Results: PCSK9 dose-dependently reduced LDLr expression in control and FH fibroblasts to similar extents, by up to 77±8% and 82±7%. Likewise, PCSK9 reduced LDLr abundance by 39±8% in non-FH and by 45±10% in HeFH lymphocytes, irrespective of their LDLr mutation status. We found positive correlations of the same magnitude between PCSK9 and LDLr-C in controls (b=0.22, p=0.0003), D206E (b=0.20, p=0.0002), V480M (b=0.24, p=0.0002), and D154N (b=0.25, p=0.048) HeFH patients. The strengths of these associations were all similar.

Conclusion: Elevated PCSK9 levels are equally detrimental for HeFH and non-FH patients: a 100ng/mL increase in PCSK9 will lead to an increase in LDL-C of 0·20-0·25mmol/L, in controls and HeFH alike, irrespective of their LDLr mutation. This explains why non-FH and HeFH patients respond equally well to monoclonal antibodies targeting PCSK9.

0169
Paraoxonase 1 activity, in the fructose-fed rats, in the presence and in the absence of an antioxidant treatment with alpha-lipoic acid

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Introduction: Paraoxonase 1 (PON1) is an esterase synthesized by the liver and secreted into the plasma, where it is associated with high density lipoproteins (HDL). Its role is to protect LDL and HDL from oxidation, thus preventing atherosclerosis. A decreased level of plasma PON1 activities has been found in diabetes mellitus, cardiovascular disorders and chronic liver diseases; but, it can also be influenced by diet and lifestyle. The purpose of this study was to assess the PON1 activities in the insulin-resistant rats fed with a fructose-enriched diet, in the presence and in the absence of an antioxidant treatment with alpha-lipoic acid (AL).

Methods: 48 male Sprague-Dawley rats were randomized into two series: rats fed for 3 months with standard chow (Control) or with standard chow supplemented with fructose (60%). In each series, a group of rats was treated intraperitoneally during 14 days/month with NaCl 0.9% and another group with 50 mg/kg/day AL. At the end of the 3 months, we assessed: 1) peripheral tissue resistance to insulin (HOMA-IR) and plasma lipid profile, 2) paraoxonase, arylesterase and lactonase activities of PON1, 3) plasma homocysteine (Hcy) level and 4) hepatic transaminase activities: aspartate-aminotransferase and alanine-aminotransferase.

Results: The fructose intake increased peripheral tissue resistance to insulin (HOMA-IR) and plasma lipid profile, less the HDL. Also, transaminase and PON1 activities, especially arylesterase and lactonase activities, and the plasma Hcy level were significantly (p<0.05) enhanced in the fructose group. The AL discontinuous treatment associated with the fructose-enriched diet improved the tissue sensitivity to insulin and decreased the plasma lipoprotein levels. Moreover, the AL treatment restored PON1 and transaminase activities, without influencing the Hcy concentration. A decrease in plasma transaminase activities was noted even when AL was associated with standard diet.

Conclusions: In our experimental conditions, the fructose intake induced an increase in plasma transaminase and PON1 activities in association with a Hyperhomocysteinemia. The AL treatment restored the enzymes’ activities and had a hepatoprotective effect, but without influence on Hcy level.

0261
Hao Ling pu-erh tea attenuates lipid accumulation in primary culture rat hepatocytes.

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Aim: Tea is one of the most consumed beverages in the world and its health-promoting effects have been widely investigated. Lipid-lowering effects of pu-erh tea have attracted growing interest. The importance of liver in lipid metabolism prompted us to investigate the lipid-lowering properties of pu-erh tea in rat primary culture hepatocytes. We tested the effect of a Hao Ling pu-erh tea extract (HLPT) and one of the major components of tea as Epigallocatechin-3-gallate (EGCG) which is largely recognized as a hypolipidemic molecule.

Methods: HLPT: an infusion of Hao Ling pu-erh tea was lyophilized and quantified for its composition in catechins by LC-MS. 24h after seeding on collagen, rat hepatocytes in primary culture were treated for 24h with various concentrations of HLPT (100, 200, 400, 600 μg/ml) and EGCG (30, 100 μM) and compared to Cyclosporin A (hyperlipidemic reference) and Clofibrate (hypolipidemic drug used in human) (n=3 in triplicate). Lipid droplet accumulation was measured by LipidTox staining and evaluated by fluorescence microscopy on an ArrayScanXTI high Content Analysis Reader (Cellomics Inc.).

Results: We found that HLPT significantly prevented hepatocyte lipid accumulation (~50%) and in the same proportion to Clofibrate. EGCG also significantly attenuated lipid accumulation (~19%) but less than HLPT.

Conclusion: The main result of this study was to point out the major implication of liver cells in the hypolipidemic effects of HLPT. Moreover, we have shown here that this effect was partly due to the EGCG, well known for its antioxidant effects. However as we reported here that HLPT has a higher hypolipidemic effect than EGCG alone, which means that EGCG acts in synergy with other HLPT components such as theaflavins but this hypothesis has to be confirmed in further experiments. In the future, the variation of expression of genes involved in lipid metabolism (THSRL, LXR, HNF-α) by qPCR induced by HLPT will allow us to improve the understanding of the effect induced by HLPT.

0211
Prevention of cardiovascular, renal and metabolic abnormalities by soluble epoxide hydrolase inhibition in a murine model of type 2 diabetes

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Objective: Epoxycosatrienoic acids (EETs) are synthesized from arachidonic acid, notably in endothelial cells, and display attractive metabolic, vasodilatory and anti-inflammatory properties. We demonstrated previously that inhibiting EET degradation mediated by soluble epoxide hydrolase (sEH) reduces hypertension and heart failure, and others reported that it improves glucose homeostasis in type 2 diabetes. However, the impact of such strategy on target organ damage in diabetes remains to be clarified.

Materials and methods: The pharmacological sEH inhibitor t-AUCB (10 mg/l in drinking water) was administered for 8 weeks in mice subjected to a high-fat diet (HFD, 60% fat) for 16 weeks. Mice on control chow diet (10% fat), non-treated HFD mice and HFD mice treated with glibenclamide (80 mg/kg) served as controls.

Results: Glibenclamide and t-AUCB similarly prevented the increased fasting glycemia in HFD mice (Control: 5.4±0.2; HFD: 8.0±0.8; HFD+G: 5.1±0.3; HFD+t-AUCB: 5.6±0.2 mmol/L; p<0.05). However, only t-AUCB improved glucose tolerance and decreased gluconegogenesis. In parallel, t-AUCB prevented adipose tissue activation and dyslipidemia. Moreover, t-AUCB improved coronary endothelial function and prevented diastolic dysfunction, as shown by echocardiography (E/A ratio; Control: 1.25±0.02; HFD: 1.05±0.03; HFD+G: 1.07±0.04; HFD+t-AUCB: 1.23±0.04, p<0.05) and invasive hemodynamics (LVEDPVR; Control: 1.90±0.55; HFD: 3.8±0.61; HFD+G: 3.1±0.8; HFD+t-AUCB: 1.88±0.2 mmHg/RVU; p<0.05). Finally, t-AUCB prevented the increased urinary albumine-to-creatinine ratio and decreased renal inflammation.

Discussion: These results demonstrate that beyond its glucose-lowering effects sEH inhibition improves coronary endothelial function, diastolic dysfunction and prevents early kidney damage in a murine model of type 2 diabetes. This positive impact on target organ damage and metabolic homeostasis prompts sEH inhibition as a promising therapeutic perspective in type 2 diabetes.