Cell Calcium 67 (2017) 138–147

Contents lists available at ScienceDirect

Cell Calcium

journal homepage: www.elsevier.com/locate/ceca

Review

Transient receptor potential (TRP) channel function in the reproductive axis

Viktoria Götz[a], Sen Qiao[a], Andreas Beck[a,b], Ulrich Boehm[a,*]

[a] Pharmacology and Toxicology, Center for Molecular Signaling (PZMS), Saarland University School of Medicine, Homburg, Germany
[b] Center of Human and Molecular Biology (ZHMB), Saarland University, Homburg, Germany

ARTICLE INFO

Article history:
Received 23 March 2017
Received in revised form 19 April 2017
Accepted 19 April 2017
Available online 3 May 2017

Keywords:
Reproduction
Hypothalamus
Pituitary
Gonads
TRP channels
TRPC channels
TRPC5
Knock-out
Plasticity
Gonadotropes
Kisspeptin neurons
GnRH neurons
Genetic labeling
Ca^{2+} imaging
Genetic Ca^{2+} indicator
GCaMP3
Whole-cell patch clamp
RNA-sequencing
Heat map

ABSTRACT

Transient receptor potential (TRP) channels play important functional roles in the signal transduction machinery of hormone-secreting cells and have recently been implicated in reproductive physiology. While expression studies have demonstrated TRP channel expression at all levels of the hypothalamic–pituitary–gonadal (hpg) axis, functional details about TRP channel action at the level of the individual cells controlling reproduction are just beginning to emerge. Canonical TRP (TRPC) channels are prominently expressed in the reproductive center of the neuroendocrine brain, *i.e.* in kisspeptin and gonadotropin-releasing hormone (GnRH) neurons. Kisspeptin neurons are depolarized by leptin *via* activation of TRPC channels and kisspeptin depolarizes GnRH neurons through TRPC4 activation. Recent studies have functionally identified TRPC channels also in gonadotrope cells in the anterior pituitary gland, which secrete gonadotropins in response to GnRH and thus regulate gonadal function. TRP channel expression in these cells exhibits remarkable plasticity and depends on the hormonal status of the animal. Subsequent functional analyses have demonstrated that TRPC5 in gonadotropes contributes to depolarization of the plasma membrane upon GnRH stimulation and increases the intracellular Ca^{2+} concentration *via* its own Ca^{2+} permeability and *via* the activation of voltage-gated Ca^{2+} channels. However, conditional gene targeting experiments will be needed to unambiguously dissect the physiological role of TRPC channels in the different cell types of the reproductive axis *in vivo*.

Contents

* Corresponding author at: Experimental Pharmacology, Center for Molecular Signaling (PZMS), Saarland University School of Medicine, Bldg 61.4, 66421 Homburg, Germany.
E-mail address: ulrich.boehm@uks.eu (U. Boehm).

http://dx.doi.org/10.1016/j.ceca.2017.04.004
0143-4160/

1. The reproductive axis

Proper functioning of the hypothalamic–pituitary–gonadal (hpg) axis (Fig. 1) ensures reproduction in vertebrates. While several major cellular players within the hpg axis have been identified and extensively characterized, important questions regarding the physiology of the reproductive axis remain unanswered. For example, how precisely releasing hormone pulses are shaped in particular in the female reproductive center of the brain and how those pulses with their different amplitudes and frequencies are decoded in the pituitary gland and integrated with steroid hormone feedback from the gonads is – despite intense research and hundreds if not thousands of research papers – still not fully understood. Recent results have implicated TRP channels in reproductive physiology with specific emphasis on the canonical TRP (TRPC) subfamily. This review summarizes our current understanding of TRP channel function within individual cells of the reproductive axis and provides an outlook on future experiments needed to dissect the role of TRP channels in reproduction *in vivo*.

1.1. The reproductive center of the neuroendocrine brain

A few hundred neurons scattered throughout the preoptic area of the hypothalamus secrete gonadotropin-releasing hormone (GnRH), the master molecule of reproduction [1,2]. Starting with the onset of puberty, GnRH is released into the hypophysial portal vasculature from axon terminals at the median eminence [1]. GnRH is secreted in pulses differing in frequency and amplitude and depending on the hormonal status of the animal [3–5]. Upstream of GnRH neurons are neurons that release kisspeptin, another neurohormone and a very potent activator of GnRH neurons *via* GPR54 (KiSS1 receptor) [6,7], a Gq/11-protein coupled receptor. GnRH and kisspeptin neurons are core components of the neural circuits underlying reproductive physiology and behavior in the vertebrate brain (Fig. 1). It is important to note however, that kisspeptin and GnRH function may not just be restricted to reproduction particularly in adult animals. The two major kisspeptin neuron populations in the anteroventral periventricular nucleus (AVPV) and in the arcuate nucleus (ARC) of the adult hypothalamus project to many brain areas not containing GnRH neurons [8]. These data raise the possibility that kisspeptin is acting on other neurons in areas not (yet) linked to reproduction. Consistent with this, GnRH neurons constitute only a minority of the GPR54 neuron population in the adult mouse brain [9]. Likewise, GnRH fibers project to many areas other than the median eminence and genetic analyses have shown that GnRH-responsive neurons expressing the GnRH receptor are located in different areas of the brain including hippocampus, amygdala and cortex [10,11]. This may be important to keep in mind when phenotyping kisspeptin and/or GnRH-specific conditional TRP knock-out mice.

1.2. The pituitary gland

Gonadotrope cells in the anterior pituitary gland integrate hormonal signals from both the brain and the gonads and provide a means of communication and thus a functional link between those tissues (Fig. 1). Gonadotropes decode GnRH pulses from the median eminence and fluctuating steroid hormone levels to adapt luteinizing hormone (LH) and follicle-stimulating hormone (FSH) production and release to the hormonal status of the animal [1,2,4,5,12]. Information about the individual ion channels involved in the physiological activation of primary gonadotropes and their adjustment to different hormonal stages are just beginning to emerge. Most of the experiments to unravel signal transduction pathways in these cells were actually not conducted in primary gonadotropes, but in cell lines [13,14] or in dissociated pituitary cells [15–17]. While the physiological relevance of data about molecular signaling in immortalized tissue culture cells is generally questionable, recent data suggest cell networks and complex cellular interactions in the anterior pituitary gland [18], indicating the necessity to study gonadotrope cells in situ.

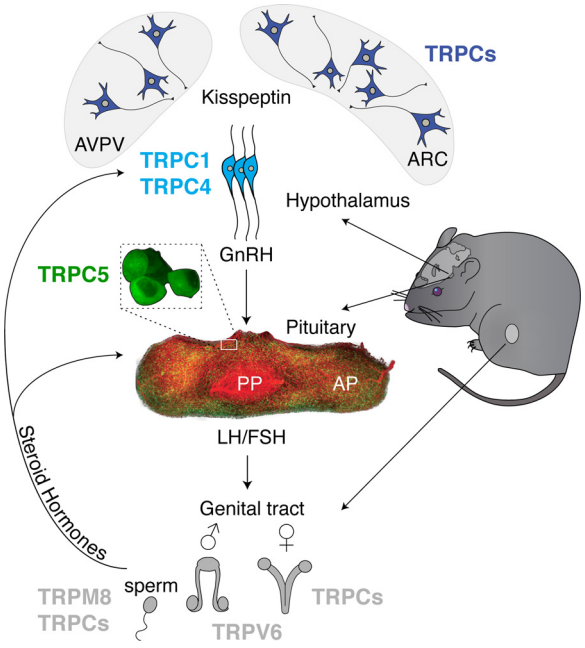

Fig. 1. The hypothalamus–pituitary–gonadal (hpg) axis. Kisspeptin neurons in the hypothalamus release kisspeptin, which acts on GnRH neurons *via* kisspeptin/GPR54 signaling. GnRH neurons release GnRH into the hypophyseal portal vasculature to act on the gonadotrope cells in the anterior pituitary gland. By binding to the GnRH receptor, GnRH triggers an increase in $[Ca^{2+}]_i$ and subsequently the release of the gonadotropins LH and FSH. LH and FSH act on the gonads to regulate gametogenesis and the estrous cycle. The gonads produce steroid hormones such as estradiol which feed back onto the hypothalamus and the pituitary. AP, anterior pituitary gland; AVPV, anteroventral periventricular nucleus of the hypothalamus; ARC, arcuate nucleus of the hypothalamus; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; PP, posterior pituitary gland; TRPC, TRP canonical channel; TRPM, TRP melastatin channel; TRPV, TRP vanilloid channel.

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