Neural control of erection

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Abstract

Penile erection is a vascular event controlled by the autonomic nervous system. The spinal cord contains the autonomic preganglionic neurons that innervate the penile erectile tissue and the pudendal motoneurons that innervate the perineal striated muscles. Sympathetic pathways are anti-erectile, sacral parasympathetic pathways are pro-erectile, and contraction of the perineal striated muscles upon activity of the pudendal nerves improves penile rigidity. Spinal neurons controlling erection are activated by information from peripheral and supraspinal origin. Both peripheral and supraspinal information is capable of either eliciting erection or modulating or inhibiting an erection already present. Sensory information from the genitals is a potent activator of pro-erectile spinal neurons and elicits reflexive erections. Some pre-motor neurons of the medulla, pons and diencephalon project directly onto spinal sympathetic, parasympathetic and pudendal motoneurons. They receive in turn sensory information from the genitals. These spinal projecting pathways release a variety of neurotransmitters, including biogenic amines (serotonin, dopamine, noradrenaline, and adrenaline) and peptides that, through interactions with many receptor subtypes, exert complex effects on the spinal network that controls penile erection. Some supraspinal structures (e.g. the paraventricular nucleus and the medial preoptic area of the hypothalamus, the medial amygdala), whose roles in erection have been demonstrated in animal models, may not project directly onto spinal pro-erectile neurons. They are nevertheless prone to regulate penile erection in more integrated and coordinated responses of the body, as those occurring during sexual behavior. The application of basic and clinical research data to treatment options for erectile dysfunction has recently proved successful. Pro-erectile effects of phosphodiesterase type 5 inhibitors, acting in the penis, and of melanocortin agonists, acting in the brain, illustrate these recent developments.

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1. Understanding penile erection: local mechanisms, peripheral neural pathways and peripheral pharmacology

Penile erection takes place when both dilation of the penile arteries and relaxation of the erectile tissue (corpus cavernosum and corpus spongiosum) occur [1]. Dilation of the penile arteries results in an increased blood flow to the penis, and erectile tissue relaxation results in an engorgement of the penis with blood. Because the erectile tissue is surrounded by the tunica albuginea, a tissue that does not distend easily, the increased blood flow to the penis increases not only the penile volume but also intrapenile pressure. Measuring intracavernous pressure is therefore a reliable index of penile erection and has been used in many experiments performed in animals. Both arterial and penile relaxations rely upon a change in the tone of the smooth muscle fibers constitutive of the walls of the arteries and of that of the erectile tissue (e.g. the trabeculae of the corpus cavernosum). It is the amount of intracellular, cytoplasmic calcium that controls the tone of smooth muscle fibers. Increasing this amount, through releasing calcium from intracellular stores (sarcoplasmic reticulum) and/or facilitating its entry from the extracellular milieu, leads to contraction. In the flaccid state, smooth muscle fibers of
the penis and penile arteries are contracted. Decreasing the amount of cytoplasmic calcium, through pumping it back into the sarcoplasmic reticulum or expelling it out of the cell, leads to relaxation. During erection, the smooth muscle fibers of the penis and penile arteries are relaxed. Depending on the smooth muscle fiber under consideration, intracellular calcium movements are either spontaneous or controlled by information from the extracellular milieu. With regards to the penis, this information is carried by chemical messengers that are released by endothelial cells and nerve terminals [2]. Both endothelial cells and nerve terminals are present in the penis and penile arteries. Chemical messengers either interact with specific receptors present at the surface of the smooth muscle fiber membrane, or directly pass into the cells. Interaction of the messengers with their receptors activates intracellular enzymes, the first step of cascades of intracellular mechanisms. Erection is mainly due to the increased synthesis of two intracellular second messengers, the cyclic nucleotides guanosine monophosphate (cGMP) and adenosine monophosphate (cAMP). cGMP and cAMP are degraded by phosphodiesterases. The pro-erectile chemicals facilitate the synthesis or the accumulation, or prevent the degradation, of cGMP and/or cAMP. Increasing the amounts of intracellular cGMP and cAMP leads to relaxation. Because smooth muscle fibers of the penis are connected with gap junctions, it is not required that chemical messengers reach all of the cells to elicit an effect. Indeed, gap junctions allow for a rapid spread of electrotonic current and intercellular diffusion of second messengers and ions [3]. This system supports the rapid propagation of information in the erectile tissue, starting with a limited amount of chemical messengers released.

In contrast with other visceral tissues (e.g. the gut, the uterus), which possess both smooth muscle cells that contract spontaneously and rhythmically (pacemaker cells) and an intrinsic innervation (autonomic ganglion cells present in the wall or at the outer surface of the organ), the penis is devoid of such autonomy. Therefore, its activity is completely dependent on the autonomic innervation that it receives from the spinal cord (Fig. 1).

The neurotransmitters released by the postganglionic nerve terminals of the sympathetic and parasympathetic pathways in the penis are the best chemical messenger candidates for the control of erection. Noradrenaline (NA) and neuropeptide Y (NPY) are released in the penis by the terminals of sympathetic fibers. NA is the major contractile agent of the smooth muscles of the penis and penile arteries, and NPY augments its effects. NA plays a role in flaccidity and detumescence [2]. The terminals of parasympathetic fibers release acetylcholine (ACh), vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) [2]. ACh contracts penile smooth muscle in vitro, and erection is rather resistant to the cholinergic antagonist atropine. Therefore, ACh cannot be the candidate to exert a direct relaxant effect on penile smooth muscle. In fact, it activates endothelial cells that in turn release NO. The relaxant effects of VIP [4] and NO [5–8] released by nerve terminals on the penis have been demonstrated. NO increases the production of cGMP in smooth muscle fibers, and it is recognized as the most important activator of the local relaxation of the penis smooth muscle. The amplification of the local relaxant effects of NO by blocking the degradation of cGMP using inhibitors of type 5 phosphodiesterases is one of the most efficient treatments of erectile dysfunction in humans [9–11]. Added to the release of transmitters by the endings of autonomic postganglionic motor fibers, there exists a release of neuropeptides by the peripheral endings of autonomic sensory fibers. Although some of these peptides [e.g. substance P (SP) and calcitonin gene-related peptide (CGRP)] display vasorelaxant effects in vitro, their physiological role in the control of erection remains to be demonstrated [2].

The penis receives motor innervation from the sympathetic and parasympathetic branches of the autonomic nervous system [12,13]. Sympathetic pathways originate in the dorsolumbar spinal cord (thoracolumbar in rats). Preganglionic sympathetic fibers reach the penis via the lumbar splanchnic nerves or via the paravertebral sympathetic chain [14]. They relay on ganglionic neurons in the hypogastric plexus or in the paravertebral sympathetic chain ganglia. Sympathetic postganglionic axons reach the penis through a variety of routes. One route begins with the hypogastric nerve, which extends to the pelvic plexus, from which the cavernous nerve extends to the penis. Another route is the paravertebral sympathetic chain, which connects via the pelvic nerve to the pelvic plexus and then via the
cavernous nerve to the penis. The last route exits from the paravertebral sympathetic chain via the pudendal nerve to the penis.

In rats, the majority of the sympathetic preganglionic cell bodies, whose axons run in the paravertebral sympathetic chain, are located in the intermediolateral cell column. If one considers that penile erection is a vascular event and that neurons of the intermediolateral cell column are mainly vasoconstrictor neurons [14], it can be hypothesized that these neurons are involved in the spinal sympathetic inhibition of penile erection. In keeping with this hypothesis, all experiments performed so far in a variety of animals (rats, rabbits, cats, dogs, monkeys) have unmasked an anti-erectile sympathetic contingent in the paravertebral sympathetic chain [15–21]. Because sympathetic pathways display spontaneous activity, it is likely that they exert an anti-erectile tone on the penis. In favour of this hypothesis are the observations that (i) the intracavernous injection of the α-adrenergic antagonists phenoxybenzamine and phenolamine elicits erection in humans [22] and that (ii) electrical stimulation of the cavernous nerve elicits better erections in rats pretreated with 6-hydroxydopamine, a neurotoxin that destroys catecholaminergic terminals [23].

The sympathetic preganglionic neurons that send fibers into the hypogastric nerve originate in the dorsal grey commissure [24]. However, depending on the conditions used (the animal species, animals with an intact or a lesioned spinal cord), either a pro-erectile, or an anti-erectile, or no role at all have been attributed to the sympathetic contingent running in the hypogastric nerve and plexus.

Sacral preganglionic parasympathetic neurons are present in the sacral parasympathetic nucleus. Their axons travel in the pelvic nerve and establish synapses in the pelvic plexus (the major pelvic ganglion in rats [25,26]). Parasympathetic postganglionic fibers reach the penis via the cavernous nerve. All stimulation applied to the sacral cord, sacral roots, sacral nerves, pelvic nerve or cavernous nerve elicits penile erection [15,27–32]. Therefore, all of these experiments provide evidence that the only pro-erectile contingent of intact subjects leaves the sacral cord and runs in the pelvic and cavernous nerves.

Pudendal motoneurons [Onufrowicz’ (Onuf) nucleus, the dorsomedial—DM (also named the spinal nucleus of the bulbocavernosus—SNB) and dorsolateral—DL nuclei located in the ventral sacral cord (lumbosacral segments in rats) innervate the perineal striated muscles (namely the bulbospongiosus and ischiocavernosus muscles) via the pudendal nerve [33,34]. The contraction of these muscles on a flaccid penis does not elicit erection. In contrast, when the muscles contract on an erect penis, penile rigidity and intrapenile pressure dramatically increase [35]. The rhythmic activity of the perineal striated muscles also participates in the saccadic expulsion of semen during ejaculation.

Alteration of peripheral neural pathways (e.g. occurring during diabetes or during pelvic surgery) has deleterious effects on penile erection. Both lesions of the sacral parasympathetic pro-erectile outflow, and surprisingly, lesions of the sympathetic outflow, alter penile erection [36]. In the first condition, treatments targeting the peripheral end organ, e.g. intracavernous, intra-urethral or per os delivery of vasoactive agents can restore erection [37]. Other approaches aiming at restoring the wiring of the sacral innervation of the penis have more recently been proposed [38]. In the second condition, a variety of hypotheses have been proposed to explain why the elimination of a sympathetic outflow, basically anti-erectile, leads in fact to erectile dysfunction. To some authors, this would be due to the elimination of a pro-erectile contingent running in the sympathetic nerves. To others, it unmasks the major contribution of the sympathetic outflow to (i) the tone of the arteries and (ii) to the dynamic distribution of blood into different areas and organs, including the pelvic ones [39]. Through the lesion of this sympathetic pathway, one would prevent the redistribution of blood to the penis, from non-erectile tissues, that is required to elicit erection.

2. The spinal network that controls erection

The spinal cord contains the three sets of motoneurons (thoracolumbar sympathetic, sacral parasympathetic and sacral pudendal) that are anatomically linked with the penis and functionally linked with erection. Recordings performed in humans and animals reveal that these spinal neural populations are closely linked; however, they are located neither in the same spinal segments (thoracolumbar and lumbosacral) nor in the same spinal areas (sacral parasympathetic nucleus and Onuf or DM and DL nuclei). Thus, it is likely that an intraspinal network extending over the lower thoracic, lumbar and sacral segments of the spinal cord connects the different areas and segments. This network has been unmasked by neuroanatomical tract tracing techniques using the trans-synaptic retrograde transport of pseudorabies virus injected in the penis of rats [40]. The question to be addressed is how this network is activated so that erection occurs. Experiments have revealed that erection can be elicited by a variety of stimuli (tactile, visual, and olfactory), applied on exteroceptive sensory receptors and integrated at the spinal cord level or in higher brain structures in various animal models and in humans. Therefore, there may be many pro-erectile reflex pathways, differing by the nature of the stimulus applied at the periphery [41], and probably sharing the same common final pro-erectile pathway, namely the sacral parasympathetic output. Other experiments have used the electrical or chemical stimulation of peripheral neural pathways, spinal cord or supraspinal nuclei [42]. The concept emerging from these experiments is that the spinal cord represents a key structure upon which excitatory and inhibitory information
from the periphery and from supraspinal nuclei impinges. Erection likely occurs when the convergence of peripheral and supraspinal information onto the spinal cord elicits a lowering of the activity of the thoracolumbar sympathetic anti-erectile pathway and an increase of the activity of both the sacral parasympathetic pro-erectile pathway and the pudendal pathway.

While the spinal cord manages the circuits of erection, it is also responsible for the coordination of erection with other sexual responses such as ejaculation, and the inhibition of the activity of other pelvic functions such as micturition and defecation. The hyperreflexias, dysynergias, altered erections and/or ejaculations recorded in patients with a lesion of the spinal cord reflect the important role of supraspinal structures in this coordination.

There exists at least one recognized input of peripheral origin that, when stimulated, elicits erection, namely reflexive erections. This input comes from the genitalia. It is mainly conveyed by the dorsal penile nerve. It carries sensory information from the glans, perhaps the corpus cavernosum, and the preputial sheath. In animals with a complete section of the spinal cord at the thoracic level, genital stimulation elicits a variety of responses: erection, emission of secretions from the accessory sex glands, and movements of the hindlimbs, that are mediated by spinal segments below the lesioned ones [43–45]. Reflexive erections are present in patients with a lesion of the spinal segments above the sacral ones [46–50]. In conscious rats, the tonic retraction of the preputial sheath triggers clusters of reflexive erections separated by minutes of silence [51,52]. Each cluster includes several glans erections and penile extensions. The cluster frequency is the same in rats with an intact spinal cord and in rats with a lesion of the spinal cord. Therefore, this parameter depends upon a purely spinal mechanism. In contrast, latency of the first erection is shorter in rats with a lesion of the spinal cord, revealing the presence of descending inhibitory pathways [52]. Finally, following anesthesia of the T4 or T10 thoracic segments of the spinal cord with tetracaine, the latency of the first erection is diminished, but the burst frequency is lowered, suggesting both excitatory and inhibitory descending influences [53].

The rat is an original and interesting model. Its spinal cord receives excitatory inputs from the genitals. Inputs are recruited by penile sheath retraction. The lumbosacral spinal cord translates this tonic input into a phasic output, expressed by the clusters of erections. Rats share with other mammals the anatomical and functional coupling of two pair of tissues involved in erection: the corpus cavernosum with the ischiocavernosus muscle and the corpus spongiosum with the bulbospongiosus muscle [54–56]. It is, however, noteworthy that, in this species, the tissues work either independently or in close association during reflexive erections. Rats display five different gradations of reflexive erections: ups (extension of the penis in the penile sheath), type 1, type 2 and type 3 ("cups" or intense) glans erections, and short and long flips (dorsiflexions of the penis) [52,57]. Physiological measures of intracavernous [58] and intraspousiosus [59] pressures and of the electromyographic activity of the ischiocavernosus and bulbospongiosus muscles [54,55,59] have revealed that reflexive erections consist of plateaus of increased intracavernous and intraspousiosus pressures, reaching sub-systolic blood pressure levels and lasting several seconds, upon which peaks of suprasystolic pressures occur. The occurrence of plateaus parallels that of bursts of reflexive erections. Peaks, lasting about 1 s, are accompanied with an intense activity of the ischiocavernosus and bulbospongiosus muscles. The occurrence of peaks parallels that of individual erections. Ups and type 1 and type 2 erections are, respectively, accompanied by intracavernous and intraspousiosus pressures to systolic levels, with low to moderate activity of the ischiocavernosus and bulbospongiosus muscles. Type 3 erections ("cups") are accompanied by suprasystolic pressure rises in the corpus spongiosum and intense activity of the bulbospongiosus muscle. Flips are accompanied by suprasystolic pressure rises in the corpus cavernosum and intense activity of the ischiocavernosus muscle. Excision of the bulbospongiosus muscle [60] and denervation of this muscle [61] suppress the "cups". Excision of the ischiocavernosus muscle eliminates the flips [60]. Section of the cavernous nerves eliminates corpus cavernosum erections (ups and flips) but not glans erections [62]. In anesthetized rats and other animals, plateau increases of penile pressure are elicited by pelvic and cavernous nerve stimulation, and stimulation of the pudendal nerve is required to record suprasystolic penile pressure rises [17,18,21]. Therefore, at least in rats, reflexive erections need a strong coordination of the sacral parasympathetic outflow to the penis with the pudendal outflow to the perineal striated muscles. Privileged connections must exist within the spinal cord between sacral parasympathetic preganglionic neurons to the corpus cavernosum and dorsolateral motoneurons to the ischiocavernosus muscle, as well as between preganglionic neurons to the corpus spongiosum and dorsomedial motoneurons to the bulbospongiosus muscle. Activation of the sacral parasympathetic outflow is the first occurring event, and may condition the participation of the other sets of spinal neurons. The nerves, and therefore preganglionic neurons, responsible for corpus cavernosum erection are different from those eliciting corpus spongiosum erections. The coordinated activity of autonomic pathways to the penis with that of somatic pathways to the perineal muscles leading to suprasystolic increases of penile pressure had been demonstrated in large animals (dogs, rams, goats, stallions, bulls) in the context of copulation (see references in Ref. [53]).

In anesthetized rabbits, the stimulation of the sacral nerves elicits reflexive erections [63]. In anesthetized rats, electrical stimulation of the dorsal penile nerve elicits reflex evoked potentials in the cavernous nerve [64], increases in penile pressure and contraction of the perineal striated
muscles [64–66]. Finally, and most importantly, in humans genital stimulation elicits a rise of penile pressure, an increased blood flow to the penis and contraction of the perineal striated muscles [67–70]. These experiments confirm that stimulation of penile sensory pathways is able to recruit the different autonomic and somatic nuclei of the spinal cord that control erection.

The main spinal projection of sensory afferents from the penis is the lumbosacral spinal cord [71–73]. A contingent of sensory fibers originating in the corpus cavernosum also project to the thoracolumbar spinal cord [74].

The network of neurons supporting pro-erectile reflex pathways is located in the sacral spinal cord (lumbosacral segments in rats [52,75,76]). The pro-erectile network is activated by stimulation of the penis and dorsal penile nerve, and also by stimulation of the urethra [77]. Sensory information from the penis reaches the spinal cord, as well as the gracile nucleus [78], the brainstem [79], the hypothalamus (medial preoptic area [80] and paraventricular nucleus [81]), the thalamus [82] and the cortex [83]. Whether these areas are only the relays of sensory pathways conveying genital information en route to the cortex, or whether they are the centers of supraspinal reflex pathways remains to be explored.

3. Spinal pharmacology

Lumbosacral neurons, either sacral parasympathetic preganglionic ones, pudendal motoneurons or interneurons, bear a great variety of receptors and are surrounded by numerous fibers from local, peripheral and supraspinal origins that release many neurotransmitters. A rapid review of the literature suggests that a theoretical sacral parasympathetic preganglionic neuron bears the adrenergic alpha-1A-a, b, d and alpha-2A-a and b receptor subtypes, the dopaminergic D2 receptor subtype, the serotonergic 5HT1A, 5HT1B and 5HT2C receptor subtypes, the oxytocin receptor, the NK1 receptor for SP, the PGE3 receptor for prostaglandins, the glutamatergic GluR1-R4 (AMPA) and the NMDA-R1 receptor subtypes, and the melanocortin MC3 and MC4 receptor subtypes [75,84,85]. It contains the ER-alpha and ER-beta estrogen receptors and the AR androgen receptor. It synthesizes, transports and releases not only acetylcholine, the classical transmitter of all preganglionic neurons, but also cholecystokinin (CCK), CGRP, Leu-enkephalin, NO and somatostatin. It is surrounded by interneurons releasing bombesin, CCK, dynorphin, Leu- and Met-enkephalins, GABA, galanin, glycine, NPY, neuropeptide Y, nociceptin, SP, somatostatin and VIP. It is closely apposed by the terminals of sensory afferents that release CGRP, CRF, galanin, NO, SP and VIP, and by the terminals of descending pathways that release 5-HT, adrenaline, arginine-vasopressin, dopamine, NA, oxytocin, SP, thyrotropin-releasing hormone-TRH and alpha-MSH. In contrast to the anatomical demonstration of so many transmission pathways converging onto sacral parasympathetic neurons, the functional roles (if any) of all these transmitters in the spinal control of penile erection is far from being demonstrated.

The control of reflexive erections by forebrain structures on has been analyzed [86,87]. The tonic inhibition exerted by some descending pathways is released by a complete section of the spinal cord at the thoracic level [52,57], by a transient inhibition of cortical activity [88], by the bilateral lesion of the nucleus paragigantocellularis of the brainstem [89], and by the chemical lesion of the serotonergic pathways using 5,7-dihydroxytryptamine [90]. In rats, reflexive erections are depressed by buspirone and by 8-OH-DPAT, two agonists of the 5-HT1A serotonergic receptor subtype [91–93]. In anesthetized animals, the reflex response of the cavernous nerve to stimulation of the dorsal penile nerve is facilitated after the complete section of the spinal cord at the thoracic level and after systemic injection of m-chlorophenylpiperazine, an agonist of the 5-HT2C receptor subtype [94]. These experiments reveal the importance of the descending raphe-spinal serotonergic inhibitory pathway. Serotonin depresses reflexive erections through the 5-HT1A receptor subtype, but facilitates the recruitment of spinal pro-erectile neurons with the 5-HT2C receptor subtype.

Reflexive erections are depressed by the intrathecal injection of apomorphine, an agonist of the D1/D2 dopaminergic receptors [95], by RDS-127 (2-N,N-di-n-propylamin-4,7-dimethoxyindane [96]) and by quinelorane (LY-163502 [97]), two agonists of the D2 receptors, by thyrotropin-releasing hormone (TRH [98]) and by baclofen, a GABA-B receptor agonist [99]. Reflexive erections are also depressed by antagonists of alpha-2 adrenoceptors (yohimbine, idazoxan, imiloxan [100]), by propranolol, a beta-adrenoceptor antagonist [101] and by morphine [102].

As confirmed by this overview of the pharmacology of reflexive erections, there exists a large gap between the great variety of neurotransmitters and receptors present in the lumbosacral spinal cord and the limited number of experiments that have revealed a role for one of them in erection. Also lacking are (i) an integrated view of the whole system (why so many neurotransmitters?) and (ii) any evidence for any specialized neurotransmission system involved in the control of one pelvic organ. The sacral parasympathetic nucleus is very likely organized according to the principle of viscerotopy [103]. That is, each pelvic organ is controlled by a subpopulation of sacral preganglionic neurons that is located in one particular area of the nucleus. It is, however, unknown whether the specialized network of neurons that controls penile erection bears a unique combination of receptors.

Finally, much more research is needed to understand how three levels of intraspinal coordination regulate the spinal control of pelvic functions. The first level is the required coordination of sacral parasympathetic pro-erectile neurons with pudendal motoneurons, and with thoracolumbar
sympathetic anti-erectile neurons. Such coordination is better understood for the spinal control of the urinary bladder [104]. The second level is the required coordination between the spinal networks that control erection with the spinal network that controls ejaculation. A spinally located, ejaculation-dedicated neural network has recently been evidenced [105]. These important data open new perspectives for investigations in this domain, and we may now expect information on the intraspinal coordination between erection and ejaculation. The third level of organization is the reciprocal inhibitory influences existing between different pelvic functions. Reciprocal inhibitory interactions have been demonstrated between the bladder and the colon [106–108], and those between the bladder or the colon and the penis have not yet been explored. The anatomical basis of the intraspinal organizations controlling pelvic functions has been revealed by the experiments in which neurotropic viruses, which are transneuronally transported, have been injected into a variety of lower digestive and urogenital organs (see for example Ref. [40]). All experiments reveal a dense network of neurons, present in the intermediate plane of the lower thoracic, lumbar and sacral segments. This population is a prominent candidate for the role of integration and redistribution of information from peripheral and supraspinal origins onto autonomic preganglionic and pudendal neurons. The function of these networks now deserves experimental investigation.

Besides measuring the effects of chemicals on reflexive erections, attempts have been made to search for the role of some neurotransmitters in the excitation of spinal pro-erectile neurons. Thus, it has been demonstrated that agonists of the 5-HT2C receptor subtype elicits penile pressure rises without any peripheral stimulation in anesthetized rats [94], as do apomorphine [109], oxytocin [110], glutamate [111] and the melanocortin receptor agonist melanotan II (MT-II [112]). Apart from glutamate, which is a strong candidate for the neurotransmission of information from the sensory fibers innervating the penis to the spinal cord, the other molecules very likely mediate an excitatory, pro-erectile input originating in supraspinal nuclei.

4. Androgens and reflexive erections

In adult animals with a complete section of the spinal cord, castration strongly depresses reflexive erections [51]. In castrated rats that display few or no reflexive erections, testosterone [51,113,114] and dihydrotestosterone, but not estradiol [115,116], delivered peripherally, restore reflexive erections. The implantation of testosterone directly into the lower spinal cord, or into the spinal canal, also reverses the deleterious effects of castration on reflexive erections [117]. The androgen receptor is present in a population of lumbar and sacral dorsal root ganglion neurons (i.e., primary sensory neurons, some of which innervate the penis) [118], in sacral spinal cord interneurons that are activated during copulation [119], in spinal neurons [120], including sacral parasympathetic preganglionic ones [121] and pudendal motoneurons [122], and in neurons of the major pelvic ganglion [123,124]. Pudendal motoneurons concentrate dihydrotestosterone [125]. The development, survival, length of dendritic extensions, and maintenance of pudendal motoneuron activity are dependent upon androgens [126]. Testosterone could act through the control of the NMDA glutamatergic receptor expression by these neurons [127]. In the major pelvic ganglion, testosterone displays trophic effects [124], activates the synthesis of pro-erectile neurotransmitters such as NO [128] and facilitates the ganglionic nicotinic transmission [129].

5. Spinal lesions, reflexive erections and treatments for erectile dysfunction

Lesions of the spinal cord, such as those occurring during multiple sclerosis, spinal cord injury, tumor, syringomyelia, transverse myelitis, arachnoiditis, disk disease and myelodysplasia, can lead to erectile dysfunction [1]. As mentioned above, reflexive erections remain if the sacral reflex arch is spared. Although the basic mechanisms through which the spinal cord controls erection in physiological conditions are better understood today, this set of information has not yet provided any track for an efficient treatment of erectile dysfunction through spinal targeting, in both spinally intact and spinally injured patients. An intriguing aspect of experimental models of spinal trauma is the report of erections in animals with a complete lesion of the lumbosacral spinal cord [130], which would remove parasympathetic influence. One possible hypothesis to explain the onset of erections in these animals is that it reflects the remaining activity of sympathetic pathways (a lowering of the activity of anti-erectile sympathetic pathways and perhaps a redirection of blood flow from non-erectile tissues) occurring in a sexually relevant context [13].

6. The supraspinal control of penile erection

In humans and animals, penile erection occurs in several contexts, some of which have nothing to do with a sexually relevant context. Erections have been observed in utero in humans [131], and in rats during copulation, in response to genital stimulation, during sleep [132], in the presence of a receptive female with no possibility to engage in copulation (“noncontact erections” [133]), and in response to the injection of centrally acting drugs [134]. It is possible that several different areas of the brain contribute to the occurrence of erections in the different contexts [135]. Each context may reflect the contribution of a unique combination of several brain nuclei. One brain nucleus may contribute to the genesis of erection in several contexts. The contribution
of each nucleus to erection depends upon the amount of excitatory and inhibitory information that it receives from the periphery and from other central nuclei, and to its hormonal environment. In the male brain, both androgens and estrogens play an important regulatory role. A final challenge is to understand whether the brain selectively and separately processes information regarding sex behavior and penile erection, with at least some interrelations between them, or if penile erection is just one of many outputs of a central network devoted to sex behavior.

The first candidates for a role in the supraspinal control of erection are those nuclei that project directly onto the sacral spinal cord. Such nuclei contain pre-motor neurons that project onto central output neurons (either autonomic or somatic motoneurons), and they largely contribute to bodily homeostasis [136]. With regards to penile erection in rats, these neurons have been localized using their trans-synaptic labeling with pseudorabies virus injected into the corpus cavernosum [40]. They are present in a variety of brainstem, pons and hypothalamic nuclei. Attempts to demonstrate the role of these brain structures in the control of erection have used, among other techniques, selective central lesions in animal models.

The medial preoptic area of the hypothalamus is a key structure in the central control of the male sexual behavior [137]. The medial preoptic area is not the source of projections to the spinal cord. Lesions of the medial preoptic area do not affect either noncontact or reflexive erections [138]. The parvocellular part of the paraventricular nucleus of the hypothalamus contains neurons that send direct oxytocinergic and vasopressinergic projections to the lumbosacral cord. Paraventricular nucleus lesions increase the latency of noncontact erections and diminish their number, but are devoid of effect upon erection during copulation, and facilitate reflexive erections [139,140]. The nucleus paragigantocellularis of the brainstem contributes descending serotonergic fibers to the lumbosacral cord. Its bilateral lesion removes an inhibition normally exerted upon reflexive erections and erections during copulation [89,140,141]. Finally, lesions of the medial nucleus of the amygdala, which have no effect upon erections during copulation, facilitate reflexive erections but depress noncontact erections [142].

Other attempts have used models that do not reflect a natural context. Among them are experiments in which electrical or pharmacological stimulation of central brain structures or pathways have been performed. Thus, it has been demonstrated that electrical stimulation of the medial preoptic area and of the paraventricular nucleus in monkeys and rats elicit complex sexual and genital responses including erection [143–146]. Some drugs injected in conscious animals elicit erection in the absence of any sexual stimulation. This is true for m-chlorophenylpiperazine, a metabolite of trazodone and a 5-HT2C serotonergic receptor subtype agonist, when it is injected in monkeys and rats [147,148]. In rats, systemic apomorphine [134] and the intracerebroventricular injection of oxytocin, glutamate, apomorphine, NO donors, adrenocorticotropic hormone (ACTH), alpha-melanocyte stimulating hormone (α-MSH), Melanotan II (MT-II) and PT-141 (these four last molecules being agonists of melanocortin receptors [110,149–154]) also elicit erections. It is recalled here that, even if erection is the final common expression of a variety of contexts, it is the result of the actions of several brain nuclei that are recruited through different stimuli that are specific for each context. Therefore, one cannot expect from the recording of a pro-erectile effect of a drug acting centrally any information on the brain nuclei that are targeted. The analysis of studies using either local microinjection directly within brain structures and of studies in which peripheral injections are made in parallel with selective central lesions provides nevertheless some clues. Thus, the paraventricular nucleus of the hypothalamus in rats is an obligatory structure in the pro-erectile effects of apomorphine and oxytocin [155].

Again, one drug may or may not affect erection, depending upon the experimental paradigm used. Apomorphine, whatever its route of delivery, elicits erection in the absence of sexual stimulation in several animal species [156]. It depresses reflexive erections when is it delivered intrathecally, and has no effect upon erections during copulation [95]. The agonists of the GABA B receptor subtype depress both reflexive erections [99] and erections elicited by apomorphine, but have no effect on erections during copulation [99].

7. Central brain lesions in humans and penile erection

Among the neurologic disorders than can cause erectile dysfunction through alteration of central pathways are tumor, stroke, encephalitis, Parkinson’s disease, dementias, the olivopontocerebellar degeneration (Shy-Drager syndrome) and epilepsy of the temporal lobe [1,157]. In contrast, erections occur after lesions of the pyriform cortex and amygdaloid complex (the Kluver-Bucy syndrome [84]).

8. Perspectives for treating erectile dysfunction in humans through a central target

The link between dopaminergic pathways and central pro-erectile pathways has been indirectly evidenced in human patients suffering from the alteration of dopaminergic transmission. Some Parkinson’s patients treated with apomorphine, L-DOPA or bromocriptine report the occurrence of erections and increased libido or an improved sexual interest [158–163]. The effects of apomorphine in these patients must be evaluated on a basis different from other patients [164]. Indeed, Parkinson’s patients undergo a dramatic decrease of central dopaminergic transmission, and therefore their response to apomorphine does not corre-
spond to the response of other patients. In some patients that do not respond to anti-Parkinsonian drugs, transcranial stimulation with AC pulsed electromagnetic field induces sexual arousal and penile erections. It is hypothesized that this stimulation results in activation of central D2 dopaminergic receptors [165]. In contrast, Parkinsonian signs are side effects of drugs that antagonize dopamine. Such drugs are used in the treatment of schizophrenia. In schizophrenic patients, amantadine and apomorphine have a positive effect on erection, and amantadine improves the patient’s desire and satisfaction from sexual performance, but does not affect ejaculation [166,167].

Pro-erectile effects of apomorphine in humans have been described in patients treated for alcoholism [168]. In this study, 63% of the apomorphine treated patients report the occurrence of erection during treatment. Apomorphine elicits erection as revealed by an enlargement of penile circumference in normal human subjects [169–171]. It increases penile volume, without any other stimulation, and enhances erections elicited by visual sexual stimulation. Side effects of sublingual apomorphine include nausea, headache, dizziness, rhinitis and pharyngitis [172]. In contrast to the pro-sexual effects of apomorphine in rats, apomorphine sublingual has no significant effect on libido in humans [173]. In humans, the pro-erectile role of another dopaminergic agonist, bromocriptine, is controversial: depending on the study, it has no effect [174] or improves the ability to obtain an erection [175, 176]. The frequency of nocturnal penile tumescence and total tumescence time during sleep is significantly increased in 50% of patients who received L-DOPA administration [177].

The use of melanocortin receptor agonists as a therapeutic option for the treatment of erectile dysfunction has drawn much attention in the recent years. The two melanocortin receptor agonists, MT-II and PT-141, have undergone early clinical trials. MT-II-induced erections were reported as the side effect of the drug administration in a preliminary clinical study [178]. Subsequently, the pro-erectile effects of MT-II were evaluated [179, 180]. The studies have provided clear evidence that MT-II exerts a pro-erectile activity in patients with erectile dysfunction of various origins. The enhanced sexual desire reported with MT-II warrants further investigation of the effect of melanocortin receptor agonists. Also, MT-II elicits side effects such as nausea, stretching and yawning and decreased appetite more frequently than does placebo. The pro-erectile effects of intranasally delivered PT-141 on penile erection in humans have been demonstrated [154]. No serious side effects were reported after PT-141 administration both in normal subjects and in patients with erectile dysfunction.

9. Androgens and the central control of penile erection

As castration depresses sexual behavior, it is not possible to record any erections during copulation in castrated male rats, although there are historical and clinical reports of castrated men keeping sexual activity and erections. In these men, it is possible that castration was performed when they were adults, a time after androgen-dependent systems have been organized during the neonatal period and activated during puberty. In rats, castration suppresses noncontact and apomorphine-induced erections [181–183]. In contrast, apomorphine restores mounts, intromissions (and the concurrent erections) and to a lesser extent ejaculation in those castrated animals [184]. Dihydrotestosterone restores apomorphine-induced erections but not erections during copulation in castrated rats [185]. Estradiol restores copulation and erection in copula but not noncontact erections in castrated rats [181]. Analysis of the sex-steroid regulation of penile erection suggests another classification of erections. A distinction exists between testosterone- and dihydrotestosterone-dependent erections, which are mainly controlled by the spinal cord, and testosterone- and estradiol-dependent erections, which are mainly controlled by supraspinal nuclei. However, this does not completely explain the presence of both androgen and estrogen receptors at all levels of the neuraxis, nor does it exclude a regulatory role of androgens in the periphery. Androgen receptors are present in the medial preoptic area and paraventricular nucleus [117,186]. The direct implantation of testosterone in the brain [187, 188] revealed that the hormone restored the sexual behavior of castrated male rats through a central effect. Thus testosterone and its metabolites, estradiol and dihydrotestosterone, act at all levels of the “sexual” neuraxis.

10. Provisory conclusions

What can we learn and what can we expect from the developments in basic and clinical research on the nervous control of penile erection? The last 20 years have seen tremendous advances in the understanding of the basic mechanisms of erection and in efficient treatments of erectile dysfunction. However, one should not forget that (i) the role of the various abdominal and pelvic nerves in the control of penile erection had been clearly stated at the end of the 19th century (see Ref. [15] as an example), and (ii) some outstanding results, mainly in the basic research field, have been unfortunately ignored. This sometimes occurs when articles were not published “at the right time”; see for example Ref. [189], a complete and elegant demonstration of the relaxant effects of NO on bovine and canine penile arteries, at a time when NO was not recognized as a molecule present in living organisms. Another cause for diminished impact is that the most appropriate audience was not targeted; see for example Ref. [134], a definitive demonstration of the central pro-erectile effects of apomorphine in rats.

With regards to the treatment of erectile dysfunction, much progress has been made, although the definitive
advances have not been discovered through the mainstream of thoughts and practices. Furthermore, a gap still exists between animal models that are used for the demonstration of drug effects and the use of the same drugs to treat erectile dysfunction in patients.

Thus, the emergence of NO as the principal pro-erectile agent at the periphery definitively refutes the concept that the effects of parasympathetic pathways are due to the release of acetylcholine by postganglionic fibers. Furthermore, it is interesting to note that, although the concept of nonadrenergic, noncholinergic (NANC) neurotransmitters was already established with regards to the activity of the autonomic nervous system, it is not one of the recognized NANC transmitters (ATP, VIP, NPY) that has proved efficient in the control of erection, but NO. Finally, the amplification of the NO effects by using phosphodiesterase-type 5 inhibitors is today a major treatment option for men with erectile dysfunction [37]. It should be recalled here that among the compounds that possess this inhibitory effect, the first one proposed for the treatment of erectile dysfunction, UK-92,480 (Viagra), was not developed for this purpose, and failed to remedy the problems for which it was first developed (angina and hypertension). Pro-erectile effects of the drug were reported only as side effects [190]. This is another illustration that there is no logical cascade of events and decisions from fundamental biology to clinical applications, and that the final outcome of a research program is not always predictable. Another important and promising area of research in the field of erectile dysfunction, which is not covered by this review, is the analysis of the role of the endothelium and vascular functions in the penis, and the endothelium dysfunction that is associated with conditions of erectile dysfunctions [191].

In contrast with the advances in the understanding of the peripheral mechanisms of penile erection, paralleled by the production of treatments targeting these mechanisms, the picture provided by the studies on the spinal and brain control of penile erection is less clear. We can today identify some brain structures that, when stimulated, elicit erection. The activity of these brain structures is regulated by a very complex milieu made of many different neurotransmitters and sex steroids. Among the neurotransmitters, some are excitatory, others inhibitory, and some are only regulatory. Each neurotransmitter can affect the activity of a brain nucleus through several receptor subtypes. It is very likely that pro-erectile brain nuclei cannot be defined on the basis of their neurotransmitter-receptor subtype specificity, making the treatment of men with erectile dysfunction with drugs acting in the brain very difficult. However, the recent results of clinical approaches using agonists of melanocortins are promising.

If one considers the several peripheral (smooth muscle, endothelium) and central (spinal cord, supraspinal nuclei) targets and several strategies (gene therapy, peripheral nerve grafts or repair, peripheral and central pharmacology) available today, one can evaluate the advances that have been achieved over the last 15 years in the possible therapies for erectile dysfunction [192,193].

References


