Editorial
Letter to the Editor

Carbonic Anhydrases: Battlefield for Enzyme Inhibitor and Activator Drugs?

Dear Editor,

In general, a substrate-binding site consists of an indentation or cleft on the surface of an enzyme molecule that is complementary in shape to the substrate. Moreover, the amino acid residues that form the binding site are arranged to interact specifically with the substrate in an attractive manner. A few enzymes are absolutely specific for only one compound. Most enzymes, however, catalyze the reactions of a small range of related compounds [1]. Although traditionally textbooks and research articles have highlighted the truly remarkable specificity of enzyme action, they have largely ignored the 'darker' side of enzyme cross-reactivity, or promiscuity. However, in the past several years, research into promiscuity leads to interesting insights, in particular with regard to how specificity and promiscuity coincide with a single active site [1 and references therein]. Early examples of enzyme promiscuity include pyruvate decarboxylase, carbonic anhydrase, pepsin, chymotrypsin, and L-asparaginase [2 and references therein].

The carbonic anhydrase enzymes (CAs, EC 4.2.1.1) are zinc containing metalloproteins, which efficiently catalyse the reversible conversion of carbon dioxide to bicarbonate and release proton. These enzymes are essentially important for biological system and play several important physiological and pathophysiological functions. About 16 different CAs are found in mammals that differ in their enzymatic properties, amino acid sequences and sites of expression [3 and references therein]. For a long time, it was believed that carbonic anhydrases exhibited absolute specificity, i.e. that they would only catalyze the inter-conversion between CO2and HCO3-. However, in the 1960s it was discovered that these enzymes also catalyze hydration of various aldehydes as well as hydrolysis of esters and based on the literature, the elements of both lyase and esterase active sites of CA are the same, see Figure 1 [4 and references therein].

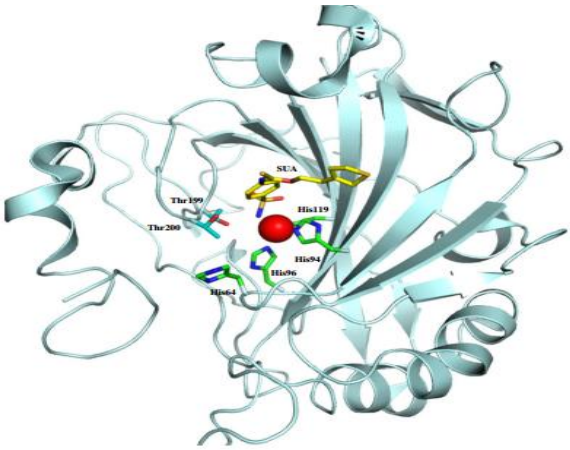

Figure 1. Structural representation of CAII in cartoon model. Centrally coordinated zinc atom is shown in red sphere. His (light green) and Thr (light pink) residues present in active site pocket are illustrated in stick model. A ligand in complex with CA is shown in yellow stick (Adopted from [2], PDB id: 3K34).

Due to their distribution and vital role in metabolism, CAs are generally considered as target of drugs. These enzymes are inhibited by two classes of compounds. One is metal complex forming anions and others are sulfonamides and their isosteres (Arylsulfonamides, aryl sulfamates) [3 and references therein].

Ethoxzolamide, acetazolamide, methazolamide and dorzolamide are specific CA inhibitors, used for the treatment of glaucoma, as antitumor agents/diagnostic tools for tumors, antiobesity agents, anticonvulsants, and antimicrobials/antifungals agents and/or altitude sickness and benign intracranial hypertension. Since many unrelated drugs such as topiramate, celecoxib, furosemide, glibenclamide can act as weak inhibitors of CAs [4 and references therein], side effects of prolonged administration of these drugs may be expectable.
On the other hand, CA activators bind at the entrance of the enzyme active site, and facilitate the proton transfer processes between active site and solvent system. A series of amines and amino acids such as L-His, L-Trp, L-Phe, dopamine, L-DOPA, serotonin, L-Tyr, 4-amino-L-Phe, and histamine are known which work as activators for CAs. Activators may be designed as useful derivatives for the enhancement of synaptic efficacy, which may represent a conceptually new approach for the treatment of Alzheimer's disease, aging and other conditions. Among different categories of drugs, sildenafil, fluoxetine, citalopram and sertraline etc are also found as activators of CAs [5 and references therein] and prolonged administration of these drugs may lead to some CA-related metabolic consequences. Taking above statements together, ongoing researches/clinical trials should consider possible CA inhibitory/activatory effects (CA cross-reactivity) of drugs in new generation therapeutics.

References

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