

Invited Speaker Plenary 3: Gene-Nutrient Interactions

Characterisation of a novel selective PPAR γ modulator (SPPAR γ M) with insulin sensitizing and glucose lowering properties

T Allen^{1†}, SA Moodie^{2†}, F Zhang^{2†}, A Smith¹, F Gregoire², E Clemens², J Luo²,
GEO Muscat^{1*}, TA Gustafson^{2*}

* Corresponding authors †joint first authors

¹Institute for Molecular Bioscience, University of Queensland, St. Lucia QLD 4072, AUSTRALIA.

²Metabolex, Inc. 3876 Bay Center Place, Hayward, CA 94545

Background - PPAR γ is a member of the Nuclear Hormone Receptor (NR) superfamily, and the NR1C subgroup that includes PPAR α and PPAR δ . Inherited mutations in the PPAR γ gene lead to dysfunctional lipid and glucose homeostasis. The NR1C subgroup functions as fatty acid (FA) sensors, and couples fluxes in low affinity dietary lipids/FAs to the transcriptional regulation of genes in lipid and glucose homeostasis. For example, the mono and polyunsaturated (but not saturated) FAs modulate PPAR γ in the μ M range. The total concentration of nonesterified FAs in human serum can exceed 1mM, and the more prevalent FAs can account for up to 20-40% of this total. The pathophysiological significance is underscored by many reports that diets rich in unsaturated FAs lower cholesterol and triglycerides levels, and elevate HDL cholesterol levels in animals and humans. Furthermore, the dietary polyunsaturated to saturated fat ratio differentially affects the body mass index in populations with common variants of the PPAR γ gene, highlighting the importance of PPAR γ (gene)-nutrient interactions.

Halofenate, a phenoxyacetic acid [(2-acetoamidoethyl (p-chloro-phenyl) (m-trifluoromethylphenoxy) acetate)] was tested clinically in the 1970's as a hypouricemic, and hypolipidemic drug. Halofenate was shown to be very effective in lowering plasma triglycerides, cholesterol, uric acid and bilirubin levels in patients with a variety of hyperlipoproteinemias. Interestingly, hypoglycemic and hypoinsulinemic effects were serendipitously observed in dyslipidemic type II diabetic (NIDDM) patients after halofenate monotherapy, and in combination with oral hypoglycemic drugs. The therapeutic (and time course of the hypoglycemic) effects of halofenate mirrored some aspects of the TZD class of insulin sensitizers that are potent synthetic activators of PPAR γ .

Objectives - We hypothesized that halofenate might act as an insulin sensitizer and we present data to show that halofenate is a selective PPAR γ modulator (SPPAR γ M) with therapeutic utility.

Outcomes - We show that halofenic acid: (i) selectively activates PPAR γ in a dose dependent manner (\sim EC₅₀ 30 μ M); (ii) binds directly to human PPAR γ (K_i of \sim 18-30 μ M); and (iii) is a partial PPAR γ agonist with \sim 20% the activity of the full agonist rosiglitazone. The partial agonism of halofenic acid reflects a unique footprint in the context of interactions with transcriptional cofactors. For example, the differential displacement of corepressors (N-CoR and SMRT) and the defective recruitment of the coactivators (p300, CBP and TRAP220). Specifically, halofenic acid displaced the co-repressors N-CoR and SMRT from PPAR γ in a dose dependent manner yet did not induce recruitment of the co-activators p300, CBP or TRAP 220, relative to the potent PPAR γ agonist, rosiglitazone. In addition, halofenic acid selectively modulated specific PPAR γ responsive genes in differentiated 3T3-L1 adipocytes. In contrast to the potent agonist, rosiglitazone, halofenic acid did not induce genes involved in fatty acid storage and transport. Moreover, halofenic acid did not induce differentiation of primary human pre-adipocytes, and neutralized rosiglitazone-mediated adipogenesis. *In vivo* studies demonstrated that halofenate displays vigorous insulin sensitizing and glucose lowering properties in *ob/ob* mice.

Conclusions - These results demonstrate that halofenate is a novel selective PPAR γ modulator that induces differential cofactor displacement and recruitment. Moreover, it demonstrates therapeutic anti-diabetic properties in the absence of adipogenic properties that lead to deleterious weight gain with TZD treatment in type II diabetic patients.