EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 5
Issue: 9
362-368
Year: 2018

ROLE OF SUGAR IN SUGAR ADDICTION: A REVIEW FOR BIOLOGICAL PLAUSIBLE REASONS

[1]*Dr. Geeta Rani, [2]Dr. Manjunath B. C., [3]Dr. Adarsh Kumar, [4]Dr. Ritu Phogat, [5]Dr. Saumya Singh and [6]Dr. Anuradhha

[1,4,5,6]PG Student, MDS Public Health Dentistry, Post Graduate Institute of Dental Sciences, Rohtak.
[2]Senior Professor & Head, Department of Public Health Dentistry, PGIDS, Rohtak.
[3]Associate Professor, Department of Public Health Dentistry, PGIDS, Rohtak.

***Corresponding Author: Dr. Geeta Rani**
PG Student, MDS Public Health Dentistry, Post Graduate Institute of Dental Sciences, Rohtak.

Article Received on 29/06/2018 **Article Revised on 19/07/2018** **Article Accepted on 08/08/2018**

ABSTRACT
Background: A lot of substances are associated with addiction and in recent times, sugars are also considered in the group but with lack of proper evidence. There is a necessity to find the plausible reasons. **Objectives:** To find out the evidences whether sugar has addiction potential in Humans or not. **Material and Methods:** A systematic literature survey was carried out in electronic databases such as PubMed, Medline, Scopus, Embase, Science direct, and Cochrane database with key words, sugar addiction, and sugar abuse. Original articles published in English language since 10 years were selected. **Results:** The search resulted in 260 research articles out of which 18 articles were selected which fulfilled the objective of the study. Most of studies for sugar addiction have been done on laboratory animals. These studies showed that sugar and other sweet substances result in production of neuro-chemical substances such as Dopamine in brain of these animals. In Humans evidences showed that sugar and other sweet substances increased cerebral blood flow in right nucleus accumbens after intake of high glycemic index meal. The evidence is limited by the difficulty in comparing different types of rewards and psychological experiences in humans. **Conclusions:** There is some evidence of sugar addiction among laboratory animal models which gives biological plausible answers but the same may not be true among humans. More research is necessary among human subjects to verify the link of sugar as addictive substance.

KEYWORDS: Sugar, Addiction, Biological plausibility, Dopamine.

INTRODUCTION
Globally, over the years dietary pattern has changed profoundly from consumption of cereals & pulses to highly palatable, rich in sugar products.[1] Sugar is known to naturally occur in all foods that contain carbohydrates, whole grains and dairy products.[2] Sugar is defined as a "Sweet crystalline substance obtained from various plants, especially sugar cane and sugar beet, consisting essentially of sucrose, and used as a sweetener in food and drink."[3]

As far as health effects of sugar are concerned research suggests that sugar can result in dental as well as the systemic effects. Dental issues can be, ranging from dental caries, periodontal problems to severe dental pain and tooth loss leading to difficulty in chewing food and dissatisfaction with esthetics, while systemic effects can be impaired glucose tolerance, diabetes, cardiovascular problems, non-alcoholic liver disease, altered platelet function, it also increases risk for breast and pancreatic cancer.[4,5]

In recent years, a new concept associated with food intake is drawing attention which is addiction of high palatable food. Addiction or substance dependence is commonly characterized by following three stages: 1.Bingeing / intoxication, 2.Withdrawal / negative effect, 3.Preoccupation / Anticipation.[5] Bingeing is defined as increase in intake of a voluntary substance with a high proportion of intake at one time, usually after a period of abstinence or deprivation. An increase in responsiveness to a repeatedly administered stimulus is called sensitization and gradual decrease in responsiveness is tolerance, such that same desired effect is produced by increased amount of substance.[6] Both are important at the beginning of the addiction cycle since both can increase responding and intake.[7] Signs of withdrawal become apparent when the abused substance is no longer available or is chemically blocked.

The concept of ''sugar addiction'' has been discussed about for many years now. Recently ''sugar addiction'' have been the topic of interest for many best-selling

books and the focus of various popular diet programs.[8,9,10] In above literature, people have described the symptoms of withdrawal whenever they were deprived of sugar-rich foods. They have also described food craving, particularly for sugar and other carbohydrates, which can further trigger impulsive eating. This leads to a perpetual cycle of self-medication with foods sweet in nature that may result in an eating disorder. Hence, Sugars are considered to have addictive properties.[8]

Moreover factors like obesity, depression, anxiety, bipolar disorders, disturbed emotional status, persons with low serotonin levels and premenstrual disorders in women have shown to make Individuals susceptible to sugar addiction.[11] So, there is a necessity to find out the plausible reasons for addictive nature of sugar, hence the present review was undertaken to find out the evidence of addiction potential of Sugar in Humans and ultimately to report the biological and psychological plausible reasons for sugar addiction.

METHODOLOGY

A systematic literature survey was carried out by two independent readers in electronic databases such as PubMed, Medline, Scopus, Embase, Science direct, Cochrane database, Google Scholar etc. using the key words "Sugar addiction" and "Sugar abuse". 260 references were identified through primary database from January 2000 to September 2016. Inclusion criteria- Randomized control trials conducted on Humans reporting changes at physiological and psychological levels after high carbohydrate intake as well as on animals reporting changes at neuro-chemical and psychological level published in English within above said time period were included in present review. Exclusion criteria- literature published in language other than English, reviews, duplicates, cross sectional studies and food addiction articles were excluded. So, 94 references were selected for screening after applying exclusion criteria. Further studies were excluded by reading the title. 38 abstracts qualified for the screening. 24 trails were selected for full text reading. Finally 18 trials were included in this review (12 Human and 6 Animal).

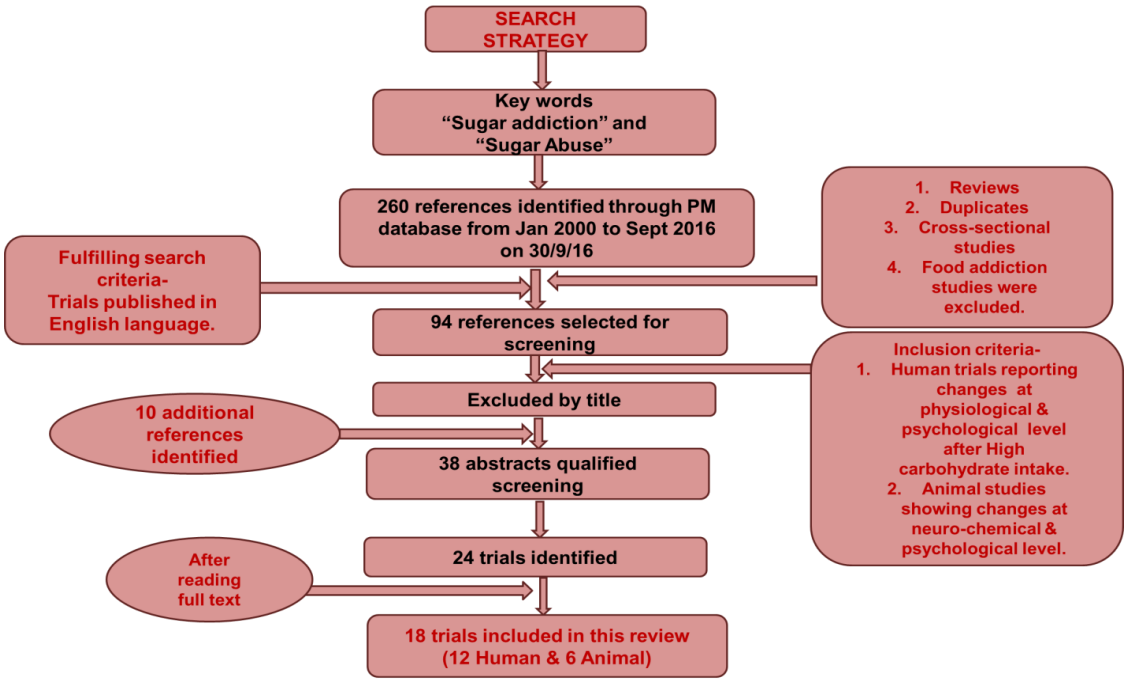


Table 1: Evidence for changes in Human Body after sugar consumption.

S.No	Author	Year	Subjects	Intervention	Findings
Physiological changes:					
1.	**Raben *et al*[12]**	**2002**	41 adults 35 female 6 male	1st gp- Sucrose 2nd gp- Artificial sweetener	**Total Energy intake, Sucrose consumption, BP, Body wt. –** Sig. increase in sucrose gp ($p<0.0001$).
2.	**Wurtman *et al*[13]**	**2003**	8 healthy adults 6 male 2 female	1st gp- Carbohydrate rich 2nd gp- Protien rich diet	**Insulin- Carb gp > protein gp ($p<0.05$)**
3.	**Stanhope *et al*[14]**	**2008**	34 Healthy adults 18 male, 16 female	1st gp- High fructose corn syrup 2nd gp- Sucrose sweetened beverage	**24-hr plasma profiles – Glucose, leptin, ghrelin, TG – NS($p>0.05$) Insulin- Sucrose beverages > HFSC. ($p<0.01$)**
4.	**Teff *et al*[15]**	**2009**	17 obese 9 male 8 female	1st gp- glucose 2nd gp- Fructose sweetened beverage	**24-hr plasma profiles – Glucose, leptin, ghrelin, TG & Insulin – Glucose gp > fructose gp ($p<0.0001$)**
5.	**Yu Z *et al*[16]**	**2013**	138 adults	1st gp- HFSC 2nd gp- Sucrose	**24-hr plasma profiles – Glucose, ghrelin – NS($p>0.05$) Insulin, Leptin, TG- sig. high in Sucrose gp ($p<0.05$)**
6.	**Heden *et al*[17]**	**2014**	40 adolescents	1st gp- Fructose 2nd gp- Glucose beverage	**Fasting level (12hr)- Glucose, Insulin, Lactate - NS($p>0.05$)**
Changes in Brain activity on MRI:					
1.	**Lennerz *etal*[18]**	2013	Healthy overweight and obese young male, aged between 18 and 35 yr,	1- High & 2- Low glycemic index meals	**Cerebral blood flow** in the right nucleus accumbens- greater after the high- than low-GI meal
2.	**Stice *etal*[19]**	2013	106 healthy-weight adolescents	1- high-fat/high-sugar, 2-high-fat/low-sugar, 3-low-fat/high-sugar, 4-low-fat/low-sugar chocolate milkshake and 5- tasteless solution	High-fat/high-sugar milkshake (compared with the tasteless solution) intake elicited robust activity in the bilateral postcentral gyrus that extended into the insula and right Rolandic operculum.
Psychological changes:					
1.	**Spring *et al*[20]**	2008	61 overweight women	1st gp- balanced protein rich 2nd gp- 100% Carbohydrate beverage	**Beverage choice- Carbohydrate beverage consumption-** Sig. increase ($p<0.0001$). **Reduction in Dysphoria-** Sig. reduction in Carb beverage gp ($p<0.05$).
2.	**Lemmens *et al*[21]**	2011	38 adults 19male 19female	1st gp- high Protein meal 2nd gp- high carbohydrate meal	**Test meal consumption- Wanting/liking of bread & drinks-** sig decrease ($p<0.001$) in both gps. More reduction in gp 1.
3.	**Lemmens *et al*[22]**	2011	27 normal weight (NW) 15 overweight adults (OW)	1st gp- high Protein meal 2nd gp- high Glucose meal Stress Vs rest condition	**Test meal consumption- Wanting/liking of dessert & snacks-** High Glucose gp > protein gp ($p<0.001$) **Stress Vs rest condition- Wanting/liking-** sig. increase in OW & Sig. decrease in NW ($p<0.02$).
5.	**Lowdens *et al*[23]**	2014	65 overweight	1st -10% Sucrose 2nd -20% Sucrose 3rd -10% Fructose 4th -20% Fructose	**Beverage consumption-** Sig increase in both 20% gps than 10% gps ($p<0.01$). 20% fructose > 10% Sucrose ($p<0.01$).

Table 2: Evidence for changes in Animals after sugar consumption.

S.No	Author	Year	Subjects	Intervention	Findings (Physiologcal changes)
1.	**Hajnal *et al*[24]**	2002	Rats	Sucrose gp v/s Plain water gp	**Dopamine release –** sucrose gp > water gp ($p<0.05$).
2.	**Avena *et al*[25]**	2006	Rats	Sham feed gp v/s Real feed gp (Sucrose water)	**Sucrose consumption-** Sham fed gp > real fed ($p<0.01$). **Acetycholine release-** real fed gp> Sham fed ($p<0.01$).
3.	**Avena *et al*[26]**	2008	Rats	Experimental gp- intermittent sugar+ chow v/s Control gp- ad libitum chow	**Dopamine release after 36 hrs-** sig. less in experiment gp ($p<0.05$).
4.	**Avena *et al*[27]**	2008	Rats	Experimental gp- sucrose bingeing v/s Control gp- ad libitum chow	**Dopamine release –** sucrose bingeing gp > control gp ($p<0.001$).
Psychological Changes:					
5.	**Lenoir *et al*[28]**	2007	Rats	Water with Saccharin v/s Intravenous Cocaine	**Preference –** Saccharin gp > cocaine ($p<0.01$).
6.	**Vendruscolo *et al*[29]**	2010	Rats	Plain water gp v/s Sucrose gp	**Preference-** Sucrose > water ($p<0.0001$).

RESULTS

Table 1: Human Trials

Physiological changes

Significant increase in total energy intake, BP and body weight were observed to be associated with increase in consumption of sucrose when compared with artificial sweetener.[12] Increase (significant) in production of Insulin in body with consumption of carbohydrate rich diet compared to protein rich diet.[13] 24 hour plasma profiles for insulin were found to be significantly increased with intake of sucrose beverage and glucose intake.[14,15,16] Associated significant increase in 24 hour plasma levels of leptin and triglycerides were observed with sucrose intake.[16] 12 hour non-significant rise in glucose, insulin levels with glucose intake was also reported by one of the authors.[17]

Brain activity after sugar intake on MRI

Increased cerebral blood flow in right nucleus accumbens after intake of high glycemic index meal.[18] Also robust activity was reported in bilateral postcentral gyrus upon intake of high fat/high sugar milkshake.[19]

Psychological changes

Significant increase in carbohydrate rich beverage as a beverage of choice than protein rich beverage, also significant reduction in dysphoria after consumption of carbohydrate rich beverage was reported.[20] With consumption of the High protein and high carbohydrate meal a pre- to post-meal decrease in 'wanting' for bread, filling, drinks, dessert, and snacks was reported ($P < 0.04$). The effect was more evident in high protein meal consumption group than the high carbohydrate group however the effect disappeared during stress.[21] During stress 'Wanting' for dessert and snacks, energy intake, carbohydrate and fat intake was found to be relatively increased in visceral overweight vs. decreased in normal weight ($p<0.02$).[22] Significant increase in beverage consumption was reported in overweight population in 20% sucrose as well as 20% fructose groups than their 10% counterparts.[23]

Table 2

Animal studies

Physiological changes

Significant amount of dopamine release in rats was observed on sucrose/sugar consumption compared to plain water, ad libitum chow by Hajnal 2002, Avena 2008, Avena 2008 respectively.[24,26,27] Significantly increased levels of acetylcholine were reported among rats in sucrose fed group by Avena in 2006.[25]

Psychological Changes

Significantly increased preference for saccharin compared to cocaine was reported among rats by Lenoir 2007.[28] Further Vendrusco in 2010 reported significantly increased preference for sucrose water compared to plain water among rats.[29]

DISCUSSION

Sugar addiction represents a specific case of food addiction. Possible reason for its addictive properties may be because of presence of a specific nutrient i.e. Sucrose.[30] This evidence is supported in present review by various animal studies which showed that sucrose intake result in production of neuro-chemical substances such as Dopamine in brain of these animals.[24,26,27,31]

Animal studies

In addiction the central role in reward and craving is played by nucleus accumbens (part of striatum), into this mesolimbic dopaminergic system of the brain converges. Nucleus accumbens plays a significant role in the cognitive processing of motivation, aversion, reward (i.e. pleasure and positive reinforcement), and reinforcement learning, hence it is assumed to have a significant role in addiction.[32,33] In animal (rat) studies, the concentrations of dopamine and its metabolites in the nucleus accumbens increased more after the consumption of

sugar rich substrates and increased preference for sugar rich beverages compared to plain water and even cocaine was also observed.[24,29] Avena 2006 reported increased secretion of acetylcholine with increased consumption of sucrose.[25] This can be supported by theory that acetylcholine is normally important for the satiation process.[34] It also suggests that by purging, one eliminates the acetylcholine response that opposes dopamine. Acetylcholine theoretically inhibits appetitive approach and stimulates the aversion-avoidance path; this could be due to synaptic effects at muscarinic M2 and M1 receptors, respectively.[34]

Clinical studies

MRI changes

Clinical studies that used functional brain imaging have reported greater activation in the nucleus accumbens or other regions of the striatum in obese than lean individuals after they consumed palatable sugar rich food.[18,19] This can be explained by the fact that increase in blood flow in right nucleus accumbens plays a central role in reward and craving and high sugar intake also elicited robust activity in the bilateral postcentral gyrus that extended into the insula and right Rolandic operculum which are known to be involved in reward, motivation and oral somato-sensation.[18,19] This is also supported by further findings of increase in likeliness or wanting for carbohydrate meal/beverage more than that for protein meals.[12,20,23]

•At Physiological level

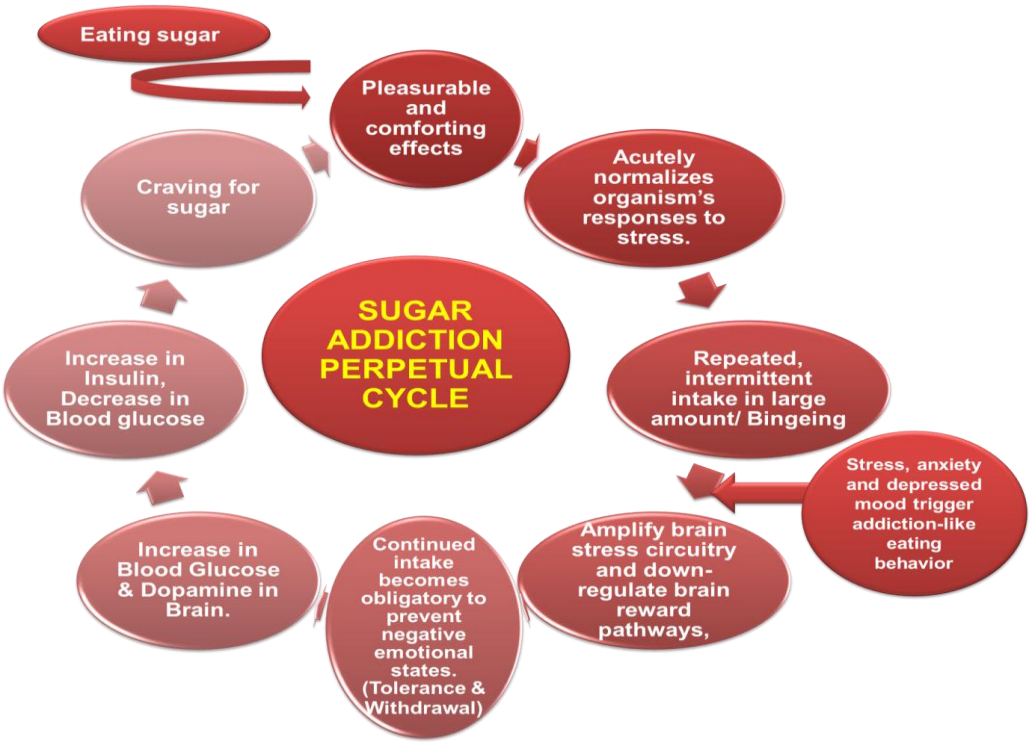
In fructose groups reduced postprandial insulin levels contribute to blunted postprandial suppression of ghrelin compared to glucose containing beverages with meals.[8] Ghrelin has been proposed to be involved in meal initiation in humans may also contribute to increased food intake.[14,15] In contrast to glucose metabolism, which is controlled by the rate limiting enzyme phosphofructokinase and subject to negative feedback control by elevated cytosolic levels of ATP and citrate, fructose metabolism is relatively unregulated. Thus, after ingestion of large amounts of fructose, increase in hepatic acetyl-CoA lead to increased production of very low density lipoprotein and triglycerides (TGs).[17]

•At Psychological level

The available evidences are limited because of difficulty in comparing different types of rewards and psychological experiences in humans. Foods with the macronutrient contents used in one study seemed ineffective in regulating the psychological stress response, the rewarding value of food, and the stress-induced food choice and food intake.[20,23]

Sugar addiction perpetual cycle to discuss biological plausibility

Introduction of sugar substrate in human as well as animal body normalizes organism's response to stress resulting in repeated intake/ bingeing of sugar. Stress, anxiety and depressed mood acts as triggering factors for addiction like behavior. Bingeing result in brain stress circuitry pathway and down regulation of brain reward pathways. This resulted in release of Dopamine in human brain which acts as pleasure hormone and elevates the mood of individual and increase in blood glucose level which is regulated by increase in insulin level in body. This is a vicious cycle resulting in addiction like behavior. This can be depicted as following:



CONCLUSION

There is some evidence of sugar addiction among laboratory animal models which gives biological plausible answers but the same may not be true among humans as there are multiple factors affecting the human behavior like stress, anxiety, depression and other systemic illness. Extensive research is necessary among human subjects to verify the link of sugar as addictive substance.

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