to enhance their mood and relieve negative emotional states \textsuperscript{170}. In an observation of rats undergoing acute stress, the provision of a sucrose solution significantly reduced levels of both ACTH and corticosterone secretion \textsuperscript{15}. Furthermore, rats
fed with a sweetener (Saccharin), also showed lower HPA axis responses to acute stress suggesting the hedonic nature of sugar may be responsible for the reduced stress response $^{15}$.

Contrastingly, a study involving nineteen women found consumption of sucrose but not the sweetener (Aspartame) resulted in reduced reduced stress-induced cortisol $^{172}$. Sucrose and not Aspartame also produced greater activity in the left hippocampus $^{172}$ suggesting the HPA negative feedback loop may assist in generating a tendency towards sugar consumption in people dealing with stress. The following section reviews the complex relationship between the HPA axis, food intake, energy stores and chronic stress.

Figure 3 here.

Any discerned acute stressor may cause engagement of the HPA axis and result in an emotional response eliciting fear, anxiety or defensive behaviours designed to maximize chances of survival $^{15}$. The relationship between stress, cortisol levels and sugar consumption is far from understood, however, it appears that high sugar diets play a significant role in HPA axis regulation and binge-like eating associated with stress. When ingested, foods high in sugar release neuropeptides, elevating mood and reinforcing desire or selective preference towards greater amounts of high caloric food $^{27}$. Sucrose and the sweetener saccharin have been shown to dampen the HPA axis response and this effect is possibly why highly palatable foods are consumed to assuage unpleasant emotions $^{27}$. Sugar consumption regulates stress-like behaviour via the HPA axis however, the precise mechanisms of action are yet to be elucidated.

Contrarily, examples of chronic stress reveal elevated levels of glucocorticoids with increased risk of developing stress related illnesses such as depression. Long term stress appears to alter brain function through changes in negative feedback loops from energy stores
and glucocorticoid modulation of neural circuits (for review see \textsuperscript{173}). As glucocorticoid levels are tightly controlled by the HPA axis, one avenue of investigation has been to examine levels of mRNA expression of 11\(\beta\)HSD-1 (a mediator of glucocorticoid metabolism in the liver) in cases of early life stress\textsuperscript{174}. Interested in the role of sugar intake on lipid homeostasis, researchers found a 53\% increase in transcriptional levels of 11\(\beta\)HSD-1 in animals permitted chronic sugar (25\% sucrose solution) consumption in contrast to controls revealing a correlation between sucrose consumption, stress and increased glucocorticoid metabolism\textsuperscript{174}. Additionally, when humans are exposed to stress at a young age, they become more likely to develop anxiety and depression associated with dysregulation of the HPA axis\textsuperscript{175}. Increased levels of cortisol (the resultant product of the HPA axis in humans) have also been positively correlated with higher visceral fat deposits and insulin resistance\textsuperscript{176}. Similarly high cortisol levels (22\% higher) were reported in overweight/obese adolescents after 2 or more sugar-sweetened beverages per day, suggesting significant increases in stress hormone were not only due to visceral fat deposits but also increased sugar consumption\textsuperscript{177}. One suggested mechanism may include morphological alteration of the adrenal glands as shown through consumption of high sugar content beverages which increased the risk of metabolic syndromes such as diabetes and lead to dysfunction of the adrenal glands\textsuperscript{178}. Young adult rats fed a 30\% sucrose solution for 12 weeks showed increased visceral fat deposits and insulin resistance\textsuperscript{178}. Interestingly, the adrenal glands showed histomorphological changes in the adrenal cortex and medulla due to sucrose consumption, suggesting hyperplasia and indicators of metabolic syndrome\textsuperscript{178}.

3.4 Developmental neuroadaptation

In rodents prenatal stress can decrease glucocorticoid and mineralocorticoid receptor levels in the hippocampus thus decreasing receptor availability for the feedback inhibition of corticosterone, which may explain why novel stressors cause an increased and longer lasting
corticosterone response \(^{179}\). Pregnant rats underwent restraint stress during the third week of gestation\(^{179}\). The HPA axis and hippocampal corticosteroid receptors in the male offspring were investigated. Plasma corticosterone was found to be significantly higher in the prenatally-stressed rats compared to controls and the receptor subtypes (hippocampal type I and type II corticosteroid receptors) were decreased in the hippocampus suggesting long term changes in the HPA axis may occur following prenatal stress\(^{179}\). Numerous studies have examined maternal stress and corticosteroids, for a comprehensive review see \(^{180}\). Fewer studies involve these neuroadaptations and diet, therefore more direct investigation of high sugar consumption in mothers may be significant in the study of childhood obesity.

Furthermore, evidence exists for the pre-programming of HPA axis hyper activation during prenatal periods \(^{180}\). In adolescents deemed to be at higher risk of becoming obese (by evaluating their parent’s body mass index), a higher functional magnetic resonance imaging (fMRI) signal was observed in brain regions associated with reward learning, processing and motivation after the consumption of high sugar milkshakes as compared to high fat milkshakes \(^{181}\). Although fat provides greater energy and therefore contributes to obesity by providing excess calories, sugar is more often associated with modulation of habitual overeating and therefore the addiction-like behaviour associated with obesity \(^{181}\).

Overconsumption during adolescence leads to long-lasting changes in the dopaminergic reward system and may cause stimuli-induced sensitization that is observed in adulthood \(^{182},^{183}\). Stimuli-induced sensitization refers to an increased effect of the stimuli, following repeated exposures eg. repeated exposure to a loud noise may create a sensitization to noise, generating an enhanced response, the same being true for repeated exposures to a drug of abuse. In drug addiction, sensitization causes changes in dopamine transmission and delta FosB expression which contributes to increased craving and relapse \(^{184}\).
Adolescent rats permitted sucrose consumption (5% sucrose solution) for sixteen days were later tested for motivation to seek either saccharin, maltodextrin or cocaine. The adult rats showed a reduction in motivation to procure saccharin and maltodextrin, however this was not the case for cocaine. Further to these findings, rats presented with a choice between a saccharin solution and intravenous cocaine demonstrated the reward provided by the sweetness surpassed the desire for cocaine; an intense debate remains as to whether sugar is in fact addictive.

It has been hypothesized the addictive-like behaviours present after long-term sucrose consumption arise from the highly palatable nature of sugar and not the neurochemical effects of sugar itself (for reviews see 90, 150, 189-192). The purpose of this review is not to debate the argument, but to examine the role of sugar in emotional dysfunction.

4. Common neurochemistry underlie consumptive behaviours and emotions

Neuroimaging studies and animal models investigating the mechanisms involved in the progression to obesity have revealed neurobiological correlates participating in the neuroadaptations of obesity and sugar consumption. Preclinical rodent models of consumption are useful for investigating neural regions and pathways underlying consumptive behaviours with intermittent access to sucrose shown to have an effect on opioid, cholinergic and, importantly, dopaminergic receptors. 53, 115, 164, 196.

4.1 Opioids

Opioid receptors are expressed throughout the limbic system and play key roles in the regulation of fear, happiness, anger, arousal, motivation and reward related feeding. Opioid-induced behaviour includes the modulation of pain, drug addiction and control of the autonomic nervous system, which includes emotions, cognitive processes and stress coping.
Opioids influence the way we process rewards through interaction with the dopamine system. The way an animal behaves towards food is also modulated by endogenous opioid neurotransmitters, which are neural substrates that create susceptibility to reward. Alterations in hedonic processing are demonstrated to be highly dependent on endogenous opioid receptors in the NAc suggesting these changes may result in the development of reward-related disorders such as obesity.

Opioid peptides (β-endorphin, enkephalins, and dynorphins), and activation of their receptor types, μ (mu), δ (delta) and κ (kappa) in the NAc cause inhibition at both pre and post synapses. Opioid agonists modulate pleasure, reward and reinforcement through activation of mu and delta receptor ligands via the mesolimbic dopamine system whereas the dysphoria associated with withdrawal relies on kappa receptors. Mu receptor binding in the NAc is significantly increased after cocaine, morphine and sucrose.

In the endeavor to define specific peptide and receptor involvement in the motivation and reward seeking behaviour characteristic of hedonistic feeding, several animal studies have combined opioid antagonists and agonists with sucrose consumption. Opioid receptor antagonists (naltrexone and naloxone), used to treat drug and alcohol dependence, were shown to use kappa and mu2 binding sites to inhibit sucrose intake, thus demonstrating the role of endogenous opioids in regulation of hedonic rewards in rats.

Substance P and the NK1 receptor system, interact with opioid receptor systems to regulate reward related behaviours, suggesting its role in addictive behaviour. Substance P is also a neuropeptide that affects the orexigenic pathway, via the NK1 receptor. Its presence in the brain assists the regulation of feeding, however, it is also located in the stomach and small intestine suggesting it may be a potential therapeutic target for obesity. Administration of a substance P antagonist (CJ 012,255) was shown to prevent weight gain in obese mice following a 2w high fat diet while treatment with CJ 012,255 in obese mice
resulted in a loss of weight loss and reduction improved insulin sensitivity, partially due to reduced food intake\textsuperscript{212}.

Using a two-bottle choice drinking paradigm, knockout mouse models (lacking either one or two opioid peptides) were used to identify opioid receptor ligands modulating sucrose preference\textsuperscript{208}. Enkephalin and dynorphin were found to modulate preference to sucrose but were not considered necessary for its consumption, supporting the role these peptides play in the motivation to consume unnecessary calories\textsuperscript{208}. A decrease in enkephalin mRNA expression was observed in the NAc after rats were provided with intermittent access to sugar\textsuperscript{111}. The link between opioids, dopamine and motivation for hedonic rewards is further reinforced with data showing rats preference for sweet taste after the introduction of morphine to the NAc\textsuperscript{213, 214}.

4.2 Acetylcholine

Neuronal nicotinic acetylcholine receptors (nAChRs) act as biological targets for ethanol, nicotine\textsuperscript{215} and sucrose\textsuperscript{53, 216} and modulate the neurotransmission of GABA, glutamate, dopamine, serotonin, acetylcholine and noradrenaline\textsuperscript{217}. Homeostatic dysregulation of acetylcholine in the limbic system has been shown to modulate the motivation and reward seeking behaviours characteristic of addiction and relapse\textsuperscript{218-220}, neurodegeneration (Alzheimer’s disease, mild cognitive impairment) and mental illness (anxiety, depression and schizophrenia)\textsuperscript{217, 221}. Within the NAc, cholinergic interneurons regulate the expression and release of enkephalin\textsuperscript{222} and many rat studies support the theory that they inhibit feeding behaviour\textsuperscript{71, 218, 223}. As increased serotonin reduces the motivation to feed, a study using rats to perform a progressive ratio task and paroxetine (a selective serotonin reuptake inhibitor) found that increased serotonergic activity decreased the appetitive-based responses to the hedonic taste of sucrose and the aversive taste of quinine\textsuperscript{116}. Withdrawal from morphine increases acetylcholine levels in the NAc, while
dopamine simultaneously remains low, leading to the assertion that this mechanism is involved in the unpleasant aspects associated with withdrawal. Arecholine (a muscarinic agonist) inhibits feeding but can be blocked by pirenzapine (a muscarinic acetylcholine 1 receptor antagonist), suggesting a role for acetylcholine in food intake.

In 2010, Lof and associates utilized rats to demonstrate the role of nAChRs in the conditioned reinforcement of lever pressing for a sucrose reward. Using a selective antagonist at α7 nAChRs (methyllycaconitine) they showed reduced lever pressing for the sucrose solution down to the level of the control, suggesting mediation of the amount of influence the cue had on the desirability of the sucrose. More recently our laboratory elucidated the effects of varenicline (an FDA-approved drug to reduce nicotine cravings) on sucrose consumption in rats. Varenicline, a partial agonist at α4β2* and antagonist α6β2* nAChRs subtypes, significantly reduced sucrose consumption in both short and long term binge like (intermittent access) drinking. While α4β2* nAChR binding sites were increased, α6β2* nAChRs were significantly decreased in the NAc as a result of both short-term and long-term sucrose consumption. By modulating dopamine release in the NAc the control of sucrose consumption by nicotinic receptors and their subtypes may provide promising therapeutic strategies for obesity.

4.3 Dopamine

Sucrose is considered a primary or natural reinforcer that does not require a learning process to be considered desirable. Primary reinforcers are known to trigger dopaminergic activation in the VTA, which act on the NAc via the medial forebrain bundles. Activation of dopaminergic neurons in the VTA modulates processes of memory, learning and motivation as well as the intense emotions associated with love, sexual desire, orgasm, fear, stress, anxiety and psychosis. Rat models of obesity display low levels of dopamine and impairment in the release of dopamine.
The mesocorticolimbic dopaminergic system has been implicated in modulation of addictive reward seeking behaviour, (for review see 240). Drugs of abuse such as alcohol, nicotine, cocaine and amphetamines that cause increased extracellular dopamine and subsequent heightened pleasure levels in humans 241, 242 also cause increases in dopamine release in the NAc in rats 152, 243. Commonly abused (opiates, ethanol, cocaine, amphetamine and nicotine) given to rats resulted in increased extracellular dopamine in the NAc and the dorsal caudate nucleus 243. Similar results were found in rats permitted intermittent access to sugar with subsequent binge drinking resulting in increased dopamine release in the NAc 71, 244.

Supporting both the hedonic potency of sucrose and its reliance on dopaminergic regulation, orosensory stimulation in sucrose sham-fed rats resulted in increased dopamine release within the NAc, thus increasing reward seeking behaviour 245, 246. Compelling evidence shows drugs not routinely abused, such as imipramine, atropine and diphenhydramine do not display rewarding properties and do not alter synaptic dopamine levels 243. Studies show an attenuated dopamine system in obesity prone rats in the NAc, PFC and dorsal striatum and suggest the reduction in hedonic response available to these animals is related to hyperphagia (increased appetite) and resultant obesity 107. These findings were similar to those of a human study showing reduced levels of dopamine D2 receptors correlated with increased body mass index in 10 obese individuals 247.

4.3.1 Dopamine sensitization

In 1993 Robinson and Berridge postulated the incentive-sensitization theory, which suggested that repeated exposure to rewarding substances sensitizes the dopaminergic system resulting in exaggerated “cue-triggered wanting” which can transform into a compulsion to seek out an associated reward 109, 242. Cue-reward learning depicts the learned association between the rewarding effects of substances of abuse and environmental cues 248, 249. This
learning contributes to obsessive overuse and the tendency to relapse after long periods of abstinence. Repeated or prolonged substance abuse can cause modifications to neurotransmitter release and alterations in synaptic strengths. For example, rats provided with intermittent access to sucrose display signs of dopamine sensitization through altered dopamine receptor function.

Behavioural sensitization or hyper-locomotion is a motor response that increases incrementally with repeated exposures to a drug. It is reflective of a hyposensitized (or attenuated) reward pathway and is said to contribute to the craving or compulsive seeking which characterizes addictive behaviour. In both human and rodent studies, behavioural sensitization has been observed as dose-dependent and shows considerable individual variation. Brain-derived neurotrophic factor (BDNF) is believed to modulate this behaviour through overexpression of the dopamine D3 receptor and has been implicated in drug addiction, schizophrenia and novelty seeking behaviour in obese rats. Animals sensitized to one drug are often cross-sensitized to other substances of abuse as well as non-drug substances. This has been demonstrated with rats exposed to amphetamines becoming sensitized to cocaine, cocaine cross-sensitizing to alcohol and cocaine cross-sensitizing with stress. Similar to these, short term sucrose consumption increases binding affinity to opiates, resulting in cross tolerance to other opioids such as morphine, while chronic sucrose consumption reduces the analgesic properties of morphine. A number of studies have also shown opioid agonists such as morphine to increase the impulsivity to feed when injected systemically or directly into the NAc, paraventricular nucleus, AMG, hypothalamus and tegmentum.

Further investigations have demonstrated how sugar access can lead to cross-sensitization of dopamine-altering drugs. Intermittent access to sugar has been found to cross-sensitize with amphetamines up to 8 days post sugar ingestion. Female rats provided with
either a 10% sucrose solution or a rotation of sucrose solution and withdrawal, displayed behavioural cross-sensitization to a small dose of amphetamine. Similar results for sucrose and cocaine and sucrose and quinpirole (a dopamine agonist) have also been found. The rats maintained on the cyclic sucrose solution responded hyperactively to amphetamine in comparison to controls, suggesting the binge-like sugar consumption leads to increased amphetamine sensitivity, which may be due to neuroadaptations of the dopamine system. Compelling evidence suggests chronic stress leads to similar cross-sensitization. As globally the consumption of sugar is on the rise an interesting avenue of investigation may be to examine the effect of sucrose consumption on stress derived cross sensitization.

4.3.2 Dopamine and impulsivity

Dopamine is released in response to food cues, making it essential for the motivational prompt to consume food. As dopamine neurons project from the VTA to the NAc, caudate, putamen, PFC, hippocampus and AMG, they modulate a wide variety of behaviours and emotions including impulsivity. In relation to eating disorders such as obesity, there appears to be an impulsive tendency to overconsume sweet foods in response to cravings for carbohydrates and sugars. When a subject is withdrawn from an addictive substance, impulsivity increases and can be quantified using a behavioural test called differential-reinforcement-of-low-rate-schedule performance (DRL). The test requires the subject to withhold a response for a set period of time before they are permitted to respond and thereby earn a reward. Deprivation after long term sugar consumption in rats resulted in impairment of DRL performance, confirming its resemblance with drug addiction and suggesting an increase in impulsive behaviour following sugar deprivation. The suggested mechanism of action for this behaviour is the dopaminergic system as dopamine receptor
antagonists (pimozide\textsuperscript{277}, raclopride \textsuperscript{278}, SCH 23390 \textsuperscript{279}) can attenuate the desirability of highly palatable foods in rats\textsuperscript{275,277}.

The progression towards obesity is linked with a decline in neural responses to reward similarly induced by cocaine and heroin, which moderate the transition from casual user to the impulsive actions of a compulsive drug-taker\textsuperscript{280}. Impulsive actions such as over eating are modulated by the excitation of D1 dopaminergic neurons and inhibition of D2 dopaminergic neurons in the dorsal striatum and the NAc \textsuperscript{280}. Preclinical and clinical studies have been conducted to investigate the role of dopamine in obesity with findings showing obese subjects have an inverse relationship between the abundance of dopamine D2Rs and body mass index, suggesting a dopaminergic role in compulsive eating\textsuperscript{247,280-282}. Male rats self-administering amphetamine showed a reduction in the ability of D2Rs to inhibit dopamine release in the NAc supporting the theory that desensitization due to short term substance abuse modulates addiction-related behaviours such as impulsivity \textsuperscript{283-285}. In a human study, twelve patients with Parkinson’s disease, a disorder of the mesolimbic dopamine system, underwent several cognitive tests designed to provide a measure of impulsivity. Increased impulsive behaviour was found to correlate with greater dopamine levels\textsuperscript{285}.

The neural mechanisms modulating motivation and drive are implicated in both the loss of self-control exhibited by over eating and addiction to drugs of abuse \textsuperscript{115,213}. Neurofunctional imaging has documented neuroadaptations in the PFC \textsuperscript{286}, hippocampus\textsuperscript{287}, AMG and NAc \textsuperscript{281}. A functional MRI study was conducted showing female adolescents an image of either highly palatable food (dessert) or a vegetable\textsuperscript{288}. In comparison to leaner adolescents, overweight adolescents had increased behavioural impulsivity and decreased neural activation in frontal inhibitory regions of the brain (e.g. medial prefrontal cortex, and orbitofrontal cortex) \textsuperscript{288}. In addition, activation of the reward region was positively correlated with body mass index when shown the picture of dessert \textsuperscript{288}. These findings suggest the
reduced functioning of inhibitory controls combined with increased responses in food reward regions are relevant to weight gain. The Stroop test requires an individual to suppress their automatic response to certain stimuli. This was used to assess the inhibitory control of overweight/obese 10 y old children in comparison to normal weight children. Results indicated changes to inhibitory control functions in overweight children suggesting less emotional self-regulation, which in conjunction with dysfunctional impulsivity control may contribute to over eating behaviour in the overweight/obese children.

5. Common anatomical structures and neural substrates of stress driven, emotional behaviour

The insular cortex and cingulate cortex (part of the limbic system) are responsible for the processing of emotions in conjunction with processes involving higher cognition. The hippocampus provides negative feedback for the HPA axis with both neuroadaptations to its volume and capacity for neurogenesis implicated in emotional disorders. The AMG processes, stores and retrieves fear memories, and initiates appropriate behavioural responses. It is responsible for the manner in which we express fear, aggression and defensive behaviour. The PFC regulates executive functions and reward processing while impulse control and mood are modulated by the orbitofrontal cortex. Emotional disorders involve a complex interconnected number of neuroendocrine, neuropeptide, neurotransmitter and neuroanatomical adaptations. These alterations may occur due to genetic predisposition or as a result of environmental influence. We assert that abundant evidence exists regarding the role overconsumption of sugar plays in altering these brain regions and contributing to emotional disorders such as depression, anxiety and fear.

5.1 Anxiety
Generalized anxiety disorder is defined by uncontrolled, exaggerated concern over numerous endeavours\(^{294}\). Treatment often consists of anxiolytic drugs that act primarily on the monoamines serotonin, noradrenalin and dopamine\(^{292}\). In the central nervous system these neurotransmitters are released in conjunction with neuropeptides that have strong links to anxiety, such as neuropeptide Y and cholecystokinin expressed in the limbic cortex where they influence emotions and stress levels\(^{292}\). Other molecular substrates involved in regulating the stress response include corticotropin-releasing factor and adrenocorticotropic hormone in the HPA axis\(^{295}\). In cases of anxiety, those carrying the short-allele of the serotonin transporter gene (5-HTTLPR) demonstrate over activation of the AMGs in response to viewing fearful and angry faces as compared to those carrying the long-allele\(^{296}\).

Two specific brain circuits are notable in anxiety disorders, the first involves the dorsolateral PFC, anterior cingulate cortex, dorsal parietal cortex and precentral gyrus, all associated with cognitive control, executive function, flexible cognition, working memory and attention\(^{297}\). The second circuit is known as the negative affect circuit and as the name suggests is activated by negative stimuli\(^{297}\). Anatomically the hippocampus, AMG, medial PFC, and the dorsal, subgenual and pregenual regions of the anterior cingulate cortex may undergo neural adaptation to skew negative bias and threat by reducing attenuation through the cognitive control circuit\(^{297}\).

Human studies show links between high caloric food consumption and anxiety. Recent evidence from epidemiological studies found a suggestive link between greater consumption of processed foods and widespread presence of anxiety disorders\(^{298-300}\). There are also numerous studies linking adverse childhood experiences (early life stress) with an increased risk of body weight gain and obesity during adolescence and adulthood\(^{301-305}\). More specific behavioural studies observing acute and chronic withdrawal from sugar in rodents show anxiety is induced when withdrawal follows extensive periods of sugar consumption\(^{115}\).
Long exposures (1 month of 12 h daily access) to palatable foods did result in rats showing increased anxiety-like behaviours on the elevated plus maze (EPM) when tested 24 h after withdrawal. Rats exposed to 12 h intermittent access to 10% sucrose solution for 28 days also displayed anxious behaviour in the EPM after 36 h withdrawal. These rats showed reduced conditioned suppression after 1 and 28 days of abstinence, measured by a failure to significantly reduce the number of lever-presses for sucrose during the presence of a tone stimulus paired with shock. Similar results have been reported using longer cycling periods whereby rats given intermittent access to a sucrose diet showed increased anxiety in the EPM and defensive withdrawal tests after 8 and 9 weeks on the diet cycle followed by 48 h withdrawal. Alternate investigations have shown rats fed a carbohydrate rich diet to have increased protein oxidation in the frontal cortex which correlated with anxiogenic behaviour. These studies suggest a high probability of long term sugar consumption may contribute to symptoms of anxiety.

A long term study has shown an opposite effect in terms of anxiety and depressive like behaviours. Findings show that sugar consumption had no significant effects on motor activity in an open field (test for locomotor and anxious like behaviour), on exploration in a T-maze, or on anxiety in an EMP. Another study looking at the anxiety effects of sugar after a 1 year intervention of sucrose and honey found that anxiety decreased after 3 months of consumption, as tested with the EPM and open field test. Importantly, this reduction was maintained until the end of the experiment at 12 months. Despite this, honey-fed rats showed significantly less anxiety throughout the study as compared with those fed sucrose. Together this data suggests that chronic (i.e., greater than 1 month) intermittent access to high energy foods may increase anxiety-like behaviour followed by a plateau observed after 3 months.

5.2 Depression
Depression is characterized by feelings of sadness, hopelessness and reduced pleasure in daily activities. Functional, structural and neurochemical factors associated with the pathophysiology of depression include dysregulation of the HPA axis resulting in reductions in hippocampal, PFC and striatal volumes. In areas of emotional processing such as the AMG and PFC abnormal metabolism of glucose and changes to cerebral blood flow have also been demonstrated. Although the association between obesity and depression is well documented, less is known about the physiological and corresponding psychological influence long-term sugar consumption has on depression. Recent research suggests a possible contributor to the incidence rate of depression is sugar overconsumption. We suggest the neuroadaptations that occur to depression-related brain regions, namely the hippocampus, PFC and AMG, following sugar intake (reviewed above) contributes to the incidence of depression.

The first study reporting a possible link between sugar and depression was conducted in 2002 by Westover and Marangell. Data collected data from 6 countries showed a correlation between the consumption of sugar (calories/capita/day) with the yearly rate of major depression disorder. Fast food further increases the potential of developing depression, and commercial baked goods are also positively correlated with depressive disorders. Not only highly palatable food, but sweetened beverages (either artificially or otherwise) also contribute to depression. Regular consumption of sweetened beverages indeed increases the occurrence of depression and suicidal tendencies.

In rats given the same high sugar/chow diet cycle for 7 weeks, highly palatable foods induce depressive-like behaviour as evidenced greater immobility in the Forced Swim Test (test for depression) and decreased preference for 0.8% sucrose (test for anhedonia). Correlations with symptoms of depression have been observed following long-term exposure to sucrose, with long term overstimulation of the dopaminergic system during adolescence,
which may occur through sucrose binging resulting in deficits in later life that affect motivation, memory and happiness. When a model designed to generate a depressed-like state (known as social defeat-induced persistent stress) was used, rats showed increased motivation to acquire a sucrose reward and reinstated sucrose-seeking induced by a cue. Importantly, these studies showed the long-term effects of stress exposure induced deficits in the ability to evaluate natural rewards.

Congenitally helpless rats, a genetic model of predisposition to major depression, were used to respond less to the reward of sucrose solution. This lack of motivation to partake in sweet rewards is conversely shown after long term sucrose consumption by adolescent rats, which results in depressive like behaviour in adulthood including symptoms of anhedonia (inability to feel pleasure) and increased anxiety-like behaviour. Adult rats consuming sucrose showed a similar depressive-like behaviour, but to a lesser degree, suggesting the critical period of brain development that occurs during adolescence can be moderated by sucrose consumption and may increase the instance of disorders related to rewards, such as depression.

As depression correlates with altered glucose metabolism, it is not surprising that comorbidity of diabetes mellitus (DM) and depression occurs quite frequently, greatly increasing the mortality risk. A study highlighting the link between glucose and depression in patients whose histories included DM and cardiac disease found there was a 34% increased chance of depression in subjects with elevated blood glucose levels. A study including 70,000 postmenopausal women found a higher risk of developing depression in women consuming a high-sugar diet than those consuming high naturally occurring sugars. However, research suggests sugar may contribute to depression more in the male population as was demonstrated by the Whitehall Study II which tracked dietary regimes and the corresponding medical health of 8,000 participants over a 22 year period. Observing a
five year duration they found a 23% increase in likelihood of men being diagnosed with depression if they consumed $\geq 67$ g of sugar per day compared to $\leq 40$ g. Cumulatively, these studies, while not able to confirm that sugar causes depression, appear to produce enough evidence to show sugar overconsumption contributes to an increased risk of developing depression.

5.4 Neurogenesis

Neurogenesis is the term given to new neurons generated from neural stem cells. The molecular substrates of stress, although not well understood are implicated in the regulation of adult neurogenesis, through molecular pathways modulated by glucocorticoids, inflammatory mediators and neurotrophic factors. Studies on antipsychotic pharmacology support these findings by linking the blockade of dopamine D2 receptors with reductions in parkinsonian symptoms, anhedonia and increased neurogenesis. The effect of diet on hippocampal neurogenesis has been relatively unexplored.

Rats given 1 month access to fructose showed almost a 40% reduction in the number of BrdU / NeuN-immunopositive cells (mature neurons) in the dentate gyrus of the hippocampus. Alternatively, rats consuming glucose had a similar number of BrdU / NeuN-immunopositive cells as the water controls. Density of immature neurons labelled with PSA-NCAM was decreased following sucrose, fructose and glucose. Sugar consumption increased the number of proliferating cells positive for Ki67 (a marker of cell proliferation) in all cases and rats offered sucrose or fructose showed more cell death in the dentate gyrus of the hippocampus.

Rats given a high fructose corn syrup solution throughout adolescence were tested for hippocampal-dependent contextual memory. Impairments in memory function were found in later in life, suggesting that sugar consumption early in life may have long-term negative
effects on memory function. High fructose consumption is also linked to insulin resistance with reduced hippocampal neurogenesis. Hence it appears convincing that a high-sugar diet negatively affects adult neurogenesis which may contribute to the anxiety and depressive like behaviour demonstrated by animals after withdrawal. Decreased neurogenesis in the hippocampus has further been implicated in memory dysfunction and cognitive impairment disorders such as Alzheimer’s disease and the learning and memory processes involved in appetitive control. The hippocampus may hold further insight into the cognitive processes by which food becomes entwined with motivation and new rewards.

5.3 Fear

The functional neuroanatomy of fear encompasses the AMG, which stimulates the HPA axis and the hippocampus, which suppresses activity of the axis. Hyper activation of the AMG was recorded in response to viewing faces construed as fearful and has been implicated in post-traumatic stress disorder (PTSD). The PFC is required for the extinction of fear memories, and in line with these findings changes in volume of the anterior cingulate cortex have been implicated in a reduced ability to extinguish fearful memories. When fear memories become dysfunctional it is thought that the intrusive, recurring thoughts result from an inability of the cognitive control circuit to repress the negative effect circuit. In patients with PTSD their information processing may be overpowered by the hyper activation of the AMG when exposed to threat related stimuli.

At the molecular level corticotrophin-releasing factor from the paraventricular nucleus of the hypothalamus initially activates the HPA axis in response to threatening stimuli. Low levels of corticosterone, which acts through binding to mineralocorticoid and glucocorticoid receptors, as well as enhanced negative feedback of the HPA axis are associated with pathological fear. Rats that underwent a single prolonged stress paradigm (a reliable animal model of PTSD) have shown a down-regulation of both these receptors in the
hippocampus, enhanced fear and altered neuronal morphology of AMG neurons. Glucocorticoid receptors and dopamine receptors have been implicated in processes within the PFC that drive extinction memory learning. Infusions of corticosterone or a glucocorticoid receptor antagonist (RU38486) into the infralimbic cortex and pretreatment with sulpiride (a dopamine D2 receptor antagonist) attenuated fear expression suggesting enhanced fear extinction. As glucocorticoid receptors are also required for glucose homeostasis and play a role in the development of hyperinsulinemia and obesity they are suspected as key players in neuroadaptations to the AMG, hippocampus and PFC that occur after long-term sucrose consumption.

Juxtaposing the combined psychological and physical effects high sugar diets have on pathological fear has, until recently, been an untouched topic of research. Although no studies have been conducted on sugar consumption alone with regards to pathological fear, some research has begun to explore the combined effect of high-fat/sugar or high sugar and high carbohydrate diets. These studies are beginning to delineate the impact high caloric foods can have on the intensity and duration of pathological fear; however research into the effect of sugar alone is required to delineate the mechanisms involved. More recent research has examined contextual fear following a standard contextual fear conditioning protocol which was contradictory to this finding. Specifically, high-sugar/carbohydrate diets significantly enhance fear-related freezing to context. Whilst both examine contextual fear memory formation, different fear conditioning protocols were used (trace fear conditioning versus contextual fear conditioning). Indeed hippocampal function in contextual fear memory has been noted as disparate, depending on the fear conditioning protocol (see recent review by). Nevertheless, these studies highlight how diet can influence hippocampal-dependent memory, as well as hippocampal function.
Fear extinction is a protocol whereby, following excessive exposure to the previously neutral fear conditioning CS (e.g. the context in contextual fear conditioning, or a tone in auditory fear conditioning), a reduction of fear-related freezing is seen\(^\text{346}\). This reduction in fear is similar to basic theories surrounding exposure therapy, whereby excessive exposure to fear-inducing stimuli (via mental imagery, for example) results in a reduction in fear-related symptoms\(^\text{346, 347}\).

Investigation into the effect of PTSD symptoms on the consumption of highly palatable ‘fast’ food and sweetened beverages was conducted to see if there was a correlation with emotional eating behaviours and body mass index\(^\text{348}\). The answers to questions regarding frequency of consuming fast food were collected from 3154 females and analyzed using regression analyses\(^\text{348}\). To determine unhealthy eating habits, participants were asked if they used diet pills, laxative, diuretics, skipped meals or vomited after eating. Findings suggested that PTSD symptoms increased the frequency of consumption of high caloric food and sodas, as well as contributing to unhealthy eating habits but did not increase overall body mass index\(^\text{348}\). Cumulatively, data from these various studies show a strong link between PTSD, fear memory and caloric foods suggesting a possible correlation with high sugar consumption that requires further investigation.

6. Sucrose Consumption Investigated

Negative states of emotion driven by substances of abuse are often shown by examining anxiety-like behaviours, decreased pain tolerance, or an increase in the point at which reward becomes sufficient to produce a stimulating effect and memory deficits\(^\text{80}\). The complexities of the systems involved, the interconnectedness of the systems and the myriad of protocols used to study sucrose dependence could potentially lead to a wide variety of outcomes and yet overall investigations into high-sugar consumption in rats, mice and humans result in similar outcomes with regards to memory, stress and emotion (see Table 3.)
7. Therapeutics for obesity, derived from studies of sucrose consumption

7.1 Pharmacological approaches

Sucrose is shown to be addictive in rodents and the studies listed in Table 3 show correlations between sucrose consumption and emotional disturbances. The NK1-(Neurokinin-1) receptor system is involved in the reinforcement mechanism that motivates the desire to have stimuli that no longer create pleasure, a characteristic of addiction, and is implicated in both anxiety and depression. Using the intermittent access model with a 5% sucrose solution, our laboratory showed the NK1-receptor antagonist ezlopitant (which possesses anxiolytic effects) was able to attenuate and inhibit sucrose intake in Long Evans rats. This finding suggests the NK1-receptor system to be a potential target for sugar-related obesity therapeutics. Other potential options include antidiabetic drugs such as sodium-glucose cotransporter 2 (SGLT2) inhibitors, which impede renal glucose reabsorption and are generally considered effective, though lose efficacy when taken long term. Indeed, a 4 week oral administration of ipragliflozin, (a SGLT2 inhibitor) with antidiabetic effects on type 2 diabetes, decreases the caloric balance and improves symptoms of diabetes, including obesity in mice fed on 20% glucose or sucrose solution.

A recent review detailing the current management for type 2 diabetes suggested a stepwise approach; including diet and exercise the patient would take metformin (which lowers high blood glucose levels by decreasing the production of hepatic glucose, increasing insulin sensitivity and lowering intestinal glucose absorption), a glucagon-like peptide 1 receptor agonist (to increase insulin output from the pancreas) or a SCLT2 inhibitor in addition to one of the approved weight-loss drugs (to control appetite or the absorption of calories).
Table 4 lists doses and mechanisms of action of therapeutics used in trials to alter sucrose consumption in an effort to discover alternate treatments for diabetes and obesity.

Table 4 here

7.2 Lifestyle Interventions

Diet and exercise are highly recommended approaches to treatment for obesity. A 2007 systematic review and meta-analysis that evaluated lifestyle interventions for patients with impaired glucose tolerance looked at 21 randomized controlled trials designed to delay or prevent the onset of type 2 diabetes. Data revealed evidence in support of interventions such as diet and exercise being at least as effective as oral diabetes drugs, a Chinese herbal remedy (jiangtang bushen) and the anti-obesity drug orlistat. The dilemma with lifestyle interventions is that regain of the weight lost is common after a period of time and often results in weight gain greater than that originally lost. Strategies that proved effective in maintaining weight loss included a consistent regular meal pattern that included breakfast, a high expectation to succeed, a good support system and behavioural self-monitoring. Mindfulness meditation is another intervention studied as a way to regulate emotional eating. A self-reported survey was conducted to examine whether mindfulness practice could alter emotional eating. Surveys conducted before and after the intervention revealed lower emotional eating scores after the meditation, suggesting a possible role for mindfulness as a treatment for emotional eating. Mindfulness studies do not show a direct effect on weight loss itself, but appear to be quite successful in lessening the addictive-like behaviours pursuant to relapse of weight gain.

7.3 Digital technology
Decreasing emotional eating has been proposed as a potential mechanism for the long-term maintenance of weight loss. Digital technology may be our best hope of achieving this goal. Interaction with online environments provide the social support often lacking during maintenance of weight loss. Apps for exercise regimes, food tracking, meditation and positive thinking all provide a support system to the user and promote networking with others in similar situations. Support networks are useful tools as increases in body weight decrease an individual’s ability to make informed decisions regarding highly palatable food, resist temptation and regulate their emotions. These challenges were supported through a study of 17 obese women and their physiological reactions to verbal food cues which found that food and beverage preferences affected physiologic responses as well as cognition and attention.

Wearable technology such as Fitbits (activity trackers), that interact directly with the individual, provide information about the individual and promote long term maintenance and support models of healthcare where the patient takes an active role in their own wellness. Wearable technologies appear to be extremely effective in assisting weight loss in patients with serious mental illness. Thirteen obese individuals diagnosed with a serious mental illness (e.g. schizophrenia and major depressive disorder) participated in 24 weeks of behavioural weight loss intervention encompassing group sessions for weight management and exercise, mobile health technology and social media for motivation, peer support and a self-monitoring tool. At the end of 6 months of interventions, 45% of participants had reduced their weight (below their baseline) and increased fitness (as measured through walking distance).

8. Discussion

The data summarized in this article suggests overconsumption of sugar can lead to brain adaptations involving many different neural systems, molecular substrates and
subsequent changes in behaviour. The ease of availability and cost effectiveness of high caloric, sweetened food and beverages appear to be a contributing factor in the world wide increase in obesity. Paradigms designed to investigate emotional eating show increases in weight gain due to higher caloric intake, nevertheless examination of the correlation between environmental and social inputs, individual thought processes and behaviour that maintains emotional eating is yet to be defined. It seems feasible to suggest the pleasurable sensations brought about through the consumption of sugar may provide a self-medicating method to deal with daily stresses. Common hedonistic mechanisms play a role in both obesity and addiction to drugs of abuse. While the root cause of obesity remains elusive, the estimated global annual healthcare cost of treating illnesses related to obesity may reach US $1.2 trillion per year by 2025.

Every day new digital applications are being developed to assist our pursuit of health and happiness. In the future it may be possible to collect personal information about the consumption of high-sugar foods and beverages in conjunction with emotions felt on a daily basis. The possibilities of personal wellness monitoring, implantable in vivo monitoring and drug delivery devices will also require further robust study before they prove to be effective treatments for obesity and food addiction. It would be interesting to investigate a possible correlation between sugar consumption, emotions and body mass index (BMI > 30 denotes obesity). It would also be significant to know if such applications combining game rewards might assist with the childhood obesity epidemic as current predictions state that globally, 2.7 billion adults will be overweight and/or obese by 2025.

Functional brain imaging studies substantiate the higher preference and increased emotional activation that occurs in response to images and verbal cues related to high sugar content foods and beverages, making it more difficult for overweight individuals to resist eating unhealthy food. Optogenetic and chemogenetic studies may assist in defining
the combination of neural pathways and substrates involved. Other tools designed to unravel
the complexities between neuronal organisation and behaviour include methods to quantify
cellular populations that are functional for particular behaviours. Using analytic methods
(including micro-binning and density mapping) to accurately compare functional neural
network activity it may be possible to produce microanatomical topography of molecular
activity resultant from the influence of long term sugar consumption on a variety of stress and
anxiety related behaviours. This would assist in demonstrating pathophysiological
neuroadaptive changes and perhaps lead to the development of enhanced pharmacotherapeutic and technological strategies to assist the reduction of excess sugar
consumption.

In conclusion, the ease of access to sugar rich diets today is an environmental contributor
to obesity, but it may be sugars ability to generate a superior neurological reward signal
which overrides self-control mechanisms and leads to obesity. Obesity and long term
sugar consumption both result in low basal levels of dopamine, particularly in the NAc,
which may be the mechanism which induces the desire to overeat in the hope to restore
homeostatic dopamine levels and avoid mild depression. Opioids, which induce feeding
through an abundance of brain regions, may be responsible for cue-induced relapse into
overeating behaviours, and binging on sugar postpones the release of acetylcholine required
to signal satiety. Each of these neuroadaptations implicates sucrose consumptions ability to
alter the way we perceive and process our emotions and consequential behaviour. Perhaps a
greater understanding of the neural mechanisms of impulsivity and overeating are required to
assist in the development of improved obesity treatments.

It has been estimated that by 2020, 1.5 million people will die each year by suicide, with
15 to 30 million attempting it. Children suffering anxiety disorders are twice as likely to
attempt suicide, while those suffering major depressive illnesses show a 3 fold chance at
attempt\textsuperscript{387}. In support of these statistics, over 300 million people were reported as suffering depression in 2016/17, with 264 million people reported to be suffering from anxiety disorders\textsuperscript{388}. This review has examined how negative emotion can exacerbate sugar overconsumption, and vice versa. If negative emotions are so prevalent in our children, and sugar intake so common, its consumption may be considered a threat to the emotional stability of our race (see reviews on mental health in children and adolescents\textsuperscript{389-391}). More importantly, reduction of sugar overconsumption may be capable of significantly reducing the prevalence of negative emotion in a vast number of individuals around the world.

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Figure Legends:

Figure 1. Reward pathway encompassing the mesocorticolimbic distribution of dopaminergic neurons. The neural regions of the reward pathway include the prefrontal cortex (PFC), amygdala (AMG), ventral tegmental area (VTA) and nucleus accumbens (NAc). Each anatomical region modulates individual behaviours and contributes to general behaviours through cross-connectivity. Regions shown and behaviours listed are consistent between human and rodent brains. 
Figure 2. Regulation of feeding behaviour and food intake by central and peripheral appetite-regulating hormones and peptides. Hypothalamic orexigenic and anorexigenic pathways and their regulation by NPY/AgRP and POMC/CART peptides, respectively, are depicted in the right-hand side panel. Peripheral appetite-stimulating (green) and –inhibiting (red) hormones and peptides crossing the blood-brain barrier (BBB), and the organs they originate from are also represented. The effect of these hormones/peptides on the stimulation or inhibition of the orexigenic (dashed green arrows) and anorexigenic (dashed red arrows) is depicted as (+) or (−), respectively.
Figure 3. Hypothalamic-pituitary-adrenal axis. Stress causes the release of corticotrophin-releasing hormone and vasopressin from the hypothalamus. These hormones are transported to the anterior pituitary. Adrenocorticotropic hormone (ACTH) is then released from the pituitary gland which stimulates the adrenal glands to release cortisol, catecholamines and aldosterone into the bloodstream. Cortisol released from the adrenal glands increases a desire for palatable foods such as sugar and targets systemic organs, including the brain where it exerts a feedback inhibition on the release of CRH by the hypothalamus and ACTH by the pituitary gland, via corticoid receptors (mostly glucocorticoid receptors (GRs), and to a lesser extent mineralocorticoid receptors).
Table 1. The effects of sugar consumption on the reward pathway.

| Sugar consumption causes neural adaptation to brain regions in the reward pathway | Sugar consumption alters activation of molecular substrates | Sugar consumption alters behaviour |
|---|---|---|
| Ventral tegmental area | ↑ Dopamine (VTA-NAc) | ↑ Sensitisation\[^{109, 110}\]↑ Reward seeking\[^{111, 112}\]↑113 |
| | ↓ Dopamine ↑ Kir2.1 ↓ CREB (NAc)\[^{114}\] | ↑ Anxiety\[^{6}\]↑ Depression\[^{115}\] |
| | ↑ Serotonin | ↓ Motivation\[^{116}\] |
| Nucleus accumbens | ↓ α6β2 nAChRs ↑ α4β2 nAChRs | ↑ Anticipation of reward ↑ Motivation\[^{53}\] |
| Amygdala | ↑ AMPAR (NAc core) | ↑ Motivational feedback ↑ Cue-triggered food seeking\[^{66}\] |
| Prefrontal cortex | IL-6↑ Leptin ↑ IL-6 ↑ TNF-α | ↑ Anxiety ↑ Fear ↑ Depression\[^{117}\] |
| | ↑ Protein oxidation (PFC) | ↓ Executive function ↑ Anxiety\[^{118}\] |
| | ↑ Delta FosB (NAc) ↑ Delta FosB (PFC) | ↑ Reward seeking\[^{72}\]↓ Fear extinction memory retention\[^{119}\] |
Table 2. The effects of sugar consumption on the orexigenic pathway.

| Sugar consumption causes neural adaptation to brain regions connected to the orexigenic pathway | Sugar consumption alters activation of molecular substrates | Sugar consumption alters behaviour |
|---|---|---|
| ↑ Dopamine | ↓ Satiety<sup>150</sup> |
| ↓ Acetylcholine |  |
| ↓ Corticosterone | ↓ Stress<sup>151</sup> |
| ↓ CRH mRNA |  |
| ↑ Orexin / hypocretin | ↑ Cue-induced consumption<sup>152</sup> over-consumption |
| ↓ BDNF | ↓ Spatial learning<sup>153</sup> |
| ↑ AgRP | ↑ Stimulation to feed<sup>131, 132</sup> |
| ↑ 5-HT2CRs | ↓ Incentive motivation<sup>154</sup> |
| ↑ Mu-1 binding | ↑ Overconsumption<sup>148</sup> |
| ↑ TNF-α | ↓ Neurogenesis<sup>155</sup> |
| ↑ NPY | ↑ Desire to feed ↑ Learned cue associations<sup>131</sup> |

Table 3. Published reports on the effect of sucrose and sweetener consumption on cognition, emotion and stress.

| Sucrose or authors | Subjects | Tasks | Brain region | Findings |
|---|---|---|---|---|

67
| sweetener consumptio n in rats | and year | involved |
|-------------------------------|----------|----------|
| 2h/day 10% sucrose for 28 days | Xu, T.J. and Reichelt, A.C., 2017 | EPM, open-field, NPR and short- and long-term NOR<sup>1</sup>, hippocampus, basolateral amygdala, increased anxiety-like behaviours |
| Rat chow supplemented with meat pies, cakes and biscuits for 10 weeks | Reichelt, A., et al., 2015 | trace fear conditioning, hippocampus, strengthened visual fears and attenuated contextual fears |
| Powdered diet: 7.9% sucrose for 52 weeks | Chepulis, L.M., et al., 2009 | <sup>1</sup>EPM, NOR Y maze, C, NA, reduced spatial memory and increased anxiety |
| 35% sucrose solution for 9 weeks | Lemos, C., et al., 2016 | open field, object displacement, NOR, forced swimming test, Hippocampus, decreased memory performance and increased helpless behaviour |
| 32% sucrose solution for eight weeks | Jurdak, N. and Kanarek, R.B., 2008 | <sup>1</sup>NOR, NA, decreased cognitive performance on object recognition, frontal cortex and hippocampus, reduced performance in the NOR test |
| 10% fructose in drinking water for 7 months | Sangüesa, G., et al., 2017 | Morris water maze, <sup>1</sup>NOR, hippocampus, - reduced ACTH by sucrose and saccharin - reduced corticosterone only after sucrose sucrose - reduced restraint-induced tachycardia and behaviour |
| 30% sucrose solution, 30m, twice daily, 2-4wk Or 0.1% saccharin | Ulrich-Lai, Y.M., et al., 2010 | Restraint stress, social interaction test, open field, EPM, hypothalamic paraventricula r nucleus, BLA, - reduced ACTH by sucrose and saccharin - reduced corticosterone only after sucrose sucrose - reduced restraint-induced tachycardia and behaviour |
| Sucrose and sweetener consumption in mice | Authors and year | Subjects | Tasks | Brain region involved | Findings |
|-----------------------------------------|------------------|----------|-------|-----------------------|----------|
| High-carbohydrate diet (45% condensed milk, 10% sugar and 45% chow) for 8 weeks | Santos, C.J., et al., 2018 | 5 – 7 week old, male BALB/c mice | restraint stress, 1 EPM, contextual fear conditioning, tail suspension test | NA | increased anxiety-like and depressive-like behaviour and aversive memory |
| 10% sucrose, 3 I2BC for four weeks, withdrawal animals received only water for one week after the four weeks | Kim, S., et al., 2017 | C57BL/6 mice | tail suspension test, 1 EPM, sucrose preference test | nucleus accumbens | withdrawal after sucrose overeating induces depression and anxiety-like behaviour. |
| Acesulfame | Ibi, D., 2018 | Male | Y-maze and frontal cortex | decrease in | |
| Sucrose and sweetener consumption in humans | Authors and year | Subjects | Tasks | Brain region involved | Findings |
|--------------------------------------------|------------------|----------|-------|-----------------------|----------|
| Sugar, sweetened beverages, and fruit intake was assessed on a servings per day basis | Cohen, J.F.W., et al., 2018 | mother and child pairings, during pregnancy and childhood mean ages 3.3 yrs, 7.7 yrs (n = 1,234) | 2 PPVT-III KBIT-II KBIT-II WRAVMA WRAML and HOME-SF | NA | adverse impact on child memory and learning |
| High-sugar content milkshakes | Shearrer, G.E., et al., 2018 | 133 adolescents | food picture exposure during fMRI | temporal gyrus, operculum, juxtapositional lobule, thalamus, caudate | increased signal in the reward learning, processing and motivation regions of the brain |
| Sucrose- or aspartame-sweetened beverage consumption three times per day for 2 weeks | Tyron, M.S., et al., 2015 | Nineteen women (age 18–40 y) | Salivary cortisol, Montreal Imaging Stress Task | hippocampus | sucrose consumption resulted in: - higher activity in the left hippocampus - reduced stress-induced cortisol - lower reactivity to naltrexone, lower nausea, and a trend toward lower cortisol |

1 EPM: elevated plus maze; NPR: novel place recognition; NOR: novel object recognition.  2 PPVT-III: Peabody Picture Vocabulary Test, third edition for maternal testing; WRAVMA: Wide Range Assessment of Visual Motor Abilities, KBIT-II: Kaufman Brief Intelligence Test, second edition, WRAML: Wide Range Assessment of Memory and Learning for childhood testing; HOME-SF: Environment short form test to evaluate home environment for cognitive stimulation and emotional support.  3 I2BC: intermittent 2 bottle choice.  4 LTP: long-term potentiation.
| Author, year | Drug / Dose | Mechanism of action | Subjects | Findings |
|-------------|-------------|---------------------|----------|---------|
| Richard, D., et al., 2000 | Topiramate (30 mg / kg) | Blocks voltage gated sodium and calcium channels, ↓ glutamate, ↑ GABA (Anticonvulsant) | Rats | ↓ Weight ↓ sucrose intake |
| Beczkowska, I.W., 1992 | Naltrexone Naloxone | Kappa and Mu2 (opioid) receptor antagonists (Treat drug and alcohol dependence) | Rats | ↓ Sucrose intake |
| Steensland, P., et al., 2010 | Ezlopitant (2,5,10 mg / kg) | NK1 receptor antagonist (Anxiolytic and antiemetic) | Rats | ↓ obesity |
| Shariff, M., 2016 | Varenicline (0.3,1,2 mg / kg) | nAChR partial agonist (Smoking cessation) | Rats | ↓ sucrose intake |
| Tahara, A., et al., 2018 | Ipragliflozin (0.1 – 3 mg / kg) | SGLT2 inhibitor (Antidiabetic) | Mice | ↓ sucrose intake |
| Muscat, R. and Willner, P., 1989 | Sulpiride (20,40 mg / kg) | D2 and D3 receptor elective antagonist (Antipsychotic) | Rats | ↓ desire for sucrose |
| Lof, E., et al., 2010 | Methyllycaconitine (0.3,1 mg/kg) | α7 nAChRs selective antagonist | Rats | ↓ sucrose preference |
| Patkar, O., et al., 2017 | Buspirone (1,2,5,5 mg / kg) | 5-HT1A/1B partial agonist (Anxiolytic) | Mice | ↓ sucrose consumption |
| Lin, Z., et al., 2013 | Curcumin (40 mg / kg) | Upregulation of PPAR-γ activation (Herbal supplement) | Rats | ↓ sucrose intake |
| Authors                  | Drug            | Mode of Action                              | Species | Effect                                      |
|-------------------------|-----------------|---------------------------------------------|---------|---------------------------------------------|
| Kurhe, Y., et al., 2014 | Ondansetron     | Serotonin receptor (5-HT3) antagonist        | Mice    | ↑ Sucrose consumption                       |
|                         | (1mg / kg)      | (Antiemetic)                                |         |                                             |
| Badia-Elder, N.E., et al., 2003 | NPY (5µg / 5µl) (10µg / 10µl) | Inhibits GAD67 expression (Vasoconstrictor) | Rats    | ↑ sucrose intake                            |
| Pandit, R., et al., 2015 | AgRP (0.66 nmol) (1 nmol) | MC 3/4 receptor inverse agonist (Decreases metabolism) | Rats    | ↑ motivation for sucrose                    |