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P-068 - The ACLY inhibitor SB204990 does not alter lysine histone acetylation in mouse liver

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Cabimer.

Resumen

Objectives: Acetyl-coenzyme A is a fundamental component of cell metabolism, which plays a role in energy production, macromolecular biosynthesis and protein modification. Within the mitochondria, acetyl-coenzyme A condensation with oxaloacetate generates citrate, which can be exported to the cytosol, where is cleaved by ATP-citrate lyase (ACLY), producing again acetyl-coenzyme A and oxaloacetate. In the nucleus and the cytoplasm acetyl-coenzyme A is used for important cellular functions such as histone acetylation or fatty acid synthesis. Silencing or inhibition of ACLY reduces tumour growth and produces blood lipid-lowering effects. Moreover, ACLY inhibitors are reasonably well tolerated in adult animals. Thus, ACLY inhibition could represent a therapeutic opportunity for the treatment of cancer and metabolic diseases, making its mechanistic understanding a promising field of study. Histone acetylation is a molecular mechanism that controls gene expression. Previous data has shown that global histone acetylation is altered in ACLY-deficient cell lines. Herein, we evaluated whether beneficial metabolic effects observed in mice exposed for 16 weeks to a pharmacological inhibitor of the ACLY are associated with modulations in histone acetylation in liver tissue lysates.

Material and methods: Mice were fed with either a standard healthy diet or a high fat diet supplemented or not with SB, a potent inhibitor of the ACLY for 16 weeks. The experimental groups were as follows: standard diet, standard diet + SB (250 mg/Kg of food), high fat diet and high fat diet + SB (250 mg/Kg of food). Metabolic and physical health was monitored during the course of the experimentation. Histological analyses were performed by haematoxylin and eosin staining in liver and white adipose tissue. A histone acid extraction was conducted using the livers of mice belonging to all experimental groups. Samples were processed and western blots were performed using specific antibodies of several histone-lysines in order to evaluate potential modulations on histone acetylation levels between the different experimental groups.

Results: ACLY inhibition reduces the size of lipid droplets in liver tissue. Current data indicates that acetylation levels of H3K9, H3K14, H3K18, H3K56, H4K5, H4K8 are not significantly altered in the different experimental conditions.

Conclusions: These results indicate that beneficial effects produced by ACLY inhibition are not caused by changes in histone acetylation levels of the residues tested in liver samples.