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The Role of Neuroendocrine in Embryo Implantation

Fenting Liu and Rong Li

Abstract

Neuroendocrine integration, an integration of the nervous system and endocrine system as its name implies, plays a critical role in the reproductive system. However, less progress has been made in the particular effects of neuroendocrine on embryo implantation. Recently, some significant knowledges have been gained on the regulation of neuroendocrine in embryo implantation. This chapter will summarize the current state of knowledges about the impaction of neuroendocrine on embryo implantation and discuss potential strategy to get higher pregnancy rate and to reduce recurrent implantation failure (RIF) possibility through modulating the neuroendocrine systems.

Keywords: neuroendocrine systems, embryo implantation, recurrent implantation failure, IVF-ET

1. Introduction

The success of mammalian pregnancy is mostly due to the smoothly embryo implantation into the maternal endometrium/decidua, which is a finely regulated process and requires the adaptation of maternal function to the needs of developing fetus. Human embryo implantation is a complex series of events involving blastocyst attachment, adhesion, and invasion into the endometrial tissue. Under normal circumstances, in order to ensure the consistency of this series, the blastocyst-stage embryo and the uterine endometrium must be collaborated during the "window of implantation" [1]. It has been long established that neuroendocrine is indispensable for mammalian reproduction [2], in which the neuroendocrine cell can synthesize and release various hormones into gonadal organ after receiving neuronal signal. Notably, the hypothalamus is the metronome of reproduction, and its main function is to receive neural signals from the brain and transform these neural signals into an endocrine output, the pulsatile release of GnRH, and other related factors. The pituitary gland, as a link between the brain and other neuroendocrine-related organs, is divided into two lobes. For the anterior lobe, it is related to the regulation of the hypothalamic-pituitary-gonadal axis (HPG axis), hypothalamic-pituitary-thyroid axis (HPT axis), and hypothalamic-pituitary-adrenal axis (HPA axis). For the posterior lobe, it is mainly about the regulation of the hypothalamic-neurohypophysis system [3]. Therefore, the description of an importance of the neuroendocrine to implantation from the aspects above is an enormous and necessary work.

Infertility affects millions of couples worldwide and its treatment has progressed immensely. As one of the most prevalent approaches of treating infertility, in vitro

fertilization and embryo transfer (IVF-ET) is always confronted with recurrent implantation failure [4], which is in the means of the situation when the transferred embryo repeatedly, failed to implant after IVF-ET [5]. A strong association between pregnancy rate following IVF-ET and recurrent implantation failure has been investigated [4], but less studies mention directly about the role of neuroendocrine in recurrent implantation failure. A thorough understanding of the processes governing human embryo implantation would be of significant benefit for the treatment of infertility. Hence, this review provides a summary of current empirical researches on the impacts of neuroendocrine aspects in implantation so that we more understand the maternal environment at the time of embryo implantation and might optimize it by altering neuroendocrine regulation to increase the success rate after IVF-ET.

2. Hypothalamic-pituitary-gonadal axis

An integrated hypothalamic-pituitary-gonadal axis with several main actors including the gonadotropin-releasing hormone (GnRH), the gonadotropins (luteinizing hormone (LH) and follicular-stimulating hormone (FSH)), and the gonadal hormones are recognized as a key mechanism on human reproduction [6]. Hypothalamic gonadotropin-releasing hormone, as a crucial regulator of the HPG axis, with characteristic pulsatile secretion pattern, plays a dominant role in the endocrine control of reproduction and its possible effects on implantation by regulating downstream hormones which have been widely concerned so far [7]. Two GnRH molecules termed GnRH I (default as GnRH) and GnRH isoform II (GnRH II) can be found in humans, and both of them play an important role during the implantation period as shown in **Figure 1** [6, 8].
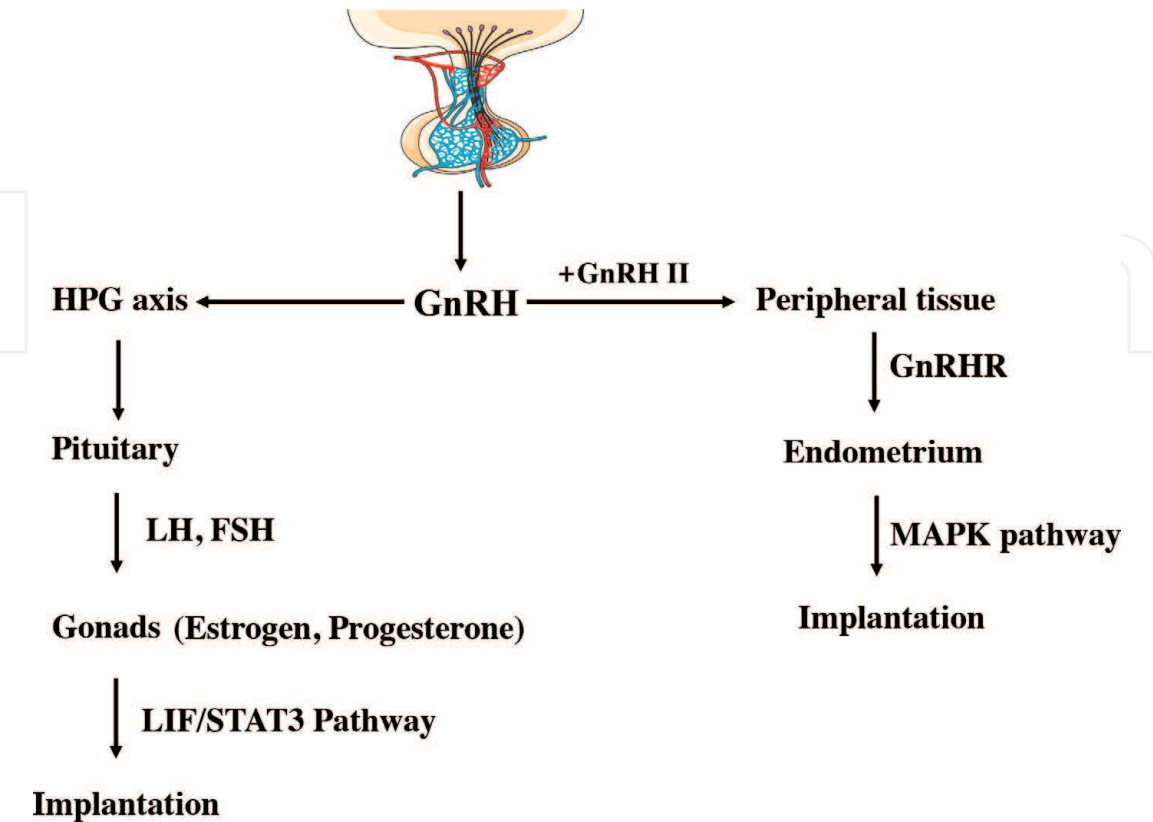

Figure 1.
Schematic of the HPG axis functions in implantation.

2.1 GnRH functions in implantation via the pituitary-gonadal axis

In the HPG axis, after releasing from the hypothalamus in a pulsatile manner, GnRH then binds to GnRH receptors (GnRHRs) on the pituitary gland, in response, that LH and FSH are synthesized and secreted in pulse by the pituitary to match the GnRH signal. Subsequently steroid hormones including progesterone and estrogen are released from the gonads and form a loop by exerting a positive or a negative feedback effect on GnRH releasing and gonadotropin [8]. Although it has been reported that human type II receptor for GnRH II shows specific expression of the receptor in the anterior pituitary and it also has been suggested that these receptors might act together to regulate the biosynthesis and secretion of both LH and FSH, further investigation should be completed [9, 10]. Thus here, we focus on the functions of GnRH in implantation via the pituitary-gonadal axis. Since natural GnRH has a short half-life, several GnRH synthetic analogues have been developed including agonists and antagonists, which can be used to stimulate or block, respectively, the pituitary-gonadal axis in an assisted reproductive technology (ART), particularly often applied to prevent premature LH surge [11]. In women undergoing IVF, GnRH agonist may improve the luteal phase support, used to trigger the final oocyte maturation and to improve implantation and live birth rates [12]. Although the effects of embryo implantation are still controversial, both of them are thought to tightly correspond to the pituitary-gonadal axis and eventually result in the fluctuation of the estrogen and progesterone level [6, 11].

Estrogen and progesterone regulate uterine cell proliferation and are necessary for the changes in both the blastocyst and uterine epithelium for successful adhesion, so an imbalance between estrogen and progesterone during the luteal phase may lead to implantation defects [13]. Thus, it is quite clear that a deep understanding of the action of estrogen and progesterone on the human endometrium will allow a clear insight into the mechanism of determining endometrial receptivity in embryo implantation.

So far, the molecular mechanism of estrogen regulation of maternal uterus in implantation remains unclear. Some studies implicated that estrogen was not essential for embryo implantation due to its receptor disappearance at the time of implantation [14, 15]. However, some studies believed that only after sufficient exposure to estrogen could progesterone exposure drive the endometrial receptivity to embryo implantation in a brief period [16, 17]. In addition, it has been proven that early growth response 1 (Egr1) as the downstream target is regulated by estrogen expression via leukemia inhibitory factor-signal transducer and activator of transcription 3 (LIF-STAT3) signaling pathway in the uterus of a mouse, and it further regulates stromal cell decidualization by regulating Wnt4 [18]. Furthermore, some studies suggested that estrogen was a trigger to close the window of implantation via insulin-like growth factor 1 pathway and made the endometrium "receptive" for blastocyst implantation [19, 20].

Progesterone production reaches its peak during the mid-luteal phase of the cycle, and this is the time when the secretory endometrium is appropriately prepared for the implantation of an embryo [8]. During the luteal phase, progesterone is produced, in turn stimulating the proliferation of the lining of the uterus to prepare for implantation by blocking the production of matrix metalloproteinase (MMP) and stimulating the production of tissue factor (TF) and plasminogen activator inhibitor 1 (PAI-1) [21, 22]. The phenomenon that a luteal phase support with progesterone can improve the implantation and pregnancy rates indicates lower progesterone and lower implantation [23, 24]. A review by Yoshinaga further confirms that progesterone is also an indispensable factor for successful implantation and pregnancy maintenance [19].

2.2 GnRH functions in implantation via peripheral reproductive tissue

The expression of GnRH/GnRH receptor (GnRHR) system and GnRH II in the female reproductive tissues has been widely reported. Therefore, in addition to its well-known function on the HPG axis, GnRH and GnRH II may also regulate extrapituitary reproductive tissues through the local GnRHRs [24]. Both GnRH and GnRH II have a dynamic pattern during the process of implantation; they may regulate the procedure of trophoblast local invasion and embryo implantation through the regulation of the proteolytic degradation of the extracellular matrix of the endometrial stroma and the motility of decidua endometrial stromal cells [6]. During the luteal phase of the menstrual cycle, high levels of both GnRH and GnRHR are expressed in the endometrium; thus the blastocyst will prefer to attach the endometrial epithelial surface and go through implantation [5, 7]. In mammals, the distribution of GnRH II is more wide in peripheral tissue than that of GnRH I, which hypothesized that GnRH II has extra functions and a possible regulator in endometrial environment [9]. Huang et al. found that GnRH II could directly regulate the behavior of endometrial cells. An embryo implantation failure may be due to the dysfunction of human decidual endometrial stromal cell motility via different pathways [25]. The hallmark events of implantation are represented by tissue remodeling and angiogenesis, which are regulated by the activity of MMPs and tissue inhibitors of MMPs (TIMPs) [26]. It has been demonstrated that GnRH II may contribute to the regulation of the cell motility of decidual endometrial stromal cells via the binding of GnRH-IRs, in turn stimulating the expression of MAPK-mediated proteinases MMP-2 and MMP-9, which specifically degrade the basement membrane and then facilitate the invasion and migration of decidual endometrial stromal cells [6].

Given the evidence above, no matter via the GnRHR in the pituitary-gonadal axis or via GnRHR in peripheral reproductive tissue, both pathways of GnRH functions on implantation are potential candidate therapeutic targets for improving the embryo implantation rate in the treatment of infertility.

3. Hypothalamus-pituitary-adrenal axis

In addition to the well-established role of the HPG axis in implantation and infertility, the role of the hypothalamic-pituitary-adrenal axis (HPA axis) in the reproductive tract also cannot be neglected. A hormone cycle also exists in the HPA axis. After receiving neuronal signals, the corticotropin-releasing hormone (CRH) secreted from the hypothalamus transports to function in the pituitary gland to release adrenocorticotropic hormone (ACTH) and subsequently acts on the adrenal cortex to produce glucocorticoid (GC) hormones (mainly cortisol in humans). Eventually, the glucocorticoid hormones will act back on the hypothalamus and pituitary (to suppress CRH and ACTH production) in a negative feedback cycle [3]. The hormone within the HPA axis can act at different levels of the HPG axis as well as the uterus and other peripheral tissues; therefore we will discuss it in the following part, respectively.

3.1 CRH functions in implantation

CRH is taking the lead in the HPA axis, and its expression is mediated by its membrane receptors including CRH-R1 and CRH-R2 [27]. According to the research, upregulating gal-1 expression by acting through the CRHR1 in Ishikawa cell line and macrophages indeed indicates that CRH plays a critical role in

implantation [28]. CRH has tremendous effects on implantation since it can impact the HPG axis at different levels. In mammals, numerous GnRH-containing neurons in the hypothalamus have been found to express both CRH receptors (CRH-R1, CRH-R2) which can exert an estradiol-dependent effect of directly influencing GnRH release in mice and rats, leading to a comparable change in serum LH levels, and eventually contribute to the difference of response during implantation procedure [29].

Besides, CRH serving as an autocrine and paracrine modulator is expressed in peripheral tissue of the female reproductive system, including the endometrium [30]. Early pregnancy, containing a higher concentration of CRH in the endometrium of a rat and killing activated T lymphocytes, can promote implantation and maintain pregnancy [31]. Furthermore, CRH can downregulate the expression of carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) by extravillous trophoblast cells, thereby controlling proper trophoblast invasion during implantation [32].

3.2 ACTH functions in implantation

Besides the downstream effects from CRH, ACTH also has its certain effects in implantation, though fewer studies have been investigated. Similar to CRH, chronic ACTH stimulation also impacts on the HPG axis by inhibiting LH secretion to impair the procedure of implantation. In the contrary, acute ACTH treatment may result in a rapid increase of progesterone which will lead to a positive feedback and induce the elevation of LH and FSH within the HPG axis [33]. A reference implied that exogenous ACTH produced postponed implantation effects and resulted in the high incidence of miscarriage and embryonic resorption [34]. However, further investigation should be performed.

3.3 Glucocorticoid functions in implantation

Glucocorticoid (GC) is a measurement of stress and leads to well-characterized profound reproduction function by suppressing the HPG axis and influencing the peripheral tissue [35]. Some studies indicated that maintaining the administration of glucocorticoids could improve pregnancy rates and outcomes both in animals and human beings [36, 37]. Therefore, to elucidate the role of glucocorticoids in implantation, the following two dimensions will be depicted.

3.3.1 Via the HPG axis

As a pivotal hormone in the HPA axis, GC has been demonstrated with the function of decreasing the release of GnRH from the hypothalamus, both directly and indirectly inhibiting GnRH pulses or inhibiting upstream regulators of GnRH release, in turn exerting direct effects on the anterior pituitary of the release of the gonadotropins, eventually influencing the steroid hormones from gonads [38].

GnRH-containing neurons also express glucocorticoid receptors (GRs) and have an effect of directly inhibiting GnRH release in mice and rats, leading to a decrease of serum LH [39]. Besides, evidences showed that chronic corticosterone (CORT) treatment could inhibit directly GnRH release in the hypothalamus and influence on implantation and reproduction [29, 40]. Another method is via modulating the hormones upstream of GnRH, mainly including kisspeptin (KISS1) and RFamide-related peptide-3 (RFRP-3) [41]. Both of these two hormones express GRs, implying that they could potentially respond to GC and suppress the release of GnRH, leading to the fluctuation of LH and FSH from the pituitary [42].

In addition to the secondary signaling effects on the pituitary, glucocorticoid can directly inhibit its secretion by different mechanisms at the level of the pituitary, including modulating the sensitivity of the pituitary to changes in GnRH secretion and further decreasing the synthesis and secretion of LH and FSH from the pituitary [43]. However, a study showed that the effects of glucocorticoid directly on the pituitary in secretion and synthesis were highly variable [44]; thereby further studies should be performed in this field.

The gonads, as the lowest level in the HPG axis, are another crucial component for glucocorticoids to regulate, which GC exhibits both stimulatory and inhibitory effects on it [45]. GC can modulate the expression of the LH receptor (LHR) on the gonads, and it also can inhibit the synthesis of testosterone (T), estrogen (E2), and progesterone (P). Hence, it can easily dysregulate these signals and cause profound fertility problems in both ovarian function during ovulation and uterine function during fertilization, implantation, and pregnancy [43].

3.3.2 Via the peripheral tissue

In addition to the effects of GC and GR on the central nervous system, GR expression also has been demonstrated in the peripheral tissue [35]. Mifepristone, a potent high-affinity GR antagonist, also implied the effects of GC regulating embryo attachment and invasion [46]. However, direct evidence implicating GR signaling in uterine biology has been described only recently. The study suggested that decreased blastocyst implantation rate and subsequent defects in stromal cell decidualization were found out in a uterine-specific glucocorticoid receptor (GR) knockout (uterine GR KO) mouse. As a master regulator, GC repressed some important gene expression and eventually influenced the uterine environment [35].

4. Hypothalamus-pituitary-thyroid axis

There are three dominant hormones within the hypothalamus-pituitary-thyroid axis (HPT axis), such as thyrotropin-releasing hormone (TRH), thyrotropin-stimulating hormone (TSH), and thyroid hormone (TH: T3 and T4) [3]. When it comes to pregnancy accompanied with thyroid disease, we always ascribe subfertility and recurrent miscarriage to either hypothyroidism or hyperthyroidism [47]. In in vivo studies, it has been demonstrated that hypothyroidism might have a dual effect on pregnancy, by influencing implantation at a very early stage and regulating placental development at the later stage [48]. Moreover, thyroid hormone receptors, expressed in the endometrium and trophoblast during implantation, can influence the feto-maternal interface [49]. In in vitro studies, it has been proven that TH is involved in the bidirectional cross talk between the blastocyst and endometrium during implantation. In hypothyroid females, lower levels of both ISP1 and ISP2 (two key regulators of embryo implantation) could be found in the uterus [48]. Furthermore, TH impacts both the endometrium and the trophoblast, via either directly or indirectly through TH effects on the synthesis and activity of implantation-mediating molecules [50]. Although a research indicated that when TSH value was below 2.5 mIU/L, no association varying TSH values and implantation was detected [51]. TH receptors (TRs) and TSH receptors (TSHRs) were broadly presented in the feto-maternal unit [50] and even increase the expression of TSHR, TRa1, TRa2, and TRb1 in endometrial cells during peri-implantation [52]. Moreover, TH synthesis is related to several transcripts, including prolyl 4-hydroxylase beta (P4HB), a molecular chaperone involved in endocytosis of immature

thyroglobulin (Tg) molecules, thyroid peroxidase (TPO), and Tg, which also could be discovered in the endometrium [53].

Beyond that, hypothyroidism can result in development of reduced endometrial thickness, because of reducing the uterine cells' estrogenic response [54]. In addition to affecting the proliferation and maturation of endometrial tissue, TH also could have profound effects on the regulation of the HPG axis and subsequently on implantation [55]. Angiogenesis and endometrium remodeling are considered as pivotal events for successful implantation, decidualization, and placentation, while it has been demonstrated that TH can exert an important role in angiogenesis via both genomic and non-genomic mechanisms in a variety of animal models [56]. Besides, TH regulates integrin $\alpha\nu\beta3$, a class of cell adhesion molecules (CAMs) that interacts with extracellular matrix (ECM) ligands, matrix metalloproteinases (MMPs), and other CAMs, playing a critical role in the cascade of events to successful implantation [57].

In summary, it is clearly suggested that both TSH and TH are essential players in the mechanism of regulating implantation based on current experimental and clinical evidences. However, less evidence shows the influence of TRH on the implantation procedure; thus further exploration needs to be continued.

5. Hypothalamo-neurohypophyseal system

Hormones from the posterior lobe of the pituitary also play an essential role in neuroendocrine and implantation. The hypothalamo-neurohypophyseal system is composed of the hypothalamus and posterior pituitary, regarded as the site for secretion of neurohypophysial hormones, classically including oxytocin and vasopressin [58].

It is well established that apt uterine contractile activity uterus is vital to successful implantation, and it has been proven that both oxytocin and vasopressin receptors are expressed in the uterus, which are closely relevant to the contractile activity of the uterus [49]. Both oxytocin and vasopressin receptors belong to the class I family of G-coupled receptors, regulating uterus contraction via a central or peripheral pathway [59]. So far, massive research literature indicated that oxytocin and vasopressin antagonist treatment was effective in priming of the uterus for implantation and consequently improved the implantation rate after IVF [58, 60–62].

Atosiban, a mixed vasopressin V1a and oxytocin receptor antagonist, have been demonstrated to improve uterine receptivity, provide a decrease in uterine contractile activity, and increase endometrial blood perfusion in women undergoing embryo transfer [58]. Another important effect of atosiban is to decrease endometrial perfusion and embryonic survival rate by inhibiting the stimulation of the endometrial production of prostaglandin F2a in an animal model [63]. With the beneficial of improving uterine environment, atosiban can be a specific treatment for the improvement of implantation rate following IVF-ET [64]. Thereby, the novel class of drugs based on these two receptors and its relative pathway for improving implantation rate and pregnancy outcomes still need to be further explored.

6. Neuroendocrine systems improve implantation rate in IVF-ET

Infertility gradually becomes an epidemic problem and brings an enormous burden on about 10% of the couples in child-bearing age [65]. Implantation concerns frequently arise in couples with infertility, especially in the setting of assisted

reproductive technology (ART) cycles [4]. Regardless of the impressive development in ART, there are still approximately 10–15% of the infertile couples suffering from recurrent implantation failure (RIF) [2].

According to the literature, factors involved in recurrent implantation failure can be summarized in three aspects such as decreased endometrial receptivity, defective embryonic developments, and others [2, 4]. However, only the evidence about different axes of hormones from neuroendocrine influencing the procedure of implantation has been concluded in this paper, and it mainly focuses on the aspect of decreasing maternal endometrium receptivity but less on blastocyst (**Table 1**).

Furthermore, the relevant literatures of ACTH, TRH, as well as TSH on implantation procedure are less, and their mechanisms are not elaborated enough. Hence, studies aiming to better define the association between neuroendocrine system and implantation processes should be further investigated, which may lead to further therapeutic intervention, thereby optimizing embryo implantation and eventually improving the success rate following IVF-ET.

HPG axis	GnRH and GnRH-II	Altered expression of adhesive molecules
	LH and FSH	–
	Estrogen and Progesterone	Endometrium thickness
		Altered expression of adhesive molecules
		Immunological factors
		Prevent thrombus formation
HPA axis	CRH	Modulating HPG axis
		Altered expression of adhesive molecules
		Immunological factors
	ACTH	Modulating HPG axis
	GCs	Modulating HPG axis
		Regulating uterine environment
		Embryo attachment and invasion
HPT axis	TRH	–
	TSH	Feto-maternal interface
	TH	Feto-maternal interface
		Endometrium thickness
		Modulating HPG axis
		Angiogenesis
		Altered expression of adhesive molecules
Hypothalamus-neurohypophyseal system	Oxytocin &Vasopressin	Uterine contractile activity
		Endometrium perfusion

Table 1.
Mainly aspects of neuroendocrine hormones involved in improving the condition of RIF.

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