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The mesolimbic system and eating addiction: what sugar does and does not do

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Obesity and obesity-related disorders are a major threat to public health. It has been suggested that food addiction is a valid clinical concept and that food addiction is a contributing factor to the obesity epidemic. Research involving restricted access 'binge' diets has shown that rodents will display sucrose-related behavior that is reminiscent of substance addiction, under certain conditions. A question that remains, however, is if food or certain components of food possess addictive qualities akin to drugs of abuse. The alternative is that 'food addiction' (or rather 'eating addiction') is not a substance use disorder in the sense that people are addicted to any specific substance or component of food, but rather an addictive disorder involving disinhibition of food intake in general that shares similarities with behavioral addictions such as problem gambling. Here we describe how sugar (a candidate addictive component of frequently consumed foods) has short and long term effects on the brain and compare this to how addictive substances functionally alter the mesolimbic dopamine system. We focus on this system since plasticity changes in the mesolimbic system have been implicated in the development of drug addiction. We conclude that sugar has a strong direct influence on the dopamine system, which underlies its profound reinforcing qualities. However, at present there is limited evidence to suggest that sugar intake induces plasticity changes comparable to those induced by drugs of abuse. Thus, based on current literature we propose that it is probably that the long term effects of sugar on the brain are both qualitatively as well as quantitatively different from those of addictive substances.

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Introduction

Obesity and its comorbidities are a major threat to public health and a serious socioeconomic burden [1,2]. It has recently been suggested that addiction-like processes might contribute to the obesity epidemic [3,4]. However, opinions differ on whether food, or components of food, themselves have addictive qualities that are comparable to those of addictive substances [5,6]. With substance addiction, there is a specific substance (e.g. cocaine) to which the subject is addicted and the exposure to cocaine is causally involved in the development of the addiction. It is currently not clear if food can play a similar role in the development of addictive behavior. Alternatively, 'food addiction' may not be a substance addiction, but rather a behavioral addiction (like problem gambling), involving disinhibition of eating in general. If so, the disorder might be more aptly described using the term 'eating addiction' [7••].

This short review is not meant to debate the clinical validity or usefulness of the concept of eating addiction. We acknowledge that there is evidence of humans and animals displaying addiction-like behavior directed at food [8–13]. It is not clear, however, if the addiction-like behavior in these examples is a consequence of exposure to a specific component of food, such as is the case for substance addiction. Therefore, we would like to limit the scope of this review to the question of whether an important component of modern food, namely sugar, has addictive qualities and if so, if these are comparable to those of drugs of abuse. Here we focus on sugar because sugar-rich foods and drinks are increasingly available in society. Many have suggested that these omnipresent 'hyper palatable' (i.e. very tasty) sugar-rich foods possess addictive qualities and that these therefore make a major contribution to the obesity epidemic [13,14]. Interestingly, this might be more so for sugar-rich drinks than for foods [15]. We have limited our review to preclinical literature dealing with the effects on sugar on the mesolimbic dopamine system. This system plays a key role in reward prediction and reinforcement learning [16–18], motivation [19] and incentive salience [20]. There is strong evidence that plasticity changes in this system facilitate the development of addictive behavior [21,22]. Furthermore, because we intend to describe the effect of sugar itself on the mesolimbic dopamine system, we do not extensively discuss research that combines sucrose exposure with stressful stimuli (such as prolonged food deprivation or painful stimuli) or high-fat/high-sucrose combination diets in this review.

Initial exposure

Sucrose, a disaccharide consisting of glucose and fructose, is commonly referred to as a 'natural reward' [23]. The reinforcing qualities of sucrose are in part due to its sweet taste. Sucrose binds the sweet taste receptors T1R2 and T1R3 which ultimately promotes dopamine release, which probably underlies its reinforcing properties [24,25]. Animals are willing to work for non-caloric sweeteners, and have been reported to initially prefer non-caloric sweeteners over cocaine [26,27]. However, when given a choice between sucrose and sucralose (which stimulates the same taste receptors but does not have any caloric value), mice will overwhelmingly prefer sucrose [28,29••]. Interestingly, mice that lack the sweet taste receptors T1R3, T1R2 or the ion channel trpm5 (necessary for sweet taste signaling) no longer prefer sucralose over water, but are perfectly capable to learn to prefer sucrose over water [30,31]. Indeed, sucrose has strong reinforcing qualities and stimulates dopamine neurotransmission *independent* of its taste [30]. For example, intragastric and intravascular infusions of glucose maintain operant behavior in rodents and raise dopamine levels in the ventral striatum [i.e. nucleus accumbens (NAc) and olfactory tubercle] [32,33,34•,35,36]. When intragastric infusions of glucose are coupled to consumption of a specific tastant, rats will learn to prefer this tastant over a control solution, even when the test solution was initially perceived as aversive (i.e. bitter-tasting) [37,38]. Furthermore, in rats, cues previously associated with sucrose evoke more dopamine release in the NAc than cues paired to saccharin (a non-caloric sweetener) [39]. Infusions of the dopamine D1 receptor antagonist SCH23390 into the NAc shell block the acquisition of glucose conditioning [40]. Conversely, although sucralose is non-caloric, when licking on a sipper of sucralose is paired to optogenetic activation of dopamine neurons, mice will prefer this sipper over a sipper that dispenses sucrose when satiated, which suggests that activation of dopamine neurons is what leads to this preference [29••].

The fact that sucrose has reinforcing properties independent of its taste is reminiscent of how psychostimulants promote positive reinforcement via their pharmacodynamic effects on the dopamine system while, in many cases, the administration process is not generally considered pleasant [e.g. IV injection (heroine), snorting (cocaine)]. It is interesting to note that all drugs of abuse influence the mesolimbic dopamine system either directly or indirectly [21,22]. Indeed, it can be considered as 'a quirk of evolutionary fate', that humans learned to 'artificially' stimulate the brain circuits that evolved to respond to natural rewards such as sucrose [23], whereby it should be noted that natural rewards such as carbohydrates and fat are crucial sources of energy, essential for survival. Thus, although there are notable differences between the pleasurable effects of substances of abuse and sucrose, initially both addictive substances as well as sucrose promote positive reinforcement presumably by their (direct or indirect) influence on the mesolimbic dopamine system. Thus, exposure to addictive substances is thought to mimic the dopamine response normally evoked by natural rewards.

A notable difference regarding cocaine-evoked and sucrose-evoked dopamine release appears after multiple exposures. Dopamine release in the NAc following sucrose or sweet food self-administration rapidly declines after initial exposure (although this is not observed when sucrose exposure is alternated with daily 12 h periods of food deprivation [41]). By contrast, cocaine administration, as a result of its direct influence on dopamine neurons (i.e. by blockade of the dopamine transporter (DAT)), continues to promote dopamine release in the NAc [42,43]. In fact, repeated exposure to psychostimulant drugs has been widely reported to cause neurochemical sensitization, that is, an augmented stimulation of NAc dopamine activity [44,45]. Thus, repeated exposure to substances of abuse evokes different effects of mesolimbic dopamine transmission than repeated exposure to palatable food. This process is thought to underlie a maladaptive learning process whereby substances-stimulus associations are continuously strengthened, and substance-predictive stimuli gain abnormal incentive value [46].

Neuronal plasticity underlying the development of sensitization and craving

As mentioned above, repeated administration of drugs of abuse promotes behavioral and neural sensitization. Sensitization can be readily observed as an increased locomotor response following repeated injections of, for instance, cocaine. This process has been hypothesized to reflect increased incentive salience of drugs and drug-associated cues [47]. Synaptic plasticity in the ventral tegmental area (VTA), where the cell bodies of dopaminergic neurons projecting to the NAc are located, is thought to play a role in the development of sensitization, which is in part maintained by synaptic plasticity in the NAc [21,48••,49•,50,51].

Even a single passive exposure to drugs of abuse (by contrast to non-addictive drugs such as fluoxetine) has been shown to potentiate glutamatergic synaptic connections on dopamine neurons in the VTA in mice [51–53], especially those projecting to the NAc [51]. Importantly, it has been demonstrated that sucrose self-administration (solid pellets) transiently increases AMPA/NMDA ratios on dopamine neurons in rats, whereas cocaine self-administration creates a robust potentiation that lasts for months [54••].

Somewhat reminiscent of drug sensitization is the finding that rodents that are exposed to a very specific binge diet

consisting of alternating 12 h periods of food deprivation and access to 10% sucrose/25% glucose, will come to binge on sucrose and become more motivated to obtain a sucrose reward [55,56]. Interestingly, in rats, cross-sensitization between an intermitted excessive sugar diet and amphetamine has been reported [57,58], hinting at the involvement of the dopamine system in sucrose binging evoked by stringent binge diets. However, it should be noted that in these same studies a control group, which received sucrose continuously, did not develop the same behavior. Thus the cross-sensitization effect was a consequence of the stringent diet criteria, and not a direct outcome of sucrose exposure *per se* [57]. In this study, the rats were challenged with an amphetamine injection after seven days of forced abstinence from sucrose. Related to this, prolonged abstinence from sucrose self-administration resulted in decreased AMPA/NMDA ratios in putative prefrontal cortex (PFC) to NAc afferents in rats [59•], reminiscent of the effects of cocaine exposure followed by abstinence on PFC afferents to the NAc in mice [48••,60]. In this respect, it is interesting to note that cross-sensitization, as well as a decreased AMPA/NMDA ratio on PFC afferents to the NAc is observed following forced abstinence from a different natural reward, namely sexual behavior in male rats [61,62].

There are notable differences between cocaine and sucrose-induced plasticity changes in the NAc, especially when observed some time after exposure. A history of cocaine self-administration followed by abstinence promotes the insertion of GluA2-lacking, calcium-permeable AMPA receptors into the cell membrane of NAc output neurons, which mediates the increase (incubation) in cocaine seeking after prolonged abstinence [48••,63,64]. Although under some conditions, a similar effect is seen after orosensory stimulation with both (non-caloric) saccharin and sucrose, this effect is transient and is not observed following prolonged abstinence from sucrose [59•,65]. Furthermore, incubation of cocaine seeking is more robust and lasts longer (>3 months) than incubation of sucrose seeking and it is associated with gene expression changes (including brain derived neurotropic factor (BDNF) up-regulation in the NAc, VTA and Amygdala) not observed after sucrose exposure [66].

In sum, drugs of abuse evoke long-lasting neuronal plasticity in the VTA and the NAc, which underlies drug sensitization and drug seeking. Current evidence suggests that sucrose and sucrose-withdrawal induced plasticity is different and transient (Figure 1).

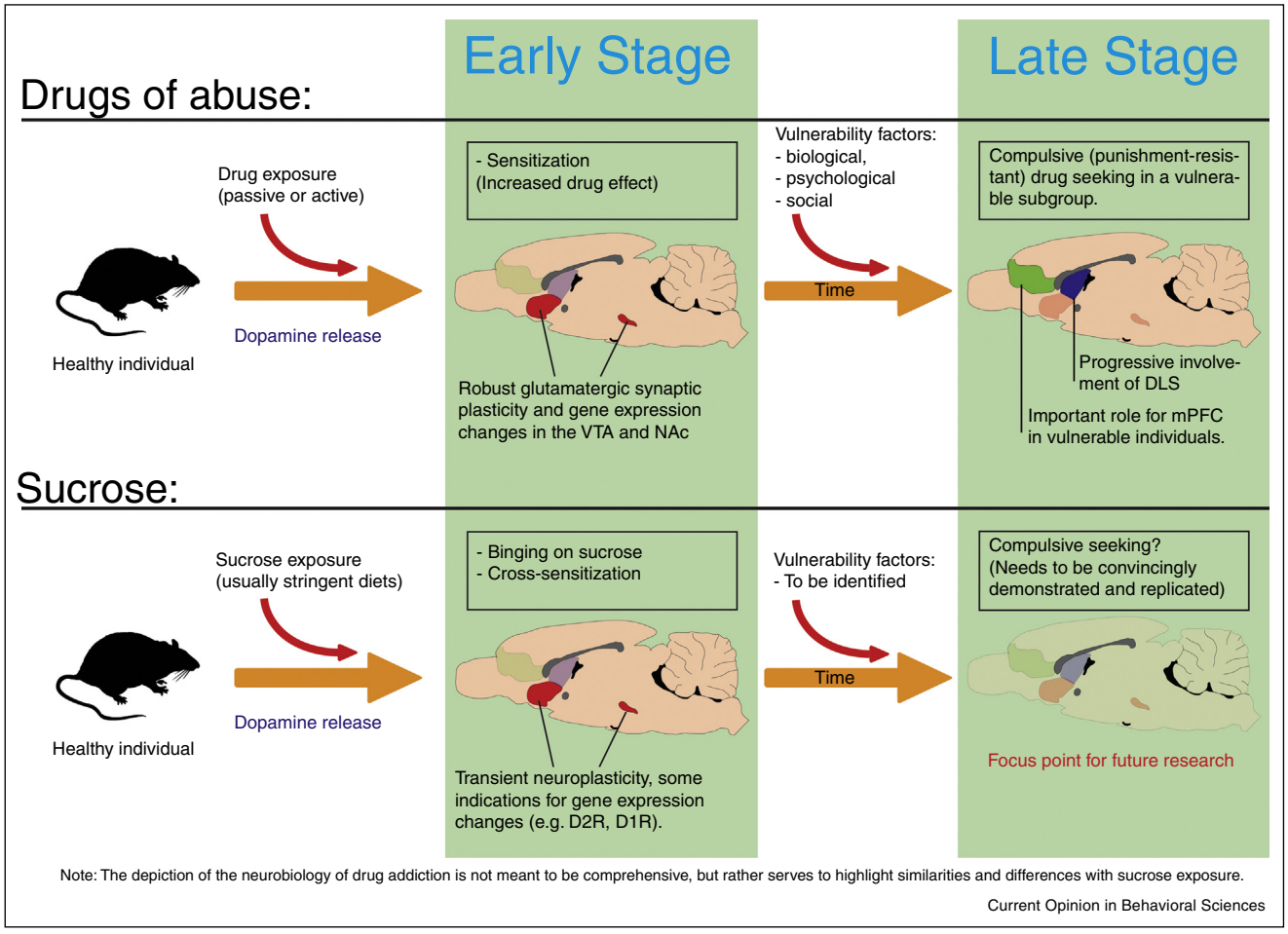
Prolonged exposure and the development of compulsive seeking

After prolonged cocaine self-administration, drug seeking and taking can become compulsive as animals continue to seek cocaine in the face of possible aversive consequences (e.g. an electric shock) [67,68•,69] (for a review see: [70]). Direct comparison of the long-lasting consequences of self-administration has shown that unlike cocaine self-administration, prolonged sucrose self-administration does not cause resistance to presentation of an aversive (footshock-associated) stimulus [65,66]. Moreover, although there are several examples of punishment-resistant sucrose seeking [9,10,71], these results are arguably not as robust as the cocaine findings, which are regularly replicated (e.g. compare [72,73] and see: [68•,69]). Whether this is a quantitative difference, reflecting the fact that sucrose is not *as* addictive as cocaine, or a qualitative difference, may be tested by investigating the neural substrate of long-term substance vs. sucrose exposure. If sucrose does indeed possess addictive qualities, even if they are not as conspicuous as those of addictive drugs, it is probably possible to identify changes in brain functioning such as those that have been described for addictive drugs.

Extended drug self-administration is characterized by a shift in functional involvement of the ventral striatum to the dorsal striatum, which is thought to underlie the development of habitual drug seeking [74–76]. Furthermore, inactivation of the dorsolateral striatum, which has been implicated in habitual behavior [77,78] selectively blocks the expression of punishment-resistant cocaine seeking in rats [79]. Future studies should investigate whether punishment-resistant sucrose seeking might involve a similar mechanism. Several recent studies have implicated hypo-activity of the prelimbic cortex in animals that displayed compulsive cocaine seeking [80,81•]. It is therefore very interesting to explore plasticity changes in the PFC in compulsive sucrose seeking, as was previously done for cocaine [82]. Further research involving animal models of uncontrolled or compulsive food seeking (e.g. [9,72]) will be necessary to identify the neuronal substrate of compulsive aspects of sucrose seeking.

A potential functional similarity following prolonged exposure to sucrose or addictive substances relates to postsynaptic dopamine D2 receptor expression in the striatum. Positron emission tomography (PET) studies in humans have shown that both drug addiction and severe obesity are associated with decreased dopamine D2 receptor availability in the striatum [83,84] (although this is not found in all studies [85]). The causal relationship between striatal D2 receptor density and drug addiction/obesity is not completely clear, as there is evidence in both directions. Decreased D2 receptor availability has been associated with increased sensitivity to methylphenidate in humans and increased cocaine reinforcement in animals [86–88]. Moreover, decreased D2 receptor availability in the striatum has been implicated in impulsive behavior, a character trait associated with both drug addiction and obesity [89–91]. Furthermore, lentiviral mediated knock-down of the

Figure 1



Concise overview of the neural substrate involved in drug addiction. Both sugar and addictive drugs are potent stimulators of the mesolimbic system and have strong reinforcing qualities. Both have been shown to transiently alter glutamatergic synaptic plasticity, as well as gene expression within the mesolimbic system. Prolonged drug exposure promotes compulsive seeking (e.g. see: [67,69]), which is associated with robust, long-lasting changes in brain plasticity. Future research will have to identify if extensive sugar exposure, whether or not in the form of stringent binge diets, can promote similar alterations in brain functioning. VTA, ventral tegmental area; NAc, nucleus accumbens; DLS, dorsolateral striatum; mPFC, medial prefrontal cortex; D1R, dopamine D1 receptor; D2R, dopamine D2 receptor.

D2 receptor in the dorsal striatum has been implicated in the development of compulsive sucrose seeking following intake of a high-caloric diet [9]. This is interesting, but at the same time illustrates the complexity of the role of the D2 receptor in addictive behavior, since D2 receptor binding studies in rodents have shown an association between cocaine reinforcement and D2 receptor density in the *ventral* striatum [87,92•]. Conversely, prolonged cocaine exposure promotes down regulation of the D2 receptors throughout the striatum [92•–94], and there is evidence that a high-fat choice diet or a limited-access sucrose diet alters striatal D2 receptor expression in rodents (albeit most convincingly in the dorsal and only in parts of the ventral striatum) [95,96]. These results, and their behavioral correlates should be further explored in the future.

Conclusion

Sucrose has historically been described as a natural reward [23]. Interestingly, even independent of its rewarding taste, sucrose and its components glucose and fructose can influence the mesolimbic dopamine system and they are reinforcing when they are infused into the stomach or directly into the circulation [36,97]. This is somewhat reminiscent of the 'chemical' reward produced by intravenous drug administration. The mesolimbic dopamine system facilitates the formation of stimulus-reward associations, motivation and incentive learning [16,18,20]. These processes are important for an organism to learn about factors in its environment that are beneficial to its survival (such as energy-rich food). Addictive substances such as nicotine, heroin, ethanol and cocaine produce robust long-lasting plasticity changes in the mesolimbic

dopamine system (both in the VTA and NAc) which are thought to underlie motivational aspects of addictive behavior [48••,51–53,63]. Ultimately, the development of habitual (automated, cue-driven) drug seeking is facilitated by alterations in the dorsolateral striatum, and in the mPFC [79,81•,82,98]. There is currently no convincing evidence that sucrose is able to 'hijack' these neural circuits to a similar extent. It should be noted that others have stated that sucrose, when given intermittently, produces behavioral symptoms that are reminiscent of substance use disorders, such as binging on sucrose (cross) sensitization and even withdrawal [57,99]. However, the animal models used in these studies employ stringent 'binge diets' that involve prolonged periods of food deprivation or other stressful stimuli, as mere sucrose exposure is apparently not sufficient to induce these behaviors (for a review see: [100,101]). This is a notable contrast with substance addiction, which depends primarily on factors influencing individual susceptibility and extensive access to the drug itself [67,73,81•,102]. Therefore, we propose that there is no reason to suppose that sucrose, *by itself*, plays a causal role in the development of addictive behavior. Rather, as was recently proposed, the phenomenon of 'food addiction' might be more appropriately captured by the term 'eating addiction', as a behavioral addiction involving disinhibition of eating in general and not an addiction to a specific substance [7••].

In conclusion, preclinical research has identified both qualitative as well as quantitative differences between how the brain is affected by sucrose and drugs of abuse. On the basis of the current literature it is therefore not tenable to characterize sucrose addiction as a substance use disorder. In this regard, it is of interest to elucidate whether extensive sucrose exposure can induce habitual and compulsive behavior (i.e. automated and insensitive to punishment) and to identify associated changes in neuronal plasticity in the mesolimbic dopamine system, the dorsal striatum, as well as in the mPFC. Distinguishing between eating addiction and substance use disorders will probably influence the development of treatment options and prevention programs as well as future research.

Conflict of interest

The authors have no conflict of interest to disclose.

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