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Somatic genital reflexes in rats with a nod to humans: Anatomy, physiology, and the role of the social neuropeptides

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ABSTRACT

Somatic genital reflexes such as ejaculation and vaginocervical contractions are produced through the striated muscles associated with the genitalia. The coordination of these reflexes is surprisingly complex and involves a number of lumbosacral spinal and supraspinal systems. The rat model has been proven to be an excellent source of information regarding these mechanisms, and many parallels to research in humans can be drawn. An understanding of the spinal systems involving the lumbosacral spinal cord, both efferent and afferent, has been generated through decades of research. Spinal and supraspinal mechanisms of descending excitation, through a spinal ejaculation generator in the lumbar spinal cord and thalamus, and descending inhibition, through the ventrolateral medulla, have been identified and characterized both anatomically and physiologically. In addition, delineation of the neural circuits whereby ascending genitosensory information regarding the regulation of somatic genital reflexes is relayed supraspinally has also been the topic of recent investigation. Lastly, the importance of the "social neuropeptides" oxytocin and vasopressin in the regulation of somatic genital reflexes, and associated sociosexual behaviors, is emerging. This work not only has implications for understanding how nervous systems generate sexual behavior but also provides treatment targets for sexual dysfunction in people.

Introduction

While advances in our knowledge of the supraspinal and spinal control of the genital musculature have been made, the neural circuits and neurochemistry underlying the regulation of somatic genital reflexes such as ejaculation in men and vaginocervical contractions in women have not been fully elucidated. In both men and women, internally or externally derived stimulation results in rhythmic contractions of genital muscles often associated with orgasm (Argiolas and Melis, 2003). All of these processes are reflexive and under the control of somatic spinal efferents (Giuliano and Clement, 2005; McKenna, 2002; Temel et al., 2005). However, these efferents are regulated by both excitatory and inhibitory controls from numerous spinal and supraspinal sites. Coordination of the various circuits controlling genital reflexes has been studied extensively in men, with recent interest in defining homologous circuits in women. From this work, a general understanding of the discrete processes underlying genital reflex control has been established. First, the autonomic nervous system plays the key role in providing the necessary signals for increased blood flow to the genitalia for both men (erection) and women (genital engorgement) as well as providing signals for the production of secretive fluids used for lubrication and seminal transfer (ejaculation, emission phase; McKenna, 2002; Temel et al., 2005; Yang and Jiang, 2009). Second, and the focus of this review, the somatic nervous system provides the signals for rhythmic contractions of the genital musculature in both men (ejaculation, expulsion phase) and women (vaginocervical contractions; Giuliano and Clement, 2005; Levin, 1998; Yang and Jiang, 2009). There is a surprisingly complex integration of ascending sensory information from the genitalia with both descending excitatory and inhibitory inputs to the spinal motor neurons. Non-human animal models, in particular the rat, have been informative in elucidating the basic anatomy and physiology of these circuits (Pfaus et al., 2003). An understanding of the anatomy and physiology of these circuits, with a special emphasis on social neuropeptides, is an important area of research with significant implications for our understanding of basic sexual processes as well as sexual dysfunction in people.

The striated genital musculature and associated motoneurons

The pelvic muscles associated with the genitalia in both humans and rats include the striated perineal muscles musculus bulbospongiosus (also known as the musculus bulbocavernosus), musculus

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ischiocavernosus, and musculus levator ani (Blaivas et al., 1981; deGroat and Booth, 1980; Holmes et al., 1991; Rand and Breedlove, 1987). These muscles, in particular the bulbospongiosus, provide the rhythmic contractions associated with orgasm and the expulsion of semen during ejaculation in males in both humans and rats (Ertekin and Reel, 1976; Gerstenberg et al., 1990; Hart and Melese-D'Hospital, 1983; Holmes et al., 1991; Sachs, 1982). In females, despite the "vestigial" description that some authors have applied (Arakawa et al., 2010; Fishman and Breedlove, 1988), these muscles are found to produce rhythmic contractions during orgasm in both humans and rats (Giraldi et al., 2004; McKenna and Nadelhaft, 1989; Meston et al., 2004; Vodusek et al., 1983).

The perineal muscles are innervated by the pelvic and pudendal nerves (Pacheco et al., 1989; Pastelin et al., 2008) from the lower lumbar and upper sacral divisions of the spinal cord (de Araujo et al., 1982; Katagiri et al., 1986; Roppolo et al., 1985) in both humans and rats. In rats, the lumbosacral spinal motoneuron pools associated with these nerves are referred to as the dorsomedial nucleus (DM; also known as the spinal nucleus of the bulbocavernosus) and the dorsolateral nucleus (DL) of the L5-S1 ventral horn (Collins et al., 1991; Katagiri et al., 1986; McKenna and Nadelhaft, 1986; Peshori et al., 1995; Schroder, 1980). The DM and DL are considered homologs of Onuf's nucleus in humans (Breedlove and Arnold, 1980; Roppolo et al., 1985; Schroder, 1981). The DM is an androgen sensitive sexually dimorphic structure with more numerous and larger cells in males in both humans (Forger and Breedlove, 1986) and rats (Breedlove and Arnold, 1980; Freeman et al., 1995; Katagiri et al., 1986).

The DM and DL nuclei are active during ejaculation in rats (Clement et al., 2007; Giuliano et al., 2007). Interneurons within the spinal cord appear to connect primary afferent somatosensory information with the DM and DL (Collins et al., 1991; Peshori et al., 1995; Wiedey et al., 2008), but a number of descending projections from other parts of the spinal cord, as well as from supraspinal sites, provide both excitatory and inhibitory drives to these motoneuron pools (Allard et al., 2005; Coolen, 2005; Marson and McKenna, 1990; Wagner and Clemens, 1991). These excitatory and inhibitory drives compete at the level of the spinal cord motoneuronal pools to regulate somatic genital reflexes.

The ejaculation generator and descending excitatory circuits

A hypothesized ejaculation generator, constituting a central pattern generator for the muscles of ejaculation, has been described in the lumbar spinal cord of rats and appears to be present in both sexes (Carro-Juarez and Rodriguez-Manzo, 2006). These galanin-immunoreactive neurons, referred to as lumbar spinothalamic (LSt) neurons, express ejaculation induced Fos (Truitt et al., 2003) and project to both a thalamic region (the parvocellular subparafascicular thalamic nucleus; SPFpc) that expresses ejaculation-induced Fos (Coolen et al., 2003a; Coolen et al., 2003b), and the autonomic nuclei responsible for the emission phase of ejaculation (Xu et al., 2006), and the DM and DL (Newton, 1993; Xu et al., 2006). This anatomical connectivity suggests a central role in the relay of sensory information from the genitals, in combination with the coordination of the emission and expulsion phases of ejaculation. In fact, lesions of these lumbar spinothalamic cells abolish the ability of male rats to ejaculate, while leaving other aspects of sexual behavior intact (Truitt and Coolen, 2002). In addition, electrical stimulation of LSt cells in male rats produces both the emission and expulsion phase of ejaculation in a coordinated fashion, as measured by elicited seminal vesicle and bulbospongiosus contractions (Borgdorff et al., 2008). Interestingly, vaginocervical stimulation does not induce Fos expression in these cells in female rats, indicating that there may be a discrete sexual dimorphism in the organization of this circuit (Truitt et al., 2003). It is also possible that descending excitation to the somatic motoneurons is relayed from these LSt cells, through the thalamus, to other forebrain regions with descending input to the DM and DL spinal motoneuronal pools.

The paraventricular hypothalamic nucleus (PVN) has direct and indirect connections to the DM and DL (Tang et al., 1999; Wagner and Clemens, 1991). The PVN has been previously implicated in the control of genital reflexes and is most likely a source of descending excitatory input to the genital musculature. Lesions of both magnocellular and parvocellular PVN cells increase ejaculation latency in rats (Liu et al., 1997), although lesions restricted to the parvocellular PVN do not (Ackerman et al., 1997). Importantly, lesions of the PVN have more dramatic effects on penile reflexes mediated by the autonomic nervous system rather than somatic efferents (Ackerman et al., 1997; Chen et al., 1997; Eaton et al., 1991; Liu et al., 1997), and it has been

Table 1
Abundance of H129 labeling in supraspinal sites of male and female rats as a result of genital inoculation.

Region	Male	Female
VO	+++	–
AIC	++	–
M1/S1	+	+
BNST	+++	–
CeM	+++	–
VP	++	–
MPG	++	–
LPG	++	–
PVN	+++	+++
LH	+++	–
MCLH	–	+
PeF	+++	++
Sub	+++	–
ZI	+++	–
VPM	++	–
VA	+++	–
SPFpc	++	–
SNR	++	–
PF	+	+
LPAG	+	+
VLPAG	+++	–
RPC	+++	+++
RMC	+++	+++
IMLF	++	+
PL	+	+
DpMe	+	–
DpG	++	–
CnF	+	–
VLTg	++	–
PB	++	–
NRM	+++	+++
DMTg	++	–
LC	+++	+++
Mo5	–	++
A5	–	++
nPGi	+++	+++
PnC	++	–
Sol	+++	–
PCRt	++	–

The relative density of H129 labeling in each region as represented by the crosses is as follows: + indicates a few cells; ++, 5–25 cells; +++, >25 cells. VO indicates ventral orbital cortex; AIC, anterior insular cortex; M1/S1, primary somatomotor cortex; BNST, bed nucleus of the stria terminalis; CeM, central amygdala; VP, ventral posterior thalamic nucleus; MPG, medial globus pallidus; LPG, lateral globus pallidus; PVN, paraventricular hypothalamic nucleus; LH, lateral hypothalamus; MCLH, magnocellular nucleus of the lateral hypothalamus; PeF, perifornical nucleus; Sub, subicular nucleus; ZI, zona incerta; VPM, posteromedial ventral nucleus of the thalamus; VA, ventral anterior thalamic nucleus; SPFpc, parvocellular subparafascicular nucleus; SNR, substantia nigra; PF, parafloccculus; LPAG, lateral periaqueductal gray; VLPAG, ventrolateral periaqueductal gray; RPC, parvocellular red nucleus; RMC, magnocellular red nucleus; IMLF, interstitial nucleus of the medial longitudinal fasciculus; PL, paralemniscal nucleus; DpMe, deep mesencephalic nucleus; DpG, deep gray layer of the superior colliculus; CnF, cuneiform nucleus; VLTg, ventrolateral tegmental area; PB, parabrachial nucleus; NRM, nucleus raphe magnus; DMTg, dorsomedial tegmental area; LC, locus coeruleus; Mo5, motor trigeminal nucleus; A5, A5 noradrenergic cell group; nPGi, nucleus paragigantocellularis; PnC, caudal pontine reticular nucleus; Sol, solitary nucleus; PCRt, parvocellular reticular nucleus.