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Role of the Kiss1/Kiss1r system in the regulation of pituitary cell function

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ABSTRACT

Kisspeptin (Kiss1) is an amidated neurohormone that belongs to the RF-amide peptide family, which has a key role in the control of reproduction. Specifically, kisspeptin regulates reproductive events, including puberty and ovulation, primarily by activating the surface receptor Kiss1r (aka GPR54), at hypothalamic gonadotropin-releasing hormone (GnRH) neurons. More recently, it has been found that kisspeptin peptide is present in the hypophyseal portal circulation and that the Kiss1/Kiss1r system is expressed in pituitary cells, which suggest that kisspeptin could exert an endocrine, paracrine or even autocrine role at the pituitary gland level. Indeed, mounting evidence is pointing towards a direct role of kisspeptin in the control of not only gonadotropins but also other pituitary secretions such as growth hormone or prolactin. In this review, we summarize the most recent advances in the study of the role that the Kiss/Kiss1r system plays in the control of pituitary gland function, paying special attention to the direct role of this neuropeptide on pituitary cells and its interactions with other relevant regulators.

1. Introduction

Kisspeptin, encoded by the Kiss1 gene, is an amidated neurohormone, which belongs to the RF-amide peptide family and is known for its key role in reproduction by regulating reproductive events, including puberty and ovulation, primarily via the tight control of gonadotropin-releasing hormone (GnRH) neurons (Pinilla et al., 2012; Roa et al., 2011). Kiss1 gene, discovered two decades ago while searching for melanoma metastasis-suppressor genes (Lee et al., 1996), has been shown to encode four N-terminal truncated and C-terminal amidated peptides with 54, 14, 13, and 10 amino acids, derived from a 145 amino acid precursor protein. These products were subsequently isolated from human placenta and designated as kisspeptin-54 (also named as metastin (Ohtaki et al., 2001)), kisspeptin-14, kisspeptin-13, and kisspeptin-10 (Muir et al., 2001; Kotani et al., 2001; Stafford et al., 2002). Several years later (2001), three independent laboratories identified the orphan G-protein-coupled receptor 54 (GPR54) as the cognate receptor for kisspeptin (Ohtaki et al., 2001; Muir et al., 2001; Kotani et al., 2001) and, consequently, it has been most recently suggested to be re-named as Kiss1r (Kirby et al., 2010; Gottsch et al., 2009). These seminal studies demonstrated that the different kisspeptin peptides bind with equal affinity and efficacy to this receptor (Kotani et al., 2001; Ramaswamy et al., 2009; Smith et al., 2008) and, for this reason, most research has been implemented using kisspeptin-10.

Further studies demonstrated that kisspeptin is the most potent activator of GnRH neuron excitability (Han et al., 2005). In particular, endogenous (Liu et al., 2011) and exogenous (Han et al., 2005; Dumalska et al., 2008; Liu et al., 2008; Pielecka-Fortuna et al., 2008; Zhang et al., 2008) kisspeptin binds with nanomolar efficacy (EC50 = 3–5 nM) to the Kiss1r expressed on the cell body and/or proximal dendrites of most GnRH neurons (Pielecka-Fortuna et al., 2008; Zhang et al., 2008), which has been shown to cause a

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depolarization of the neuron *in vitro* and *in vivo* (Constantin et al., 2013).

However, kisspeptins have also been shown to be able to modulate the activity of other hypothalamic and brain neurons such as those located at the supraoptic (SON) and paraventricular (PVN) nuclei (Scott and Brown, 2013; Zmora et al., 2014). In addition, kisspeptin gene products were found to be present in ovine hypophyseal portal blood (Smith et al., 2008), and Kiss1 and Kiss1r are widely distributed not only in the brain but also in other tissues including the pituitary gland (Clarkson et al., 2009), suggesting that kisspeptins might also act as endocrine, paracrine and/or autocrine mediators in the modulation of hormonal secretions from the anterior pituitary.

In this review, we summarize the most recent advances in the study of the role that the kisspeptin/Kiss1r system plays in the control of pituitary gland functioning, paying special attention to the direct role of this neuropeptide on pituitary cells and its interactions with other relevant regulators.

2. Presence of Kiss1 and Kiss1r in pituitary gland

The expression of Kiss1 and Kiss1r is not restricted to the central nervous system inasmuch as it has been reported by different laboratories that this system is expressed in numerous tissues including pituitary gland (Clarkson et al., 2009). Indeed, the presence of the Kiss/Kiss1r system has been described in the pituitary gland of different species such as rodents, goldfish, ewes, primates and humans (Muir et al., 2001; Kotani et al., 2001; Ramaswamy et al., 2009; Smith et al., 2008; Gutierrez-Pascual et al., 2007; Richard et al., 2008; Yang et al., 2010; Quennell et al., 2010). Of note, one of the first studies exploring the expression pattern of KISS1/KISS1R system was carried out by quantitative PCR analysis in a wide set of human tissues (Muir et al., 2001). Therein, the authors demonstrated that KISS1R mRNA was extensively present in human tissues, with high expression levels in the brain and placenta and a more modest expression in other tissues, including the pituitary gland. On the contrary, KISS1 mRNA was detected at low levels in different human tissues including the pituitary, but was absent in the placenta and central nervous system (Muir et al., 2001). Remarkably, similar results were reported in rodents by several independent studies (Gutierrez-Pascual et al., 2007; Richard et al., 2008; Kinoshita et al., 2005), which demonstrated a low, but detectable, expression levels of Kiss1 and Kiss1r in rat pituitaries.

To complement these data, additional studies were implemented to localize the production of kisspeptins in the different areas of the rat pituitary by immunohistochemistry, which demonstrated that kisspeptin-10 immunoreactive cells were mainly restricted to the anterior lobe, with some positive cells in pars intermedia; while immunoreactive cells were absent in pars nervosa (Richard et al., 2008). Furthermore, dual fluorescence labeling assays performed in rats showed that some kisspeptin-10 immunoreactive cells were not stained with luteinizing hormone (LH) beta polypeptide (LHβ) antibody while all LHβ-immunoreactive cells were stained with kisspeptin-10 antibody (Richard et al., 2008), suggesting that kisspeptins could be expressed in other types of pituitary cells. However, a posterior study on pituitary glands from male baboons (*Macaca mulatta*) using dual immunofluorescence showed a restricted localization of kisspeptin cells in the intermediate lobe with some immunopositive cells scattered in the periphery of the anterior lobe. In this study, kisspeptin co-localized with alpha-melanocyte-stimulating hormone (alpha-MSH) cells in the intermediate lobe and with adrenocorticotropic hormone (ACTH)-immunopositive cells in the adenohypophysis with no evidence for co-localization of kisspeptin with gonadotropes, somatotropes or lactotropes in male baboons (Ramaswamy et al., 2009).

Of note, the presence of Kiss1r was also studied in rats with a similar approach showing that Kiss1r immunoreactive cells were present in anterior lobe but absent in pars intermedia and pars nervosa. In addition, dual immunofluorescence revealed that all Kiss1r-immunoreactive cells were co-localized with LHβ-immunoreactive cells and that Kiss1r co-localized with Kiss1 in gonadotropes (Richard et al., 2008). Alternatively, Kiss1r transcript levels have been also detected by RT-PCR analysis in enriched cellular fractions of ovine pituitary cells (lactotropes, somatotropes and gonadotropes) (Smith et al., 2008), indicating that the receptor is expressed in gonadotrope-enriched cell fraction, but also in lactotropes and somatotropes fractions (Smith et al., 2008). Indeed, these results are consistent with a more recent study implemented in goldfish that demonstrated that Kiss1r expression was present in immuno-identified gonadotropes, lactotropes, and somatotropes (Yang et al., 2010).

Although partially contradictory, these observations suggest the presence of the Kiss1/Kiss1r system at the pituitary gland of a wide variety of species and provide evidence of a possible paracrine and/or autocrine loop of the Kiss1/Kiss1r system in several pituitary cell subtypes. However, further studies would need to be implemented in order to precisely identify the specific pituitary cell subtypes expressing Kiss1 and Kiss1r and to determine if the components of the Kiss1/Kiss1r could exhibit a species-dependent and pituitary cell-type specific pattern of expression.

3. Effects of kisspeptins in the control of the function of different pituitary cell types

The pituitary gland is comprised by the neurohypophysis (posterior lobe) and the adenohypophysis (consisting of the anterior and intermediate lobes), which are morphologically distinct structures that exhibit remarkable functional interplays (Asa De Grootet al, 2000). The pituitary gland is a central regulator of reproduction but also growth and endocrine physiology and conveys signals from the hypothalamus to various target organs (Musumeci et al., 2015). Indeed, since the pituitary synthesizes and/or releases various hormones that modulate the function of multiple peripheral organs to regulate vital processes such as growth, puberty, metabolism, stress responses, reproduction, and lactation (Musumeci et al., 2015), the functioning of this gland is strictly controlled by central, peripheral and local factors (Schwartz, 2000), wherein Kiss/Kiss1r systems is emerging as a novel pivotal regulator (Liu and Herbison, 2016).

3.1. Effects on neurohypophysis

The neurohypophysis or posterior pituitary is a large collection of axonal projections from the magnocellular neurons localized at the SON and PVN nuclei of the hypothalamus that store and release the neurohypophyseal hormones oxytocin and vasopressin (Pearson and Placzek, 2013).

Interestingly, one of the first neuroendocrine observations associated to intravenous administration of kisspeptin was the stimulation of oxytocin secretion in rats (Kotani et al., 2001), which is consistent with the fact that intravenous kisspeptin increases the firing rate of oxytocin neurons in the hypothalamic SON of rats (Scott and Brown, 2011, 2013). However, intracerebroventricular (icv) administration of kisspeptin does not alter oxytocin firing in female rats under normal conditions (Scott and Brown, 2011, 2013), while icv treatment of kisspeptin is able to activate oxytocin neuron firing during the late-pregnancy and lactation (Scott and Brown, 2013). Remarkably, Kiss1r does not seem to be expressed in oxytocin neurons of the SON in rats or mice (Lee et al., 1999;