**Diet Induced Fatty Liver is Prevented and Reversed by Fatty Acid Bile Acid Conjugates (FABACs) via Inhibition of Stearoyl Coenzyme A Desaturase1 in Rodents**

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**Abstract**

NAFLD is currently the most common chronic liver disease worldwide. It is devoid of an accepted medical treatment. Aramchol (a conjugate of Arachidic and Cholic Acid) was shown to prevent diet induced NAFLD as well as to treat pre-established NAFLD [1,2]. We investigated its hepatic, metabolic and molecular effects during treatment of established NAFLD by oral Aramchol (150 mg/kg/day) in C57Bl6 mice maintained on a 50% High Fat Diet (HFD) liver fat decreased by ca 32 % (2) while SCD1 activity in the liver microsomes decreased by 84 % (Fig 2). In the same study of liver maintained on a 100% HFD with and without oral treatment of established NAFLD by Aramchol (150mg/kg/d) liver fat decreased by ca 42 % (2) while SCD1 activity in the liver microsomes decreased by 62 % (2). In a comparison of similar concentrations with the established SCD1 inhibitor – Conjugated Linoleic Acid (CLA) T10C12 – Aramchol inhibited SCD1 to a greater degree. The target CLA isomer T10 C12 did not inhibit SCD1 activity serving as a negative control (Fig.3). Analysis of mRNA in the above 2 groups of mice livers at the end of the periods of Aramchol treatment showed no significant changes in a number of the lipid genes (Fig.4). Analysis of transcription FXR did not show any direct response but there was competitive agonist activity with site acida (not shown).

**Methods**

Liver tissue was measured chemically. SCD1 activity was measured by the conversion of [14C] Palmitic acid (16:0) and [14C] Palmitoleic acid (16:1) to [14C] Palmitic acid. Liver homogenates, hepatic cells and microsomes were studied.

Aramchol reduces liver triglycerides via incomplete, probably direct, inhibition of SCD1 activity without affecting the mRNA of this or other lipogenic liver genes. The increase in beta oxidation and decrease in the synthesis of fatty acids associated with SCD1 inhibition contribute to the decrease in liver triglycerides.

**Results**

**Fig.1.** Effects of Aramchol and Steamchol on SCD1 activity in vivo in C57Bl6/J mice. A-Mice maintained on a 50% High Fat Diet for 6 weeks +/- Aramchol or Steamchol (150 mg/kg/day). B-Mice maintained on a 100% High Fat Diet for 13.5 weeks +/- Aramchol (150 mg/kg/day).

**Fig.2.** A-Liver Microsomes of C57Bl6/J mice incubated in vitro with increasing concentrations of Aramchol. SCDD1 activity measured. B-Same microsomes incubated in vitro with equimolar amount of Aramchol,CLA T10,12c (inhibitor) or CLA 9c,11t (inactive as inhibitor).

**Fig.3.** Effects of Aramchol (µg/ml) on β oxidation using [14C] acetate incorporation into fatty acids.

**Fig.4.** Fatty Acid Synthesis in HepG2 cells in vitro. Effect of increasing doses of Aramchol (µg/ml) on [14C] acetate incorporation into fatty acids.

**Fig.5.** Relative luciferase activity. Effect of increasing doses of Aramchol compared to against GW 3965.

**Fig.6.** mRNA expression of DHT, SCD1, SCD2, SREBP1c, ABCA1, ABCG1, FAT, SREBP1c, SREBP2, LXRα, LXRβ, PPARγ/β in HepG2 cells. Relative luciferase activity. Effect of increasing doses of Aramchol compared to against GW 3965.

**Fig.7.** Effects of Aramchol and Arachidic acid on SCD1 activity in vitro in HepG2 cell line. Relative luciferase activity. Effect of increasing doses of Aramchol compared to against GW 3965.

**Conclusions**

Aramchol reduces liver triglycerides via incomplete, probably direct, inhibition of SCD1 activity without affecting the mRNA of this or other lipogenic liver genes. The increase in beta oxidation and decrease in the synthesis of fatty acids associated with SCD1 inhibition contribute to the decrease in liver triglycerides.

**References**
