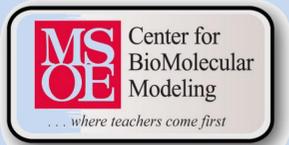


Hydrochlorothiazide: A comprehensive review of the drug's history, drug development, medicinal chemistry, adverse reactions, and current research



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Abstract:

Hydrochlorothiazide (HCTZ) is traditionally a diuretic drug, but a new use has recently been discovered. Namely, HCTZ is potentially useful in the treatment of neurological disorders. This poster illustrates the importance of HCTZ through a case study, describes its new use, explains the mechanism behind its new use, and addresses some clinical issues as well.

Introduction:

A 79 year old male arrives at the emergency department for Torsades de Pointes (TdP). The patient is on HCTZ, dofetilide, lisinopril, and simvastatin. Additionally, the patient is suffering from hypokalemia and hypomagnesemia. The potassium depleting effects of HCTZ can potentiate dofetilide-induced TdP. Today, HCTZ is considered a potential neuroscience medication targeting a receptor entirely different from the diuretic targets it has been known to effect.

Discovery:

Cyclothiazide (CTZ) was the first drug in HCTZ's class to be discovered to interact with ionotropic glutamate receptors (iGluRs) (see Figure 1). HCTZ was investigated after CTZ because it lacks an additional hydrophobic group, which alters the position in the binding pocket (Figure 2) [1].

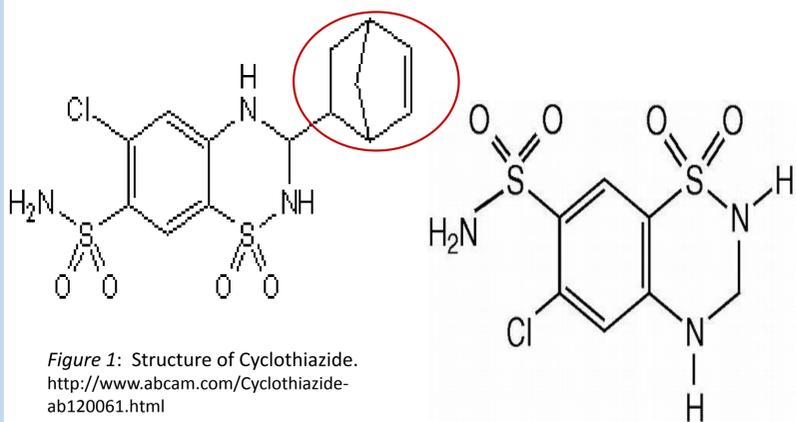


Figure 1: Structure of Cyclothiazide.
<http://www.abcam.com/Cyclothiazide-ab120061.html>

Figure 2: Structure of Hydrochlorothiazide
http://www.theodora.com/drugs/avalide_tablets_sanofi_aventis.html

Mechanism of Action:

HCTZ binds to the iGluRs. Glutamate receptors are normally excitatory nerve pathways. HCTZ acts like an allosteric modulator, keeping the glutamate receptor in a stable position which allows it to stay active, or in the excitatory state, longer [1].

Our Model:

HCTZ bound to iGluR, specifically binding to Ser108 and Lys218.

Molecular Story:

The molecular interaction of interest involves the structural properties of HCTZ and iGluRs. iGluRs are found throughout the body, playing a role in mediating fast excitatory neurotransmissions in the brain. Benzothiazide diuretics, including HCTZ, have been found to bind to iGluR2-AMPA receptors and enhance neurotransmission and the activity of glutamate agonists [1]. We explored the molecular structure of HCTZ and iGluR2-AMPA to find out how that binding occurs:

- iGluR2-AMPA receptors are ligand-gated ion channels with four subunits, each containing a ligand binding domain with two lobes that remain open in a state of inactivation, blocking conduction (Figure 3). The subunits form a U-shaped crevice in which HCTZ can bind [1].

Figure 3: Structure of the iGluR2-AMPA receptor.
http://proteopedia.org/wiki/index.php/Glutamate_receptor_%28GluA2%29

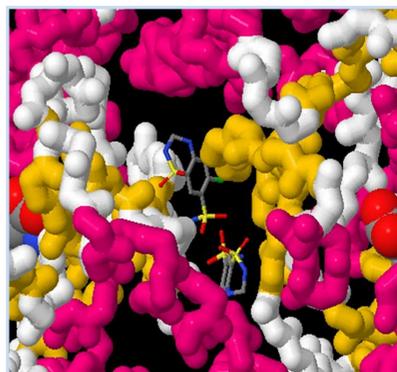
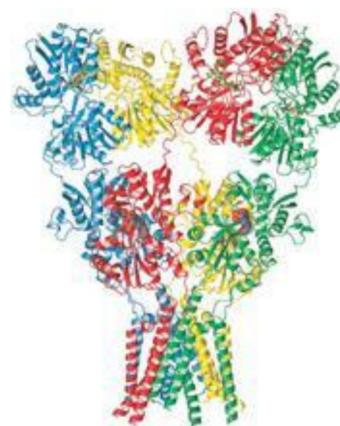


Figure 4: The figure illustrates HCTZ at an allosteric binding site while glutamate is bound at its normal site on the receptor.
<http://www.pdb.org/pdb/explore/explore.do?structureId=3IJX>

- The sulfonamide on HCTZ forms a hydrogen bond with Lys218 (Figure 5) in the binding pocket [1].
- The hydrogen substitute on the 3-carbon rotates HCTZ and allosterically modulates the receptor, leaving the B subunit open (Figure 4). Water molecules subsequently fill this space, indicating that this site is hydrophilic. This could be key in drug development as it relates to glutamate receptor binding affinity [1].
- With the hydrobenzothiazide ring now in the C subunit, the stoichiometry of the receptor is also altered and the sulfonamide group on the 7-carbon of HCTZ is now exposed [1].
- The Ser108 residue on the receptor forms a hydrogen bond (Figure 5) to the sulfonamide group [1].

Clinical Issue:

HCTZ is a renowned member of the thiazide diuretics (Figure 2). It is commonly used to treat hypertension and water retention and is often the drug of choice due to its low side effects.

Adverse drug reactions:

HCTZ interacts with dofetilide. Dofetilide is an anti-arrhythmic that can cause severe cardiac side effects and is monitored closely [2]. It works by blocking the ion channel in the heart that carries the delayed rectifier potassium current. The drug is eliminated via cation exchange in the kidneys.

Why is this a problem?

- HCTZ interferes with the elimination of dofetilide by reducing cation reabsorption.
- High levels of dofetilide may cause Torsades de Pointes (TdP) which is often triggered by hypokalemia [2].
- HCTZ can also cause hypokalemia due to increased potassium excretion.
- Increased K⁺ excretion occurs because an increase in sodium retention in the renal tubule indirectly causes an increase in Na⁺/K⁺ exchange.
- When these two medications are combined, the chance of hypokalemia is greatly increased [3].
- If hypokalemia is increased, chances of TdP are increased as well.

Summary:

HCTZ has previously been known for its use as a diuretic, for which it remains safe and effective. Due to its competitive binding, this drug is being considered for other uses for more severe conditions. Recently, it has been found that this drug binds to the iGluRs which have been linked to other disease states. It is currently being researched as a potential treatment for neurodegenerative diseases such as Alzheimer's and Parkinson's. Through further research of HCTZ and its binding pocket, advancements in drug therapy for many hard-to-treat diseases may be forthcoming.

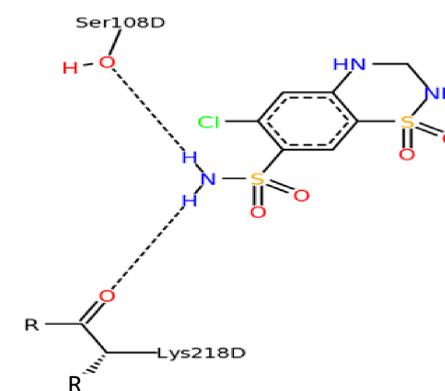


Figure 5: HCTZ interactions with amino acid residues in AMPA Subunit GluR2
<http://www.pdb.org/pdb/explore/explore.do?structureId=3IJX>

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