INVITED REVIEW

Erectile dysfunction: from biochemical pharmacology to advances in medical therapy

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Abstract

Research on penile smooth muscle physiology has increased the number of drugs available for treating erectile dysfunction (ED). Penile erection involves the relaxation of smooth muscle in the corpus cavernosum. The key mediator of smooth muscle relaxation is nitric oxide (NO), which acts by increasing the cellular level of cGMP. Another cyclic nucleotide, cAMP, is involved in smooth muscle cell relaxation; cAMP formation is stimulated by a number of compounds, such as alprostadil. An increase in cAMP and/or cGMP levels can also be induced by inhibition of phosphodiesterases (PDEs), the enzymes involved in cyclic nucleotide breakdown. Both papaverine and sildenafil are PDE inhibitors. Papaverine is a non-specific inhibitor of these enzymes; sildenafil is an orally active, potent and selective inhibitor of GMP-specific PDE5, the predominant isoenzyme metabolizing cGMP in the cells of the corpus cavernosum. Penile smooth muscle contraction, induced by adrenergic fibers through α₁ adrenoceptors, produces detumescence, thus making α₁ adrenoceptor antagonists suitable for maintenance of penile erection. The orally active drug yohimbine is a mixed α₁-α₂ adrenoceptor antagonist that works by a dual mechanism; it facilitates sexual arousal by acting on α₂ adrenoceptors in the central nervous system and blocks adrenergic influences at peripheral level.


Introduction

In the 1960s and early 1970s it was widely assumed that almost all sexual disorders, including erectile dysfunction (ED), had a psychogenic basis. Therefore sex or behaviour therapies were the only possible therapeutic strategies for ED (1, 2). However, it is now generally believed that the majority of patients with ED have an underlying organic disorder that contributes, at least in part, to the erectile problem. However, it is the authors’ opinion that ED, defined as the consistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual performance or intercourse (3), is a frequent symptom, which, in nearly all cases, underlies a mixed etiology. Indeed, a vascular or neurological impairment for penile erection is frequently coupled with a psychological and relational problem. Recognized risk factors for ED are reported in Table 1. For an accurate therapeutic approach to ED, it is important to recognize and remove one or several of these risk factors, when present. For example, changing the type of antihypertensive treatment may improve ED. However, in routine daily practice a definite aetiological diagnosis for patients with ED is often difficult to establish or, when established, is difficult to reverse. Therefore, the therapeutic pharmacological approach is mainly symptomatic. Only ED due to hypogonadism or hyperprolactinaemia can be rationally treated with the appropriate therapy, i.e. androgen or gonadotrophin supplementation for hypogonadism and dopaminergic drugs for hyperprolactinaemia.

During the last two decades, a greater understanding of the biochemical basis of penile erection has drastically increased the number of therapeutic options available to clinicians for treating the symptoms of ED. Basic research into penile smooth muscle physiology and the central neurotransmitters involved in male sexual response has culminated in effective oral agents that can satisfactorily treat the majority of patients. However, the intrapsychic and cognitive processes underlying sexual dysfunction are so complicated that effective medical interventions for sexual arousal and desire are still lacking.

In this article we focus on the main biochemical events leading to penile erection and detumescence as well as on the potential manipulation of these events for therapeutic purposes.
Biochemical events underlying penile erection

The principal mechanism of human penile erection involves the relaxation of arterial and trabecular smooth muscle in the corpus cavernosum. Conversely, penile smooth muscle contraction maintains baseline flaccidity and causes detumescence (Fig. 1). For several years, it has been clear that detumescence is mediated by the tonic signaling of sympathetic nerves. However, the factor(s) mediating cavernosal body relaxation and penile erection have only recently been discovered.

Figure 2 shows a typical experiment performed in isolated rabbit corpora cavernosa. Electrical field stimulation (EFS; 10 Hz, 100 mA, 10 s) of the tissue in basal conditions induces a transient contraction of the preparation (Fig. 2A). This indicates that stimulation of the nerve endings induces smooth muscle cell contraction (and therefore detumescence). Chemical stimulation of adrenergic receptors with phenylephrine evokes a sustained increase in basal tone (Fig. 2A), confirming that activation of the sympathetic system allows smooth cell contraction. However, after repeating EFS in a preparation precontracted with phenylephrine, a biphasic response is observed; after transient stimulation relaxation is present (Fig. 2A). This relaxation is further magnified by the addition of guanethidine (1 M), which abolishes sympathetic tone activity (Fig. 2A). A similar result is also obtained by increasing concentrations of acetylcholine (ACh; Fig. 2B). However the relaxant effect of EFS is not affected by a cholinergic antagonist such as atropine (not shown). This implies the presence of non-adrenergic, non-cholinergic (NANC) relaxing factors. The main NANC relaxing factor has been identified as the labile gas nitric oxide (NO; 4±7). NO is produced as the enzymatic byproduct of molecular oxygen (O₂) and L-arginine under the control of nitric oxide synthase (NOS). So far, three distinct isoforms of NOS have been identified: neuronal (nNOS); endothelial (eNOS); and inducible (iNOS). All three isoforms are present in corpora cavernosa, although with a different cellular localization. NANC neurones express nNOS (8), while endothelial and smooth muscle cells express the other isoforms (9, 10). NOS inhibitors such as N-nitro-L-arginine-methyl-ester (L-NAME) completely block the relaxing

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<th>Table 1 Risk factors for erectile dysfunction.</th>
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<td>• Antihypertensive drugs: thiazide diuretics, reserpine, α methyl Dopa, clonidine</td>
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<td>• Psychotropic drugs: phenothiazine, butyrophenone, antidepressants</td>
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<td>• Hormonal drugs: oestrogen, progesterone, antiandrogens, GnRH analogues, finasteride, ketoconazole</td>
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effect of both EFS (11) and ACh (12). In addition, an NO donor such as sodium nitroprusside (SNP) completely relaxes pre-contracted human corpora cavernosa. These findings indicate that NO is a key physiological mediator of smooth muscle relaxation and penile erection.

After release from nerve endings and vascular endothelial cells, NO diffuses to neighbouring vascular and trabecular smooth muscle cells and binds to guanylate cyclase. This induces a conformational change in the enzyme and the subsequent catalytic production of 3'-5'-cyclic guanosine monophosphate

Figure 1 Left side: During flaccidity, constrictor tone in arterioles and sinuses causes a low blood flow in lacunar spaces. During erection, relaxation of arterioles and cavernosal sinuses allows a maximum flow to dilated sinusoidal spaces in the meanwhile venous outflow is reduced to the minimum. Right side: The predominance of constrictor tone, causing a low flow state, induces detumescence and allows venous outflow.

Figure 2 (A) Typical experiment showing the effect of electrical field stimulation (EFS; 10 Hz, 100 mA, 10 s) in a normal rabbit corpus cavernosum preparation (left) and in a preparation precontracted by phenylephrine (PHE; 3 μM) in the absence (centre) and in the presence (right) of guanethidine (1 μM). (B) Relaxant effect induced by increasing concentrations of acetylcholine (ACh) in a rabbit corpus cavernosum preparation pre-contracted by PHE (3 μM). Arrows indicate the addition of the substances.
(cGMP) from its precursor nucleotide, guanosine 5'-triphosphate (Fig. 3). Data from our laboratory indicate that inhibitors of cGMP production, such as LY 83583, blunt the relaxing effect of NO donors. Indeed, increased cGMP levels induce a series of protein kinase interactions that culminate in a decrease in intracellular calcium levels and smooth muscle cell relaxation.

Besides cGMP, another cyclic nucleotide, cAMP, is directly involved in decreasing intracellular calcium concentration, therefore allowing smooth muscle cell relaxation. Cyclic AMP formation is stimulated by the binding of several neurotransmitters and hormones to their respective G protein-coupled receptors (Fig. 3). Among vasoactive substances mediating adenylate cyclase activity and cAMP formation in the penile corpora cavernosa are vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), prostaglandin E1 (PGE1) and adenosine. Figure 4 shows the dose-dependent relaxant effect of PGE1 and adenosine in human corpora cavernosa.

The intracellular cGMP and cAMP levels are finely tuned (Fig. 3) by a family of enzymes termed phosphodiesterases (PDEs). This family of enzymes is composed of at least nine different gene groups (13), that differ for substrate specificity, sensitivity to inhibitors and organ localization. In human corpus cavernosum the presence of several members of this family have been demonstrated, including the cAMP/cGMP non-selective PDE2, the cAMP-selective PDE2 and PDE4 and cGMP-selective PDE5 (14).

**Figure 3** (A) Mechanism of detumescence. Stimulation by catecholamines of G protein-coupled α-adrenoceptors activates phospholipase C; inositoltrisphosphate (IP3), released from precursors by the enzyme, induces the release of Ca2+ from endoplasmic reticulum stores, thus causing detumescence. (B) Mechanism of erection. Stimulation of G protein-coupled receptors by endogenous or exogenous substances activates adenylate cyclase which, in turn, increases cAMP production from precursors. Moreover, NO diffusion into the cells leads to guanylate cyclase activation and consequent production of cGMP. Both cyclic nucleotides are involved in decreasing free Ca2+ concentration and therefore in causing relaxation. cAMP and cGMP are substrates of phosphodiesterases with the production of inactive compounds. Examples of drugs interfering with the above mechanisms are shown in italics. Rec, receptor; G, G protein; PLC, phospholipase C; SR, sarcoplasmic reticulum; AC, adenylate cyclase; GC, guanylate cyclase; PDEs, phosphodiesterases; NO, nitric oxide.

**Figure 4** Effects of increasing concentrations of prostaglandin E1 (PGE1) and adenosine in human corpora cavernosa preparations from three patients. Corpora cavernosa were pre-contracted by phenylephrine (Phe, 3 μM). Ordinate axis indicates the percentage of relaxation. Points represent mean values of six experiments; vertical bars indicate S.E.M. values.
Clinical results with vasoactive substances in ED

The penile prosthesis (and sex therapies) represented the gold standard of therapy for ED up to the late 1970s. They were progressively replaced in the 1980s by the introduction of intracavernosal injections of vasoactive substances, and by the vacuum constriction device. The latter is a safe and effective form of therapy. It essentially consists of a plastic cylinder connected to a vacuum pump that allows a negative pressure to induce erection by increasing corporal blood flow. Erections are thereafter prolonged by a constricting ring applied to the base of the penis. Although vacuum constriction devices might improve erection adequately for sexual intercourse in the majority of cases (15), they do not meet the expectations of the patient or his partner and therefore the long-term satisfaction rate is not high (16). Problems with vacuum devices include pain from the constriction ring, lack of spontaneity, decrease in the quality of orgasm and ejaculatory discomfort.

Intracavernosal injection of vasoactive substances is another important therapeutic option for the treatment of ED. It made the successful treatment of the condition possible on a large scale, because it is relatively easy to perform and results in efficient and normal-looking erection. The technique is based on the local (intracavernous) administration of drugs that directly or indirectly relax smooth muscle cells. Injections should be performed dorsolaterally into the proximal half of the penis. The first injection should always be performed by the therapist, explaining and demonstrating in detail the injection technique. Several vasoactive substances have been proposed for this kind of therapy, including medications that increase either the cAMP- or the cGMP-mediated pathways. Among agents that increase cGMP levels, NO donors represent the most physiological candidate for the ideal drug. However, despite their effects in vitro, contrasting results have been obtained in vivo by directly injecting NO donors into the corpora cavernosa (17–19). Therefore, NO donors are not widely used in the therapy of ED. Similarly inconsistent results were obtained with the intracavernosal administration of neurotransmitters that mediate their effect through an increase in the cAMP-mediated pathway, such as CGRP (20, 21), VIP (22) and adenosine (23, 24). Conversely, interesting results were obtained by blocking cAMP breakdown using a non-specific inhibitor of PDE, such as papaverine. Since the first report by Virag in 1982 (25), papaverine have been used extensively because of effectiveness (success rate 55%) and low cost. The usual dosage is 20–80 mg. However, important local side effects such as penile fibrosis (6%) and prolonged erection (5%) limited its popularity (26). It is still employed in combination with other vasoactive drugs to increase their effectiveness in selected poor-responder patients.

Up to now PGE1 (alprostadil) has given the best results as a mono-dose pharmacotherapy for ED. In a 6-month study of intracavernosal self-injection with alprostadil in 683 men, the study participants and their partners reported a satisfactory sexual activity for almost 90% of the injections, with relatively few side effects (27). The most common was a burning sensation during injection and painful erection, occurring in 15% of patients (26). In contrast to papaverine, alprostadil injections carry a small risk of prolonged erection and fibrosis at the injection site (1–2%). The general dosage is 5–40 µg. The initial testing dose is usually 10 µg, although in patients with neurological disease it should be lowered to 5 µg (26). Although the average success rate of alprostadil injection can be as high as 73% (26), this type of treatment is only rarely chosen as initial therapy (16), and up to 50% of men eventually discontinue treatment for reasons relating to pain, lack of confidence in self-administration, loss of effectiveness or loss of spontaneity of love-making. Hence the initial enthusiasm for intracavernosal alprostadil was in fact dampened by the number of patients that refused or discontinued therapy. This is the rationale for alternative, local, routes of administration of alprostadil. Although topical gel containing PGE1 has been proposed (28), its effectiveness needs to be further validated. An interesting alternative route introduced recently was MUSE (medicated urethral system for erection). It is based on the ability of alprostadil to diffuse from the corpus spongiosum of the urethra to the corpora cavernosa via vascular interconnections. Alprostadil is deposited in the urethra through a syringe-like device containing a pellet of the vasoactive substance. In placebo controlled studies, nearly 60% of the patients achieved efficient erections (29). Another study reported a lower success rate (30). The reported risk of fibrosis and priapism is very low (29); however, some patients are reluctant to accept this treatment because of burning sensation at the site of applicator insertion.

Although the introduction of intercavernosal injections and MUSE offered a great opportunity for achieving erections in patients otherwise unable to have sexual intercourse, only oral medications are readily accepted by the majority of men because of ease and non-disclosure of use. Among the oral agents currently available, sildenafil represents the cornerstone for ED therapy.

Sildenafil is an orally active, potent and selective inhibitor of PDE5, the predominant PDE isoenzyme metabolizing cGMP in the smooth muscle cells of the corpus cavernosum. As cGMP levels are improved, there is an increased vasodilatation and dilation of the sinuses in the corpus cavernosum, allowing for greater erection (Fig. 5). This compound was originally tested in the UK as an anti-anginal agent. In clinical trials, it was noted that although it was ineffective for the treatment of angina pectoris, it
improved penile erection. Sildenafil was finally approved from the US Food and Drug Administration (FDA) for the treatment of ED in March 1998. Since that date there has been extensive media coverage of the drug as it was the first effective oral agent for ED. Its introduction has indeed revolutionized the field of sexual healthcare, shifting the domain of the field from urologists to primary care and non-urology specialists. One of the main advantages of sildenafil is its selectivity for PDE5, an isoenzyme that is not only present in corpus cavernosum but also in platelets and in visceral and tracheal smooth muscle (14, 31). The affinity of sildenafil for the other PDEs is much lower than for PDE5, with the exception of PDE6 (10-fold selectivity), the isoenzyme found in the photoreceptors of the retina. Indeed, while sildenafil binds to PDE5 in the nanomolar range, it inhibits PDE2 (adrenal cortex), PDE3 (cardiac muscle, platelets, other smooth muscle cells) and PDE4 (brain and lung lymphocytes) in the high micromolar range. It shows an intermediate affinity for PDE1 (300 nM), the isoenzyme present in brain, renal tissue and other smooth muscle cells. This pharmacological profile shows that the vasodilatation induced by sildenafil is mainly limited to the corpus cavernosum and side effects are generally few. Blood pressure is reduced transiently, even at supratherapeutic doses (32). Other common adverse effects are headache (14–30%), flushing (10–27%), dyspepsia (3–16%), nasal congestion (1–11%), abnormal vision (2–11%) and dizziness (2%) (33–36). However, some severe cardiovascular events were observed in postmarketing surveillance, although these have not been confirmed in controlled studies (37). As both sildenafil and nitrates (or other NO donors) increase cGMP levels in the systemic circulation, although at different points along the NO-cGMP pathway, the combination of the two agents is contraindicated because of symptomatic hypotension (38). A retrospective subanalysis of data from double-blind, placebo-controlled trials with sildenafil in patients with ED and ischemic heart disease, who were not taking nitrates, suggests that it is well tolerated (35). However, a recent study has shown that sildenafil, at supraphysiological concentrations, is able to increase cAMP levels in human cardiac tissues obtained from patients admitted coronary bypass surgery (39). This observation may provide a potential mechanism for the cardiovascular side effects, such as arrhythmogenesis, observed with the drug.

Moreover, because sexual activity is associated per se with a cardiac risk, physicians should be aware of the cardiovascular status of the patient who plans to resume sexual activity before initiating sildenafil, as with other therapies for sexual dysfunction (35, 40, 41).

In fasting subjects, sildenafil is rapidly absorbed, with dose-proportional peak plasma concentration within 1 h of administration. The mean terminal half-life is 3–5 h. A high fat meal can reduce its rate of absorption by 25% (31). Because sildenafil is metabolized by the P450 3A4 pathway, drugs like cimetidine, erythromycin, ketoconazole, rotonavir and saquinavir that inhibit the pathway may increase its plasma concentration. Therefore the lower dose of sildenafil (25 mg) should be administered concomitantly with those agents. Caution should also be observed in patients with severe renal impairment or hepatic dysfunction (41). Otherwise, dosages start at 50 mg 1 h before sexual intercourse and the maximum dose is 100 mg. More than 4000 patients with ED of different etiologies have been treated up to now with sildenafil or placebo in fixed- or titrated-dose trials (29, 33, 34, 36, 42). In all of the studies, sildenafil was associated with dose-related improvements in the frequency, hardness and duration of erection and in patient abilities to achieve and maintain erection adequate for successful sexual intercourse (average success rate, 50–70%). An improvement in the quality of life for patients and their sexual partners is therefore achieved. In general, patients with a predominant neurogenic cause of ED (including diabetes and prostatic surgery) had the poorest response rate (36, 42, 43). This indicates that an adequate nerve supply, more than blood supply, is crucial for sildenafil.

Figure 5 Mechanism of action of sildenafil. Sildenafil, by inhibiting phosphodiesterase 5 (PDE5) activity in corporal smooth muscle cells, leads to an accumulation of cGMP levels, thus amplifying the cyclic nucleotide effect on relaxation and enhancing erectile response.
responsiveness. Although sildenafil substantially improves many parameters of the male sexual response, it does not affect sexual desire (34, 36, 43). In conclusion, sildenafil is an effective oral agent for the treatment of ED and seems to represent the first-line therapy for this sexual problem.

Biochemical events underlying penile flaccidity

As previously mentioned, flaccidity is maintained by adrenergic fibers and receptors present in the cavernous trabeculae and in the cavernous arteries (Fig. 3). The pharmacological characterization of such receptors indicates that the $\alpha$ subtype is at least 10-times more abundant than the $\beta$ subtype (44). Indeed, in human corpora cavernosa preparations in the presence of L-NAME, the contractile response to EFS was completely blocked by the addition the $\alpha$ adrenoceptor antagonist prazosin (1 $\mu$M: data not shown). All three subtypes of $\alpha_1$ adrenoceptor so far characterized (1a, 1b and 1d) are present in human corpora cavernosa in terms of genes and protein expression (45). Similar results have been reported for the three subtypes of $\alpha_2$ adrenoceptors (2a, 2b and 2c) (46). Both $\alpha_1$ and $\alpha_2$ are present in penile tissue; however, they are differentially expressed. Figure 6 (insert panel) shows the effect of $\alpha_1$ (phenylephrine) and $\alpha_2$ (clonidine and UK 14,304) adrenoceptor agonists in rabbit corpora cavernosa preparations. Although the different agonists elicited contractions with similar EC$_{50}$ values, the maximum contractile response to the $\alpha_2$ agonists was about 58% of the value obtained with phenylephrine, indicating the functional predominance in this tissue of $\alpha_1$ adrenoceptors, as previously described (47–49). Hence, post-junctional adrenoceptors have a clear anti-erectile effect. However, the role of pre-junctional $\alpha_2$ adrenoceptors is less clear. These receptors are usually involved in a negative regulation of norepinephrine outflow from sympathetic nerve endings (autoreceptors). However, experiments in horse penile arteries indicate that, in the presence of NG-nitro-L-arginine (to block nitricergic transmission), an $\alpha_2$ antagonist, rauwolscine, inconsistently enhanced EFS-induced contractions (50). Similar results have been obtained in human corpora cavernosa. After blocking NO formation, contractions induced by EFS are not inhibited by the $\alpha_2$ agonist clonidine and not enhanced.

Figure 6 Insert shows the effect of increasing concentrations of different $\alpha$ adrenoceptor agonists on basal tone of rabbit corporal muscle. The $\alpha_1$ agonist phenylephrine induces the maximal increase in tone with an EC$_{50}$ of 5 $\mu$M. The $\alpha_2$ agonists UK 14,304 and clonidine induce contractions (EC$_{50}$ values of 6 $\mu$M and 2 $\mu$M, respectively) similar to that phenylephrine, but with lower maximal effects. Points represent the mean values of at least six experiments. Vertical bars indicate S.E.M. values. (A) Effect of increasing concentrations (0.1–1 $\mu$M) of the $\alpha_2$ agonist clonidine and (B) of the $\alpha_2$ antagonist yohimbine (0.1–1 $\mu$M) on the response induced by EFS (10 Hz, 100 mA, 10 s) in human corporal muscle treated with L-NAME (100 $\mu$M). Histograms show the mean values of six experiments; vertical bars indicate S.E.M. values; $^*$ $P<0.05$. C, control.

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by the $\alpha_2$ antagonist yohimbine (Fig. 6A and B). Surprisingly, the latter treatment induced relaxation of the preparation. These findings indicate that pre-junctional $\alpha_2$ adrenoceptors in penile tissues are not functionally present in adrenergic nerve endings and therefore do not negatively modulate norepinephrine release. However, experiments performed in horse penile arteries suggest that $\alpha_2$ receptors may be functionally present in NANC nerves. In fact, after blockade of sympathetic outflow with guanethidine, EFS-induced relaxation was inhibited by the $\alpha_2$ agonist BHT920 and this effect was antagonized by rauwolscine (51). In conclusion, while post-junctional adrenoceptors mediate penile smooth muscle cell contractility and detumescence, pre-junctional $\alpha_2$ receptors might enhance the maintenance of detumescence, inhibiting nitrergic transmission.

It is, however, important to note that despite the peripheral anti-erectile effect of sympathetic activity, several lines of evidence indicate that noradrenergic transmission in the brain and spinal cord is important for sexual behaviour (52, 53). In particular, it has been demonstrated that in the rat brain $\alpha_2$ inhibits, while $\alpha_1$ stimulates, sexual arousal (54). Therefore the ideal drug for the treatment of ED would be an $\alpha_2$ antagonist (increasing sexual arousal and decreasing detumescence) with peripheral $\alpha_1$ antagonistic activity (blocking sympathetic transmission).

**Clinical results with $\alpha$ adrenoceptor antagonists in ED**

It has been shown that the employment of $\alpha$ adrenoceptor antagonists for induction and/or maintenance of penile erection should be efficacious in treating ED. Indeed, this class of drug has been successfully used for this purpose since the early 1980s (55, 56).

Phenoxybenzamine (57) and phentolamine (58) administered intracavernosally alone or in combination with other vasoactive substances have been a breakthrough in the treatment of ED, and are still employed to treat PGE$_1$-unresponsive patients. Nowadays injection of phentolamine (0.25–1 mg) in combination with papaverine (7.5–30 mg), PGE$_1$ (5–40 $\mu$g) or papaverine and PGE$_1$ (triple drug) results in a greater than 70% success rate (59). Promising results are also obtained with intracavernosal injection of a combination of phentolamine and VIP (60, 61). Conversely, intracavernous administration of phenoxybenzamine is not still in use due to local side effects as fibrosis and prolonged erection.

Preliminary clinical trials indicate that oral administration of phentolamine is useful in treating ED, with limited side effects (56, 62, 63). In patients with predominant organogenic etiology, oral phentolamine (20–60 mg) induced full erections in 20–40% of the subjects, while the success rate in the placebo group was only 14% (63). This effect was dose-dependent. Clinical results with other $\alpha$ adrenoceptor antagonists are limited. It has been reported that in hypertensive subjects, treatment with the $\alpha_1$ antagonist doxazosin prevents the incidence of ED (64). In addition, oral administration of a single dose (4 mg) of $\alpha_1$ antagonists such as doxazosin (65) and prazosin (66) increase the effectiveness of intracavernosal or intraurethral therapies with alprostadil in patients with ED.

In folk medicine the $\alpha$ adrenoceptor antagonist yohimbine was used extensively for the treatment of sexual dysfunction. It is an alkaloid derived from the bark of the Central African tree *Corynanthe johimbe* and shows relatively high affinity (3–4 nM) for human $\alpha_{2A}$ and $\alpha_{2C}$ receptors, and moderate affinity (14 nM) for the $\alpha_{2B}$ receptor subtype (67). It has been known for many years that this drug facilitates sexual activity in several experimental models, acting on $\alpha_2$ adrenoceptors present in the central nervous system (68, 69). At the penile level, yohimbine does not enhance, but indeed blocks, contractions induced by EFS (Fig. 6). This effect is partially mediated by a blockade of the post-junctional $\alpha_2$ receptors but might be mediated also by a relative antagonism of $\alpha_1$ receptors. Indeed, in rabbit corpora cavernosa, yohimbine not only antagonizes the contractile activity induced by the selective $\alpha_2$ agonist UK 14,304 (10 $\mu$M), but also blocks (with a similar IC$_{50}$) contractions induced by an equimolar concentration of the selective $\alpha_1$ agonist phenylephrine (Fig. 7). An enhancement of nitrergic transmission is also possible, as in isolated rat aorta yohimbine induces a $\alpha_2$-mediated, endothelium-dependent, relaxation by enhancing the release of NO (70).

Yohimbine has been used for many years as an oral agent for the treatment of ED (71). Subsequently, many clinical trials have shown that it is able to improve erectile function (72–78), although a negative study has been also reported (79).

**Figure 7** Relaxant effect of increasing concentrations of yohimbine on rabbit corporal muscle pre-contracted by the $\alpha_1$ agonist phenylephrine (10 $\mu$M) or by the $\alpha_2$ agonist UK 14,304 (10 $\mu$M). Points represent the mean values of six experiments; vertical bars indicate S.E.M. values.
A recent meta-analysis of double-blind, randomized, placebo-controlled clinical trials employing this drug indicated that yohimbine is superior to placebo, with an odds ratio of 3.85 (confidence interval 2.22 to 6.67; 38). In the majority of the studies, yohimbine is administered at variable doses ranging from 5 to 10 mg three times daily. Positive effects might be apparent also after a 2–3-week latency period. The pharmacokinetic profile after oral administration is quite variable among subjects, possibly because of variable hepatic metabolism (80). Terminal elimination half-life ranges from 0.94 to 8.27 h, with a maximal blood concentration in the micromolar range (80). Side effects of yohimbine are very limited (79, 80). Interestingly, although yohimbine induces an increase in norepinephrine plasma concentration (80–82), it does not significantly affect heart rate or blood pressure (79, 80). In some studies agitation and anxiety have been reported (73, 76). Although no significant change in anxiety- and mood-inventory testing was found after different doses of yohimbine (up to 40 mg/day), in patients with psychiatric diseases, such as agoraphobia and panic attacks, it may induce panic episodes (83).

Conclusions

Although pharmacological research has made significant inroads into the understanding and treatment of ED, clinical management of the patient remains problematic. Negative interactions of biological, psychological and lifestyle risk factors underlie many cases of ED. Excessive fear of sexual failure can so deeply influence penile erection and the ejaculatory process that even the more recent treatments are sometimes ineffective. Therefore, psychologists and physicians should work together towards a multidisciplinary approach to a problem that indeed involves conflicts and anxieties rooted in the mind, but that also implies changes in the cell-to-cell communication in the central nervous system and penis.

The first line of ED therapy is understanding who the patient and his partner are and what the sexual problem(s) of the couple is (are). Indeed, the clinician often should reassess the male erectile complaint as a couple’s concern, because relationship factors exert a very important influence. This may require partner consultation.

The second point is to identify (and if possible, remove) risk factors for ED, such as drug-related and lifestyle-related risk factors. Other concomitant or determinant systemic diseases should also be identified and treated. Endocrine disorders must be adequately investigated, because hypogonadism and hyperprolactinemia could be easily and satisfactorily treated with an appropriate therapy.

If a symptomatic therapy for ED is to be established, pharmacological agents are indicated. A list of available drugs is provided in Table 2. Oral therapy is the first choice and the effective drugs presently available are sildenafil and yohimbine. Although yohimbine is more cost-effective than sildenafil, its success rate is relatively lower. Yohimbine should be reserved for younger patients with a predominant fear of sexual failure and psychological distress. Sildenafil, although ineffective on sexual desire, may resolve many of the problems coupled with ED in the majority of patients. Its cardiovascular profile is relatively safe. However, recommendations recently published by the American College of Cardiology/American Heart Association (41) should be taken into consideration before prescribing sildenafil. These include contraindication of a concomitant use of sildenafil and nitrates, and potentially hazardous effects of sildenafil in patients with active coronary ischemia and congestive heart failure. Caution should also be observed in patients with borderline low blood pressure, borderline low volume status, or in patients in a

<table>
<thead>
<tr>
<th>Drug</th>
<th>Administration</th>
<th>Target</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papaverine</td>
<td>Intracavernosal</td>
<td>PDEs (unselective inhibitor)</td>
<td>Relaxation of CC due to ↑ cAMP and ↑ cGMP levels</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Intracavernosal</td>
<td>α₁ and α₂ adrenoceptors (noncompetitive antagonist)</td>
<td>Block of adrenergic influences on CC (peripheral effect)</td>
</tr>
<tr>
<td>Alprostadil</td>
<td>Intracavernosal</td>
<td>Prostanoid EP receptors (agonist)</td>
<td>Relaxation of CC due to ↑ cAMP levels</td>
</tr>
<tr>
<td>Phenotolamine</td>
<td>Intracavernosal</td>
<td>α₁ and α₂ adrenoceptors (competitive antagonist)</td>
<td>Block of adrenergic influences on CC (peripheral effect)</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Oral</td>
<td>PDE5 (selective inhibitor)</td>
<td>Relaxation of CC due to ↑ cGMP levels</td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Oral</td>
<td>α₁ and α₂ adrenoceptors (competitive antagonist)</td>
<td>↑ Sexual arousal (central effect) block of adrenergic influences on CC (peripheral effect)</td>
</tr>
</tbody>
</table>

CC, corpus cavernosum; PDEs, phosphodiesterases; ↑, increase.
complicated, multidrug antihypertensive program. In addition a long list of drugs that may potentially prolong sildenafil half-life is provided (41).

In patients for whom oral therapy is ineffective or contraindicated, intracavernosal vasodilators acting locally on the penile tissue should be prescribed. Papaverine with or without phentolamine is relatively cost-effective over PGE1; however, the use of papaverine alone or in combination with other vasoactive drugs has not been approved by the FDA and is associated with more serious side effects than PGE1. Therefore in recent years intracavernosal administration of PGE1 has supplanted the use of other vasoactive drugs. PGE1 might also be administered by an intraurethral route, such as MUSE. However, this method of drug delivery appears to be less effective and more expensive than the intracavernosal route.

Prosthesis implantation is the last choice and is reserved for patients who do not respond or who are unable to tolerate other forms of therapy. It is an expensive and invasive procedure but it provides the ability to engage in sexual activity in otherwise unresponsive patients. Improvements over the past decade have resulted in excellent patient and partner satisfaction with a relatively low complication rate (84).

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