Journal of Food Bioactives
International Society for Nutraceuticals and Functional Foods
Original Research
J. Food Bioact. 2018;3:161–167

Chronic increase in sugar consumption and visual attention in Wistar rats

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DOI: 10.31665/JFB.2018.3159
Received: September 04, 2018; **Revised received & accepted:** September 14, 2018
Citation: Lange, K.W., Hauser, J., Kaunzinger, I., Nakamura, Y., Reissmann, A., Stollberg, E., Guo, J., and Li, S. (2018). Chronic increase in sugar consumption and visual attention in Wistar rats. J. Food Bioact. 3: 161–167.

Abstract

High sugar consumption is known to elevate the risk of obesity and related metabolic disturbances, but far less is known about its effects on cognition, learned behavior and mental health. Experimental findings in rodents indicate that increased sugar intake can induce cognitive impairment, most consistently in regard to memory functions. Studies examining the effects of an increase in dietary sugars on attention are lacking. The present study investigated the effects on visual attention of chronic high intake of sucrose and glucose in Wistar rats. Two groups of Wistar dams and their offspring were fed either a diet high in sugar, containing a high percentage of sucrose and glucose, or a standard sucrose/glucose diet. Attention was examined using a 3-choice-serial-reaction-time task. The present results demonstrated detrimental effects of high pre- and postnatal sugar consumption on visual attention in rats. The previously demonstrated memory impairments following increased sugar consumption may be mediated, at least partly, by attentional deficits. Future studies should investigate the translational relevance of these findings in humans, particularly in regard to mental disorders such as attention deficit/hyperactivity disorder (ADHD). Emerging evidence suggests that the mechanisms underlying the behavioral impairments related to diets high in sugar and/or fat may include neuroinflammation, changes of the blood–brain barrier and altered levels of brain-derived neurotrophic factor (BDNF). The elucidation of these mechanisms requires further investigations.

Keywords: Attention; Cognition; Attention deficit/hyperactivity disorder; Sugar; Rat.

1. Introduction

Nutrition and diet play a significant role in the development and progression of many non-communicable diseases, such as obesity, type 2 diabetes mellitus, dyslipoproteinaemia, metabolic syndrome, hypertension, cardiovascular diseases, and cancer (Lange, 2017). Furthermore, the relative contribution of nutrition-related non-communicable diseases to the total disease burden of society and health care expenditure has risen steadily over recent decades. Overweight and obesity trends have been rising worldwide. For example, a tenfold increase in obesity in children and adolescents between 1975 and 2016 has been shown (NCD Risk Factor Collaboration, 2017). Carbohydrates, in particular, may be relevant in the pathophysiology of non-communicable diseases (Evans, 2017). The findings of numerous studies have suggested a direct association between the intake of free sugars or sugar sweetened

beverages and weight gain, overweight and obesity (for review see Te Morenga et al., 2012; Malik et al., 2013; Keller and Bucher Della Torre, 2015). The epidemiological evidence of the associations between the consumption of sugars and the incidence of obesity and type 2 diabetes mellitus have led to national and international recommendations regarding sugar intake for adults and children (Hauner et al., 2012; World Health Organization, 2015; Tappy et al., 2018). The World Health Organization (WHO) recommends a reduced sugar consumption throughout the life course, with a reduction of the intake of free sugars to less than 10% and preferably below 5% of the total energy intake in both adults and children (World Health Organization, 2015).

While high dietary sugar intake is known to increase the risk of obesity and related metabolic disturbances, much less is known about the cognitive and behavioral effects of high sugar consumption. A clear association between mid-life obesity and cognition, cognitive decline, and risk of dementia in later life has been demonstrated (for review see Dye et al. 2017). Furthermore, the intake of diets high in processed, high-fat, high-sugar foods during adolescence and adulthood have been shown to be associated with mental disorders, such as depression and anxiety (Lai et al., 2014; O'Neil et al., 2014). Cross-sectional studies have shown an association of depression with the consumption of sweet foods (Jeffery et al., 2009) or of foods with a high glycemic index (Mwamburi et al., 2011). However, cross-sectional studies do not provide evidence of causality, and the relationship between sugar consumption and depression may be bidirectional. Random assignment to diets with a higher carbohydrate content and glycemic load has been shown to have negative effects on mood (Cheatham et al., 2009; Micha et al., 2011).

Some early studies have suggested that increased intake of added sugars may be a factor in ADHD. For example, hyperactive children ingesting larger amounts of sugar were reported to show greater hyperactivity (Prinz et al., 1980). A dose-response relationship between ADHD and the consumption of sugar-sweetened beverages could also be shown (Yu et al., 2016). Furthermore, inattention was shown to increase following acute ingestion of sugar in individuals with ADHD (Wender and Solanto, 1991). However, other studies were unable to provide convincing evidence that sugar intake is related to symptoms of ADHD (Kim and Chang, 2011; White and Wolraich, 1995; Wolraich et al., 1985; Wolraich et al., 1994). In a meta-analysis examining the effects of sugar consumption, no effects could be found on the behavior and cognition of children, while small sugar effects or effects on subgroups of children could not be ruled out (Wolraich et al., 1995).

The findings of investigations in rodents indicate that sugar intake can induce cognitive impairment, with deficits related to spatial learning and memory most consistently observed, and younger animals were found to be particularly sensitive to the effects of sugar on reward processing (for review see Kendig, 2014). For example, short-term exposure to a diet rich in sugar impaired place recognition memory prior to the emergence of weight differences (Beilharz et al., 2014) while diet-induced obesity resulting from excess sucrose intake, but not fat intake, in young rats impaired spatial learning and memory (Jurdak et al., 2008). Chronic sucrose consumption in rats led to a metabolic condition suggestive of a prediabetic state which was associated with short- and long-term spatial memory deficits (Soares et al., 2013). A diet high in fructose, accompanied by a reduction of omega-3 polyunsaturated fatty acids, resulted in a marked decline in spatial memory functions (Agrawal and Gomez-Pinilla, 2012). Transgenerational administration of a Western diet with increased amounts of sugar and saturated fatty acids impaired local discrimination in rats (Lange et al., 2018). Intake of excess sugar was shown to induce insulin resistance and to exacerbate memory deficits and amyloidosis in a transgenic mouse model of Alzheimer's disease (Cao et al., 2007).

Taken together, the available research findings indicate an association between high dietary intake of sugar and an impairment of cognitive functions such as spatial memory. Investigations assessing the effects of sugar consumption on attentional functions have focused primarily on ADHD. However, the small number of available studies differed widely in their methodology, the types of employed samples and the parameters measured. Moreover, it is difficult to control and quantify the dietary intake of sugars and to distinguish the effects of diet from other sociocultural influences in human studies. Therefore, the present study has investigated whether visual attention of rats can be impaired by a diet high in sucrose and glucose.

2. Methods

2.1. Apparatus and testing procedure

The 3-choice-serial-reaction-time task (3-CSRTT) used in this study is a modification of the 5-CSRTT (Bari et al., 2008), an established test for the assessment of visual attention in rodents. It requires subjects to detect brief flashes of light presented in a pseudorandom order in one of three spatial locations over a large number of trials. Both the apparatus used and the 3-CSRTT have been described in detail elsewhere (Hauser et al., 2018a; Hauser et al., 2018b; Stollberg et al., 2018).

2.2. Animals and feeding procedure

Wistar rats were used in this experiment. Dams and their offspring were fed an experimental diet high in sucrose and glucose or a standard diet normally used for keeping and breeding. Both diets were delivered by Ssniff (Soest, Germany; high sucrose/glucose diet based on AIN93G); for details see Table 1. Female and male Wistar rats were delivered by Charles River Laboratories (Sulzbach, Germany). Dams were randomly assigned to the diet groups. The behavioral experiment was performed with the male offspring of the high sucrose/glucose diet (n = 17), or the standard sucrose/glucose diet (n = 12) fed dams. The specific experimental diets were provided to the dams during prenatal, perinatal and lactation periods, and, after weaning, to the male offspring until the end of the experiment.

At the beginning of the experiment, male rats of the experimental groups were eight weeks old (body weight approximately 250–300 g). The rats were housed in standard cages under standard animal laboratory conditions (12:12 h light/dark cycle, room temperature 22 °C, humidity 50%) in the animal laboratories of the University of Regensburg. All treatments, trainings and testings were performed during the light phase between 9 a.m. and 4 p.m. During the behavioral experiments, access to food was restricted since the behavioral paradigm used in this study (3-CSRTT) is based on food reinforcement. Water was provided ad libitum. After the training or testing procedures, the rats had free access to food for at least three hours a day. The rats' weight was carefully controlled, and weight reduction was avoided in order to prevent stress (Deroche et al., 1995) and subsequent changes in the dopaminergic system (Pothos et al., 1995). Rats were monitored daily for health concerns and body weight. After the experiments, rats

Table 1. Composition of the experimental diets

	High sucrose/glucose diet *Experimental customized*	**Standard sucrose/glucose diet** *Standard control*
Energy (Atwater), MJ/kg*	16.0	13.6
Protein, kJ%	19	25
Carbohydrates, kJ%	69	65.5
Fat, kJ%	12	9.5
Sucrose/glucose (1:2 by weight) composition, % of diet	30.8	5.5

*Physiological fuel value

were sacrificed using carbon dioxide.

2.3. Statistical analysis

All findings concerning group differences and comparisons between the diet groups are expressed as means ± standard errors. The statistical analysis of differences between the diet groups was performed using the Mann-Whitney U-test; an α-level of 0.05 was applied. All statistical analyses were performed using the Statistical Package for Social Sciences 21.0 (SPSS) for Windows.

2.3.1. Attention parameters

The following attention-related parameters were analyzed: (1) number of correct responses (a reaction in an illuminated hole), (2) number of incorrect responses (errors of commission, i.e. a reaction in a non-illuminated hole), (3) number of omissions (no reaction to a presented stimulus), (4) percentage of correct responses (number of correct responses/total number of responses [correct and incorrect]) and (5) percentage of omissions (total number of missed responses/total trials presented expressed as percent).

2.3.2. Impulsivity parameters

The following parameters in regard to behaviors associated with impulsivity were analyzed: (6) number of premature responses, i.e. nose poke responses during intertrial intervals (ITI), (7) number of food tray panel pushes during ITI, (8) number of time-out responses, i.e. nose poke responses during time-out period, and (9) total number of perseverative responses following a correct response (in correct hole and in incorrect hole).

2.3.4. Activity parameters

In order to compare general activity between the two diet groups, the following parameters were analyzed: (10) number of trials completed, (11) the correct response latency, (12) the commission error latency, and (13) the reward collection latency.

2.4. Ethics

All experiments were performed in accordance with national laws (German law on protection of animals) and the principles of laboratory animal care (NIH publication No. 86- 23, revised 1996). The rats were handled according to the guidelines of the Federation for European Laboratory Animal Science Associations (FELASA). The rats were monitored daily for health concerns and body weight. Body weight was assessed in order to avoid a reduction of body weight as a consequence of restricted food access. In case of weight loss, the rats were fed individually and were given free access to food for more than 3 hours a day.

3. Results

In regard to body weight, none of the differences between the high sucrose/glucose diet group and the standard sucrose/glucose group were statistically significant. At the beginning of the training, the animals of the high sugar group weighed 403.87 ± 12.61 g (mean ± standard error) and those of the standard sugar group 367.80 ± 9.53 g ($Z = -1.816$, $p = 0.069$). At the beginning of the testing sessions, the high sugar group weighed 444.65 ± 13.34 g, and the standard sugar group 421.18 ± 8.37 g ($Z = -1.638$, $p = 0.101$).

The present results show differences between the high sucrose/glucose and standard sucrose/glucose groups in parameters associated with attentional processes, as measured by the 3-CSRTT. The rats of the high sugar group made a statistically significant fewer number of correct responses ($Z = -2.526$, $p = 0.012$), fewer incorrect responses ($Z = -2.468$, $p = 0.014$) and more omissions ($Z = -1.996$, $p = 0.046$) compared to the standard sugar group. The percentage of omissions was also significantly higher in the high sugar group ($Z = -2.745$, $p = 0.006$).

With regard to parameters associated with impulsive behavior, the data show a reduction in the high sucrose/glucose group compared to the standard sugar group. The standard sucrose/glucose group made more panel pushes during ITI ($Z = -2.591$, $p = 0.010$), more premature responses, more timeout responses and more perseverative responses. The latter three comparisons failed to reach statistical significance. Concerning the activity parameters, only the reward collection latency ($Z = -4.428$, $p < 0.001$) and the number of trials completed ($Z = -2.208$; $p = 0.027$) showed statistically significant differences between the two groups. All other comparisons between the groups failed to attain statistical significance. Detailed data are provided in Table 2.

4. Discussion

The available scientific literature clearly indicates that sugar consumption in rodents can induce cognitive dysfunction, especially impaired spatial learning and memory. In particular, cognitive impairments were seen when sugar intake in animals was similar to that in humans (Kendig, 2014). This study aimed to investigate the chronic effects of a diet rich in sucrose and glucose on visual

Table 2. Test performance of the high and standard sucrose/glucose groups as measured using the 3-CSRTT (mean ± standard error), stimulus duration 2.5 s

	High sucrose/glucose diet *Experimental customized*	**Standard sucrose/glucose diet** *Standard control*
Attention parameters		
No. of correct responses	37.85 ± 3.18#	49.88 ± 2.87
No. of commission errors	2.74 ± 0.49#	4.96 ± 0.62
No. of omission errors	16.09 ± 1.39#	10.67 ± 1.72
Correct responses, %	92.79 ± 1.38	90.80 ± 1.18
Omissions, %	29.97 ± 3.06#	16.39 ± 2.72
Impulsivity parameters		
No. of premature responses	11.76 ± 2.01	18.54 ± 3.30
No. of panel pushes during ITI	41.06 ± 6.90#	78.63 ± 11.78
No. of time-out responses	9.38 ± 2.02	15.17 ± 2.78
No. of perseverative responses	1.44 ± 0.32	2.21 ± 0.55
Activity parameters		
No. of trials completed	56.68 ± 3.23#	65.50 ± 2.61
Correct response latency (s)	1.35 ± 0.07	1.12 ± 0.07
Commission error latency (s)	1.59 ± 0.25	1.37 ± 0.27
Reward collection latency (s)	1.72 ± 0.13#	1.07 ± 0.04

#p ≤ 0.05 compared with standard sucrose/glucose diet

attention in Wistar rats. For this purpose, Wistar dams were fed one of two different diets, either a standard diet containing 5.5% of a sucrose/glucose composition or an experimental diet with 30.8% sucrose/glucose. These diets were maintained in the offspring. Visual attention was assessed in the male offspring using the 3-CSRTT, which also assesses premature responding as a form of motor impulsivity.

In comparison with the standard sucrose/glucose group, the rats of the high sugar group made significantly fewer correct responses and more omission errors, and the percentage of omissions was significantly higher. These findings indicate impaired visual attention following chronic pre- and postnatal intake of a high sugar diet. The significantly fewer incorrect responses in the high sugar group may be explained by the fact that this group was less active, as was shown by the significantly smaller number of completed trials (see Table 2). In regard to 3-CSRTT parameters assessing motor impulsivity, only the number of panel pushes during ITI differed significantly between the two groups. Since other measures of premature responding failed to show statistically significant differencs between groups (see Table 2), a major effect of sucrose/glucose consumption on motor impulsivity could not be found.

The body weight of the animals tested was measured to determine whether the two diets used led to different levels of weight gain. Mean body weight of the rats fed the diet high in sucrose and glucose was higher, though not significantly, than those on the standard diet, both at the beginning of the training (by about 10%) and during the testing period (by about 5%, see Table 2).

Overweight and obesity are important determinants of various diseases (e.g. Kopelman, 2000). In regard to cognitive decline, overweight in middle-age predicted reduced performance in several cognitive functions, such as long- and short-term memory as well as verbal and spatial ability, in later life (Dahl et al., 2010). Obesity has been shown to be associated with cognitive impairment and an increased risk of dementia (Haslam and James, 2005; Bruce-Keller et al., 2009; Dye et al., 2017). Explanations of the association between obesity and cognition are related to aspects of metabolic syndrome including inflammation (Yaffe et al., 2004) or of cardiovascular disease including hypertension (Elias et al., 2003; Waldstein and Katzel, 2006).

It has been proposed that cognition is not directly influenced by obesity, but that the consumption of diets high in sugar and/or fat induces more rapidly occurring central and peripheral changes, including inflammation, which mediate the effects on cognition (Beilharz et al., 2015). Increased intake of simple sugars has been found to be associated with a decline in cognitive functioning. For example, a prospective cohort study of elderly people demonstrated the impact of the relative intake of the macronutrients sugar and fat (Roberts et al., 2012). Participants who derived a relatively high amount of energy from carbohydrates showed an elevated risk of mild cognitive impairment or dementia, while the risk was reduced in those with a high percentage of energy intake from fat and protein (Roberts et al., 2012). In a cross-sectional study of elementary school children, an inverse relationship between the intake of refined sugars and non-verbal intelligence was found, even following adjustment for body mass index (Abargouei et al., 2012).

The effects of high sucrose intake during pregnancy on ADHD-like behavioral phenotypes were studied in mouse offspring (Choi et al., 2015). While the high sucrose-exposed offspring showed no obvious changes in gross development, such as body weight gain, significantly increased locomotor activity as well as a dose-dependent decrease in attention and increase in impulsivity were observed (Choi et al., 2015). These findings correspond with the present results of impaired visual attention in rat offspring following a prenatal (and postnatal) exposure to large amounts of dietary sucrose/glucose. This points to sugar consumption prenatally and

during early development as a risk factor of ADHD, which warrants further investigations in humans. A dose-response relationship between the consumption of sugar-sweetened beverages and ADHD in children has been shown (Yu et al., 2016). However, the interrelationship of dietary macronutrients such as sugars with other lifestyle factors including physical exercise needs to be considered (Lange, 2018).

Several investigations have demonstrated the negative impact on brain function of an excessive intake of high sugar and high fat foods during adolescence, causing impaired cognition and altered reward processing (for review see Reichelt and Rank, 2017). Increased neuroplasticity in the adolescent brain may be associated with an increased vulnerability to the effects of poor dietary choices including the consumption of "junk" foods high in fat and sugar. These foods may adversely influence maturational processes underlying cognitive control and behavior by causing alterations in dopamine-mediated reward signaling and inhibitory neurotransmission controlled by γ-aminobutyric acid (Reichelt, 2016). The brain regions affected by such dietary effects may include the prefrontal cortex, which is involved not only in the activation of neural circuits mediating reward but also in the control of cognitive functions, such as attention and learning (Bechara et al., 1999; Reichelt, 2016). Other mechanisms linking poor diet to cognitive impairment include oxidative stress and inflammation (Beilharz et al., 2014), decreased levels of neurotrophic factors (Molteni et al., 2002), an increase in the permeability of the blood-brain barrier (Kanoski et al., 2010; Davidson et al., 2012), and insulin insensitivity (Calvo-Ochoa et al., 2014; Wu et al., 2015). Chronic low-grade inflammation has been suggested to be involved in many diet-related diseases (e.g. Dantzer et al., 2008; Figaro et al., 2006; Halaris, 2013). Diet-induced inflammation may also provide an explanation for a specific impact of high fat-sugar diets on cognitive processes related to the hippocampus and other brain areas. For example, rats on high fat-sugar diets showed elevated levels of inflammatory markers (Pistell et al. 2010) and specific neuroinflammatory responses in the hippocampus (Boitard et al., 2014; Castanon et al., 2015). It needs to be investigated whether the molecular effects of diets high in sugar and/or fat act independently or whether they are related to one another. For example, an impaired blood–brain barrier could contribute to neuroinflammation which might reduce the production of brain-derived neurotrophic factor (BDNF).

Diet-induced gut dysbiosis may play a role in the development of cognitive alterations, and the microbiota-gut-brain axis may constitute a mechanistic link between impaired cognition and the consumption of diets high in added sugar and/or saturated fat (Noble et al., 2017; Proctor et al., 2017). Gut bacteria have been linked to alterations in intestinal permeability and integrity of the blood-brain barrier, thereby rendering the brain more vulnerable to the influx of deleterious substances from the bloodstream. For example, consumption of a "Western" diet may increase the production of endotoxins by commensal bacteria, which could promote neuroinflammation and consequent cognitive dysfunction (Noble et al., 2017). Diet-induced alterations in gut microbiota can also impair peripheral insulin sensitivity, which is associated with neuronal alterations in the hippocampus and mnemonic impairments (Noble et al., 2017). The microbiome could be a useful target when treating diet-associated cognitive decline, since specific probiotics or prebiotics have been shown to be able to prevent or reverse some of the negative effects of a Western diet on neuropsychological measures (see Noble et al., 2017).

In summary, the results of the present study demonstrate detrimental effects of chronic high sugar intake on visual attention in rats. The sugar-induced memory impairments demonstrated in previous studies may be mediated, at least partly, by attentional deficits. In the present study, a sugar-rich diet was consumed both pre- and postnatally. Future studies should investigate dietary influences in the prenatal and postnatal phases of development respectively. Increased neuroplasticity during intrauterine development, early childhood and adolescence may render the brain particularly vulnerable to deleterious effects of environmental factors such as diet. The effects of acute versus chronic exposure to dietary sugar are also of interest. Moreover, the neurochemical and physiological mechanisms mediating these dietary effects on the brain need further investigation. As well as a reduction in the intake of sugars, other interventions seeking to prevent and reverse diet-induced cognitive deficits require further study. For example, an increase in the consumption of polyunsaturated fatty acids, an increased ratio of polyunsaturated to saturated fatty acids, and physical activity may be associated with improved cognitive functions (e.g. Kalmijn et al., 2004; Molteni et al., 2004; Morris et al., 2004). Caution is needed when extrapolating the effects of sugar on cognition in animals to humans, and the translational relevance of the present findings for human conditions such as ADHD, depression and dementia should be examined.

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