

The promiscuous mineralocorticoid receptor

Hormones and nerves are the key communication systems in the human body. Nerves are like a fixed-line telephone network, capable of very fast messaging: think of the pianist's fingers playing the Minute Waltz. Hormones are like radio, you need a receiver – in biology, a receptor- to pick them up. Their concentrations in blood are very low, so you need powerful receivers to pick them up – in biology, high affinity receptors. Their actions can be fast through very slow, but not as fast as nerves: it takes ~45 seconds for the blood to go around, and then the receptor has to do its thing, so they start at least a minute behind.

Mineralocorticoid receptors in the kidney and colon have high affinity for the salt-retaining hormone aldosterone. In evolution aldosterone first appears in lungfish, which as their name suggests can manage life in and out of water: curiously, mineralocorticoid receptors appeared much earlier, in both bony (e.g. trout) and cartilaginous (e.g. sharks, rays) fish: food for thought. In humans, aldosterone levels rise when salt intake falls, and are low when salt is plentiful, as in most western diets. This was not always the case – think of the salt routes in Europe, and how Salzburg made its money for centuries.

Aldosterone and mineralocorticoid receptors have another life in addition to salt and water. When we stand up from lying down, we need blood vessels to constrict, quite acutely, to the redistribution of blood. Part of the mechanism for doing this is for acute release of aldosterone to rapidly activate mineralocorticoid receptors in the vessel wall to constrict. Aldosterone is made in the adrenal glands, sitting on top of the kidney. If they are shot (Addison's disease) subjects have so-called postural hypertension, that is an acute blood pressure drop on standing up, often culminating in fainting.

It all sounds pretty straight to date: no hint of promiscuity yet. Where it comes in is other steroid hormones (progesterone; cortisol, often called hydrocortisone) which bind equally well to mineralocorticoid receptors. The problem is that cortisol circulates at ~ 1000 fold higher concentrations than aldosterone – very inconvenient, but cortisol was *the* steroid in fish. Progesterone acts as an antagonist of aldosterone in pregnancy: aldosterone levels rise 3-10 fold, in an attempt to overcome the sodium loss caused by the elevated progesterone.

Cortisol is something else. In the kidney and colon cortisol occupies most mineralocorticoid receptors, but does not activate them like aldosterone does, due to the workings of an enzyme abbreviated to 11β HSD2. If the enzyme is congenitally absent, or partially blocked by your eating too much liquorice, then cortisol activates these otherwise 'protected' mineralocorticoid receptors, and you retain too much salt and water.

Fast forward to the heart, where the only 11β HSD2 is in the coronary arteries: the muscle cells have unprotected mineralocorticoid receptors, normally filled with the much higher levels of cortisol. Aldosterone, if it can get in, is very bad news in various experimental situations. These are conditions in which the heart muscle is damaged – and under these conditions cortisol becomes a mineralocorticoid receptor agonist, mimicking aldosterone and causing even further tissue damage.

So cortisol is what is known as bivalent – an aldosterone blocker under normal circumstances, but a mimic in damaged tissues. Mineralocorticoid receptors occur in many tissues not primarily concerned with salt and water, and if and when they are damaged – by trauma, infection, whatever – cortisol can be a mischief-

maker. We still don't know what evolutionary advantage this confers – or exactly what cortisol does in fish, or why we didn't evolve a truly specific receptor for aldosterone (mineralocorticoid receptors are part of a large family, with 47 relatives), rather than processing an existing receptor protected by an enzyme as we came out of the water. We don't know why men have progesterone receptors. The more we know, the more we know how much we don't know.

Funder JW

*Department of Steroid Biology, Hudson Institute of Medical Research and Monash University,
Clayton, Victoria, Australia*

Publication

[The Promiscuous Mineralocorticoid Receptor.](#)

Funder JW

Hypertension. 2016 May