Male erectile dysfunction

The biochemistry of Viagra™

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The chances are that you'll have heard something about sildenafil — marketed under the trade name Viagra™ (Figure 1). Launched in 1998 as a tablet for treating male erectile dysfunction (MED), it's now been used by over 15 million men and has attracted plenty of publicity. As a biochemist however, you'll probably want to go one step further. This review will take a closer look at the interesting biochemical details of how sildenafil works.

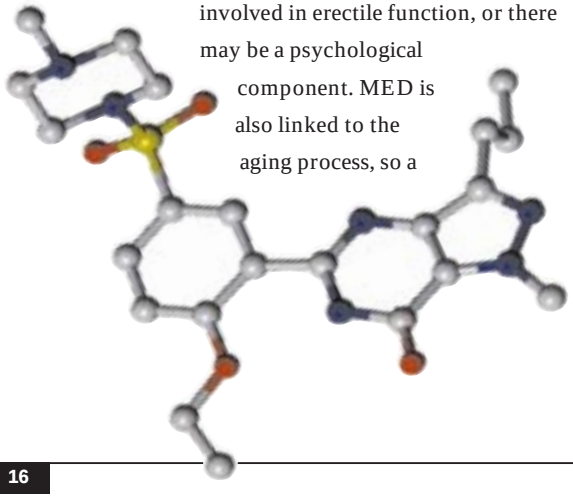
Impotence

Male impotence, or erectile dysfunction, affects a large number of men throughout the world[1]. Its precise definition and estimated prevalence vary, but one well regarded study showed that about 50% of men aged 40–70 experience some difficulty in obtaining an erection sufficient for intercourse[2]. It's recognized as being an important disorder since it can be distressing for sufferers and puts significant strain on their relationships.

Causes

MED may have a variety of causes[1]. These can be direct, as a result of neuronal damage (e.g. from a spinal injury or prostate operation), indirect, as a consequence of disorders such as diabetes or hypertension, which can damage the vasculature involved in erectile function, or there may be a psychological component. MED is also linked to the aging process, so a man in his sixties is approximately four times more likely to have moderate or complete MED than a man in his forties. Another important risk factor is smoking, which is linked to impaired blood flow in the penis.

Figure 1. Sildenafil chemical structure. Grey, C; red, O; blue, N; yellow, S



Therapy

Treatment of MED has traditionally relied on physical or invasive methods such as vacuum pumps, prosthetic implants or the use of prostanoids injected directly into the penis. While these therapies work in most cases, they are clearly far from ideal, and with the availability of an oral medicine like sildenafil[3], it's not difficult to see why these older treatments are becoming less popular.

Physiology of erection

In order to understand the biochemistry of the erectile response and the mechanism of action of sildenafil, we should consider how an erection works at a biomechanical level. The penis is composed largely of a sponge-like smooth muscle called the corpus cavernosum (CC) (Figure 2). During arousal, the smooth muscle of the CC relaxes, allowing more blood to enter and fill the lacunar spaces in the muscle. The CC is encased in a tough coat called the tunica albuginea and therefore, as the penis becomes engorged, the pressure of the blood against the tunica forms a rigid structure. The vasculature architecture in the penis further ensures that when erect, blood outflow is physically restricted, helping to maintain the erection. The penis returns to its flaccid state after arousal by contraction of the CC smooth muscle, forcing blood to leave the penis.

Control

The relaxation of the CC smooth muscle is controlled neuronally via a spinal reflex regulated by the central nervous system (CNS)[4]. The CNS integrates a variety of mental, tactile, visual, and olfactory stimuli which contribute to sexual arousal.

Not unexpectedly, the present understanding of the biochemical details of the CNS control of arousal is incomplete, but several key molecules including oxytocin, serotonin (5-hydroxytryptamine; 5-HT) and dopamine are known to be involved.

More is understood about the biochemical events that occur locally in the penis, the site of action of sildenafil.

NO and cGMP

The result of sexual stimulation is a release of the potent smooth muscle relaxant nitric oxide (NO) from non-adrenergic, non-cholinergic nerves that innervate the penis. NO diffuses into the smooth muscle cells of the CC where it binds to and activates

soluble guanylate cyclase. This enzyme synthesizes the key second messenger cGMP, which has several direct effects in these cells (Figure 3). Most importantly, it binds and activates cGMP-dependent protein kinase (cGK), which then phosphorylates a number of key regulatory proteins involved in the relaxation response. These cGK targets are thought to include K^+- and Ca^{2+}-channels, myosin light-chain phosphatase, the inositol trisphosphate receptor, phospholamban and the sarcoplasmic reticulum Ca^{2+} ATPase[5]. The net effect of cGMP elevation and cGK activation is to trigger a decrease in intracellular Ca^{2+} levels, which stimulates relaxation of smooth muscle cells, and hence allows increased blood flow into the spaces of the penis, all of which results in an erection.

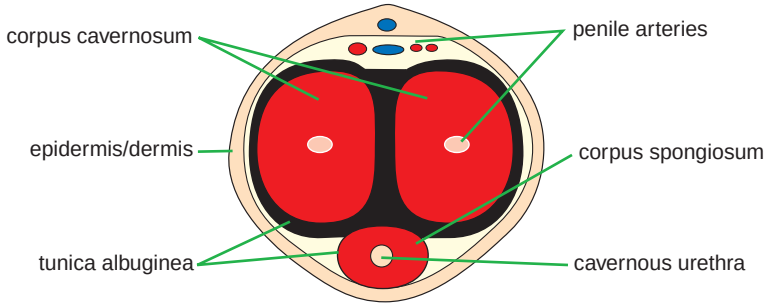


Figure 2. A section through a human penis showing key features relevant to the erectile response

Phosphodiesterase type 5

Levels of cGMP in the cells of the CC are finely controlled by a balance of synthesis and degradation. This is crucial since elevated cGMP is the signal for smooth-muscle relaxation and subsequent erection, whereas hydrolysis into GMP promotes a return to the contractile, flaccid state. Phosphodiesterase type 5 (PDE5)[6,7] is the principal enzyme that degrades cGMP in the CC; it inactivates it by hydrolysis to GMP. Sildenafil works by directly inhibiting PDE5[3,6]; it binds reversibly to the enzyme's active site through competition with it's natural substrate, cGMP. In the presence of sildenafil therefore, cGMP breakdown is decreased and the effects of the natural signals transmitted to the penis during arousal are enhanced. This potentiation of the endogenous signal cascade enables erectile function to be restored in patients whose nerve or vascular damage results in inadequate NO/cGMP release. Sildenafil works by enhancing the effect of the natural arousal signals without affecting libido.

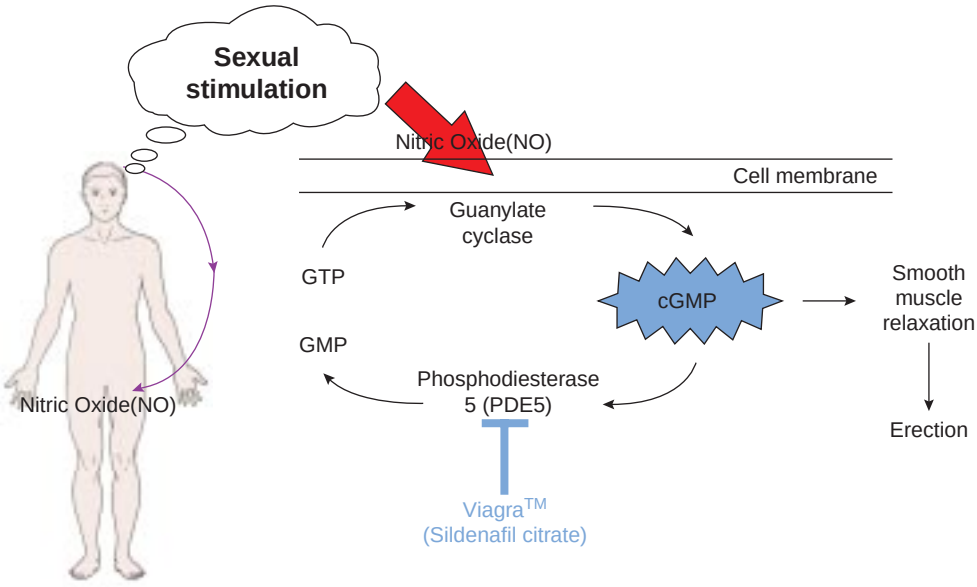


Figure 3. Mechanism of action of sildenafil

The potency of sildenafil as a PDE5 inhibitor is measured *in vitro* in a high throughput 96-well format assay, using enzyme purified by anion exchange chromatography from human platelets or CC. This was used to screen many small molecules, leading to the discovery of sildenafil as a potent PDE5 inhibitor. The assay is configured with a low substrate concentration, such that the IC_{50} (3.5 nM for sildenafil; Figure 4), is approximately equal to the inhibition constant K_i (3.8 nM)[8]. This correlates well with sildenafil's potency *in vivo*. Other experiments *in vitro*, using strips of CC tissue, have confirmed that sildenafil acts functionally to enhance the smooth muscle relaxation elicited by electrical nerve stimulation[8] (Figure 5).

Side effects

PDE5, the target of sildenafil, can also be found in smooth muscle in tissues other than the penis, particularly in the vasculature. Inhibition of PDE5 in these tissues is thought to contribute to some of the side effects experienced by some sildenafil users. These effects include facial flushing, headache and slight lowering of blood pressure. The biochemical mechanism of action also explains why sildenafil must not be taken by patients with heart disease who are taking nitrate drugs. The NO pathway of their vasculature is already stimulated by NO donors and sildenafil potentiates this, which could lead to excessive decreases in blood pressure.

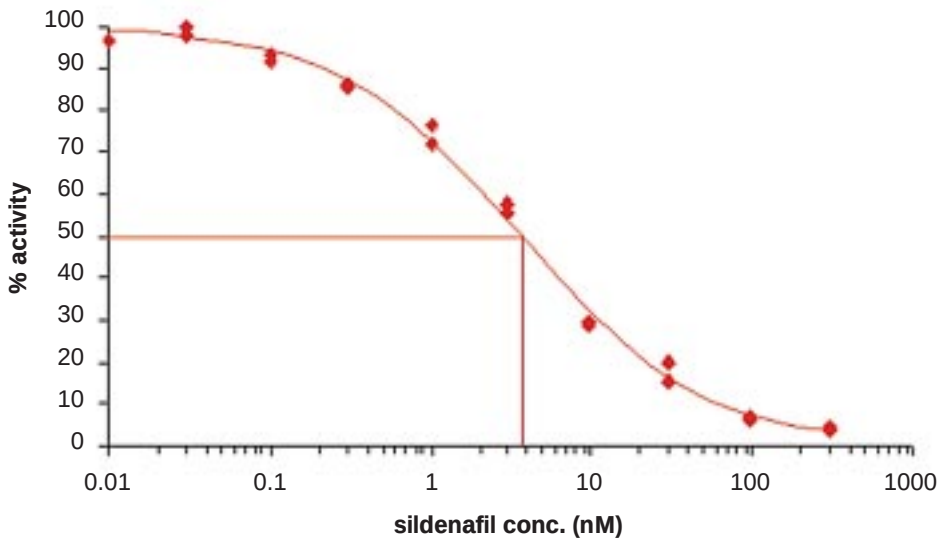


Figure 4. Typical enzyme inhibition curve from an experiment demonstrating the potency (IC_{50}) of sildenafil against purified PDE5 *in vitro*.

PDE family

PDE5 is a member of a superfamily of related phosphodiesterases. Molecular biologists have discovered 21 human genes that encode PDEs. These have been classified into 11 gene families based on sequence similarity. Sildenafil was designed as a selective PDE5 inhibitor and shows excellent selectivity (>80-fold) over the remainder of the PDE family, with the exception of PDE6 for which selectivity is approximately 10-fold[8]. A slight inhibition of PDE6 probably explains the transient change in colour vision reported by some patients at high doses of sildenafil.

Members of the PDE family have shown themselves to be amenable to inhibition by drug-like molecules. Since they occupy pivotal positions in important signalling pathways in a variety of tissues, it is likely they will yield drugs for disorders other than MED. For example, work has already been reported on the use of PDE4 inhibitors for respiratory disorders including asthma[9].

The future

The introduction of sildenafil has revolutionized the treatment and awareness of male erectile dysfunction. As our understanding of the biochemical pathways involved in sexual function increases further, pharmaceutical companies will undoubtedly produce other drugs that will correct sexual disorders by intervening in other biochemical mechanisms in both men and women.

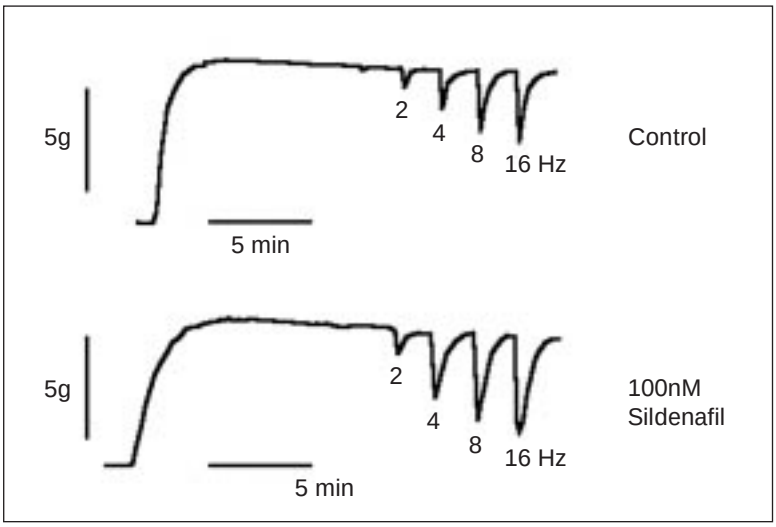


Figure 5. Typical chart trace showing the effects of sildenafil (100 nM) on the magnitude and duration of relaxation of phenylephrine precontracted human CC tissue strips, induced by EFS for 10 s at frequencies of 1–16 Hz. Reproduced, with permission, from Ballard, S.A. et al. (1998) J. Urol. **159**, 2164–2171.

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