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Are sweetened drinks a gateway to alcohol, opiate and stimulant addiction? Summary of evidence and therapeutic strategies

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A B S T R A C T

1. Drinks sweetened with both sugar and artificial additives lead to dopamine release at the nucleus accumbens (NAc) in rat models; the basis of experiences of pleasure in humans, resulting in impulsive binging behaviour at times.
2. Evidence from rat models show cross sensitisation between sweetened drinks, alcohol, opiates and stimulants. Therefore, it could be hypothesised that sweetened drinks could be a gateway to multiple substance abuse among humans via 'alcopops'.
3. Identification of an allelic variant of the cyclic adenosine monophosphate responsive element modulator gene (*CREM*), linking impulsivity and multiple substance abuse, opens up prospects of mass screening to advice on harm reduction.
4. Furthermore, therapies involving cannabinoid receptor antagonists and transcranial brain stimulation are being currently investigated; of benefit to limit binge use of sweetened drinks.

Context – are sweetened drinks addictive?

Globally, increased consumption of sweetened drinks have been recorded over the last 20 years, matched by a rise in obesity [1]. Currently, Europeans consume on average 2 lb of sugar a week [2] largely through carbonated sweetened drinks.

Taxation on drinks with added sugar was introduced in England recently due to awareness of increasing obesity and non-alcoholic steatohepatitis (NASH); the world's commonest killer due to its potential to cause myocardial infarcts [3]. Furthermore, a large study of middle aged adults consuming both sugar and artificially sweetened drinks showed premature mortality [4].

The finding of increasing consumption of such drinks globally has raised the question whether sugar itself – 50% fructose, 50% glucose in composition – is an addictive substance; as characterised by craving, binging, tolerance and withdrawal features. Despite this suggestion being confirmed in rodents [5,6], it has not been replicated in humans [7]. However, there is evidence of fructose ingestion in humans producing a pattern of regional blood flow in the brain associated with food seeking behaviour compared to the pattern produced by Glucose ingestion, which is typical of satiety [8]. The finding confirms the 'appetiser' effect of high fructose corn syrup, a common ingredient in sweetened drinks [9].

However, there is also evidence that the addictive potential of sweetened drinks is due to the perception of intense sweetness rather than sugar or sweeteners. In rodents, artificial sweeteners including sucralose, aspartame and high fructose corn syrup appear to be equally addictive as cocaine [10]. Furthermore, an allelic variant of a gene termed cyclic adenosine monophosphate responsive element modulator (*CREM*) gene has been found, associated with behaviours of impulsiveness and multiple substance abuse [11].

Neuroscience findings – The brain reward circuit (BRC)

Neuroanatomical research has led to identification of a brain reward circuit [12], centred on the shell of the nucleus accumbens (NAc); with input via dopaminergic neurones from the ventral tegmental area [13]. The NAc shell has both dopamine type 1 and 2 receptors (D1 and D2). More upstream, the ventral tegmental area receives inhibitory input from the lateral hypothalamus; which controls feeding for hunger and for recreational purposes via serotonergic neurones. Downstream, the nucleus accumbens has interconnections with the dorsomedial prefrontal cortex [14]; associated with compulsive searching. On specific receptor subtypes, the accumbens based dopamine 2 receptors appear to have a damping effect on substance abuse, with dopamine 1 receptors related to increased use. Consistent with this, drugs of abuse appears to downregulate D2 and upregulate D1 [15].

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Box 1

Behavioural stages of addiction [16]
1. Acute drug effects (thrill and pleasure)
2. Transition from recreational use to binge use
3. Overwhelming desire to use the drug (planning daily use)
4. Diminished ability to control drug seeking
5. Reduced pleasure from other daily rewards.

Hypotheses

1. Sugary or artificially sweetened drink use, despite not being inherently addictive, can be a gateway to alcohol, opiate and stimulant addiction in humans.
2. These drinks lead to multiple addictive behaviours by activating the brain reward circuit in 'at risk' people (CREM gene variant for example).

Evidence

1. *Cross sensitisation in rodents.* Rats given daily access to sugar show alterations of dopamine and opioid receptors, cross sensitisation with amphetamine and alcohol, as well as behavioural signs of naloxone precipitated withdrawal [17]. Compared to control rats, experimental rats increased their daily consumption of a sugar solution three fold, with extracellular dopamine rising by 130%. There is evidence of delayed satiation, compared to rapid satiation in control rats. In rodents, artificial sweeteners sucralose, aspartame and high fructose corn syrup appear to be equally addictive as cocaine [10].
2. *Long term activation the brain reward circuit.* The lateral hypothalamus commences the brain reward circuit activation with serotonin release at the hypothalamus, leading to opiate release in the ventral tegmental area thereby causing inhibition of dopaminergic supply at the nucleus accumbens [18]. In situations of drug and sugar use, additional gamma aminobutyric acid (GABA) input to the ventral tegmental area disinhibits the release of dopamine; rapidly increasing concentration of dopamine at the accumbence shell. There is evidence in rats of escalating consumption of readily available sugar to achieve bursts of dopamine release in the accumbens shell [19] the process leading to sensitisation and consequent tolerance.
3. *Influence of the endocannabinoid system.* Recently researchers have discovered an additional pathway impacting on dopaminergic input to the brain reward circuit; the endocannabinoid system [20]. Endogenous cannabinoids are small molecules derived from arachidonic acid, with anandamide and 2-arachidonyl-glycerol present in the brain, binding to cannabinoid receptors. The cannabinoid receptor type 1 is the commonest in the brain; impacting on areas associated with motor control, cognition, emotional responses and motivation.

Alternative hypotheses

The main alternative hypothesis is that processed foods are addictive [9], and act as a gateway to alcohol, opiate and stimulant use. The addictive potential of processed food is difficult to test, as consumption is often accompanied by sweetened carbonated beverages. Furthermore processed food contains high fructose corn syrup as a preservative. There is no evidence from rodent research that processed food is addictive or capable of producing cross sensitisation to alcohol or substance use.

Implications on public health

1. It is anticipated that the tax on sugary drinks would reduce consumption. However, artificial sweetener based drinks are not taxed in most nations, despite similar obesity rates [21] and equally increased mortality compared to sugary drinks [4]. This inconsistency needs review by governments, despite resistance by soft drinks and alcopops manufacturers who moved to artificially sweetened ('diet') drinks to avoid taxation.
2. Identification of the *CREM* gene variant suggests the potential for genetic screening of volunteers to prevent the risk of multiple addictive behaviours. Gene testing is becoming increasingly viable, and could be a routine part of a general psychiatry clinic, with education, harm reduction and potential therapies available including motivational interviewing [22].

Therapeutic approaches

1. On drug based approaches, dopamine antagonists have a beneficial impact on reducing cue induced response to sugar [23]. However bromocriptine (a dopamine type 2 antagonist) used as a satiation agent in diabetes management, has side effects such as hypertension and migraine. Aripiprazole is a partial dopamine type 2 antagonist, therefore potentially of value in avoiding side effects.
2. Regarding the endocannabinoid system, it is known that administration of cannabinoid type 1 receptor antagonists block cue induced reinstatement of heroin and cocaine use [24]. These drugs also appear to decrease alcohol self-administration in animals with a history of alcohol dependence [25]. Studies involving the effectiveness of cannabinoid type 1 receptor antagonist use in binge use of sweetened drinks are awaited.
3. Finally, the latest non-drug approach is transcranial stimulation involving direct current applied to the pre frontal areas of the brain, with reduced impulsivity in a range of addictive behaviours after stimulation [26]. However, frequency and duration of treatment remains unclear.

Conclusion

The potential risk of sweetened drinks increasing addiction to alcohol, opiates and stimulants in genetically vulnerable people is a serious public health issue. It is likely that the pathophysiology is via the sensation of intense sweetness leading to activation of the brain reward circuit. Furthermore the relevance of the endocannabinoid system is starting to be understood, leading to therapeutic agents to reduce craving.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.109469.

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