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FOOD ADDICTION (E SCHULTE, SECTION EDITOR)

Preliminary Evidence that Tolerance and Withdrawal Occur in Response to Ultra-processed Foods

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Abstract

Purpose of Review Food addiction posits that the nature of ultra-processed food (UPF) contributes to addiction. Tolerance and withdrawal are core addiction symptoms that have received little attention in the food addiction literature. This review aimed to summarize evidence for tolerance and withdrawal in the UPF context.

Recent Findings Following repeated UPF consumption, animals show mesolimbic dopamine receptor downregulation and behavioral changes consistent with tolerance. Humans show weaker neural reward responses to UPF following frequent consumption. Following abstinence from UPF after heavy consumption, animals exhibit behavioral and neural indicators consistent with withdrawal. Humans report withdrawal symptoms when reducing UPF consumption, with the exception of a recent study that demonstrated symptom improvement during early abstinence.

Summary Preliminary evidence suggests that tolerance and withdrawal may occur in response to UPF. However, human research has been mostly limited to self-report and retrospective recall. Future experimental research is needed to further evaluate these constructs' validity.

Keywords Withdrawal · Tolerance · Addiction · Substance-use disorders · Food addiction · Ultra-processed food

Introduction

Ultra-processed food (UPF; industrially created food that contains high levels of refined carbohydrates, fats, and other additives such as flavor enhancers) dominates the current food environment [1]. Once considered novelty items reserved for special occasions, UPFs are now part of the everyday repertoire for people of all ages. UPF consumption is associated with several negative physical and mental health outcomes, including obesity [2], cardiovascular disease [3], metabolic syndrome [4], and depressive symptoms [5, 6].

Food addiction theory posits the addictive nature of UPF contributes to its overconsumption and rising rates of associated negative health outcomes. UPF activates neural reward systems more strongly than naturally occurring, minimally processed foods, even those with relatively high levels of carbohydrates (e.g., fruit) or fat (e.g., avocado) [7–9]. Intake of UPF is associated with indicators of addiction in a subset of vulnerable individuals [10]. The Yale Food Addiction Scale 2.0 (YFAS), which applies the substance-use disorder criteria in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) to UPF, is the primary measure for these addictive indicators [10, 11]. Substance-use disorders (and thus, food addiction) are indicated by eleven possible symptoms [11]. One must endorse at least two of these symptoms, in addition to clinically significant impairment and/or distress, in order to meet criteria for a substance-use disorder [11]. Approximately 3–15% of adults in community samples and 20–50% of samples with obesity, and up to 60% of samples with eating disorders meet criteria for "diagnosable" food addiction [12]. There is currently strong evidence that some symptoms of addiction occur with UPF, including loss of control over consumption (e.g., eating much more UPF than intended in one sitting) and repeated unsuccessful attempts to cut down (e.g., attempting to reduce consumption of UPF, but returning to baseline levels after a period of days or weeks). Approximately

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94% of adolescents seeking weight loss treatment and 98% of adults with obesity and binge eating disorder endorse being unable to cut down or stop consuming UPF [13, 14].

Tolerance and withdrawal, which are other substance-use disorder symptoms, have received relatively less attention in food addiction research. Although tolerance and withdrawal are not necessary or sufficient for a substance-use disorder (there are nine other potential indicators), tolerance and withdrawal are key elements of addiction for several substances [11]. Tolerance refers to the tendency to need more and more of an addictive substance to achieve the same desired effect [15, 16]. Withdrawal refers to the cascade of unpleasant physical and psychological symptoms that emerge when trying to reduce or abstain from use of an addictive substance [17, 18]. Withdrawal symptoms often have qualities opposite of the substance (e.g., hypersomnia during cocaine withdrawal, anxiety during alcohol withdrawal) [11]. Tolerance and withdrawal are considered related, as they are driven by the body seeking to maintain equilibrium in the context of repeated administrations of an addictive substance [19, 20]. These adaptations can lessen the cognitive, affective, and physical effects of taking the substance over time, which can then lead to more and more of the substance being needed to achieve the same effects (i.e., tolerance) [20]. The development of tolerance may have clinically important implications by driving increasingly larger quantities of the drug (or more potent forms of the drug) to be consumed, which may then increase the likelihood of advancing the progression of addiction and increasing the harm associated with intake [11]. Abstaining from or reducing intake of the substance can reverse tolerance-related adaptations and lead to a loss of tolerance to the substance. When the substance intake is initially reduced or stopped, withdrawal can result from the removal of the substance from the biopsychological system that has become accustomed to functioning with the substance [20].

However, withdrawal and tolerance are not thought to be driven by identical mechanisms. The incentive sensitization theory of addiction posits that although both tolerance and withdrawal are associated with downregulation of neural receptors in response to continued use of an addictive substance, withdrawal is additionally driven by sensitization to substance cues (i.e., increased "wanting" despite stable or decreased "liking") [19]. This can lead to enhanced cravings and urges for the substance during withdrawal. Although the word "withdrawal" often conjures images of severe physical symptoms observed in opioid and alcohol withdrawal, many withdrawal symptoms relevant for relapse are psychological (e.g., dysphoric mood, irritability, increased cravings) [21]. These aversive withdrawal symptoms contribute to relapse because resuming use of the addictive substance can quickly ameliorate them. Withdrawal also predicts greater substance-use disorder severity and increased rates of relapse [22–24].

Despite the ongoing debate about whether UPFs are truly "addictive," it is widely accepted that they are difficult to quit despite contributing to widespread negative health outcomes—most diets fail and attrition rates for diet change interventions are high [25, 26]. Tolerance and withdrawal may be key overlooked contributors to diet change failure. This review will discuss preliminary evidence that withdrawal and tolerance occur in the context of UPF.

Current Evidence for UPF Tolerance

Animal Models

Animal models provide a useful scientific approach to understanding the impact of UPF intake, as they provide controlled settings where dietary exposures can be tightly manipulated. Further, animal models of addiction have strong face validity for understanding addiction in humans, as the neurochemical and neuroanatomical systems impacted by addictive substances appear to be similar in non-human animals and humans [27]. Animal models provide evidence of the development of tolerance in response to UPF (or ingredients common in UPFs like sugar) in biological and behavioral domains. Animals exposed to UPF demonstrate changes in the mesolimbic dopaminergic system, which plays a key role in reward and motivational processes [28–33]. Frequent UPF intake leads to downregulation of striatal dopamine D2 receptors, which is an adaptation that also occurs with addictive drugs [34]. This dopamine D2 receptor reduction in response to UPF intake was associated with deficits in brain reward functioning [34]. Behaviorally, these animals would no longer consume their standard chow even when it was easily accessible to them in their cage, but they would risk aversive consequences (i.e., electric shock) to seek out UPF [34]. These animals may have exhibited tolerance to the reward level provided by standard chow, which may have contributed to their increased motivation to seek out the more highly rewarding UPF options. Other animal models that focus on specific ingredients are also consistent with the development of tolerance. Research by Avena and colleagues [35] has demonstrated that rats exposed to sugar will show a progressive increase in binge intake of sugar over time, potentially demonstrating the need for larger and larger quantities of intake in response to tolerance. Thus, there is evidence of hedonic adaptations in response to UPF and sugar intake that is consistent with the development of tolerance in animal models.

Human Studies

The literature on the development of tolerance in response to UPF in humans is relatively small and has focused

predominantly on adults. Given that initial exposure to UPF occurs in the first years of life and the majority of children receive a large proportion of their daily calories from UPF [36, 37], it is likely that measurable tolerance effects to UPF occur much earlier than adulthood. The ability to detect additional tolerance effects in adulthood after decades of UPF exposure may be limited by a ceiling effect. Despite this limitation, studies in adults have still found evidence consistent with tolerance. In addiction research, one piece of evidence for tolerance is that frequent substance users experience less hedonic impact from the substance than occasional or infrequent users [38]. Consistent with this idea, adolescents who frequently consume ice cream (compared to infrequent consumers) exhibited a weaker reward-related neural response (i.e., activation in the striatum) when consuming a milkshake [39]. This study was followed by a within-subject experimental design where 20 individuals who did not frequently consume sugar-sweetened beverages (SSB) were asked to have daily intake for 21 weeks [40]. After this increased exposure, individuals exhibited less striatal response when consuming an SSB compared to their baseline scans [40]. Further, a larger study of 100 young adults found that higher consumption of sugar calories from SSBs was related to decreased activation of dopamine-related brain regions (posterior midbrain, dorsolateral/orbitofrontal cortices) during receipt of an SSB (relative to a rinse) [41•]. Thus, repeated exposure to at least some types of UPF appears to lead to adaptations in hedonic neural systems in a manner consistent with the development of tolerance.

Taste-related adaptations may be particularly associated with the development of tolerance in response to UPF intake. The taste of palatable UPFs (as well as sugar and fat) are capable of rapidly inducing dopamine release in the striatum at a magnitude that is similar to substances like nicotine and ethanol [28–31]. The chemosensory system involved in taste is plastic and changes based on patterns of dietary intake [42•]. In humans, intake of higher sodium foods can lead to a greater preference for more intense salty tastes [43]. Reducing exposure to salty foods can reverse this adaptation and people can learn to enjoy less salty foods over time [42•]. Diets high in fat are also associated with a decrease in fat sensation and an increased preference for higher fat foods in humans [42•, 44]. A higher level of sugar intake also appears to alter taste preferences in humans to increase preferences for more intense sweetness [42•]. Thus, it is plausible that repeated exposure to UPFs with unnaturally intense levels of salt, fat, and sugar shape taste preferences over time. This may reduce the hedonic impact of naturally occurring tastes associated with minimally processed foods that have lower levels of salt, fat, and sugar (as well as artificial flavor enhancers). These adaptations may drive food preferences away from nutritious, minimally processed foods and towards UPFs with intense tastes. However, more research is needed to investigate this possibility.

The development of tolerance to the aversive experiences of a substance is also important and can allow for greater substance intake. For example, initial experiences of using tobacco products can trigger aversive experiences, like nausea and dizziness, which can serve as obstacles to continued use [45]. However, repeated tobacco intake causes tolerance adaptations that diminish these aversive effects, thus minimizing a potential obstacle to continued tobacco use [46]. In the context of UPF, there is evidence that the stomach adapts to the large quantities of foods (typically UPFs) [47] consumed in binge eating episodes by increasing gastric capacity [48]. This may lead individuals to consume a larger amount of food prior to feeling physical discomfort from gastric distention. Further, many UPFs are high in rapidly absorbed sugar and refined carbohydrates, which have a high glycemic load (i.e., can lead to elevated blood glucose levels) [49]. Binge intake of UPFs can cause spikes in blood glucose, which have been implicated in aversive experiences, such as increased negative affect, headaches, and fatigue [50]. Insulin is a hormone released to stabilize blood glucose levels and bring the body back to homeostasis (although this process can become dysregulated in the context of diabetes and metabolic syndrome) [51]. There is some evidence that insulin levels may be higher for individuals with binge eating disorder relative to controls [48], which may be an adaptive response developed to diminish the disruptive impact of high blood glucose levels resulting from binge eating episodes. Investigating how blood glucose, insulin, and other gut hormones are impacted by binge eating and other addictive patterns of UPF intake is an important future direction.

Future Directions

Overall, there is evidence in both animals and humans that adaptations can occur in response to frequent intake of UPF (and ingredients in UPFs) that is consistent with the development of tolerance. Tolerance may shift hedonic and taste preferences away from nourishing minimally processed foods and towards more intensely rewarding UPF that negatively impact health. There is also evidence of adaptations that reduce the aversive experiences associated with overeating (e.g., gastric distention), which may allow for greater UPF intake.

There are several important future directions to more fully understand the role of tolerance in addictive eating. It is essential to investigate whether adaptations related to tolerance occur in children, given the high levels of UPF intake within the first years of life [36, 37]. It is also important to consider that there are individual differences in the propensity to develop tolerance and not all individuals with

addictive patterns of intake of a substance will clearly demonstrate evidence of tolerance [52]. In contrast, some individuals are especially prone to develop tolerance. For example, individuals with a family history of alcohol problems are more likely to exhibit an innate tolerance to the sedative effects of alcohol and may be able to consume greater quantities of alcohol during initial drinking episodes (before tolerance would be acquired) [53]. Familial history of alcohol problems is also associated with increased sweet preferences and reward-driven eating [54, 55]. Thus, a family history of alcohol problems may be a potential predictor of individual differences to develop tolerance to UPF intake.

An understudied domain is the role of opponent-process responses to UPF. For addictive substances, cues that become coupled with intake of a substance can elicit the opposite physiological reaction in an attempt to diminish the degree of disturbance to the body (i.e., opponent-process responses) [56]. For example, cues repeatedly associated with the ingestion of stimulants (that increase heart rate and autonomic activity) will trigger a slowing of the heart rate and other physiological systems even before the drug is consumed [56]. This opponent-process can lead to a diminished effect of the substance, which may then motivate greater intake of the substance to overcome this reduction [20]. If the opponent-process response is triggered by substance-related cues, but the substance is not consumed, this places the body out of equilibrium and can induce withdrawal-like symptoms [56]. There is evidence that the body begins to prepare for the disequilibrium associated with food intake by secreting insulin in response to cues that have previously predicted eating behavior (prior to the food actually being consumed) [57]. It is plausible that UPFs (particularly those with a higher glycemic load) may be more likely to cause opponent-process responses to cues, which may contribute to the development of tolerance and addictive eating. However, limited research has been conducted on this topic.

Finally, it is clearly documented that on a population level the portion sizes of UPFs have increased over time [58]. In contrast, there has been little evidence that the portion sizes of minimally processed foods (e.g., bags of salads, cans of beans) have had notable increases in portion size. There are many factors that contribute to increasing UPF portion size (e.g., consumer demand, marketing strategies, shelf stability), but one potentially overlooked contributor is tolerance. If UPFs are associated with adaptations in hedonic, taste, and hormonal systems that lead to tolerance, this would lead individuals to seek out greater quantities of UPF to receive the same effects. This could contribute to the desire for larger UPF portion sizes. In contrast, minimally processed foods may not lead to tolerance-based adaptations, which may contribute to the relative stability in their portion sizes. Systematic research is needed to investigate the ability of different food types to be able to trigger tolerance processes.

Current Evidence for UPF Withdrawal

Animal Models

Animal models provide strong experimental evidence that cessation of UPF consumption can induce withdrawal. Although several specific methodologies have been used to examine withdrawal in this context, the core method involves measuring animal behavior while exposed to a high-UPF diet over time and then switched to a more nutritionally balanced diet. Animals exhibit physical symptoms during UPF withdrawal, including paw tremors, teeth chattering, and head shaking [59]. Animals also display affective indicators of withdrawal during UPF withdrawal, including indicators of anxiety (e.g. decreased time spent on the open arm of an elevated plus-maze), depression (e.g., increased immobility during the tail suspension test), and anhedonia (e.g., decreased spontaneous exploration) [60–62]. Interestingly, although animals exhibit general signs of low motivation during UPF withdrawal, they show enhanced motivational drive/craving to consume UPF [34, 63, 64]. One other interesting behavior that animals exhibit during UPF withdrawal is increased binge eating behavior [65]. Although this behavior does not directly map onto a withdrawal symptom for substances currently recognized in the DSM-5, each substance has unique withdrawal indicators for that substance (e.g., nose running in opioids) DSM-5. Binge eating may be a symptom that is unique to withdrawal from UPF.

Animal research has also examined the biological mechanisms of withdrawal in the context of UPF. Animals show neural reward dysfunction during UPF withdrawal [34, 60, 62, 65]. As in humans and animals withdrawing from other substances, animals withdrawing from UPF show decreased dopamine in the nucleus accumbens, a key neural reward region [34, 60, 62, 65]. Animals subjected to UPF withdrawal also show increased expression of the corticotropin-releasing factor (CRF) system, which is responsible for the body's stress response [66].

In sum, current animal evidence for UPF withdrawal is strong. The credibility and reliability of this research are bolstered by strong experimental designs and the replication of several findings by independent research groups.

Human Research

Research regarding UPF withdrawal in humans has only recently begun. However, several qualitative and quantitative studies suggest that UPF withdrawal warrants further study in humans. In a recent qualitative study examining consumer messages about diet change in an online

community setting, consumers referred to withdrawal symptoms in personal narratives and when advising other community members on how to reduce their sugar intake [67]. A recent qualitative study that interviewed individuals with food addiction found that several participants reported experiences of withdrawal when trying to reduce their consumption of UPF [68]. Further, parents who were interviewed about their experiences trying to restrict their children's SSB intake reported withdrawal-like symptoms in their children (i.e., headaches, social withdrawal, irritability) [69].

Quantitative research also suggests UPF withdrawal may be relevant for humans.

Research in community samples has found that 18.5–29.7% of participants endorse questions on the Yale Food Addiction Scale (YFAS) designed to capture withdrawal [10, 70]. In more clinical samples (e.g., individuals with binge eating disorder and obesity), endorsement rates of withdrawal items have ranged from 26 to 54.9% [13, 14]. Another study of adults in a community setting found that participants reported strong UPF cravings (a key withdrawal symptom) when trying to limit their consumption [10]. Evidence is conflicting regarding whether these findings generalize to adolescents. A study of adolescent withdrawal from SSB found that participants reported increased craving for sugar-sweetened beverages and decreased motivation for schoolwork during the early period of abstinence [71••]. However, another recent study with similar methods found that adolescents reported overall improvements in symptoms during the period when withdrawal would be expected to occur [72••].

Preliminary evidence suggesting withdrawal may be an important element of UPF addiction has driven interest in creating measures to specifically assess UPF withdrawal symptoms. The Highly Processed Food Withdrawal Scale (ProWS) is a self-report measure that was developed based on measures of withdrawal from tobacco to assess for UPF withdrawal symptoms in adults [73]. In a preliminary validation study, the ProWS showed good convergent, discriminant, and incremental validity. Importantly, ProWS scores were associated with more failed lifetime weight loss attempts and less self-reported success at reducing UPF consumption. A second measure was recently developed to measure UPF withdrawal in children. The Highly Processed Food Withdrawal Scale for Children (ProWS-C) utilizes parent-report to assess for common indicators of withdrawal in children when parents attempt to restrict their UPF intake [74]. The ProWS-C has also demonstrated good psychometric properties in a preliminary validation study and was associated with lower parent-reported success at changing their child's diet. The preliminary validation studies for each of these measures asked participants to report the timeline during which withdrawal symptoms peaked following the reduction of UPF. Each study found that self-reported UPF withdrawal symptoms appeared to follow a similar time course to withdrawal from other addictive substances (e.g., peaking around days 2–5 on average) [73, 74].

Future Directions

Overall, findings from human research suggest the construct validity of UPF withdrawal. Participants report experiencing withdrawal when they have attempted to reduce their or their children's consumption of UPFs. However, there is some conflicting evidence regarding the occurrence of withdrawal in adolescents when attempting to reduce their SSB consumption. Most prior research has utilized self-report and retrospective recall. The current lack of controlled experimental research leaves many remaining questions regarding the true validity of the construct. Future research should use experimental and longitudinal methods to examine whether withdrawal symptoms emerge in response to a controlled intervention and whether the time course follows a similar pattern to addictive substances. Future research should also aim to experimentally investigate whether self-reported symptoms of withdrawal may indicate some other process (e.g., hunger due to caloric restriction, responses to feeling deprived that would manifest if another pleasant stimulus was reduced in individuals' lives). To help rule out potential alternative explanations, future experimental research should examine whether withdrawal symptoms emerge when UPFs are removed from the diet, while maintaining isocaloric intake of foods not implicated in food addiction (i.e., minimally processed, naturally occurring whole foods).

Conclusions

Preliminary evidence, especially in animal models, suggests that tolerance and withdrawal are important components of UPF addiction. The investigation of how foods may differentially trigger tolerance adaptations, particularly in children, is an important area of future study. Human evidence supports the construct validity of UPF withdrawal but is limited to self-report and retrospective recall. If tolerance and withdrawal do occur with UPFs, this has important implications for prevention and treatment of food addiction. Tolerance and withdrawal may play key roles in maintaining widespread overconsumption of UPFs and their associated negative health outcomes. Well-designed experimental and longitudinal research with human participants is vital for understanding the role of tolerance and withdrawal in food addiction. Further understanding of these processes is a key part of resolving the ongoing debate regarding whether UPFs can be addictive, and an important step for identifying

individual and systemic interventions to reduce the negative impact of UPF on human health.

Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain original data from any studies with human or animal subjects performed by the authors.

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