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REGULATION OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS BY PHYTOSTEROL: ACTIONS AND MECHANISM OF ACTION

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ABSTRACT:
Phytosterols (PS), commonly referred to as plant sterols, are naturally occurring chemicals found in plants that resemble cholesterol in structure but have an additional methyl (campesterol) or ethyl (β-sitosterol) group in the side chain. The present review was based on the regulation of the hypothalamic-pituitary-adrenal axis by phytosterol: actions and mechanism of action. PS have been shown to have endocrine-disrupting properties, and studies on humans, rats, mice, goldfish (*Carassius auratus*), and Japanese quail have all reported experiencing this effect. Dietary PS has been shown to accumulate in the brain lately. Dietary β-sitosterol has the ability to cross the blood–brain barrier (BBB) and build up permanently in the membranes of brain cells. The stress response, which consists of a complex interplay between elements of the central nervous system (CNS) and peripheral systems such the endocrine, immunological, and cardiovascular systems, is triggered by exposure to environmental, physical, or physiological stressors. Under stressful circumstances, the HPA axis mediates the physiological maintenance of homeostasis. In conclusion, adult male quails fed PS alone had lower testosterone concentrations in their plasma and pituitary without appreciably changing their levels of LH. Furthermore, LH release from the pituitary gland and testosterone release from the testes were both markedly increased by cGnRH-1 stimulation. In contrast to control animals, quails fed PS had lower amounts of testosterone and LH.

Keywords: Phytosterols, hypothalamic-pituitary-adrenal axis, hypothalamic GnRH-1 expression, testosterone.

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INTRODUCTION

Phytosterols (PS), commonly referred to as plant sterols, are naturally occurring chemicals found in plants that resemble cholesterol in structure but have an additional methyl (campesterol) or ethyl (β-sitosterol) group in the side chain [1]. Although more than 200 distinct forms of PS have been identified in plants, β-sitosterol, campesterol, stigmasterol, and brassicasterol are the most prevalent PS [2][3]. PS, which influences intestinal cholesterol absorption, has been referred to as plasma cholesterol reduction since 1950. While having no discernible effect on triglyceride or high-density lipoprotein cholesterol (HDL-C) levels, PS lowers total cholesterol, especially LDL-C levels [4].

PS have been shown to have endocrine-disrupting properties [5], and studies on humans [6], rats [7], mice [8], goldfish (*Carassius auratus*), and Japanese quail [9][10] have all reported experiencing this effect. Dietary PS has been shown to accumulate in the brain lately [11]. Dietary β-sitosterol has the ability to cross the blood–brain barrier (BBB) and build up permanently in the membranes of brain cells [12]. According to Shi et al., membrane β-sitosterol can stop the gonadotropin-releasing hormone (GnRH) secretion from declining when TNF-α is present [13]. GnRH, a hypothalamic decapeptide, is essential to the reproductive systems of both mammals and birds. GnRH causes the anterior pituitary to release the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn causes the gonads to release steroid hormones [14]. Furthermore, the pituitary glands' secretion and release of gonadotropins are inhibited by the hypothalamic dodecapetide gonadotropin-inhibitory hormones (GnIH). According to recent research, the hypothalamic-pituitary-gonadal (HPG) axis, which includes the testes of birds, expresses both GnRH and GnIH. Nonetheless, there is ongoing debate over PS's disruptive effects on reproductive processes mediated by the HPG axis [15].

Hypothalamic-pituitary-adrenal (HPA) axis

The stress response, which consists of a complex interplay between elements of the central nervous system (CNS) and peripheral systems such the endocrine, immunological, and cardiovascular systems, is triggered by exposure to environmental, physical, or physiological stressors [16]. The anterior pituitary gland, the cortex of the adrenal gland, and the paraventricular nucleus (PVN) of the hypothalamus regulate how the body reacts to stress in normal physiology. The hypothalamic-pituitary-adrenal (HPA) axis is the collective name for these structures [17]. The control of adrenal hormones that aid in maintaining or reestablishing homeostasis is largely dependent on the HPA axis.

When the hypophysiotropic neurons located in the hypothalamic ventral plexus (PVN) are stimulated to synthesis and produce corticotropin-releasing hormone (CRH) [18] and arginine vasopressin (AVP) [19], the HPA axis is activated. The hypophyseal portal arteries then release CRH and AVP into the median eminence and carry them to the anterior pituitary gland. After entering the anterior pituitary gland, CRH binds to the pituitary corticotrophs' corticotropin receptor factor (CRF) type 1 receptors (CRFR1). Adrenocorticotropic hormone (ACTH) is produced from pre-pro-opiomelanocortin (pre-POMC) when CRH binds to CRFR1, which then causes ACTH release into the systemic circulation. AVP increases the production and secretion of ACTH through a number of different processes, which are covered in more detail later in this article. The principal stress hormones, glucocorticoids

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(cortisol in humans and corticosterone in rats), are synthesized and released when adrenal cortex zona fasciculata contains melanocortin type 2 receptors (MC2-R), which ACTH binds to after release. In reaction to both internal and external stressors, the body responds best by increasing glucocorticoid levels, which helps the body regain equilibrium. In response to stress, glucocorticoids have positive effects on the immune system, secondary metabolism, and cardiovascular health. Pathologies, such as a higher risk of cardiovascular disease, will arise if glucocorticoid levels are persistently raised as a result of pharmaceutical therapies, endocrine problems, or exposure to chronic stress [20]. Hence, a negative feedback loop at the level of the hypothalamus and pituitary gland closely controls activation of the HPA axis and glucocorticoid release. The latter is the primary mechanism by which glucocorticoids suppress the synthesis and release of ACTH, hence suppressing the adrenal glands' output of glucocorticoids.

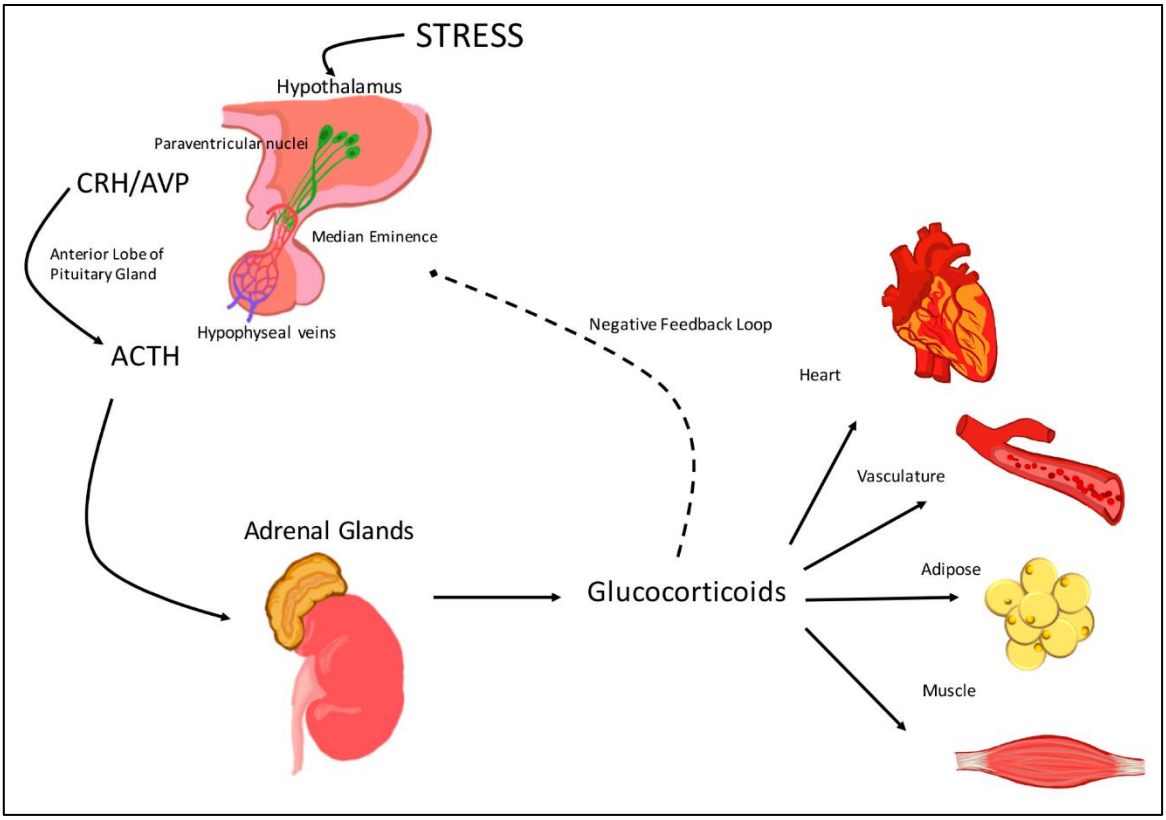

Fig 1. The activation of the hypothalamic-pituitary-adrenal (HPA) axis

Under stressful circumstances, the HPA axis mediates the physiological maintenance of homeostasis. The endocrine, neurological, and immunological systems are all involved in a complex regulatory mechanism that is activated in reaction to this. Numerous diseases, including hypercortisolism, hypertension, and the ensuing vascular damage and cardiac collapse, are associated with dysregulation of these systems. The main hormones regulated by the HPA axis and their effects were outlined in this review, with an emphasis on the function

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of glucocorticoids in the heart and vasculature. Understanding the functions of each of these systems and regulatory mechanisms will help us better understand how the body reacts physiologically to stress, which could ultimately help us identify novel targets for treatment.

Biological response and mechanism of action of phytosterol [21] on Hypothalamic-pituitary-adrenal (HPA) axis

- Testosterone and LH Concentrations in Plasma and Pituitary:

Chronic feeding of PS reduced testosterone levels, particularly at the 800 mg/kg BW dose. Analysis by 2-way ANOVA indicated that testosterone levels were increased after cGnRH-1 injection compared to sham controls ($P < 0.001$); however, testosterone levels were low in PS-treated animals 30 min after cGnRH-1 injection as compared to controls. Although a slight decrease was found in LH levels after long-term PS treatments, the concentrations were not statistically different among the groups before cGnRH-1 injection.

- PS Effects on GnRH and GnIH Gene Expression

Through the regulation of the anterior pituitary gonadotropins (LH and FSH), hypothalamic GnRH and GnIH play crucial roles in reproductive performance. A study shown that hypothalamic GnRH-1 expression was slightly reduced in PS-treated male quails (sham control) compared to controls. However, the expression of GnRH-1 in the brain was significantly improved after a 30-minute cGnRH-1 injection. Moreover, a dose-dependent decrease was found in testicular GnRH-1 expression with or without cGnRH-1 stimulation, particularly at the dose of 800 mg/kg BW after stimulation

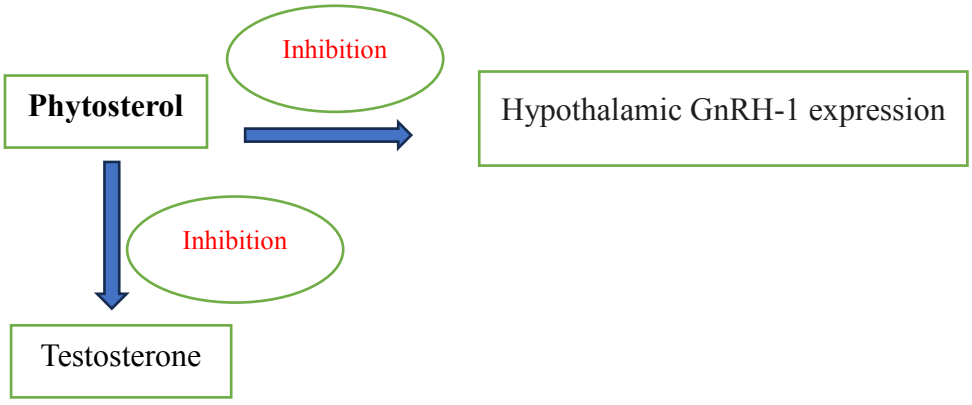

Fig 2. Mechanism of action of phytosterol in Hypothalamic-pituitary-adrenal (HPA) axis

In male rats, administration of β-sitosterol derived from Barleria prionitis roots resulted in a dose-dependent decrease in testosterone, LH, FSH, and sperm quality. However, testosterone, FSH, and sex hormone-binding globulin levels in males, as well as estradiol, FSH, and sex hormone-binding globulin levels in women, were not significantly affected by a daily intake of 2 g of PS for a period of two weeks [22]. In male Japanese quails, we previously discovered that long-term PS gavage dramatically decreased testicular weights and testosterone levels during the developing period (particularly at the dose of 800 mg/kg BW) (unpublished data). Furthermore, during adulthood, leydig cell counts and testosterone

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concentrations were likewise decreased [23]. These results supported our earlier research and revealed that PS feeding in Japanese quail directly lowers testosterone in the testes as opposed to indirectly through the HPG axis.

In a study, male quails given PS showed reduced expression of GnRH-1 in the brain and testes; additionally, testicular expression was much lower in PS-treated animals, even though the injection of cGnRH-1 to male quails did not alter GnRH-1 expression in the brain. These findings contradict a prior study that discovered brain membrane accumulation of β-sitosterol inhibited an inflammatory decrease in GnRH in vitro. While circulating cholesterol cannot enter the brain, PS's lipophilic nature enables it to pass through the BBB efficiently and accumulate in brain cell membranes [24]. Therefore, it is plausible that membrane PS might modify the GnRH response to feedback by reducing the amount of testosterone produced by the testes, or that local aromatization of testosterone to estrogen could downregulate the expression of GnRH-1 in the hypothalamus [25] as a result of PS's estrogenic action, as previously noted [26]. Moreover, elevated GnIH expression in PS-treated mice may also lower GnRH and LH expression.

Male quails fed PS over an extended period of time showed increased expression of GnIH in the testicles and hypothalamus. The earliest evidence of the hypothalamic dodecapeptide GnIH's inhibitory effect on the anterior pituitary gland's production of gonadotropin was found in Japanese quails [27]. GnIH and its receptors are mostly found in Leydig cells and germ cells (spermatocytes and spermatids) in the testicles, as well as in the epididymis of birds, suggesting a potential role for this peptide in the control of gonadal functions. The previous in vitro finding that GnIH and its receptor (GPR147) expression in the gonadotropin-stimulated testis culture significantly reduced testosterone production in house sparrows (Passer domesticus) [28] is further supported by the high expression of GnIH in the testicles even after cGnRH-1 injection. Furthermore, the elevated expression of GnIH in the testicles and brain of male quails treated with PS (800 mg/kg BW) may indicate the autocrine and paracrine activity of GnIH in testicular function. As was previously shown, local expression of GnIH in the testes may also decrease Leydig cell functions, such as the generation of testosterone.

CONCLUSION

In conclusion, adult male quails fed PS alone had lower testosterone concentrations in their plasma and pituitary without appreciably changing their levels of LH. Furthermore, LH release from the pituitary gland and testosterone release from the testes were both markedly increased by cGnRH-1 stimulation. In contrast to control animals, quails fed PS had lower amounts of testosterone and LH.

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CONFLICT OF INTEREST

Authors declared for none conflict of interest.

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