REDUCTION OF ESTABLISHED FATTY LIVER IN RODENTS BY ORAL FATTY ACID BILE ACID CONJUGATES (FABACs)

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ABSTRACT

Fatty Acid Bile Acid Conjugates – FABACs were shown to have multiple metabolic effects. They prevented the development of Fatty Liver in animals on high fat diets. The present study was initiated to test whether they are able to reduce liver fat in preestablished Fatty Liver – i.e. in a therapeutic setting. Fatty Liver was induced by a high fat diet or by a high fat high cholesterol diet. Subsequently rats were maintained on various proportions of fat in the same diet with or without oral FABAC therapy at 150 or 25 mg/kg/day. On a 25% HFD in mice FABACs reduced total liver fat (TLL) significantly within 4 weeks (p<0.03). On a 50% HFD the reduction was noted at 8 weeks (p<0.05). On a 100% HFD in rats TLL was significantly reduced after 12 weeks. Triglycerides and Diglycerides were the neutral lipids reduced by FABAC therapy. In mice and rats FABAC therapy reduced the serum 16:1/16:0 + 16:1 fatty acid ratio, a surrogate marker of Stearoyl CoA Desaturase activity. De novo fatty acid synthesis was reduced by FABACs in HepG2 cells. The above effects may be part of the MOA of the FABACs. FABACs may serve as potential therapeutic agents for human NAFLD and NASH.

INTRODUCTION

FABACs were previously shown to have multiple metabolic effects. They prevent and dissolve cholesterol gallstones1. They markedly reduce plasma cholesterol by several mechanisms: increased cholesterol efflux from cells via the ABCA1 transporter2, increased fecal sterol loss3 and other mechanisms of cholesterol catabolism. They were also shown to prevent diet induced Fatty Liver in several animal species4. The Aim of the present study was to investigate whether they would also be effective in reducing preexisting Fatty Liver (NAFLD) in a therapeutic setting.

RESULTS

When the maintenance diet contained only 25% of the fat present in the HFD, FABACs, after 4 weeks, significantly (p<0.03) reduced TLL (Fig 2). The effect was similar with Steamchol and Aramchol treatment consistently reduced this ratio, indicating a down regulation of the enzyme Stearoyl CoA Desaturase. De novo fatty acid synthesis from labeled acetate moieties was measured in HepG2 cells. Aramchol in the medium rapidly down regulated it. The changes in serum 16:1/16:0 + 16:1 fatty acids (a surrogate marker of SCD activity) following FABAC therapy are shown in Fig.6 for mice and Fig.7 for rats. FABAC treatment significantly reduced this ratio, indicating a down regulation of the enzyme Stearoyl CoA Desaturase. De novo fatty acid synthesis from labeled acetate moieties was measured in HepG2 cells. Steamchol treated mice. With a 50% HFD the effect was similar with Steamchol and Aramchol and at both dose levels. After 6.5 weeks the TLL declined further in the 25% HFD controls. The decrease in the FABAC treated group was greater but remained significant only in the Steamchol treated mice. With a 50% HFD the TLL in the controls remained steady at 4 and 8 weeks. The effects of Aramchol became apparent only at 8 weeks (p<0.05) (Fig.3). When the 100% HFD was given throughout the 12 week treatment period in rats (Fig.4) the TLL in the controls increased very markedly. Aramchol treatment decreased the TLL significantly (p<0.01). The results were similar when expressed as mg lipid/gm liver or mg lipid/mg protein.

Liver lipid classes were analyzed at the end of the 12 weeks of treatment, in rats (Fig.5). The main decrease was noted in diglycerides and triglycerides. The changes in serum and TLL are shown in Fig.6 for mice and Fig.7 for rats. FABAC treatment consistently reduced this ratio, indicating a down regulation of the enzyme Stearoyl CoA Desaturase. De novo fatty acid synthesis from labeled acetate moieties was measured in HepG2 cells. Aramchol and Steamchol treatment reduced the TLL in the FABAC treated group was greater but remained significant only in the Steamchol treated mice. With a 50% HFD the TLL in the controls remained steady at 4 and 8 weeks. The effects of Aramchol became apparent only at 8 weeks (p<0.05) (Fig.3). When the 100% HFD was given throughout the 12 week treatment period in rats (Fig.4) the TLL in the controls increased very markedly. Aramchol treatment decreased the TLL significantly (p<0.01). The results were similar when expressed as mg lipid/gm liver or mg lipid/mg protein.

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CONCLUSIONS

• FABACs reduce liver fat in preexisting Fatty Liver
• The rapidity of the effect is in inverse proportion to the fat concentration of the diet fed during the treatment period.
• Diglycerides and Triglycerides were the main neutral lipids affected
• FABACs reduce the activity of Stearoyl CoA Desaturase and fatty acid synthesis which may represent one of their mechanisms of action
• FABACs may be considered potential therapeutic agents in human NAFLD and NASH

REFERENCES