The Structure of Spironolactone: Binding and Interaction with the Mineralocorticoid Receptor

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Abstract

The mineralocorticoid receptor is a steroid receptor that assists in balance of fluid and electrolytes. The binding of endogenous aldosterone to the active site results in the retention of electrolytes and fluid. Spironolactone, an aldosterone antagonist, binds and affects DNA transcription which results in the opposite effect. It increases serum potassium levels by inhibiting aldosterone at the mineralocorticoid receptor by competing for the aldosterone-dependent sodium-potassium exchange site in the distal tubule cells. This leads to an increase in secretion of water and sodium while decreasing the excretion of potassium. Interactions between spironolactone and the C-terminal activation function 2-helix allow binding of the drug without activation of the mineralocorticoid receptor. This decrease in potassium excretion can lead to potentially dangerous increases in serum potassium. Spironolactone is currently used or is being investigated for use for a variety of conditions. While spironolactone is a very safe and effective medication with strong evidence supporting its use, it is important to monitor for signs of possible side effects such as hyperkalemia that may result from its use.

Introduction

The mineralocorticoid receptor is a steroid hormone regulated receptor that helps to balance fluid and electrolytes in the distal convoluted tubule of nephrons. Aldosterone was identified as one of the endogenous ligands for the mineralocorticoid receptor in 1953 and scientific efforts have been made ever since to find compounds that will act as aldosterone antagonists.[1] Other endogenous ligands include cortisol, cortisone, progesterone, and deoxycorticosterone. Deoxycorticosterone and aldosterone have been linked as the most relevant endogenous ligands of this receptor as they display the most effect on its function. This led to research of medications which would antagonize the mineralocorticoid receptor. These efforts resulted in the creation of spironolactone. Spironolactone acts on a nuclear receptor directly acting on DNA transcription, which in turn indirectly affects fluid and electrolyte balance.

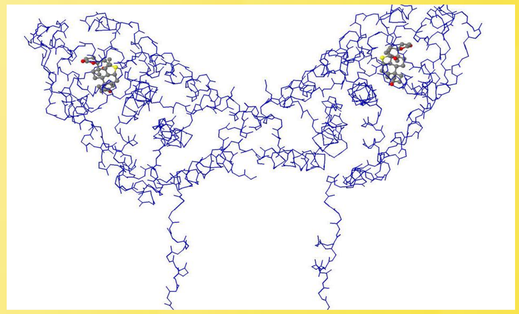

Figure 1 (right): *Spironolactone bound to the mineralocorticoid receptor.*

Spironolactone is a potent antagonist of the mineralocorticoid receptor. It was synthetically designed and is primarily characterized by the presence of a C17 γ-lactone which is responsible for its antagonist character. Various substituents at different positions of the steroid skeleton were modified during development to increase potency. Over the last 30 years, spironolactone has remained one of the most widely used mineralocorticoid receptor antagonists.[2] Its treatment use ranges from ascites, congestive heart failure, edema, and hypertension to hypokalemia, primary aldosteronism, and acne vulgaris.[3] Overall, spironolactone has been regarded as a generally well-tolerated medication. As with any medication, however, there is potential for adverse effects.

Molecular Story

- Spironolactone, a synthetically derived passive antagonist of mineralocorticoid receptor (MR).

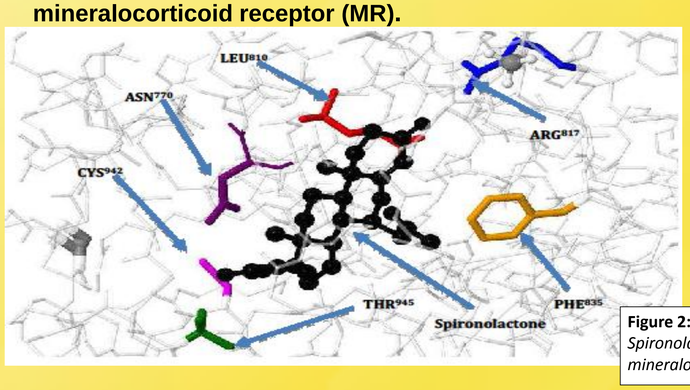

Figure 2: *A Close-up image of Spironolactone bound to the mineralocorticoid receptor*

- In order for MR to become activated it must undergo a conformational change in which AF-2 must be correctly positioned in order to properly recruit coactivators for transcription.
- In order for AF-2 to become correctly positioned, multiple interactions must occur.
  - The loop preceding the AF-2 must be stabilized via hydrogen bonds between ASN770 and SER767 on helix 3 and GLU955 present on the loop.
  - Additionally, there must be an interaction with THR945 via hydrogen bonds or hydrophobic interactions in order to stabilize helix 3.
- The distance between the lactone keto group of spironolactone and ASN770, as well as the distance between the lactone keto moiety and the hydroxyl group of THR945 suggest weakened binding capabilities compared to MR's endogenous ligands.
- These weakened bonding potentials do not allow for proper positioning of the AF-2, enabling spironolactone to bind to MR without activating it, yet provide spironolactone with its great affinity for the receptor.

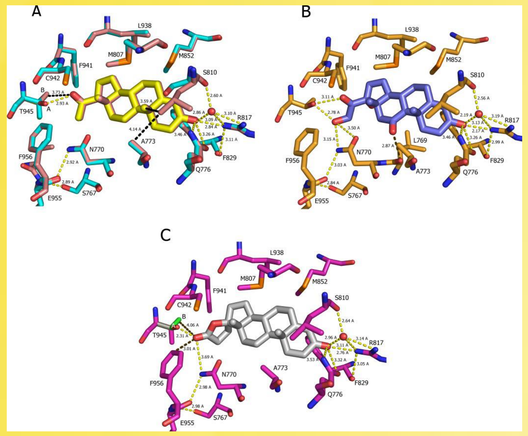

Figure 3[4]: *Close-up views of the MR C808S/S810L mutant bound to progesterone, cortisone, and spironolactone.[4] Here we have the drug; spironolactone bound to a mineralocorticoid receptor (MR). In order for this receptor to become activated, it needs the ligand to form hydrogen bonds to both ASN770 and THR945, which results in a conformation change that allows coactivators of transcription to bind. Spironolactone is an antihypertensive medication that is passively antagonistic to MR. How this drug provides its antagonistic effect, is by preventing MR from adapting its conformational change where it forms hydrogen bonds to ASN770 and THR945. Image C depicts spironolactone binding to MR, while images A and B were included to demonstrate how progesterone and cortisone similarly bind MR.*

Future Clinical Scenario

Spironolactone has been implicated in incidence of gynecomastia or swelling of the breasts. It is believed this interaction occurs through interference of endogenous testosterones and estrogens. Medicinal chemists should look for ways to improve the structure of the molecule to make it more specific for the mineralocorticoid receptor while minimizing the effect on endogenous hormones, although this reaction can still be utilized moving forward. New research suggests that spironolactone may treat female alopecia, likely through hormonal modification.

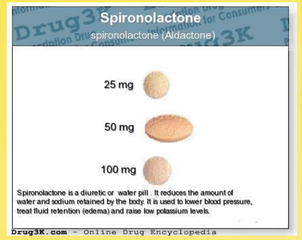

Figure 4: *Spironolactone tablet formulations*

Summary

Spironolactone exerts its effect by passively antagonizing the mineralocorticoid receptor (MR). MR is a large protein comprised of 784 amino acids and must undergo a conformational change in order to properly recruit coactivators for transcription. By blocking this receptor, spironolactone produces blood pressure lowering effects that are useful in hypertension and certain cases of heart failure. Spironolactone also increases serum potassium levels by competing for the aldosterone-dependent sodium-potassium exchange site in the distal tubules. This effect can be beneficial or troublesome depending on patient potassium levels, since levels out of range may lead to arrhythmias.

References

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