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Review Article

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Role of human carbonic anhydrase isoforms VA and VB in obesity: Implications, mechanisms, and therapeutic prospects

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ABSTRACT: Carbonic anhydrases (CAs, EC 4.2.1.1) are metalloenzymes ubiquitous in both prokaryotes and eukaryotes and catalyze a very basic physiological reaction. In particular, hCA VA and hCA VB isoenzymes are mitochondrial isoforms that are involved in metabolic processes such as ureagenesis, gluconeogenesis, and *de novo* lipogenesis by providing bicarbonate. The development of inhibitors for hCA VA and hCA VB commenced following the observation of weight loss, a metabolic adverse effect, in epileptic patients who were using antiepileptic medicines such as topiramate, zonisamide, and acetazolamide. Based on the structures of these drugs, the rational drug design technique, together with the famous "tail approach" was applied to develop novel hCA VA and hCA VB inhibitors that have potential as anti-obesity drug candidates. This review summarizes the implication of hCA VA and hCA VB in the pathophysiology of obesity and the inhibitory activities of small molecules developed against hCA VA and hCA VB as potential anti-obesity agents.

KEYWORDS: Carbonic anhydrase, obesity, lipogenesis, gluconeogenesis, mitochondrial enzymes

1. INTRODUCTION

Obesity is generally defined as an excessive accumulation of fat compared to lean mass such as bone, muscle, and water. Excessive daily energy intake exceeding energy expenditure results in the accumulation of unspent energy as adipose tissue, leading to obesity. One of the criteria for obesity is body mass index (BMI) being greater than 30 kg/m^2. The United States has the highest prevalence of obesity globally. In the United States, approximately 2/3 of the population is outside the ideal weight[1]. Obesity is a multifaceted disease that reduces the quality of life as the average life expectancy increases. It is classified as a chronic and degenerative disease and has many metabolic and psychological aspects. Therefore, it is necessary to address treatment both medically and socially[1–3]. Obese individuals may also experience symptoms such as snoring, excessive sweating, sleep apnea, pain in the joints and back, skin infection due to irritation, and feeling out of breath due to fatigue even with the slightest movement[1,2].

The primary contributors to obesity include Western style eating habits, sedentary lifestyles, and genetic factors [4]. The fact that obesity causes many comorbidities is a factor that increases the health expenditures of countries and consequently imposes a serious health burden on countries [5]. Since obesity is a multifaceted health problem, its treatment should also be multifaceted. Currently, there are different therapeutic approaches for the treatment of obesity. Among these approaches, diet is the most important [6]. However, the extent to which patients adhere to diet treatment and the success rates are controversial. Furthermore, bariatric surgery and various stomach operations are common surgical practices in the management of obesity, however, it should be thoroughly investigated whether these surgical practices are effective on each patient profile. In addition to bariatric surgery and diet, various medical treatments are also available [1,3,7,8]. Aside from the current existing drugs, many drugs have been approved and subsequently withdrawn due to their serious side effects that have been reported [1,3]. Nevertheless, the

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approved that are still in use also exhibit potential side effects that have not been completely corrected .The use of these medications may have serious consequences, especially for patients in some risk groups. Consequently, this warrants the need for the development of novel anti-obesity drugs that have different targets or mechanisms of action with fewer side effects. Recently, CA V has been among the most explored targets in the quest for developing new anti-obesity agents. Interestingly, many studies have reported CA V inhibitors as potential candidates for the management of obesity[9]. We hope that the carbonic anhydrase inhibitor compounds discussed in this review may shed new light on obesity treatment.

2. CURRENT DRUGS IN OBESITY

Although bariatric surgery, diet, and lifestyle changes are very important for the treatment of obesity, their effectiveness and maintenance of weight loss are controversial[6]. Since not every patient has the same willpower, it is imperative to provide additional support for these methods. An effective pharmacological treatment may be the most important element to support these methods. Unfortunately, the drugs available today for the treatment of obesity are limited and have serious side effects. In addition, the incomplete understanding of their pharmacological mechanisms of action questions their safety[6]. Some of the mechanisms on which current drugs are based are as follows; restricting calorie intake by reducing appetite, increasing energy consumption by inducing metabolism, restricting fat absorption from the intestines, and preventing fat storage. As can be understood from the general characteristics of these mechanisms, these antiobesity drugs are versatile drugs from the brain to the liver[6]. These drugs available and used in the treatment of obesity are phentermine, sibutramine, orlistat, and rimonabant (**Figure 1**).

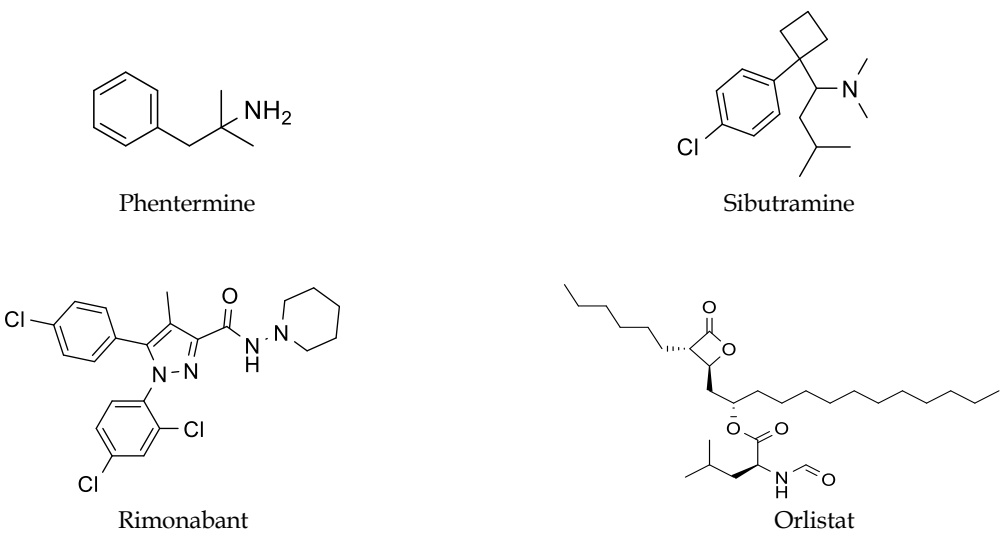

Figure 1. Molecular structures of anti-obesity drugs.

Phentermine is an amphetamine-derived drug that was approved by the FDA in 1959. It is an effective appetite suppressant used in the short-term treatment of obesity; however, serious side effects have been reported including cardiotoxicity. Therefore, obese patients at risk of cardiovascular disease should not use this drug[10].

Sibutramine is another drug approved by the FDA in 1997 for the treatment of obesity. It is a serotonin, noradrenaline, and dopamine reuptake inhibitor. Although it was developed as an antidepressant, it was not effective in this field. The basis of its mechanism of action is related to increasing the feeling of fullness. They stimulate thermogenesis by activating B-adrenoreceptors, especially on brown adipose tissue[10]. Dry mouth, nausea, and constipation may be considered as mild side effects of sibutramine. These side effects are related to the activation of the sympathetic system. However, some potential side effects include, but not limited to, cardiotoxicity, have been reported, causing a restriction on its usage [11].

Orlistat is a semi-synthetic lipostatin derivative that can be considered relatively safe compared to both phentermine and sibutramine. It reduces fat absorption in the gastrointestinal tract by approximately 30%. It is indicated for the treatment of type 2 diabetes as well as obesity[12]. Patients using orlistat experienced an approximately 10% decrease in body weight after 1 year of treatment. It does not have life-threatening toxic

side effects compared to sibutramine and phentermine. General side effects mostly affect the gastrointestinal tract and include oily stools, sudden defecation, and flatulence[11,13,14].

Rimonabant, a relatively new antiobesity drug, is a cannabinoid CB1 receptor blocker. It shows its effect by suppressing appetite. It was developed after seeing the effect of Anandamide, an endogenous cannabinoid, on increasing appetite[15]. It has shown promising results in clinical studies. Psychiatric disorders such as depression and anxiety are among the most important side effects[16,17].

Recently, semaglutide and tirzepatide which were initially approved for the treatment of type 2 diabetes are licensed to be used for the treatment of obesity [18,19]. However, considering the side effect profiles and potential adverse effects of these available drugs previously mentioned, it becomes evident that there is a necessity to explore novel anti-obesity agents with new mechanisms of action. Many ongoing research have identified various targets that are implicated in the pathophysiology of obesity and CA V has been a promising target for the management of obesity[9].

3. CARBONIC ANHYDRASES: AN OVERVIEW

Carbonic anhydrases (CAs) are metalloenzymes found in both prokaryotes and eukaryotes[1]. Their catalytic activities play a crucial role in catalyzing very basic and important physiological reactions, mainly by catalyzing the conversion between carbon dioxide and a bicarbonate ion . Consequently, they play an essential role in maintaining pH and CO_2 homeostasis. In addition, CAs are in (**Figure 2**)volved in multiple essential physiological processes such as electrolyte secretion, biosynthetic reactions (gluconeogenesis, lipogenesis, etc.), bone resorption and calcification, and many other processes in tissues and organs [2,20].

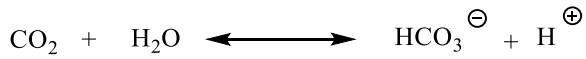

Figure 2. Reaction catalyzed by carbonic anhydrases.

The functions of carbonic anhydrases in advanced organisms are broader and more complex, especially in humans. CAs are categorized into eight distinct families according to their evolutionary trend. The families of CAs include alpha (α), beta (β), gamma (γ), delta (δ), zeta (ζ), eta (η), theta (θ), and ι iota (ι)[21]. Among them, the alpha (α) family is the most extensively studied and is the only class found in mammals, including humans. There are 16 different α-CA isoforms in mammals that have been isolated and characterized. They are grouped according to their location and function. Isoforms CA I, CA II, CA III, CA VII, and CA XIII are cytosolic; isoforms CA IV, CA IX, CA XII, CA XIV, and CA XV are membrane-bound; isoforms CA VA and CA VB are mitochondrial and isoform CA VI is secreted protein. In addition, there are three acatalytic forms known as the CA-related proteins (CARP VIII, CARPX, CARP XI) which are also cytosolic[1–3].

CA isoforms have various tissue and organ distribution with a variety of vital physiological functions. They are involved in respiration and regulation of the acid/base homeostasis[1]. Homeostasis is maintained through many different processes including the transportation of both CO_2/bicarbonate between metabolizing tissues and excretion sites (lungs, kidneys). This process helps eliminate CO_2 in capillaries and pulmonary microvasculature, eliminates H^+ ions in the renal tubules and collecting ducts, and reabsorbs HCO_3^- in kidneys[22]. However, CA VA and VB, the only mitochondrial isoforms in particular, are involved in metabolic processes like gluconeogenesis and ureagenesis and molecular signaling processes such as insulin secretion signaling from β cells of the pancreas[23].

3.1. Carbonic Anhydrases as Drug Targets

As previously mentioned, CA isozymes are found in different organs and tissues and play a crucial role in a wide range of physiological processes including the maintenance of homeostasis, vision, gustation, olfaction, bone resorption, gluconeogenesis, ureagenesis, bile production and oncogenesis[24]. Consequently, any disturbance in these processes can initiate the overexpression or downexpression of the associated isoenzymes. Besides, many pathological conditions affect the normal distribution and expression of these isoenzymes, resulting in their overexpression in unexpected regions. As a result, these CA isoenzymes serve as biomarkers and druggable targets for novel drug candidates in different diseases[25].

Glaucoma is an optic disease that is seen worldwide and causes irreversible blindness[26]. Increased intraocular pressure is the primary risk factor for the development and progression of glaucoma. Lowering intraocular pressure is the main strategy in the treatment of glaucoma. An increase in intraocular pressure is caused by aqueous humor. Studies on the chemistry of aqueous humor have shown that the main ingredient of this fluid is sodium bicarbonate[27–29]. CAs present in the anterior uvea of the eye are responsible for the

secretion of bicarbonate secretion. Hence, CA inhibitors (CAI) inhibit the ciliary-process enzyme causing a decrease in the intraocular pressure[30].

Cancer is another group of diseases in which CAs can be a potential target. Hypoxia is a common feature of many tumors and is strongly associated with tumor proliferation, progression, and resistance to treatment[31–36]. Hypoxia also affects the regulation of membrane-bound CA IX and CA XII isoforms in tissues. These two isoforms are potential targets in tumor progression[37]. CA IX has been associated with poor prognosis caused by the tumor's resistance to classical radiotherapy and chemotherapy[21,32,38]. Many studies are showing that CA IX plays a role in the growth, survival, and spread of tumor cells[39] by neutralizing the intracellular pH and acidifying the extracellular environment[32,40]. With CA IX inhibition, tumor cells are unable to maintain neutral intracellular pH and acidic extracellular pH, leading to the death of tumor cells [32,41–43]. Therefore, CA IX inhibitors may be potential and useful agents with anticancer effects. On the other hand, CA XII, which is overexpressed in renal cell carcinoma (RCC) is also induced by hypoxia[31,44–46]. However, contrary to CA IX, the overexpression of CA XII has been associated with higher survival, especially in patients with non-small cell lung cancer (NSCLC)[47]. Since CA XII is not associated with a poor prognosis as CA IX, studies on its inhibitors and activators are less. So far, there are few studies related to the tumor physiology of CA XII[32]. However, more studies on the tumor physiology of CA XII are needed.

3.2. Carbonic Anhydrase Inhibitors

Sulfonamides (RSO_2NH_2) are a group of antibiotics discovered by Domagk in 1935[48]. After the discovery of sulfanilamide as a bacteriostatic agent, a number of its analogues were developed and used as antibacterial. For example, Prontosil **(Figure 3)**, a sulfanilamide derivative, is an old prodrug with antibacterial action [49].

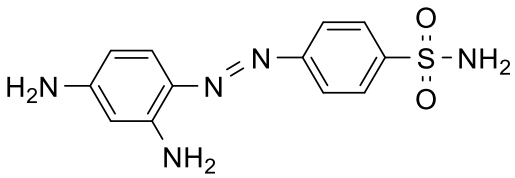

Figure 3. Molecular structure of Prontosil.

Sulfonamides come first among the classical CAIs. They have been used for more than 50 years, especially as antiglaucoma and diuretic agents[7]. In addition, CAIs have anticonvulsant, antiobesity, anticancer, and antiinfective potentials[1–3]. Nevertheless, these CAIs are non-selective and can cause potential side effects by inhibiting off-targets. Recently, significant progress has been made in the development of sulfonamide derivatives and their bioisosteres as isoform-selective CAIs[3].

Acetazolamide is the first CAI diuretic, which was introduced in 1956 and served as the prototype for the subsequent development of thiazide diuretics and loop diuretics[50]. Acetazolamide increases the volume of urine and alkalinity by increasing bicarbonate concentration, thereby facilitating the excretion of Na^+ and K^+ ions. In addition, the amount of excreted chloride ions is reduced through the inhibition of H^+ secretion from the proximal tubule portion of the nephron[50]. Acetazolamide, methazolamide, ethoxazolamide and dichlorphenamide have the same mechanism of action. These drugs are used to relieve edema[51]. The other diuretics, such as benzothiadiazines, metolazone, chlorthalidone, indapamide, furosemide, and bumetanide act as CA inhibitors[50]

Furthermore, systemic acetazolamide, methazolamide, ethoxazolamide, and dichlorophenamide (**Figure 4**) are extensively used to treat glaucoma[28]. However, since CAs are abundant in vertebrates, their systemic use causes undesirable side effects. These side effects may include fatigue, metallic taste, weight loss, decreased libido, and gastrointestinal irritation. Dorzolamide and Brinzolamide were found to avoid these side effects in the early 1990s. Thus, a topical treatment for glaucoma was developed. These two drugs are effective in lowering intraocular pressure and their side-effect profiles are safer than the systemically administered drugs[28].

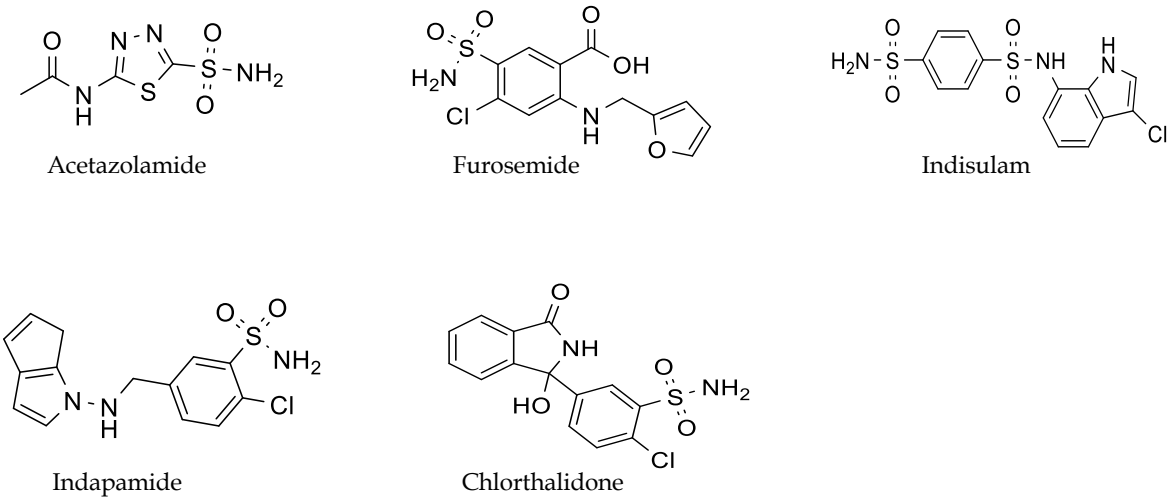

Figure 4. Some carbonic anhydrase inhibitors.

Indisulam is a CA IX inhibitor, a sulfonamide derivative with anticancer activity (**Figure 4**). The mechanism of action has not been fully elucidated however, it has been shown to have significant antitumor efficacy in vivo mice experiments, and Phase 1 and Phase 2 clinical studies are progressing [52–54].

4. THE MITOCHONDRIAL ISOENZYMES: hCA VA AND hCA VB

There are 15 isoenzymes of CAs in humans (hCA I – hCA XIV). These isoforms have been studied as diuretic, antiglaucoma, anticancer, and antiepileptic agents. Recently, CAs have been studied not only in pH regulation and buffering but also as metabolic enzymes, as they play a role in various metabolic activities in cells[55]. These isoenzymes have different subcellular localizations, however, only hCA VA and hCA VB are located within mitochondria.

The first CA isoenzyme localized in the mitochondria was discovered in the liver and kidney of rats in 1959, however, it was later extracted from a guinea pig liver in 1980. Subsequently, it was designated as CA V based on the order of its discovery, until the discovery of another homologous mitochondrial CA, currently referred to as CA VB[56]. In humans, both the mitochondrial hCA VA and hCA VB show different distributions in different tissues. hCA VA is mostly found in the liver (hepatocytes), skeletal muscle, and distribution of the kidneys, whereas hCA VB is absent in the liver but present in the pancreas, kidneys, and glands[1,3]. Similar to other carbonic anhydrases, hCA VA and hCA VB catalyze the conversion of CO_2 to HCO_3^- with hCA VA showing moderate catalytic activity of k_{cat}/K_m = 2.9 × 10^7 M^{-1} s^{-1}, whereas hCA VB shows a high catalytic activity of k_{cat}/K_m =9.8× 10^7 M^{-1} s^{-1}[25,57,58].

4.1. hCA VA and hCA VB and Their Metabolic Roles

hCA VA and VB are also known as metabolic enzymes since they participate in essential biosynthetic processes including gluconeogenesis, lipogenesis, ureagenesis, and insulin secretion[24,25]. These two isoenzymes are very important in terms of supplying bicarbonate ions to biosynthetic processes in mitochondria. In gluconeogenesis, *de novo* lipogenesis and ureagenesis, pyruvate carboxylase (PC), acetyl coenzyme A carboxylase (ACC) and carbamoyl phosphate synthetase I and II processes are the main enzymes, respectively[59]. These enzymes require CA-provided HCO_3^- as their key substrate for their respective activities.[56] The lipid profile in mitochondria is closely linked to metabolic disorders, making mitochondrial enzymes directly associated with obesity[60].

In the urea cycle, carbamoyl phosphate synthetase I (CPS I) catalyzes the synthesis of carbamoyl phosphate (CP) using NH_3 and HCO_3^- as substrates. However, cytosolic HCO_3^- cannot penetrated the membrane of mitochondria and hence CPS I relies on hCA V for the production HCO_3^-. CP is an essential compound that is required in the synthesis of citrulline, which is a rate-limitig step in ureagenesis, emphasizing the crucial involvement of hCA V in the process of ureagenesis[61,62].

During gluconeogenesis, the first step involves the transformation of pyruvate into oxaloacetate with the help of the mitochondrial pyruvate carboxylase (PC) and hCA V-provided HCO_3^- used as a substrate[46]. Pyruvate is also converted to Acetyl CoA (acetyl CoA) by the action of pyruvate dehydrogenase with the

release of CO_2. However, both oxaloacetate and acetyl CoA cannot be transported from the mitochondria. As a result, these two substrates (oxaloacetate and acetyl CoA) are converted to citrate in the mitochondria by the citrate synthase. Citrate formed in mitochondria either participates in the Krebs cycle or passes into the cytosol via the tricarboxylate transporter[50,62].

Fatty acid biosynthesis (lipogenesis) occurs in the cytosol and requires Acetyl CoA. In the cytosol, citrate translocated from mitochondria is converted to oxaloacetate and Acetyl CoA in the presence of ATP citrate lyase and CoA. The oxaloacetate is converted to pyruvate, which is subsequently translocated back to the mitochondrio via the pyruvate transporter, whereas, Acetyl CoA is converted to malonyl CoA in the presence of acetyl-CoA carboxylase (ACC) and HCO_3^-. Malonyl-CoA is converted into fatty acids with the release of carbon dioxide by the fatty acid synthase enzyme (**Figure 5**)[50,62].

As can be understood from these processes, the biosynthesis of oxaloacetate in the mitochondria and malonyl CoA in the cytosol from pyruvate and Acetyl CoA, respectively, require the presence of HCO_3^-. These bicarbonates are produced from the catalytic activity of hCA VA/VB in the mitochondria and by hCA II in the cytosol. Therefore, inhibition of these CAs reduced the biosynthesis of citrate, thereby reducing the biosynthesis of fatty acids (lipogenesis) as reported by multiple studies[50,62].

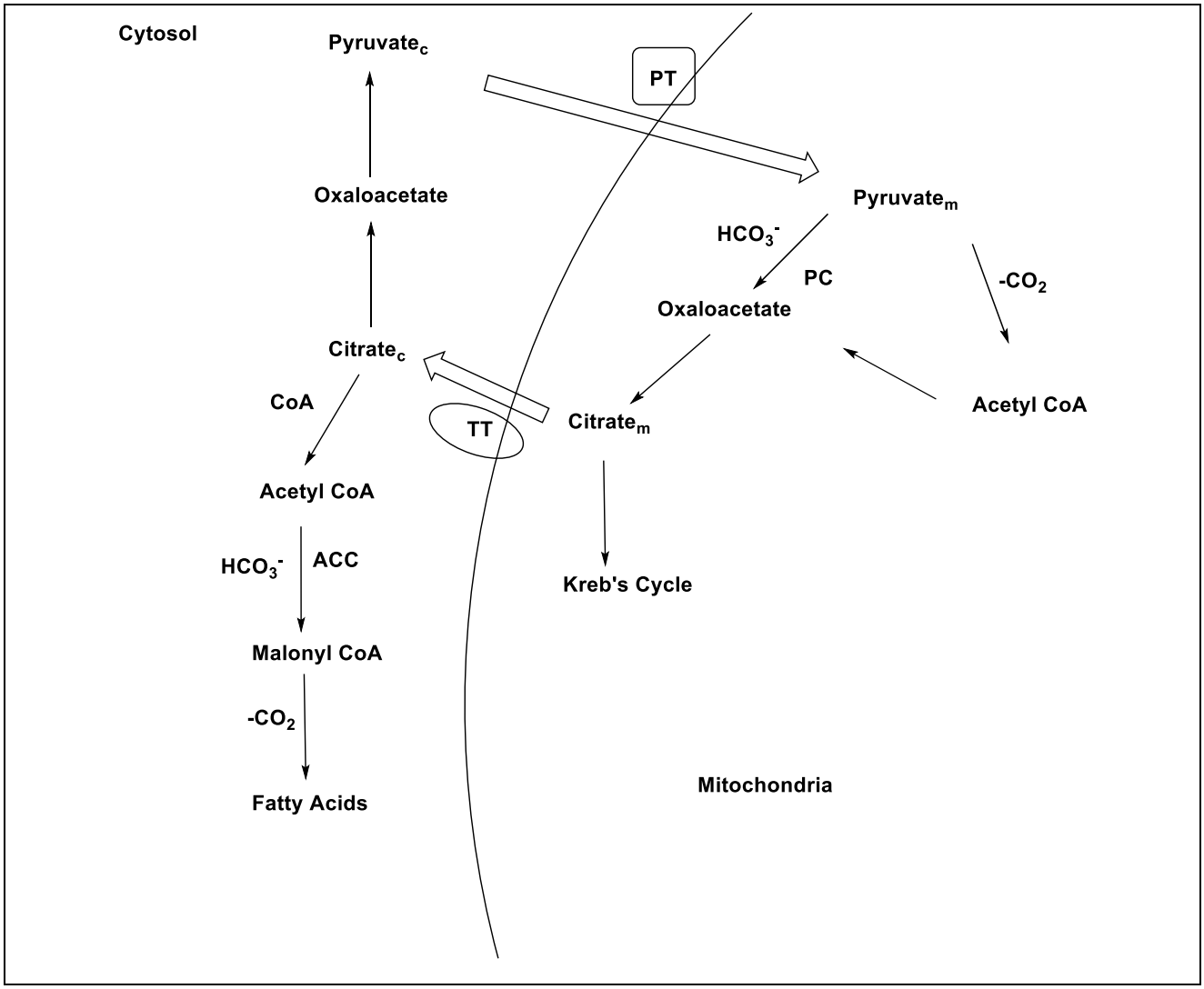

Figure 5. The transfer of acetyl groups from the mitochondrion to the cytosol (as citrate) for the provision of substrate for de novo lipogenesis. PT: Pyruvte transporter, TT: Tricarboxylate transporter, PC: Pyruvate carboxylate, ACC: Acetyl CoA carboxylase

4.2. Carbonic Anhydrase Inhibitors as Antiobesity Agents

Since CAs are widely distributed in the body and have important roles in maintaining basic physiological functioning, many studies have been conducted to date. CAIs and activators developed thanks to these studies are used in the treatment of many diseases. These diseases include glaucoma, epilepsy, cancer, neuropathic pain, and infectious diseases[25]. However, there is still an area that has received less scientific investigation compared to these diseases, and that is obesity. Today, there are three main approaches to developing obesity-effective carbonic anhydrases. These are the repurposing of drugs, screening of natural products/synthetic libraries, and *de novo* drug design[63].

Sulfonamide and its isostere derivatives are the most widely used and researched CAIs. They have been used clinically for decades as antiepileptic, antiglaucoma, diuretic and antiinfective. Among these derivatives, Topiramate and Zonisamide (**Figure 6**) have strong antiepileptic effects, as well as side effects due to their non-selective nature. In particular, their ability to induce weight loss has also been reported from multiple studies conducted on animal models[64]. Therefore, it is suggested that these drugs can be used especially in the management of obesity. Studies based on this have found that topiramate, in particular, has a strong affinity for hCA VA and hCA II[65].

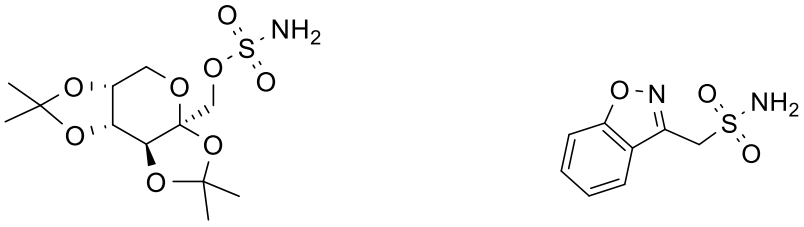

Figure 6. Molecular structure of Topiramate and Zonisamide.

The idea that CAIs could be a potential antiobesity drug stemmed from the fact that antiepileptic drugs such as topiramate and zonisamide cause weight loss as a side effect. Significant weight loss has been observed in obese and epileptic patients using these drugs. An average of 7.3% of body weight loss was observed in patients treated with topiramate after one year. For patients with a body mass index above 30, the average weight loss was 11% of body weight. Moreover, this effect is independent of the appetite-suppressing effect of Topiramate[66]. Based on these effects, various studies have been conducted on the metabolic effects of CAs. Understanding the metabolic effects of CA isoforms, especially in mitochondria, is crucial to understanding how they can be potential targets.

4.3. De Novo Drug Design

After it was understood that CAIs such as topiramate and zonisamide inhibit mitochondrial CA and may be effective in obesity, new derivatives began to be investigated based on the skeletal structure of sulfonamide-derived CAIs used in the clinic. Generally, the SO_2NH_2 that binds the Zn^{2+} ion present in the binding site of CAs is attached to a heterocyclic ring system. Attached to the ring is a tail section that interacts with the hydrophobic and hydrophilic halves of CAs which contain the non-conserved amino acid residues. These interactions lead to the development of selective inhibitors. Some researchers have applied this "tail approach" to develop selective hCA VA and VB inhibitors. Guzel et al. synthesized a series of aromatic/heterocyclic sulfonamides incorporating phenacetyl and thienylacetyl tails (**Compounds 1 – 5**). Some of these molecules showed potent inhibitory effects against hCA VA and hCA VB[67,68]. These inhibitors have shown the highest inhibition so far and hold promise as antiobesity drug candidates (**Table 1**).

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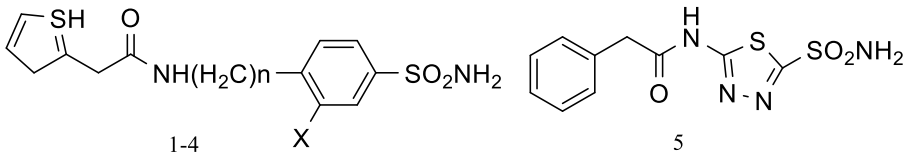
Table 1. Benzenesulfonamides and 1,3,4-thiadiazole-sulfonamides acting as low nanomolar hCA VA and VB inhibitors [67,68].



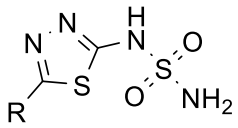
1-4 5

			K_I (nM)	
Compound	**n**	**x**	**hCA VA**	**hCA VB**
1	0	-	7.2	7.0
2	0	Cl	7.7	8.6
3	1	-	9.1	7.2
4	2	-	10.2	8.0
5	-	-	8.4	6.1

In another study, Smaine et al. reported hCA VA/VB inhibitory properties of small series of 2-substitued-1,3,4-thiadiazole-5-sulfamides derivatives. These derivatives showed selectivity towards hCA VA/VB over hCA I, II, and IV. The compounds inhibited hCA VA and VB at low nanomolar concentrations with a range of *K*i values of 4.2 – 32 nM and 1.3-74 nM, respectively (**Table 2**) [68,69].

Table 2. Substituted thiadiazole derivatives and their inhibitory.

		K_I(nM)	
Compound	**R**	**hCA VA(μM)**	**hCA VB(μM)**
6a	H	28.3	74
6b	Et	18.7	63
6c	t-Bu	10.4	2.8
6d	CF_3	7.3	3.9
6e	MeS	32	2.9
6f	EtS	9.3	23.1
6g	Ph	9.2	7.5
6h	4-$MeOC_6H_4$	8.0	1.3
6i	4-Br- C_6H_4	4.2	4.5
6j	$MeSO_2$	8.7	2.7
AZA	-	63	54
ZNS	-	20	6033
TPM	-	63	30



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In another study, Poli et.al reported the synthesis of a series of N-aryl-N'-ureido-O-sulfamates of (Compounds **7, 8,** and **9)** and tested them against the hCA VA and hCA VB. One of these derivatives, compound **7o,** had interesting selectivity towards hCA VB (K_i = 515 nM) over hCA VA (K_I > 10μM) (**Table 3**). According to molecular modeling studies, the tail region of the inhibitor has been shown to be extremely important in terms of interaction and selectivity with the mitochondrial isoform carbonic anhydrases[70,71].

Table 3. Sulfamates 7-9 reported as hCA VA/VB inhibitors[70].

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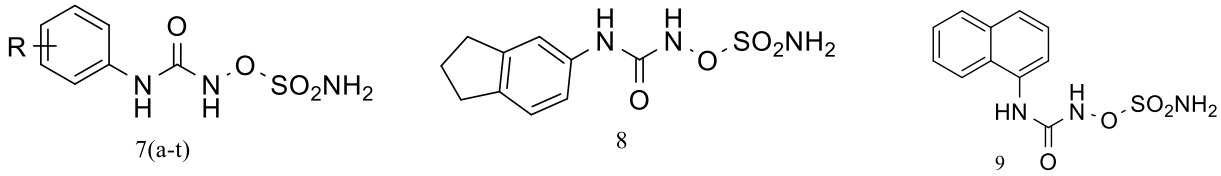

Compound	R	Compund	R
7a	H	7k	2-OEt
7b	4-CH_3	7m	4-OPh
7c	2-CH_3	7n	3-COOEt
7d	4-Cl	7o	2,5-Me_2
7e	3-Cl	7p	3,5-Me_2
7f	2-Cl	7q	4-CF_3
7g	4-F	7r	4-F- 3-Me
7h	4-NO_2	7t	2,3,4,5,6-F_5
7j	2-OMe	7s	4-CF_3-2Cl

In another study, Maresca and Supuran communicated the synthesis and hCA VA/VB inhibitory activities of a series of (R)- and (S)-10-camphorsulfony-substituted aromatic/heterocyclic sulfonamides (**10** and **11)**. They showed effectiveness in inhibiting hCA VA/VB. The (R) enantiomers were generally more effective than (S) enantiomers (**Figure 7**) [68,72].

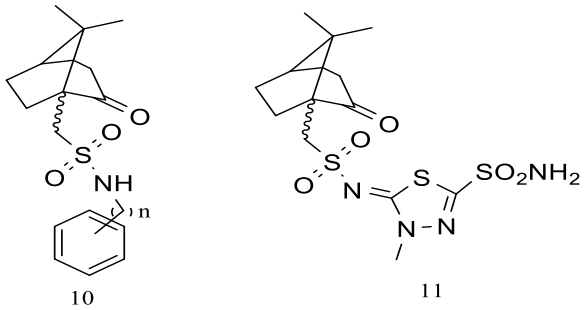

Figure 7. Aromatic/heterocyclic sulfonamides 10 and 11 incorporating 10-camphorsulfonyl tails. In derivatives 10, n=0,1[72]

Poulsen et al. prepared derivatives of triazole-sulfonamides **12** using click chemistry (**Figure 8**). These molecules showed promising nanomolar inhibition of hCA VA/VB, however, they also lack selectivity by potentially inhibiting hCA II. One of the most effective derivatives (R =3-Me) displayed an inhibition value of K_I=12.8 nM against CA VA and K_I =10.6 nM against CA VB. However, this derivative lacked selectivity against against CA II.(K_I=18.6 nM) [68,73].

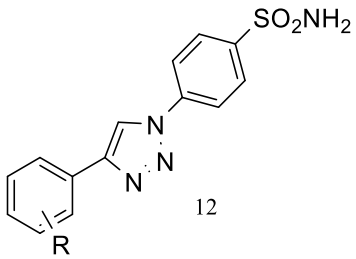

Figure 8. Triazole-sulfonamides derivatives.

In another study, Carta F. et al. synthesized a series of new sulfonamide derivatives based on the Pritelivir molecule. Pritelivir is an antiviral agent that is in phase II clinical development against herpes simplex virus (HSV) infections. Unlike other antiviral agents, it contains a sulfonamide group and exhibit inhibitory activity against CAs. These pritelivir derivatives exhibited significant inhibitions against hCA

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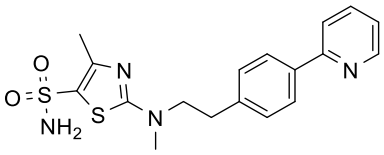
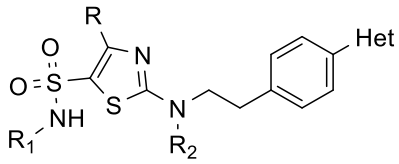
VA/VB compared to acetazolamide (**Table 4**). It is noteworthy to mention that compound **13d**, which is the most effective compound, has a bulky R_2 group [74].

Table 4. hCA VA and hCA VB inhibition values of some Pritelivir derivatives against acetazolamide [74].



Pritelivir

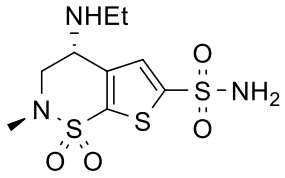


13

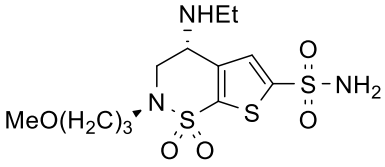
Compound	R	R1	R2	Het	hCA VA(μM)	hCA VB(μM)
13a	R=Me	R_1=H	R_2=Me	Het=Phenyl	67.6	55.1
13b	R=Me	R_1=H	R_2=Me	Het= N-Pyrazoyl	32.0	58.0
13c	R=Me	R_1=H	R_2=Me	Het=2-Pyrazyl	61.7	45.6
13d	R=Me	R_1=H	R_2=$(CH_3)_2NCH_2CH_2$-	Het= Phenyl	29.0	47.0
13e	R=Me	R_1=H	R_2=Me	Het=3-Fluorophenyl	58.9	49.1
13f	R=Me	R_1=H	R_2=Me	Het=3-Fluoro-2-methoxyphenyl	37.4	56.7
13g	R=Me	R_1=Me	R_2=Me	Het=2-Fluorophenyl	32.8	79.4
13h	R=Me	R_1=Me	R_2=Me	Het=2-Pyridyl hydrochloride salt	64.8	37.8
AAZ					63.1	54.2

Furthermore, Vullo et al. communicated the hCA VA inhibitory properties of sulfonamide derivatives **14** and **15.** These compounds demonstrated a better activity than topiramate (**Table 5**) [75].

Table 5. Heterocyclic sulfonamide derivatives and hCA VA inhibition values.[75]



14

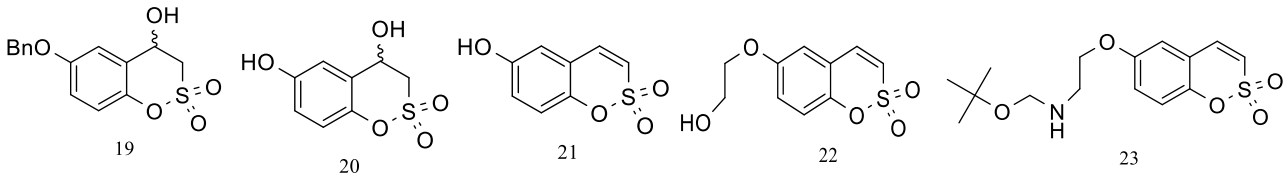


15

Compound	hCA VA(μM)
14	48
15	51
Topiramate	63

In another study, Mahapatra et al. synthesized a group of 5-(4H)-oxazolone derivatives without the famous zinc-binding sulfonamide group. The inhibitory activities of these compounds were evaluated against hCA VA. These compounds exhibited selectivity towards hCA VA over hCA II and hCA IX with low micromolar concentrations (**Table 6**) [76].

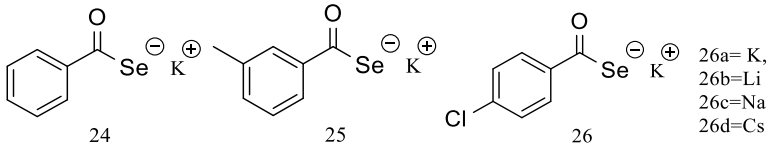
Table 6. Inhibition values of some sulfocoumarin derivatives [76].



Compound	K_I hCA VA(μM)
19	89
20	42
21	96
22	0.06
23	87
Acetazolamide	0.06

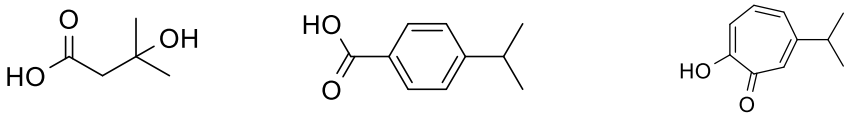
Similar to Mahapatra et al, Tanini D. et al. went beyond the classical sulfonamide derivatives by developing selenium derivatives that have a remarkable inhibitory activity against CAs. These new derivatives called benzoselenoates, constitute a new class of CAIs. However, these compounds lacked selectivity towards hCA VA and are therefore, unlikely to be potential antiobesity agents. However, the inhibition values on other isoforms of CA were promising (**Table 7**) [77].

Table 7. Some benzoselenoate derivatives and their inhibition values[77].

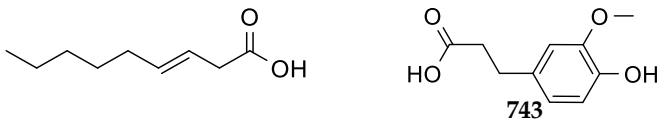


Compound	hCA I	hCA II	hCA IV	hCA VA	hCA VII	hCA IX
24	4.04	20.57	5.97	14.68	0.96	1.40
25	1.38	9.67	7.63	11.54	1.01	1.57
26a	8.40	7.13	4.79	9.87	0.42	0.87
26b	8.97	4.59	5.83	8.88	0.35	0.99
26c	8.36	5.43	5.09	10.42	0.39	1.02
26d	8.01	4.20	4.98	11.49	0.48	0.98
Acetazolamide	0.25	0.012	0.074	0.063	0.003	0.026

Costa G. and his colleagues developed a CAIs using an alternative method. They utilized essential oils as the basis for developing compounds that displayed efficacy against hCA VA through the *in silico* technique. Although essential oils have traditionally been used as antibacterial, antifungal and insecticide, it can be said that this study is a novel perspective. Approximately 2690 compounds from the chemical natural products library were screened using the *in silico* method and compounds demonstrating high efficacy against hCA VA were identified. However, their toxicity and selectivity toward other enzymes have not been sufficiently investigated. Nevertheless, the inhibitory activity of these compounds against hCA VA were promising. The most effective compounds from these screenings and their inhibition values against hCA VA are given below [78].



27 (7.5μM) 28 (3.8μM) 29 (7.38 μM)



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30 (4.52 μM 31 (9.69 μM)

Figure 9. Some most effective compounds from the chemical natural products library.

5. CONCLUSION

Obesity is currently one of the most important health problems globally. Obesity with other comorbidities significantly impairs the quality of life. Rapid changes in eating style, increasing prevalence of fast-food consumption, and preference for sedentary lifestyles indicate that obesity is emerging as a significant health concern in the future. Efforts to prevent and treat such an important disease would greatly contribute to the improvement of many lives. Therefore, it is imperative to conduct comprehensive investigations into the various mechanisms underlying obesity and its treatment. The phenomenon of weight loss, observed as a side effect in patients undergoing treatment for epilepsy with certain CAIs, has been comprehensively studied. Subsequently, it has been observed that these drugs exert their activities via the inhibition of metabolic hCA VA and VB present in the mitochondria. In light of this, various researchers have endeavored to develop novel compounds using rational drug design and by screening natural products that have inhibitory effects against hCA VA and hCA VB. However, the ubiquitous nature of CAs causes selectivity problems for the developed inhibitors, causing many side effects. Hence, it is imperative to design selective hCA VA and hCA VB inhibitors with minimal side effects. However, up to date, few studies on the design of selective inhibitors inducing weight loss with minimal side effects have been reported. Therefore, more comprehensive research is needed to address this.

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