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Hormone oscillations in the HPA axis: dynamical diseases and beyond

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Abstract

Aim: Hormone pulsatility is an important aspect of the hypothalamic-pituitary-adrenal (HPA) axis in health and disease. We use the properties of simple mathematical models to determine whether hormone pulsatility reflects the presence of a time delay in the production of hormones and/or is related to the impulsive nature of hormone secretion.

Methods: The predictions of two models for HPA pulsatility are compared. The first model assumes pulsatility arises because of a time delay in the synthesis of glucocorticoids (GCs). The second model suggests that pulsatility reflects the impulsive nature of hormone secretion. The generation of oscillations by the second mechanism does not require a time delay.

Results: The time delay for the synthesis of GC (0–10 minutes) may not be long enough to account for the oscillations in adrenocorticotrophin (ACTH) and GC observed with constant corticotrophin-releasing hormone (CRH) infusion in rats. A simple mechanism for hormone release, illustrated using an integrate-and-fire mechanism, reproduces the observed hormone pulsatility.

Conclusions: The water solubility of CRH and ACTH draws attention to the role played by soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins in the calcium-dependent exocytosis of peptide hormones. Abnormalities in SNARE proteins are anticipated to cause changes in the amplitude modulation of ACTH and CRH hormone pulses. In mice, a mutation in a SNARE protein causes abnormalities in the HPA axis. Mutations in SNARE proteins occur in many neurodegenerative and neuropsychiatric diseases. Abnormalities in HPA function also occur in these disorders. The identification of SNARE protein mutations in exosomes in serum and cerebrospinal fluid in humans may make it possible to determine whether there exists a causal relationship between an SNARE protein mutation and abnormalities in the HPA axis in this patient group.

Keywords

Hypothalamic-pituitary-adrenal axis, pulsatility, time delay, secretion, soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor proteins

Introduction

The attention of physicians is often attracted to patients whose symptoms recur in a rhythmic fashion. For example, periodic patterns of seizure recurrence can often be detected in seizure diaries maintained by patients [1, 2]. However, the periodic recurrence of symptoms is not only seen in patients with epilepsy but can be observed in a wide range of medical conditions collectively referred to as "periodic diseases" [3–5] or more recently as "dynamical" [6, 7] or "dynamic" [8] diseases. The importance of recognizing the oscillatory features of dynamical diseases is because the number of plausible physiological mechanisms capable of producing the observed dynamical behaviors is relatively small. Thus, teams formed of physicians and mathematically oriented scientists working together have become very successful in identifying more clearly the nature of the underlying pathologies leading to the development of effective therapeutic strategies. In many cases, it appeared that a longer-than-normal time delay in a relevant feedback control mechanism provided an explanation for the observed dynamical behaviors.

Surprisingly, diseases of the hypothalamic-pituitary-adrenal (HPA) did not appear in initial discussions of dynamical diseases. In retrospect, this is surprising, since a striking feature of the HPA axis is the presence of a wide range of oscillatory behaviors [9]. Moreover, it has been suggested that these oscillatory behaviors are essential for maintaining optimal responsiveness of GC (glucocorticoid)-sensitive neural processes [10].

A puzzling observation is the occurrence of abnormal hormone dynamics in patients with neurodegenerative and neuropsychiatric diseases including but not limited to ADHD (attention-deficit/hyperactivity disorder) [11, 12], ALS (amyotrophic lateral sclerosis) [13, 14], Alzheimer's disease [15–17], major depression [18–20], Huntington's disease [21], Parkinson's disease [15], schizophrenia [22, 23]. Most often, the endocrine abnormalities are reflected by abnormal cortisol levels. Although these observations may be related to the "stresses'' associated with chronic illness [24], here we suggest another possibility. The quantal release of neurotransmitters and the regulated release of peptide hormones are processes that are both mediated by a molecular motor generated through the actions of SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) proteins [25, 26]. SNARE protein mutations occur in neurodegenerative and neuropsychiatric diseases [27, 28]. Thus, it would be anticipated that certain SNARE protein mutations could present clinically with problems related to both nervous system function and hormone secretion. Indeed, abnormalities in the HPA regulation have been demonstrated in the SNARE protein syntaxin 1A (STX1A) knockout mice [29]. It was observed that the knockout mice had lower GC and ACTH (adrenocorticotrophin) levels than wild-type mice. Moreover, the stress-induced response of ACTH and GC was reduced. These observations are consistent with the concept that a SNARE protein mutation would affect the release of peptide hormones.

Here we explore this possibility by examining the HPA axis from the point of view of dynamical diseases. First, we discuss the effects of a time delay on hormone dynamics [30–32]. A time delay occurs in the HPA axis because GC is only synthesized by the adrenocortical cells following stimulation by ACTH [30]. We suggest that this time delay may not be large enough to account for the observed periods of the oscillations in ACTH that occur in rats with constant infusion of CRH (corticotrophin-releasing hormone) in agreement with [32].

Next, we explore the effects of the impulsive nature of the secretion of the water-soluble peptide hormones, CRH and ACTH [33–37]. Abnormalities in hormone secretion are expected to affect the amplitude modulation of ACTH and CRH pulses. These observations raise the possibility that mutations in the SNARE protein may contribute to the HPA dysfunction seen in patients with neurodegenerative and neuropsychiatric disorders.

Materials and methods

The role of the presence of a time delay in the synthesis of GC was examined under the condition of high constant CRH infusion. Under these conditions, the dynamics of GC can be approximated by the first-order delay differential equation

$$\frac{dx}{dt} = f(x(t-\tau)) - kx(t)$$

where $f(x(t-\tau))$ describes the action of time-delayed feedback on GC production. In mathematics, this equation is referred to as the Hayes equation [38]. Mathematical models of this form have been used to model the dynamics of the pupil light reflex [39] and certain blood cell populations [40]. These equations, in turn, were instrumental in establishing the concept of a dynamical disease [6–8]. In dynamical diseases, the appearance of oscillations was often related to changes in the length of the time delay.

Next, we examined the effect of DCV (dense core vesicle)-mediated secretion of ACTH and CRH on the dynamics of the HPA axis. In mathematical terms, the secretion of these hormones is impulsive [33–37]. We used an integrate-and-fire (IF) model to illustrate the dynamics of the hormone pulsatile release from the secretory vesicle pool, as shown in Figure 1.

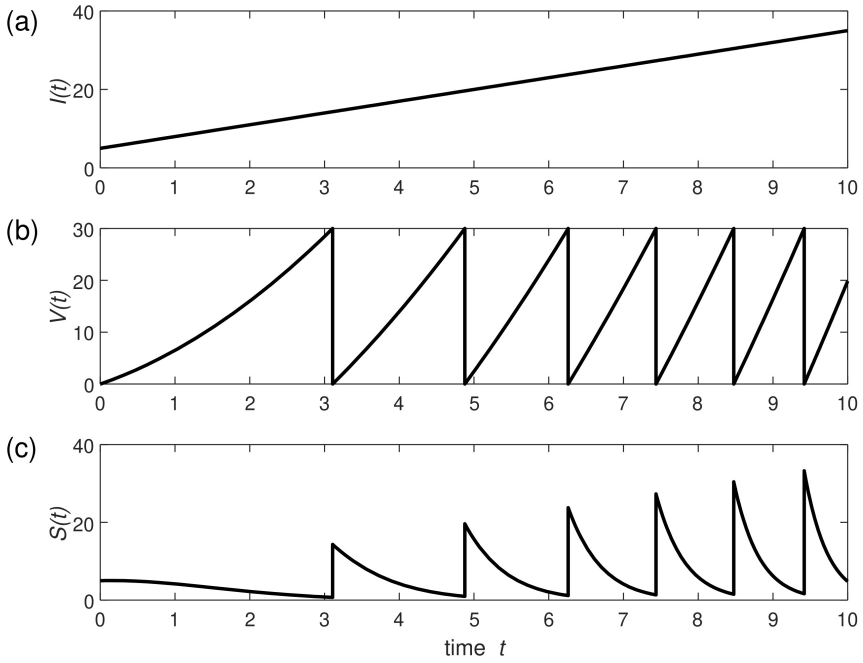

Figure 1. Impulsive model for hormone pulse generation [35, 36]. See text for description

Figure 1a shows the input, $I(t)$, to the hormone secretory pool. Although $I(t)$ could be constant, in general, it will be non-constant. For illustrative purposes, we assume that the increase in $I(t)$ is linear in time.

Figure 1b describes the timing of the pulses generated by the IF oscillator to the input $I(t)$. The time that the impulse is generated corresponds to the time when the potential, V, of the IF oscillator, reaches the threshold. If the threshold is not reached, pulsativity fails. When the threshold is attained, the action potential is reset to zero. This event describes the "jump condition" for the impulsive event. The term "impulsive" arises because the generation of the spike is associated with a discontinuity of the action potential. The sequence of firing times describes the frequency modulation of $V(t)$ by the input $I(t)$. Obviously, the greater the input stimulus $I(t)$, the faster the threshold will be reached. Note that there are two impulse generators in the HPA axis since there are two water-soluble peptide hormones: CRH and ACTH.

Figure 1c shows the hormone secretion rate, $S(t)$. It can be defined in many ways. For simplicity, we have assumed that $S(t)$ depends on the stimulus $I(t)$ and on the timing found in the previous step. It is important to note that with an increase in the stimulus (top panel), pulses are emitted more frequently (Figure 1b), and their peaks increase (Figure 1c). Since GC has a suppressive effect on hormones of the hypothalamus and the pituitary, as GC increases, $I(t)$ decreases. This, in turn, causes pulse amplitudes and frequencies to decrease.

The secretion rate $S(t)$ constitutes a train of secretory pulses, which should not be confused with the train of hormone pulses. The latter can be obtained by an integration of $S(t)$. The shape of the hormone pulses, as well as the sensitivity of their parameters to $I(t)$, will depend on the details of the Ca^{2+}-dependent exocytosis. Thus, we anticipate that these shapes and sensitivities can be modified by mutations in SNARE proteins and/or CAPS (calcium-activator protein for secretion), which affect exocytosis. We anticipate that the effect of SNARE mutations will cause changes in the shapes and amplitudes of hormone pulses, but not necessarily affect the timing of pulses.

Results

Time-delays and the HPA axis

Under conditions of high constant CRH, GC levels in rats change rhythmically over a period of about 60 minutes (Figure 2). In general, all that can be said about the period, T, of oscillations generated by the Hayes equation is that $T > 2\tau$ [38]. However, if we assume that the oscillations in Figure 1 are approximately sinusoidal, then $f(x(t-\tau)) \approx x(t-\tau)$ and the Hayes equation becomes the Wright equation [41] and $2\tau < T < 4\tau$ .Thus the time delay required to generate an oscillation with a period of approximately 60 minutes would be between 15 and 30 minutes.

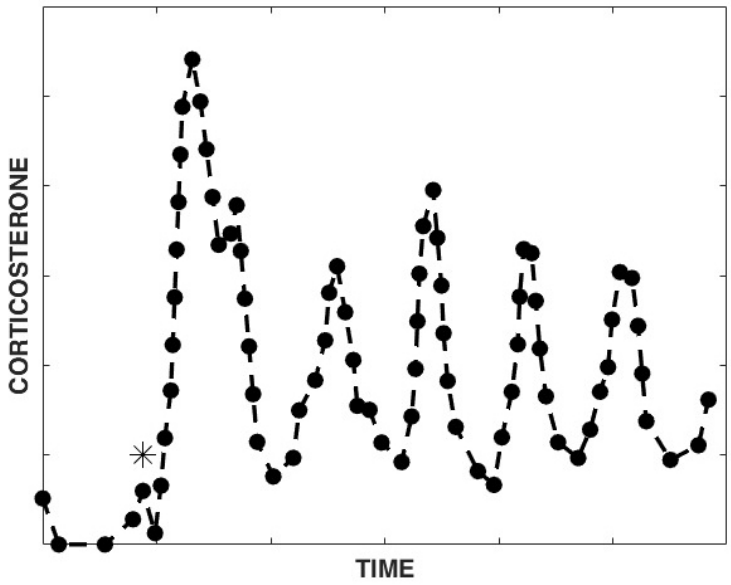

Figure 2. GC oscillations in a rat in response to a constant CRH infusion with a sampling time of 10 minutes. The period of the CRH oscillations is approximately 60 minutes. The • indicates measured values of GC, and the * denotes the time when the CRH infusion began. The figure is based on data obtained by [45]; however, the sampling times are hypothetical. CRH: corticotrophin-releasing hormone; GC: glucocorticoid

Estimates of the delay for GC synthesis range from 0 minutes [42] to 2 minutes [43] to 3–6 minutes [44] to 10 minutes [45]. Thus, we agree with [45] that the period of the GC oscillations when CRH is constant cannot be completely accounted for by the measured time delay.

One possible explanation is that the observed oscillation is not generated by one negative feedback loop but arises from the interaction of two or more positive and negative feedback loops [32, 45, 46]. However, we show that GC pulsativity does not depend on the presence of a time delay but instead arises because of the impulsive nature of hormone secretion [34].

Impulsive model for peptide hormone secretion

Figure 3a illustrates the dynamics of the impulsive HPA axis. Impulsive hormone release is superimposed on the well-known 24-hour modulation of the amplitude of ACTH and GC secretion. The important point is that a time delay is not important for the generation of these dynamics. The time delay only introduces a

small phase shift [34]. Figure 3b shows the effect of a constant CRH infusion on HPA dynamics when circadian input is absent. As can be seen, there is a rhythmic release of GC (Figure 3). The parameters in this model can readily be adjusted so that the pulse period is about 60 minutes. These observations support our observation that the oscillations in GC shown in Figure 2 do not depend on the presence of a time delay.

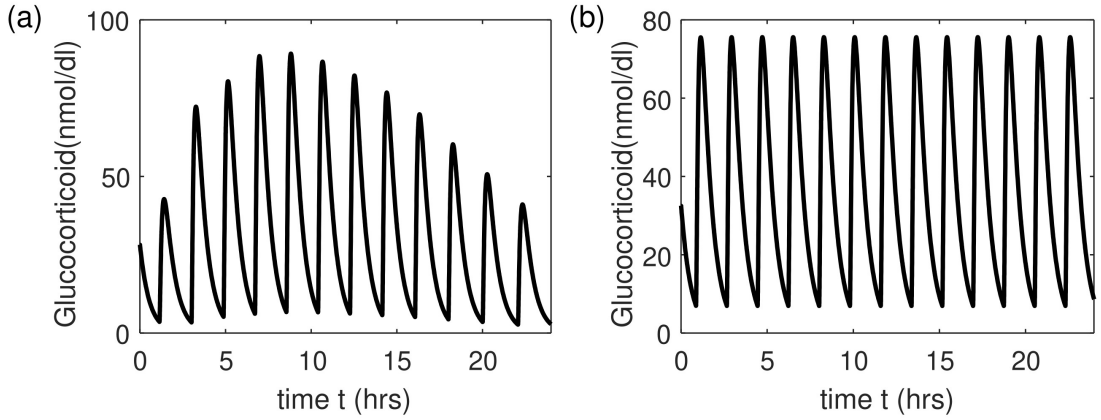

Figure 3. GC oscillations in an impulsive model for hormone secretion. (**a**) Profile for GC for 24 hours under normal conditions. (**b**) Profile for GC when CRH is infused at a constant level. We have also removed the input from the SCN. For details concerning the full model, see [29, 30]. CRH: corticotrophin-releasing hormone; GC: glucocorticoid; hrs: hours; SCN: suprachiasmatic nucleus

Amplitude modulation

The impulsive nature of the release of CRH (and ACTH) raises the question: What constitutes a hormone pulse? In Figure 2, we indicated the experimentally measured concentration of ACTH using a •. What is the nature of changes in hormone concentration for the times between the •'s, i.e., the times represented by the dashed lines?

For many neurodegenerative and psychiatric diseases, including Alzheimer's disease [15], major depression [18–20], Parkinson's disease [15], and schizophrenia [22], the timing of the GC pulses is like that observed for healthy controls. However, the amplitudes of the pulses are different. Thus, namely the shapes and amplitudes may play a role in the HPA dysfunction observed in these diseases. Abnormalities in the shapes and amplitudes of hormone pulses, but not necessarily in their timing, would be expected to occur if there were defects that affect exocytosis.

SNARE peptide hormone exocytosis

The peptide hormones CRH and ACTH are water soluble and are secreted by a DCV-dependent exocytotic process. The molecular motor that makes the exocytotic process possible is generated by the SNARE proteins. The exocytotic process is a multistep mechanism that involves: 1) packaging the hormones into DCVs, 2) transporting the DCVs from the cytoplasm to the cell plasma membrane, 3) "priming" and "docking" the DCVs, and 4) a Ca^{2+}-dependent mechanism which releases the peptide hormones into the extracellular environment [25, 47–49]. This process is thought to occur through the agency of cup-shaped structures in the cell membrane referred to as porosomes [50, 51].

SNARE proteins are divided into two groups: the v-SNARE proteins located in the vesicle membrane and the t-SNARE proteins located on the target membrane. It is well established that three canonical SNARE protein families are essential for Ca^{2+}-dependent peptide hormone release: 1) t-SNARE proteins (SNAP-25 and STX1A, STX1B, Munc-1 families), 2) v-SNARE proteins (the VAMP family) [52–56]. The driving force for exocytosis comes from the energy released during the assembly of the SNARE complexes, which in turn pull the vesicle and target membranes together, leading to fusion and content release. Biophysical studies using the atomic force microscope indicate that the "docked" vesicle swells slightly before it "pops" to release its contents extracellularly [50].

The Ca^{2+}-dependent release of peptide hormones is not as well characterized as the release of neurotransmitters. The differences between the exocytosis of neuropeptides and neurotransmitters are mainly related to the role played by Ca^{2+}, e.g., latencies, calcium concentrations, etc. (see [25, 57] for reviews). CAPS have been identified for the secretion of peptide hormones [58]. However, given the delicate nature of a molecular motor, it is unlikely that there are differences in the role of the SNARE proteins for exocytosis between neurons and neuroendocrine cells [25, 59].

Although abnormalities in HPA regulation have been demonstrated in STX1A knockout mice [29], the co-existence of an SNARE protein mutation and an abnormality in the HPA axis has yet to be reported for humans. The observations in the STX1A knockout are consistent with the concept that a SNARE protein mutation would affect the release of ACTH. This suggestion is also supported by calculations of the "energy landscape" of a SNARE complex for neural transmission due to mutations in SNAP-25 [60]. It was observed that the SNAP-25 mutation produced two effects: 1) unregulated membrane fusion of the vesicles with the cell membrane and 2) reduction in spontaneous and Ca^{2+}-evoked vesicle fusion. At present, SNARE protein mutations in humans are detected post-mortem. However, assays to detect the presence of SNARE protein mutations in blood [61, 62] and cerebrospinal fluid [63] are being developed. Thus, it may eventually be possible to determine the nature of the relationships between SNARE protein mutation and HPA dysfunction in humans.

Discussion

It is well established that the characteristics of the fluctuations in ACTH and GC depend on how frequently blood is sampled [64–67]. As the sampling interval is decreased, the inter-peak interval becomes shorter, but the variance in the amplitude becomes more marked. For example, as the sampling intervals decreased from 12 minutes to 2 minutes, the inter-peak interval decreased from 73 minutes to 18 minutes [65] and hence appears to approach the period of ACTH release for isolated human pituitary glands, i.e., approximately 15 minutes [68]. For each sampling frequency, the inter-peak intervals remained the same; however, the amplitude of the pulses varied. Thus, amplitude modulation of hormone pulses is an important aspect of HPA dynamics in humans [64, 65]. Similar trends are observed in rats [66] and monkeys [67]. These observations indicate that a "hormone pulse" observed when blood is sampled at intervals of 10 minutes or longer is more complex than a single pulse.

A SNARE protein mutation that affects the secretion of water-soluble hormones would be expected to be related to changes in the amplitude modulation of peptide hormone pulses in the HPA axis. The amplitude modulation of hormone pulses in the HPA axis is most clearly seen when blood is sampled frequently: 1-minute intervals in animal models [66, 67], and 2–4-minute intervals in human subjects [64, 65]. These sampling intervals are much shorter than those commonly employed in human studies, typically 10 minutes [10, 18–20, 22, 69–71], and the sampling time for implanted monitoring systems, e.g., about 20 minutes for U-rhythm [72]. However, it must be emphasized that the purpose of short sampling times is to detect the possible presence of a SNARE protein mutation that affects hormone release, not for long-term monitoring. A study period ranging from 2 hours to about 4 hours may be sufficient to characterize the amplitude modulation of ACTH pulses. The development of nanopore technologies may make it possible to detect peptide hormone molecules as they cross the plasma membrane and hence make it possible to refine the description of hormone pulse generation and possibly enable therapeutic strategies [73].

The possibility of a SNARE protein mutation suggests that patients with neurodegenerative and psychiatric disorders might have problems related to both neurotransmission and peptide hormone secretion to varying extents. This may explain why the management of the HPA axis in patients with these disorders remains so challenging [74]. Although the reaction of the HPA axis to acute stress is beneficial, the effects of chronic stress are harmful. The dynamics of the HPA axis are affected by compensating changes in the mass of hormone-producing glands [24], increased adrenal sensitivity to hormonal inputs, and decreased GC metabolism [74]. The outcome can be a "viscous cycle of stress" in which stress drives the disease, and the disease drives the stress [17, 75].

Often overlooked by benchtop and blackboard researchers is the role played by physicians and health care workers. However, their role is critical since they are best positioned to detect abnormalities related to disease dynamics at the bedside that do not fit the norm. It is possible that the presence of a SNARE protein mutation related to peptide hormone secretion would take the form of atypical mood changes and responses to stressful situations. The analysis of patient diaries and questionnaires by physicians has already played an important role in showing how shift work [76] and depression [77, 78] lead to "flattened cortisol rhythms". Thus, input from physicians, healthcare workers, and patients will continue to be important for guiding researchers at the benchtop and at the chalkboard.

Abbreviations

ACTH: adrenocorticotropin

CAPS: calcium-activator protein for secretion

CRH: corticotrophin-releasing hormone

DCV: dense core vesicle

GC: glucocorticoid

HPA: hypothalamic-pituitary-adrenal

IF: integrate-and-fire

SNARE: soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor

STX1A: syntaxin 1A

Declarations

Author contributions

JM: Conceptualization, Writing—original draft, Writing—review & editing, Investigation. AC: Conceptualization, Formal analysis, Software. Both authors read and approved the submitted version.

Conflicts of interest

Both authors declare that they have no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

All data analyzed in this study were obtained from published sources cited in the references. The custom computational scripts used for modeling will be made available upon reasonable request to the corresponding author.

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