高果糖引起的脂肪肝大鼠肾脏脂质合成相关基因和蛋白的表达

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摘要 大量研究表明, 高果糖可引起脂肪肝, 但对肾脏脂质代谢的影响尚不清楚。该实验研究给予10%果糖水5周后诱导的脂肪肝大鼠肾脏的脂质代谢情况, 并探讨其可能机制。将16只雄性SD大鼠随机分为正常组(con)和果糖组(fru), 果糖组给予10%(W/V)果糖水, 第5周末称体重、取血、处死, 检测血浆GLU、TG、TC和INSULIN含量。取肾脏、肝脏和白色脂肪称重, 采用形态学方法观察肝脏和肾脏脂质沉积情况, 酶法测其TG、TC含量, 以Real time-PCR检测肾脏、肝脏中脂质合成和脂质氧化相关基因水平, 以Western blot检测肾、肝细胞核脂质合成转录因子的蛋白表达。结果显示, 果糖组大鼠血浆TG、INSULIN明显升高, 并出现肥胖体征, 肝脏脂质沉积严重, 其调控脂质合成的两个关键的转录因子ChREBP和SREBP1c mRNA和核蛋白表达都明显升高, 并且它们靶向的脂质合成相关酶*FAS*、*ACC1*、*SCD1* mRNA表达也显著增加。但是, 在肾脏中, 高果糖没有引起TG含量的变化, 调控脂质重新合成的基因和蛋白的表达也未发生变化。因此, 与果糖致脂肪肝不同, 高果糖饮食并没有造成肾脏的脂质沉积和脂质合成相关基因、蛋白的变化。

关键词 果糖; 肾脏; 肝脏; 脂质代谢; 基因表达

Renal Lipid Accumulation and Expression of the Proteins/Genes Responsible for Fatty Acid Synthesis in Rats with Fatty Liver Induced by Fructose Overconsumption

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Abstract Chronically high consumption of fructose in rodents leads to fatty liver. However, it is still unknown whether fructose overconsumption affects renal lipid metabolism. Here, we found that treatment of rats with 10% fructose in drinking water over 5 weeks induced excess hepatic triglyceride deposition, further investigated the effects and mechanisms of fructose overconsumption on renal lipid metabolism by comparing to

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those in the liver in rats. Sixteen male SD rats were divided into two groups: (1) water control with free access to water; (2) fructose with free access to 10% fructose in drinking water (W/V, prepared daily). The duration of the experiment was 5 weeks. On day 35, animals were weighed, then blood samples were collected by retroorbital venous puncture under ether anesthesia for determination of plasma concentrations of glucose, insulin, total cholesterol and triglyceride. Immediately thereafter, animals were killed. Livers, kidneys, epididymal and perirenal white adipose tissues were collected and weighed. The indexes of lipid in liver and kidney were determined histologically and enzymatically. Gene expressions involved in lipid synthesis and oxidation were analyzed by Real time-PCR. Protein expressions of transcriptional regulators involved in lipid metabolism were analyzed by Western blot. The results showed that treatment of rats with 10% fructose in drinking water over 5 weeks induced excess hepatic triglyceride deposition, accompanied by increases in plasma concentrations of triglyceride and insulin, as well as adiposity. Further, hepatic mRNA and/or nuclear protein expressions of two key transcriptional regulators carbohydrate response element binding protein (ChREBP) and sterol regulatory element-binding protein (SREBP)1c, and their targeted genes responsible for *de novo* fatty acid synthesis, were activated. Surprisingly, the lipid content and expression of these proteins/genes in the kidneys were not altered by fructose feeding. Therefore, unlike the liver, fructose overconsumption does not alter renal lipid accumulation and expression of the proteins/genes responsible for *de novo* fatty acid synthesis in rats.

Key words fructose; kidney; liver; lipid metabolism; gene expression

代谢综合征和糖尿病患者非脂肪组织器官中的脂质代谢平衡被打破, 致细胞内脂质堆积过多, 使细胞功能失调、细胞结构破坏甚至死亡[1-3], 这种现象称为脂毒性。脂毒性会发生于心脏、肝脏、胰腺、肾脏和肌肉等多种非脂肪组织器官中[1-4]。尽管截止目前, 肾脏脂毒性发生的相关机制尚不明确, 但大量研究表明, 在某些代谢性疾病的动物模型中, 肾脏的脂质沉积十分明显[5-17]。

果糖是目前应用最为广泛的甜味剂, 但高果糖饮食会对机体造成不利的影响。长期过量摄入果糖会导致代谢综合征和肝内的脂质代谢异常[18-20]。虽然有研究表明, 过度地摄入果糖会引起大鼠和小鼠肾脏的损伤[21], 但是, 它是否会影响肾脏的脂质代谢尚不清楚。我们研究小组前期的工作表明, 10%果糖水喂养大鼠5周后引起明显的代谢紊乱和脂肪肝[22], 以及肾脏的一些病理改变, 但是相对于肝脏脂毒性的发生, 果糖是否也能同时引起肾脏脂质代谢异常是一个值得探讨的重要问题。本研究旨在通过比较肾脏与肝脏脂质代谢相关指标, 观察果糖对大鼠肾脏的作用, 为高果糖所致肾脏损伤的机制研究提供新证据。

1 材料与方法

1.1 动物分组与处理

16只SPF级雄性SD大鼠, 购于重庆医科大学动物中心, 体重210~230 g, 适应性喂养一周后, 随机分为对照组(control, con)和果糖组(fructose, fru), 每组8只。对照组给予正常饮食饮水, 果糖组给予10%的果糖水[23], 两组均给予标准饲料, 每天记录进水量和进食量, 每3 d记录大鼠体重。第5周末处死动物, 采集血浆保存于–20 °C。取肝脏、肾脏、附睾和肾周脂 肪(epididymal and perirenal white adipose tissue, e+p WAT)称重, 部分肝、肾组织以10%甲醛固定, 其余组织存于液氮, 随后转移至–80 °C冰箱保存以备生化、基因和蛋白检测。

1.2 血生化检测

按试剂盒说明书分别检测血浆血糖(glucose, GLU, 上海科欣生物技术研究所葡萄糖检测试剂盒)、胰岛素(INSULIN, 日本东京森永胰岛素检测试剂盒)、总胆固醇(total cholesterol, TC, 上海科欣生物技术研究所胆固醇检测试剂盒)、甘油三酯(triglyceride, TG, 日本大阪和光甘油三酯检测试剂盒)。

1.3 肝脏和肾脏的脂质提取和TG、TC检测

本实验采用Rong等[24]的方法, 称取100 mg组织, 加入2 mL异丙醇并充分匀浆后, 放入4 °C冰箱过夜, 隔日3 000 r/min离心15 min, 取上清, 按照试剂盒说明书分别检测肝脏、肾脏TG、TC含量。

1.4 肝脏和肾脏的组织形态学观察

将10%甲醛固定的肝脏和肾脏组织分别制作成

6 μm的冰冻切片, 常温干燥20 min, 流水冲洗1~10 min, 60%异丙醇浸洗1~5 min, 然后将切片入油红O工作液(现配现用)染色15 min, 60%异丙醇分色至背景无色, 蒸馏水洗, Mayer苏木精复染, 自来水洗(蓝化)1~3 min, 甘油明胶封片, 光镜下观察并拍照。

1.5 Real time-PCR检测基因表达

参照试剂盒说明书, 使用TRIzol(购于中国大连宝生物公司)提取肝脏和肾脏总RNA。采用大连宝生物公司M-MLV反转录酶试剂盒合成cDNA。应用美国伯乐CFX 96 Real-Time PCR和大连宝生物SYBR® Premix Ex Taq™ II试剂盒, 检测脂质合成相关基因碳水化合物反应元件结合蛋白(carbohydrate response element binding protein, *ChREBP*)、固醇调节元件结合蛋白1c(sterol regulatory element binding protein 1c, *SREBP1c*)、脂肪酸合成酶(fatty acid synthase, *FAS*)、乙酰辅酶A羧化酶1(acetyl-CoA carboxylase 1, *ACC1*)、硬脂酰辅酶A去饱和酶1(stearoyl-CoA desaturase 1, *SCD1*)和脂质氧化基因过氧化物酶体增殖物激活受体(peroxisome proliferator activated receptor α, *PPARα*)、肉碱棕榈酰转移酶1α(carnitine palmitoyltransferase 1α, *CPT1α*)、酰基辅酶A氧化酶(acyl-CoA oxidase, *ACO*)、*CD36*的mRNA表达情况, 引物序列详见表1。以*β-actin*为内参基因, 用目的基因与*β-actin*的起始拷贝数比值表示目的基因的相对表达量。

1.6 Western blot

按照美国皮尔斯蛋白提取试剂盒说明书, 提取肝、肾组织细胞核蛋白, 常规方法进行SDS-PAGE凝胶电泳, 电转至PVDF膜, 5%脱脂奶粉封闭2 h, 加入Lamin A/C一抗(封闭液1:1 000稀释)、ChREBP一抗(封闭液1:200稀释)和SREBP1c一抗(封闭液1:1 000稀释), 4 °C摇床过夜, TBST洗膜3次, 每次15 min, 二抗孵育1 h, TBST洗膜3次, 每次15 min, 加入美国皮尔斯ECL发光底物, X胶片显影。用ImageJ 1.43软件, 以目的蛋白与Lamin A/C的灰度比值表示目的蛋白的表达量。

1.7 统计学处理

应用StatView软件进行统计学分析, 所有数据以均数±标准误($\bar{x}\pm s$)表示, 两组数据差异比较进行t检验, $P<0.05$为差异有统计学意义。

2 结果

2.1 果糖对大鼠脂代谢相关指标影响

与正常组相比, 果糖组进食量减少[正常组: (28.45±2.91) g/只/天, 果糖组: (16.86±2.12) g/只/天], 对照组与果糖组的进水量分别为(32.33±0.56) mL/只/天和(108.73±7.25) mL/只/天。果糖组血浆GLU(图1A)、INSULIN(图1B)、TC(图1C)和TG(图1D)含量都升高。

虽然果糖摄入没有影响体重(图2A), 但是大鼠附睾和肾周白色脂肪组织的重量(图2B)、肝脏重量(图2C)和肝脏重量与体重比(图2D)都增加。与此相反, 肾脏重量和肾脏重量与体重比下降(图2C和图2D)。更重要的是, 果糖诱导大鼠肝脏TG的大量沉积, 是对照组的2.5倍, 但肾脏TG含量无明显改变(图3A和图3B)。油红O染色可见果糖组肝细胞大量的脂肪滴(图4A), 而肾脏细胞没有变化(图4B)。果糖对肝脏和肾脏的TC含量(图3C和3D)没有显著影响。

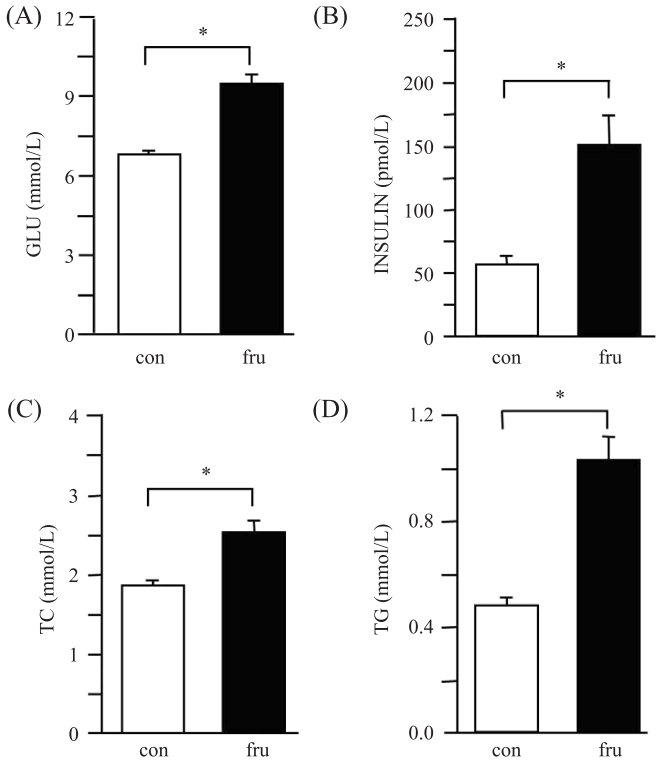
2.2 果糖对大鼠肝脏和肾脏脂质代谢相关基因表达的影响

Real time-PCR检测肝脏和肾脏的脂肪酸重新合成相关基因的表达, 结果显示, 果糖组大鼠肝脏

表1 实时荧光定量PCR相关基因引物序列

Table 1 Primer sequences for Real time-PCR assays

基因 Gene	上游引物(5′-3′) Forward primers (5′-3′)	下游引物(5′-3′) Reverse primers (5′-3′)
β-actin	ACG GTC AGG TCA TCA CTA TCG	GGC ATA GAG GTC TTT ACG GAT G
ChREBP	GAA GAC CCA AAG ACC AAG ATG C	TCT GAC AAC AAA GCA GGA GGT G
SREBP1c	CTG TCG TCT ACC ATA AGC TGC AC	ATA GCA TCT CCT GCA CAC TCA GC
FAS	ACC TCA TCA CTA GAA GCC ACC AG	GTG GTA CTT GGC CTT GGG TTT A
ACC1	AAC ATC CCG CAC CTT CTT CTA C	CTT CCA CAA ACC AGC GTC TC
SCD1	CAG TTC CTA CAC GAC CAC CAC TA	GGA CGG ATG TCT TCT TCC AGA T
PPARα	GTC ATC ACA GAC ACC CTC TCC C	TGT CCC CAC ATA TTC GAC ACT C
CPT1α	CTG CTG TAT CGT CGC ACA TTA G	GTT GGA TGG TGT CTG TCT CTT CC
ACO	CCC AAG ACC CAA GAG TTC ATT C	TCA CGG ATA GGG ACA ACA AAG G
CD36	AAC CCA GAG GAA GTG GCA AAG	GAC AGT GAA GGC TCA AAG ATG G

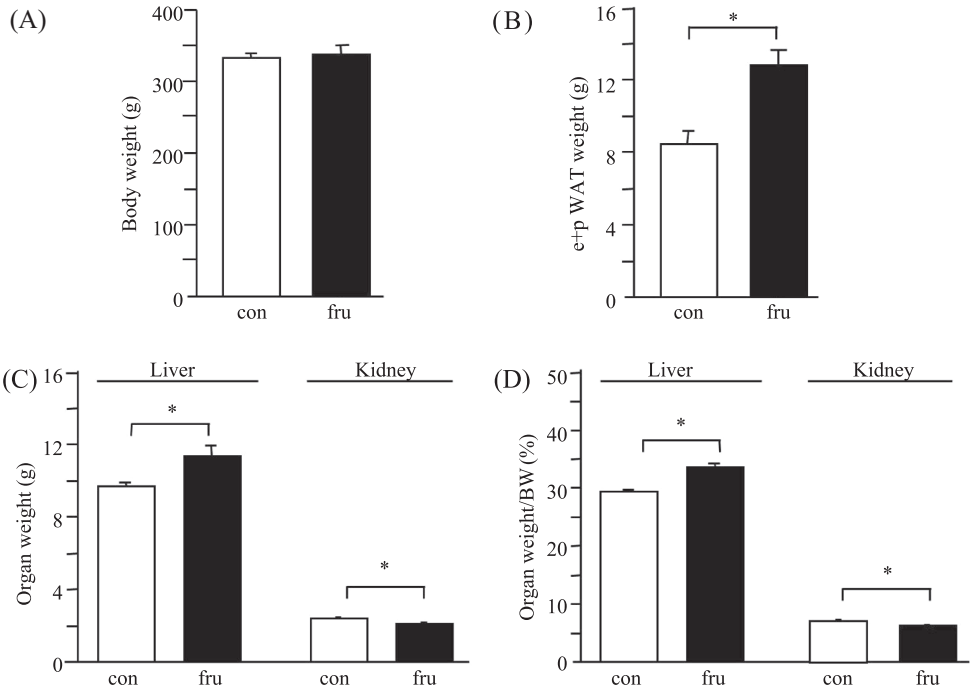


A: 血浆GLU浓度; B: 血浆INSULIN浓度; C: 血浆TC浓度; D: 血浆TG浓度。*P<0.05, 与对照组比较。

A: plasma concentrations of GLU; B: plasma concentrations of INSULIN; C: plasma concentrations of TC; D: Plasma concentrations of TG. *P<0.05 *vs* control group.

图1 果糖对大鼠血浆生化指标的影响

Fig.1 Effects of fructose on plasma biochemical parameters in rats

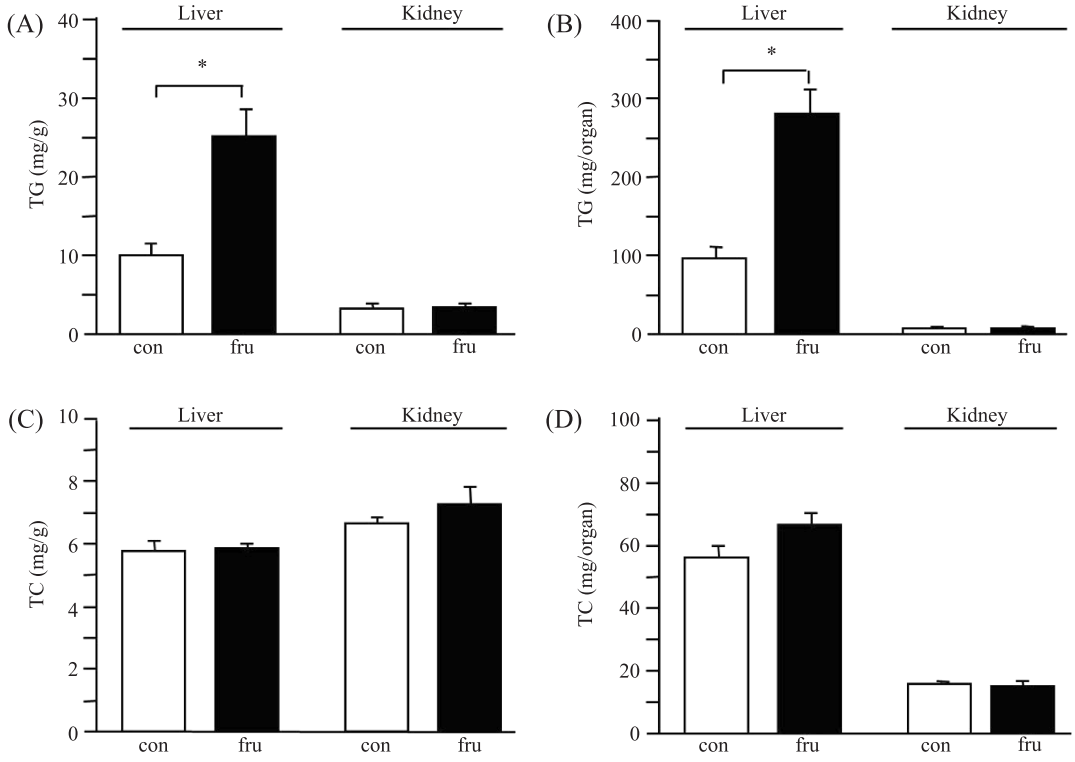


A: 体重; B: 附睾与肾周白色脂肪总重量; C: 肝脏和肾脏重量; D: 肝脏和肾脏重量与体重之比。*P<0.05, 与对照组比较。

A: body weight; B: epididymal and perirenal white adipose tissue weight; C: liver and kidney weights; D: ratios of liver and kidney weights to body weight. *P<0.05 *vs* control group.

图2 高果糖对大鼠体重和器官重量的影响

Fig.2 Effects of fructose on body weight and organ weight in rats



A: 肝脏、肾脏的TG含量; B: 器官(肝脏、肾脏)TG与器官(肝脏、肾脏)重量的比值; C: 肝脏、肾脏的TC含量; D: 器官(肝脏、肾脏)TC与器官(肝脏、肾脏)重量的比值。*P<0.05, 与对照组比较。

A: liver and kidney contents of TG; B: ratios of liver and kidney TG contents to liver and kidney weight; C: liver and kidney contents of TC; D: ratios of liver and kidney TC contents to liver and kidney weight. *P<0.05 *vs* control group.

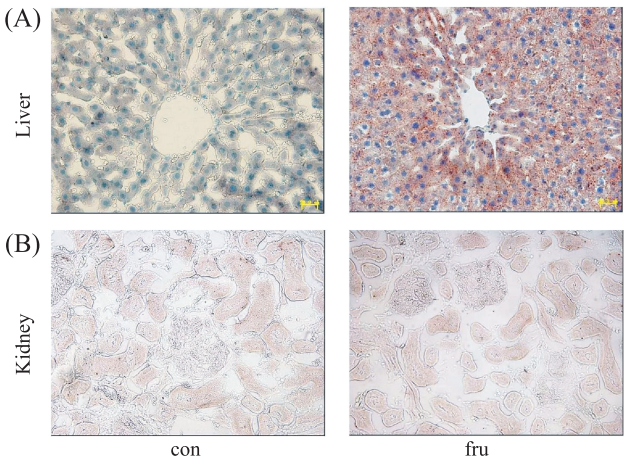
图3 果糖对大鼠肝脏、肾脏TG和TC的影响

Fig.3 Effects of fructose on TG and TC contents in liver and kidney

ChREBP mRNA(图5A)和*SREBP1c* mRNA(图5C)表达量分别为对照组的2倍和3倍, 其下游靶基因*ACC1*(图6A)、*FAS*(图6B)和*SCD1*(图6C)的mRNA表达量分别是对照组的10倍、8倍和9倍; 相反, 这些基因在肾脏的表达甚低, 果糖组大鼠肝脏*ChREBP*、*SREBP1c*、*ACC1*、*FAS*和*SCD1*的mRNA表达量分别是肾脏的7倍、8倍、52倍、10倍和506倍(图5A~图5D和图6A-图6C); 而且, 在肾脏中, 果糖也并没有引起这些基因表达的变化(图5A~图5D和图6A~图6C)。肾脏中脂质氧化相关基因*PPARα*(图7A)、*CPT1α*(图7B)、*ACO*(图7C)和*CD36*(图7D)的表达量也远低于肝脏。与脂肪酸合成基因的表达变化相反, 5周的果糖摄入没有对肝脏和肾脏中这些脂质氧化相关基因产生影响(图7A~图7D)。

2.3 果糖对大鼠肝脏和肾脏ChREBP和SREBP1c蛋白表达的影响

已知ChREBP和SREBP1c是脂质合成通路中两个关键的转录因子, 它们发挥作用的方式是首先从

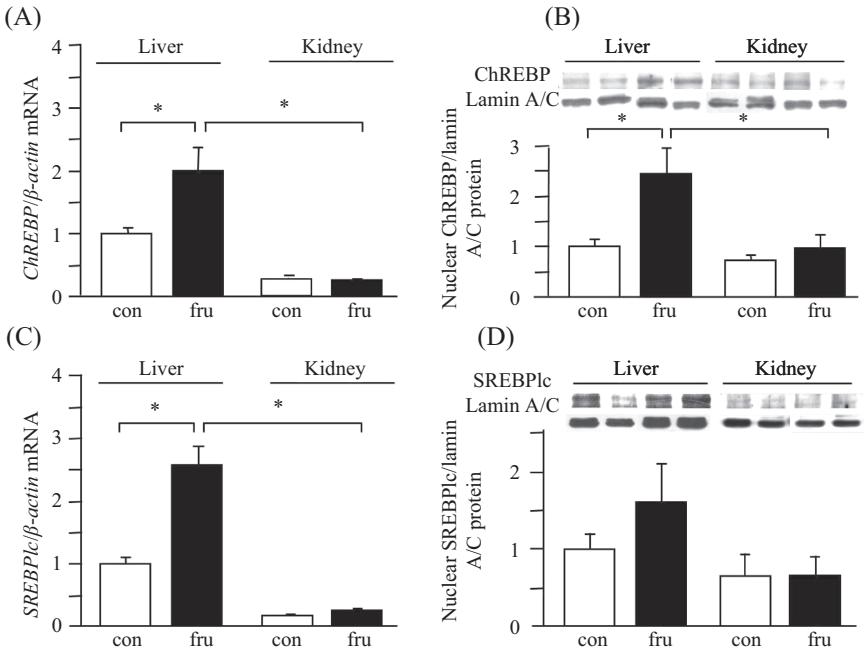


A: 正常组和果糖组肝脏脂质沉积情况; B: 正常组和果糖组肾脏脂质沉积情况。

A: the liver lipid deposition of water-control and fructose-fed rats; B: the renal lipid deposition of water-control and fructose-fed rats.

图4 油红O染色检测肝脏和肾脏脂滴沉积(200×)

Fig.4 Representative images showing lipid droplet accumulation (oil red O staining) in liver and kidney (200×)

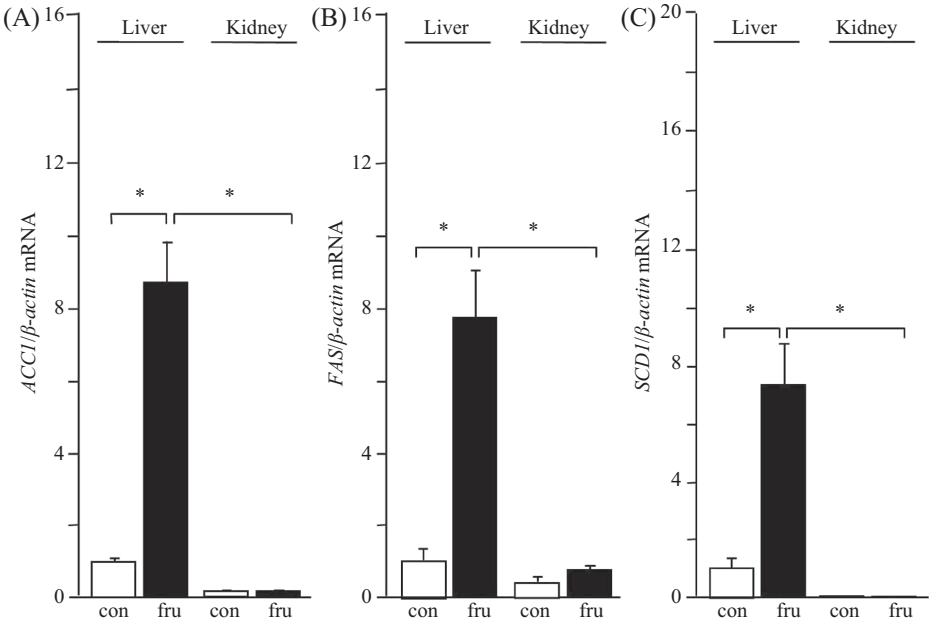


A: 肝脏、肾脏的*ChREBP* mRNA水平; B: 肝脏、肾脏的ChREBP蛋白表达水平; C: 肝脏、肾脏的*SREBP1c* mRNA水平; D: 肝脏、肾脏的SREBP1c蛋白表达水平。*P<0.05, 与对照组比较。

A: hepatic and renal mRNA expression of *ChREBP*; B: hepatic and renal protein expression of *ChREBP*; C: hepatic and renal mRNA expression of *SREBP1c*; D: hepatic and renal protein expression of SREBP1c. *P<0.05 *vs* control group.

图5 果糖对大鼠肝脏和肾脏ChREBP、SREBP1c表达的影响

Fig.5 Effects of fructose on hepatic and renal mRNA and protein expression of ChREBP and SREBP1c



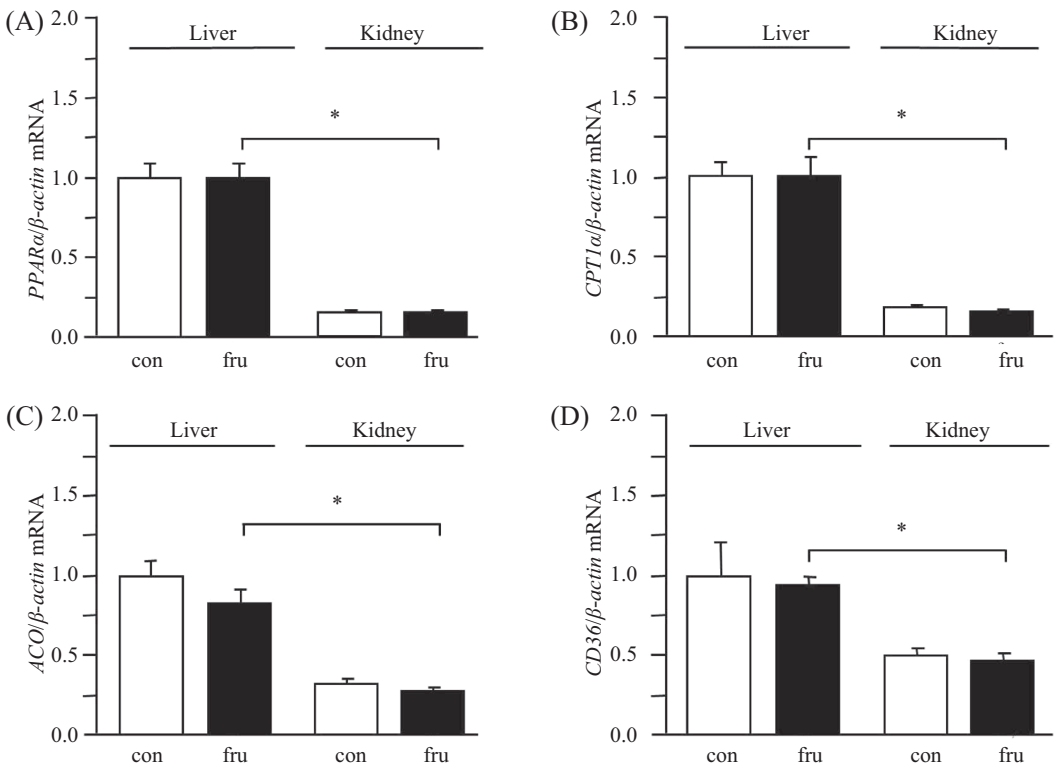
A: 肝脏和肾脏的*ACC1* mRNA水平; B: 肝脏和肾脏的*FAS* mRNA水平; C: 肝脏和肾脏的*SCD1* mRNA水平。*P<0.05, 与对照组比较。

A: hepatic and renal mRNA expression of *ACC1*; B: hepatic and renal mRNA expression of *FAS*; C: hepatic and renal mRNA expression of *SCD1*. *P<0.05 *vs* control group.

图6 果糖对大鼠肝脏和肾脏脂质合成相关基因mRNA水平的影响

Fig.6 Effects of fructose on hepatic and renal mRNA expression of lipid synthesis-related gene

细胞质转移到细胞核, 结合到相应基因的启动子上, 激活目的基因转录, 启动基因表达。因此, 本实验重点观察了肝脏和肾脏细胞核中ChREBP和SREBP1c蛋白的表达变化。Western blot检测结果显示, 果糖组大鼠肝脏细胞核内ChREBP表达明显增加, SREBP1c蛋白表达也有增高的趋势(图5B和图5D), 但它们在肾脏中的表达甚低, 而且果糖也没有引起这些蛋白表达的变化(图5A~图5D和图6A~图6C)。



A: 肝脏和肾脏的*PPARα* mRNA水平; B: 肝脏和肾脏的*CPT1α* mRNA水平; C: 肝脏和肾脏的*ACO* mRNA水平; D: 肝脏和肾脏的*CD36* mRNA水平。*P<0.05, 与对照组比较。

A: hepatic and renal mRNA expression of *PPARα*; B: hepatic and renal mRNA expression of *CPT1α*; C: hepatic and renal mRNA expression of *ACO*; D: hepatic and renal mRNA expression of *CD36*. *P<0.05 *vs* control group.

图7 果糖对大鼠肝脏和肾脏脂质氧化相关基因mRNA水平的影响

Fig.7 Effects of fructose on hepatic and renal mRNA expression of lipid oxidation-related genes

3 讨论

本实验结果表明, 5周10%果糖水诱发大鼠肝脏甘油三酯过度沉积, 同时伴高血糖、高胰岛素血症、高胆固醇血症、高甘油三酯血症和肥胖, 这与以往诸多报道[18-20]相一致。出乎预料的是, 在我们的实验中, 高果糖没有影响肾脏甘油三酯的含量, 这不同于其他代谢性疾病、急性和慢性肾损伤、年老动物模型等的结果[5-17]。

研究发现, 肝脏脂肪酸重新合成的增加在果糖诱发的脂质紊乱中占据重要地位[19-20,25]。SREBP1c是肝脏葡萄糖和脂质代谢的重要转录因子之一, 介导脂肪酸的重新合成, 调节过剩的脂质沉积[20,26]。ChREBP是另一个调控葡萄糖与脂质代谢的关键转录因子, 在将过多的碳水化合物转变形成甘油三酯的过程中发挥重要作用。果糖激活ChREBP, 与SREBP协同作用增加脂质合成基因(*ACC1*、*FAS*和*SCD1*)的表达[20]。已知ChREBP和SREBP1c这两个重要的转录因子发挥作用的方式是, 它们首先从细胞质转移到细胞核, 然后分别结合到糖酵解和脂肪合成酶相关基因启动子区的糖类应答元件(ChRE)与固醇调节元件(SRE)上, 调节糖酵解和脂肪合成酶相关基因(如*LPK*、*FAS*、*ACC*、*SCD1*)的表达, 从而引起甘油三酯的合成。在高脂饮食、链脲佐菌素、基因工程和衰老的动物模型中, 肾脏有类似的脂质沉积现象; 在这些模型中, 肾脏重新合成脂肪酸的相关基因(*FAS*、*ACC1*、*SCD1*)被激活, 并伴有肾甘油三

酯积累增加[5,8-13,15-16]。本研究结果显示, 这两个关键的转录因子, 尤其是ChREBP, 以及它下游的靶基因*ACC1*、*FAS*和*SCD1*, 在肝脏中高表达, 但在肾脏中表达甚低。果糖引起脂肪肝伴有这些蛋白与基因的明显激活, 相反, 果糖没有使肾脏中这些基因与蛋白发生变化。因此, 高果糖不能激活肾脏ChREBP和*SREBP1c*以及它们靶向的下游脂肪酸合成基因, 与肾脏脂质沉积未发生变化有密切关系。

有研究发现, 肝脏SREBP1c受胰岛素调节, 介导胰岛素对脂肪酸合成酶和甘油三酯合成酶的转录影响[26]。但是, 也有报道指出, 在果糖代谢中, SREBP1c的表达不受胰岛素调控[27]。与之一致, 在本研究中, 果糖诱导的高胰岛素血症也没有明显改变肝细胞核SREBP1c蛋白的表达。

脂质β-氧化对肝脏甘油三酯沉积的影响较小[26]。PPARα主要表达于肝脏, 而在心脏和肌肉表达较少, 它在控制脂肪酸氧化途径起重要作用[28-29]。本实验对照组肾脏PPARα及其靶基因*CPT1α*、*ACO*和*CD36*的表达量远低于肝脏, 但是果糖没有影响这些基因在肝脏和肾脏的表达。

有报道称, 在有蛋白尿的肾疾病和肾病综合征中, 游离脂肪酸与白蛋白相结合的复合体滤出过多, 由于近端肾小管内吞作用, 这些复合体被重新吸收, 这可能是造成肾脏脂质沉积的主要原因[19]。也有研究证实, 用含66%果糖的饲料喂养16周并不改变C57Bl/6J、CBA/JN和DBA/2N小鼠的尿白蛋白排泄量[21]。因此, 在本研究中, 10%果糖水喂养5周的大鼠很有可能没有改变其尿白蛋白排泄, 这可能也是本实验中未发现肾脏脂质异常沉积的原因之一。

综上所述, 本研究结果表明, 与肝脏脂质沉积显著增加相比, 大鼠给予果糖水5周未能引起肾脏的脂质沉积, 肾脏脂肪酸重新合成的基因、蛋白的表达水平也未发生变化, 提示在此种情况下果糖没有引起肾脏的脂质代谢异常, 尽管我们前期工作观察到肾脏已经发生其他病理改变, 但是脂毒性不是果糖致肾脏损伤的原因。我们的这一发现很可能为果糖导致相关肾脏损害的研究提供重要信息。

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