Neuroscience and Biobehavioral Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

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

Review

Unraveling the modulatory actions of serotonin on male rat sexual responses

A. Rubio-Casillas [a], C.M. Rodríguez-Quintero [a], G. Rodríguez-Manzo [b], A. Fernández-Guasti [b,*]

[a] Laboratorio de Biología, Escuela Preparatoria Regional de Autlán, Universidad de Guadalajara, Guadalajara, Jalisco, Mexico
[b] Departamento de Farmacobiología, CINVESTAV-Sede Sur, México, DF, Mexico

ARTICLE INFO

Article history:
Received 26 June 2014
Received in revised form 25 March 2015
Accepted 4 May 2015
Available online xxx

Keywords:
Masculine sexual responses
Serotonin
5-HT receptors
Interneurons
Inhibitory and facilitative actions
Biphasic effects

ABSTRACT

Animal studies and clinical investigations reveal that serotonin plays a central role in the control of the ejaculatory threshold. The chronic use of selective serotonin reuptake inhibitors (SSRIs) frequently results in sexual dysfunction, inviting to analyze the modulatory actions of serotonin on male sexual function in depth. Even though the main effect of serotonin on male sexual responses is inhibitory, this neuromodulator also mediates brief important stimulatory actions. Serotonin (5-HT) can activate two intracellular signaling pathways: a lower-threshold facilitatory pathway, and a higher-threshold inhibitory pathway, leading to biphasic effects. We propose that these divergent actions are related to the stimulation or inhibition of glutamatergic and GABAergic interneurons. Experimental evidence suggests that low 5-HT concentrations produce stimulatory actions on male ejaculatory aspects that might be mediated by the blockade of the GABAergic neurotransmission in the MPOA and spinal cord, which in turn releases a tonic inhibition that allows other neurotransmitters such as glutamate, noradrenaline, oxytocin and dopamine to initiate a sequence of molecular events resulting in the expression of ejaculation. Similar serotonin actions, mediated via interneurons, have been proposed for the regulation of other processes and occur in many central nervous system areas, indicating that it is not an isolated phenomenon.

Contents

1. Introduction

The biochemical mechanisms that regulate animal sexual responses have been recently studied and involve the participation of steroids, neuromodulators, neurotransmitters and other

* Corresponding author. Tel.: +52 55 54 83 28 70; fax: +52 55 54 83 28 63.
E-mail address: jfernand@cinvestav.mx (A. Fernández-Guasti).

http://dx.doi.org/10.1016/j.neubiorev.2015.05.003
0149-7634/

important molecules, thus improving our understanding of these complex responses (Traish et al., 2002; Bancroft, 2005; Carro-Juárez and Rodríguez-Manzo, 2008; Hull and Rodríguez-Manzo, 2009; Pfaus, 2009; Corona et al., 2012). Serotonin (5-HT), a neurotransmitter and a neuromodulator, is widely distributed in the mammalian central nervous system (CNS), where it plays a role in sleep, cognition, sensory perception, motor activity, temperature regulation, appetite, hormone secretion, nociception and sexual responses (Jacobs and Azmitia, 1992; Daubert and Condron, 2010). To date, at least fourteen different 5-HT receptor subtypes have been identified in mammals and are grouped into seven families (5-HT1 to 5-HT7) (Barnes and Sharp, 1999; Hoyer et al., 2002).

It is worth clarifying that sexual responses include many aspects that usually are expressed in concert during sexual behavior. However, sexual behavior in many species, including humans, may take place although lacking other components such as seminal emission or ejaculation (Agmo, 1997; Lucio et al., 2014). Conversely, ejaculation may occur in other contexts not necessarily related with behavior, for example as nocturnal emissions (Janssen, 2007). Furthermore, the terminology used to name such independent processes does not help to understand them individually; for example, the term "ejaculation" is frequently used as synonym of seminal emission, which in most tests is not verified. In behavioral observations, "ejaculation" refers to a series of motor behavioral acts that usually (but not always) accompany seminal emission (Rodríguez-Manzo and Fernández-Guasti, 1995). Even worse is the human definition of orgasm independently of ejaculation or seminal emission (for review see Komisaruk et al., 2006). Another example refers to "intromission" which habitually denotes the penile intravaginal insertion. Again, in behavioral tests usually the penile insertion is not directly observed but inferred from the animal behavior (Sachs and Meisel, 1988). In addition to this source of controversy all these sexual responses have a highly complex regulation by the central nervous system at encephalic and spinal levels, the peripheral nervous system and the autonomic nervous system through its sympathetic and parasympathetic branches (Sachs and Meisel, 1988; Steers, 1990; Coolen, 2005; Hull and Rodríguez-Manzo, 2009). Serotonin, the main mediator studied in the present review, is involved in the regulation of these events at almost all their anatomo-physiological control points. That is, it directly or indirectly participates, among many other neurotransmitters or modulators, in the control of all these sexual aspects at central and peripheral levels. This review intends to analyze the controversial role of 5-HT in the regulation of various aspects of the sexual response, primarily in the rat because it has been the most studied species.

Experts agree that brain dopamine (DA) constitutes the excitatory system core, while serotonergic transmission seems to be activated during periods of sexual inhibition (Pfaus, 2009). This affirmation is correct, but just in part because the serotonergic system may be also active during sexual arousal, erection and ejaculation. Although 5-HT mediates predominantly inhibitory effects on various aspects of the sexual response (Bitran and Hull, 1987; Finberg and Vardi, 1990; Hull et al., 2004), particularly under physiological conditions, this fact should not obscure the important stimulatory effects mediated by this neurotransmitter in erection and ejaculation (Mendelson and Gorzalka, 1985; Mendelson, 1985, 1992; Yonezawa et al., 2000, 2008; Carro-Juárez et al., 2003; Stafford et al., 2006a, 2006b; Ishigami et al., 2013).

Ejaculation – defined as a reflex mediated by a spinal generator (Carro-Juárez et al., 2003) – has an important control by lumbar spinotalamic cells (LSt) and their projections to autonomic and motor areas within the lumbosacral spinal cord (Truitt and Coolen, 2002; Coolen et al., 2004; Allard et al., 2005; Coolen, 2005; Young et al., 2009). LSt cells are essential for ejaculation since their lesions ablate the ejaculatory reflex in intact mating animals (Truitt and Coolen, 2002). In addition, electrical microstimulation of the LSt cells triggers ejaculation (Borgdorff et al., 2008). LSt cells receive glutamatergic input and express NMDA receptors, activation of which is required for producing the ejaculatory reflex (Coolen, 2011). The serotonin-glutamate interaction at the spinal cord, besides controlling pain transmission, plays a role in motor control. Ejaculation involves motor events, i.e. expulsion, which consists of an emissive phase and an ejection phase (Newman et al., 1982). Emission involves the closure of the bladder neck and contraction of the sexual accessory glands while ejection consists of the forceful ejection of semen from the urethra to the urethral meatus, due to coordinated and rhythmic contractions of the striated perineal muscles, in particular the bulbo-spongiosus (BSM) and ischiocavernosus muscles (ICM) together with the anal and urethral sphincters, all innervated by motoneurons (McKenna and Nadelhaft, 1986). At a cellular level, 5-HT is able to increase glutamate-induced excitability of spinal motoneurons (White, 1985; Jackson and White, 1990). Latest research provided biochemical, pharmacological and electrophysiological evidence that stimulation of Src tyrosine kinase is induced by activation of 5HT2C receptors, revealing that 5-HT-activated intracellular signaling events are linked with NMDA-mediated functional activity (Bigford et al., 2012).

In addition, it has been confirmed that in the male rat, the intraurethral 5-HT infusion produced a dose-dependent facilitation of the urethrogenital reflex (UGR), i.e., a decreased urethral perfusion pressure (UPP) threshold and an increased number of ejaculatory-like reflexes (ELRs). These results suggest that in the male rat urethra, peripheral 5-HT2 receptors are also involved in the 5HT-induced facilitation of the seminal expulsion associated to ejaculation (Ishigami et al., 2013). In the same sense, acute fluoxetine-induced inhibitory effects on the ejaculatory response of spinal rats have been interpreted to be due to the 5-HT2C antagonistic actions of this selective serotonin reuptake inhibitor (SSRI) (Hueletl-Soto et al., 2012). Moreover, 5-HT acting at a genital level modulates among other important physiological processes: seminiferous tubule fluid transit, seminal production and clearance, sexual accessory glands contraction, epididymal fluid composition and testicular blood flow (Killam et al., 1995; Collin et al., 1996; Leung et al., 1999; Kim and Paick, 2004). There is also evidence that the serotonergic system plays a stimulatory role upon the neuroendocrine system, which regulates puberty onset and spermatogenesis in the prepubertal rat, since 5-HT depletion reduces germ cells in the testes (Aragón et al., 2005).

Contrary to the aforementioned stimulatory effects on reproductive organs and processes, it is also clear that 5-HT mediates an inhibition of testosterone synthesis in the adult rat by promoting corticotropin-releasing factor (CRF) secretion (Tinajero et al., 1992; Frungieri et al., 1999, 2002). It is also believed that 5-HT inhibits seminal fluids secretion into the urethra by inhibiting the sympathetic nerve stimulation required to contract the seminal vesicle and vas deferens (Kim et al., 2000, 2004; Hsieh et al., 2011). In contrast to these findings, a recent work demonstrated that activation of lumbosacral 5-HT2C receptor elicits burst pattern responses in the sympathetic branch of the vas deferens nerve (VDN) and evokes emission associated with ejaculatory-like responses (Stafford et al., 2006b). Furthermore, the largest body of evidence indicates that serotonin plays an inhibitory role in the regulation of masculine sexual behavior in many species ranging from rodents to humans (Bitran and Hull, 1987; Hull and Rodríguez-Manzo, 2009; Phillips-Farfán and Fernández-Guasti, 2009), although the careful analysis of this literature shows controversial results (vide infra). Such opposite findings suggest an interesting biphasic effect of serotonergic neurotransmission. A seminal idea from a very recent work (Snoeren et al., 2014), suggested that serotonin is involved both in the inhibitory control of sexual behavior and in the disinhibition to induce sexual behaviors. Thus, the aim of this review is to propose

Please cite this article in press as: Rubio-Casillas, A., et al., Unraveling the modulatory actions of serotonin on male rat sexual responses. Neurosci. Biobehav. Rev. (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.05.003