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Review Article

Pivotal Roles of Diacylglycerol O-Acyltransferase 1 (DGAT1) and Carbonic Anhydrase Enzymes in Obesity and Diabetes

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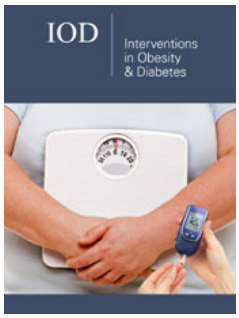

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Abstract

All around the world, the prevalence of diabetes mellitus is rising at an alarming rate. Obesity has been found to be crucial in the management of diabetes mellitus because it prolongs the period between becoming pre-diabetic and developing diabetes. The development of obesity is brought on by the buildup of lipids in adipocytes, which is facilitated by the Diacylglycerol O-Acyltransferase 1 (DGAT1). Increased DGAT1 levels in adipose tissue have been linked to insulin resistance and adipocyte hypertrophy in obese individuals. Diarylglycerol O-Acyltransferase 1 (DGAT1) is a key player in the control of diabetes and obesity. There are 16 known human carbonic anhydrase isoforms, and CA IX has also been linked to diabetes and obesity. According to research, obese people have higher levels of CA IX expression in their adipose tissue. CA IX inhibition has been demonstrated to diminish adipocyte differentiation and fat storage in vitro. The main functions of two pharmacologically significant enzymes, DGAT1 and carbonic anhydrase, are discussed in this review article. To demonstrate the potential of these enzymes as anti-obesity and anti-diabetic targets, some prospective inhibitors and various adverse effects of anti-obesity drugs are also discussed.

Keywords: Diacylglycerol O-acyltransferase 1; Carbonic anhydrase; CA IX isoform; Obesity; Diabetes

Introduction

Diabetes Mellitus (DM) is a chronic metabolic disorder in which human body cannot utilize glucose properly owing to decreased insulin secretion or absence of insulin responsiveness or both of them. Despite of the induction of new types of drugs and approaches still global diabetes crises has not been addressed. Various studies assessed that 8.8% of the world's population between the ages of 20-79 are suffering from diabetes [1-3]. There is convincing evidence that controlling obesity helps to manage type-2 diabetes by delaying from pre-diabetic to become diabetic and thus is extremely helpful in treating type-2 diabetes [4,5]. Modest and sustained weight loss has been demonstrated to improve glycemic control and lessen the requirement for glucose-lowering drugs in individuals with type-2 diabetes who are also overweight or obese [6]. More extensive dietary energy restriction with very-low-calorie diets has been shown to significantly lower A1C and fasting glucose in patients with type-2 diabetes and obesity and to induce sustained diabetic remission for at least two years [7-9]. Novel, efficient therapeutic approaches are highly inevitable to address these problems of global concern [10].

Role of Diacylglycerol O-Acyltransferase 1 (DGAT1) in Obesity and Diabetes

Diacylglycerol O-acyltransferase 1 (DGAT1) is an enzyme that plays a key role in triglyceride synthesis. It is a member of the DGAT family of enzymes and is primarily expressed in the small intestine, adipose tissue, and the liver [11,12]. DGAT1 catalyzes the final step in the synthesis of triglycerides, which involves the transfer of an acyl group from acyl-CoA to Diacylglycerol (DAG) to form a Triacylglycerol (TAG) molecule. This reaction is important for the storage of energy in adipose tissue and the production of lipoproteins in the liver [13,14]. DGAT1 has been the focus of research as a potential therapeutic target for the treatment of

obesity, type 2 diabetes, and other metabolic disorders. Several DGAT1 inhibitors have been developed and tested in preclinical and clinical studies, with promising results. Additionally, DGAT1 gene variants have been associated with altered lipid metabolism and risk of metabolic diseases in humans [15-17]. DGAT1 is also found in milk and is important for the synthesis of milk fat. Inhibition of DGAT1 in dairy cows has been shown to reduce milk fat content, which could have implications for the dairy industry [18-20].

DGAT1 enzyme plays its vital role in the synthesis of Triacylglycerol (TAG) from Diacylglycerol (DAG) and fatty acyl-CoA. This enzyme is found in many tissues, including adipose tissue, liver, and intestine, and is known to be up regulated in obesity and type 2 diabetes [21-23]. In obesity, increased levels of DGAT1 in adipose tissue have been shown to contribute to adipocyte hypertrophy and insulin resistance. Specifically, DGAT1 promotes the synthesis of TAG, which leads to the accumulation of lipids in adipocytes and the subsequent development of obesity. This lipid accumulation is thought to contribute to the development of insulin resistance, as the excess lipid can interfere with insulin signalling pathways [24-26]. In addition to its role in obesity, DGAT1 has also been implicated in the development of type 2 diabetes. Studies have shown that DGAT1 expression is upregulated in the liver of obese and diabetic mice and humans, and that this upregulation is associated with increased hepatic lipid accumulation, inflammation, and insulin resistance. Furthermore, genetic deletion of DGAT1 in mice has been shown to improve glucose homeostasis and insulin sensitivity, highlighting the potential therapeutic benefits of targeting DGAT1 for the treatment of type 2 diabetes [27-30].

Identification of DGAT1 inhibitors by Tschapalda and co-worker

Tschapalda and colleagues investigated hundreds of lipid storage inhibitors in a study and discovered three structurally diverse and powerful chemical classes that were active in cells of many species, including human cells, as DGAT1 inhibitors with low cytotoxicity, as shown in Figure 1. Compounds 4,5 and 6 the analogues of compounds 1, 2 and 3 exhibited potent DGAT1 inhibitory activity with EC50 values of 0.34nM, 9nM and 250nM, respectively [31].

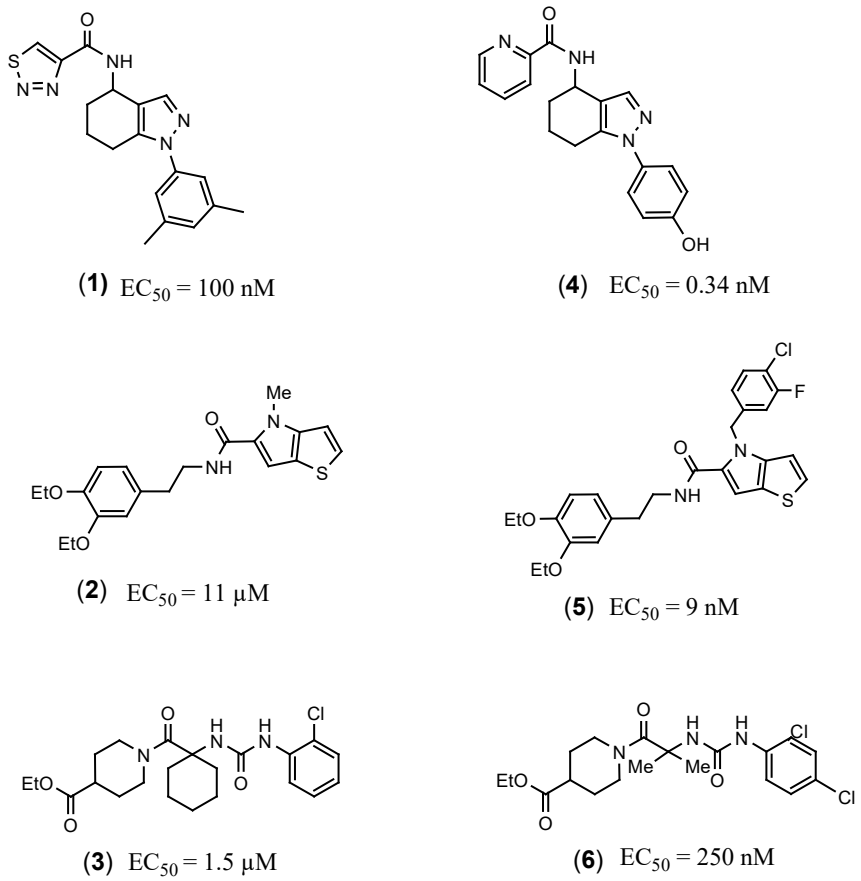
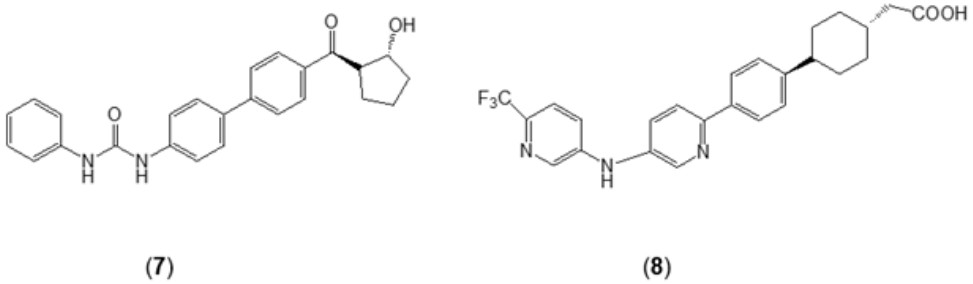


Figure 1: Potent DGAT 1 inhibitors.

Identification of DGAT1 inhibitors by Huang and co-workers

In another study, Huang and co-workers assessed the prospective therapeutic effects of DGAT1 inhibitors 7 and 8 (Figure 2) on pancreatic β-cells, and further proved their antidiabetic effects in db/db mice. This study confirmed that DGAT1 inhibitors compounds 7 and 8 have significantly reduced the apoptosis of pancreatic islets in db/db mice and considerably decreased fasting blood glucose and triglyceride levels [32]. Overall, DGAT1 plays an

important role in the development of obesity and type 2 diabetes, primarily through its role in promoting the synthesis of TAG and the subsequent accumulation of lipids in adipose tissue and liver. Targeting DGAT1 may therefore be a promising therapeutic approach for the treatment of these metabolic disorders.



(7) (8)

Figure 2: DGAT1 inhibitors with antidiabetic effects on obese diabetic db/db mice.

Role of Carbonic Anhydrase Enzymes in Obesity and Diabetes

A group of metalloenzymes known as Carbonic Anhydrases (CAs) catalyze the reversible conversion of carbon dioxide (CO2) into bicarbonate (HCO3-) and protons (H+). Numerous physiological systems, including acid-base balance, respiration, and electrolyte transport, depend on this interaction [33,34]. Carbonic anhydrases are found in many tissues, including the lungs, kidneys, liver, and pancreas, and have been identified in various organisms, including bacteria, algae, and animals [35]. There are currently 16 known isoforms of carbonic anhydrases in humans, which are classified into three main groups: cytosolic (CA I, II, III, VII, XIII, and XV), mitochondrial (CA VA and VB), and membrane-bound (CA IV, IX, XII, XIV, and XVII-XVIII) [36]. Carbonic anhydrases have been the subject of extensive research due to their importance in various physiological processes and their potential as therapeutic targets for a range of diseases, including glaucoma, cancer, and epilepsy. Carbonic anhydrase inhibitors are also used clinically for the treatment of conditions such as glaucoma, altitude sickness, and epilepsy [37,38].

There is emerging evidence suggesting a potential role for Carbonic Anhydrases (CAs) in the development of obesity and diabetes. Some studies have shown that the expression levels of certain isoforms of CAs are altered in obese and diabetic individuals compared to healthy controls. One isoform that has been implicated in obesity and diabetes is CA III. Studies have shown that the expression of CA III is increased in the skeletal muscles of obese and diabetic individuals and that this increase may contribute to insulin resistance and impaired glucose metabolism. Furthermore, inhibition of CA III has been shown to improve glucose uptake in skeletal muscle cells and improve glucose tolerance in obese and diabetic animal models [39,40]. Another isoform, CA IX, has also been implicated in obesity and diabetes. Studies have shown that CA IX expression is increased in adipose tissue of obese individuals, and that CA IX inhibition can reduce adipocyte differentiation and fat accumulation *in vitro* [41].

Identification of CAs inhibitors by Huang and co-workers

Costa and co-workers for the first time investigated essential oils against mitochondrial isoform VA of the carbonic anhydrase enzyme [42]. Prior to this a structure-based virtual screening was conducted to identify new anti-obesity drug. As a result, some active compounds (9-14) of essential oils were identified with anti-obesity potential against three isoforms of carbonic anhydrase enzyme *in vitro*, as shown in Table 1. In this study, new scaffold was identified that will be useful in optimization studies to develop novel anti-obesity drugs as shown in Figure 3. The role of CAs in obesity and diabetes is still being elucidated, there is growing evidence to suggest that these enzymes may be involved in the pathogenesis of these diseases and may be potential targets for therapeutic intervention. Overall, carbonic anhydrases are important enzymes with a wide range of physiological roles, and their study has significant implications for both basic science and clinical applications.

Table 1: Active components of essential oils as inhibitors of carbonic anhydrase as per potential anti-obesity drugs.

Compound Name	Targets		
	CAI	CAII	CAVA
β-Thujaplicin (9)	4.98	90.60	7.50
4-Isopropylbenzoic acid (10)	3.44	85.40	7.38
3-Phenylpropyl benzoate (11)	3.75	>100	7.83
Z-Geranic acid (12)	8.81	18.90	9.07
2-Methylhexanoic acid (13)	5.06	3.71	43.10
Acetazolamide (14) (used a standard)	0.25	0.01	0.06

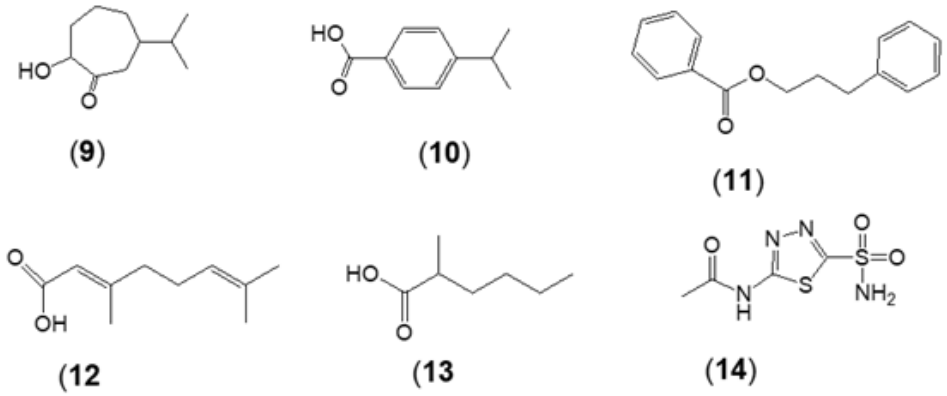


Figure 3: Structure of the CA inhibitors isolated form the essential oils as potential anti-obesity drugs.

Safety, Selectivity and Potential Side Effects of DGTA1 and Carbonic Anhydrase Inhibitors

Many effective weight-loss drugs have been pulled off the market because of potentially fatal adverse effects. These medications include phenylpropanolamine (stroke), fenfluramine (cardiac valvulopathy), dexfenfluramine (valvulopathy), aminorex (pulmonary hypertension), rimonabant (suicidal ideation and behavior), sibutramine (myocardial infarction and stroke), and the most recent medication, lorcaserin (cancer). Following the sibutramine withdrawal in 2010, the FDA requested cardiovascular safety information for new anti-obesity medications. Clinical trial results and novel drug development for effective anti-obesity medications must be carefully analyzed in light of potential safety issues and side effects, bearing in mind that obese people may regularly consume them [43,44]. Similarly, how topiramate in combination with phentermine was approved by the FDA in 2012 for a second use in the management of obesity, clinical trials are currently being conducted on the use of zonisamide, either alone or in combination with other medications (bupropion, metformin), for a similar purpose. However, although being efficacious, these pharmaceuticals are rarely employed as antiobesity therapies because of the side effects brought on by the non-selective inhibition of the target carbonic anhydrase enzyme isoforms and the polypharmacology of these medications [45].

Conclusion

In brief, these findings demonstrate that both Diacylglycerol O-Acyltransferase 1 (DGAT1) and carbonic anhydrase enzymes play vital roles in obesity and diabetes. The inhibitors of DGAT 1 and carbonic anhydrase have significant implications and are promising therapeutic approaches for the management of obesity and diabetes. Moreover, effective anti-obesity and anti-diabetic inhibitors must be prudently evaluated in light of potential safety issues and side effects.

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