



The regulation of the menstrual cycle does not depend solely on hormonal interactions within the hypothalamic-pituitary-ovarian axis, but is also influenced by many external factors, including neurotransmitters and environmental factors. These factors can modulate the pulsatile secretion of GnRH by the hypothalamus, thus affecting the synthesis and release of pituitary gonadotropins (FSH and LH) and, consequently, ovarian function.

Among the neurotransmitters involved in the regulation of the gonadotropic axis, the main ones are catecholamines (dopamine, norepinephrine), serotonin, GABA, and endogenous opioids. Dopamine has an inhibitory effect on the secretion of GnRH, mainly via D2 receptors. Hyperprolactinemia, often due to a pituitary adenoma, can thus slow down the activity of GnRH neurons through an inhibitory effect of prolactin on dopamine, resulting in gonadotropic insufficiency and amenorrhea. Conversely, norepinephrine stimulates the secretion of GnRH, particularly during the peri-ovulatory period, promoting the LH peak and ovulation.

Serotonin has a variable effect on the secretion of GnRH depending on the receptors activated and the cycle phase. In the follicular phase, it tends to inhibit GnRH secretion, while in the luteal phase, it stimulates it. Abnormalities in serotonin neurotransmission could thus be involved in certain menstrual cycle disorders, such as premenstrual syndrome or dysmenorrhea. GABA, the main inhibitory neurotransmitter of the central nervous system, slows down the secretion of GnRH, particularly by modulating the activity of kisspeptin neurons, key stimulators of GnRH neurons. Finally, endogenous opioids (enkephalins, endorphins) have an inhibitory effect on the secretion of GnRH, which could explain the amenorrhea observed in women suffering from anorexia nervosa or bulimia, due to chronic activation of the endogenous opioid system.

Environmental factors, such as stress, nutrition, physical activity or exposure to toxins, can also influence the regulation of the menstrual cycle by acting on the HPO axis. Chronic stress, whether physical or psychological, activates the corticotropic axis and stimulates the secretion of cortisol by the adrenal glands. Cortisol has an inhibitory effect on the secretion of GnRH, which can lead to gonadotropic insufficiency and functional amenorrhea. This is particularly the case for stress related to intense and prolonged physical exercise, as in high-level athletes, or severe psychological stress, as in eating disorders.

Nutrition also plays a key role in the regulation of the menstrual cycle, particularly the availability of energy and essential nutrients. Severe caloric restriction or a deficiency in certain micronutrients (iron, zinc, vitamin D) can disrupt the pulsatile secretion of GnRH and lead to hypothalamic amenorrhea. Conversely, obesity and insulin resistance are often associated with hyperandrogenism and polycystic ovary syndrome (PCOS), characterized by chronic anovulation and infertility. Studies suggest that leptin, a hormone secreted by adipose tissue, could be a link between nutritional status and reproductive function, by modulating the secretion of GnRH.

Finally, exposure to environmental toxins, such as endocrine disruptors, can interfere with the hormonal regulation of the menstrual cycle. Endocrine disruptors are exogenous chemical substances that mimic or block the action of natural hormones, by binding to their receptors or disrupting their synthesis and metabolism. These substances are found in many common consumer products, such as plastics, cosmetics, pesticides or flame retardants. Epidemiological studies suggest that chronic exposure to certain endocrine disruptors, such as bisphenol A or phthalates, could be associated with early puberty, menstrual disorders, infertility or hormone-dependent cancers.

Understanding the mechanisms by which neurotransmitters and environmental factors influence the regulation of the menstrual cycle is essential for the comprehensive management of female reproductive endocrine disorders. It allows for the identification of modifiable risk factors and the proposal of adapted preventive and therapeutic measures, such as stress management, optimization of nutritional status or reduction of exposure to endocrine disruptors. This integrative approach, taking into account the complex interactions between the environment and the endocrine system, is at the heart of functional medicine and public health strategy aimed at promoting women's reproductive health and well-being.

Key points to remember:

- The regulation of the menstrual cycle involves complex interactions between the hypothalamic-pituitary-ovarian axis, neurotransmitters, and environmental factors.
- Neurotransmitters such as dopamine, norepinephrine, serotonin, GABA, and endogenous opioids modulate the secretion of GnRH by the hypothalamus, thus influencing the

synthesis and release of pituitary gonadotropins (FSH and LH) and ovarian function.

- Environmental factors like stress, nutrition, physical activity and exposure to toxins can disrupt the regulation of the menstrual cycle by acting on the HPO axis.

- Chronic stress activates the corticotropic axis and stimulates the secretion of cortisol, which has an inhibitory effect on GnRH secretion, potentially leading to gonadotropic insufficiency and functional amenorrhea.

- Severe caloric restriction or a deficiency in essential micronutrients can disrupt the pulsatile secretion of GnRH and cause hypothalamic amenorrhea, while obesity and insulin resistance are often associated with polycystic ovary syndrome (PCOS).

- Chronic exposure to certain endocrine disruptors could be associated with menstrual disorders, infertility or hormone-dependent cancers.

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