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The effect of maternal intake of sucrose or high-fructose corn syrup (HFCS)-55 during gestation and lactation on lipogenic gene expression in rat offspring at 3 and 12 weeks of age

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Brief Report

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Abstract

Perinatal exposure to sucrose or high-fructose corn syrup-55 (HFCS-55) in rats has previously been associated with altered hepatic fat content and composition post-weaning, although the effects on hepatic metabolism are unknown. The current study aimed to determine the sex-specific effects of maternal consumption of sucrose or HFCS-55 on the expression of hepatic lipogenic genes in the offspring. Liver samples were collected from offspring of albino Wistar rats provided with *ad libitum* access to either water (control), 10% sucrose or 10% HFCS-55 solution during pregnancy and lactation at 3 weeks (control $n = 16$, sucrose $n = 22$, HFCS-55 $n = 16$) and 12 weeks (control $n = 16$, sucrose $n = 10$, HFCS-55 $n = 16$) of age. Hepatic expression of the transcription factors such as carbohydrate response element-binding protein, sterol regulatory element-binding protein-1c and downstream genes was determined by quantitative real-time PCR. Sucrose-exposed offspring had higher hepatic SREBP-1c messenger RNA expression compared with control and HFCS-55 groups at both 3 weeks ($P = 0.01$) and 12 weeks ($P = 0.03$) of age. There were no differences in the expression of other hepatic lipogenic genes between groups at either 3 or 12 weeks. Thus, perinatal exposure to sucrose may be more detrimental to offspring hepatic metabolism compared with HFCS-55, independent of sex, and it will be important to evaluate the longer-term effects of perinatal sucrose exposure in future studies.

Introduction

The global prevalence of obesity and type 2 diabetes mellitus (T2DM) has doubled over the past 30 years,[1] and is now a major public health issue. The intake of excess added sugars in foods and beverages is recognized as being an important contributor to the current epidemics of obesity and T2DM.[2] Sugar-sweetened beverages (SSBs) are the principal source of excess sugar intake in the typical Western diet and epidemiological studies have identified regular consumption of one or more serves of SSBs per day as a risk factor for both obesity and insulin resistance.[3]

The most common sweeteners used in SSBs are high-fructose corn syrup-55 (HFCS-55) and sucrose.[4] Both these sweeteners consist of a mixture of glucose and fructose, but subtle differences in their structure (sucrose is a disaccharide; HFCS-55 contains free monosaccharides) and the glucose:fructose ratio (1:1 in sucrose, 1:3.1 in HFCS-55) result in notable differences in their metabolism and downstream physiological effects. The negative metabolic effects of both HFCS-55 and sucrose have been attributed largely to the fructose component.[5] This is because fructose metabolism, unlike that of glucose, is largely unregulated, resulting in greater uptake of fructose by the liver and increased hepatic fatty acid synthesis via the *de novo* lipogenesis pathway.[6] Hepatic *de novo* lipogenesis is regulated by two key transcription factors: carbohydrate response element-binding protein (ChREBP) and sterol regulatory element-binding protein-1c (SREBP-1c). Hepatic expression of these transcription factors has previously been shown to be upregulated by fructose administration, resulting in increased expression of downstream lipogenic genes including acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS) and stearoyl-CoA desaturase (SCD1) in rodents.[7–10] This, in turn, results in hepatic triglyceride (TG) accumulation, inflammation and reduced insulin sensitivity,[11] and can ultimately lead to non-alcoholic fatty liver disease, which is also associated with whole-body insulin resistance and T2DM.[5]

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The majority of studies examining the effects of excess consumption of either HFCS-55 or sucrose have been conducted in adult humans and animal models,[12,13] and there is limited understanding of the effects of exposure to these sugars during development (before birth/early infancy) on the short- and long-term metabolic health of the offspring. Recent findings in experimental animal models, however, have clearly demonstrated that perinatal exposure to elevated levels of either fructose or sucrose are associated with altered metabolic regulation in the offspring, including increased plasma glucose, insulin and leptin concentrations.[7,10,14] Furthermore, in one study performed in a rat model, maternal fructose administration throughout gestation was reported to result in significantly higher maternal and fetal hepatic SREBP-1c messenger RNA (mRNA) and protein levels compared with controls.[7] In addition, hepatic mRNA expression of the downstream lipogenic gene FAS was also higher in the fructose-treated dams, although not the fetuses, in this study.[7] Of direct relevance to the current study, we have previously found that maternal consumption of HFCS-55, but not sucrose, during gestation resulted in lower relative liver weight and plasma free fatty acid (FFA) concentrations in rat pups at birth.[15] By 3 weeks of age, however, FFA concentrations were elevated in offspring prenatally exposed to HFCS-55. Interestingly, even after being weaned onto a standard rodent chow and tap water, plasma FFA concentrations at 12 weeks of age remained elevated in offspring exposed to HFCS-55 before birth, and a similar increase was also noted in sucrose-exposed offspring.[15,16] Furthermore, perinatal exposure to either sucrose or HFCS-55 also resulted in significant alterations in hepatic lipid composition, most notably increased hepatic concentrations of monounsaturated (omega-7 and omega-9) fatty acids.[16] Therefore, these findings suggest that the effects of perinatal exposure to added sweeteners on the offspring liver are sugar specific, and also differ according to the age at which the offspring are assessed.

Based on our previous findings, we hypothesized that perinatal exposure to either sucrose or HFCS-55 would result in altered expression of key hepatic genes regulating hepatic lipid synthesis/metabolism in the offspring. Due to differences in offspring outcomes observed between the sugar groups in our previous studies, we further hypothesized that the changes in gene expression would be sugar specific. In the current study, we therefore aimed to determine the effect of maternal consumption of a 10% w/v beverage containing sucrose or HFCS-55 during pregnancy and lactation on the hepatic expression of key lipogenic genes ACC, FAS, SCD1, their transcription regulators ChREBP and SREBP-1c, as well as a factor involved in lipid packaging, apolipoprotein B100 (ApoB), in the offspring at 3 (weaning) and 12 (young adult) weeks of age.

Methods

Animals and experimental design

This study utilizes tissues previously collected from a sub-set of the offspring from a study previously published by our group.[15] All procedures were approved by the Animal Ethics Committee of SA Pathology for the University of South Australia, in accordance with the Australian Code for the Care and Use of Animals for Scientific Purposes. In brief, 61 virgin female and 12 male albino Wistar rats (8 weeks old) were obtained from Laboratory Animal Services (outbred albino Wistar rats; SA, Australia) and housed in individually ventilated cages under a 12-h light–dark cycle at a room temperature of 22°C. Following 1 week acclimatization with *ad libitum* access to standard rat and mouse cubes (Specialty Feeds, Glen Forrest, WA, Australia; 14 kJ/g) and water, rats were randomly assigned (based on an independently generated random number sequence) to receive a control diet with *ad libitum* access to standard laboratory rat chow and water ($n = 25$ dams), or *ad libitum* access to chow and a SSB containing either 10% w/v sucrose (CSR, Australia; $n = 19$ dams) or HFCS-55 (Nature's Flavors, Orange, CA, USA; $n = 17$ dams), made fresh in the animal facility using autoclaved water, and replaced every 48 h or when required.[15] Offspring were born naturally at day 22.4 ± 0.07 gestation. Within 24 h of birth, litters were culled to eight pups per litter, four males and four females where possible, and all offspring used in the current study were cross-fostered to another dam in the same treatment group, and were therefore exposed to either the control, fructose or sucrose diet both before birth and during the suckling period. All pups were weighed every 2 days from birth until 3 weeks of age, at offspring were weaned onto standard rat and mouse cubes (Specialty Feeds, Glen Forrest, WA, Australia; 14 kJ/g) and had *ad libitum* access to this diet and tap water. The weaned offspring were weighed weekly until 12 weeks of age. At 3 and 12 weeks of age, one male and one female from each litter were killed via an overdose of CO_2 (3 weeks, male: control $n = 8$; sucrose $n = 8$, HFCS-55 $n = 8$ offspring; 3 weeks, female: control $n = 8$, sucrose $n = 11$, HFCS-55 $n = 8$; 12 weeks, male: control $n = 8$, sucrose $n = 5$, HFCS-55 $n = 8$; 12 weeks, female: control $n = 8$, sucrose $n = 5$, HFCS-55 $n = 8$ offspring). The liver was dissected out and weighed, then a sample was snap frozen in liquid nitrogen and stored at −80°C for subsequent molecular analyses.

Hepatic lipid content and composition determination

Hepatic lipids were extracted from samples of liver collected from offspring at 3 and 12 weeks according to previously established and described methods.[16,17] Hepatic TG, FFA and phospholipids were separated on thin layer chromatography plates, and the fatty acid composition of each of these lipid classes was determined separately by gas chromatography-flame ionization detection as previously described.[15]

RNA extraction and reverse transcription

Total RNA was extracted from ~100 mg of liver samples using TRIzol reagent (Sigma-Aldrich Co., St. Louis, MO, USA) and RNAeasy Mini Kit (Qiagen Pty Ltd, Doncaster, Australia) as per the manufacturers' instructions. RNA integrity was assessed by agarose gel electrophoresis and RNA concentration was determined using a NanoDrop ND-1000 Spectrophotometer (Thermo Fisher Scientific, Waltham, MA, USA). Complementary DNA was synthesized from ~1 µg total RNA using Superscript III reverse transcriptase and random hexamers (Invitrogen Australia Pty Ltd, Mount Waverley, Australia).

Hepatic gene expression

The relative hepatic mRNA expression of key genes involved in hepatic lipid metabolism (SREBP-1c,[18] ChREBP,[19] ACC1, FAS, SCD1 and ApoB[20]) was determined by quantitative real-time PCR (qRT-PCR) using SYBR Green (Bio-Rad Laboratories, Hercules, CA, USA) and the Viia™ 7 Real-Time PCR system (Applied Biosystems, Foster City, CA, USA). The mean C_t values obtained for all genes were normalized to mean C_t values of two

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housekeeping genes, HPRT[21] and β-actin (QT00193473; Qiagen Pty Ltd) for each sample using DataAssist software (Applied Biosystems)[21] to determine the mean normalized expression of each target gene for each experimental animal.

Statistical analysis

All data are presented as mean ± S.E.M. All data were assessed for normality using the Shapiro–Wilk test and the dam (mother) was used as the unit of analysis. There was a significant effect of age on all measures, therefore data were analyzed separately at 3 and 12 weeks of age. The effect of maternal sucrose or HFCS-55 exposure during pregnancy and lactation on maternal and pregnancy outcomes and on offspring body weight, relative liver weight, hepatic fat content and composition and hepatic mRNA expression of SREBP-1c, ChREBP, FAS, SCD1, ACC1 and ApoB in the offspring at 3 and 12 weeks of age was determined using a one-way analysis of variance. Where a significant effect of treatment was found, a Bonferroni *post-hoc* analysis was used to determine between-group differences. There was no effect of offspring sex nor interactions between sex and treatment for any of the genes evaluated, and thus data from males and females were combined for all analyses.

Regression analysis, controlling for the covariates of treatment and sex, was used to determine the relationship between hepatic mRNA expression of the target genes listed above, and the relationship between mRNA expression and offspring hepatic lipid concentrations. Regression coefficient and 95% confidence intervals are presented for all regression analyses. All statistical analyses were performed using Stata13 (StatCorp LP, USA), and a probability of <5% ($P < 0.05$) was considered statistically significant.

Results

Maternal and pregnancy outcomes

As previously reported, dams in the sucrose and HFCS-55 groups consumed a greater daily fluid volume than controls, and this was associated with a compensatory decrease in average daily chow consumption in both sucrose and HFCS-55 dams.[15] Daily energy intake was higher in HFCS-55 dams during both pregnancy and lactation and in sucrose dams during pregnancy and 1st week of lactation, compared with control dams. Body weight was not different between groups at the commencement of the interventions. There was also no effect of treatment on maternal body weight during pregnancy or lactation, however sucrose, but not HFCS-55, dams had an increased relative fat mass at the end of lactation compared with controls.[15]

There was no effect of maternal sucrose or HFCS-55 consumption before and during pregnancy on average litter size (control, 13.6 ± 0.5; sucrose, 12.6 ± 0.8; HFCS-55, 12.4 ± 0.4 pups per litter) or the ratio of male:female pups per litter (control, 1.2 ± 0.2; sucrose, 1.2 ± 0.1; HFCS-55, 1.2 ± 0.1).[15]

Offspring growth and hepatic fatty acid composition

There were no differences in offspring body weight between control, sucrose and HFCS-55 offspring at either 3 or 12 weeks of age in either males (3 weeks: control, 45.4 ± 2.0 g; sucrose, 42.1 ± 0.9 g; HFCS-55, 45.2 ± 1.5 g, $P = 0.18$; 12 weeks: control, 409.2 ± 11.0 g; sucrose, 410.1 ± 6.6 g; HFCS-55, 393.3 ± 7.3 g, $P = 0.30$) or females (3 weeks: control, 44.4 ± 1.4 g; sucrose, 41.1 ± 1.1 g; HFCS-55, 43.1 ± 1.4 g, $P = 0.21$; 12 weeks: control, 266.1 ± 5.4 g; sucrose, 255.3 ± 6.5 g; HFCS-55, 269.4 ± 13.2 g, $P = 0.46$).

There were no differences in relative liver weight between groups at either 3 or 12 weeks of age, independent of sex (3 weeks: control, 3.74 ± 0.04 g/kg; sucrose, 3.62 ± 0.05 g/kg; HFCS-55, 3.64 ± 0.04 g/kg, $P = 0.68$; 12 weeks: control, 3.70 ± 0.07 g/kg; sucrose, 3.79 ± 0.07 g/kg; HFCS-55, 3.83 ± 0.05 g/kg, $P = 0.39$). Hepatic fat content at 3 weeks of age tended ($P = 0.07$) to be lower in the HFCS-55 group compared with the sucrose group, independent of sex, but was not different between groups at 12 weeks (Table 1). At 3 weeks of age, hepatic omega-7 and omega-9 monounsaturated fatty acids were increased in both sucrose and HFCS-55 offspring compared with controls (Table 1). Hepatic omega-7 monounsaturated fatty acids were, however, lower in the sucrose group at 12 weeks of age (Table 1). Hepatic omega-6 and omega-3 polyunsaturated fatty acid contents were not different between groups at either 3 or 12 weeks (Table 1).

Effect of sucrose and HFCS-55 exposure on hepatic mRNA expression

Hepatic SREBP-1c mRNA was higher in offspring of sucrose-fed dams compared with both the control and HFCS-55 groups at both 3 and 12 weeks of age, independent of sex (Fig. 1).

There were no significant differences in ChREBP mRNA expression between groups at either 3 or 12 weeks of age (Table 2). At 12 weeks of age, however, ChREBP mRNA expression tended ($P = 0.09$) to be lower in the sucrose offspring compared with both the control and HFCS-55 groups. There was no effect of exposure to maternal sucrose or HFCS-55 consumption during pregnancy and lactation on hepatic ACC1, ApoB, FAS or SCD1 mRNA expression at either 3 or 12 weeks of age (Table 2).

Table 1. Hepatic fat content and composition in offspring of control, sucrose and HFCS-55 fed dams at 3 and 12 weeks of age

	Treatment			
	Control	Sucrose	HFCS-55	*P*-
Measure	*n* = 11	*n* = 11	*n* = 10	value
3 weeks				
Fat content (%)	7.1 ± 0.4	8.0 ± 0.5	6.5 ± 0.3	0.07
Omega-9 (mg/100 g)	509.2 ± 38.8	719.2 ± 42.1	625.2 ± 36.4	0.003
Omega-7 (mg/100 g)	82.2 ± 5.2	146.4 ± 10.1	116.2 ± 5.6	<0.001
Omega-3 (mg/100 g)	347.5 ± 9.4	361.0 ± 30.0	367.6 ± 17.2	0.73
Omega-6 (mg/100 g)	1139.3 ± 56.3	1109.6 ± 68.8	1083.2 ± 33.3	0.75
	n = 12	*n* = 9	*n* = 12	
12 weeks				
Fat content (%)	6.4 ± 1.1	5.4 ± 0.6	5.9 ± 0.6	0.71
Omega-9 (mg/100 g)	608.9 ± 93.0	505.7 ± 97.8	625.3 ± 56.1	0.61
Omega-7 (mg/100 g)	114.9 ± 10.8	91.2 ± 4.01	134.9 ± 10.9	0.02
Omega-3 (mg/100 g)	303.9 ± 28.5	256.1 ± 11.8	306.3 ± 15.8	0.30
Omega-6 (mg/100 g)	1416.1 ± 124.6	1221.8 ± 46.0	1332.0 ± 81.0	0.43

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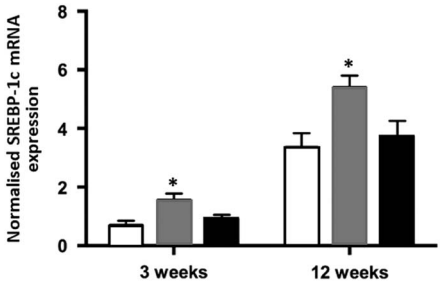

Fig. 1. Effect of developmental exposure to sucrose or high-fructose corn syrup-55 (HFCS-55) on hepatic sterol regulatory element-binding protein-1c (SREBP-1c) messenger RNA (mRNA) expression in offspring of control (open bars), sucrose (grey bars) and HFCS-55 (closed bars) dams at 3 (control, $n=16$; sucrose, $n=22$; HFCS-55, $n=16$) and 12 (control, $n=16$; sucrose, $n=10$; HFCS-55, $n=16$) weeks of age. Data were pooled for sex and presented as mean ± S.E.M. *Mean values that were significantly different across the treatment groups ($P<0.05$).

Table 2. Hepatic acetyl-CoA carboxylase 1 (ACC1), apolipoprotein B100 (ApoB), carbohydrate response element-binding protein (ChREBP), fatty acid synthase (FAS) and stearoyl-CoA desaturase (SCD1) mRNA expression (mean ± S.E.M.) in offspring of control, sucrose and high-fructose corn syrup-55 fed dams at 3 and 12 weeks of age

	Treatment			
	Control	Sucrose	HFCS-55	
Gene	$n=16$	$n=22$	$n=16$	*P*-value
3 weeks				
ACC1	0.31 ± 0.31	0.39 ± 0.47	0.35 ± 0.06	0.463
ApoB	5.28 ± 0.28	5.20 ± 0.28	4.63 ± 0.14	0.182
ChREBP	0.97 ± 0.09	0.85 ± 0.09	0.81 ± 0.12	0.545
FAS	0.36 ± 0.06	0.34 ± 0.07	0.29 ± 0.51	0.728
SCD1	3.49 ± 0.73	6.93 ± 1.41	5.79 ± 1.51	0.166
	$n=16$	$n=10$	$n=16$	
12 weeks				
ACC1	2.0 ± 0.19	2.47 ± 0.27	2.15 ± 0.24	0.448
ApoB	12.03 ± 0.77	13.0 ± 0.81	12.40 ± 0.56	0.679
ChREBP	3.54 ± 0.51	2.01 ± 0.17	3.41 ± 0.52	0.094
FAS	1.34 ± 0.12	1.68 ± 0.31	1.17 ± 0.22	0.279
SCD1	10.30 ± 2.28	15.40 ± 5.06	21.5 ± 4.47	0.111

Relationship between hepatic mRNA expression and hepatic fatty acid concentrations at 3 and 12 weeks of age

At 3 weeks of age, hepatic mRNA expression of ChREBP, SCD1, FAS and ACC1 were all negatively correlated with hepatic omega-3 concentrations (Table 3). The expression of ACC1 mRNA in the liver at 3 weeks of age was also negatively correlated with hepatic omega-6 fatty acid content. Conversely, SREBP-1c mRNA expression at 3 weeks of age was positively correlated with hepatic omega-3 and trans-fatty acid content when data from all animals were combined.

There were no significant relationships between mRNA expression of any hepatic genes and any measures of hepatic fatty acid composition in offspring at 12 weeks (data not shown).

Table 3. Relationships between hepatic mRNA expression of acetyl-CoA carboxylase 1 (ACC1), carbohydrate response element-binding protein (ChREBP), fatty acid synthase (FAS), stearoyl-CoA desaturase (SCD1) and sterol regulatory element-binding protein-1c (SREBP-1c) and measures of hepatic fat content in offspring at 3 weeks, independent of sex, when offspring in all treatment groups were combined

Independent–dependent variable	Regression coefficient (95% CI)	r^2	$P>\|t\|$
ACC1-total omega-3	−230.33 (−315.04, −145.62)	0.537	0.0001
ACC1-total omega-3 TG	−141.57 (−220.38, −60.75)	0.317	0.001
ACC1-total omega-6	−516.03 (−828.16, −203.91)	0.291	0.002
ChREBP-total omega-3	−67.79 (−108.72, −26.85)	0.328	0.002
FAS-total omega-3	−149.13 (−208.46, −89.80)	0.513	0.0001
SCD1-total omega-3	−7.83 (−10.74, −4.92)	0.522	0.0001
SREBP-1c-total trans	0.95 (0.26, 1.64)	0.302	0.008
SREBP-1c-total omega-3	35.0 (15.86, 54.13)	0.359	0.001

Correlations are expressed as regression coefficient (95% CI), r^2 and *P*-value.

Discussion

The key finding of the current study was that maternal consumption of sucrose, but not HFCS-55, during pregnancy and lactation led to increased hepatic mRNA expression of SREBP-1c, one of the major transcription factors involved in promoting hepatic lipogenesis in the offspring. This effect was still present at 12 weeks of age after offspring had consumed a standard rodent chow and water for 9 weeks since weaning. Somewhat unexpectedly, we found no effects of perinatal sucrose exposure on hepatic mRNA expression of downstream lipogenic genes at either 3 or 12 weeks of age, and further studies are required to determine whether the alterations in SREBP-1c mRNA expression translate into functional effects on hepatic metabolism, in particular an increased propensity towards lipid storage when exposed to a high-calorie/high-fat/high-sugar diet.

The markedly different effects of perinatal sucrose and HFCS-55 exposure on SREBP-1c mRNA expression were unexpected given their similar compositions. However, this sugar-specific effect could be related to the higher relative glucose content in sucrose compared with HFCS-55 (50 *v.* 42% glucose, respectively), since glucose has the capacity to induce SREBP-1c mRNA expression via additional metabolic pathways to fructose.[22] Thus, while fructose induces SREBP-1c mRNA expression principally via the *de novo* lipogenic pathway, independently of insulin,[22] glucose can stimulate SREBP-1c mRNA expression via both insulin-independent and insulin-dependent pathways.[23] The latter involves activation of the insulin signalling pathway and specifically the master growth regulator mammalian target of rapamycin complex 1 (mTORC1).[24] In addition, there is emerging evidence that glucose can directly activate mTORC1 through an additional separate pathway, and via other factors, including phospholipase D and adenosine monophosphate-activated protein kinase.[25] Therefore, compared with fructose, glucose has at least two additional pathways by which it can induce hepatic SREBP-1c mRNA expression.

Despite SREBP-1c being one of the major transcription factors induced by downstream hepatic lipogenic genes, including ACC1, ACL, FAS and SCD1, we found no effect of perinatal sucrose exposure on the hepatic expression of these genes in the offspring.

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One possibility is that there was insufficient availability of substrates (citrate, acetyl-coA, etc.) available for SREBP-1c mediated activation of these downstream genes, since a previous study reported that SREBP-1c did not induce expression of ACC and FAS, in the absence of an adequate supply of these substrates.[9] In the same study, oleate produced by SCD1 was shown to be required for fructose-mediated induction of lipogenic gene expression through SREBP-1c,[9] suggesting the lack of increase in mRNA expression of ACC1, ApoB and FAS in the sucrose offspring may have been secondary to inappropriate/altered regulation of SCD1. At the age of 12 weeks, it is also possible that the trend towards lower ChREBP mRNA in the sucrose-exposed offspring may have opposed the effect of the higher SREBP-1c expression and 'cancelled out' the effects of increased SREBP-1c mRNA. It is also important to note, however, the current study only investigated the mRNA expression of these lipogenic genes, and it is therefore possible that the levels of precursor, nuclear or activated proteins encoded by these genes may have be altered.

We previously reported that the offspring of dams that consumed sucrose during pregnancy and lactation had an altered hepatic lipid profile at weaning, including higher levels of hepatic omega-7 and -9 fatty acids, compared with controls.[16] Given the role of SCD1 in the regulation of hepatic lipid composition, and specifically the synthesis of omega-7 and omega-9 fatty acids,[26] we had hypothesized that perinatal sucrose exposure would be associated with increased hepatic SCD1 mRNA expression. Additionally, postnatal fructose administration has previously been linked to increased hepatic SCD1 mRNA expression.[9] However, the results of the current study provide no evidence to support this hypothesis. Our finding of negative correlations of hepatic mRNA expression of ACC1, ChREBP, FAS and SCD1 with hepatic omega-3 fatty acid concentrations at 3 weeks of age are, however, consistent with previous reports that demonstrated an inhibitory effect of omega-3 fats on hepatic lipogenic gene expression.[27] Thus, it appears that there is appropriate regulation of these genes by omega-3 fatty acids in the offspring in our study, independent of whether they were exposed to a sucrose, HFCS-55 or control treatment during the perinatal period. However, our finding that SREBP-1c hepatic mRNA expression was positively correlated with hepatic total omega-3 content in this study is unexpected, and may potentially indicate altered regulation of SREBP-1c mRNA expression in these offspring.

Conclusion and implications

Developmental exposure to increased amounts of sucrose via the mother has the potential to significantly alter the long-term hepatic metabolic outcomes in the offspring, even when the sugar stimulus does not persist beyond weaning. High basal expression of hepatic SREBP-1c mRNA in these offspring may translate into increased *de novo* lipogenesis and increased fatty acid production in the liver, resulting in increased hepatic TG concentrations and, ultimately, insulin resistance, although further studies are required to investigate this directly.

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Conflicts of Interest. None.

Ethical Standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guides on the care and use of laboratory animals (albino Wistar rats) and has been approved by the institutional committee (Animal Ethics Committee of SA Pathology for the University of South Australia).

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