



The information provided by the adrenal cortical steroids: A hypothesis

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HIGHLIGHTS

- ▶ Hormones are selected to test the level of physiological parameters.
- ▶ Glucocorticoids test the cells' potential to increase mitochondrial activity.
- ▶ Mineralocorticoids test the potential of sodium transporters to increase activity.
- ▶ The closed blood system in vertebrates facilitated the evolution of the adrenal gland.

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ABSTRACT

We present the hypothesis that in vertebrates their closed blood circulation facilitated the evolution of the adrenal cortex as a central processing unit that provides the rest of the body with information on the effect of changes in the blood glucose and sodium levels on the functioning of the mitochondria, and of sodium transporters in the adrenal cortex.

When cells in the glomerulosa can no longer increase the synthesis of aldosterone, the message to the body is that a higher level of sodium in the blood may damage the cells. When the fasciculata cells cannot increase the synthesis of glucocorticoids, the message to the body is that their mitochondria cannot produce more ATP, and that higher levels of glucose in the blood may harm the organism.

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1. Introduction

Following an earlier paper (Zahavi and Perel, 2011) that explored the reliability of the message encoded in the sex steroids, we used the same approach to explore the message encoded by the adrenal corticosteroids. We base our hypothesis and discussion on the theory of signal selection (Zahavi and Zahavi, 1997), which suggests that even signals within the multicellular organism provide evidence that the information encoded in them is reliable. This suggestion was supported by a model produced by Krakauer and Pagel (1996) on the function of acetyl choline in morphogenesis. We also suggest that the synthesis and the properties of the chemical signal are tests of the reliability of the information encoded in the signal.

In text books the corticosteroids are described as a node in the transference of signals from the hypophysis to the whole organism, in order to stimulate the synthesis of glucocorticoids that promote the introduction of glucose from endogenous stores (Malcher-Lopes and Buzzi, 2009), and from the kidney to the whole organism in order to stimulate the adrenal to synthesize

more aldosterone, which increases the absorption of more sodium into the blood (Diliberto et al., 1983; Schild, 2010).

In the following we present the hypothesis that corticosteroids are not solely a node in transferring information, but that they also add information not presented by the hypophysis or the kidney.

The adrenal cortex is stimulated to produce corticosteroids by ACTH, a peptide synthesized in the hypophysis. The production of ACTH in the hypophysis is stimulated by another peptide, CRH, which is produced in the hypothalamus. This is not the only signaling pathway in the vertebrate body that stimulates the organism to introduce more glucose into the plasma. For example, glucagon and adrenalin also increase the level of glucose transport into the blood through a stimulatory effect on hepatic glycogenolysis and gluconeogenesis (Bray, 1993). Hence the question arises as to the advantage in evolving corticosterone as an additional signal that increases glucose levels in the blood. Is the adrenal cortex solely a node in transferring information from the brain to the rest of the body? Why can the brain or the hypophysis not send its message directly? Or, perhaps, might the adrenal cortex add important information, not available via the other stimulatory pathways that raise glucose levels.

Aldosterone poses a similar problem. The sensors that detect the need to send more sodium to the blood are present in the

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kidney (Schild, 2010). Kidney is also an organ that absorbs sodium from the urine. Why then should the kidney send the peptide hormone angiotensin I, which is cleaved in the blood to form angiotensin II, to stimulate the adrenal cortex to secrete aldosterone, which in turn arrives back at the kidney and stimulates it to reabsorb more sodium? (Kubzansky and Adler, 2010; Siliprandi et al., 1979).

2. Information encoded in the corticosteroids

A study of the available literature has led us to the hypothesis that an important function of steroid hormones of the adrenal cortex is to provide the brain and hypophysis with information on when to stop stimulating an increase in glucose levels, and to the kidney as to when to stop increasing the transport of sodium into the blood.

2.1. Corticosterone synthesis

The glucocorticoids cortisol and corticosterone are synthesized in the mitochondria of the fasciculata cells in the adrenal cortex. The final step in the synthesis of both cortisol and corticosterone takes place in the mitochondria of the cells in question (Yanagibashi et al., 1990). Glucocorticoids are secreted in all vertebrates, but not in other life forms. In mammals and bony fish, the main glucocorticoid is cortisol, except in some rodents, in which it is corticosterone. In birds, reptiles, amphibians, and cartilaginous fish, the main glucocorticoid is corticosterone (Murphy, 2007). The first step of corticosterone synthesis from cholesterol takes place in the mitochondria, in which cholesterol is cleaved to form pregnenolone. Pregnenolone is then transported into the endoplasmic reticulum (ER) in which it is oxidized into progesterone, and progesterone is then hydroxylated to form DOC (11-deoxycorticosterone). DOC is later transported back into the mitochondria, where it is further hydroxylated to form corticosterone (Yanagibashi et al., 1990). It is interesting to note that the sex steroid hormones are oxidized from progesterone in the ER. Hence it is intriguing as to why natural selection preferred to shift the final step in the synthesis of corticosterone back into the mitochondria. We posit the following hypothesis.

Corticosterone is produced from DOC using electrons donated by intramitochondrial NADPH (Natarajan and Harding, 1987), an electron donor whose synthesis is directly dependent on the activity of the Krebs cycle. Due to this dependence, an increase in corticosterone level informs the body that the mitochondria are able to use more substrates to generate ATP. Once the activity of the Krebs cycle reaches its upper limits, corticosterone levels cease to rise, and the message to the organism's body is that the organism should stop sending glucose into the blood since glucose that cannot be metabolized by mitochondria may damage the cells (Choi et al., 2008).

Fluorocitrate and 2,4-DNP inhibit the Krebs cycle activity and corticosterone production. This indicates that operation of the Krebs cycle is important for the synthesis of corticosterone, because the NADH produced by the cycle generates ATP via the respiratory chain for the energy-linked transdehydrogenase which produces intramitochondrial NADPH (Lin et al., 1974).

Under chronic stress, when the brain continues to signal a demand for more glucose by secreting ACTH, the adrenal cortex responds by hypertrophy (Hornsby, 1987; Vinson et al., 2000), increasing the number of cells that synthesize steroids in order to synthesize more corticosterone. This supports our suggestion that the existing cells are not able to increase the synthesis of steroids.

We suggest that the synthesis of corticosterone in the mitochondria, in the closest proximity to the Krebs cycle, evolved

because it provided the body with more and the most detailed information on the activity level of the Krebs cycle.

2.2. Aldosterone synthesis

In many vertebrates the mineralocorticoid function is served by aldosterone (McCormick et al., 2008). Aldosterone is synthesized from DOC in the mitochondria of the glomerulosa cells by electrons donated by ascorbate (Mitani et al., 2005). Ascorbate serves as an auxiliary electron donor, especially in the last two steps of aldosterone synthesis (Mitani et al., 2005).

Ascorbic acid, in its reduced form, is taken up into the cells via the sodium-dependent ascorbate transporter SVCT-2. SVCT-2 expression appears to be localized to regions with a strong requirement for ascorbate and with the ability to concentrate it. Among the various tissues, the adrenal gland contains the highest levels of ascorbate (Harrison and May, 2009; Wu et al., 2007).

Sodium influx into the cells is a consequence of its higher concentration in the blood than in the cytosol (Diliberto et al., 1983). Sodium is secreted out of cells in order to stabilize sodium levels in the cytosol, and to avoid damage caused by a surplus of sodium (Mejia-Alvarez and Marban, 1992). The sodium transport out of the cell is essential for the secretion of protons and other unwanted metabolites which are co-transported with sodium (Jaitovich and Bertorello, 2010). Sodium is secreted by the Na^+K^+ -ATPase transporter (Schild, 2010). The inhibition of Na^+K^+ -ATPase, which secretes sodium out of the cell, results in the inhibition of ascorbate uptake (Corti et al., 2010).

When the capacity of these sodium transporters to secrete sodium reaches its peak, uptake of sodium into the cell via SVCT-2 ceases (Corti et al., 2010), and with it ceases the uptake of ascorbate and the synthesis of aldosterone. Since aldosterone synthesis is dependent on ascorbate, the upper limit of aldosterone synthesis reflects the upper limit of the activity of the sodium transporters in glomerulosa cells, and provides information on the ability of these cells to eliminate waste products generated by higher activity of mitochondria.

Hence, as long as the aldosterone level increases, the message conveyed by aldosterone is that the sodium transporters in the glomerulosa cells are able to increase their activity, and higher sodium import into the blood within the kidney is desirable. When aldosterone levels stop rising, the message to the kidney is to stop sending more sodium into the blood.

3. Discussion

We suggest that the adrenal cortex evolved as a central processing unit that tests the impact of raised glucose levels in the blood on the function of mitochondria and of the level of sodium on sodium transporters. The evolution of the closed blood system in vertebrates provided the option for rapid transference of the results of tests conducted in one central organ to all cells in the organism, including the brain and the hypophysis. Cells in the organism can then increase or decrease their activities in relation to the information provided by the fluctuations in steroid production in the adrenal cortex, and save themselves the investment required in providing feedback information on the level of their own activities, since all cells are affected in the same direction by changes in the blood composition which surrounds them.

The information carried by the adrenal cortex steroids regarding the activity of the adrenal mitochondria and sodium transporters is reliable, since corticosterone synthesis is dependent on the activity of the Krebs cycle, and aldosterone synthesis is dependent on the activity of the sodium transporters.

To conclude: the adrenal cortex does not function solely as a node that transfers information from the hypophysis or the kidneys to the rest of the organism in order to increase the levels of glucose and sodium in the blood. Rather, we suggest that the adrenal cortex also tests the potential of its cells and mitochondria to increase their activities if provided with more glucose and/or sodium. The synthesis of corticosterone provides information on the ability of mitochondria in the adrenal cortex to increase the activity of the Krebs cycle. The synthesis of aldosterone provides information on the ability of the adrenal cortical cells to increase the activity of their sodium transporters to secrete sodium, and with it the waste products generated by the activity of mitochondria

We thus suggest that an important function of the steroid hormones of the adrenal cortex is to provide information to the brain and hypophysis on when to stop stimulating an increase in glucose levels, and to the kidney on when to stop increasing the transport of sodium into the blood.

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