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Neurophysiology of Erectile Function: Androgenic Effects

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Penile erection is a highly specialized vascular biologic process that requires regulatory control. Among the regulatory mechanisms contributing to this regulation, the nervous system is perceived to be the primary regulatory mechanism affording this control. Multiple levels of the neuroaxis, from the brain and spinal cord to nerves terminating within the penis, originate and relay neurochemical impulses that produce the erectile response.

At the same time, it is known that androgens exert prominent roles in the development and maintenance of assorted neuronal circuits involved in male sexual function. These roles are exerted both at central and peripheral nervous system levels. The study of androgenic effects has primarily examined central mechanisms, with a focus on sexual differentiation of the vertebrate brain. Cellular mechanisms under androgenic control include neurogenesis, cell differentiation, cell migration, synapse formation, synapse elimination, and cell death. Additional emphasis has been given recently to androgenic effects on peripheral neuronal pathways. Characterization of androgenic effects on peripheral neurons has primarily pertained to structural and biochemical changes occurring most notably at puberty and after castration, although recent investigation has also identified electrophysiologic changes amid these perturbations.

This presentation provides a brief contemporary review of the neural control of penile erection at central and peripheral levels, with special consideration given to the androgenic influence on the neuroanatomy, neural pathways, and neurological mechanisms involved in the erectile response. Accordingly, the extent to which androgens exert a humoral regulatory basis on the primary control system for erection will be assessed. Insights drawn from this review may reveal whether pharmacotherapeutic interventions involving the nervous system using testosterone supplementation are possible to treat male erectile dysfunction. It is recognized that most of the knowledge base regarding this subject matter is derived from laboratory animal studies, and direct evidence of androgenic effects on human penile erection remains fairly limited. Furthermore, real differences in androgenic effects are known to exist between commonly used laboratory animals and primates, such as the distinction that aromatized metabolites androgens do not influence sexual dimorphism in primates (Cooke et al, 1998). Nonetheless, the information presented herein offers an opportunity to consider

aspects of androgenic control of neurophysiologically mediated penile erection. Limited inferences regarding human erectile function may best be drawn at this time.

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Several brain nuclei are proposed to participate in the supraspinal control of penile erections (Burnett, 2000). Coordinating centers (in descending order of the neuroaxis) include the cortical and subcortical areas, the diencephalon consisting of the medial hypothalamic area (the paraventricular nucleus, the medial preoptic area [MPOA], and the dorsal hypothalamic area), and the brain stem (see Table). At the spinal cord level, important nuclei include the intermediolateral cell column (referred to as the sacral parasympathetic nucleus at lumbosacral levels), which governs autonomic input to the pelvis; the medial dorsal horn and dorsal commissural nucleus, as the sensory input circuit for spinal reflexes; and the Onuf's nucleus (also known as the spinal nucleus of the bulbocavernosus) located in the ventral horn at lumbosacral levels, which innervates the penile-associated striated muscles. In the brain, nuclei of the diencephalon likely connect with spinal cord levels that mediate reflexive penile erections as well as with various other brain sites that suggests its function in integrating ascending and descending neural information. The spinal cord mediates neural reflexive loops between penile afferents and both autonomic and somatic efferents required for reflexive erectile responses. The central neurochemistry mediating sexual behaviors include diverse agents, established through various morphological and pharmacological studies in animals. Putative roles exist for monoamines (dopamine, norepinephrine, and 5-hydroxytrypatmine), decarboxylated amino acids, neuropeptides (oxytocin, prolactin, adrenocorticotropin, opioids), and gaseous molecules.

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Supraspinal centers regulating sexual function

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The neuroregulation of penile erection peripherally requires the coordination of the parasympathetic, sympathetic, and somatosensory neural pathways (Burnett, 2000). These pathways describe efferent and afferent projections. The efferent projection relevant to penile erection refers to the thoracolumbar sympathetic (T_{10}-L_2) and sacral parasympathetic (S_2-S_4) divisions of the autonomic nervous system, and the sacral somatic (S_2-S_4) nervous system. The autonomic input is primarily represented by the cavernous nerves, arising from the inferior hypogastric plexus, and the somatic input is represented by the pudendal nerves, which course from the sacral plexus. The afferent projection relevant to penile erection involves sacral innervation (S_2-S_4) and is represented by the dorsal nerves of the penis, sensory branches of the pudendal nerves.

In combination, these neural pathways regulate the sequence of blood inflow and engorgement of the

penis, and they also coordinate the activity of the penile-associated striated muscles, which contract to augment penile rigidity. The effector sites of action within the penis are the vascular smooth muscle components, the vasculature supplying the penis, and the trabeculae comprising erectile tissue of the penis (Burnett, 2000). These components respond to the appropriate neuronal stimulus by generating a degree of vascular smooth muscle tone that influences the erection state of the penis. During penile tumescence and erection, the penile vasculature vasodilates and the trabecular tissue becomes relaxed. During the tonic state of flaccidity, the penile vasculature is vasoconstricted and the trabecular tissue is contracted. Current concepts support the predominant role of nitric oxide, a gaseous messenger molecule, as the principal mediator of penile erection serving both as a neurotransmitter and as an endothelial effector (Burnett, 2002), although other neurotransmitters are known to influence the neuroregulation of penile erection. The facilitation of proerectile neurotransmitter mechanisms and inhibition of antierectile neurotransmitter mechanisms are together involved in producing maximal penile erection.

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The concept of steroid-sensitive neurons and neuronal regulatory pathways is well established in the central nervous system. A major area of study pertains to sexual dimorphism, which associates hormone influences with brain regions that govern male or female behaviors. Androgens and estrogens exert effects via regions expressing steroid receptors that regulate diverse neuronal properties during maturation and throughout adulthood. These regions are represented throughout the nervous system without concentration to a single structure or neuronal center.

Probably the best characterized sexual dimorphic neuromuscular system in mammals involves the spinal nucleus of the bulbocavernosus muscle (SNB). This nucleus describes a group of motoneurons in the lower lumbar spinal cord that innervate striated ischiocavernosus, bulbocavernosus, and levator ani muscles attached to the penis. The rat has served as a primary animal model to investigate this nucleus, located in the dorsomedial portion of the ventral horn in lumbar segments 5 and 6 in this species. Male rats possess at least 3 times as many SNB motoneurons as do females, and these motoneurons are twice the size in males compared with females (Breedlove and Arnold, 1980). Although both male and female rats possess SNB cells that synapse upon bulbocavernosus muscles before birth, the muscles and their respective motoneurons normally degenerate shortly after birth in female rats (Breedlove and Arnold, 1983). This developmental process establishes the adult sex differences in SNB motoneurons and target muscle fibers. Various lines of evidence involving hormone exposure and withdrawal perinatally in genetically male and female rats resulting in distinct morphological changes have reinforced these observations (for additional review, see Cooke et al, 1998).

Such experimental evidence strongly indicates that androgens affect the mediation of penile reflexes associated with the SNB. What is the mechanism for such regulation? Developmental studies favor the hypothesis that SNB motoneurons preserved under the influence of androgens spare the target muscles, thereby resulting in the sparing of all related innervation (Breedlove and Arnold, 1983). Neurotrophic factors are thought to be regulated or sensitized by androgens to maintain the muscles and their associated motoneurons (Forger et al, 1995; Al-Shamma and Arnold, 1997). An androgenic influence is also believed to exert a maintenance role in adulthood (Rand and Breedlove, 1995; Nanasaki and Sakuma, 2000). The basis for the trophic effects in adulthood relates not only to androgenic support of penile-associated striated muscles. At this maturation level, SNB motoneurons have also developed to express androgenic receptors such that they react directly to androgen exposure to maintain somata size (Freeman et al, 1996).

Perhaps the most studied sexually dimorphic neural center is the MPOA, with information drawn from various species, including humans. Within this nucleus, a sexually dimorphic group of neurons have been identified across various species, and in rats they are as much as 5 times greater in size in males than in females (Gorski et al, 1980). The cytoarchitecture of these neurons is also divergent between genders in rodents, with respect to synaptic fields and connections (Raisman and Field, 1973). Receptor-binding studies have localized steroid sites to these specific neurons, with a greater concentration of nuclear estrogen receptor-binding sites in female rats than in male rats and a greater extent of androgen receptor-binding sites in male rats than in female rats (Jacobson et al, 1987). However, the function of this sexually dimorphic neural center in mammals remains uncertain, with equivocal data even at the rodent level: after lesioning the area, there are no changes in male copulatory behaviors in rats, whereas a diminution of these behaviors results in gerbils (Cooke et al, 1998).

The androgenic regulation of MPOA sexually dimorphic neurons adheres to both organizational (developmental) and aromatization hypotheses in studies of the rat. The humoral influence on neurogenesis and neuronal growth in fetal and early postnatal life implies developmental effects (Gorski et al, 1980). Changes in gonadal steroid exposure in adulthood do not affect the morphology of this nucleus (Gorski et al, 1980). However, the long-term testosterone replacement in aged rats has been shown to preserve mounting behavior as well as dopaminergic activity in the MPOA (Sato et al, 1998), implying that at least sustained androgenic exposure may exert effects in adulthood beyond the morphological level. Interestingly, estrogen treatment more effectively elicits normal maturation of this select population of neurons than does androgen treatment in rats, indicating that aromatized metabolites of androgen sufficiently masculinize these neurons (Dohler et al, 1984).

Other sexually dimorphic central nuclei have also been described mostly along morphological grounds and primarily in rodent species. These include the olfactory limbic system (medial amygdala, bed nucleus of the stria terminalis, preoptic area), hippocampus, and assorted hypothalamic nuclei.

The association of androgens and the function of peripheral autonomic neurons have only recently come under study. Androgen receptors and androgenic sensitivity have been demonstrated for lumbosacral preganglionic neurons, sympathetic and parasympathetic postganglionic neurons, and sensory postganglionic neurons (Schirar et al, 1997b). A great deal of interest has been given to the autonomic ganglion cells of the pelvic ganglion, which comprises a mixture of sympathetic and parasympathetic neurons. In rats, sympathetic neurons change in size most markedly after castration or testosterone administration (Keast and Saunders, 1998). In parallel with this observation, testosterone exposure is directly related to membrane capacitance of sympathetic neurons in pelvic ganglia of rats (Kanjhan et al, 2003). Although evidence suggests that androgens primarily influence neuronal cell body growth and size, additional evidence points to their effect on ion channels and second messenger pathways associated with pelvic ganglion neurons. For instance, in rats, castration results in a depleted neurochemical content of nitric oxide synthase, which generates nitric oxide neuronally, whereas testosterone replacement after castration restores this neurochemical level (Schirar et al, 1997a). Similar effects have been demonstrated for postganglionic cavernous and dorsal nerve terminations in the rat penis (Giuliano et al, 1993; Baba et al, 2000).

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Multiple lines of experimental evidence establish the major role of steroid hormones in the sexual differentiation of neural systems in animals. Aside

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from the morphological evidence, to what extent do sexually dimorphic neural centers exert functional effects in humans? A definite issue in this matter is that it is difficult to distinguish in the adult human brain whether circulating gonadal steroids account for a sexual dimorphism unrelated to early, fetal steroid action. In addition, sexually dimorphic structural differences may be explained on the basis of human experience, either during development or in adulthood, again without relation to fetal steroid action. Resolution of such difficulties could be achieved if sexual dimorphisms are obvious at birth, although limited examples exist to support this contention. The concern that the weight of the human brain is greater in males, as an example, could be associated with an effect of androgens on the release and action of other factors such as growth hormone other than by direct action of steroids. Conceivably, many of the sexually dimorphic differences in humans could indeed result from androgen exposure at some significant time postnatally. Evidence in humans is entirely inconclusive to render a statement as to whether exposure to fetal hormones determines sexually dimorphic behaviors. There is no evidence to support the aromatization hypothesis in humans, and the example of the androgen-insensitive XY individual who does not display masculine behaviors despite a feminine exterior would certainly argue against this hypothesis. Thus, definitive proof that steroids acting early in development directly masculinize the human brain remains lacking.

Accordingly, on the basis of the experimental evidence on this subject, determinations about androgenic control over the neuroregulation of human erection should be restrained. On the other hand, because it is clinically apparent that androgens do influence male sexual behaviors, there remains an obvious interest to explore how and where steroid hormones regulate the adult human brain. Evidence in favor of androgenic effects on the neuroregulation of erection in humans is provided by clinical data that show the importance of androgens on erections measured during nocturnal penile tumescence testing in the sleep laboratory (Cunningham et al, 1990). The current understanding is that sleep-related erections involve activation of supraspinal regulatory influences operating during rapid-eye-movement sleep (Lue, 2002). The preservation of sleep-related erections to a greater extent in men with eugonadism than in men with hypogonadism strongly suggests androgenic modulation of this mechanism. However, other manifestations of erection neurophysiology, such as responses to visual sexual stimulation or sexual partner stimulation, may not operate under such obvious androgenic control. Indeed, men with hypogonadism may achieve erections to permit sexual activity, and men with eugonadism may experience difficulty in achieving erections to perform sexually. A range of regulatory factors may certainly be involved under these various circumstances and exert predominant roles irrespective of the degree of androgenic support.

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