Abstract

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. 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.

Molecular Story

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

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. 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.

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. It treatment use ranges from ascites, congestive heart failure, edema, and hypertension to hypokalemia, primary aldosteronism, and acne vulgaris. Overall, spironolactone has been regarded as a generally well-tolerated medication. As with any medication, however, there is potential for adverse effects.

References