Long-term excess fat and/or fructose ingestion causes changes in small artery K^+ transporter expression and function with effects on blood pressure

INTRODUCTION: Excess visceral fat may lead to serious disease such as hypertension, type-2 diabetes, myocardial infarcts and stroke. Obesity is recognized as a world-wide problem reaching epidemic proportions. Genetic rodent models of obesity and hypertension may not reflect the same pathophysiological mechanisms as rodents fed a high-calorie diet for > 10 weeks. The precise role of fat vs. sugar or its combination in cardiovascular diseases must be elucidated using more realistic models. K^+ is the most important ion for controlling the membrane potential in vascular smooth muscle and thus K^+ channels, Na/K-ATPase, and voltage-gated Ca^{2+} channels are crucial determinants of resistance artery tone. Only scarce information is available on the role of K^+ transporters in pathophysiological mechanisms induced by long-term feeding of laboratory rats with either high-fat, high-fructose or high-fat/high-fructose diet. HYPOTHESIS: A 28-week diet consisting of high-fat or high-fructose, or both, will lead to changes in K^+ transporter expression and function, which will be linked with changes in blood pressure, arterial smooth muscle function, endothelial function and passive structural/mechanical properties. METHODS: Male Sprague Dawley rats (4 weeks) were randomized into 4 diet groups receiving a diet with normal chow (CTR, N=19), high-fat chow (60% saturated fat, FAT, N=18), high-fructose (10% in drinking water; FRUC, N=15), or a combination of fat/fructose (FAT/FRUC, N=15) for 28 weeks. Systolic blood pressure (SBP) was measured by tail-cuff plethysmography once weekly. Gene expression in small mesenteric arteries (2^{nd}-3^{rd} order SMA) was measured at the end of study using real-time quantitative PCR (q-PCR). Arterial function and passive structure, mechanical properties were measured by pressure and wire myography. Pharmacological modulators of K^+ transporters were used to assess their potential role. RESULTS: Body weight was significantly ($P<0.05$) increased in the FAT and FAT/FRUC groups vs. CTR. SBP measured from 11-28 weeks of age was significantly increased in FRUC and FAT/FRUC vs. CTR ($P<0.05$). A comparison of mRNA expression of K_{ATP}, K_{ir}, $K_V1.2$, $K_V1.5$, $K_V7.4$, SK_{Ca}, IK_{Ca}, BK_{Ca}, Na/K-α_1, Na/K-α_2, and $Ca_V1.2$ transporters in the 4 diet groups revealed an up-regulation of K_{ir} and $K_V7.4$ channels in FAT vs. CTR, and a down-regulation of SK_{Ca} and IK_{Ca} channels in FAT/FRUC vs. CTR ($P<0.05$). Testing of endothelial function with pressure myography showed no difference between diet groups for flow-mediated vasodilatation or SK/IK channel activation using NS309 (1 µM). Wire myography showed a reduced EDH-type relaxation to increasing ACh concentrations in the presence of L-Name (100 µM) and Indomethacin (10 µM) in the FAT/FRUC group vs. CTR ($P<0.05$), consistent with reduced SK/IK channel expression. Pressure myography showed no diet-induced differences in constrictions to high-KCl (75 mM), increasing phenylephrine (PE) concentrations, or the K_V7 channel blocker XE-991 (10 µM). XE-991 reduced the Log(EC_{50}) of PE to a similar extent in all diet groups. XE-991 significantly increased vasomotion amplitude and reduced vasomotion frequency measured at a half-maximal [PE] in FRUC vs. CTR ($P<0.05$). Dilatation to excess bath [KCl] was significantly impaired in the FAT (at 9.5 mM KCl, $P<0.05$), FRUC ($P<0.05$), and FAT/FRUC groups (both at 12 mM KCl, $P<0.01$) vs. CTR. In age-matched lean control rats (N=7) $BaCl_2$ (50 µM) and $BaCl_2$ + Ouabain (100 µM) (but not Ouabain alone), significantly inhibited the excess KCl dilatations ($P<0.05$). There were no major effects of the different diets concerning structural remodelling or arterial stiffness. CONCLUSION: Our data indicates that transcriptional and/or functional changes in SK/IK and K_{ir} channels may lead to discrete functional changes in small arteries that may cause hypertension in rats fed a long-term high-fructose or a high-fat/high-fructose diet. A high-fat diet may lead to compensatory changes that prevent an increase in SBP.