Molecular and Cellular Endocrinology xxx (2017) 1–10

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

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

Role of the androgen receptor in the central nervous system

Sakina Mhaouty-Kodja

Sorbonne Universités, UPMC Univ Paris 06, INSERM, CNRS, Neuroscience Paris Seine – Institut de Biologie Paris Seine, 7 Quai St Bernard, 75005 Paris, France

ARTICLE INFO

Article history:
Received 23 March 2017
Received in revised form
30 July 2017
Accepted 2 August 2017
Available online xxx

Keywords:
Androgen receptor
Nervous system
Brain
Behavior
Sex steroid
Hormone

ABSTRACT

The involvement of gonadal androgens in functions of the central nervous system was suggested for the first time about half a century ago. Since then, the number of functions attributed to androgens has steadily increased, ranging from regulation of the hypothalamic-pituitary-gonadal axis and reproductive behaviors to modulation of cognition, anxiety and other non-reproductive functions. This review focuses on the implication of the neural androgen receptor in these androgen-sensitive functions and behaviors.

Contents

1. Introduction

Androgens have been shown to regulate several neural functions ranging from reproduction to mood and cognitive abilities.

E-mail address: sakina.mhaouty-kodja@upmc.fr.

http://dx.doi.org/10.1016/j.mce.2017.08.001
0303-7207/

This property starts as early as the perinatal period, which is characterized by prenatal and postnatal surges of gonadal testosterone, and continues through puberty and even adulthood. In the nervous system, the effects of testosterone are mediated either by androgen receptors (AR), or, after neural aromatization to 17β-estradiol, by estrogen receptors (ER) α and Erβ. Local synthesis of neuro-steroids has been reported in several cerebral regions such as the hippocampus, where they modulate hippocampal synaptic plasticity and healthy memory processes (Ooishi et al., 2012). AR and ER receptors are members of the nuclear receptor superfamily and act mainly through regulation of target genes at the transcriptional level, although several studies show rapid membrane and cytoplasmic changes. The present review focuses on studies in rodents that address the neural AR role in androgen-induced regulation of central nervous system (CNS) functions.

2. Pharmacological and genetic tools to assess neural AR function

2.1. Pharmacological tools

To discriminate between the androgenic and estrogenic pathways in testosterone-mediated regulation of CNS functions, gonadectomy and supplementation with 5-α-dihydrotestosterone (DHT) are used. However, this non-aromatizable metabolite of testosterone does not exclusively activate AR. Indeed, it can be metabolized to 5α-androstan-3β, which binds ERs and triggers neural responses (Handa et al., 2008). Systemic or local treatments in specific CNS regions with AR-antagonists, such as flutamide and cyproterone acetate, are also used to confirm an AR-dependent mechanism. These anti-androgens can act as partial agonists for neural AR in some situations (Nguyen et al., 2007). The use of selective AR modulators (SARM; Narayanan et al., 2017) has also been reported in a few studies.

2.2. Genetic models

Table 1 summarizes the different models used or generated in order to delineate the role of *AR* gene in CNS functions. The Testicular Feminization Mutation (Tfm) of the *AR* gene, which resides on the X chromosome, has been described in both rats and mice (Allison et al., 1971; Lyon and Hawkes, 1970). These spontaneous genetic models are widely used in studies addressing neural AR functions. Both rat and mouse mutations result in a similar, entirely feminine, external phenotype, but they inactivate *AR* to different extents. The rat mutation decreases AR function by 85–90% (Yarbrough et al., 1990). In the mouse model, a single nucleotide deletion introduces a reading frame shift and premature stop codon, thereby resulting in a shortened transcript and absence of AR protein (Charest et al., 1991; He et al., 1991). High testosterone levels are reported in Tfm rats while almost no secretion occurs in mutant mice (Yarbrough et al., 1990).

The global *AR* knock-out mouse models generated by Cre recombinase-mediated excision of Exon 1 or 2 display an androgen insensitivity phenotype comparable to that of Tfm mice (De Gendt et al., 2004; Sato et al., 2003; Yeh et al., 2002). Genetic (XY) males exhibit a typical female external appearance, small cryptorchidic azoospermic testes and very low levels of circulating testosterone. In both Tfm and global knock-out mice, it is difficult to distinguish between CNS and peripheral-mediated effects of testosterone through the AR, given the critical role of this hormone in several peripheral functions related, or not, to reproduction.

This observation motivated the generation of the first mouse line selectively invalidated for the neural *AR* by using mice with floxed *AR* Exon 2 and transgenic animals carrying Cre recombinase driven by the nestin promoter and nervous system-specific enhancer (Raskin et al., 2009, Fig. 1). This conditional mutation, targeting *AR* in neuronal and glial precursor cells as early as embryonic day (ED) 10.5, does not interfere with the normal development of the urogenital tract. The same mouse line was generated and reported by other groups (Chen et al., 2016; Juntti et al., 2010; Karlsson et al., 2016). Deletion of the *AR* gene in neurons was also performed using synapsin-I-Cre transgenic mice (Yu et al., 2013). Two mouse models overexpressing *AR* either globally or selectively at neural sites (neuronal and glial) were recently reported by Swift-Gallant et al. (2016a).

3. Neuroendocrine functions and behavior related to reproduction

Perinatal testosterone permanently potentiates male (masculinization) and inhibits female (de-feminization) neuroanatomical and behavioral characteristics (Morris et al., 2004; Phoenix et al., 1959). These organizational effects of testosterone suppress the

Table 1
Genetic models used to delineate the role of AR in CNS functions. Models with global or selective (neural, neuronal) *AR* mutation or overexpression are presented. For each genetically engineered model, the two mouse lines crossed to induce Cre-loxP-mediated invalidation or overexpression are shown. The genetic background of mouse lines is indicated when available. ACTB: actin beta; AR: androgen receptor; CMV: cytomegalovirus, PKG: phosphoglycerate kinase-1; Tfm: Testicular feminization mutation.

AR mutation	Spontaneous		Transgenic mouse lines crossed		
	Tfm	Reference	Floxed *AR*	Cre recombinase	Reference
Global	Rat	Allison et al., 1971	Exon 2	ACTB-Cre	Yeh et al., 2002
	Mouse	Lyon and Hawkes, 1970	Exon 1	CMV-Cre	Sato et al., 2003; Sato et al., 2004
			Exon 2	PGK-Cre^{m}	De Gendt et al., 2004
Neural knockout: neuronal and glial			Exon 2 (De Gendt et al., 2004)	Nestin-Cre (Tronche et al., 1999)	Raskin et al., 2009 (C57BL/6 x 129SvEv) Juntti et al., 2010 (C57BL/6 x 129SvEv) Raskin et al., 2012 (C57BL/6) Marie-Luce et al., 2013 (C57BL/6) Picot et al., 2014 (C57BL/6) Picot et al., 2016 (C57BL/6) Karlsson et al., 2016 (C57BL/6) Chen et al. 2016 Dombret et al., In press(C57BL/6)
Neuronal knockout			Exon 2 (Yeh et al., 2002)	Synapsin-I-Cre (Cohen et al., 2001)	Yu et al., 2013
***AR* overexpression**			**Transgenic mouse lines**		**Reference**
Global Neural: neuronal and glial			CMV-Stop-AR	CMV-Cre	Swift-Gallant et al., 2016a (C57BL/6)
			CMV-Stop-AR	Nestin-Cre (Tronche et al., 1999)	Swift-Gallant et al., 2016b (C57BL/6)

Please cite this article in press as: Mhaouty-Kodja, S., Role of the androgen receptor in the central nervous system, Molecular and Cellular Endocrinology (2017), http://dx.doi.org/10.1016/j.mce.2017.08.001