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Dynamics of the HPA axis and inflammatory cytokines: Insights from mathematical modeling

Hamed Malek [a], Mohammad Mehdi Ebadzadeh [a,*], Reza Safabakhsh [a], Alireza Razavi [b], Jalal Zaringhalam [c]

[a] Biocomputing Laboratory, Computer and Information Technology Engineering Department, Amirkabir University of Technology, Tehran, Iran
[b] Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran
[c] Neurophysiology Research Center, Department of Physiology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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ABSTRACT

In the work presented here, a novel mathematical model was developed to explore the bi-directional communication between the hypothalamic-pituitary-adrenal (HPA) axis and inflammatory cytokines in acute inflammation. The dynamic model consists of five delay differential equations 5D for two main pro-inflammatory cytokines (TNF-α and IL-6) and two hormones of the HPA axis (ACTH and cortisol) and LPS endotoxin. The model is an attempt to increase the understanding of the role of primary hormones and cytokines in this complex relationship by demonstrating the influence of different organs and hormones in the regulation of the inflammatory response. The model captures the main qualitative features of cytokine and hormone dynamics when a toxic challenge is introduced. Moreover, in this work a new simple delayed model of the HPA axis is introduced which supports the understanding of the ultradian rhythm of HPA hormones both in normal and infection conditions. Through simulations using the model, the role of key inflammatory cytokines and cortisol in transition from acute to persistent inflammation through stability analysis is investigated. Also, by employing a Markov chain Monte Carlo (MCMC) method, parameter uncertainty and the effects of parameter variations on each other are analyzed. This model confirms the important role of the HPA axis in acute and prolonged inflammation and can be a useful tool in further investigation of the role of stress on the immune response to infectious diseases.

1. Introduction

1.1. Background

For decades, the following general concept concerning the endocrine system has been accepted: the regulation of the immune system by the nervous system is achieved through an interaction between various hormones and cytokines in different organs of the body. Perhaps, the best known of the early studies was performed by Selye who noted the relation between stress and substantial decrease of circulating lymphocytes and shrinkage of the thymus and lymph nodes in rats [36]. Since then, the idea of bidirectional communication between the immune and the central nervous system and the role of hormones and cytokines in this interaction have been supported by various experiments and studies [40].

During the last decade, much attention has been given to the role of the interaction between the immune and nervous systems in immune diseases, such as autoimmune, allergy, inflammatory, and viral infections, or nervous system disorders such as major depression [22]. Although much has been done in identifying the different aspects of this network, the complex bidirectional communication system of the HPA is poorly understood [19].

During injury, disease, or infection, the immune system is activated and releases a group of proteins called cytokines, which act as mediators of the innate immune response. Inflammatory cytokines are a type of cytokines that are produced and secreted locally from different immune cells in the inflammatory area during the first phase of immune response. Some examples of these cytokines are tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), and interleukin-6 (IL-6). Among all cytokines, these three have the most modulating effects on the hypothalamic-pituitary-adrenal (HPA) axis activation associated with immune response [11], and as a result of which, cortisol and other glucocorticoid hormones are released by the adrenal glands. The HPA axis has an important role in regulating different organs of the body during exposure to threatening stress. The activation of the HPA axis involves the release of corticotropin-releasing hormone (CRH) by the paraventricular nucleus of the hypothalamus, stimulating the production of adrenocorticotropic hormone (ACTH) in

* Corresponding author.
E-mail address: ebadzadeh@aut.ac.ir (M.M. Ebadzadeh).

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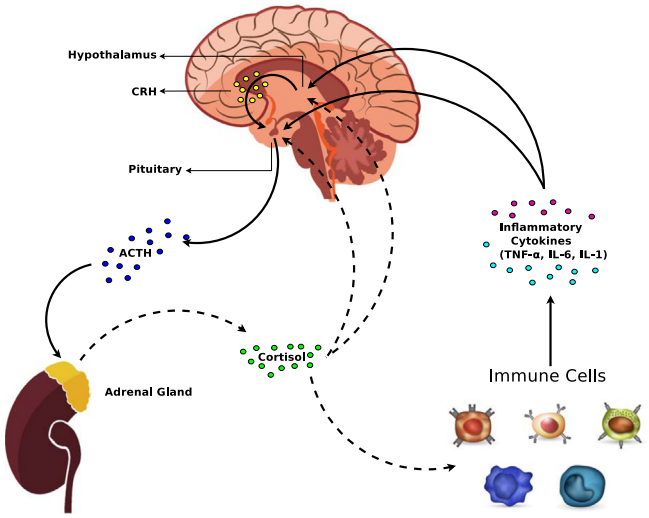

Fig. 1. Schematic diagram of the interaction of innate immune cells with the HPA axis through inflammatory cytokines. Solid arrows indicate stimulation and dashed arrows indicate inhibition.

the anterior lobe of the pituitary gland. Secreted ACTH in the peripheral circulation stimulates the adrenal cortex, releasing glucocorticoids and, in particular, cortisol into the blood. It is commonly known that glucocorticoids inhibit the activity of the HPA axis by negative feedback on CRH and ACTH secretion [35].

During an infection, pro-inflammatory cytokines are produced and released by immune cells such as macrophages, and T and B lymphocytes. They act on all three levels of the HPA axis (hypothalamus, pituitary, and adrenal glands) and through the activation of the HPA axis, stimulate the release of glucocorticoids, in turn suppressing further production and release of pro-inflammatory cytokines [37]. The effect of the HPA axis on inflammatory/immune response and the roles of the main parts of these systems in this interaction are illustrated in Fig. 1.

Beside the stimulating effects of inflammatory cytokines in activating the HPA axis, a number of these cytokines may act differently in various situations. For example, IL-6 is a multifunctional cytokine and has been shown to elicit both pro- and anti-inflammatory effects. It acts as a pro-inflammatory cytokine in activating of the HPA axis, but at the same time, inhibits the production of TNF-α and IL-1 [47]. As well, in contrast to the stimulating effect of TNF-α on the HPA axis [14] in humans, it has been shown in a series of animal experiments or human fetal cell experiments that TNF-α has an inhibitory effect on cortisol release [37,5,17,24]. These multifunctional properties and the complex communication between hormones and cells make understanding the interactions between the immune and nervous systems more difficult.

1.2. The proposed model

In the last decade, several mathematical models of the HPA axis and acute inflammation have been introduced. However, although various cell culture, animal or, human experiments have been carried out, no mathematical model has been proposed for modeling the bidirectional interaction between the HPA axis and inflammatory cytokines in acute inflammation and, specifically, the effects of circadian and ultradian rhythms of the HPA axis in this interaction.

In the work presented here, a delay-differential equation model is proposed for the interaction between the immune system and the HPA axis through two main pro-inflammatory cytokines (TNF-α and IL-6) and two main endocrine hormones of the HPA axis (ACTH and cortisol). The authors demonstrate how the model correctly captures the ultradian rhythm of cortisol and ACTH in blood plasma and how it can be used to simulate the behavior of the HPA axis and inflammatory cytokines in response to injected LPS. They also show how a few changes in the production rates of pro-inflammatory cytokines can lead to a persistent inflammation in the body.

The proposed model is elaborated upon in two stages in Sections 2.1 and 2.2. In the first stage, a new simple 2-D delayed model of the HPA axis is developed. Using physiologically reasonable parameters, it is demonstrated in Section 3 that the model is able to capture ultradian and circadian rhythms of the HPA axis. In the next stage, the complete model of the inflammatory cytokines and the HPA axis with the addition of endotoxin to initiate the immune response is constructed. A number of parameters of the main model are extracted from the clinical published data, and others are estimated using a global optimization algorithm in Section 2.3. An analysis of uncertainty of the estimated parameters using a Markov chain Monte Carlo (MCMC) algorithm is also presented. Finally a discussion on the physiological implications of a positive steady state of the model, and the role of cortisol on controlling the inflammation and robustness of the HPA model is described in Section 4.

1.3. Related works

So far, no investigation of the interaction between the HPA axis and inflammatory cytokines through mathematical models has been performed, but there are several works in the literature for which modeling has been proposed for each of the components of this interaction.

Different mathematical models of the HPA axis have been developed aiming to describe the interaction of CRH, ACTH, and cortisol and the role of the HPA axis in circadian and ultradian (short period) rhythms of cortisol concentration.

Usually, 3 or 4 main hormones of the axis have been utilized. Vinther et al. [42] introduced a simple model for the interaction of the three main hormones of the HPA axis, i.e. CRH, ACTH, and cortisol. Their mathematical analysis demonstrated that without considering delay equations, these hormones cannot exhibit periodic behavior by themselves. In order to simulate the ultradian behavior of the HPA axis, other models have added glucocorticoid receptors (GR) to the equations in addition to these hormones, and have exhibited that ultradian behavior can be expressed by including GR [16,1,13,39,44]. On the other hand, a number of studies have suggested delay equations for modeling of the HPA axis [3,21,44]. The delay parameter has been employed to various degrees in these models. For example, in [21] and [3], the delay parameters were applied at all three major levels of the axis. However, in the model proposed in [44], the delay parameter was only considered for the effects of ACTH on cortisol release. Applying delay in mathematical models results in instability and hence periodic behavior in the model.

In the previously described models of the HPA axis, the ultradian rhythm of the HPA axis has been modeled through at least three variables. This would result in increasing model complexity, more data for parameter estimation, and more difficulties in model analysis. Generally, low dimensional models are always preferable, especially, when the model is intended to be included in other models.

Mathematical modeling of acute and chronic inflammation has also been the subject of quite a few papers. In [9], a four-dimensional differential equations model of inflammation response to bacterial lipopolysaccharide (LPS) endotoxin was put forth. A two-variable model for the interaction between pro-inflammatory and anti-inflammatory cytokines for rheumatoid arthritis, a chronic inflammatory disease, is proposed in [4]. In