Exploring the structure-activity relationship of various sEH inhibitors in promoting brown adipogenesis

Sue Choi, Yang Yang, Christophe Morisseau, Bruce D Hammock, and Ling Zhao

1 Department of Biochemistry and Cellular & Molecular Biology, 2 Department of Nutrition, University of Tennessee, Knoxville, 3 Department of Entomology, University of California, Davis

Introduction

Brown adipose tissue has emerged as a novel target for obesity prevention and treatment due to its responsibility for heat production. Pharmaceutical agents that can promote brown adipogenesis, i.e. formation of new brown adipocytes, will be beneficial for this purpose. Soluble epoxide hydrolase (sEH) is a cytosolic enzyme that degrades epoxy fatty acids (EpFAs) (lipid signaling molecules) into inactive diols.1 Potent sEH inhibitors (sEHIs) are beneficial for many chronic diseases as they stabilize endogenous EpFAs by blocking their degradation.1 Our preliminary results have shown that trans-4-[4-(3-adamantan-1-yl-ureido)-cyclohexyl]-benzoic acid (t-AUCB) and trans-4-[4-[4-(trifluoromethoxyphenyl)-ureido] cyclohexyl] benzoic acid (t-TUCB), both potent sEH inhibitors, dose-dependently promote brown adipogenesis.

The objective of this study is to investigate the structure and activity relationship (SAR) of various sEHIs with variations to those of t-AUCB and t-TUCB to identify the structure properties that make a potent drug to promote brown adipogenesis. Oil Red O (ORO) stained lipids accumulation was used as a marker to evaluate brown adipogenesis.

Methods

- Murine brown adipogenesis: murine brown pre-adipocytes were induced to differentiate in the presence of various doses of sEHIs during the differentiation process
- ORO staining and absorbance: the cells were fixed after differentiation and were stained with ORO dye; ORO absorbance was measured at 500 nm wavelength
- Statistical analysis: ANOVA with RM was used to detect the significance of various sEHIs compared to the controls

Effects of t-AUCB-derived sEHIs

Effects of t-TUCB-derived sEHIs

Effect of t-AUCB and t-TUCB

**References:**


3 Unpublished results.