Central Nervous System Agents and Erectile Dysfunction

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KEYWORDS

• Apomorphine • Melanocortin • Serotonin
• Erectile dysfunction • Central agents

Cortical regions act as centers for integration of sensory stimuli and hormonal influences to initiate sexual desire and libido. These stimuli and hormones then act through sympathetic and parasympathetic pathways to control the peripheral activities that result in a penile erection. These cortical pathways explain the occurrence of erections without genital stimulation such as those occurring during fantasy, visual stimuli, and sleep. Whereas the role of nitric oxide (NO) as an end effector has been well established, the role of the central nervous system (CNS) in mediating penile erections remains unclear despite several laboratory and animal studies attesting to its importance. Initial studies were based on animal models with retrograde labeling of pathways, but more recent reports have used newer techniques such as the positron emission tomographic scan.[1,2]

Among a large variety of areas that may potentially be involved within the cortex, the medial preoptic area and the paraventricular nucleus (PVN) of the hypothalamus along with the hippocampus seem to be the principal areas of interest.[3] The PVN contains dopaminergic neurons whose stimulation is associated with penile erection. Whereas injection of dopaminergic agents in this region potentiates erections, lesions in this region result in a loss of erectile ability.[4,5] In further attempts to characterize the role of the PVN in erectile functioning, Richards and colleagues[6] recorded potentials from individual neurons in the PVN as well as local field potential activity in anesthetized rats during erectile activity. Apomorphine in erectogenic doses was injected peripherally and resulted in variable firing patterns of the neurons in the preerectile and erectile phases (**Figs. 1** and **2**).

The melanocortinergic system also has multiple sites of action within this complex network. This system consists of neuropeptides such as adrenocorticotropic hormone, β-endorphin, and α, β and γ melanocyte-stimulating hormones (MSHs) apart from their receptors and various antagonists. The melanocortins are posttranslational products of the prohormone pro-opiomelanocortin (POMC), which produces 8 different peptides based on the site of cleavage. POMC messenger RNA exists in several human tissues including the genitourinary tract. Among the various melanocortin receptors (MCRs), MCR3 and MCR4 have been found in the hypothalamus and MCR4 primarily has been seen to be involved in modulating sexual function.[7,8]

The CNS administration of α-MSH induces penile erections and yawning, somewhat similar to that seen with apomorphine. Mizusawa and colleagues[9] implanted catheters in the lateral cerebral ventricle or the subarachnoid space in 78 male Sprague-Dawley rats and injected α-MSH. These injections resulted in penile erections and an increase in intracavernosal pressure, which was abolished by the administration of NO inhibitors. Similar responses were produced by intracerebroventricular oxytocin, but intrathecal α-MSH did not produce any erectile response, suggesting a central role for α-MSH.

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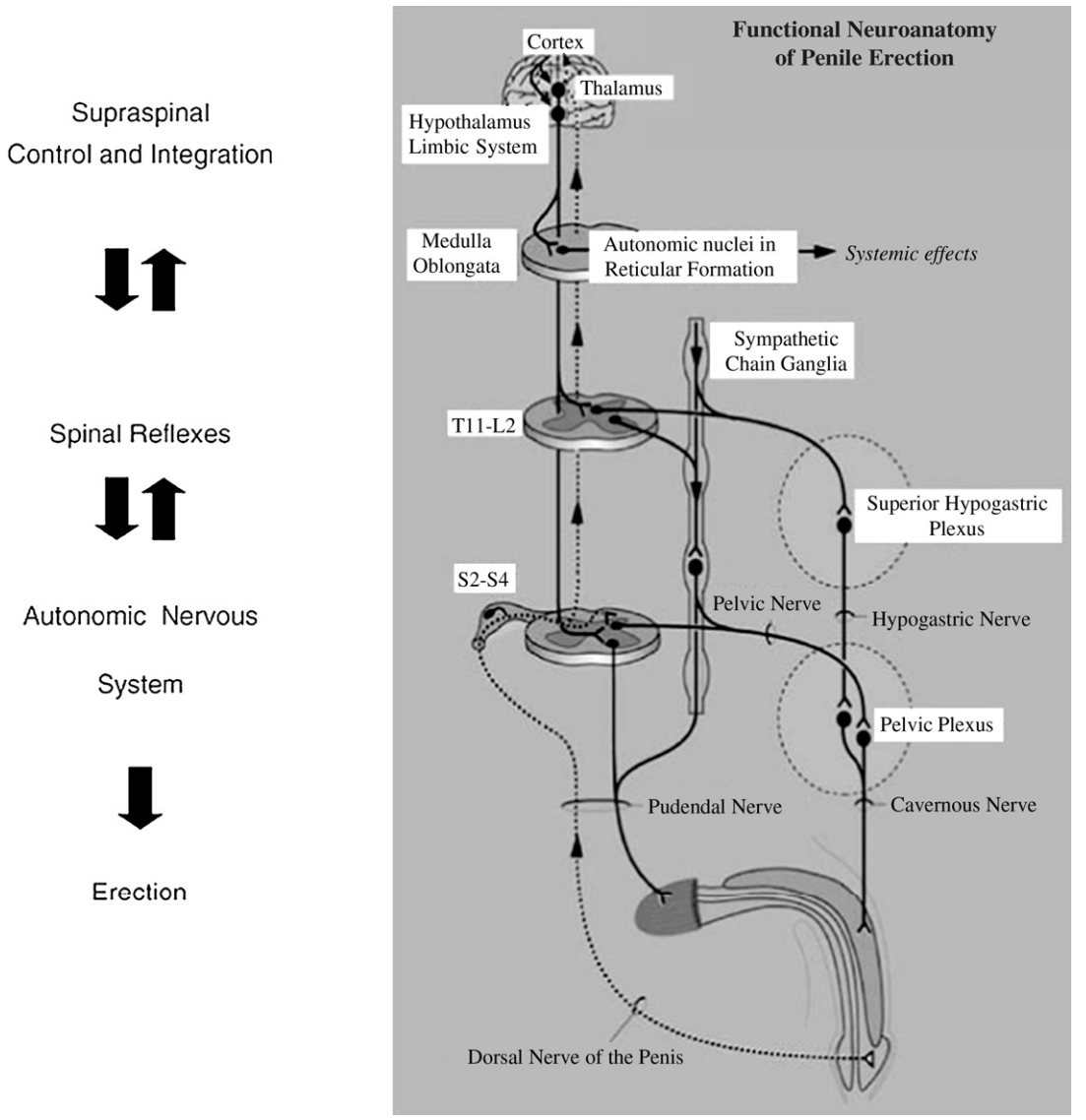

Fig. 1. Functional neuroanatomy of penile erection. (*From* Graugaard C, Hertoft P, Møhl B, editors. Hjerne & Seksualitet: Aspekter af Teori & Klinik. Copenhagen: Munksgaard Denmark 1997; with permission.)

Centrally acting agents are not among the currently recommended treatments for erectile dysfunction (ED) in the guidelines of the American Urological Association and the European Association of Urology.[10,11] These guidelines recommend phosphodiesterase 5 inhibitors (PDE5i) sildenafil, tadalafil, and vardenafil as first-line therapies with options including prostaglandin E_1, intracavernosal vasoactive agents, vacuum constriction devices, and penile prosthesis. The guidelines recommended switching from an oral to an alternate therapy among nonresponders.

PDE5i have a significant failure rate, including both primary and secondary failures among patients who may have initially responded to therapy. Further, some patient groups, such as in those after radical prostatectomy, have poorer outcomes with PDE5i. Adverse effects, time to onset of action, and lack of spontaneity are additional concerns with these agents. The current guidelines leave little oral options for these men, and there is clearly a potential for the development of alternative therapies. The principal reason for the recommendation against centrally acting