Autonomic Neuroscience: Basic and Clinical 187 (2015) 1–17

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

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

Review

Estrogen and female reproductive tract innervation: Cellular and molecular mechanisms of autonomic neuroplasticity

M. Mónica Brauer [a,*], Peter G. Smith [b,c,**]

[a] Laboratory of Cell Biology, Instituto de Investigaciones Biológicas Clemente Estable, Montevideo 11600, Uruguay
[b] Department of Molecular and Integrative Physiology, University of Kansas Medical Center, Kansas City, KS 66160, United States
[c] Institute for Neurological Discoveries, University of Kansas Medical Center, Kansas City, KS 66160, United States

ARTICLE INFO

Article history:
Received 23 July 2014
Received in revised form 18 November 2014
Accepted 20 November 2014

Keywords:
Female reproductive tract
Estrogen
Sympathetic nerves
Parasympathetic nerves
Sensory nerves
Neuroplasticity

ABSTRACT

The female reproductive tract undergoes remarkable functional and structural changes associated with cycling, conception and pregnancy, and it is likely advantageous to both individual and species to alter relationships between reproductive tissues and innervation. For several decades, it has been appreciated that the mammalian uterus undergoes massive sympathetic axon depletion in late pregnancy, possibly representing an adaptation to promote smooth muscle quiescence and sustained blood flow. Innervation to other structures such as cervix and vagina also undergo pregnancy-related changes in innervation that may facilitate parturition. These tissues provide highly tractable models for examining cellular and molecular mechanisms underlying peripheral nervous system plasticity. Studies show that estrogen elicits rapid degeneration of sympathetic terminal axons in myometrium, which regenerate under low-estrogen conditions. Degeneration is mediated by the target tissue: under estrogen's influence, the myometrium produces proteins repulsive to sympathetic axons including BDNF, neurotrimin, semaphorins, and pro-NGF, and extracellular matrix components are remodeled. Interestingly, nerve depletion does not involve diminished levels of classical sympathetic neurotrophins that promote axon growth. Estrogen also affects sympathetic neuron neurotrophin receptor expression in ways that appear to favor pro-degenerative effects of the target tissue. In contrast to the uterus, estrogen depletes vaginal autonomic and nociceptive axons, with the latter driven in part by estrogen-induced suppression of BMP4 synthesis. These findings illustrate that hormonally mediated physiological plasticity is a highly complex phenomenon involving multiple, predominantly repulsive target-derived factors acting in concert to achieve rapid and selective reductions in innervation.

Contents

* Corresponding author. Tel.: +598 24871623; fax: +598 24875461.
** Corresponding author. Tel.: +1 913 588 5970; fax: +1 913 588 5677.
E-mail addresses: brauer2009@gmail.com (M. Mónica Brauer), psmith@kumc.edu (P.G. Smith).

http://dx.doi.org/10.1016/j.autneu.2014.11.009
1566-0702/

1. Introduction

The ability to reproduce is essential to the survival of all species. Even in the simplest of organisms, reproduction is a highly complex phenomenon. As we advance along the evolutionary spectrum, the challenges and complexity become greater. As organismal development in utero becomes more advanced, increasingly sophisticated homeostatic mechanisms are presumably required. In the case of humans, the highly developed nervous system creates special challenges in terms of how precisely the uterine environment must be maintained and the degree to which the system must rapidly adapt in order to shift from maintaining pregnancy to completing parturition. In the case of the female reproductive tract, maintaining the environment requires the dynamic interplay of nerves and hormones.

The female reproductive tract is imbued with a rich ground plexus of autonomic nerves that regulate vascular and nonvascular smooth muscle contractile activity, glandular secretions and immune cell interactions, and convey information to the central nervous system (CNS) regarding the internal environment and potential noxious stimuli. In transitioning from nonpregnant to gravid states, it is advantageous for reproductive tract innervation to alter its properties in ways that accommodate reproductive needs. For example, while activation of excitatory uterine sympathetic pathways during a fight or flight response may be beneficial in the nonpregnant female, doing so in an advanced state of pregnancy could result in deprivation of blood flow to the placenta or premature delivery. How does innervation of the female reproductive tract adapt to meet the needs of dramatically changing target tissues?

This review covers some 40 years of research beginning with reports by Owman and colleagues of changes in uterine sympathetic innervation during pregnancy (Owman et al., 1976). In this period, our knowledge of the extent to which autonomic innervation changes as a function of reproductive status has grown significantly. Moreover, we now have a richer understanding of the hormonal, cellular and molecular mechanisms through which reproductive tract neural plasticity takes place. In addition to the importance of this process to the survival of the species, the female reproductive tract provides a unique model for understanding the processes underlying physiological neural plasticity. While it is now generally well accepted that remodeling is ongoing within both the central and peripheral nervous systems of adult mammals, these processes typically occur asynchronously and randomly over long periods. The ability to trigger synchronous nerve degeneration or regeneration simply by altering the hormonal milieu provides a highly tractable model system in which to study how target innervation is regulated.

In this review, we first provide an overview of the innervation of the female reproductive tract. We then examine how this innervation is modulated under normal physiological conditions such as puberty, the menstrual or estrous cycle, and pregnancy, as well as following hormonal manipulations. We conclude by summarizing what is known regarding molecular mechanisms mediating changes in target innervation. While the picture remains incomplete, results point to surprisingly complex multifactorial processes by which reproductive tract innervation is regulated.

2. Innervation of the female reproductive tract: an overview (Fig. 1)

2.1. Ovary

The ovary receives sympathetic innervation from the upper lumbar spinal segments via splanchnic nerve fibers and parasympathetic innervation via the vagus nerves. Autonomic axons travel to the ovary via the ovarian nerve plexus and the superior ovarian nerve (Papka and Traurig, 1993; Traurig and Papka, 1993). Sympathetic innervation appears to play an important role in the prepubertal development of ovarian function (Lara et al., 1990; Albuquerque-Araujo et al., 1995). The ovaries are also well imbued with sensory axons containing calcitonin gene-related peptide (CGRP) as well as other neuropeptides (Ghatei et al., 1985) and may be involved in vasomotor regulation. The organization and functions of ovarian innervation is addressed in more detail by Uchida (this issue).

2.2. Oviduct

Many oviductal functions are under the control of autonomic and sensory nerves, which innervate the muscularis, vasculature and to a lesser extent the oviductal mucosa (Owman et al., 1986a; Owman and Stjernquist, 1988; Papka and Traurig, 1993; Traurig and Papka, 1993). Sympathetic nerves arising from the thoraco-lumbar sympathetic chain and prevertebral ganglia densely innervate the oviduct. In the pig, the paracervical ganglia also supply sympathetic innervation to the oviducts (Czaja et al., 2001a,b), while in the rat, this plexus does not innervate the upper genital tract (Houdeau et al., 1998a,b). Oviductal sympathetic innervation shows regional variations; most nerves associate with blood vessels in the ampulla, whereas in the isthmus fibers mainly innervate the prominent circular muscle layer and are involved in neural control of the sphincter. Interestingly, in women with hydrosalpinx a loss of adrenergic nerves occurs at the isthmus and leads to a distal fluid-filled dilation of the Fallopian tube causing infertility (Zhu et al., 2013).

Parasympathetic nerves are relatively scarce in the oviduct and mainly confined to the vasculature and muscularis (Wrobel and Kujat, 1993; Jankovic et al., 2004). These nerves are particularly well developed in the tubo-uterine junction, suggesting a role in sphincter control