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Pharmacology of Penile Erection

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Abstract*——Erection is basically a spinal reflex that can be initiated by recruitment of penile afferents, but also by visual, olfactory, and imaginary stimuli. The reflex involves both autonomic and somatic efferents and is modulated by supraspinal influences. Several central transmitters involved in the erectile control have been identified. Dopamine, acetylcholine, nitric oxide (NO), and peptides, such as oxytocin and adrenocorticotropic/α-melanocyte-stimulating hormone, seem to have a facilitatory role, whereas serotonin may be either facilitatory or inhibitory, and enkephalins are inhibitory. Peripherally, the balance between contractant and relaxant factors controls the degree of contraction of the smooth muscle of the corpora cavernosa and determines the functional state of the penis. Noradrenaline contracts both corpus cavernosum and penile vessels via stimulation of α_1-adrenoceptors. Neurogenic NO is considered the most important factor for relaxation of penile vessels and corpus cavernosum. The role of other mediators released from nerves or endothelium has not been definitely established. Erectile dysfunction (ED) may be due to inability of penile smooth muscles to relax. This inability can have multiple causes. However, patients with ED respond well to the pharmacological treatments that are currently available. The drugs used are able to substitute, partially or completely, the malfunctioning endogenous mechanisms that control penile erection. Most drugs have a direct action on penile tissue facilitating penile smooth muscle relaxation, including prostaglandin E_1, NO donors, phosphodiesterase inhibitors, and α-adrenoceptor antagonists. Dopamine receptors in central nervous centers participating in the initiation of erection have been targeted for the treatment of ED. Apomorphine, administered sublingually, is the first of such drugs.

I. Introduction

Penile erection is the end result of smooth muscle relaxation in the penis. It is basically mediated by a spinal reflex and involves central nervous processing and integration of tactile, olfactory, auditory, and mental stimuli (Fig. 1). Many central nervous transmitters and transmitter systems participate in the regulation. This is also the case peripherally, where both autonomic and somatic efferents are involved. The different steps of neurotransmission, impulse propagation, and intracellular transduction of neural signals in penile smooth muscles are still only partly known. However, it is well

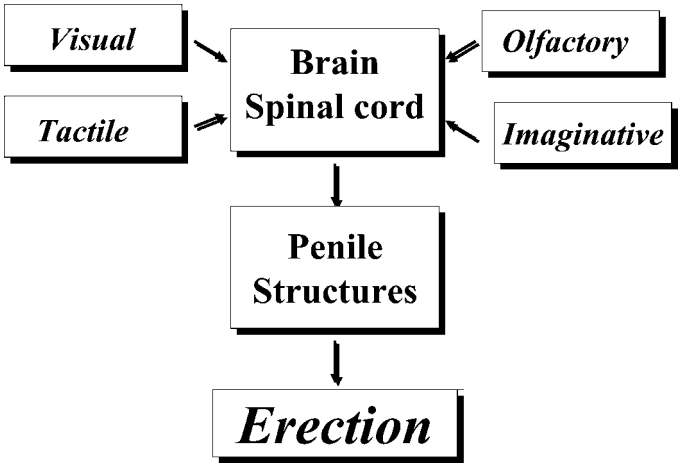

FIG. 1. Centrally evoked erections occur in response to various stimuli. Together with the input from tactile stimulation, these stimuli are processed and integrated supraspinally (e.g., medial preoptic area, paraventricular nucleus) as well as spinally. The integrated signal reaches the penile erectile tissues and starts the erection.

established that the balance between contractant and relaxant factors controls the degree of tone of the penile vasculature and of the smooth muscle of the corpora cavernosa and determines the functional state of the penis: detumescence and flaccidity, tumescence and erection.

The field of erectile function and dysfunction has undergone a rapid development during the last decade, and several pharmacological, physiological, and clinical aspects have been reviewed previously (e.g., Andersson, 1993; de Groat and Booth, 1993; Andersson and Wagner, 1995; Giuliano et al., 1995, 1997; Rampin et al., 1997; McKenna, 1999; Giuliano and Rampin, 2000a,b; Heaton, 2000a,b; Levy et al., 2000; Lue, 2000; Lue et al., 2000; Maggi et al., 2000; Steers, 2000; Moreland et al., 2001). The present review is an attempt to update the rapidly expanding information on some of the transmitters/modulators believed to be involved in the control of erectile mechanisms centrally and peripherally, and that are the basis for the currently used treatments of erectile dysfunction (ED[2]). ED is defined as the "inability to achieve or maintain an erection adequate for sexual satisfaction" (National Institutes of Health Consensus Statement, 1993).

[2] Abbreviations: ED, erectile dysfunction; ACTH, adrenocorticotropic hormone; α-MSH, α-melanocyte stimulating hormone; AR, adrenoceptor; cGK, cyclic GMP-dependent protein kinase; CGRP, calcitonin gene-related peptide; NO, nitric oxide; NOS, nitric-oxide synthase; eNOS, endothelial NOS; iNOS, inducible NOS; nNOS, neuronal NOS; ET, endothelin; GABA, γ-aminobutyric acid; GC, guanylyl cyclase; HO, heme oxygenase; 5-HT, 5-hydroxytryptamine, serotonin; IP_3, inositol 1,4,5-trisphosphate; K_{ATP}, adenosine triphosphate-dependent K channel; K_{Ca}, calcium-dependent K channel; MLC_{20}, regulatory light-chain subunit of myosin; MLCK, myosin light-chain kinase; MPOA, medial preoptic area; NA, noradrenaline; NANC, nonadrenergic, noncholinergic; L-NAME, N^G-nitro-L-arginine methyl ester; m-CPP, 1-(3-chlorophenyl)-piperazine; NMDA, *N*-methyl-D-aspartate; PDE, phosphodiesterase; PVN, paraventricular nucleus; PG, prostaglandin; PHM, peptide histidine methionine; sGC, soluble guanylyl cyclase; SNO-Glu, *S*-nitrosoglutathione; TFMPP, *N*-trifluoromethylphenyl-piperazine; TX, thromboxane; VIP, vasoactive intestinal polypeptide; YC-1, 3-(5′-hydroxymethyl-2′-furyl)-1-benzylindazole.

II. Central Regulation

A. Central Mediators

The central nervous regulation of erectile function involves both spinal and supraspinal pathways and mechanisms. Not unexpectedly, the central neurotransmission of penile erection is complex and only partly known. However, progress continues to be made to identify effectors involved in this function. Much of the knowledge gained in this area relates to morphological and pharmacological studies in experimental animal models (e.g., rodents, primates). In these models, neurochemical perturbations can be performed and responses monitored in a reasonably meaningful way. Results of such investigations must be interpreted with caution, because they encompass a wide range of types and modes of elicitation of sexual function (Sachs, 2000). Species differences, drug-dependent effects, and multiple drug sites of action must also be considered (McKenna, 1999; Giuliano and Rampin, 2000a,b; Steers, 2000).

1. 5-Hydroxytryptamine. It is well established that 5-hydroxytryptamine (5-HT; serotonin) neurons participate in the control of sexual behavior, both in humans and in animals. The amine has been implicated in the supraspinal as well as the spinal pharmacology of erectile function and involves both sympathetic, parasympathetic, and somatic outflow mechanisms. 5-HT pathways are considered to exert a general inhibitory effect on male sexual behavior (Bitran and Hull, 1987). However, these pathways may be inhibitory or facilitatory depending upon the action of the amine at different subtypes of 5-HT receptors located at different sites in the central nervous system (de Groat and Booth, 1993). The effects also seem to be species specific (Paredes et al., 2000).

5-HT-positive nerve terminals are present throughout the central nervous system, and 5-HT-containing neurons can be found in the medullary raphe nuclei and ventral medullary reticular formation, including the rostral nucleus paragigantocellularis, as well as the lumbosacral spinal cord in association with mainly somatic and autonomic outflow projections to the pelvis (Loewy and McKellar, 1981; Steinbusch, 1981; Monroe and Smith, 1983; Skagerberg and Bjorklund, 1985; Fischette et al., 1987; Marson and McKenna, 1992; Tang et al., 1998; Bancila et al., 1999). A decreased amount of 5-HT in these structures, occurring experimentally with the inhibition of serotonin synthesis (parachlorophenylalanine), destruction of 5-HT-containing axons (5,7-dihydroxytryptamine), or electrolytic destruction of the dorsal raphe nucleus, enhances sexual activity (McIntosh and Barfield, 1984; Kondo et al., 1993). Conversely, sexual activity is attenuated following the intracerebroven-

tricular (i.c.v.) or intrathecal (i.t.) administration of 5-HT and drugs that increase central release or synthesis of amine (Ahlenius et al., 1981; Svensson and Hansen, 1984; Szele et al., 1988).

Thus, 5-HT appears to serve various functions in male sexual function and is likely to act as a major modulator of the central neuroregulatory control of penile erection. As indicated above, the predominant role of 5-HT in the central neuromediation of erectile function appears to be associated with inhibitory control of spinal sexual reflexes involving the brain stem level (Marson and McKenna, 1992). Intrathecal injection of 5-HT in the spinalized anesthetized male rat blocked the appearance of the coitus reflex, suggesting that endogenous 5-HT may act in the descending input to the lumbar spinal cord that inhibits sexual reflexes (Marson and McKenna, 1992). A similar procedure in other experiments also inhibited ejaculation as well as penile intromission in rats, suggesting an alternative role of 5-HT in the transmission of sensory feedback information necessary for sexual responses (Svensson and Hansen, 1984). Similarly, penile reflexes are inhibited by i.t. 8-hydroxy-2-(di-*n*-propylamino)tetraline and buspirone (Mas et al., 1985; Lee et al., 1990; Mathes et al., 1990).

Many 5-HT receptor subtypes have been identified, which can rationally be divided into G-protein-coupled and ligand-gated ion channel-related subfamilies (Gerhardt and van Heerikhuizen, 1997; Barnes and Sharp, 1999). The receptors use different effector systems in different cells, which may explain the conflicting reports on the effects of 5-HT agonists and antagonists on sexual functions. For example agonists may either enhance or depress sexual function, which has been attributed to the involvement of multiple 5-HT receptors. 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A}, and 5-HT_{2C} receptor subtypes have been found at different levels of the spinal cord (Marlier et al., 1991; Thor et al., 1993; Ridet et al., 1994). In accordance with the selective use of 5-HT receptor agonists and antagonists, components of male copulatory behavior were found to be displayed variably. For example, 5-HT_{1A} receptor activation may have contrasting effects on sexual function, depending on the dose of administration and location of the receptor in the brain (Ahlenius et al., 1997; Rehman et al., 1999). Based on their findings, Bancila et al. (1999), using immunohistochemistry, suggested that the supraspinal serotonergic control of erection at the lumbosacral level appeared to be strongly associated with activation of 5-HT_{2C} receptors. 1-(3-Chlorophenyl)-piperazine (m-CPP), a trazodone metabolite, and *N*-trifluoromethylphenyl-piperazine (TFMPP) are considered partial agonists at 5-HT_{2C} receptors and usually display 5-HT_{2A} receptor antagonistic actions (Barnes and Sharp, 1999). They both induce erection in rodents, but they also significantly inhibit ejaculation and sexual behavior (Aloi et al., 1984; Berendsen and Broekkamp, 1987; Szele et al., 1988; Steers and de Groat, 1989; Berendsen et al., 1990, 1991; de Groat and Booth 1993; Pomerantz et al., 1993; Millan et al., 1997). RSD 992, an agonist at 5-HT_{2C} receptors, induced erections and facilitated male copulative behavior (Hayes et al., 2000) suggesting an important role for the 5-HT_{2C} receptor in the control of erectile mechanisms.

NOS inhibitors, given by i.c.v. administration, prevented m-CPP- and TFMPP-induced erectile responses (Melis and Argiolas, 1995).

Drugs that act through 5-HT mechanisms may affect sexual behavior. Thus, melatonin, which increases all aspects of sexual activity in rats, possesses 5-HT_{2A} antagonistic properties (Drago et al., 1999). Evidence for a facilitatory role of melatonin in sexual behavior has been presented, suggesting that its mechanism of action may involve the 5-HT_{2A} receptor (Brotto and Gorzalka, 2000).

2. Dopamine. Central dopaminergic neurons comprise an incertohypothalamic system with projections to the medial preoptic area (MPOA) and paraventricular nucleus (PVN) (Bjorklund et al., 1975). Dopaminergic neurons have also been identified, traveling from the caudal hypothalamus within the diencephalospinal dopamine pathway to innervate the lumbosacral spinal cord (Skagerberg et al., 1982; Skagerberg and Lindvall, 1985). Thus, dopamine may be expected to participate in the central regulation of both the autonomic and somatic components of the penile reflexes. Supporting this view, the dopamine receptor agonist apomorphine, administered systemically to male rats, was found to induce penile erection (Benassi-Benelli et al., 1979), simultaneously producing yawning and seminal emission. The effect of apomorphine was biphasic in the freely moving rat, with low doses facilitating and high doses inhibiting erection (Pehek et al., 1988a). These observations were subsequently extended to investigations involving low dose systemic administration of other dopamine agonists such as piribedil, lisuride, and quinelorane to rats and other animals (for review, see Andersson and Wagner, 1995). The effects of these agonists were attenuated by centrally, but not peripherally, acting dopamine receptor antagonists. Dopamine-receptor agonist-induced erections were abolished by castration in rodents, and testosterone replacement restored erectile function (Scaletta and Hull, 1990; Heaton and Varrin, 1994; Melis et al., 1994; Szczypka et al., 1998; Brien et al., 2000). Interestingly, rhesus monkeys did not respond to apomorphine, suggesting that there are basic differences between rats and rhesus monkeys in the systems mediating sexual behavior (Chambers and Phoenix, 1989). Whether the proerectile effects of apomorphine in humans are dependent on the androgenic state has not been clarified.

Dopamine receptors are distributed to various regions in the brain, with a high density particularly in the basal ganglia. Both the two major families of dopamine receptors, D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and

D_4) receptors (Sibley, 1999), have been associated with central erectile functions. The D_2 receptor seems to be responsible for most of the behavioral effects of dopamine, whereas the effects of D_1 receptors are more difficult to define. The dopamine-induced stretching, yawning, and penile erection syndrome seem to involve particularly the D_2 receptor subtype.

Apomorphine is a nonselective D_1/D_2 receptor agonist with more potent D_2- than D_1-like activity. The injection of apomorphine into the MPOA showed that low levels of dopaminergic stimulation, via D_1 receptors in particular, facilitated erections (Bazzett et al., 1991; Hull et al., 1992). In contrast, dopaminergic antagonists injected into the MPOA decreased the number of penile reflexes (Pehek et al., 1988b; Warner et al., 1991). In the PVN, similar experiments have established that D_2 rather than D_1 receptors primarily facilitate erections (Melis et al., 1987).

The erection following paraventricular D_2 receptor stimulation apparently involves oxytocinergic neurotransmission (Carter, 1992). Dopaminergic neurons impinge on oxytocinergic cell bodies in the PVN (Buijs, 1978; Lindvall et al., 1984), and apomorphine-induced penile erection is prevented dose dependently by oxytocin receptor antagonists (Argiolas et al., 1987b; Melis et al., 1989) or by electrolytic lesions of the PVN that deplete central oxytocin content (Lang et al., 1983; Hawthorn et al., 1985; Argiolas et al., 1987a). Conversely, injection of oxytocin into the PVN induced erections that were not attenuated by dopamine receptor blockade, suggesting that dopaminergic neurons activate oxytocinergic neurons in the PVN and that released oxytocin then accounts for the erectile response (see *Section II.1.6.*).

Injection of apomorphine into the lumbosacral subarachnoid space was reported to impair ex copula penile reflexes, slow the rate of copulation, and decrease the number of intromissions preceding ejaculation (Pehek et al., 1989a,b), suggesting an inhibitory effect on spinal erectile mechanisms. This is in contrast to recent findings, showing that injection of apomorphine intrathecally in rats evoked erection in both normal (Giuliano et al., 2000a,b) and spinalized animals (Giuliani et al., 2000b). The difference in the result is difficult to explain. However, most probably stimulation of the dopaminergic system can produce erection at both supraspinal and spinal sites.

As mentioned above, systemically administered apomorphine, enhances seminal emission. Pehek et al. (1989b) found that apomorphine injected into the PVN, but not in the MPOA, enhanced seminal emission. Recording of intravesical pressure in the nonanesthetized rat after administration of apomorphine showed that the pressure response consisted of both smooth and striated muscle components (Andersson et al., 1999). This implies that apomorphine has effects not only on the sacral parasympathetic output, but also on somatic pathways. Systemically administered apomorphine induces both penile erection and bladder overactivity in male rats (K.-E. Andersson and R. K. Pandita, unpublished results). Thus, at least in rats, apomorphine has effects not only on erection but also on seminal emission and bladder function.

3. Noradrenaline. Evidence for noradrenergic mechanisms involved in the supraspinal mediation of penile erection is sparse. Noradrenergic neurons from the A5 region and from the locus coeruleus project to the nuclei in the spinal cord involved in erection (Giuliano and Rampin, 2000b). Available data suggest that increased noradrenergic activity stimulates, whereas decreased noradrenergic activity inhibits, sexual function (Bitran and Hull, 1987). Insights have almost exclusively drawn from experimental work involving the administration of agents that interact through α-adrenoceptor (AR) pathways. Furthermore, accurate conclusions can only be drawn from work that suggests that central adrenergic receptors have been selectively stimulated. In rats given the α_2-AR agonist, clonidine, by direct injection into the MPOA, male sexual behavior was suppressed (Clark, 1988). The suppression was inhibited by pretreatment with selective α_2-AR antagonists (Clark et al., 1985), consistent with established facilitatory effects of these agents on erectile responses in rats (Clark et al., 1985). However, although several α_2-AR antagonists, most notably yohimbine, have been shown to increase sexual responses in rats, the relatively poor therapeutic efficacy of yohimbine in clinical use among men with ED (see below), casts doubt on the significance of central noradrenergic mechanisms in erectile function.

4. Excitatory Amino Acids. Excitatory amino acids appear to exert a role in penile erection. Thus, microinjections of L-glutamate into the MPOA elicited an increase in intracavernous pressure (Giuliano et al., 1996). Behavioral studies have shown that *N*-methyl-D-aspartate (NMDA) increases the number of penile erections when injected in the PVN (Melis et al., 1994a–c). NMDA, amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid, or *trans*-1-amino-1,3-cyclo-pentadicarboxylic acid, increased intracavernous pressures when injected into the PVN (Zahran et al., 2000). The effect of NMDA was prevented by i.c.v. administration of an oxytocin antagonist (Melis et al., 1994a). The NO synthase signal transduction pathway is considered to mediate the effect of NMDA, since the administration of NOS inhibitors into the PVN and i.c.v. blocked the NMDA effect (Argiolas, 1994; Melis et al., 1994c). Further support was provided by findings that NMDA injected into the PVN also leads to an increased concentration of NO metabolites in this region (Melis et al., 1997c). The mechanism for NOS activation would conceivably involve increased calcium influx through previously described calcium channel-coupled NMDA receptors (Snyder, 1992). However, the ineffectiveness of ω-conotoxin injected into the PVN in blocking erections induced by NMDA injected in this

nucleus indicates that ω-conotoxin-sensitive N-type calcium channels are not responsible for this mediation (Succu et al., 1998).

5. γ-Aminobutyric Acid. Cumulative data resulting from investigations on the role of γ-aminobutyric acid (GABA) in penile erection indicate that this neurotransmitter may function as an inhibitory modulator in the autonomic and somatic reflex pathways involved in penile erection (de Groat and Booth, 1993). In male rats, high concentrations of GABA have been measured in the MPOA (Elekes et al., 1986), and GABAergic fibers and receptor sites have been localized to the sacral parasympathetic nucleus and bulbocavernosus motor nucleus (Bowery et al., 1987; Magoul et al., 1987). The injection of $GABA_A$ agonists into the MPOA decreases (Fernandez-Guasti et al., 1986), whereas the injection of $GABA_A$ antagonists into this region increases copulatory behavior of male rats (Fernandez-Guasti et al., 1985). Systemic administration or i.t. injection at the lumbosacral level of the $GABA_B$ receptor agonist, baclofen, decreased the frequency of erections in rats (Bitran and Hull, 1987). Recent investigations showed that activation of $GABA_A$ receptors in the PVN reduced apomorphine-, NMDA-, and oxytocin-induced penile erection and yawning in male rats (Rosaria Melis et al., 2000).

6. Oxytocin. Experiments using retrograde labeling have shown that oxytocin-containing neurons in the PVN project to spinal autonomic nuclei (Swanson and Kuypers, 1980; Sawchenko and Swanson, 1982). This was confirmed by Tang et al. (1999) using retrograde transneuronal tracing with rabies virus. They found that oxytocinergic spinal projections from the PVN are more likely to influence the sacral autonomic rather than the somatic outflow. Plasma oxytocin concentrations are known to be elevated in humans following sexual stimulation (Carmichael et al., 1987; Murphy et al., 1987).

Oxytocin was found to be a potent inducer of penile erection when injected into the lateral cerebral ventricle, the PVN, or hippocampus in laboratory animals (Argiolas et al., 1986; Argiolas, 1992; Melis et al., 1997d). The erectile response was blocked by oxytocin antagonists and by electrolytic lesion of the PVN (Argiolas et al., 1987a,b). The oxytocin-induced erections were also abolished by castration, and testosterone replacement restored erectile function (Melis et al., 1994)

Immunoreactive oxytocin-containing spinal neurons associating with sacral preganglionic neurons, confirmed by retrograde labeling, support the role of oxytocin in the autonomic spinal circuitry that mediates penile erection (Tang et al., 1998; Veronneau-Longueville et al., 1999).

Oxytocin appears to exert an autoactivation mechanism involving stimulation of oxytocinergic receptors located on the cell bodies of the same oxytocinergic neurons in the PVN (Argiolas et al., 1986; Argiolas, 1992). In support of this view, immunoreactive cell bodies of oxytocinergic synapses have been found to impinge upon the cell bodies of oxytocinergic neurons in both hypothalamic supraoptic and PVN nuclei (Theodosis, 1985). Several central neurotransmitters may also converge upon the oxytocinergic system as activators (e.g., dopamine) or inhibitors (e.g., opioid peptides) of its transmission. Evidence supports calcium as a second messenger mediating oxytocin-induced penile erection in the PVN and oxytocinergic receptor coupling with calcium channels through a pertussis toxin-sensitive G-protein (Argiolas et al., 1990b; Stancampiano et al., 1992). The oxytocinergic system may also be influenced by the NO synthase signal transduction pathway since inhibitors of this pathway prevent penile erection and yawning in rats induced by oxytocin, dopamine, and NMDA stimulation (Melis and Argiolas, 1993; Melis et al., 1994b,c).

Recent studies have explored the physiologic basis for central oxytocin release. Thus, electrical stimulation of the dorsal penile nerve in rats, presumed to represent physiological tactile stimulation during copulation, produced orthodromic excitation in about half the oxytocin-containing cells in the PVN (Yanagimoto et al., 1996).

7. Adrenocorticotropin and Related Peptides. Proteolytic cleavage of the precursor, pro-opiomelanocortin, gives rise to several peptides including adrenocorticotropic (ACTH) and the α-melanocyte-stimulating hormones (α-MSH), which both have been associated with erectile responses. After i.c.v. or hypothalamic periventricular injection into various animal models, ACTH and α-MSH induce penile erection and ejaculation, grooming, stretching and yawning (Ferrari et al., 1963; Bertolini et al., 1975; Mains et al., 1977; Poggioli et al., 1998; Argiolas et al., 2000). These effects were shown to be androgen-dependent, since they were abolished by castration and could be fully restored by treating castrated animals with testosterone (Bertolini et al., 1975). Interestingly, ACTH and the ACTH-like peptides do not enhance social interaction, since during periods of sexual stimulation the animals did not seek to copulate with partners (Bertolini and Gessa, 1981).

It is now clear that most, if not all, of the effects of the α-MSH/ACTH peptides are mediated via specific subtypes of melanocortin (MC) receptors. The cloning of five different subtypes of MC receptor (Wikberg, 1999; Wikberg et al., 2000) has recently opened up new possibilities for drug development. α-MSH/ACTH peptides seem to act in the hypothalamic periventricular region, and grooming, stretching and yawning, but not penile erection, appear to be mediated by MC_4 receptors (Vergoni et al., 1998; Argiolas et al., 2000). Interestingly, the MC_3 receptor showed a high density in the hypothalamus and limbic systems (Wikberg, 1999), regions known to be important for erectile functions.

Calcium channels seem to mediate the effects of ACTH since i.c.v. injection of the N-type calcium channel blocker ω-conotoxin prevents the actions of ACTH (Argiolas et al., 1990a,b). Intracerebroventricular injection

of L-NAME significantly inhibited ACTH-induced erections but not stretching and grooming. Both lesions of the PVN (Argiolas et al., 1987a) and injections of ω-conotoxin into this nucleus (Argiolas et al., 1990a) failed to alter erection induction by ACTH. This observation, combined with evidence that excitatory amino acids do not affect ACTH effects (Melis et al., 1992a), suggests that the hypothalamic site or mechanism of action responsible for ACTH induction of erection is different from that involving dopamine or oxytocin action in the PVN (Argiolas and Melis, 1995). However, NO seems to be involved in the ACTH effects (Poggioli et al., 1995).

In men with ED, a synthetic analog of α-MSH, Melanotan II, given subcutaneously had proerectile effects but also induced yawning and stretching (see Wessels et al., 1998, 2000).

8. Opioid Peptides. Endogenous opioid peptides have long been assumed to be involved in the regulation of male sexual responses, since sexual dysfunction has been observed clinically in men chronically using opiates (Cushman, 1972; Crowley and Simpson, 1978). Copulatory behavior in male rats is depressed experimentally with the systemic administration of morphine or other opioids (McIntosh et al., 1980; Pfaus and Gorzalka, 1987). β-Endorphin injection into the cerebral ventricles or MPOA of male rats attenuates copulatory behavior (McIntosh et al., 1980; Hughes et al., 1987). Morphine, injected systemically or into the PVN of male rats, prevents penile erection induced by i.c.v. administration of oxytocin or subcutaneous dopamine (Melis et al., 1992b) or NMDA injected into the PVN (Melis et al., 1997a). However, similar application of a selective agonist of the κ-opioid receptor does not alter apomorphine- or oxytocin-induced erectile responses (Melis et al., 1997b). This evidence and the demonstration that the opiate antagonist naloxone administered systemically abolishes the central morphine preventative effect on erections in rats, have supported the belief that μ receptors in the PVN account for the morphine effect (Melis et al., 1997b). NO metabolite concentrations that are increased in the PVN following apomorphine, oxytocin, or NMDA local administration, become reduced following morphine administration into the PVN, indicating that the morphine effect depresses an NO-mediated erection induction mechanism at this level (Melis et al., 1997a,b; 1999). Current data support the hypothesis that μ-opioid receptor stimulation centrally prevents penile erection by inhibiting mechanisms that converge upon central oxytocinergic neurotransmission.

9. Acetylcholine. The role of acetylcholine (ACh) at central levels in the regulation of penile erection is mostly inferred from limited neuropharmacologic studies involving systemically and/or intracerebrally administered muscarinic agonists and antagonists and lesioning studies in the brain (Hull et al., 1988a,b; Maeda et al., 1990, 1994a,b). These studies have suggested that cholinergic mechanisms operating seemingly at the hippocampus and MPOA may have a regulatory role in erectile function.

10. Nitric Oxide. The role of NO in the central neuromediation of penile erection followed observations that the injection of NOS inhibitors i.c.v. or into the PVN prevented penile erectile responses induced by dopamine agonists, oxytocin, ACTH, 5-HT_{2C} agonists, or NMDA in rats (Melis and Argiolas, 1993, 1995, 1997; Melis et al., 1994c, 1997d; Poggioli et al., 1995; Fig. 2). The inhibitory effect of NOS inhibitors was not observed when these compounds were injected concomitantly with L-arginine, the substrate for NO.

The PVN has been implicated as a prime site for NO interacting with the oxytocinergic mechanisms of penile erection (Melis et al., 1994b). This brain nucleus (Fig. 3) was earlier identified to contain one of the highest concentrations of NOS in the brain (Bredt et al., 1990). Nitroglycerin, an NO donor, induces penile erection in the rat when injected into the PVN (Melis and Argiolas, 1995). The MPOA is also purported to liberate NO with sexual activity in rats. Direct measurements of NO in the MPOA showed NO release associated with copulatory behavior. Local administration of an NOS inhibitor decreased NO release and copulatory behavior (Sato et al., 1998, 1999). NO production increased in the PVN during noncontact erection and copulation (Melis et al., 1998).

Interestingly, since guanylyl cyclase (GC) inhibitors (e.g., methylene blue) injected into the PVN fail to prevent drug-induced penile erection, and 8-bromo-cGMP injected into the PVN fails to elicit erections, it has been proposed that the mechanism of NO action is not associated with the activation of GC (Melis and Argiolas, 1997). The additional finding that the NO scavenger, hemoglobin, does not prevent penile erection in spite of its ability to block NO production in the PVN, suggested that NO acts as an intracellular rather than an intercellular modulator of erectile responses involving the PVN (Melis and Argiolas, 1997).

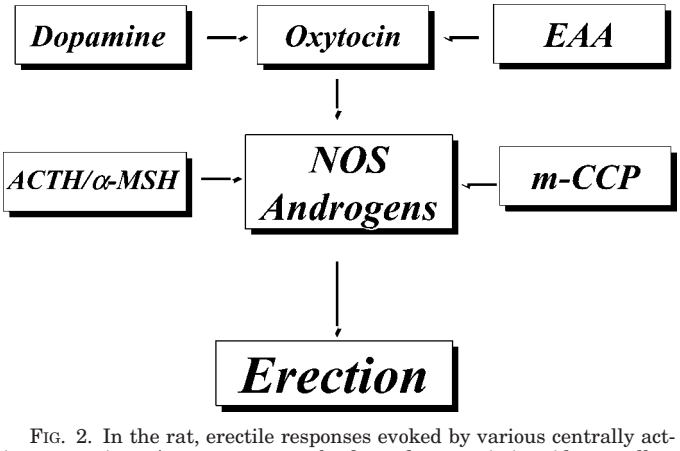

FIG. 2. In the rat, erectile responses evoked by various centrally acting transmitters/agents appear to be dependent on nitric oxide as well as androgens.

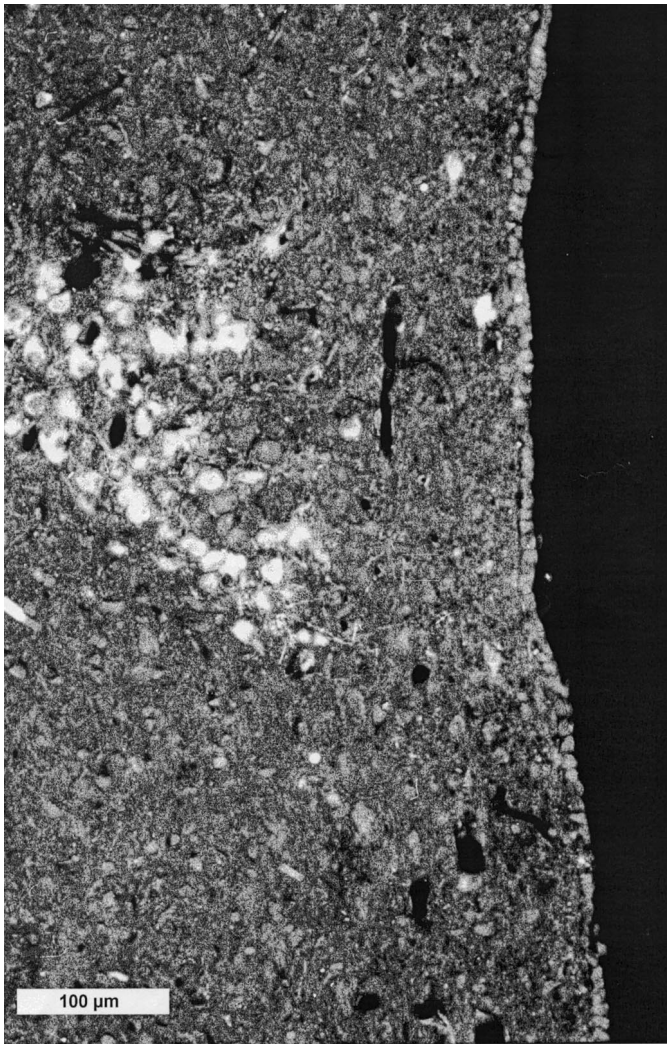

FIG. 3. Nitric-oxide synthase within the paraventricular nucleus of the rat. Bar = 100 μm.

In the spinal cord, the distribution of NOS-containing neurons suggests that nitric oxide plays a role in spinal cord neurotransmission including preganglionic sympathetic and parasympathetic, somatosensory, visceral sensory, and possibly motor pathways (Valtschanoff et al., 1992; Dun et al., 1993; Saito et al., 1994; Burnett et al., 1995). At the spinal cord level, the functional role of NO for erection is not known.

III. Peripheral Regulation

The different structures of the penis receive sympathetic, parasympathetic, somatic, and sensory innervation (Dail, 1993). The nerves contain different transmitters, and the nerve populations have been categorized as adrenergic, cholinergic, and nonadrenergic, noncholinergic (NANC). The latter nerves may contain not only neuropeptides, but also transmitters and transmitter/modulator-generating enzymes, such as NOS and heme oxygenases (HO). NANC transmitters/modulators may be found in adrenergic and cholinergic nerves (Lundberg, 1996), which should make it more meaningful to define nerve populations based on their transmitter content. Thus, it seems that one important population of nerves in the corpora cavernosa contain not only ACh, but also NOS, VIP, and neuropeptide Y (Hedlund et al., 1999, 2000a,b).

The nerves and endothelium of sinusoids and vessels in the penis produce and release transmitters and modulators, which interact in their control of the contractile state of the penile smooth muscles. In addition, they may also have other important functions, some of which are discussed below.

A. Contraction-Mediating Transmitters/Modulators

1. Noradrenaline. Penile arteries and veins, and cavernosal smooth muscle receive a rich adrenergic innervation, and it is generally accepted that the penis is kept in the flaccid state mainly via a tonic activity in these nerves. Released noradrenaline (NA) stimulates α-ARs in the penile vasculature, contracting the helicine vessels, and in the corpus cavernosum, contracting the trabecular smooth muscle (Andersson and Wagner, 1995). NA stimulates not only α- but also β-ARs. However, in the human corpus cavernosum, receptor binding studies have revealed that the density of α-ARs is almost 10 times higher than that of β-ARs (Levin and Wein, 1980); the number of α-AR binding sites per cell was estimated to 650,000 (Costa et al., 1993).

Several factors, including androgens, may regulate the α-AR responsiveness of cavernous smooth muscle. Compared with normal rats, castrated animals showed an enhanced reactivity to α_1-AR stimulation (Reilly et al., 1997b). In long-term (1 year) diabetic animals (streptozotocin-induced diabetes), there was a failure to respond to α_1-AR stimulation in the cavernous circulation (Mills et al., 1998a,b).

Functionally and in receptor binding studies, both α_1- and α_2-ARs have been demonstrated in human corpus cavernosum tissue (Andersson and Wagner 1995; Traish et al., 1995a,b, 1997b; Goepel et al., 1999), but available information supports the view of a functional predominance of α_1-ARs. This may be the case also in the penile vasculature, although a contribution of α_2-ARs to the contraction induced by exogenous NA or NA released by electrical stimulation of nerves cannot be excluded (see below). In horse penile resistance arteries, NA activated predominantly α_1-ARs, whereas postjunctional α_2-ARs seemed to play a minor role (Simonsen et al., 1997a,b).

All the subtypes of α_1-AR with high affinity for prazosin (Hieble et al., 1995) have been demonstrated in human corporal tissue. In a preliminary communication, Price et al. (1993) reported that in human corporal tissue, mRNAs for α_{1A}, α_{1B}, and α_{1D} could be identified, with the α_{1A}- and α_{1D}-ARs predominating. This was confirmed by other investigators (Traish et al., 1995b; Dausse et al., 1998). However, Goepel et al. (1999) showed that human corpus cavernosum expressed pre-

dominantly α_{1A}, α_{1B}, and α_{2A} receptor protein and found the α_{1D}-AR was present only at the mRNA level.

Traish et al. (1995b) characterized the functional α_1-AR proteins in human corpus cavernosum tissue, using receptor binding and isometric tension experiments. Their results demonstrated the presence of α_{1A}-, α_{1B}-, and α_{1D}-ARs, and they suggested that the NA-induced contraction in this tissue is mediated by two or possibly three receptor subtypes. There is increasing evidence that an additional α_1-AR subtype with low affinity for prazosin (α_{1L}), which is not yet fully characterized, may occur in vascular smooth muscle for example (Muramatsu et al., 1995). It cannot be excluded that this receptor subtype represents a conformational state of the α_{1A}-AR (Daniels et al., 1999). The possibility that the α_{1L}-AR subtype may be of importance in human penile erectile tissues was recently suggested (Davis et al., 1999). Choppin et al. (2000) reported that the highly selective and orally active α_{1A}-AR antagonist Ro 70-0004/003 did not improve erection in men with ED, indicating that the role of the different α_1-AR subtypes for erectile function and dysfunction still remains to be established.

In vivo experiments in rats and dogs suggested that the α_{1B}- and α_{1L}-AR subtypes were functionally relevant for erectile function (Sironi et al., 2000), and the authors suggested that antagonists of these subtypes could represent an advantage in ED therapy. This may not necessarily be the case, since in humans the distribution of α_1-AR subtypes in penile erectile tissues and the vasculature may not be the same as in rats and dogs (Rudner et al., 1999).

Traish et al. (1997b) demonstrated expression of mRNAs for α_{2A}-, α_{2B}-, and α_{2C}-ARs in whole human corpus cavernosum tissue. A homogeneous population of α_{2A}-ARs was found in human tissue by Goepel et al. (1999). Radioligand binding studies with a highly selective ligand for α_2-ARs revealed specific α_2-AR binding sites, and functional experiments showed that the selective α_2-AR agonist, UK 14,304, induced concentration-dependent contractions of isolated strips of corpus cavernosum smooth muscle (Traish et al., 1997b). These results support previous functional data (Andersson and Wagner, 1995) suggesting the occurrence of postjunctional α_2-ARs in the human corpus cavernosum. However, whether or not these α_2-ARs are of importance for the contractile regulation of tone in corpus cavernosum smooth muscle is still unclear. Prejunctional α_2-ARs have been shown to modulate stimulus-evoked release of NA from nerves in the human corpus cavernosum, stimulation inhibiting the release of the amine (Molderings et al., 1989). However, stimulation of prejunctional α_2-ARs in horse penile resistance arteries was shown also to inhibit NANC transmitter release (Simonsen et al., 1997b). This might be one of the mechanisms by which NA maintains detumescence and suggests that combined α_1- and α_2-AR blockade may enhance the release of NO (de Tejada et al., 2000). Cellek and Moncada (1997) found that human corpus cavernosum has a nitrergic innervation that does not merely modulate, but actually controls, the sympathetic responses. They suggested that there is a balance between the nitrergic and sympathetic systems in the human corpus cavernosum, disruption of which may contribute to certain pathological conditions.

2. Endothelins. On the basis of functional, autoradiographical, and immunohistochemical studies, endothelins (ETs) have been suggested to contribute to the maintenance of corporal smooth muscle tone (Andersson and Wagner, 1995). Cultured endothelial cells from the human corpus cavernosum, but not nonendothelial cells, were found to express ET-1 mRNA (Saenz de Tejada et al., 1991a). ET-like immunoreactivity was observed in the sinusoidal and also in cavernous smooth muscle (Saenz de Tejada et al., 1991a). Binding sites for ET-1 were demonstrated both in the vasculature and trabecular tissue of the human corpus cavernosum by autoradiography (Holmquist et al., 1990, 1992a).

Both ET_A and ET_B receptors have been found in human corporal smooth muscle membranes (Christ et al., 1995). In rat corpus cavernosum, ET-1 and ET_A receptor binding sites were primarily localized to the endothelium lining the cavernosal lacunar spaces (Bell et al., 1995). Parkkisenniemi and Klinge (1996) suggested that ET_B receptors were located on the inhibitory nerves that mediate relaxation via activation of the L-arginine/NO/cGMP pathway. They confirmed their initial findings (Parkkisenniemi et al., 2000) but concluded that the ET_B receptors most probably had little effect on the function of the penile erection-mediating nitrergic nerves.

ET-1 potently induces slowly developing, long-lasting contractions in different penile smooth muscles: corpus cavernosum, cavernous artery, deep dorsal vein, and penile circumflex veins (Andersson and Wagner, 1995; Becker et al., 2000b) Contractions can be evoked in human corpus cavernosus tissue also by ET-2 and ET-3, although these peptides have a lower potency than ET-1 (Saenz de Tejada et al., 1991a). The contractions induced by ET-1 may be dependent on both transmembrane calcium flux (through voltage-dependent and/or receptor-operated calcium channels) and on the mobilization of inositol 1,4,5-trisphosphate (IP_3)-sensitive intracellular calcium stores (Holmquist et al., 1990, 1992b).

In bovine retractor penis muscle and penile artery, the contraction induced by ET-1 was mediated primarily by ET_A receptors (Parkkisenniemi and Klinge 1996). In the pithed rat, intravenously injected ET-1 had a vasodilator action (increase in corporal pressure) at low doses, but a vasoconstrictor action at high doses (Ari et al., 1996). ET-3 had mainly vasodilator effects, and it was suggested that the vasodilator actions were mediated by activation of ET_B receptors on the endothelium and local release of NO, since these actions were inhibited by

L-NAME. Dai et al. (2000) used specific receptor antagonists to examine the role of ET-1 in erection in rats. Blockade of the ET_A or the ET_B receptor had no effect on the erectile response induced by maximal ganglionic stimulation. Their results confirmed that cavernosal tissue of the rat penis is highly responsive to ET-1. The failure of the ET-1 antagonists to affect penile erection in response to ganglionic stimulation seemed to reflect a minimal role of ET-1 in the erectile response in the rat. However, the results do not rule out that ETs may play a role in keeping the penis in a flaccid state, nor that ETs may be associated with ED. ET-1 and ET_A receptor binding was found to be increased in diabetic rat cavernosal tissue (Bell et al., 1995). On the other hand, Christ et al. (1995) found no detectable age- or diabetes-related changes in contractile effects in human corpus cavernosum tissue. Francavilla et al. (1997) found no differences in plasma concentrations of ET-1 in diabetic and nondiabetic patients with ED, and the concentrations of ET-1 in cavernous body blood were no different following intracavernous PGE_1 injection. Negative results we also found by Kadioglu et al. (1998) in men with arteriogenic impotence after papaverine-induced penile erection –no changes in intracavernosal ET-levels were found. The levels of ET-1 were determined in peripheral and cavernosal blood during flaccidity, tumescence, rigidity, and detumescence in healthy volunteers by Becker et al. (2000b). No significant changes were demonstrated.

Even if accumulated information suggests that ETs may have a role in the mechanisms of flaccidity and detumescence, their exact role in penile physiology and pathophysiology remains to be established. ETs may function not only as a long-term regulator of corporal smooth muscle tone, but also as modulator of the contractile effect of other agents, e.g., NA (Holmquist et al., 1990; Christ et al., 1995; Kim et al., 1996), or as a modulator of cellular proliferation and phenotypic expression (Zhao and Christ, 1995).

3. Angiotensins. During detumescence, there is an increase in the level of angiotensin II in cavernous blood compared with the levels in the flaccid state (Becker et al., 2000a). Human corpus cavernosum was found to produce and secrete physiologically relevant amounts of angiotensin II (Kifor et al., 1997). In vitro, angiotensin II contracted human (Becker et al., 2000a) and canine (Comiter et al., 1997) corpus cavernosum smooth muscle. In canine corpus cavernosum, the effect was increased by NOS inhibition (Comiter et al., 1997). Intracavernosal injection of angiotensin II caused contraction and terminated spontaneous erections in anesthetized dogs, whereas administration of losartan, selectively blocking angiotensin II receptors (subtype AT1), resulted in smooth muscle relaxation and erection (Kifor et al., 1997). Also in the rabbit corpus cavernosum, results were obtained suggesting involvement of the renin-angiotensin system in the regulation of corpus cavernosum smooth muscle tone and that the angiotensin II receptor subtype AT1 is important for mediation of the response (Park et al., 1997).

Whether or not angiotensin II is an important regulator of tone in penile erectile tissues is unclear. Studies using angiotensin II receptor antagonists, for example losartan, designed to elucidate this question, would be of interest.

B. Relaxation-Mediating Transmitters/Modulators

1. Acetylcholine. Penile tissues from animals and humans receive a rich cholinergic innervation as shown by histochemistry (ACh esterase staining) or immunohistochemistry (Dail, 1993; Hedlund et al., 1999, 2000a,b). ACh released from these nerves acts on muscarinic receptors located on cavernosal smooth muscle and endothelium. Four muscarinic receptor subtypes (M_1–M_4) were shown to be expressed in human corpus cavernosum tissue (Traish et al., 1995c); the receptor on smooth muscle was suggested to be of the M_2 subtype (Toselli et al., 1994; Traish et al., 1995c), whereas that on the endothelium was of the M_3 subtype (Traish et al., 1995c).

Costa et al. (1993) calculated the number of binding sites for ACh on isolated corpus cavernosum smooth muscle cells to be 45,000, which was about 15 times less than the number of α-ARs. In these cells, the nonsubtype selective muscarinic receptor agonist, carbachol, consistently produced contraction. This means that relaxation induced by ACh is indirect and can be obtained either by inhibition of release of a contractant factor, e.g., NA, and/or is produced by the release of a relaxation-producing factor, e.g., NO. It is important to stress that parasympathetic activity is not equivalent with the actions of ACh; other transmitters may be released from cholinergic nerves (Lundberg, 1996). Parasympathetic activity may produce penile tumescence and erection by inhibiting the release of NA through stimulation of muscarinic receptors on adrenergic nerve terminals (Klinge and Sjöstrand, 1977), and/or by releasing NO and e.g., vasodilating peptides from nerves and endothelium (Andersson and Wagner, 1995).

2. Nitric Oxide and the Guanylyl Cyclase/cGMP Pathway. Synthesis of NO and the consequences of NO binding to soluble guanylyl cyclase is essential for the erectile process. There are several steps in the pathway (Fig. 4) that may be interesting targets for pharmacological intervention.

a. Nitric-Oxide Synthases. An important role for NO in the relaxation of corpus cavernosum smooth muscle and vasculature is widely accepted (Andersson and Wagner, 1995; Burnett 1997). Both the endothelium and/or the nerves innervating the corpus cavernosum may be the source of NO, and thus, more than one isoform of NOS can be involved. There seems to be no doubt about the presence of neuronal NOS (nNOS) in the cavernous nerves and their terminal endings within the corpora cavernosa, and in the branches of the dorsal penile

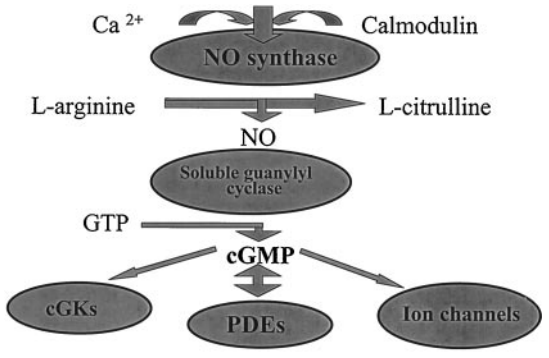

FIG. 4. The L-arginine/nitric oxide/guanylate cyclase/cGMP pathway.

nerves and nerve plexuses in the adventitia of the deep cavernous arteries (Burnett et al., 1992, 1993, 1996; Alm et al., 1993; Dail et al., 1995; Burnett, 1997; Hedlund et al., 2000b). It was therefore surprising to find that mice lacking nNOS (Huang et al., 1993) had erections, showed normal mating behavior, and responded with erection to electrical stimulation of the cavernous nerves (Burnett et al., 1996). However, it was shown that these mice are still able to express an alternatively spliced mRNA of nNOS, which could be the source of NO in nNOS mutant mice (Eliasson et al., 1997). A variant of nNOS (penile nNOS, P nNOS) has been identified as two distinct isoforms in the penis of rat and mouse (Magee et al., 1996; Gonzalez-Cadavid et al., 1999, 2000).

In the rat, Dail et al. (1995) found that all smooth muscle regions of the penis were richly innervated by nerves containing nNOS, and that the endothelium of vessels stained for both endothelial NOS (eNOS) and NADPH diaphorase. However, the endothelium of cavernous sinuses did not contain eNOS and did not stain for NADPH diaphorase. This is in contrast to findings in humans and several other species (Burnett et al., 1996; Bloch et al., 1998; Hedlund et al., 2000a,b). Bloch et al. (1998) examined activities of NOS enzymes in specimens of potent and impotent patients by means of light and electron microscopy using NADPH diaphorase staining and immunohistochemical eNOS-specific, smooth muscle actin-specific, and nNOS-specific markers. They found a distinct expression of eNOS in cavernosal smooth muscle and in the small intracavernosal helicine arteries. No overall correlation between NOS expression and erectile function was observed. In human penile cavernosal smooth muscle cells in culture, Rajasekaran et al. (1998) found mRNA expression of both eNOS and inducible NOS. Localization studies showed positive signals for NADPH diaphorase, eNOS, and calmodulin, and electron microscopic evaluation confirmed the localization of eNOS to the cytoplasm and small vesicles in the cells. Stanarius et al. (1999), using electron microscopy and immunohistochemistry, found eNOS to be present in the endothelial cells covering the cavernous spaces and in the endothelial cells of arteries branching within human erectile tissue. They found no eNOS activity in cavernous smooth muscle cells and cavernous nerves. The difference in the results concerning the occurrence of eNOS in cavernous smooth muscle cells is difficult to explain. If there are eNOS binding sites in the cavernous smooth muscle, they may represent the caveolae described in vascular endothelial tissue (Feron et al., 1998, 1999). The expression of caveolins, caveolin-1 and caveolin-3, which are inhibitory proteins for NOS, were investigated in human corpus cavernosum by Tsutsui et al. (1999). Caveolin-1, which preferentially binds to eNOS, appeared to be diffusely located within the smooth muscle of the corpus cavernosum and endothelium of the vasculature, whereas caveolin-3, which binds to nNOS, was located close to NADPH-positive nerve fibers (Tsutsui et al., 1999).

Functional studies support the occurrence and importance of eNOS in human cavernous tissue (Andersson and Wagner, 1995), and this also seems to be the case in rat (Cartledge et al., 2000b) and mouse (Mizusawa et al., 2001) corpus cavernosum. If the occurrence of nonendothelial eNOS in the corpus cavernosum can be confirmed, its functional significance should be established.

The influence of androgens on erectile function might be mediated by the NO/cGMP pathway (Zvara et al., 1995; Lugg et al., 1996; Penson et al., 1996; Schirar et al., 1997; Mills et al., 1998a; Mills and Lewis, 1999), even if non-NO-dependent pathways have been demonstrated (Reilly et al., 1997; Mills et al., 1999; Mills and Lewis, 1999). Castration of rats and treatment with the anti-androgen, flutamide, reduced constitutive penile NOS activity (Chamness et al., 1995; Lugg et al., 1996; Penson et al., 1996).

Compared with young rats, NOS-containing nerves, NOS mRNA expression, and NOS activity decreased in old animals (Garban et al., 1995; Carrier et al., 1997; Dahiya et al., 1997). ED associated with for example diabetes was found to be associated by a decreased nNOS content and activity in the rat corpus cavernosum (Vernet et al., 1995; Autieri et al., 1996; Rehman et al., 1997). In humans, the diabetic ED was suggested to be related to the effects of advanced glycation end products on NO formation (Seftel et al., 1997). In rats, Cartledge et al. (2000a) found that glycosylated human hemoglobin impaired corpus cavernosal smooth muscle relaxation by generation of superoxide anions and extracellular activation of NO.

b. Soluble Guanylyl Cyclases. The GCs comprising both membrane bound (particulate) and soluble isoforms are expressed in nearly all cell types (Lucas et al., 2000). Kim et al. (1998) demonstrated production of cGMP by particulate GC in the corpus cavernosum membranes of rabbit and rat stimulated by C-type natriuretic peptide 1–22, atrial natriuretic peptide 1–28, and brain natriuretic peptide 1–26. In addition, C-type natriuretic peptide 1–22, but not atrial natriuretic peptide 1–28 relaxed precontracted isolated preparations of rabbit corpus cavernosum. However, in the penis, soluble GC (sGC) is

probably the most important receptor for NO as a signaling molecule. The enzyme, which catalyzes the conversion of GTP into cyclic GMP, consists of two different subunits and contains a prosthetic heme group that mediates up to 400-fold activation by NO.

YC-1 [3-(5′-hydroxymethyl-2′-furyl)-1-benzylindazole] was shown to elicit a direct activation of sGC by increasing the affinity for GTP and increasing the maximal enzyme activity, leading to increased cGMP levels in smooth muscle cells (Mulsch et al., 1997). Moreover, YC-1 caused a large activation in the presence of the NO donor, sodium nitroprusside, which led to a remarkable 2200-fold stimulation of the human recombinant sGC (Lee et al., 2000). In addition, YC-1 enhances the sGC-stimulating effect of carbon monoxide (31- to 34-fold above carbon monoxide alone; Friebe and Koesling, 1998). Besides NO, YC-1 represents the first drug activating sGC in a biological environment. In addition, YC-1 seems to be able to stimulate NO synthesis and release (Wohlfart et al., 1999), and to inhibit cGMP-hydrolyzing phosphodiesterases (Friebe et al., 1998), enhancing the overall effect of cGMP.

YC-1 caused concentration-dependent relaxant responses in NA-contracted rat corpus cavernosum preparations, and enhanced responses to electrical field stimulation. YC-1 also enhanced the relaxant response induced by carbachol. In vivo, YC-1 elicited not only dose-dependent erectile responses when administered intracavernously, but also increased the effects on intracavernous pressure produced by stimulation of the cavernous nerve (H. Mizusawa, P. Hedlund, J. D. Brioni, J. P. Sullivan, and K.-E. Anderson, unpublished results).

c. Cyclic GMP-Dependent Signaling. cGMP signals via three main receptors in eukaryotic cell ion channels, phosphodiesterases, and protein kinases (Lucas et al., 2000). At present, however, the molecular targets that are activated by cGMP and finally execute the relaxation of penile smooth muscle are only partly known.

Two different cGMP-dependent protein kinases (cGK I and II) have been identified in mammals. Inactivation of cGK I in mice abolished both NO/cGMP-dependent relaxation of vascular and intestinal smooth muscle and inhibition of platelet aggregation, causing hypertension, intestinal dysmotility, and abnormal hemostasis (Pfeifer et al., 1998). cGK I-deficient (cGK I−/−) mice show a very low ability to reproduce. Corpus cavernosum tissue from these mice has an inability or markedly reduced ability to relax in response to neuronally or endothelially released or exogenously administered NO (Hedlund et al., 2000a). The expression of cGK I in penile tissue fom cGK I+/+ mice, as revealed by immunohistochemistry, was confined to the smooth muscle of the walls of the central and helicine arteries, and to the smooth muscle of the trabecular septa surrounding the cavernous spaces. This is in line with its presumed role in the erectile events. The total innervation (PGP immunoreactivity) and distribution of nerve populations containing transmitters or transmitter-forming enzymes believed to be important in the regulation of tone in corpus cavernosum tissue (Andersson and Wagner, 1995), were similar in normal and cGK I null mice.

Analysis of the NO/cGMP-induced relaxation clearly showed that cGK I is the major mediator of the cGMP signaling cascade in corpus cavernosum tissue. Its absence cannot be compensated for by the cAMP signaling cascade that relaxes normal and cGK I null penile erectile tissue to a similar extent. Taken together, these findings suggest that activation of cGK I is a key step in the signal cascade leading to penile erection.

The expression of cGK I was examined in corpus cavernosum specimens from patients with and without ED (Klotz et al., 2000). In all specimens of cavernosal tissue, a distinct immunoreactivity was observed in different parts and structures, with a high expression in smooth muscle cells of vessels and in the fibromuscular stroma. No clear immunoreactivity against cGK I was found in the endothelium. There was no distinct difference in immunoreactivity and cellular distribution between potent and impotent patients. This does not exclude the facts that dysfunction of cGK I can be a cause of ED in humans and that cGK I can be an interesting target for pharmacological intervention.

Phosphodiesterases (PDEs) catalyze the hydrolysis of the second messengers cAMP and cGMP, which are involved in signal pathways of cavernous smooth muscle. The protein superfamily of cyclic nucleotide PDEs can be subdivided into at least 11 families of structurally and functionally related enzymes. More than 40 isoforms have been characterized so far, all differing in their primary structures, specificity for cAMP and cGMP, cofactor requirements, kinetic properties, mechanisms of regulation, and tissue distributions (Beavo, 1995; Polson and Strada, 1996; Dousa,1999; Küthe et al., 1999, 2000, 2001; Fawcett et al., 2000; Hetman et al., 2000; Soderling and Beavo, 2000). Because of their central role in smooth muscle tone regulation and the considerable variation of PDE isoenzymes with respect to species and tissues, PDEs have become an attractive target for drug development. In human cavernous tissue, at least 13 isoenzymes have been identified, including PDE3 (cGMP-inhibited cAMP PDE), PDE4 (cAMP-specific PDE), and PDE5 (cGMP-specific PDE) (Ballard et al., 1996, 1998; Bivalacqua et al., 1999; Küthe et al., 2000, 2001). Functionally, PDE3A and PDE5A seem to be the most important (Ballard et al., 1998; Stief et al., 1998; Küthe et al., 2000, 2001). Lin et al. (2000) reported cloning of three PDE5 isoforms from human penile tissues. Two of the isoforms were identical to PDE5A1 and PDE5A2, respectively, which had previously been isolated from nonpenile tissues. The third isoform was novel and called PDE5A3; this isoform was confined to tissues with a smooth muscle or cardiac muscle component. PDE5A3 should be an interesting target for future drug developments.

The identification of the various PDE families has been paralleled by the synthesis of selective or partially selective inhibitors. Sildenafil is a highly selective inhibitor of PDE type 5 (Boolell et al., 1996a,b). It enhances NO-mediated relaxation of rabbit, rat, and human corpus cavernosum in vitro (Ballard et al., 1996, 1998; Tang et al., 1996; Chuang et al., 1998; Stief et al., 1998; Gemalmaz et al., 2001) and increases dose dependently the intracavernous pressure in anesthetized dogs (Carter et al., 1998). Sildenafil increases the intracellular concentrations of cyclic GMP (Chuang et al., 1998; Jeremy et al., 1997) due to an amplification of the endogenous NO-cyclic GMP pathway. This seems to involve a novel cellular signal transduction pathway in which force is dissociated from myosin light chain phosphorylation (Chuang et al., 1998). Several other selective PDE5 inhibitors are in different stages of development (Meuleman et al., 1999; Giuliano et al., 2000c; Noto et al., 2000; Oh et al., 2000; Stark et al., 2000).

3. Vasoactive Intestinal Polypeptide. The penis of humans as well as animals is richly supplied with nerves containing VIP (Dail, 1993). The majority of these nerves also contain immunoreactivity to NOS, and colocalization of NOS and VIP within nerves innervating the penis of both animals and humans has been demonstrated by many investigators (Ehmke et al., 1995; Hedlund et al., 1995a,b, Tamura et al., 1995; Vanhatalo et al., 1996, 1997; Dail et al., 1997; Schirar et al., 1997). It seems that most of these NO- and VIP-containing neurons are cholinergic, since they also contain vesicular acetylcholine transporter (Hedlund et al., 1999), which is a specific marker for cholinergic neurons (Arvidsson et al., 1997).

VIP receptors (types 1 and 2), linked via a stimulatory G-protein to adenylyl cyclase, are considered to mediate the actions of the peptide (Fahrenkrug, 1993; Harmar et al., 1998). The importance of the different subtypes of VIP receptor in penile tissues have not been clarified. VIP-related peptides, e.g., pituitary adenylyl cyclase-activating peptide, which has been found to be colocalized with VIP in penile nerves (Hedlund et al., 1994, 1995a), seem to act through one of the VIP receptors.

The stimulatory effect of VIP on adenylyl cyclase leads to an increase in cAMP, which in turn activates cAMP-dependent protein kinase. In corporal tissue from humans (Hedlund et al., 1995a), rats, and rabbits (Miller et al., 1995), VIP increased cAMP concentrations without affecting the cGMP levels.

In rats with experimentally induced diabetes, Maher et al. (1996) found that the VIP content of the major pelvic ganglion and penis was markedly increased, whereas intracavernous injection of VIP, which caused erection in control rats, had no effect in diabetic animals. Since forskolin, which directly activates adenylyl cyclase, induced erection in both controls and diabetic rats, it was concluded that there was a defect at the level of the VIP receptor or of the associated G-protein. This is in contrast to previous findings in diabetic rats, showing that VIP-stimulated cAMP generation was significantly increased (Miller et al., 1995). They are also in contrast to observations in human diabetes (Gu et al., 1984; Lincoln et al., 1987) showing that in patients with impotence, there was a marked reduction of VIP-like immunoreactivity in nerves associated with the cavernous smooth muscle. However, the latter observation has not been confirmed by other investigators (Haberman et al., 1991).

Undeniably, VIP has an inhibitory and relaxation-producing effect on strips of human corpus cavernosum tissue and cavernosal vessels in vitro, but it has been difficult to convincingly show that VIP released from nerves is responsible for relaxation of penile smooth muscle in vitro or in vivo (Andersson and Wagner, 1995). VIP antiserum (Adaikan et al., 1986) and α-chymotrypsin (Pickard et al., 1993) reduced or abolished the relaxant effect of exogenous VIP on isolated human corpus cavernosum tissue but had no effect on relaxation induced by electrical stimulation of nerves. Kim et al. (1995) reported that in rabbit corpus cavernosum, a VIP antagonist inhibited electrically induced contractions, suggesting that the peptide was released from nerves during stimulation. They concluded that VIP appeared to contribute to NANC-mediated corpus cavernosum relaxation and that its mechanism of relaxation was dependent on prostanoids and involved the generation of NO. This is in contrast to the conclusion drawn by Hayashida et al. (1996), who found no evidence for a role of VIP in the regulation of tone in the canine corpus cavernosum.

As mentioned previously, many penile nerves contain NO, VIP, and ACh, and the possible interactions between these agents should be of particular interest. The effects of NO and the NO donor linsidomine (SIN-1) were studied on human isolated cavernous artery and corpus cavernosum (Hempelmann et al., 1995). They found nonsynergistic independent relaxant effects in both types of preparation. Suh et al. (1995) investigated the effect of VIP and VIP combined with ACh given intracavernously in rats. They found that VIP and ACh, individually or in combination, did not produce full erection and concluded that neither VIP nor ACh were likely to be principal transmitters.

Not only NOS, but also other peptides, seem to be colocalized with VIP. Peptide histidine methionine, which is derived from the same precursor as VIP (Yiangou et al., 1985; Kirkeby et al., 1992; Hauser-Kronberger et al., 1994a,b), and the VIP-related pituitary adenylyl cyclase-activating peptide and helospectin (Hauser-Kronberger et al., 1994a,b; Hedlund et al., 1994, 1995a) have been found to be colocalized with VIP. Even if Hedlund et al. (1995a) demonstrated that some of these peptides were effective relaxants of human corpus cavernosum preparations, a role for them as neuro-

transmitters and/or neuromodulators has yet to be demonstrated.

Thus, whether or not VIP has a role as a neurotransmitter or modulator of neurotransmission in the penis has not been established. Even if its physiological role in penile erection and in ED remains to be settled, VIP receptors in the penis are an interesting therapeutic target. Particularly, the combination of VIP and phentolamine seems to be effective in the treatment of ED (see below).

4. Prostanoids. Human corpus cavernosum tissue has the ability to synthesize various prostanoids and also has the ability to locally metabolize them (Miller and Morgan, 1994; Andersson and Wagner, 1995; Porst, 1996; Minhas et al., 2000). The production of prostanoids can be modulated by oxygen tension and suppressed by hypoxia (Daley et al., 1996a,b). Corresponding to the five primary active prostanoid metabolites: PGD_2, PGE_2, $PGF_{2\alpha}$, PGI_2, and thromboxane A_2, there are five major groups of receptors that mediate their effects, namely DP, EP, FP, IP, and TP receptors. cDNAs encoding representatives of each of these groups of receptors have been cloned, including several subtypes of EP receptors, which are expressed in human corpus cavernosum (Moreland et al., 1999b). The prostanoid receptors are G-protein-coupled with differing transduction systems (Coleman et al., 1994; Pierce et al., 1995; Narumiya et al., 1999) .

The role of the different prostanoid receptors in penile physiology is still far from established (Khan et al., 1999). Prostanoids may be involved in contraction of erectile tissues via $PGF_{2\alpha}$ and thromboxane A_2, stimulating thromboxane and FP receptors and initiating phosphoinositide turnover, as well as in relaxation via PGE_1 and PGE_2, stimulating EP receptors (EP2/EP4) and initiating an increase in the intracellular concentration of cAMP. PGE_1-induced relaxation of human corporal smooth muscle was also suggested to be related to activation of K_{Ca} channels, resulting in hyperpolarization (Lee et al., 1999b). Escrig et al. (1999) found that repeated PGE_1 treatment enhances erectile responses to nerve stimulation in the rat penis by up-regulating constitutive NOS isoforms.

Prostanoids may also be involved in inhibition of platelet aggregation and white cell adhesion, and recent data suggest that prostanoids and transforming growth factor-β_1 (TGF-β_1) may have a role in modulation of collagen synthesis and in the regulation of fibrosis of the corpus cavernosum (Moreland et al., 1995).

Palmer et al. (1994) found that forskolin, which directly stimulates adenylate cyclase, was a potent stimulant of intracellular cAMP formation in cultured human corporal smooth muscle cells. Threshold forskolin doses were found to significantly increase the production of cAMP by PGE_1, which suggested a possible synergistic effect. Traish et al. (1997a) confirmed this synergistic effect of forskolin and PGE_1 in cultured human corpus cavernosum cells. They also demonstrated that the augmentation of the forskolin-induced cAMP generation by PGE_1 and PGE_0 was mediated by EP receptors and attributable to interactions at the adenylyl cyclase and G-protein levels. Both forskolin and PGE_1 elicited concentration-dependent increases in the magnitude and duration of intracorporal pressure in dogs without systemic effects (Cahn et al., 1996). Mulhall et al. (1997) injected forskolin intracavernously to patients with ED who had failed to respond to standard injection therapy and found improvement of erection in 61% of the cases. These results suggest that it is possible to enhance the relaxant corporal effects of PGE_1, and possibly other vasodilators, by forskolin and analogs (Laurenza et al., 1992), and it cannot be excluded that this may provide new strategies for pharmacologic treatment of ED. Another way of enhancing the effects of PGE_1 may be to combine with α-AR antagonists, such as doxazosin (Kaplan et al., 1998).

5. ATP and Adenosine. ATP and other purines were shown to decrease both basal tension and phenylephrine-stimulated tension in isolated rabbit corpus cavernosum preparations (Tong et al., 1992; Wu et al., 1993). It was suggested that ATP is a NANC transmitter in the corpora cavernosa, and that purinergic transmission may be an important component involved in the initiation and maintenance of penile erection (Tong et al., 1992). However, none of the purines tested facilitated or inhibited the response of corporal smooth muscle to electrical field stimulation, and therefore their role may be in the modulation of erection rather than as neurotransmitters (Wu et al., 1993). ATP injected intracavernously in dogs was found to produce increases in intracavernous pressure and erection (Takahashi et al., 1992a). This effect, which was unaffected by atropine and hexamethonium, could be obtained without changes in systemic blood pressure. In addition, adenosine produced full erection on intracavernous administration (Takahashi et al., 1992b).

The relaxant activity of ATP may be mediated either by its interaction with ATP receptors, or by adenosine generated through the endonucleotidase-mediated breakdown of ATP. Adenosine was suggested to act through stimulation of receptors belonging to the A_{2a} subtype (Mantelli et al., 1995). Filippi et al. (1999) found that ATP acted as a potent and NO-independent relaxant agent of human and rabbit corpus cavernosum. They also showed that the ATP effect was partially attributable to the metabolic breakdown of ATP to adenosine but was also due to a direct stimulation of P2 receptors, seemingly different from the classical P2Yand P2X receptor subtypes. Shalev et al. (1999) showed that human corporal cavernosal strips can be relaxed by stimulation of P2Y purinoceptors via NO release. This relaxation was mediated by an endothelium-dependent mechanism. They suggested that purines may be implicated in physiological erection in man. However, the roles of ATP

or adenosine in the physiological mechanisms of erection still remain to be established.

6. Other Agents.

a. Adrenomedullin and Calcitonin Gene-Related Peptide. Adrenomedullin, which has been suggested to serve as a circulating hormone-regulating systemic arterial pressure, consists of 52 amino acids and has structural similarities to calcitonin-gene-related peptide (CGRP) (Kitamura et al., 1993). Injected intracavernously in cats, adrenomedullin caused increases in intracavernous pressure and in penile length (Champion et al., 1997a–c). Since the erectile responses to adrenomedullin or CGRP were unaffected by NO synthase inhibition with L-NAME or by K_{ATP} channel inhibition with glibenclamide, it was suggested that NO or K_{ATP} channels were not involved in the response. The responses to CGRP were reduced by the CGRP antagonist CGRP (8–37) at doses having no effects on the adrenomedullin response, suggesting that the peptides acted on different receptors. Adrenomedullin and CGRP reduced blood pressure in the highest doses used. CGRP may be useful in the treatment of ED (Stief et al., 1990). However, whether or not adrenomedullin can be used or whether it has any advantages over CGRP remains to be established. A limiting factor for both agents is that they have to be injected intracavernously.

b. Nociceptin. Nociceptin is a 17-amino acid peptide that shares structural homology with the dynorphin family of peptides. It differs from other opioid peptides by not having the NH_2-terminal residue, which is essential for activity at μ, δ, and κ opioid receptors (Henderson and McKnight, 1997; Calo et al., 2000). The drug is an endogenous ligand for the orphan opioid receptor that has been identified in several species: the human clone is called ORL1. Its function is not established; it may be involved in hyperalgesia or analgesia (Henderson and McKnight, 1997).

Champion et al. (1997a) compared the erectile responses to intracavernously given nociceptin with those of a triple drug combination, VIP, adrenomedullin, and an NO donor in cats. Nociceptin in doses of 0.3 to 3 nM elicited dose-related increases in intracavernous pressure and penile length comparable with that of the triple drug combination, but the duration of the response was shorter. Whether nociceptin is involved in erectile mechanisms and whether the ORL1 receptor may be a target for drugs improving erectile function remains to be established.

C. Impulse Transmission

1. Electrophysiology. Although a variety of ion channels have been identified in corpus cavernosum smooth muscle cells (Christ et al., 1993; Noack and Noack, 1997; Christ, 2000), there have been few electrophysiological investigations of whole corporal smooth muscle preparations. However, electrical activity of the human corpus cavernosum in vivo as revealed by electromyographic studies is well synchronized, and corporal smooth muscle cells behave as a functional syncytium (Andersson and Wagner, 1995). In the proximal part of the rat corpus spongiosum (penile bulb), Hashitani (2000) demonstrated spontaneous action potentials in the inner muscle layer. On the other hand, no action potentials could be detected by electrophysiological investigation of cultured human corpus cavernosum smooth muscle cells (Christ et al., 1993). If this is valid for the cells in vivo, it calls for an alternative mechanism for impulse propagation. Such a mechanism may be provided by gap junctions.

2. Gap Junctions. As underlined by Christ (2000), signal transduction in corporal smooth muscle is more a network event than the simple activation of a physiological cascade or pathway in individual myocytes. Gap junctions may contribute to the modulation of corporal smooth muscle tone, and thus, erectile capacity, and intercellular communication through gap junctions can provide the corpora with a significant "safety factor" or capacity for plasticity/adaptability of erectile responses.

Gap junctions constitute an ion channel gene family in corporal smooth muscle. The pore-forming units are formed by hexamers of connexin. Connexin43 is the predominant gap junction protein found in corporal myocytes (Campos de Carvalho et al., 1993; Moreno et al., 1993; Christ, 1995; Brink et al., 1996; Christ et al., 1996; Serels et al., 1998; Christ and Brink, 1999). Gap junctions represent aggregates of intercellular channels where each channel is formed by the union, across the extracellular space of two hemichannels or connexons, one contributed by each cell of an adjacent pair. Rafts of these individual channels (i.e., hundreds to thousands) aligned in adjacent cell membranes form the structural basis for the gap junctional plaques that are frequently, but not always, observed between smooth muscle myocytes. The functional correlate of these structures is that corporal smooth muscle cells function as a network (Christ, 2000).

3. Signal Coordination. Coordination of activity among the corporal smooth muscle cells is an important prerequisite to normal erectile function. The autonomic nervous system plays an important role in this process by supplying a heterogeneous neural input to the penis. The density, distribution, and roles of the various neuroeffector pathways are not completely understood, and in fact, may vary significantly between individuals as well as over time within the same individual. For example, the activity of the various parts of the autonomic nervous system differs dramatically during erection, detumescence, and flaccidity (Becker et al., 2000c). As such, it is increasingly clear that the role of the autonomic nervous system in normal penile function must be coordinated with the phenotype and activity of the constituent corporal and arterial myocytes. That is, the firing rate of the autonomic nervous system, myocyte excitability and signal transduction processes and the extent of cell-to-cell communication between corporal

smooth muscle cells must be carefully integrated to ensure normal erectile function.

Such an integrative mechanism for the coordination of tissue responses has been suggested (Christ et al., 1993, 1997; Christ, 1997) and referred to as the "Syncytial Tissue Triad". The principles that govern the coordination of corporal smooth muscle responses exist at three levels: 1) the signal, direct activation of a fraction of the corporal smooth muscle cells by first messengers; i.e., neurotransmitters, neurohumors, or hormones, etc.; 2) signal spread, electrotonic current spread and intercellular diffusion of relevant second messenger molecules/ions via gap junctions; and 3) signal transduction, intracellular signal transduction within corporal smooth muscle cells mediated by activation of transducer G-proteins, i.e., second and third messengers, etc. (Christ et al., 1993; Christ, 1997).

D. Excitation-Contraction Coupling

1. Ionic Distribution. The distribution of ions across the corporal smooth muscle cell membrane is critical to the understanding of ion channel function. In conjunction with resting membrane potential of the corporal smooth muscle cell, this distribution ultimately determines the direction of ion flow during the opening of any given ion channel. These ionic gradients are maintained by a series of active membrane ion pumps and cotransporters and are absolutely critical to the normal function of the corporal smooth muscle cell.

2. K^+ Channels. At least four distinct K^+ currents have been described in human corporal smooth muscle (Christ, 2000): 1) a calcium-sensitive maxi-K (i.e., K_{Ca}) channel; 2) a metabolically regulated K channel (i.e., K_{ATP}); 3) a delayed rectifier K channel (i.e., K_{DR}); and 4) an "A"-type K current. The K_{Ca} channel and the K_{ATP} channel (see Baukrowitz and Fakler, 2000) are the most well characterized and probably the most physiologically relevant.

The distribution of K^+ across the corporal smooth muscle cell membrane ensures that the opening of potassium channels will lead to efflux of K^+ from the smooth muscle cell, down their electrochemical gradient. The movement of positive charge out of the cell results in hyperpolarization and an inhibitory effect on transmembrane Ca^{2+} flux through voltage-dependent calcium channels.

a. The K_{Ca} Channel. The calcium-sensitive K channel has been well characterized in both human and rat corporal smooth muscle (Wang et al., 2000). K_{Ca} channel mRNA and protein have been detected in both freshly isolated human corporal tissues and cultured corporal smooth muscle cells (Christ et al., 1999). Consistent with such observations, the single channel conductance (≈180 pS), whole cell outward currents, and voltage and calcium sensitivity of the K_{Ca} channel are remarkably similar when comparing data collected with patch clamp techniques on freshly isolated corporal smooth muscle myocytes versus similar experiments on short-term explant-cultured corporal smooth muscle cells (see Fan et al., 1995; Lee et al., 1999a,b).

The K_{Ca} channel appears to be an important convergence point in modulating the degree of corporal smooth muscle contraction. The activity of this channel is increased following cellular activation of either the cAMP pathway by 8-Br-cAMP or PGE_1 (Lee et al., 1999a) or the cGMP pathway by 8-Br-cGMP (Wang et al., 2000). It seems clear that the two most physiologically relevant endogenous second messenger pathways act to modulate corporal smooth muscle tone (i.e., elicit relaxation), at least in part, via activation of the K_{Ca} channel subtype. The resulting hyperpolarization, in turn, is coupled to decreased transmembrane calcium flux through L-type voltage-dependent calcium channels (see below) and, ultimately, smooth muscle relaxation.

b. The K_{ATP} Channel. Western blots on isolated tissue strips, and immunocytochemistry of cultured corporal smooth muscle cells, using antibodies to the K_{ATP} channel, have documented the presence of the K_{ATP} channel protein (Christ et al., 1999). Consistent with these observations, several studies have documented that K channel modulators, putative activators of the K_{ATP} channel subtype, elicit a concentration-dependent relaxation of isolated human corporal smooth muscle (Andersson and Wagner, 1995). Recent experiments on freshly isolated corporal smooth muscle cells have documented the presence of two distinct ATP-sensitive K^+ currents in cultured and freshly dissociated human corporal smooth muscle cells (Lee et al., 1999a). Consistent with observations at the single channel level, whole cell patch clamp studies documented a significant glibenclamide-sensitive increase in the whole cell outward K^+ currents in the presence of the K channel modulator levcromakalim (see Lee et al., 1999a). These data, ranging from the molecular, through the cellular and whole tissue levels, clearly document the presence and physiological relevance of the K_{ATP} channel subtype(s) to the modulation of human corporal smooth muscle tone.

3. L-Type Voltage-Dependent Calcium Channels. The distribution of calcium ions across the corporal smooth muscle cell membrane ensures that opening of calcium channels will lead to influx of calcium ions into the corporal smooth muscle cell down their electrochemical gradient. The movement of positive charge into the smooth muscle cell has the opposite effect of the movement of K^+ out of the cell, and therefore, will lead to depolarization. Several studies have documented the importance of continuous transmembrane calcium influx through L-type voltage-dependent calcium channels to the sustained contraction of human corporal smooth muscle (Fovaeus et al., 1987; Christ et al., 1989, 1990, 1991, 1992a,b). There seems to be only one published report of inward Ca^{2+} currents in corporal smooth muscle using direct patch clamp methods (Noack and Noack, 1997). However, much of the most compelling mechanistic data concerning the role of calcium

channels in modulating human corporal smooth muscle tone have been established using digital imaging microscopy of Fura-2-loaded cultured corporal smooth muscle cells. These studies have provided strong evidence for the presence and physiological relevance of transmembrane calcium flux through the L-type voltage-dependent calcium channel in response to cellular activation with ET-1 ($ET_{A/B}$ receptor subtype) and phenylephrine (α_1-adrenergic receptor subtype (Christ et al., 1992b; Zhao and Christ, 1995; Staerman et al., 1997).

4. Chloride Channels. The contribution of chloride channels/currents to the modulation of human corporal smooth muscle tone is less well understood than that of the other ion channels. Although rigorous analysis of Cl^- channels is hindered by the lack of truly selective channel blockers, there is still strong evidence for the presence of at least two subtypes of Cl^- channels on corporal myocytes (Christ et al., 1993), one calcium-sensitive and one stretch-sensitive. The calcium-sensitive Cl^- channel has a very small open probability, making assessment of its potential physiological significance a difficult task. The stretch-sensitive Cl^- channel may well provide an important servo-mechanism for length maintenance of the corporal smooth muscle cell in the face of differential hydrostatic gradients, or additionally, during the rapid corporal pressure changes that occur during alterations in the flow of blood to and from the penis during normal penile erection and detumescence (Fan et al., 1999).

5. Contractile Machinery.

a. Contraction. Changes in the sarcoplasmic Ca^{2+} concentration, and thereby in the contractile state of the smooth muscle cell, can occur with or without changes in the membrane potential (Somlyo and Somlyo, 1994; Stief et al., 1997). Action potentials or long-lasting changes in the resting membrane depolarize the membrane potential, thus opening voltage-gated L-type Ca^{2+} channels (Kuriyama et al., 1998). Thus, Ca^{2+} enters the sarcoplasm driven by the concentration gradient and triggers contraction. Changes in the membrane potential may also be induced by membrane channels other than Ca^{2+} channels. Opening of K^+ channels (see above) can produce hyperpolarization of the cell membrane. This hyperpolarization inactivates the L-type calcium channels, resulting in a decreased Ca^{2+} influx and subsequent smooth muscle relaxation.

The major mechanisms involved in smooth muscle contractions, not associated with changes in membrane potential, are the release of IP_3 and the regulation of Ca^{2+} sensitivity. Both mechanisms may be important for the activation of corporal smooth muscle. With regard to the physiologically important phosphatidylinositol cascade, many agonists (e.g., α_1-AR agonists, ACh, angiotensins, vasopressin) bind to specific membrane-bound receptors that are coupled to phosphoinositide-specific phospholipase C via GTP-binding proteins. Phospholipase C then hydrolyzes phosphatidylinositol 4,5-biphosphate to 1,2-diacylglycerol (this activates protein kinase C) and IP_3. The water-soluble IP_3 binds to its specific receptor (Berridge and Irvine, 1984; Ferris and Snyder, 1992) on the membrane of the sarcoplasmic reticulum (intracellular compartment for Ca^{2+} storage), thereby opening this Ca^{2+} channel. Since the Ca^{2+} concentration in the sarcoplasmic reticulum is about 1 mM, Ca^{2+} is thus driven into the sarcoplasm by the concentration gradient, triggering smooth muscle contraction. This increase in sarcoplasmic Ca^{2+} concentration may activate a distinct Ca^{2+} release channel of the sarcoplasmic reticulum (i.e., perhaps the ryanodine receptor-operated channel), leading to a further increase in the Ca^{2+} concentration of the sarcoplasm muscle (Somlyo and Somlyo, 1994; Karaki et al., 1997).

As in striated muscle, the amount of intracellular free Ca^{2+} is the key to regulation of smooth muscle tone. In the resting state, the level of sarcoplasmic free Ca^{2+} amounts to about ≈100 nM, whereas in the extracellular fluid the level of Ca^{2+} is in the range of 1.5 to 2 mM. This 10,000-fold gradient is maintained by the cell-membrane Ca^{2+} pump and the Na^+/Ca^{2+} exchanger. A rather modest increase in the level of free sarcoplasmic Ca^{2+} by a factor of 3 to 5 to 550 to 700 nM then triggers myosin phosphorylation (see below) and subsequent smooth muscle contraction.

In the smooth muscle cell, Ca^{2+} binds to calmodulin, which is in contrast to striated muscles, where $Ca^{2+}{}_i$ binds to the thin filament-associated protein troponin (Chacko and Longhurst, 1994; Karaki et al., 1997). The calcium-calmodulin complex activates myosin light chain kinase (MLCK) by association with the catalytic subunit of the enzyme. The active MLCK catalyzes the phosphorylation of the regulatory light chain subunits of myosin (MLC_{20}). Phosphorylated MLC_{20} activates myosin ATPase, thus triggering cycling of the myosin heads (cross-bridges) along the actin filaments, resulting in contraction of the smooth muscle. A decrease in the intracellular level of Ca^{2+} induces a dissociation of the calcium-calmodulin MLCK complex, resulting in dephosphorylation of the MLC_{20} by myosin light chain phosphatase and in relaxation of the smooth muscle (Somlyo and Somlyo, 1994; Karaki et al., 1997). A specific long lasting state of contraction with reduced cycling frequency and low energy (ATP) consumption is termed a *latch state*. The mechanism of this high-force and low-energy consumption state is not known.

In corpus cavernosum smooth muscle, which unlike most smooth muscles, spends the majority of its time in the contracted state, an overall myosin isoform composition was found that was intermediate between aorta and bladder smooth muscles, which generally express tonic- and phasic-like characteristics (Di Santo et al., 1998), respectively.

In smooth muscle, the force/Ca^{2+} ratio is variable and depends partly on specific activation mechanisms. For example, α-AR agonists induce a higher force/Ca^{2+} ratio

than does a depolarization-induced increase (i.e., KCl) in intracellular Ca^{2+}, suggesting a "calcium-sensitizing" effect of agonists. Furthermore, it has been shown that at a constant sarcoplasmic Ca^{2+} level, decrease of force ("calcium desensitization") can be observed. The effect of calcium-sensitizing agonists are mediated by GTP-binding proteins that generate protein kinase C or arachidonic acid as second messengers (Karaki et al., 1997; Kuriyama et al., 1998). The major mechanism of Ca^{2+} sensitization of smooth muscle contraction is through inhibition of the smooth muscle myosin phosphatase, thus increasing MLC_{20} phosphorylation by basal level activity of MLCK. The resulting myosin phosphorylation and subsequent smooth muscle contraction therefore occurs without a change in sarcoplasmic Ca^{2+} concentration. Ca^{2+} sensitization by the Rho-A/Rho-kinase pathway contributes to the tonic phase of the agonist-induced contraction in smooth muscle, and abnormally increased activation of myosin by this mechanism may play a role in certain diseases (Somlyo and Somlyo, 2000). This calcium-sensitizing Rho-A/Rho-kinase pathway may also play a synergistic role in cavernosal vasoconstriction to maintain penile flaccidity. Rho-kinase is known to inhibit myosin light chain phosphatase and to directly phosphorylate myosin light chain, altogether resulting in a net increase in activated myosin and the promotion of cellular contraction. Although Rho-kinase protein and mRNA have been detected in cavernosal tissue, the role of Rho-kinase in the regulation of cavernosal tone is unknown. Using the Rho-kinase antagonist Y-27632, Chitaley et al. (2001) examined the role of Rho-kinase in cavernosal tone, based on the hypothesis that antagonism of Rho-kinase results in increased corpus cavernosum pressure, initiating the erectile response independently of NO. They found that Rho-kinase antagonism stimulated rat penile erection independently of NO and suggested that this principle could be a potential alternate avenue for the treatment of ED (Chitaley et al., 2001).

b. Relaxation. Like in other smooth muscles, corporal smooth muscle relaxation is mediated via the intracellular cyclic nucleotide/protein kinase messenger systems. Via specific receptors, e.g., β-ARs, agonists activate membrane-bound adenylyl cyclase, which generates cAMP. cAMP then activates protein kinase A (or cAK) and, to a lesser extent, protein kinase G (or cGK). Atrial natriuretic factor (ANF) acts via the membrane-bound GC (Lucas et al. 2000), whereas NO stimulates the soluble form of GC (see above); both generate cGMP, which activates cGKI and, to a lesser extent, cAK. Activated cGKI and cAK phosphorylate phospholamban, a protein that normally inhibits the Ca^{2+} pump within the membrane of the sarcoplasmic reticulum. The Ca^{2+} pump is then activated and, consequently, the level of free cytoplasmic Ca^{2+} is reduced, resulting in smooth muscle relaxation. Similarly, the protein kinases activate the cell-membrane Ca^{2+} pump, leading to a decreased sarcoplasmic Ca^{2+} concentration and to subsequent relaxation (Somlyo and Somlyo, 1994; Karaki et al., 1997).

IV. Pharmacology of Current and Future Therapies

A. Erectile Dysfunction—Risk Factors

ED is often classified into four different types: psychogenic, vasculogenic or organic, neurologic, and endocrinologic. It may also be iatrogenic and result as a side effect of different pharmacological treatments. For long time, it was believed that psychogenic factors were predominant. However, although it is difficult to separate psychogenic factors from organic disease, vasculogenic ED was found to account for about 75% of ED patients (National Institutes of Health Consensus Statement, 1993).

ED may be due to inability of penile smooth muscle to relax. This inability can have multiple causes, including nerve damage, endothelial damage, alteration in receptor expression/function, or in the transduction pathways that are implicated in the relaxation and contraction of the smooth muscle cell. Generally, patients with ED respond well to the pharmacological treatments that are currently available. In those who do not respond to pharmacological treatment (10 to 15% of patients with ED), a structural alteration in the components of the erectile mechanism can be suspected. Various diseases commonly associated with impotence can alter the mechanisms that control penile smooth muscle tone. Often, changes in the L-arginine/NO/cGMP system are involved.

Aging is an important risk factor for ED, and it has been estimated that 55% of men are impotent at the age of 75 (Kaiser, 1991; Melman and Gingell, 1999; Johannet et al., 2000). Garban et al. (1995) found that the soluble NOS activity decreased significantly in penile tissue from senescent rats. Lower NOS mRNA expression was found in older rats than in younger rats (Dahiya et al., 1997). In another rat model of aging, the number of NOS-containing nerve fibers in the penis decreased significantly, and the erectile response to both central and peripheral stimulation decreased (Carrier et al., 1997). In the aging rabbit, endothelium-dependent corpus cavernosum relaxation was attenuated; however, eNOS was up-regulated both in vascular endothelium and corporal smooth muscle (Haas et al., 1998).

Diabetes mellitus is often associated with ED (Saenz de Tejada and Goldstein, 1988; Melman and Gingell, 1999; Johannes et al., 2000) and with impaired NOS-dependent erectile mechanisms. In isolated corpus cavernosum from diabetic patients with impotence, both neurogenic and endothelium-dependent relaxation was impaired (Saenz de Tejada et al., 1989), and this was also found in rabbits where diabetes was induced by alloxan (Azadzoi and Saenz de Tejada, 1992). Penile NOS activity and penile NOS content were reduced in rat models of both type I and type II diabetes with ED

(Vernet et al., 1995). However, in streptozotocin-induced diabetic rats, NOS binding increased (Sullivan et al., 1996), and NOS activity in penile tissue was significantly higher than in controls, despite a significant degradation of mating behavior and indications of defective erectile potency (Elabbady et al., 1995). In humans, the diabetic ED was suggested to be related to the effects of advanced glycation end products on NO formation (Seftel et al., 1997).

Atherosclerosis and hypercholesterolemia are significant risk factors involved in the development of vasculogenic ED. Hypercholesterolemia was also found to impair endothelium-mediated relaxation of rabbit corpus cavernosum smooth muscle (Azadzoi and Saenz de Tejada, 1991; Azadzoi et al., 1998). Hypercholesterolemia did not affect NOS activity, but impaired the endothelium-dependent, but not the neurogenic, relaxation of rabbit corpus cavernosum tissue. Since the endothelium-dependent relaxation was improved after treatment with L-arginine, it was speculated that there was a deficient NO formation due to lack of availability of L-arginine in the hypercholesterolemic animals.

In a rabbit model of atherosclerotic ED (Azadzoi and Goldstein, 1992; Azadzoi et al., 1997), it was shown that chronic cavernosal ischemia impaired not only endothelium-dependent, but also neurogenic corpus cavernosum relaxation and NOS activity (Azadzoi et al., 1998). There was also an increased output of constrictor eicosanoids in the corpus cavernosum. L-Arginine administration failed to improve corpus cavernosum relaxation, which was suggested to be due to impairment of the NOS activity and and reduction of NO formation.

Smoking is a major risk factor in the development of impotence (Mannino et al., 1994). In rats, passive chronic smoking caused age-independent moderate systemic hypertension and marked decreases in penile NOS activity and nNOS content (Xie et al., 1997). This was not reflected in a reduction of the erectile response to electrical nerve stimulation or by a decrease in penile eNOS.

B. Drugs for Treatment of Erectile Dysfunction

A wide variety of drugs have been used for treatment of ED. Major advances have been made in our understanding of the mechanisms of drug action and of the mechanisms of penile erection, and presently, there seems to be a rational basis for a therapeutic classification of currently used drugs. Such a useful classification was suggested by Heaton et al. (1997), in which ED treatments were divided into five major classes by their mode of action: I) central initiators; II) peripheral initiators; III) central conditioners; IV) peripheral conditioners; and V) other. Drugs can be further subdivided by the routes of administration, for example.

C. Drugs for Intracavernous Administration

Among the many drugs tested (Jünemann and Alken, 1989; Jünemann, 1992; Gregoire, 1992; Linet and Ogrinc,1996; Porst, 1996; Bivalacqua et al., 2000; Levy et al., 2000; Lue et al.; 2000), only three, used alone or in combination, have become widely accepted and administered on a long-term basis, namely papaverine, phentolamine, and PGE_1 (alprostadil). The experimental and clinical experiences with several other agents used for treatment and discussed below are limited.

1. Papaverine. Papaverine is often classified as a phosphodiesterase inhibitor, but the drug has a very complex mode of action and may be regarded as a "multilevel acting drug" (Andersson, 1994). It is difficult to establish which of its several possible mechanisms of action is the one that predominates at the high concentrations that can be expected when the drug is injected intracavernously. In vitro, it has been shown that papaverine relaxes the penile arteries, the cavernous sinusoids, and the penile veins (Kirkeby et al., 1990). In dogs, Juenemann et al. (1986) demonstrated that papaverine had a dual hemodynamic effect, decreasing the resistance to arterial inflow and increasing the resistance to venous outflow. The latter effect, which has been demonstrated also in man (Delcour et al., 1987), may be related to activation by papaverine of a veno-occlusive mechanism.

Since the main mechanism of action of papaverine is nonselective PDE inhibition, and the main PDE activities in the human corpus cavernosum appear to be PDE3 and PDE5, injectable PDE inhibitors with actions on these isoenzymes, but which lack the "nonspecific" side effects of papaverine, would be an interesting alternative.

2. α-Adrenoceptor Antagonists.

a. Phentolamine. Phentolamine is a competitive α-AR antagonist with similar affinity for α_1- and α_2-ARs, and this is its main mechanism of action. However, the drug can block receptors for 5-HT and cause release of histamine from mast cells. Phentolamine also seems to have another action, possibly involving NOS activation (Traish et al., 1998). Since phentolamine nonselectively blocks α-ARs, it can be expected that by blocking prejunctional α_2-ARs, it would increase the NA release from adrenergic nerves, thus counteracting its own postjunctional α_1-AR blocking actions. It is not known whether or not such an action contributes to the limited efficacy of intracavernously administered phentolamine to produce erection.

In dogs, phentolamine like papaverine decreased the resistance to arterial inflow to the penis. However, papaverine, but not phentolamine, increased the resistance to venous outflow (Juenemann et al., 1986). Lack of effect on venous outflow by intracavernous phentolamine has also been demonstrated in man (Wespes et al., 1989).

There is a general lack of information about the pharmacokinetics of phentolamine. The drug has a reduced efficacy when given orally, probably due to extensive first-pass metabolism. A discrepancy between the plasma half-life (30 min) and effect duration (2.5–4 h) has been demonstrated (Imhof et al., 1975); whether this can be attributed to active metabolites is not known. When the drug is given intracavernously, the serum concentration of phentolamine will reach a maximum within 20 to 30 min and then rapidly decline to undetectable levels (Hakenberg et al., 1990).

The most common side effects of phentolamine after intravenous administration are orthostatic hypotension and tachycardia. Cardiac arrhythmias and myocardial infarction have been reported, but these are very rare events. Theoretically, such effects may be encountered also after intracorporal administration, but so far this does not seem to be the case. Since a single intracavernous phentolamine injection does not result in a satisfactory erectile response in most cases, the drug is widely used in combination with papaverine (Zorgniotti and Lefleur, 1985; Jünemann and Alken, 1989) or VIP (Gerstenberg et al., 1992).

b. Thymoxamine. Thymoxamine (moxisylyte) has a competitive and relatively selective blocking action on α_1-ARs. In addition, it may have antihistaminic actions. In vitro, moxisylyte relaxed NA-contracted human corpus cavernosum preparations (Imagawa et al., 1989) but was less potent than prazosin and phentolamine.

Little is known about its pharmacokinetics, but after systemic administration, it has an effect duration of 3 to 4 h. Moxisylyte is a prodrug, rapidly transformed into an active metabolite in plasma (deacetylmoxisylyte). Elimination of the active metabolite occurs by *N*-demethylation, sulfo-, and glucuroconjugation. The *N*-demethylated metabolite is sulfoconjugated only. Urine is the main route of excretion (Marquer and Bressole, 1998).

Moxisylyte was shown to produce erection when injected intracavernously (Brindley, 1986), and in a double blind crossover study, Buvat et al. (1989) showed it to be more active than saline but less active than papaverine. Buvat et al. (1989) reported on the experiences of intracavernous injections of moxisylyte in 170 patients with impotence and pointed out that the drug did not initiate, but facilitated, erection by inducing prolonged tumescence. They also stressed that the main advantage of the drug was its safety. Only two of the 170 patients injected had prolonged erections. Buvat et al. (1991), comparing papaverine and moxisylyte, also found that moxisylyte had less tendency to produce corporal fibrosis than papaverine (1.3 versus 32%). The positive safety aspects were underlined by Arvis et al. (1996), who reported no serious side effects among 104 men followed for 11 months and performing 7507 self-administrations.

In a comparative study between moxisylyte and PGE_1, Buvat et al. (1996) showed that PGE_1 was significantly more effective than moxisylyte (71 versus 50% responders), especially in patients with arteriogenic dysfunction (96 versus 46%). However, moxisylyte was significantly better tolerated than PGE_1 causing fewer prolonged erections and fewer painful reactions.

As a facilitating drug, moxisylyte may be a reasonable alternative for treatment of ED. An interesting development is nitrosylated moxisylyte, which may act as a combined NO donor and α_1-AR antagonist (de Tejada et al., 1999). Clinical studies experiences with this drug are so far lacking.

3. Prostaglandin E_1 (Alprostadil). PGE_1, injected intracavernously or administered intraurethrally, is currently one of the most widely used drugs for treatment of ED (Linet and Ogrinc, 1996; Porst, 1996; Hellstrom et al., 1996; Padma-Nathan et al., 1997), and several aspects of its effects and clinical use have been reviewed (Linet and Ogrinc, 1996; Porst, 1996). In clinical trials, 40 to 70% of patients with ED respond to intracavernosal injection of PGE_1. The reason why a considerable number of patients do not respond is not known. Angulo et al. (2000) characterized the responses to PGE_1 in human trabecular smooth muscle and penile resistance arteries, which both showed large variability in response to PGE_1. They found a correlation of the in vitro response with the clinical erectile response and suggested that their results may explain why some patients respond and others do not to intracavernous PGE_1.

PGE_1 is metabolized in penile tissue to PHE_0 (Hatzinger et al., 1995), which is biologically active and may contribute to the effect of PGE_1 (Traish et al., 1997a). PGE_1 may act partially by inhibiting the release of NA (Molderings et al., 1992), but the main action of PGE_1 and PGE_0 is probably to increase the intracellular concentrations of cAMP in the corpus cavernosum smooth muscle cells through EP receptor stimulation (Palmer et al., 1994; Lin et al., 1995; Cahn et al., 1996; Traish et al., 1997a).

PGE_1 is known to have a variety of pharmacological effects. For instance, it produces systemic vasodilatation, prevents platelet aggregation, and stimulates intestinal activity. Administered systemically, the drug has been used clinically to a limited extent. Little is known about its pharmacokinetics, but it has a short duration of action and is extensively metabolized. As much as 70% may be metabolized in one pass through the lungs (Gloub et al., 1975), which may partly explain why it seldom causes circulatory side effects when injected intracavernously.

Angulo et al. (2000) demonstrated that the combination of PGE_1 with *S*-nitrosoglutathione (SNO-Glu) consistently relaxed penile smooth muscle whether or not it relaxed well to PGE_1. They suggested that the clinical response to PGE_1 may be limited in some patients by the specific lack of response of penile smooth muscle to PGE_1 while maintaining the ability to relax in response to agents that activate alternative relaxant pathways. A combination of PGE_1 and SNO-Glu had a synergistic

interaction to relax penile trabecular smooth muscle, and it was speculated that such a combination might have significant therapeutic advantages in the treatment of male ED.

4. Vasoactive Intestinal Polypeptide. As discussed previously, a role for VIP as neurotransmitter and/or neuromodulator in the penis has been postulated by several investigators, but its importance for penile erection has not been established (Andersson and Wagner, 1995; Andersson and Stief, 1997). However, the inability of VIP to produce erection when injected intracavernously in potent (Wagner and Gerstenberg, 1988) or impotent men (Adaikan et al., 1986; Kiely et al., 1989; Roy et al., 1990) indicates that it cannot be the main NANC mediator for relaxation of penile erectile tissues.

VIP has been shown to produce a wide range of effects. It is a potent vasodilator, inhibits contractile activity in many types of smooth muscle, stimulates cardiac contractility, and many exocrine secretions. It stimulates adenylate cyclase and the formation of cyclic AMP (Fahrenkrug, 1993).

Wagner and Gerstenberg (1988) found that even in high doses (60 ug), VIP was unable to induce erection on intracavernous injection in potent men. On the other hand, when used in conjunction with visual or vibratory stimulation, intracavernous VIP facilitated normal erection. Kiely et al. (1989) injected VIP, papaverine, and combinations of these drugs with phentolamine intracorporeally in twelve men with impotence of varying etiology. They confirmed that VIP alone is poor at inducing human penile erections. However, in combination with papaverine, VIP produced penile rigidity similar to that obtained with papaverine and phentolamine. Gerstenberg et al. (1992) administered VIP together with phentolamine intracavernously to 52 patients with erectile failure. Forty percent of the patients had previously received treatment with papaverine alone or with papaverine and phentolamine. After sexual stimulation, all patients obtained erection sufficient for penetration. Those patients previously treated with papaverine or papaverine/phentolamine stated that the action of the VIP combination was more like the normal coital cycle. No patient developed priapism, corporal fibrosis, or any other serious complication (Gerstenberg et al., 1992). These positive results have been confirmed by other investigators (McMahon,1996; Dinsmore and Alderdice, 1998; Sandhu et al., 1999). Thus, Sandhu et al. (1999) found that using a novel auto-injector in a double blind placebo-controlled study on 304 patients with psychogenic ED, over 81% of patients and 76% of partners reported an improved quality of life.

VIP given intravenously can produce hypotension, tachycardia and flushing (Palmer et al., 1986; Frase et al., 1987; Krejs,1988). However, the plasma half-life of the peptide is short, which may contribute to the fact that systemic side effects are rare when it is administered intracavernously (McMahon, 1996; Sandhu et al., 1999). The principal adverse event seemed to be transient facial flushing.

It seems that VIP administered intracavernously with phentolamine may be an alternative to the more established treatments with papaverine/phentolamine or PGE_1, but more experience is needed to give a fair evaluation of the advantages and disadvantages of this combination.

5. Calcitonin Gene-Related Peptide. Stief et al. (1990) demonstrated CGRP in nerves of the human corpus cavernosum and suggested its use in ED. In human blood vessels from various regions, CGRP is known to be a potent vasodilator. Its effect may be dependent or independent of the vascular endothelium (Crossman et al., 1987; Persson et al., 1991). The peptide relaxed the bovine penile artery by a direct action on the smooth muscle cells (Alaranta et al., 1991), which suggests that it may have important effects on the penile vasculature.

In patients, intracavernosal injection of CGRP induced dose-related increases in penile arterial inflow, cavernous smooth muscle relaxation, cavernous outflow occlusion, and in erectile responses. The combination of CGRP and PGE_1 may be more effective than PGE_1 alone (Stief et al., 1991b; Djamilian et al., 1993; Truss et al., 1994b).

As an initiator of erection, CGRP can be useful for therapeutic purposes and cannot be excluded as a facilitating drug, alone or in combination with other drugs, but to assess its potential, more experience is needed.

6. Linsidomine Chlorhydrate. It is reasonable to assume that drugs acting via NO may be useful for treatment of ED. Linsidomine, the active metabolite of the antianginal drug molsidomine, is believed to act by nonenzymatic liberation of NO (Feelisch, 1992; Rosenkranz et al., 1996), which by stimulating soluble GC increases the content of cyclic GMP in the smooth muscle cells and produces relaxation. Linsidomine also inhibits platelet aggregation (Reden 1990), and in some countries, it is registered for treatment of coronary vasospasm and coronary angiography. The drug was reported to have a plasma half-life of approximately 1 to 2 h (Wildgrube et al., 1986; Rosenkranz et al., 1996).

Linsidomine was found to effectively relax preparations of rabbit and human corpus cavernosum contracted by NA or ET-1 in a concentration-dependent way (Holmquist et al., 1992a). In preliminary studies, Stief et al. (1991a, 1992), and Truss et al. (1994a) studied the effect of linsidomine injected intracorporeally in impotent patients and found that the drug induced an erectile response by increasing the arterial inflow and relaxing cavernous smooth muscle. There were no systemic or local side effects, and no patient had a prolonged erection. These promising results have not been confirmed by other investigators (Porst, 1993; Wegner et al., 1994). Placebo-controlled randomized clinical trials must be performed to ascertain whether linsidomine is a useful

therapeutic alternative to existing drugs available for intracorporal injection.

Another NO donor, sodium nitroprusside (SNP), has been given intracorporeally for treatment of ED, but has been shown not to be effective (Martinez-Pineiro et al., 1995; Tarhan et al., 1996, 1998) and caused profound hypotension. These rather discouraging results with donors of NO do not rule out that drugs acting through the L-arginine/NO/GC/cGMP pathway can be effective for treatment of ED (see below).

D. Drugs for Nonintracavernous Administration

Drugs that can be given by modes other than intracavernously may have several advantages in the treatment of ED (Morales et al., 1995; Burnett, 1999; Morales, 2000a). There is a generally a high placebo response (30 to 50%) to nonintracavernously administered drugs. Therefore, placebo-controlled trials and valid instruments used to measure response are mandatory to adequately assess effects.

1. Organic Nitrates. Nitroglycerin and other organic nitrates are believed to cause smooth muscle relaxation by stimulating soluble GC via enzymatic liberation of NO (Feelisch,1992). Both nitroglycerin and isosorbide nitrate were found to relax isolated strips of human corpus cavernosum (Heaton, 1989).

Transdermal administration of nitroglycerin is well established in the treatment of angina pectoris. The observation that topical application of nitroglycerin to the penis may lead to erection adequate for sexual intercourse (Talley and Crawley, 1985) has stimulated several investigations on the efficacy of this potential mode of treatment of ED.

Owen et al. (1989) performed a placebo-controlled double blind study on the effect of nitroglycerin ointment applied to the penis of 26 impotent patients with a diagnosis of organic, psychogenic, or mixed-type impotence. In relation to placebo, nitroglycerin increased penile circumference significantly in 18 of 26 patients, and in 7 of 20 patients it increased blood flow in the cavernous arteries. Hypotension and headache were observed in one patient. In a double blind, randomized, placebo-controlled trial, Claes and Bart (1989) treated 26 impotent men with nitroglycerin patches. They observed a positive response to nitroglycerin with return to satisfactory sexual function in 12 (46%) patients, and some erectile improvement in 9 (35%). Only 1 of the 26 reported restoration of potency with placebo patches. Twelve of the patients reported mild to moderate headache during nitroglycerin treatment.

The effects of nitroglycerin plaster applied to the penis were also investigated in 10 impotent patients by Meyhoff et al. (1992). They found that when tested in the laboratory, all patients achieved an erectile response. When the plaster was self-administered, potency was restored in four, semirigidity insufficient for intercourse was seen in two, tumescence in three, and no effect in one. Seven patients complained of headache. A sufficient erectile response to the same nitroglycerin plaster was found in 5 of 17 patients with spinal cord injury (Sønksen and Biering-Sørensen, 1992).

Comparing transdermal nitroglycerin and intracavernous injection of papaverine in 28 patients with spinal cord lesions and ED, Renganathan et al. (1997) found that 61% responded to nitroglycerin and 93% to papaverine. Nine patients had complications with papaverine, whereas the only side effect of transdermal nitroglycerin was mild headache (21%). Even if the efficacy is limited and headache seems to be a common side effect, transdermal nitroglycerin may be an effective treatment in selected patients.

2. Phosphodiesterase Inhibitors. The L-arginine/NO/GC/cGMP pathway seems to be the most important for penile erection in some species (see above), and recent results with sildenafil, a selective inhibitor of the cGMP-specific PDE5, further support the view that this may be the case also in humans (Boolell et al., 1996a,b). Sildenafil is 4000 times more selective for PDE5 than for PDE3, 70 times more selective for PDE5 than PDE4, but only 10 times more selective for PDE5 than for PDE6 (Ballard et al., 1998; Moreland et al., 1998, 1999a). Sildenafil is rapidly absorbed after oral administration (bioavailability 41%) and has a plasma half-life of 3 to 5 h.

A large number of placebo-controlled, randomized, double blind trials have shown that sildenafil can improve erections in men with ED, regardless of whether the cause is due to psychogenic, organic, or mixed factors (Steers, 1999; Levy et al., 2000). Since PDE5 is not restricted to the penis, but can be found in other tissues as well, side effects such as nasal congestion, dyspepsia, headache, facial and chest flushing, and diarrhea may develop. Possible cardiovascular and visual side effects have dominated the safety discussions. An absolute contraindication to sildenafil is the use of nitrates, and several, but not all, of the deaths associated with sildenafil use have been attributed to concomitant use of nitrates. However, based on experience so far, sildenafil must be considered a safe drug (Conti et al., 1999; Steers, 1999; Zusman et al., 1999).

Sildenafil appears to be one of the most promising orally active agents for the treatment of ED. The high response rate and good tolerance makes it an attractive first alternative to patients who would previously have been considered candidates for injection therapy.

As mentioned previously, several other selective PDE5 inhibitors are in development (Meuleman et al., 1999; Giuliano et al., 2000c; Noto et al., 2000; Oh et al., 2000; Rotella et al., 2000; Stark et al., 2000), but the amount of clinical data available for evaluation is limited.

3. Prostaglandin E_1. Vasoactive agents can be administered topically to the urethral mucosa and can apparently be absorbed into the corpus spongiosum and transferred to the corpora cavernosa. PGE_1 (alprostadil)

and a PGE_1/prazosin combination was demonstrated to produce erections in a majority of patients with chronic organic ED (Peterson et al., 1998). In a prospective, multicenter, double blind placebo-controlled study on 68 patients with long-standing ED of primarily organic origin (Hellstrom et al., 1996), transurethrally administered alprostadil produced full enlargement of the penis in 75.4%, and 63.6% of the patients reported intercourse. The most common side effect was penile pain, experienced by 9.1 to 18.3% of the patients receiving alprostadil. There were no episodes of priapism. In another double blind placebo-controlled study on 1511 men with chronic ED from various organic causes, 64.9% had intercourse successfully when taking transurethral alprostadil compared with 18.6% on placebo (Padma-Nathan et al., 1997). Again the most common side effect was mild penile pain (10.8%). Positive experiences were also reported by Guay et al. (2000) retrospectively reviewing 270 patients. For men finding intracavernous injections problematic, the ease of intraurethral administration alprostadil is an option. Penile pain remains a problem in many patients.

4. K^+ Channel Openers. Several K^+ channel openers (pinacidil, cromakalim, lemakalim, and nicorandil) have been shown to be effective in causing relaxation of isolated cavernous tissue from both animals and man, and to produce erection when injected intracavernously in monkeys and humans (Andersson, 1992; Benevides et al., 1999). However, only minoxidil, an arteriolar vasodilator used as an antihypertensive agents in patients with severe hypertension, seems to have been tried in man. Minoxidil is a prodrug not active in vitro but is metabolized in the liver to the active molecule, minoxidil NO sulfate (McCall et al., 1983). It has been shown that minoxidil sulfate has the properties of a K^+ channel opener. Minoxidil is well absorbed, both from the gastrointestinal tract and transdermally, but its biotransformation to the active metabolite has not been evaluated in man. The drug has a half-life in plasma of 3 to 4 h, but the duration of its vascular effects is 24 h or even longer.

In a double blind trial, minoxidil was given to 33 patients with neurogenic and/or arterial impotence and compared with placebo (lubricating gel) and nitroglycerin (2.5 g of 10% ointment). Minoxidil was applied on the glans penis as 1 ml of a 2% solution. Minoxidil was superior to both placebo and nitroglycerin in increasing penile rigidity, and it was suggested that the drug might be considered for long-term treatment of organic impotence (Cavallini, 1991, 1994).

The main side effects of the drug, when used in the treatment of hypertension, are fluid and salt retention, cardiovascular effects secondary to baroreflex activation, and hypertrichosis. Side effects have not been reported when the drug is used for treatment of ED, but the experiences are limited.

The principle of K^+ channel opening is interesting, and the preliminary experiences with minoxidil seem promising, but more controlled clinical trials are needed to confirm and assess the efficacy and side effects of the drug in patients with ED.

5. α-Adrenoceptor Antagonists.

a. Phentolamine. Early studies with oral phentolamine showed some success in patients with nonspecific erectile insufficiency (Gwinup, 1988; Zorgniotti, 1992, 1994; Zorgnotti and Lizza, 1994). Zorgniotti (1992) considered nonintracavernous, "on demand" administration of phentolamine a promising approach for treatment of impotence. Becker et al. (1998) performed a double blind placebo-controlled trial with 20, 40, and 60 mg of oral phentolamine in patients with ED and a high likelihood of organogenic etiology and found the drug to be of benefit. There were no serious complications, but some circulatory side effects were seen after 60 mg.

According to textbooks (Hoffman and Lefkowitz, 1996), phentolamine use may be associated with a considerable cardiac risk, producing hypotension, tachycardia, cardiac arrhythmias, and ischemic cardiac events. However, these actions refer to intravenous use of the drug. Oral phentolamine, in doses up to 150 mg, seems to have moderate beneficial hemodynamic short-term effects in patients with congestive heart failure (Gould and Reddy, 1979; Schreiber et al., 1979). In the doses needed for enhancing erectile responses (20–40 mg), few adverse cardiovascular effects have been observed (Goldstein, 2000; Goldstein et al., 2001).

Goldstein (2000) and Goldstein et al. (2001) reviewed experiences with oral phentolamine in ED and reported the results of large multicenter placebo-controlled pivotal phase III clinical trials. The mean change in the erectile function as estimated by erectile function scores was significantly higher following the use of active drug (40 mg and 80 mg) compared with placebo. Three to four times as many patients receiving phentolamine reported being satisfied or very satisfied compared with those receiving placebo. At doses of 40 and 80 mg, respectively, 55 and 59% of men were able to achieve vaginal penetration with 51 and 53% achieving penetration on 75% of attempts. The correction of ED or improvement to a less severe category of dysfunction was experienced by 53% of men with the 80-mg dose and 40% with the 40-mg dose of phentolamine. All trends of response were the same regardless of any concomitant medication. There were no severe adverse events. The most common side effects observed were nasal congestion (10%), headache (3%), dizziness (3%), and tachycardia (3%). Goldstein (2000) and Goldstein et al. (2000) concluded that phentolamine is safe, well tolerated, and efficacious for the treatment of ED. Whether or not phentolamine is a competitive alternative to other oral treatments of ED has to be demonstrated in comparative clinical trials.

b. Yohimbine. Yohimbine is a pharmacologically well characterized α_2-AR antagonist that has been used for over a century in the treatment of ED (Morales, 2000b). The drug is relatively selective for α_2-ARs, and even if other actions have been demonstrated (Goldberg and Robertson, 1983), these can be demonstrated only in concentrations that most probably cannot be obtained in man. The site of action of yohimbine as a pro-erectile agent is probably not peripheral, since the predominant subtype of α-ARs in penile erectile tissue is of α_1-type (Andersson, 1993) and intracavernosal injection of another more potent α_2-AR antagonist, idazoxan, did not produce penile erection in man (Brindley, 1986). In normal healthy volunteers, Danjou et al. (1988) found that intravenous infusion of yohimbine had no erectogenic effects, which does not exclude that orally administered yohimbine may be effective. The plasma half-life of yohimbine was found to be 0.6 h (Owen et al., 1987), whereas the plasma NA-increasing effects of the drug lasted for 12 h (Galitzky et al., 1990). This discrepancy may be explained by the presence of an active metabolite (Owen et al., 1987).

The effects of yohimbine have been investigated in controlled trials on patients with organic (Morales et al., 1987), psychogenic (Reid et al., 1987), and mixed (Riley et al., 1989; Susset et al., 1989) etiology to their impotence. In organically impotent patients, marginal effects of the drug were demonstrated, i.e., 43% responded (complete or partial response) to yohimbine and 28% to placebo (difference not significant) (Morales et al., 1987). In studies of the same design, similar figures were obtained in patients with psychogenic impotence, although this time the difference between active treatment and placebo was significant (Morales et al., 1987; Reid et al., 1987). Positive responses in patients with impotence of mixed etiologies were reported in approximately one-third of the cases (Riley et al., 1989; Susset et al., 1989).

A crossover double blind study on 62 patients with impotence, where the efficacy of yohimbine ointment administered locally on the penis was compared with that of placebo, suggested positive results in a subgroup of patients (Turchi et al., 1992), but in the total population, no significant effects were found.

High dose yohimbine (36 mg per day) was found to have no positive effect in a prospective, randomized, controlled double blind, crossover study of 29 patients with mixed type ED (Kunelius et al., 1997). Another double blind placebo-controlled study of 86 patients without clearly detectable organic or psychologic causes (Vogt et al., 1997) revealed that yohimbine was significantly more effective than placebo (71 versus 45%) in terms of response rate.

In a randomized, double blind, placebo-controlled study, Montorsi et al. (1994) found that combination treatment with yohimbine and trazodone was more effective than placebo for the treatment of psychogenic impotence. Meta-analyses have demonstrated that yohimbine is superior to placebo in the treatment of ED (Carey and Johnson, 1996; Ernst and Pittler, 1998).

Jacobsen (1992) found in a pilot study that eight of nine patients with impotence associated with antidepressive treatment with the serotonin reuptake blocker, fluoxetine, responded favorably to oral yohimbine. A potentiation of yohimbine effects by the opioid receptor antagonist naltrexone has been demonstrated (Charney and Heninger, 1986).

The reported side effects of yohimbine, when used for purposes other than ED, include increases in heart rate and blood pressure, orthostatic hypotension, anxiety, agitation, and manic reactions (Charney et al., 1982, 1983; Price et al., 1984). The side effects observed in patients with ED are usually mild (Morales, 2000b).

It cannot be excluded that orally administered yohimbine can have a beneficial effect in some patients with ED. The conflicting results available may be attributed to differences in drug design, patient selection, and definitions of positive response. However, generally, available results of treatment are not impressive (Morales, 2000b).

6. Opioid Receptor Antagonists. It is well documented that chronic injection of opioids can lead to decreased libido and impotence (Parr, 1976; Crowley and Simpson, 1978; Mirin et al., 1980; Abs et al., 2000), possibly due to hypogonadotropic hypogonadism (Mirin et al., 1980; Abs et al., 2000). Assuming that endogenous opioids may be involved in sexual dysfunction, opioid antagonists have been suggested to be effective as a treatment (Fabbri et al., 1989; Billington et al., 1990). In anesthetized cats, naloxone caused erections (Domer et al. (1988), and it was suggested the erection could be due either to altered levels of hormones released from the central nervous system or to removal of reflex inhibitory tone in the spinal cord or sacral parasympathetic ganglia. Interestingly, naloxone can potentiate the erectile effects of apomorphine in rats (Berendsen and Gower, 1986).

Intravenous naloxone was found to have no effect on arousal in normal subjects (Goldstein and Hansteen, 1977). Naltrexone has effects similar to those of naloxone, but can be given orally and has a higher potency and a longer duration of action (24–72 h) than naloxone. It is well absorbed from the gastrointestinal tract but is subject to an extensive first-pass metabolism, metabolized in the liver and recycled by enterohepatic circulation. The major metabolite of naltrexone, 6-β-naltrexone, also possesses opioid receptor antagonist activity and probably contributes to the effects of naltrexone.

In an open pilot study, Goldstein (1986) found that naltrexone (25–50 mg/day) restored erectile function in six of seven men with "idiopathic" ED. In a single blind randomized study, Fabbri et al. (1989) compared naltrexone with placebo in 30 men with idiopathic erectile impotence. It was found that sexual performance was improved in 11 of the 15 naltrexone-treated patients,

whereas placebo had no significant effects; libido was not affected and there were no side effects. In general, the adverse effects of naltrexone are transient and mild, but hepatocellular injury may be produced with high doses.

In a randomized, placebo-controlled, double blind pilot study of 20 patients with idiopathic, nonvascular, nonneurogenic ED, van Ahlen et al. (1995) found no significant effect on libido or frequency of sexual intercourse, but early morning erections increased significantly.

Increased inhibition by opioid peptides cannot be excluded as a contributing factor in nonorganic erectile failure and that naltrexone therapy in these cases may be a useful therapeutic agent. However, well controlled studies confirming this are lacking.

7. Dopamine Receptor Agonists. It is well established that dopaminergic mechanisms may be involved in the regulation of male sexual behavior in animals (Bitran and Hull, 1987; Foreman and Hall, 1987). As discussed previously, apomorphine, a dopamine receptor agonist which stimulates both dopamine D_1 and D_2 receptors, has been shown to induce penile erection in rats (Mogilnicka and Klimek, 1977; Benassi-Benelli et al., 1979) as well as in normal (Lal et al., 1984) and impotent (Lal et al., 1987, 1989) men. L-Dopa may also stimulate erection in patients with Parkinson's disease (Vogel and Schiffter, 1983). It has been suggested that dopamine D_2 receptor stimulation may induce penile erection in rats, whereas activation of D_1 receptors has the opposite effect (Zarrindast et al., 1992). In rhesus monkeys, quinelorane, a dopamine D_2 receptor agonist, produced penile erection (Pomerantz, 1991), favoring the view that D_2 receptor stimulation is important for this response. This may be the case also in man (Lal et al., 1989). However, clinical trials with the selective D_2 receptor agonist, quinelorane, were discontinued prematurely before its efficacy could be assessed.

a. Injected Apomorphine. Lal et al. (1984) showed in a placebo-controlled double blind study on healthy volunteers that apomorphine injected subcutaneously (0.25–0.75 mg) was able to induce erection. This was confirmed by Danjou et al. (1988), showing that apomorphine induced erection and potentiated the erection induced by visual erotic stimulation. There was no increase in libido, which was in agreement with previous observations (Julien and Over, 1984). In 28 patients with impotence, Lal et al. (1989) found that 17 responded with erection after subcutaneous apomorphine (0.25–1.0 g); no erection developed after placebo. Segraves et al. (1991) also administered apomorphine subcutaneously (0.25–1.0 g) to 12 men with psychogenic impotence in a double blind and placebo-controlled study. They found a dose-related increase in maximal penile circumference. An erection exceeding 1 cm was obtained in 11 of the 12 patients.

It cannot be excluded that a subgroup of impotent patients may have an impairment of central dopaminergic functions and that the principle of dopamine receptor stimulation can be used not only diagnostically but also therapeutically. The therapeutic potential of subcutaneous apomorphine, however, seems to be limited mainly because of frequently occurring side effects. High doses (i.e., up to 5–6 mg in adult patients) may cause respiratory depression, and in the low dose range (0.25–0.75 mg) where effects on penile erection can be demonstrated, emesis, yawning, drowsiness, transient nausea, lacrimation, flushing, and dizziness (Lal et al., 1984; Segraves et al., 1991) may occur. In addition, apomorphine is not effective orally and has a short duration of action. Lal et al. (1987) observed that nonresponders, but not responders, experienced side effects. However, apomorphine administered subcutaneously does not seem to have an acceptable effect/side effect ratio.

b. Oral Apomorphine. Heaton and coworkers (1995) reported that apomorphine, absorbed through the oral mucosa will act as an erectogenic agent. In 12 impotent patients with proven erectile potential but with no documentable organic disease, 3 or 4 mg of apomorphine in a sublingual controlled release form produced significantly durable erections in 67% without adverse effects.

These results have been largely confirmed in randomized double blind studies (Padma-Nathan et al., 1999; Dula et al., 2000). In the study of Padma-Nathan et al. (1999), doses of 2, 4, 5, and 6 mg were investigated, with optimum effects (best effect and less side effects) obtained with 4 mg (apomorphine 58.1% versus placebo 36.6%). The occurrence of nausea (not severe) with 4 mg was 21.4%. Similar results were obtained in two randomized double blind studies including 977 patients with hypertension (Lewis et al., 1999).

Extensive clinical experiences with sublingual apomorphine 2 and 3 mg have recently led to approval for clinical use in several countries. Available information (Heaton, 2000) suggests that sublingual apomorphine is an effective and reasonable alternative for patients with ED.

8. Trazodone. Trazodone is an "atypical" antidepressive agent, chemically and pharmacologically distinct from other currently available antidepressants (Haria et al., 1994). The drug selectively inhibits central 5-HT uptake and increases the turnover of brain dopamine but does not prevent the peripheral re-uptake of NA (Georgotas et al., 1982). Trazodone has also been demonstrated to block receptors for 5-HT and dopamine, whereas its major metabolite, m-CCP, has agonist activity at 5-HT_{2C} receptors (Monsma et al., 1993). This metabolite induces erection in rats and selectively increases the spontaneous firing rate of the cavernous nerves (Steers and de Groat, 1989). The mode of action of trazodone in depression is not fully understood; it has a marked sedative action. Trazodone has a serum half-life of about 6 h and is extensively metabolized (Haria et al., 1994).

Trazodone and its major metabolite were shown to have an α-AR blocking effect in isolated human cavernous tissue (Blanco and Azadzoi, 1987; Saenz de Tejada et al., 1991b). Krege et al. (2000) showed trazodone to have high to moderate affinity for human α_1- and α_2-ARs, respectively, and that the drug did not discriminate between subtypes of α_1- and α_2-ARs. The active metabolite, m-CCP, seemed to have no significant peripheral effects.

Orally administered trazodone has been associated with priapism in potent men (Azadzoi et al., 1990) and with increased nocturnal erectile activity in healthy volunteers (Saenz de Tejada et al., 1991b). When injected intracavernously to patients with impotence, trazodone caused tumescence but not full erection (Azadzoi et al., 1990). Intracavernosal trazodone acted as an α-AR antagonist but was not as effective as papaverine or a combination of papaverine and phentolamine (Azadzoi et al., 1990). Positive clinical experience with the drug has been reported (Lance et al., 1995). However, in double blind placebo-controlled trials on patients with a different etiology of their ED, no effect of trazodone (150–200 mg/day) could be demonstrated (Meinhardt et al., 1997; Enzlin et al., 2000).

Even if the information from randomized controlled clinical trials do not support the view that trazodone is an effective treatment for most men with ED, the drug may be an alternative in some anxious or depressed men.

9. Melanocortin Receptor Agonists. Melanotan II is a cyclic nonselective melanocortin receptor agonist, and injected subcutaneously, was found to be a potent initiator of penile erection in men with nonorganic ED (Wessels et al., 1998, 2000). However, yawning/stretching and in some cases severe nausea and vomiting limited its use. Nevertheless, the principle of melanocortin receptor agonism with subtype selective drugs is a new and potentially useful therapeutic option.

V. Conclusions

The important role of the central nervous system for erectile mechanisms is being recognized. The spinal and supraspinal regulation of the erectile process involves several transmitters, including dopamine, serotonin, noradrenaline, nitric oxide, and peptides, such as oxytocin and ACTH/α-MSH, but is still only partly known. Detailed knowledge of these systems will be important in the discovery of novel pharmacological agents for the treatment of ED. Even if research has focused mainly on the peripheral pathways of erection and has led to recognition of a predominantly organic basis for ED, the different steps involved in neurotransmission, impulse propagation, and intracellular transduction of neural signals in penile smooth muscles need further investigation. Continued studies of interactions between different transmitters/modulators may be the basis for new combination therapies. Increased knowledge of changes in penile tissues associated with ED may lead to increased understanding of pathogenetic mechanisms and to prevention of the disorder.

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