PHARMACO-PHYSIOLOGY OF EJACULATORY DISTURBANCES

THESIS

SUBMITTED IN PARTIAL FULFILMEMT FOR MASTER DEGREE
IN

DERMATOLOGY AND VENEROLOGY

BY

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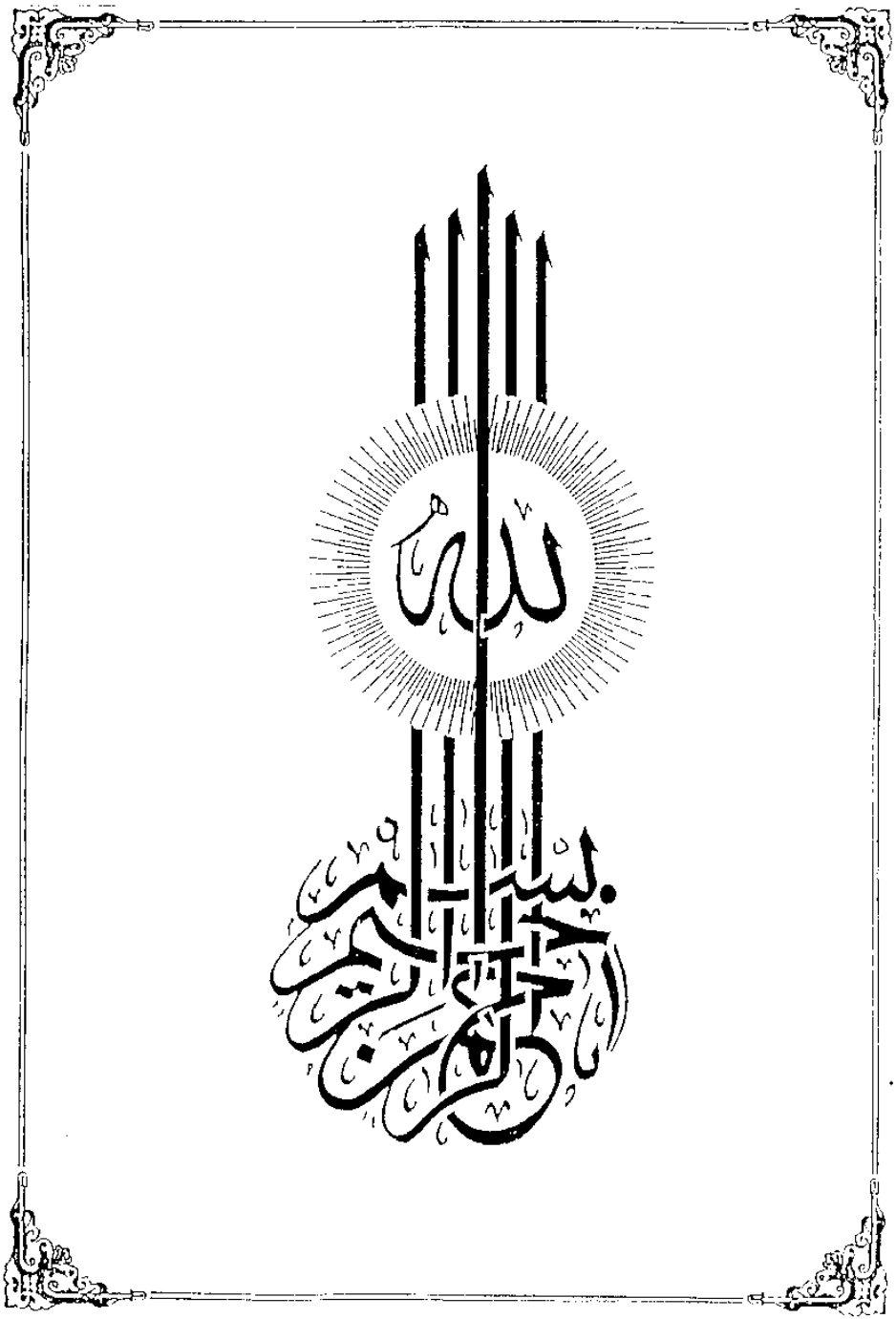
1991

ACKNOWLEDGMENT

The present work has been suggested and planned by Prof. Dr. MOHAMMED HABIB, Professor of Dermatology and Venerology, Faculty of Medicine, Ain Shams University, to whom I wish to offer my sincere thanks and gratitude for keen supervision, continuous guidance, pertinent observations on this work and whose kind encouragement and fruitful criticism were of utmost help .

My profound gratitude should be expressed to Dr. MOHSEN **EL-BAHRAWY** , Lecturer of Dermatology and Venerology, Faculty of Medicine, Ain Shams University . His efforts are invaluable through the whole steps till this thesis has come to light .



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Introduction

I N T R O D U C T I O N

One of the most obvious changes at puberty is the onset of ejaculation (Bancroft, 1983) . Normal ejaculation is defined as the expulsion of seminal fluid to the exterior by the rhythmic contraction of the genital tract muscles . The mechanism of normal ejaculation depends on the intact autonomic nervous system . Either chemical or surgical sympathectomy can interfere with ejaculation (Kedia & Markland, 1976) .

Various drugs, specially antiadrenergic compounds like guanethidine and certain tranquilisers such as thioridazine, sometimes lead to failure of ejaculation as a side effect for these drugs . This pharmacological inhibition of ejaculation has been exploited to treat premature ejaculation (Bancroft, 1983) . Much more attention has been paid to the sexual side effects of drugs to minimize iatrogenic disability .

Review of Literature

NEUROANATOMY OF EJACULATION

The events of ejaculation are dependent on a reflex neural process (Kedia & Markland, 1976) . In this reflex, afferent sensory stimuli are initially relayed from the genitalia via the pudendal nerve to the cerebral cortex (Fig. 1) . The efferent neural fibers travel through the anterolateral column to the thoracolumbar sympathetic outflow (T12 - L3), and pass through sympathetic chain and inferior mesenteric ganglion and form hypogastric nerve . There is no relay of preganglionic fibers in inferior mesenteric ganglion . Preganglionic fibers relay into

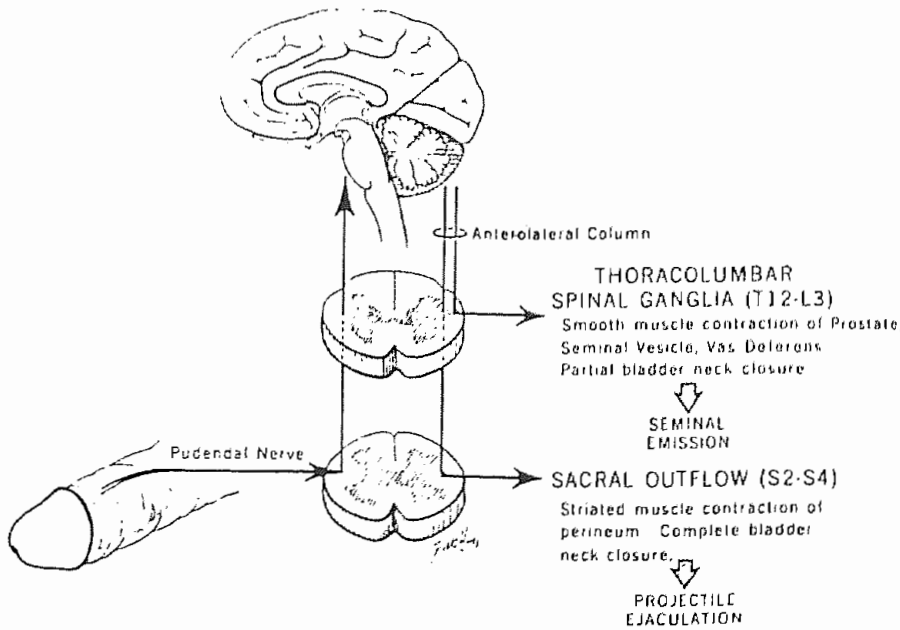

Fig. 1 : The afferent and efferent pathways of the reflex of ejaculation.

ganglia located on the ductus deferens, seminal vesicles, prostate, and base of bladder and innervate by so-called short adrenergic neurons (Sjostrand, 1965) . This sympathetic neural output produces smooth muscle contraction of the ductus deferens, which is mediated primarily through stimulation of α_1 -adrenergic receptors, stimulating peristalsis with propulsion of semen from the cauda epididymis to the ampulla and smooth muscle contraction of the ampulla, prostate, and seminal vesicles, with partial closure of the bladder neck, resulting in seminal emission into the posterior urethra (Kedia & Markland, 1976) (Fig. 2) .

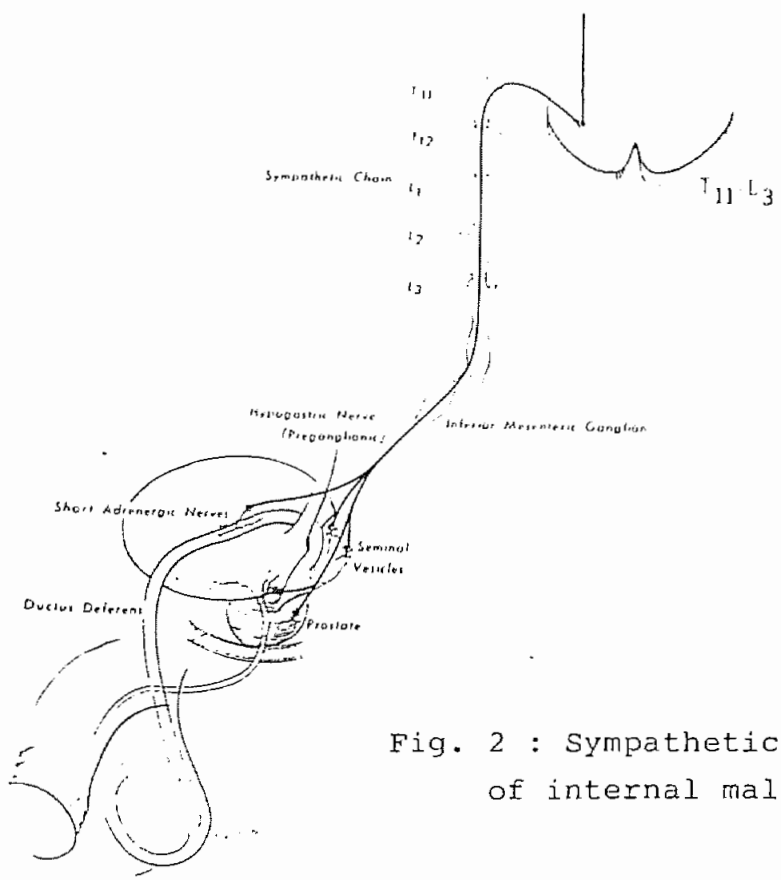

Fig. 2 : Sympathetic innervation of internal male genitalia.

The short adrenergic neurons innervating the internal male genital organs differ in several physiological and pharmacological properties from the conventional long adrenergic neurons . They have more sensitivity in-vitro to guanethidine (adrenergic neuronal blocker) (Burnstock et al., 1971) and react differently to immunosympathectomy (destruction of sympathetic nerve terminals by means of specific antibodies) (Hamberger et al., 1965) . Their endogenous noradrenaline content is not increased after decentralization, nor is it reduced by nerve stimulation (Blakeley et al., 1970) . This suggests that short adrenergic neurons are a unique entity of the sympathetic nervous system in innervating the pelvic organs .

Further efferent neural control is mediated through the parasympathetic sacral outflow (S2 - S4) and pudendal nerve, which causes clonic contraction of the striated bulbocavernosus and ischiocavernosus muscles and associated movements of the remaining striated muscles of the pelvic floor, lower extremities, and trunk; these responses, together with complete closure of the bladder neck, result in rhythmic projectile ejaculation through the urethra (Kuntz, 1965) (Fig. 3) .

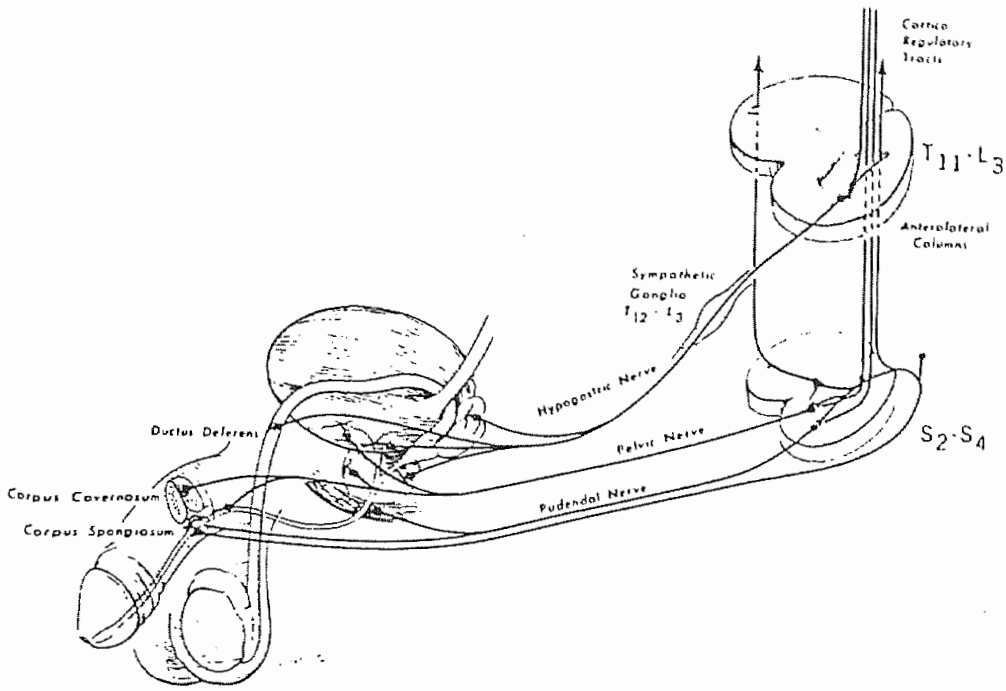

Fig. 3 : Sympathetic, parasympathetic and somatic innervation of internal male genitalia .

Central Nervous Structures Concerned in Ejaculation :

Reflex ejaculation in men with complete transection of the spinal cord formerly thought to be rare, but is now known to be common if the correct stimulus is applied. The spinal centres for reflexive ejaculation are situated in a number of segments of the cord, from S3 up to L1 or higher (Brindley, 1983) .

Orgasm is a cortical sensory experience with efferent input from contraction of the smooth muscles of the internal sexual organs as well as the pelvic striated muscles (Kedia & Markland, 1976) .

The precise location of the fibers involved in the control of sexual responses as they descend and ascend in the spinal cord is not known . Men who have received bilateral anterolateral cordotomies, usually at an upper thoracic level, for the relief of intractable pain, often report loss of erection and ejaculation, though their tactile, two point discrimination and vibration sense in the penis is unchanged . This suggests that close to the spinothalamic pathways for pain and temperature run fibers either from above, involved in the central control of erection and ejaculation or from the periphery involved in the specifically erotic components of genital sensation (Bancroft, 1983) .

Within the brain, there is evidence from a variety of sources that the limbic system is the neural substrate for sexuality as it is for other appetitive functions (Maclean, 1976) . Studies with implanted electrodes in various parts of the limbic system of Squirrel or Rhesus monkeys have

demonstrated that there are a number of sites, not necessarily contiguous, where stimulation produces either erection or ejaculation . These include the anterior part of the conjugate gyrus, pre-optic region, lateral hypothalamus and tegmentum . In contrast, stimulation is consistently ineffective in the hippocampus, fornix, mammillary bodies, posterior cingulate gyrus, caudate nucleus, ansa lenticularis and the genital receiving area of the post central gyrus (Brindley, 1983) . As yet, therefore, it is premature to suggest any precise localisation of sexual function in the human brain .

It has long been assumed that the brain stem exerts a tonic descending inhibitory influence on spinal sexual reflexes, but the source of this inhibition is unknown (Bancroft, 1983) . Marson and Mc Kenna, (1990) by using brain stem transections and electrolytic and neurotoxic lesions, have identified a group of neurons in the paragigantocellular reticular nucleus in the ventral medulla which mediates this descending inhibition via a direct projection to pelvic efferent neurons and interneurons .

Adrenergic Receptors & Drugs affecting Sympathetic Function:

The process of ejaculation is mainly a function of the sympathetic nervous system . The ultimate effects of sympathetic stimulation are mediated by release of noradrenaline from nerve terminals that serves to activate the adrenoceptors on postsynaptic sites . When this occurs, the organ responds characteristically . There are two main kinds of adrenergic receptors; alpha (α) and beta (β) receptors . The effects of noradrenaline released by adrenergic nerve impulses at various organs are listed in table (1) (Flattery & Spero, 1989) .

Alpha adrenoceptors are subclassified into two types, α_1 and α_2 . α_1-receptors are located on postsynaptic membranes and thereby modify cell function . α_2-receptors are in part located on presynaptic nerve terminals (Fig. 4); activation of these receptors results in inhibition of the release of transmitter (i.e. -ve feedback effect) . α_1-receptors are selectively stimulated by phenylephrine and methoxamine and α_2-receptors are selectively stimulated by clonidine (Catapress) and α-methyl dopa (Aldomet) which are used as antihypertensive drugs . Noradrenaline and adrenaline stimulate both equally (Hoffman, 1989) .

TABLE 1 Responses of Effector Organs to Autonomic Transmitters

Effector Organs	Adrenergic Receptors*	Adrenergic Responses	Muscarinic Cholinergic Responses
Eye			
Radial muscle of iris	α_1	Contr (mydriasis)	–
Sphincter muscle of iris		–	Contr (miosis, strong)
Ciliary muscle	β_2	Relax (slight)†	Contr (strong)‡
Heart			
Heart rate	β_1§	↑	↓
Atrial contractility/conduction	β_1	↑	↓
A-V conduction	β_1	↑	↓ (block)
Ventricular contractility/conduction	β_1	↑	↓
Blood Vessels#			
Coronary	α_1 β_2 α_2#	Constr Dilat (β_2)	
Skin and mucous membranes	α_1 α_2	Constr (strong)	
Skeletal muscle	α_1 β_2	Constr Dilat (β_2)	Dilat
Cerebral	α_1	Constr (slight)	
Pulmonary	α_1 β_2	Constr Dilat (β_2)	
Abdominal viscera	α_1 β_2	Constr Dilat (β_2)	
Lung			
Bronchial smooth muscle	β_2	Relax	Contr
Bronchial glands		Inhibition (?)	Stimulation
Stomach and Intestine			
Motility and tone	α_1 β_2 α_2**	↓	↑ (strong)
Sphincters	α_1	Contr (?)	Relax (usually)
Secretion		Inhibition (?)	Stimulation
Gall Bladder and Ducts		Relax	Contr
Urinary Bladder			
Detrusor muscle	β_2	Relax (usually)	Contr
Trigone and sphincter	α_1	Contr	Relax
Ureter			
Motility and tone	α_1	↑ (usually)	↑ (?)
Uterus	α_1 β_2	α_1 = contr†† β_2 = relax	Variable
Skeletal Muscle	β_2	Increased contractility, glycogenolysis	–
Sex Organs Male	α_1	Ejaculation	Erection
Skin			
Sweat glands	α_1	Slight secretion	Profuse secretion
Pilomotor muscles	α_1	Contr	
Spleen Capsule	α_1 β_2	Contr (strong)	
Adrenal Medulla		–	Secretion of adrenaline and noradrenaline (*nicotinic* effect)
Pineal Gland	β	Melatonin synthesis	–
Posterior Pituitary	β_1	ADH secretion	–
Fat Cells	β_1	Lipolysis	–
Liver	α β_2	Glycogenolysis and gluconeogenesis	Glycogen synthesis
Pancreas			
Acini	α_1	Decreased secretion	Secretion
Islet cells	α_2 β_2	α_2 = decreased secr n β_2 = increased secr n	–
Salivary Glands	α_1	Potassium and water secretion (slight)	Potassium and water secretion (profuse)
Lacrimal Glands		–	Secretion (profuse)
Nasopharyngeal Glands		–	Secretion
Kidneys	α_1 β_1	α_1 = ↓ renin release β_1 = ↑ renin release	–
Adrenergic Nerve Terminals	α_2 (pre-synaptic)	↓ Release of noradrenaline	
Cholinergic Nerve Terminals	α_2 (pre-synaptic)		↓ Release of acetylcholine at some sites

* Where known
† For far vision
‡ For near vision
§ β_2 and α Adrenoceptors are present in the heart also but they are less important than β_1 receptors
# Renal and mesenteric blood vessels have dopamine receptors which cause dilatation when stimulated. α_2 Adrenoceptors in blood vessels cause contraction when stimulated
** α_2 Adrenoceptors in the myenteric plexus inhibit acetylcholine release when stimulated
†† α_1-Adrenoceptor stimulation contracts the uterus during pregnancy
↑ = Increase ↓ = Decrease Constr = Constriction Dilat = Dilatation Contr = Contraction Relax = Relaxation – = No effect