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Research review

Cognitive and behavioural effects of sugar consumption in rodents. A review ☆

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ABSTRACT

The pronounced global rise in sugar consumption in recent years has been driven largely by increased consumption of sugar-sweetened beverages. Although high sugar intakes are recognised to increase the risk of obesity and related metabolic disturbances, less is known about how sugar might also impair cognition and learned behaviour. This review considers the effects of sugar in rodents on measures of learning and memory, reward processing, anxiety and mood. The parallels between sugar consumption and addictive behaviours are also discussed. The available evidence clearly indicates that sugar consumption can induce cognitive dysfunction. Deficits have been found most consistently on tasks measuring spatial learning and memory. Younger animals appear to be particularly sensitive to the effects of sugar on reward processing, yet results vary according to what reward-related behaviour is assessed. Sugar does not appear to produce long-term effects on anxiety or mood. Importantly, cognitive impairments have been found when intake approximates levels of sugar consumption in people and without changes to weight gain. There remain several caveats when extrapolating from animal models to putative effects of sugar on cognitive function in people. These issues are discussed in conjunction with potential underlying neural mechanisms and directions for future research.

Introduction

A significant change to human diet composition in recent centuries has been the increase in intake of sugars, with an estimated rise in per capita consumption from 5 kg to 70 kg per year from 1800 to 2006 (Tappy, 2012). Rising sugar consumption is no longer unique to North America and now affects the majority of the developed and developing world (Basu, McKee, Galea, & Stuckler, 2013; Lustig, Schmidt, & Brindis, 2012). This increase is largely attributable to rising consumption of *sugar-sweetened beverages* (SSBs), which contributed to 80% of the increase in added sugar consumption during the period 1962–2000 in the USA (Popkin & Nielsen, 2003) and which today are easily the largest single source of added sugar consumption (Yang et al., 2014). The percent contribution of SSBs to total caloric intake has also increased for both adults (Duffey & Popkin, 2007) and children and adolescents (Wang, Bleich, & Gortmaker, 2008). Today most individuals draw between 5% and 20% of total calories from added sugar, although this proportion is over 25% for 13% of the American population (Marriott, Olsho, Hadden, & Connor, 2010) and above 20% for many adolescents (Krebs-Smith, 2001).

Consuming too much sugar is increasingly viewed as a risk factor for many chronic diseases and not simply obesity and dental caries (Schmidt, 2014). Meta-analyses have found higher levels of sugar intake to be associated not only with weight gain (Te Morenga, Mallard, & Mann, 2013) but also with metabolic syndrome and type-2 diabetes (Malik & Hu, 2012) and cardiovascular disease incidence and mortality (Malik et al., 2010; Yang et al., 2014). Additionally, intervention studies have reported SSB-induced metabolic damage in the absence of total body weight change or total energy intake (Aeberli et al., 2011; Maersk et al., 2012). In light of this research, calls for public health interventions targeted at reducing the disease burden associated with sugar (e.g. Brownell et al., 2009; Lustig et al., 2012) have been followed by changes to public policy. A well-documented example is the introduction of taxes on SSBs by several governments in recent years, with a recent meta-analysis suggesting that this approach is effective (Escobar, Veerman, Tollman, Bertram, & Hofman, 2013). Additionally, the World Health Organization's current draft guidelines on sugar now advise that sugar comprise <5% of total energy intake, beyond the stated upper limit of 10% introduced in the 2003 guidelines (World Health Organization, 2014). Lastly, some epidemiological studies (Bray, Nielsen & Popkin, 2004) and studies in animals (e.g. Thresher, Podolin, Wei, Mazzeo, & Pagliassotti, 2000) have suggested that the harmful metabolic effects of sugar are primarily attributable to the monosaccharide fruc-

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tose, which, together with glucose, form one-half of sucrose. However, others contend that the experimental conditions used to elicit these effects are not representative of fructose consumption in the human diet, and that the effects of fructose are often equivocal when consumed at more moderate levels (Tappy & Mittendorfer, 2012; White, 2013).

Animal models, which allow for stricter control over diet and extraneous variables than studies in people, have found that rodents given free access to highly concentrated sugar solutions (above 30% w/vol) commonly show accelerated body weight gain and adiposity amongst other metabolic impairments (Chen et al., 2011; Kanarek & Orthen-Gambill, 1982; Kawasaki et al., 2005; Lindqvist, Baelemans, & Erlanson-Albertsson, 2008; Sclafani, 1987), and can also develop metabolic impairments without changes to body weight gain (Soares et al., 2013). Rodents fed lower concentrations comparable with those of SSBs, such as 10% sucrose solution, can also develop metabolic damage, although weight gain is normally unchanged as animals compensate for the calories in solution by reducing their consumption of solid chow (e.g. Avena, Bocarsly, & Hoebel, 2012; Sheludiakova, Rooney, & Boakes, 2012), with some exceptions (e.g. Chan, Kendig, Boakes, & Rooney, 2013; Kendig, Rooney, Corbit & Boakes, 2014b). Feeding sugar as part of a solid diet can induce metabolic disturbances, reduce reproductive success and lower lifespan in rodents (Chicco et al., 2003; Hulman & Falkner, 1994; Preuss et al., 1991; Ruff et al., 2013), but this method is less reliably associated with hyperphagia and obesity (Sclafani, 1987).

Sugar and behaviour

In contrast to extensive research on the physical health effects of sugar consumption, less is known about how sugar affects behaviour and cognition. A popular and persisting theory is that sugar fosters hyperactive or aggressive behaviour, particularly in children. This view was informed by early studies reporting positive associations between sugar consumption and levels of restless and "destructive–aggressive" behaviours in children (e.g. Prinz, Roberts, & Hantman, 1980), and that removing sugar from the diet improved the behaviour of juvenile prison inmates (Schoenthaler, 1983) and hyperactive children (Crook, 1974). A more recent cross-sectional study of adolescents found that the odds ratios for mental difficulties (encompassing measures of mental distress, hyperactivity and conduct problems) were highest in those reporting the greatest levels of SSB consumption (~800 ml or more/day; Lien, Lien, Heyerdahl, Thoresen, & Bjertness, 2006). However, in a sample of Korean fifth-grade children, Kim and Chang (2011) found no relationship between consumption of simple sugars and the development of ADHD.

The relationship between sugar and hyperactivity/aggression seen in some correlational studies contrasts the results of the bulk of experimental studies, which have found no effect of sucrose on behaviour and cognition. A meta-analysis of 23 double-blind intervention studies found no significant effects of sugar on 14 behavioural measures (Wolraich, Wilson, & White, 1995). Null effects of sugar ingestion have been reported in laboratory-based studies of "sugar-responsive" children (e.g. Kruesi, Rapoport, Cummings, & Berg, 1987) and in children diagnosed with ADHD as well as age-matched children without ADHD (Wender & Solanto, 1991). Studies conducted over the longer term and in the home environment report similar results; for example, a home-based dietary intervention study where "sugar-sensitive" children were fed sucrose-, aspartame- or saccharin-sweetened diets for 3-week periods found no differences on 31 cognitive and behavioural outcomes measured weekly (Wolraich et al., 1994). A review by Benton (2008) concluded that there was no evidence for any negative effects of sugar on behaviour, and reported that three putative mechanisms by which sugar is thought to cause behavioural problems – intolerance to sugar, reactive hypoglycaemia following ingestion, and reduced intake of essential micronutrients – were not supported in literature.

Thus, there does not appear to be a causal relationship between sugar consumption and hyperactive, aggressive or antisocial behaviours. Although this is inconsistent with the positive correlations found in some cross-sectional, population-based studies, it has been suggested that the latter effects are explained by reverse causation, such that children who are hyperactive or who have behavioural difficulties are more inclined to consume greater levels of sugar (Bellisle, 2004; Benton, 2008). As outlined in this review, however, increasing evidence from animal models indicates that other aspects of behaviour and cognition can be affected in animals fed a diet supplemented with sugar.

Sugar, reward and addiction

As a highly palatable and calorie-dense food, sugar activates brain regions involved in reward processing as well as energy regulation (Kenny, 2011). Indeed, the activation of brain reward circuitry by palatable foods is thought to override homeostatic signals and stimulate unnecessary eating to promote obesity development (Volkow & Wise, 2005). When lever-pressing for sucrose, rats show enhanced c-fos protein activation in limbic brain regions involved in reward as well as in hypothalamic areas involved in feeding behaviour (Figlewicz, Bennett-Jay, Kittleson, Sipols, & Zavosh, 2011). Furthermore, consumption of a sucrose solution triggers opioid and dopamine release in the nucleus accumbens, with downstream effects on other limbic and forebrain regions (Pomonis et al., 2000) and dopamine and opioid antagonists can selectively block the reinforcing properties of sucrose (for review, see Levine, Kotz, & Gosnell, 2003). Additionally, the hedonic properties of sweet tastes may outcompete those of drugs of abuse. A frequently cited example is the finding that in a two-lever choice task, an overwhelming majority of rats (94%) preferred to lever-press for sucrose and saccharin solutions than for intravenous cocaine (Lenoir, Serre, Cantin, & Ahmed, 2007).

Much has been made of observations that similar neural circuitry is activated by food and drug rewards. This has prompted consideration of the parallels between obesity and drug addiction, although this comparison has received criticism (see Ziauddeen, Farooqi, & Fletcher, 2012). Arguably a more pertinent question is to consider whether palatable foods themselves, such as sugar, can come to elicit addiction-like behaviours. To this end, Hoebel and colleagues developed an animal model in which rats are maintained on a cycle involving 12 h access to a sucrose or glucose solution and chow (commencing 4 h into the dark cycle) followed by a 12 h period of food and sugar deprivation. Consumption of the sugar solution increases over days and is defined as "bingeing", as rats with intermittent access come to consume large amounts within the first hour of access and consume as much sugar in 12-h as rats given *ad-libitum* access do in 24-h (Avena, Rada, & Hoebel, 2008b). Animals exposed to this intermittent access protocol demonstrate behavioural and neurochemical withdrawal symptoms (e.g. elevated plus-maze anxiety and teeth chattering; dopamine/acetylcholine imbalance; Avena, Bocarsly, Rada, Kim, & Hoebel, 2008a; Colantuoni et al., 2002); cross-sensitisation to amphetamine (Avena & Hoebel, 2003); craving for sucrose (responding at a greater rate to obtain it) and sensitisation of opioid and dopamine receptors in the striatum, hippocampus, and other midbrain areas (Colantuoni et al., 2001).

While these findings are suggestive of an addiction-like profile induced by sucrose consumption, an important point is that since rats fed sucrose continuously do not show this phenotype, it appears to be driven not by the consumption of sucrose *per se*, but rather by the intermittent access conditions under which it is presented (Corsica & Pelchat, 2010; Corwin & Grigson, 2009). Benton (2010) considered data from the Avena/Hoebel model to evaluate evi-