

## Carnitine Palmitoyltransferase Inhibitor in Diabetes

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### Abstract

This review addresses progress of carnitine palmitoyltransferase targeted pharmaceuticals in diabetes and the challenges ahead. Since the discovery of carnitine palmitoyltransferase (CPT), there are lots of publications on its role in disease. The wide tissue expression, functional and biological roles have documented the physiological importance of these enzymes both in health and disease. Thus, over the years, studies have revealed essential importance of CPT1 in mammalian pathophysiology revealing CPT1 as potential drug targets. Starting from a brief description of the main functional features of CPTs, their roles in physiology and pathophysiology of different human diseases, this review describes the main classes of small molecules which are able to regulate CPT1 for diagnostic and therapeutic applications.

**Keywords:** Carnitine palmitoyltransferase (CPT); Fatty acid oxidation (FAO); Diabetes

### Pathophysiology of CPT involving in FAO

Fatty acid  $\beta$ -oxidation mainly occurs in mitochondria and is controlled by CPT1, which is a key regulator to facilitate the transfer of long-chain fatty acids across the mitochondrial membrane for  $\beta$ -oxidation in mammals. Besides CPT1 is a key factor to regulate the fatty acids beta-oxidation, it is also an energy sensor to meet the body energy need by regulate fatty acids oxidation process. The activity and expression level of CPT1 varies by tissues, depending on the energy substrate tempo-spatially. There are 3 isoforms of CPT1: CPT1a in liver, CPT1b in muscle and CPT1c in neuron. CPT1a and b show differences in their kinetics and tissue expression, while CPT1c is a sensor of lipid metabolism in neurons, where it appears to impact ceramide and triacylglycerol metabolism [1].

The variation of CPT1 gene expression has tight relationship with the disease, like obesity, diabetes and cardiac disease [2]. Several report on CPT1 modulators, mostly inhibitors, related pharmaceutical formulations, being used for treatments of diabetes disorders. Numerous studies have shown that the overexpression of CPT1 is tightly associated with tumor progression in breast cancer [3,4], gastric cancer [5], prostate cancer [6], CPT1 serves to activate fatty acid oxidation (FAO) that increases ATP and NADPH reserves, protecting cancer against the environmental stress such as glucose deprivation and hypoxia [7]. These novel studies point to an important role that CPT1 had in promoting cancer angiogenesis. In the future, further efforts should be directed to interpret the precise molecular mechanism of CPT1 in cancer and the potential of CPT1 inhibition in cancer intervention.

### CPT Inhibitors and Diabetes

Metabolic modulators are a newer class of drugs by modulating tissue metabolism without altering hemodynamics. CPT inhibitor is one kind of metabolic modulators. In the past years efforts worked on CPT inhibitors trying to treat diabetes, such as malonyl-CoA analogue, glycidic acid analogues and substrate inhibitor. CPT2 inhibitors was used seldom because it effected tissue widely and was nonspecific. CPT1a inhibitor works on liver specific, affecting heart weakly. While CPT1b mainly affect the skeletal muscle, heart and adipose tissue.

CPT1a decrease gluconeogenesis while CPT1b increase the glucose uptake by peripheral tissues. It is positive in diabetes treatment, while being negative in cardiac disease control.

Elomoxir and 2-tetradecylglycidic acid (TDGA) are two prototypes of glycidic acid analogues used in treatment of diabetes. Etomoxir was originally developed as an oral hypoglycemic agent and is also an irreversible CPT-1 inhibitor [3]. Etomoxir works well in animal models and come into clinical trial II. However, its clinical trial was stopped due to its cardiac hypertrophic side effect.

ST1326, 3(R)-3-(Tetradecyl ureido)-4-(trimethylammonium) butyrate, a selective inhibitor of CPT1a, is an aminocarnitine derivative. ST1326 was initially selected by Sigma-Tau laboratories as a candidate for diabetes and ketoacidosis therapy [8]. More data suggest ST1326 plays a role in the therapy of cancer. ST1326 is highly selective for the CPT1a, a favorable characteristic when compared with etomoxir, which is irreversibly inhibits both CPT1a and CPT1b.

Teglicar is an oral formulation of ST1326. It inhibits CPT1a selectively and reversibly. *In vitro* and in animal models, it reduces gluconeogenesis and improves glucose homeostasis, refreshing the interest in selective and reversible CPT1a inhibition as a potential antihyperglycemic approach. It is a promising chemical because it modulates glucose balance in type 2 diabetes and obesity, as tested in phase 2 studies for the treatment of type 2 diabetes, in which it demonstrated an excellent safety profile [9].

However, some references reported that prolonged CPT1b inhibition poses severe cardiac risk and to improve insulin sensitivity by targeting CPT1 with current inhibitors is not viable [10,11].

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Future randomized controlled trials are warranted to reconcile the discrepancies between preclinical efficacies and inconclusive clinic outcomes of these chemicals.

## Future Scope

CPT1-targeted therapies for diabetes, enhancement of CPT1 function for diabetes and obesity are needed. The Teglicar represents promising therapies that deserve further investigation by clinical trials. Noteworthy, a unique class of gold-based compounds as selective inhibitors of CPT1 isoforms may provide new chemical tools for therapeutic applications. X-ray crystallography models and the thermodynamic measure will help to refine new molecules and to optimize inhibitors. Several pharmacological agents are in development for diabetes, cardiac disorders and cancer which act at least in part through metabolic mechanisms.

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