Published in final edited form as:

J Sex Med. 2009 March ; 6(Suppl 3): 221–228. doi:10.1111/j.1743-6109.2008.01180.x.

CLINICAL AUTONOMIC NEUROPHYSIOLOGY AND THE MALE SEXUAL RESPONSE: AN OVERVIEW

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Abstract

Introduction—Clinical neurophysiology is the study of the human nervous system through the recording of bioelectrical activity. In the realm of male sexual functioning, this includes using electrophysiologic techniques to study the nerves subserving erection, emission, ejaculation, and orgasm.

Aim—To introduce the reader to the principles of clinical neurophysiology as they relate to the male sexual response, particularly erection.

Methods—We review the pertinent autonomic neuroanatomy and neurophysiology of reflexes relevant to the male sexual response, as well as summarize the genital electrodiagnostic tests that are being used to interrogate the autonomic innervation pertinent to male sexual functioning.

Conclusions—The male sexual response is a coordinated series of interactions between the somatic and the autonomic nervous systems. Measurement of the autonomically mediated portions of the sexual reflexes is of great clinical interest, particularly in relation to erection. Advances in clinical electrodiagnostics now allow for consistent recording of evoked and spontaneous intra-penile electrical activity. However, before broad and widespread use of these techniques is possible, more investigations are needed.

Clinical neurophysiology is the study of the human nervous system through the recording of bioelectrical activity. In the realm of male sexual functioning, this includes using electrodiagnostic techniques to study the nerves subserving erection, emission, ejaculation, and orgasm. Most current physiological research in sexual medicine focuses on the molecular and cell biological mechanisms of sexual function and dysfunction. However, there is much to be learned from “circuit-testing” the nerve pathways subserving the sexual response, using electrodiagnostic techniques. The nervous system is intricately involved with sexual function, but how the central nervous system and peripheral nerves mediate the sexual response is still largely unknown. Clinical neurophysiology utilizes electrodiagnostic methods such as evoked potential studies and electromyography (EMG). These can be modified and used in clinical and research settings not only to define genital neuropathology, but to clarify the physiology of the sexual response. From this knowledge, applications for the diagnosis and treatment of neurogenic sexual dysfunction can be generated.

Standard electrodiagnostic medicine pertains to the study of the somatic nerves. However, in sexual medicine, the most important aspects of the sexual response are mediated by autonomic nerves. In healthy men, autonomic neural impulses travel through the cavernous nerves to effect penile vascular changes during erection and detumescence. In most

instances of neurogenic erectile dysfunction (ED), the cavernous nerve pathways are impaired; however, an accurate diagnosis is difficult without some means of assessing the extent of nerve impairment. A reliable, easy-to-use diagnostic method to accurately confirm cavernous nerve impairment would improve urologists' ability to accurately diagnose and treat neurogenic ED.

In the text that follows, we will briefly review the pertinent autonomic neuroanatomy and neurophysiology of reflexes pertinent to the male sexual response, as well as summarize the genital electrodiagnostic tests that are being used to interrogate the autonomic innervation pertinent to male sexual functioning.

I. GENITAL NEUROANATOMY

The male genitalia are innervated by both somatic and autonomic nerve fibers (Figure 1).

A. Somatic innervation

Somatic nerves are myelinated, and thus of large diameter, and conduct neural impulses relatively rapidly. Somatic motor fibers mediate impulses to skeletal muscles (under *voluntary* control), and somatic sensory fibers mediate information from the skin, skeletal muscles, and joints.

The somatic sensory and motor innervation of the male genitalia is carried via branches of the pudendal nerve.¹ The pudendal nerve arises from sacral spinal segments 2–4 (S₂–S₄). The nerve enters the perineum after traveling through the Alcock's canal. There are three branches of the pudendal nerve (dorsal nerve of the penis, perineal and inferior rectal), each carrying sensory input to the S₂–S₄ spinal levels from the genital structures, which is relayed through the central nervous system via ascending spinal tracts.^{2, 3} The skeletal pelvic floor muscles receive somatic innervation mainly from the motor branches of the pudendal nerve (perineal, inferior rectal).⁴

B. Autonomic innervation

Autonomic fibers are small diameter, poorly or non-myelinated, and conduct neural impulses relatively slowly. Their motor impulses mediate *involuntary* responses such as sweat gland release, blood flow, and gut peristalsis. Autonomic sensory fibers are known as visceral afferents, and conduct sensory information from the viscera and blood vessels to the central nervous system (CNS).

The exact pathways of the genital autonomic fibers within the human have not been documented, but they generally follow the major arteries of the abdomen and pelvis. The pelvic plexus is the main crossroad for genital autonomic nerves, consisting of parasympathetic fibers from the sacral nerve roots (S₂–S₄) and sympathetic nerve fibers from the thoracolumbar sympathetic nerve roots (T₁₁–L₂). The plexus lies on either side of the bladder and rectum, and supplies all the pelvic viscera, including the bladder and urethral sphincter, and the male genital tissue. The autonomic fibers to the penis are collectively called the cavernous nerve, and regulate blood flow to the erectile tissue.

II. SEXUAL REFLEXES

In neurophysiological terms, bodily functions such as the sexual response can be considered reflex events. A reflex is an involuntary event in response to a stimulus. The male sexual response can be considered as four events— erection, emission, ejaculation, and orgasm— and each of these can be considered as part of a reflex. A reflex arc is comprised of an afferent arm, through which stimuli enters the central nervous system, and an efferent arm, through

which motor signals generate a particular response. Understanding the reflex concept can provide a foundation for some of the electrodiagnostic tests that will be described below.

One manner to consider the male sexual reflexes is diagrammed in Figure 2. Sources of sexual stimuli into the CNS (the afferent arms of the reflex arcs) can arise from: the special senses (e.g., vision, hearing) or sexual fantasy; non-genital erogenous areas of the body (e.g., nipples, neck); and from the genitals. The resultant responses (efferent arms) can be emotional and psychological changes (e.g., pleasure); systemic non-genital responses (e.g., heart rate and respiration increases, skin flushing; and genital changes (e.g., erection, ejaculation). Any of the afferent signals or inputs to the nervous system can theoretically result in an efferent response, illustrating that the sexual response is a *series* of reflexes: genital stimulation can result in a genital response, but can also result in systemic non-genital responses, which from a neurophysiological standpoint, is a separate reflex.

Urologists and urologic investigators are primarily concerned with the role of the genitals in the sexual response. Of particular interest is the vascular engorgement of erectile tissue resulting in erection. This genital response can be measured in a number of ways, including penile dimension changes via tumescence and rigidity monitoring, or blood flow changes using doppler studies or cavernosometry/cavernosography. But what is missing from the clinical armamentarium is a method to directly interrogate the neurological integrity of the genital response— that is, a measurement of whether the penile cavernous nerves are working or not. Such a test must be able to measure autonomic electrical activity in the genital end-organs. Several examples are presented in the following section.

III. CLINICAL ELECTRODIAGNOSTIC TESTING OF GENITAL AUTONOMIC NERVES

Electrodiagnostic testing is an extension of the genital physical examination, and is used to search for evidence of motor and sensory nerve disruption. When used appropriately, these tests can provide objective, precise and quantitative data. These tests generally fall into two categories: measurements of electrical activity following stimulation of an area distant from the recording site (e.g., evoked potentials), and measurements of electrical activity without exogenous stimulation (e.g., electroencephalography, electromyography, electrocardiography). Although the neurophysiologic *principles* are essentially the same as for somatic innervation, autonomic nerve assessments differ in *technique* from somatic nerve electrodiagnostic tests due to the fact that autonomic fibers are smaller and the electrical stimuli necessary to depolarize the fibers is different, and the recorded signals are much more difficult to consistently capture.

Most sexual medicine investigators interested in erectile physiology acknowledge the need for a measure of genital autonomic integrity. The autonomic nervous system plays an important role in the male sexual response. Autonomic neuropathy, such as occurs in diabetes, is presumed to be a leading cause of erectile dysfunction in the US.^{5, 6} Therefore, the assessment of autonomic pathways bears critical importance in the evaluation of sexual dysfunction. Over the last generation, several tests of genital autonomic innervation have been developed.

A. Sympathetic skin response

The sympathetic skin response (SSR) is a test that measures conductance changes in the palmar and plantar skin, in response to a noxious stimulus. It is widely accepted as a functional test of the autonomic (sympathetic) nervous system as an assessment of small fiber neuropathy.^{7, 8} The reflex arc involves a myelinated somatosensory nerve, the central

autonomic network and a sympathetic efferent limb with postganglionic nonmyelinated C fibers.

In the most commonly performed version of the SSR, changes in sweat gland activity are recorded with surface electrodes placed on the palmar, plantar and dorsal sides of the hands and feet. A noxious stimulus, such as a sudden noise or an electrical impulse, results in a systemic sympathetic discharge. The discharge causes a brief release of sweat from apocrine sweat glands, which alters the voltage differential between apocrine sweat gland bearing skin and non-apocrine sweat gland bearing skin, and the change can be recorded with surface electrodes. The response is known as the SSR of the corresponding area (Figure 3).

SSR tests have been applied to evaluate the autonomic innervation of the genital skin. Because the autonomic innervation of the genital skin generally approximates the autonomic innervation of the erectile tissue, it was thought that genital SSR could be a surrogate measure of genital autonomic innervation. SSRs are recordable using surface electrodes on the skin of the perineum and the penis, and abnormal responses are associated with male erectile dysfunction.^{9–11} However, some investigators do not believe this to be a valid measure of genital innervation.¹² Furthermore, the SSR rapidly habituates, and is critically dependent on many variables, such as skin temperature. Only an absent SSR can be considered abnormal.¹³

B. Tests of Autonomic Innervation of Erectile Tissue

The sexual arousal response of penile engorgement is mediated by the autonomic fibers of the cavernous and pelvic nerves.¹⁴ In men, corpus cavernosum electromyography^{15, 16} and evoked cavernous activity^{17, 18} have been proposed for the assessment of penile autonomic innervation. These tests are presumed to assess the *sympathetic* autonomic pathways to the corpus cavernosum. Although the sympathetic innervation to the penis primarily mediates detumescence rather than erections¹⁹, most processes that disrupt the autonomic innervation of the penis (such as iatrogenic injury or neuropathy) are not specific for sympathetic or parasympathetic fibers. The neuropathy affects both types of fibers. Consequently, a technique identifying penile sympathetic denervation is likely identifying parasympathetic denervation as well. At the present time, we are limited by the lack of technology to discern neuropathy specific to parasympathetic fibers. The tests can be performed on commercially available electrodiagnostic machines.

1. Evoked Cavernous Activity—The sympathetic innervation of the penis is similar to the sudomotor fibers to the sweat glands: they are both part of a polysynaptic reflex involving pre- and post-ganglionic sympathetic nerve fibers. It is this principle that provides the foundation for the evoked cavernous activity (ECA) test, which was initially described by Yarnitsky in 1995¹⁷, and revisited by Yilmaz in 2002.²⁰

Briefly, the technique involves stimulating the median nerve with a brief pulse to evoke a generalized sympathetic discharge, similar to the procedure applied in SSR testing (Figure 4). In contrast to SSR testing, concentric needle recording electrodes are placed into each corpus cavernosum, rather than using surface electrodes. The frequency filters for recording are set within 0.2 and 100 Hz. The recorded responses have an onset latency ranging 410 – 3080 ms, requiring a sweep of 1 s/div (Figure 3).

ECA is temporally associated with hand and foot SSRs, which confirms the sympathetic nature of ECA.^{18, 21} Other characteristics corroborating the autonomic nature of ECA are its slow wave morphology, habituating nature and induction of responses with a startling stimulus. As with the SSR, the presence or absence of the response is likely the most important aspect of the test, with the latency and amplitude measurements having less

significance. Its appeal as a clinical diagnostic tool lies in the ease of performance and waveform interpretation, but it has not been widely validated. ECA is also remarkably similar to the electrical activity measured in female erectile tissue in the clitoris and bulb 22, indicating that patterns of genital innervation between the sexes may be very similar.

2. Corpus Cavernosum Electromyography—In 1989, Wagner et al. proposed the registration of electrical activity originating from the corpus cavernosum.¹⁵ Since then, this method has been intensively investigated by several groups^{23–25}, and has been coined corpus cavernosum electromyography (CC-EMG). Studies from different centers indicate that the recorded signals indeed reflect the sympathetically mediated electrical activity of the cavernous smooth muscle.²⁶ CC-EMG is believed to be able to diagnose cavernous myo- and neuropathy in patients with ED caused by cavernous smooth muscle degeneration, diabetes mellitus, radical prostatectomy, and it may play an important role in selecting candidates for invasive therapies.

Recording CC-EMG does not require any stimulus, since it is a measurement of spontaneous activity. Using either surface or needle electrodes, CC-EMG can be measured using bipolar or monopolar techniques. The former method measures potential differences between two monopolar electrodes (or between two poles of a bipolar electrode) on/in the cavernous bodies. The latter method uses one active electrode on/in the cavernous body and one reference electrode located on another part of the body. The advantages and disadvantages of these two recording methods have been discussed previously.²⁷ The recorded CC-potentials are low frequency signals, with the most significant part of the power content below 1 Hz. Figure 5 shows a portion of a CC-EMG recording from a man with normal erectile function.

For signal analysis, typically recordings of 20–30 minutes are needed. Wagner et al. evaluated the global pattern of a whole recording, mainly focusing on presence and absence of electrical activity.¹⁵ Truss and co-workers analyzed individual CC-potentials and defined parameters such as amplitude, duration, and polyphasicity.²³ Recently Jiang et al. applied correlation techniques, in which both the features of individual CC-potentials and the mutual relation of CC-potentials simultaneously recorded at different sites of the CC can be analyzed.²⁸ This method has been demonstrated to be easy-to-use, objective and comprehensive.

Notwithstanding these promising findings, the application of CC-EMG as a diagnostic tool has never reached the level of routine clinical practice, due to a series of technical and practical difficulties. The insufficient understanding of the electrophysiology of the corpus cavernosum makes precise interpretation of the recorded signals problematic. Furthermore, research activities from different centers were poorly coordinated. The lack of a standardization of devices, signal recording and analysis methods makes CC-EMG results from different centers difficult to compare. This is one of the major reasons that CC-EMG fails to draw more enthusiasm from investigators and physicians. The introduction of software to easily analyze the signal traces may help to popularize the technique.

Conclusion

The male sexual response is a coordinated series of interactions between the somatic and the autonomic nervous systems. Measurement of the autonomically mediated portions of the sexual reflexes is of great clinical interest, particularly in relation to erection. Advances in clinical electrodiagnostics now allow for consistent recording of evoked and spontaneous intra-penile electrical activity. However, before broad and widespread use of these techniques is possible, more investigations are needed to obtain a better understanding of the

features of the recorded signals, and correlate different signal patterns with specific pathological changes of the corpus cavernosum. In addition to being diagnostic tools, these tests can be helpful for investigating the autonomic electrophysiology of cavernous smooth muscle and, in a broader context, the electrophysiology of smooth muscle in general.

Acknowledgments

Support provided by NIH/NIDDK R21 DK069315

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Figure 1.

Autonomic fibers from the sympathetic and parasympathetic outflow converge in the pelvic plexus between the bladder and rectum, and then distribute to the penis as the cavernous nerve. Somatic innervation is mediated through the branches of the pudendal nerve. (from Atlas of Urosurgical Anatomy, by Frank Hinman, W.B.Saunders Co., 1993)

Sexual reflexes

Figure 2. Sexual reflex arcs diagrammatically represented. The afferent arms of the arcs are depicted on the left side of the brain and spinal cord, and the right side shows the efferent arms of the reflexes.

Figure 3. ECA and SSR. The top two traces represent evoked cavernous activity waveforms from the left and right corpus cavernosum, respectively. The third trace is a sympathetic skin response from the right hand. The bottom trace is a sympathetic skin response from the right foot. Arrows denote the time of onset of the response, from time zero at the left hand side of the figure. Note the temporal relationship of the four responses. Time base: 1 sec/div; amplitude 100 uV/div for the ECA traces, 1 mV/div for the SSR traces.

Figure 4.

Neural pathways involved in ECA. Stimulation at the median nerve results in afferent signals sent along somatosensory pathways to the autonomic portion of the central nervous system (central autonomic network). Efferent signals exit from the thoracolumbar and sacral cord in fibers that coalesce in the pelvic plexus. Autonomic fibers travel as visceral efferents (cavernous nerves) to the erectile tissue of the penis. The sympathetic response is recorded as evoked cavernous activity (ECA).

Figure 5. CC-EMG in a man with reported normal erectile function. The top trace is recorded from the proximal left CC, the second trace is from the distal left CC, the third trace is from the distal right CC, and the bottom trace is from the proximal right CC. CC potentials with typical polyphasic spindle-like waveforms are seen. CC potentials from different areas are highly similar but not identical. (Reprinted from Meuleman E, Jiang X, et al. Corpus cavernosum electromyography with revised methodology: an explorative study in patients with erectile dysfunction and men with reported normal erectile function. *J Sex Med* 2007;4:191–8, Wiley Blackwell Publishing.)