

How stress affects female reproduction: An overview

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Abstract

Chronic anxiety, depression and physical exertion-related stress consistently activate the hypothalamic-pituitary-adrenal axis. Almost each component of this activated axis, such as CRH, ACTH, β -endorphin and glucocorticoids exerts profound inhibitory effects on the hypothalamic-pituitary-ovarian axis and subsequently leads to reproductive failure in females.

The pulsatile secretion of GnRH and the response of gonadotrophs to GnRH stimulation are severely impaired. Increased levels of glucocorticoids moreover inhibit gonadal axis at the hypothalamic, pituitary and ovarian levels and concurrently result in deficient ovarian steroidogenesis, amenorrhea, anovulation, defective endometrial decidualization and implantation, abnormal fetal outcome and delayed parturition.

Stress-associated growth hormone deficiency with a corresponding deficiency of insulin-like growth factor-1 at the level of the pituitary, ovary and uterine endometrium also leads to defective reproductive outcome in females. Moreover, stress-related imbalance between prooxidant and antioxidant forces may cause damage to the released ovum, embryo fragmentation, implantation failure or abortion.

Key words: Stress, Female Reproduction

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Introduction

Individuals frequently encounter stressful conditions. In vertebrates, a major universal response of stress is hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis. Since female hypothalamus contains higher concentration of corticotrophin-releasing hormone (CRH) than the male [1], the reactivity of the HPA axis to stress could reasonably be higher in females than the males [2]. Sustained/prolonged activation of the HPA axis in psychological stress at work place in the women [3], prisoner awaiting execution [4], malnutrition in anorexia nervosa prolonged intense exercise in humans [6],

crowded and long distance transportation of the non-rodent mammals [7], stress of chair restraint in monkeys [8], and restraint stress in laboratory animals [9] all have been shown to inhibit the hypothalamic-pituitary-ovarian (HPO) axis. Hypothalamic-pituitary-adrenal responses increase after chronic or repeated stress despite robust levels of circulating glucocorticoids [11]. Chronic hyperactivation of any of the components of the HPA axis such as, corticotrophin-releasing hormone [12], corticotropin [13], β -endorphin [8], glucocorticoids [14], other associated substances, such as pro-inflammatory cytokines [15], or deficiency of GH-induced insulin-like growth factor-1 [IGF-1] [16] results in reproductive failure in females.

CRH and female reproduction

Stress is a potent activator of CRH release from the hypothalamus and extrahypothalamic sites [17]. CRH type- I receptor knockout mice have however, been shown to have a deficient ability to mount an effective stress response [18]. A direct neural connection between CRH and GnRH has been documented [6]. CRH, the major regulator of the HPA axis and the CRH-induced proopiomelanocortin peptide, such as β -endorphin reduce the hypothalamic GnRH pulse generator activity [8] and concurrently inhibit GnRH secretion [19]. The resulting decrease in pulsatile release of LH [20] subsequently leads to anovulation [21], interruption of endometrial decidualisation [22] and pregnancy wastage [23]. Receptors for CRH are identified in most of the female reproductive tissues including the ovary, uterus and placental trophoblast [24]. CRH in the ovarian theca and granulosa cells [25] is found to reduce ovarian steroidogenesis in a dose-dependent manner [26] which suggests that the ovarian CRH may lead to ovarian failure in women exposed to high psychological stress [27]. At the uterine level, an excess of CRH may induce infertility [28] and at the placental level it may induce premature labor, because stress-induced premature labor due to an excess placental CRH is reversed by CRH antagonist [29]. However, locally produced normal concentration of CRH is proposed to be essential in promoting endometrial decidualisation and implantation [30].

Proopiomelanocortin-derived ACTH, β -endorphin and female reproduction

Stress-induced elevated levels of ACTH inhibit pulsatile release of LH [31] by decreasing responsiveness of the pituitary gonadotrophs to GnRH [13]. Suppressive effect of ACTH on gonadotropin secretion has been recorded in Cushing's disease [32]. CRH activated β -endorphin moreover suppresses GnRH pulses [8] and pulsatile release of LH (33). All these changes result in depression of the pituitary-ovarian axis.

Glucocorticoids and female reproduction

Persistent increase in serum concentration of glucocorticoids in humans [35], rhesus monkeys [35], cattle [36], pigs [37], sheep (38), and laboratory rodents [39] evidently suppresses the hypothalamic-pituitary-ovarian (HPO) axis. Glucocorticoids receptors are found in the hypothalamic GnRH neurons [40] and in the pituitary gonadotrophs [41]. Stress-like glucocorticoid concentration blocks pituitary tissue concentration of GnRH [35] and the responsiveness of the gonadotrophs to GnRH (42) with a resulting

attenuation of LH pulse frequency [34]. An impaired generation of LH surge subsequently results in anovulation (43) as well as menstrual disorders [34]. Glucocorticoids receptors have been demonstrated in the ovaries [44] and ovarian granulosa cell cytosol [45). A direct effect of glucocorticoids could possibly result in follicular atresia [46] by suppressing the action of LH at the receptor level [47]. Glucocorticoids also induce estrogen deficiency by suppressing granulosa cell aromatase activity [48]. As a result, estrogen deficiency is found in anxiety and depression-related stress [49]. Glucocorticoids reduce the number of estrogen receptor [50], tissue uptake of estrogen [51] and estrogen-stimulated DNA synthesis in the uterus [52]. Glucocorticoids also reduce blood flow protein synthesis [54], IGF-1 m-RNA expression [16] and prostaglandins synthesis [55] in the uterus. Most of these estrogen-induced uterine profiles are essentially important for blastocyst implantation [56], endometrial decidualization [22], pregnancy maintenance [57] and parturition [58]. Estrogen deficiency not only impairs luteal steroidogenesis [59], it also jeopardizes receptor expression of estrogen and progesterone in the uterus [60] which may subsequently result in pregnancy wastage [61] or delayed parturition [58] Parental stress-associated shorter gestation, smaller birth weight in humans [62] could possibly be linked to the free access of excess glucocorticoids through placental barrier

GH-IGF-1 axis suppression and female reproduction

Attenuated release of growth hormone (GH) in panic disorder patients (64) has also been recorded in stressed primates [65] and laboratory animals [66]. In humans, elevated levels of glucocorticoids concurrently suppress GH secretion and the effects of IGF-1 on its target tissues Laron dwarfism, sexual maturity is always found to be delayed [68]. GH insensitivity similarly impairs formation of functional corpus luteum of pregnancy [69]. It is therefore proposed that full reproductive potential requires adequate levels of GH-induced IGF-1 in peripheral circulation [70]. IGF-1 receptors have been located in the hypothalamus, pituitary, ovaries and reproductive tract [71]. IGF-1 is found to influence the release of GnRH [72], gonadotropins secretion [70], follicular growth, steroidogenesis and ovulation [73]. Therefore, induction of ovulation in Laron dwarfism by IGF-1 treatment is often successful [74].

Interleukins and female reproduction

Pro-inflammatory cytokine, such as IL-18 [75] acts as a regulator of the HPA axis during stress. Serum levels of IL-18 are found to be elevated in depression and panic disorders [76]. Stressors are found to induce hypothalamic IL expression [15] and elevate pituitary IL-18 synthesis [77] and TNF α in particular suppresses the secretion [78] and surge [79] of LH. Prolonged cytokine exposure directly activates corticotropin and glucocorticoids release [80]. Cytokines, therefore suppress female reproduction directly or indirectly by activating hypothalamic secretion of CRH, pituitary secretion of ACTH and β -endorphin as well as by peripheral elevation of glucocorticoids and inhibition of ovarian steroidogenesis [15].

Oxidative stress and female reproduction

In a healthy body, reactive oxygen species (ROS) and antioxidant remain in balance. When this balance is disturbed, oxidative stress (OS) develops [81]. Stressful conditions depress the cellular antioxidant mechanism and subsequently develop OS [82]. Elevated levels of glucocorticoids in stress cause free radical formation [83] and subsequently decrease sex steroids synthesis [84]. Estrogens have antioxidant effects, therefore its deficiency during stress may lead to an overproduction of ROS [85] which subsequently interferes with oocyte maturation induces embryo fragmentation, implantation failure or abortion [87].

Conclusion

Stress-related hyperactivation of the HPA axis with a corresponding inhibition of the HPO axis may possibly act as the major cause of impaired fecundity in women. The National Survey for Family Growth of USA indicates that the number of women with impaired fecundity has increased to about 35% from 1982 to 1995.

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