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Abstract

Researchers are currently debating whether theories of addiction explain compulsive overeating of highly processed (HP) foods (i.e., industrially created foods high in refined carbohydrates and/or fat), which contributes to obesity and diet-related disease. A subset of individuals consumes HP foods with behavioral phenotypes that mirror substance use disorders. Withdrawal, the emergence of aversive physical and psychological symptoms upon reduction or cessation of substance use, is a core component of addiction that was central to historical debates about other substances' addictive potential (e.g., nicotine and cocaine). However, no one has systematically considered evidence for whether HP foods cause withdrawal, which represents a key knowledge gap regarding the utility of addiction models for understanding compulsive overeating. Thus, we reviewed evidence for whether animals and humans exhibit withdrawal when reducing or eliminating HP food intake. Controlled experimental evidence indicates animals experience HP food withdrawal marked by neural reward changes and behaviors consistent with withdrawal from other addictive substances. In humans, preliminary evidence supports subjective withdrawal-like experiences. However, most current human research is limited to retrospective recall. Further experimental research is needed to evaluate this construct. We outline future research directions to investigate HP food withdrawal in humans and consider potential clinical implications.

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Withdrawal: A Key Consideration in Evaluating whether Highly Processed Foods are Addictive

Addictive substances have long played a role in the human experience. However, what it takes to label a substance or behavior as "addictive" has been a source of heated debate over the last century. Through industrial advances, humans have mastered the ability to inexpensively and effectively produce large quantities of highly-rewarding food ingredients that are then combined with scores of other additives to create thousands of novel and palatable food combinations that do not naturally occur.[1] Highly processed (HP) foods refer to industrially created foods that contain unnaturally high levels of refined carbohydrates (e.g., sugar, white flour) and/or fat.[2] HP foods are now the dominant source of calories for the average United States resident.[3] HP foods typically contain high levels of saturated fats and refined carbohydrates (i.e., added sugars), and are often high on the glycemic index (GI) (i.e., they cause rapid spikes in blood glucose).[2-4] HP foods are more effective than minimally processed foods (e.g., whole fruits and vegetables) at activating reward-related neural systems that are also activated during substance use.[5,6] A subset of individuals experiences HP food addiction, which refers to the experience of core behavioral indicators of substance use disorders (SUD; e.g., loss of control, continued use despite negative consequences) in response to HP foods.[7] HP food addiction is associated with increased rates of

obesity [8] and is elevated in populations with obesity.[9] Further, a recent study identified HP food addiction as the strongest psychosocial predictor of obesity treatment attrition and poor weight loss outcomes following treatment.[10]

The withdrawal syndrome, which refers to aversive physical, cognitive, and affective symptoms that emerge following the reduction or discontinuation of an addictive substance, is another key indicator of addiction, but its role in HP food addiction has received less attention. Withdrawal has major clinical relevance as a predictor of relapse and is an intervention target in SUD.[11,12] If withdrawal occurs when HP food intake is reduced, it may contribute to high rates of dietary change failure and be a novel intervention target to improve obesity treatment outcomes.[13]

A review of the HP food withdrawal literature could provide definitive evidence that withdrawal exists in this context. If further research is needed, a review could provide guidance regarding future research directions to clarify the existence of HP food withdrawal and understand its role in obesity and obesity treatment. This is the first review to examine these questions. To advance the study of HP food withdrawal, this review 1) outlines the current evidence for HP food withdrawal from basic science and human research, 2) highlights key research questions for the next steps in evaluating HP food withdrawal, 3) discusses important alternative explanations for current human evidence and recommends methodological best practices for future study of HP food withdrawal, and 4) concludes with a discussion of the clinical implications of HP food withdrawal.

Withdrawal and Addiction

The withdrawal syndrome is a core element of the current conceptualization of SUD.[14] The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) includes a withdrawal section for substances that have an associated withdrawal syndrome (alcohol, caffeine, cannabis, opioids, sedatives, hypnotics, and anxiolytics, stimulants, and tobacco) and gambling disorder.[14] **Table 1** shows withdrawal symptoms listed in the DSM-5, organized by most cross-cutting symptoms (symptoms seen across the most addictive disorders) to least cross-cutting symptoms. Physical withdrawal symptoms from some substances (e.g., alcohol and cocaine) can be particularly salient because they can be life threatening and debilitating (e.g., seizures, vomiting). However, withdrawal from most substances is indicated more by psychological symptoms, such as anxiety, depressed or dysphoric mood, and irritability, with minimal physical symptoms. For example, nicotine withdrawal may include irritability, anxiety, difficulty concentrating, increased appetite, restlessness, depressed mood, and/or insomnia.

Controversy about the Addictiveness of HP Foods

As with historical debates about the addictive potential of cocaine and cigarettes, the ability of HP foods to trigger a withdrawal syndrome contributes to the ongoing debate about the addictive potential of HP foods.[15,16] Chronic overconsumption of HP food is associated with a wide range of public health consequences, including rising rates of obesity, diet-related disease (e.g., diabetes), and binge eating (i.e., episodes of eating marked by loss of control).[17-19] As with addictive substances (e.g., alcohol), many people consume HP foods to experience pleasure and

are able to do so in moderation.[20] However, approximately 10 to 15% of adults in the United States consume HP foods in a manner that is indicative of a SUD (i.e., an escalating, compulsive pattern of intake that continues despite negative consequences).[21]

Despite significant evidence that HP foods can trigger addictive processes (e.g., loss of control over consumption, continued use despite negative consequences, intense cravings), the existence of a withdrawal syndrome when HP food intake is reduced is not yet well understood. Comprehensive examination of withdrawal in the context of HP food consumption will be a major step toward resolving the debate about whether these foods are addictive. As with nicotine, understanding which components of HP foods (e.g., refined carbohydrates, fats) are most strongly implicated in withdrawal may aid in the identification of the addictive agent in these complex products. Further, withdrawal has major clinical relevance as a predictor of relapse and is an intervention target in SUD.[11,12] If withdrawal occurs when HP food intake is reduced, it may contribute to high rates of dietary change failure.[13] Research on this topic has been conducted but has never been scientifically reviewed.

Current Evidence for HP Food Withdrawal

Current evidence for HP food withdrawal from animal models and human research is described below. Key findings from animal research are outlined in **Table 2**. Key information from human research, including methodology, sample size, key findings and effect sizes, are outlined in **Table 3.**

Animal Models of HP Food Withdrawal

Animals demonstrate affective and physical symptoms during withdrawal from several addictive substances, including nicotine, alcohol, and cannabis.[22-24] Most animal models of substance withdrawal have been investigated in rodents.[25] Common physical indicators of withdrawal in rodents include teeth chattering, paw and body tremors, and wet dog shakes.[26,27] Common affective indicators of withdrawal in rodents include increased anxiety (often measured by decreased time spent in the open area of an elevated plus maze and more marbles buried during a marble burying test) and depression (often measured by decreased spontaneous locomotor activity and more immobile time in a tail suspension test).[27-29]

Like other addictive substances, animal models provide evidence that HP foods or ingredients in these foods (i.e., sugar or fat) can change the reward system in a manner that makes removal of these foods from the diet aversive due to the physical and affective symptoms that emerge.[30] Neural reward changes in response to HP food withdrawal are particularly salient for adolescent rodents due to higher cortical and subcortical concentrations of dopamine during this stage.[31] Importantly, animals only demonstrate withdrawal-like symptoms after exposure to HP food and not following consumption of less rewarding, more nutritious foods like standard chow.[32,33] Sugar is particularly effective in activating the mesolimbic dopamine system and the removal of added sugar from the diet triggers higher intensity and more aversive symptoms of withdrawal relative to other macronutrients found in HP foods, like fat.[34-37] However, patterns of withdrawal have also been observed in animals exposed to high-fat diets and cafeteria diets that include a range of HP foods with elevated sugar and fat content (e.g., bread with cheese, muffins,

sausages).[38,39]

Animals that are exposed to high levels of HP food, then returned to a standard diet demonstrate aversive physical and affective symptoms that mirror core withdrawal symptoms in animal models of substance withdrawal. Rats who have consumed high levels of sucrose exhibit physical signs of opioid-like withdrawal, such as teeth chattering and paw tremors when returned to standard chow.[36,40] Young rats that have consumed a cafeteria diet show increased indicators of anxiety in an open field test (measured by time spent in the central area) following a shift to standard chow for one week.[38] Mice that received ad-libitum access to a 10% sucrose solution and water for four weeks, followed by access to water only for one week, showed increased depressive-like symptoms (more immobile time in a tail suspension test) and anxiety-like symptoms (less time in the open arms of the elevated plus maze) compared to mice that only ever received water.[41] Withdrawal from sucrose in these mice was associated with decreased dopamine concentration in the nucleus accumbens, a key neural reward region.[41] Importantly, reinstatement of a 2% sucrose solution reversed both depressive- and anxiety-like symptoms.[41] Notably, the timeframe of emergence of withdrawal symptoms observed in these studies (within 24-36 hours after last consumption of HP foods) mirrors the timeframe observed in animal studies of withdrawal from other addictive substances.[22,23]

Another core component of withdrawal demonstrated by animal models is enhanced motivational drive to consume the substance, which can also be conceptualized as craving.[42] Animals exhibit craving for a substance by engaging in behavioral indicators that have

previously been paired with administration of the substance (e.g., nose pokes, lever presses).[42,43] This behavior is also seen when animals are withdrawn from HP foods. When HP foods are removed from the diet, rats exhibit general signs of anhedonia and low overall motivational drive. [32,41,44] However, motivational drive to consume HP food increases. Animals given ad-libitum access to a high-fat, high-sugar diet for four weeks, then switched to standard chow demonstrated increased craving for sucrose (measured by motivation to respond in an operant lever-press response task) at two weeks post diet change.[45] Interestingly, animals that are obesity prone (i.e., those that gain significant weight in response to HP foods in the diet, in contrast to those that do not gain weight when exposed to the same diet), appear to experience more craving than those that are not obesity-prone, which suggests weight gain may have a moderating effect on experiences of HP food withdrawal.[45]

Animal models of addictive substances have found increased motivation to seek out and consume the substance despite negative consequences in withdrawal states.[46] Similarly, rats who are withdrawn from high levels of HP food exhibit an increased desire for highly rewarding HP food at the expense of more nutritious (but less rewarding) options.[32,44] For example, when rats are withdrawn from a cafeteria diet, they exhibit little motivation to consume chow, and will risk receiving electric shocks to seek out HP food.[32]

The corticotropin-releasing factor (CRF) system, a neural system which plays a key role in the biological stress response, is a key factor in animal models of substance withdrawal.[47] Frequent consumption of HP foods leads to withdrawal symptoms that are driven by the CRF

system.[48,49] After frequent HP food exposure, removal of HP food from the diet leads to increased biological (i.e., increased CRF expression) and behavioral (i.e., reduced exploratory behavior, increased aggression) indicators of stress.[36,50,51] As with craving, obesity-prone animals appear to experience increased stress during HP food withdrawal, which further suggests weight gain may moderate experiences of HP food withdrawal.[49] The reintroduction of HP food appears to have a calming effect that reduces stress responses, indicating suppression of withdrawal symptoms by reinstatement of the addictive agent, which is a critical processes observed in withdrawal syndromes across substances in animals and humans.[50]

Increased food intake is another known indicator of withdrawal in animal models of nicotine and stimulant withdrawal.[52,53] Although binge eating behavior is not specifically recognized as a withdrawal symptom for established SUDs, increased appetite is a withdrawal symptom for tobacco and stimulants,[14] and may represent animals' attempts to reverse withdrawal symptoms through intake of a rewarding HP food. When animals that were previously exposed to a high-fat diet, then switched to standard chow, were presented with an HP food at one week post-diet change, female rats showed binge behavior that persisted at four weeks after the diet change.[39] Interestingly, rats that were exposed to a high-fat diet beginning in adolescence showed more binge behavior during withdrawal than for those that were exposed beginning in adulthood, which suggests that earlier consumption of HP food contributes to more adverse outcomes. For both age groups, binge behavior was accompanied by decreased expression of dopamine receptors in the nucleus accumbens, which did not normalize after four

weeks on chow. This pattern is consistent with withdrawal in humans, as individuals who begin using substances earlier in life are at greater risk for experiencing SUD symptoms in adulthood, including withdrawal.[54,55]

A recent review summarized the literature regarding animal models of withdrawal from obesogenic diets (most of which were high in HP foods).[30] The authors identified several animal models consistent with early withdrawal, including behavioral and stress responses, and elaborated upon effects of these diets during long-term withdrawal. The review concluded that although many negative outcomes of obesogenic diets (e.g., metabolic syndrome) normalize with long-term withdrawal, reward dysfunction appears not to normalize over time. The authors also highlight important sex differences in withdrawal effects (e.g., dopaminergic downregulation in certain neural reward regions recover following withdrawal for males, but not females).

While beneficial for building a preliminary understanding of biological and behavioral effects of HP food withdrawal, it is important to acknowledge that animal models are not directly analogous to the human experience. Although animal models often have strong internal validity, their external validity, or the degree to which they can be generalized to human experiences, is limited.[56] Aside from the obvious physiological differences between animals and humans, human are subject to several psychosocial factors that are absent in animal models (e.g., dieting histories, shape and weight concerns). Thus, human research is necessary to examine whether animal findings translate to humans.

Human Models of HP Food Withdrawal

In humans, some behavioral indicators of HP food withdrawal have been investigated. However, these studies have been subject to significant methodological limitations (most notably, a lack of experimental research). Biological indicators of withdrawal have not yet been investigated in humans. Here we review the state of the literature, which is based mainly on qualitative and retrospective recall (see Table 3) and highlight the need for additional research in this area.

Anecdotal and self-report evidence for HP food withdrawal is common. Popular diets (i.e., Atkins, Whole30) instruct dieters to prepare for a "withdrawal" syndrome marked by headaches, fatigue, irritability, and cravings that follows the timeline of drug withdrawal (i.e., emerges in the first days after dietary change and peaks on days two to five).[57,58] In recent years, scientists have conducted more research examining individuals' experiences of withdrawal when attempting to change their diets.

The recently developed Highly Processed Food Withdrawal Scale (ProWS) [59] assesses a range of physical (e.g., headaches, fatigue), cognitive (e.g., difficulty concentrating) and affective (e.g., irritability, anxiety, anhedonia, cravings) indicators of withdrawal in response to HP food reduction. Participants, particularly those with a higher body mass index (BMI) and a more addictive-like pattern of eating on the YFAS, reported that withdrawal symptoms across all domains were common when they attempted to reduce their HP food intake. The intensity of HP food withdrawal on the ProWS also appears to follow the time course of substance withdrawal with the peak intensity of symptoms occurring 2 to 5 days after cutting down on HP foods.

Greater endorsement of HP food withdrawal on the ProWS is associated with more failed lifetime weight loss attempts and less self-reported success in cutting down on HP foods.

The ProWS has also been adapted for parent-report of HP food withdrawal symptoms in children aged 3-11.[60] The Highly Processed Food Withdrawal Scale for Children (ProWS-C) measures the same range of physical, cognitive, and affective indicators of withdrawal, in a developmentally appropriate way that is observable by parents. Parents who reported attempting to cut down on "junk food" in the past year were asked to report on their children's response to this dietary change. Parents endorsed a wide range of withdrawal indicators and those who reported more ProWS-C withdrawal symptoms following a diet change attempt perceived themselves as less successful at changing their child's diet. The ProWS-C accounted for unique variance in diet change success over and above children's BMI and other symptoms of addictive-like eating. The peak intensity of ProWS-C symptoms appeared to mirror the timeline of substance withdrawal and the ProWS, occurring 2-5 days after cutting down on HP foods. This is consistent with the possibility that withdrawal-like symptoms may be contributing to the high rates of failure in the earlier stages of dietary change across the lifespan.

Self-report measures also provide preliminary evidence for HP food withdrawal. The Yale Food Addiction Scale (YFAS) is a commonly used measure that uses the diagnostic criteria for SUD (including withdrawal) to assess features associated with excessive or uncontrolled HP food consumption.[61] Endorsement of withdrawal is common on the YFAS. Specifically, 18.5-29.7% of participants in community samples[61,62] and 26–54.9% in samples with overweight,

obesity, and binge eating disorder[63,64] report that when they cut down on HP foods they "feel irritable, nervous, or sad" or "have physical symptoms like headache or fatigue" and these aversive experiences drive a return to prior levels of HP food consumption. 20.3% of adults also report experiencing strong cravings for HP foods when they try to limit them.[61]

A recent experimental study of adolescents who drank three or more sugar-sweetened beverages per day showed increased craving and decreased motivation to do work following three days of abstaining from sugar-sweetened beverages, with similar results for low and high caffeine consumers.[65] In contrast, another experimental study with similar methods found that adolescents' symptoms (as measured by the ProWS-C, Caffeine Withdrawal Symptom Questionnaire, and qualitative interviews) improved overall following three days of abstinence from sugar-sweetened bevergaes.[66] These conflicting results call into question whether HP food withdrawal occurs in adolescents. However, both studies were limited by a lack of a randomized control group and lack of blinding.

Several qualitative studies suggest individuals report withdrawal-like symptoms when attempting to reduce their consumption of HP foods. A recent study showed that consumers regularly referred to withdrawal symptoms when sharing personal stories or advising others on how to reduce their sugar intake.[67] Some consumers directly compared cutting down on sugar intake to quitting an addictive drug: "I went cold turkey and went through physical withdrawal symptoms – it was like I was giving up a drug." Some qualitative research studies have not found that people spontaneously identify withdrawal as a factor.[68] However, in a recent qualitative

study where people with food addiction were directly asked about the experience of withdrawal, individuals did report experiencing it.[69] For example, a female participant (age 45, severe food addiction) described the experience of negative physical and emotional consequences when eliminating sugar and carbohydrates from her diet: *"It's usually when we cut carbs. So, the first couple of days, you kinda feel sluggish. And I was irritable, cutting away those sugar items….. I have zero patience or tolerance for things that normally wouldn't bother me. And then stopping carbohydrates, you get the headaches, being lethargic about it. So the first four to six days of stopping eating anything, I think that's the bulk of when that happens."* Most participants who endorsed withdrawal symptoms reported experiencing negative emotions and physical reactions as a result of removing HP foods. Another recent qualitative study examining parents' perceived barriers to reducing their children and adolescents' sugar-sweetened beverage consumption found that parents described withdrawal-like symptoms in their children, including headaches, becoming more "moody," and socially isolating, when they attempted to restrict their use.[70]

Summary of Existing Evidence of HP Food Withdrawal

In summary, evidence suggests that HP food withdrawal occurs in animals. Well-controlled experimental animal studies have demonstrated behavioral and biological indicators of HP food withdrawal, which follow a similar time course to other addictive substances. Anecdotal and self-report evidence also suggests that humans experience withdrawal-like symptoms when they attempt to reduce their intake of HP foods. The reported symptoms and time course mirror withdrawal from other addictive substances. However, most current research on HP food

withdrawal in humans is limited by a reliance on retrospective, self-report data. The two experimental studies conducted on the topic of withdrawal from sugar-sweetened beverages in adolescents have yielded mixed findings and both lacked a randomized control group.[65,66] Thus, the current human evidence is not sufficient to establish the validity of HP food withdrawal. What remains unknown but important is whether indicators of HP food withdrawal can be observed in humans in real time and distinguished from other factors that may mimic withdrawal effects. Below we outline future directions to address current gaps in research examining HP food withdrawal in humans, with consideration for alternative explanations and confounding factors.

Future Research Directions on HP Food Withdrawal

Key future directions into the construct of HP food withdrawal are summarized in **Table 4.**

Phenomenology and Assessment of Withdrawal Symptoms

In SUD, although many withdrawal symptoms are observed across several substances, some withdrawal symptoms are unique to one specific substance (e.g., hypersomnia in stimulants).[14] Scales that have been developed to measure HP food withdrawal are based on existing measures of tobacco and cannabis withdrawal, and have met basic thresholds for content, convergent, and discriminant validity in preliminary validation studies.[59,60] However, if HP food withdrawal exists, there may be symptoms that are specific to this type of withdrawal that these scales currently miss (e.g., hypoglycemia). Qualitative studies may allow for identification of specific withdrawal presentations that may be unique to HP foods that could

improve the validity of assessments.

Time Course of HP Food Withdrawal

Prospectively evaluating if and when withdrawal symptoms emerge in response to reduced HP food intake is another important step toward evaluating the validity of this construct. To establish the time course of HP food withdrawal, experimental studies may prospectively administer the ProWS or other assessments of withdrawal repeatedly during a controlled dietary change intervention. Ecological momentary assessment (EMA), where participants report their symptoms in real time, in their natural environment, may also illuminate fine-grained temporal changes in withdrawal symptoms.[71-73] In other addictive substances, physical symptoms tend to peak earlier, while psychological symptoms can last for months after a quit attempt.[74] If HP food withdrawal does not follow a similar time course to other addictive substances, it may call into question whether symptoms experienced during diet change are indicative of withdrawal or some other phenomenon.

Identify Specific Foods or Ingredients That Produce Withdrawal Upon Cessation/Reduction of Consumption

Addictive substances are typically processed to alter their potency and speed of absorption into the bloodstream (i.e., processed from the coca leaf into powder cocaine). A substance's addictive potential (including potential for withdrawal) is increased by increasing the dose of the addictive ingredient and increasing the speed of absorption into the bloodstream.[75,76] HP foods are similar to other addictive substances in that foods that are more processed and

contain high concentrations of rapidly absorbed carbohydrates and fat are more commonly implicated in addictive-like eating than minimally processed foods.[2] Further research is needed to determine what specific component of HP food (e.g., degree of processing, macronutrient combinations, rapidly absorbed refined carbohydrates) may be most strongly associated with withdrawal symptoms in humans. As with nicotine and cigarettes,[77] this may be beneficial in identifying what is the most addictive component in a substance as complex as HP foods. This may also point to novel interventions. Just as slow-release nicotine patch or gum was helpful in reducing withdrawal for smokers trying to quit,[77] there may be dietary parallels for individuals trying to cut down on HP food intake. For example, foods associated with rapid spikes and crashes in blood glucose (i.e., high GI foods) have been associated with greater indicators of addictive eating.[2] It is plausible that consuming a diet that is composed of regular intake low GI carbohydrates (e.g., steel-cut oats, apples) that stabilize blood sugar and provide a lower dose and slower absorption of carbohydrates may be beneficial in reducing HP food withdrawal. Future research is needed to investigate these possibilities. If HP food withdrawal does not emerge in the context of removal of specific ingredients or combinations of ingredients, it may indicate that withdrawal-like symptoms experienced by people attempting to change their diets emerge in response to a process other than withdrawal.

Biological Correlates of HP Food Withdrawal

Withdrawal in SUD is associated with biological correlates in humans, including neurobiological differences. For example, SUD withdrawal is associated with elevated activation

in reward-related brain regions (e.g., ACC, amygdala) in response to drug cues.[78,79] Similarly, individuals show greater reactivity to food cues when fasting or calorically restricted.[80,81] To expand upon this work, researchers may specifically examine whether withdrawal from HP foods, without caloric restriction, produces patterns of reward-related neural activation and cue reactivity similar to withdrawal from other addictive substances. This research would provide important information regarding the convergent validity of the HP food withdrawal construct.

It will also be important to examine hormonal changes during reduction of HP food consumption. Cortisol is significant due to its key role in the HPA axis and regulation of stress and blood glucose utilization,[82] and cortisol dysfunction during drug withdrawal is associated with greater likelihood of relapse.[83,84] There is evidence that cortisol increases in response to caloric restriction,[85] but there has been less examination of cortisol changes in response to changing the type of food consumed. Investigating whether reducing HP food intake also leads to dysfunction in cortisol response is an important future direction to test the validity of the HP food withdrawal construct.

HP Food Withdrawal in the Maintenance of HP Food Consumption

Withdrawal may also contribute to the motivation to maintain frequent intake of HP foods. Individuals with SUD that are not trying to quit often experience withdrawal symptoms between uses of a substance, that emerge within hours of the last use.[86,87] For example, a consistent pattern of smoking throughout the day (i.e., chain smoking) is thought to be driven in part by a desire to avoid aversive withdrawal symptoms that occur when nicotine levels drop

between cigarettes.[88] Although these symptoms may not reach the same level of intensity that they would following multiple days of abstinence, they play an important role in facilitating the next use of the substance.[74] Thus, HP food withdrawal, if it exists, may motivate frequent HP food intake among individuals not attempting to change their diet. Many HP foods are high GI and can cause spikes in blood glucose that are then followed by rapid decline in blood glucose.[89] This postprandial blood glucose dip has been associated with increases in negative affect (e.g., irritability, agitation).[90,91] Thus, like chain smoking, blood glucose spikes and crashes associated with high GI HP foods may drive a consistent and regular pattern of "chain snacking" to avoid aversive withdrawal symptoms. This idea is supported by recent research that found that dips in blood glucose driven by intake of high-carbohydrate HP foods predict sooner period to next eating and higher subsequent caloric intake.[92] Future research may examine whether a relationship exists between glucose fluctuations, experiences of withdrawal, and continued consumption of HP foods. If this relationship does not exist, it may call into question the validity of the HP food withdrawal construct.

Alternative Explanations and Methodological Considerations for HP Food Withdrawal Research

Experimentally controlled animal research allows for increased confidence in evidence for HP food withdrawal in animals. However, there are some important alternative explanations for current evidence of HP food withdrawal in humans. Future studies of HP food withdrawal should be designed to consider and account for these alternatives.

First, studies must be designed to distinguish between the effects of caloric deprivation and effects of specifically reducing HP foods, as participants may express withdrawal-like symptoms in response to caloric deprivation (e.g., irritability).[108] Further, given that increased appetite and subjective experiences of hunger are documented withdrawal symptoms for various substances,[14] it will be important to understand whether these experiences are due to caloric deprivation or HP food withdrawal. Researchers can address this by providing intervention diets that are isocaloric (i.e., stable in calories) to the baseline diet and differ only in the proportion of HP foods. A recent study that found that reducing the proportion of added sugars in an isocaloric diet increased the reward value of high-sugar foods is an example of a study design that could be adapted to probe these questions.[109]

Expectancy effects may also partially explain self-reported HP food withdrawal. Participants who have more negative expectancies about quitting a substance (i.e., expect to feel more discomfort) are more likely to experience withdrawal symptoms.[110] Double blind placebo-controlled studies have been used to mitigate expectancy effects on withdrawal. For example, participants who were aware that they were switched from caffeinated to decaffeinated coffee experienced more withdrawal symptoms than those that were not aware of the change.[111] The ability to create a double-blind placebo-controlled diet is very challenging, as participants can see and taste what food they are consuming. Replacing sugar with artificial sweeteners may also be problematic, as artificial sweeteners also impact reward functioning.[112] While the development of a completely double-blind placebo-controlled methodology may be challenging

to study changes in dietary intake, it will be important for experimenters interacting with participants to be blind to study hypotheses and for all study materials to be carefully reviewed to make sure they do not unintentionally increase negative expectancies about the experience of dietary change.

Several other alternative explanations for self-reported withdrawal symptoms should be considered in future research. Reported symptoms may be related to differences in cost and convenience between HP foods and minimally processed foods, which are more expensive and require more time and energy to plan and prepare. The effects of cost and convenience can be mitigated by ensuring experimental groups do not differ in these ways, by directly providing food to participants. Withdrawal-like symptoms may also be driven by the experience of deprivation itself. Perhaps removing desirable foods initiates withdrawal-like symptoms, regardless of the processing level or content of the food. Research might account for this by comparing withdrawal symptoms when HP foods versus calorically equivalent, equally desirable minimally processed foods are removed from the diet. Withdrawal-like symptoms may also be related to social effects of abstaining from socially sanctioned HP foods (e.g., not being able to eat a piece of cake at a birthday party or missing social events to avoid HP foods). This effect may be more difficult to control for in non-laboratory-based settings. However, if studies are not able to fully control for these factors, they can be measured and analyzed to determine their impact on HP food withdrawal outcomes in more ecologically valid settings.

Unique alternative explanations may explain current evidence for HP food withdrawal in

children, which currently relies on parent report. Parents are responsible for restricting their children's access to HP foods, and often attempt to reduce HP food intake as a family. Thus, they may experience discomfort, fatigue, or their own symptoms of withdrawal that bias their perceptions of their children's behavior. Data collection from multiple informants (e.g., child self-report, teacher observation, laboratory observation) will help mitigate the impact of parental bias. Additionally, if children do experience withdrawal-like symptoms when their access to HP food is restricted, these symptoms may be caused by experiences other than HP food withdrawal. For example, social isolation may result from children's perceptions that their new eating patterns make them different from their peers. Similarly, changes in children's mood could be due to difficulty with change in general, rather than the specific reduction of HP food. Controlled studies comparing the effects of reduction of HP food intake and other changes to children's daily lives will help distinguish HP food withdrawal from these alternative explanations.

Conclusion

In conclusion, this review found compelling animal evidence for a withdrawal syndrome when HP foods are removed from the diet. These studies were well controlled and demonstrated behavioral and neural indicators of withdrawal in response to HP foods but not nutritionally balanced chow. Thus, we confidently conclude that HP food withdrawal occurs in animals. To date, every substance that elicits signs of addiction in animals also elicits an addictive response in humans.[77] However, current research in humans is not yet adequate to establish a withdrawal syndrome for HP foods. Compelling preliminary evidence shows that humans subjectively

experience withdrawal-like symptoms when reducing their consumption of HP foods, which is associated with perceived decreased success at maintaining a healthier diet. However, human research thus far has been mostly limited to retrospective self-report and experimental studies are mixed, allowing for several potential alternative explanations for results. This highlights the need for further prospective and experimental research. Expanding our understanding of whether HP food withdrawal exists in humans represents a crucial step toward determining the addictive potential of HP foods and may aid in the development of novel approaches to address the widespread overconsumption of HP foods to prevent and treat obesity. Future prospective and experimental research examining HP food withdrawal in humans is an important future direction to investigate the validity and clinical utility of considering HP food withdrawal and addiction.

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Tables