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Endocrine Cell Function and Dysfunction

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Definition

The endocrine system refers to the cells and tissue that release hormones into the blood. Unlike synaptic chemical communication, which is localized to the target cell, endocrine communication is global. The hormones act on other endocrine glands such as the adrenal gland, ovaries, testes, and others, as well as on the heart, kidneys, muscle, and the brain. Mathematical modeling has been used to understand network interactions mediated by the endocrine system, as well as the effects of hormones on single cells.

Detailed Description

Background

Like neurons, many endocrine cells are electrically excitable and release hormones through Ca^{2+}-mediated exocytosis (Stojilkovic et al. 2010). These have been the focus of mathematical modeling and computer simulation to better understand the mechanisms through which the cells operate. Several endocrine cell types are involved in diseases with substantial morbidity and mortality, making them an important target for model-assisted investigation.

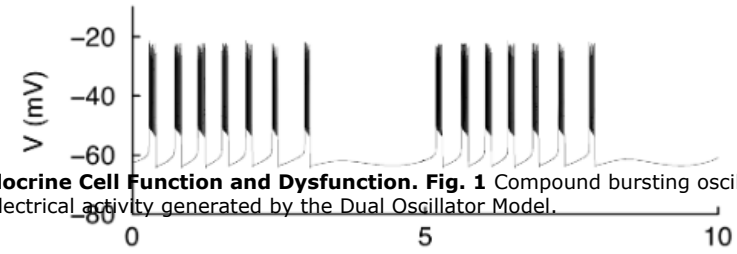
The most computational work to date has focused on the endocrine cells located within the pancreas in micro-organs called **islets of Langerhans**, and cells in the anterior region of the pituitary gland. There has also been modeling work done on the interaction between endocrine cells of different glands, and between an endocrine gland and the brain. However, modeling of the endocrine system is still in its infancy, so there is much potential for future work. Here, we consider two examples. The first illustrates cellular-level modeling of endocrine cells, and the second illustrates mean-field modeling of interactions between two endocrine glands.

Models of Pancreatic Islets

Islets are clusters of endocrine cells coupled together by gap junctions. They serve as endocrine micro-organs, and the pancreas contains hundreds of thousands of them. An islet consists of glucagon-secreting α-cells, insulin-secreting β-cells, somatostatin-secreting δ-cells, and cells that secrete pancreatic polypeptide. The gap junctions that connect neighboring cells provides electrical coupling among cells of the same type, which has the effect of synchronizing their activity.

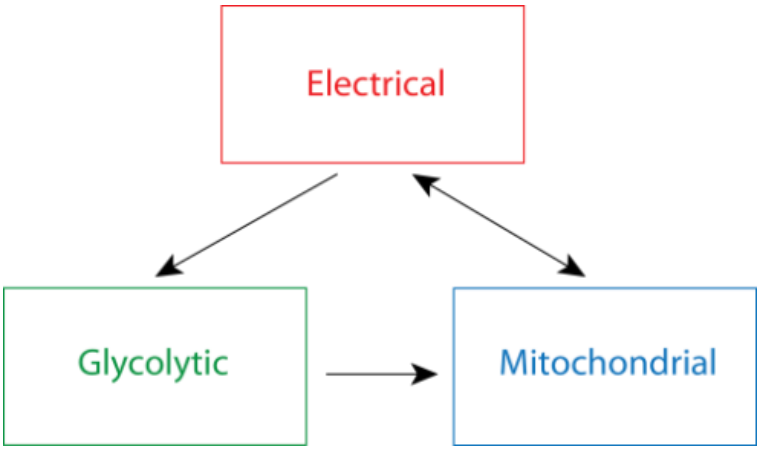
Almost all of the computational modeling that has been done on islets has focused on the β-cells. These cells sense the blood glucose concentration, and when the concentration is sufficiently high they produce a rhythmic pattern of electrical activity called **bursting,** cycles of electrical impulses separated by quiescent periods. Insulin is secreted during the active phase of the burst, which acts on target tissue such as muscle and the liver to take up glucose from the blood and metabolize it. The physiological importance of insulin secretion from β-cells, and the interesting question of how this periodic electrical activity could be produced, prompted Teresa Chay and Joel Keizer to develop the first mathematical model of β-cell electrical activity in 1983 (Chay and Keizer 1983). This model provided key insights into biophysical mechanisms for burst generation, and initiated a several-decades long series of models by them and others for pancreatic β-cells, each differing primarily in the mechanism for burst generation.

A key prediction of the **Chay-Keizer model** is that the intracellular Ca^{2+} concentration should have a sawtooth shape. This prediction was falsified when fura-2 fluorescent dye was used to measure the intracellular Ca^{2+} concentration and it was demonstrated that it has more of a square-wave shape. Other data has continued to drive revisions in the β-cell models. As the models have grown in complexity, they have grown in explanatory capacity.



Endocrine Cell Function and Dysfunction. Fig. 1 Compound bursting oscillations in electrical activity generated by the Dual Oscillator Model.

A good model of islet β-cells should be capable of explaining the 5-min oscillations in the blood insulin concentration that is typical in non-diabetic humans, mice, rats, and dogs. These oscillations correspond to either **slow bursting** or **compound bursting** activity in islets. The latter consists of bursts of electrical bursts (Fig. 1). Both slow and compound bursting oscillations have been observed frequently in isolated islets when the patch clamp technique is used to measure β-cell voltage (rather than a sharp electrode, as was used earlier). A model capable of producing slow and compound bursting oscillations, as well as the faster bursting oscillations often seen in islets, is the **Dual Oscillator Model** (Fig. 2) (Bertram et al. 2004, 2007a).

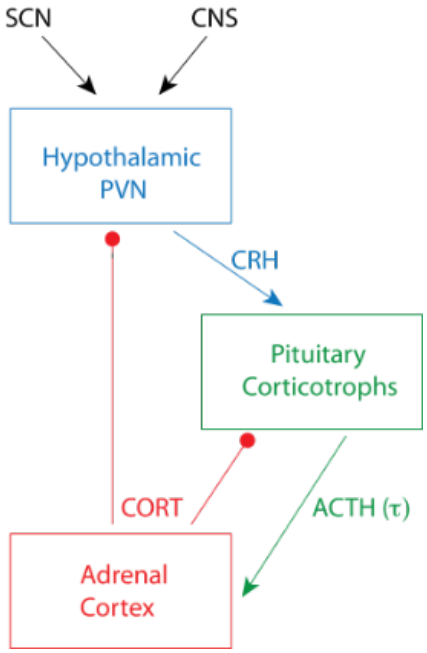


Endocrine Cell Function and Dysfunction. Fig. 2 The three main components of the Dual Oscillator Model and the interaction flow.

The first element of this model is an electrical component that also takes care of Ca^{2+} handling. This is a descendent of the Chay-Keizer model, with significant modification, and can account for the fast bursting oscillations often seen in islets. The second element describes a portion of the glycolytic pathway containing the allosteric enzyme phosphofructokinase. The product of this enzyme stimulates the enzyme's own catalytic activity and can produce slow oscillations in glycolytic activity. The third element describes portions of the citric acid cycle and oxidative phosphorylation, both of which occur in mitochondria. In the model, either slow or compound bursting oscillations are produced when the glycolytic subsystem is in an oscillatory state, which results in packaging of electrical activity into episodes. The effect of glycolytic oscillations on the electrical activity are mediated via the mitochondrial production of adenosine triphosphate (ATP), which acts on ATP-sensitive potassium ion channels in the plasma membrane. This model is able to account for the different types of bursting observed in islets, the ability of changes in glucose to convert the islet from one type of bursting pattern to another, and the effects of several pharmacological manipulations. Importantly, the model has been used to design experiments and to interpret experimental results in unintuitive ways. See (Sherman 2010) and (Bertram et al. 2007b) for details.

A Model for Glucocorticoid Pulsatility

Glucocorticoids (cortisol in humans and corticosterone in rats and mice) are released from the adrenal cortex and are key stress hormones that regulate the cardiovascular, cognitive, metabolic, and immunological state of the animal. Like many hormones, glucocorticoids are released in a pulsatile manner. This **ultradian rhythm**, with period of about 1 hour, is superimposed on a **circadian rhythm** of glucocorticoide release so that the ultradian pulse amplitude is high during the active period of the animal and low during sleep. It has been demonstrated that the physiological response to a stressor is determined in part by the time of onset of the stressor in relation to the phase of the rhythm (Windle et al. 1998). It has also been demonstrated that glucocorticoid responsive genes respond differently to pulses of glucocorticoids versus constant application of the hormone (Stavreva et al. 2009).



Endocrine Cell Function and Dysfunction. Fig. 3 Diagram of the stimulatory (arrows) and inhbitory (ball and stick) interactions responsible for the control of glucocorticoid (CORT) release. The effect of corticotrophin (ACTH) has a delay time τ reflecting the time required to synthesize CORT.

The network of interactions controlling the release of glucocorticoids is illustrated in Figure 3. Time of day information is provided by the suprachiasmatic nucleus (SCN) of the hypothalamus, and information on cognitive and physical stressors is provided by the central nervous system (CNS). A set of neurons in the paraventricular nucleus (PVN) of the hypothalamus receives and integrates this information and then releases the neurohormone corticotropin releasing hormone (CRH) into portal blood vessels that project to cells of the anterior pituitary gland. Corticotroph cells are stimulated by CRH and in response release corticotropin (ACTH) into the general circulation. This hormone acts on cells of the adrenal cortex to produce and release glucocorticoids (CORT). Because CORT is not stored, but is synthesized only in response to ACTH, there is a time delay between ACTH stimulation and CORT release. Once released, the CORT feeds back onto and inhibits both the CRH-releasing neurons in the hypothalamus and the ACTH-releasing corticotrophs in the pituitary gland.

Computer simulations with a mathematical model demonstrated that the ultradian rhythm in CORT can be produced by the mutual interactions of cotricotrophs with adrenal cells (Walker et al. 2010). That is, the rhythm can be generated even with a constant input from the hypothalamus, as long as the strength of that input is in the right range and the time delay is long enough. To demonstrate this, they used a mean-field model with three variables: a=ACTH concentration, r=glucocorticoid receptor availability in the corticotrophs, and c=corticosterone. The variables change in time according to the differential equations

$$\frac{da}{dt} = \frac{p_1}{1 + p_2 rc} - p_3 a$$

$$\frac{dr}{dt} = \frac{(cr)^2}{p_4 + (cr)^2} + p_5 - p_6 r$$

$$\frac{dc}{dt} = a(t - \tau) - c$$

where the p_j are parameters. The first equation includes the negative feedback of CORT onto ACTH release (c in the denominator of the first term). The second equation includes the positive influence of CORT on glucocorticoid receptors; the receptor number increases when CORT levels increase. The third equation includes the positive influence of ACTH on CORT synthesis and release. This has an explicit time delay of τ time units, representing the time required for the synthesis of CORT following the receipt of ACTH by the adrenal gland. These equations were constructed in dimensionless form.

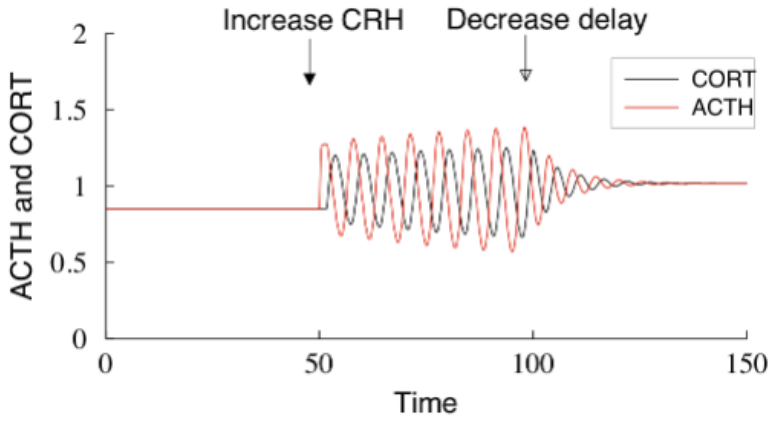


Fig. 4 Oscillations in CORT and ACTH due to the delayed positive feedback of ACTH onto CORT production. These oscillations require sufficient drive from the hypothalamus (closed arrow) and they die away if the time delay is too short (open arrow). All variables are dimensionless.

Figure 4 shows the results of computer simulations with this model, with parameters chosen as in Walker et al. (2010). In these simulations the CRH level is fixed and is represented by the parameter p_1. This is initially set at a low value of 10 and no oscillations are produced. Then, at the closed arrow, the CRH drive is increased to 15. This initiates oscillations in CORT (black), as well as oscillations in ACTH (red) that are phase shifted with the CORT oscillations. When the time delay is later decreased from 1.5 to 1 time units (open arrow) the oscillations die out and the system approaches a steady state. Thus, this simple model elegantly demonstrates several important predictions: (1) ultradian oscillations can be generated even if the output from the hypothalamus is held constant at a sufficiently high level, (2) the ACTH oscillations will be phase shifted relative to the CORT oscillations, and (3) oscillations only occur if the time lag between ACTH release and CORT synthesis and release is sufficiently large.

The essential ingredient for rhythm generation in this model is the delayed positive feedback of one component onto its inhibitor. Another model in which this occurs describes a semicircadian rhythm in the secretion of prolactin from pituitary lactotrophs (Bertram et al. 2006). This rhythm occurs during the first half of pregnancy in the rat and, according to the mathematical model, is produced by the delayed positive feedback of prolactin onto the dopamine-secreting neurons of the hypothalamic paraventricular nucleus. The dopamine is synthesized in response to prolactin activation with a time delay. Once released into the portal blood vessels connecting the hypothalamus to the pituitary, dopamine acts on lactotrophs and inhibits prolactin secretion, just as CORT inhibits ACTH secretion from corticotrophs.

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Further Reading

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