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Biochemical and Microanatomical Mechanism of Erectile Dysfunction

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The important details in the unraveling of penile erection are an understanding that it is a complex neurovascular event dependant upon proper functioning of the distributing arteries, neural structures, and neural transmission. At the molecular basis lies the proper relaxation and contraction of the supportive smooth muscle trabecular network, in part mediated by the relaxant and antithrombotic properties of the endothelial cells that line the sinusoids of the cavernous bodies.

It is the tone of the smooth muscles of the corporal bodies that keeps the penis, when it is contracted, in a flaccid state. If one considers that the penis is erect about one hour each night during REM sleep and anywhere from one to four hours each week during sexual activity, depending upon age and sexual habits, it is evident that contraction and flaccidity of the penis is the norm. Relaxation of the penile smooth muscles is an active process that enables the penis to become erect. Ageing, various diseases including diabetes mellitus, anxiety, and depression, as well as a long list of medications, interfere with this process and cause the penis to remain in the contracted state. The result of the loss of balance between flaccidity and erection is known as erectile dysfunction, or ED.

Over the past quarter century at the Urological Research Laboratory at the Albert Einstein College of Medicine, the scientist members of the department have attempted to understand some of the key components of the erectile mechanisms, particularly in relationship to the effects of aging and diabetes mellitus on smooth muscle relaxation and contraction [1-6]. During that time, there have been significant observations from several other centers interested in erectile function that have added to the overall depth of knowledge in the field.

A few of them include:

- Virag's discovery in the early 1980s that Papaverine, a non-specific phosphodiesterase inhibitor, causes erection when injected into the penis [7].
- Similarly, Brindley's injection of the alpha-blocker phenoxybenzamine induced long-lasting erection, and others showed a similar result with prostaglandin E1 injections [8].
- The discovery that Nitric Oxide, the endothelial-derived relaxing factor described by Furchgott, was a (or the) prime relaxant neurotransmitter that caused erection. This was first promoted in urologic publications by Rajfer, Burnett, and Saenz de Tejada [9-11].

Our primary goal has been to increase the understanding of the unique aspects of the smooth muscle of the penis that allow it to function. Several of these findings will be described.

Ultimately, the smooth muscle cell is under the control of the calcium ion concentration within the cytoplasm (fig. 1). In order

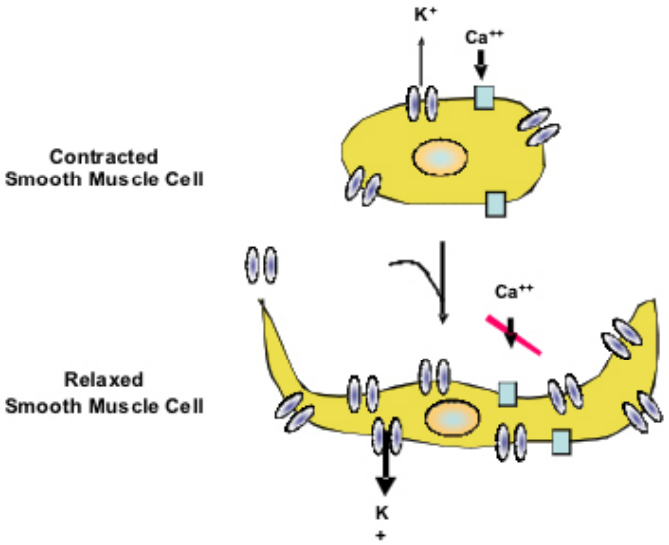

Figure 1
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for the cell to remain contracted, there must be a constant influx of calcium into the cell. If this does not happen, then the cell will relax. In opposition to that, nature has provided a mechanism to counteract the constant inflow of calcium and to lower the intracellular calcium ion concentration (Ca^{2+}) by the efflux of the potassium ion from the cell's interior down its electrochemical gradient.

The intracellular potassium ion concentration is about 40x higher than that in plasma. There are at least 4 primary potassium channels on the cell membrane (fig. 2). Most of the time they are closed, but in the presence of an appropriate signal (e.g. high local calcium ion concentration), they open and allow potassium to flow out of the cell. This hyperpolarizes the cell membrane (making it more negative) thereby closing the voltage sensitive calcium channel, stopping influx, and ultimately decreasing the action of the contractile proteins allowing cross-bridges to dissociate, causing the cell to relax.

Several members of our lab contributed to the discovery in the early 1990s that the smooth muscle cells of the penis are connected through an intracellular connection system known as gap junctions [12]. The gap junctions in the penis (fig. 3) are composed of connexin, a protein that forms a six-protein channel that lines up with other similar proteins on opposite or opposing cells to form a plaque of many connexin 43 gap junctions. This allows rapid intercellular communication of second messengers such as cyclic AMP and cyclic GMP and ions, which are present in the cytoplasm.

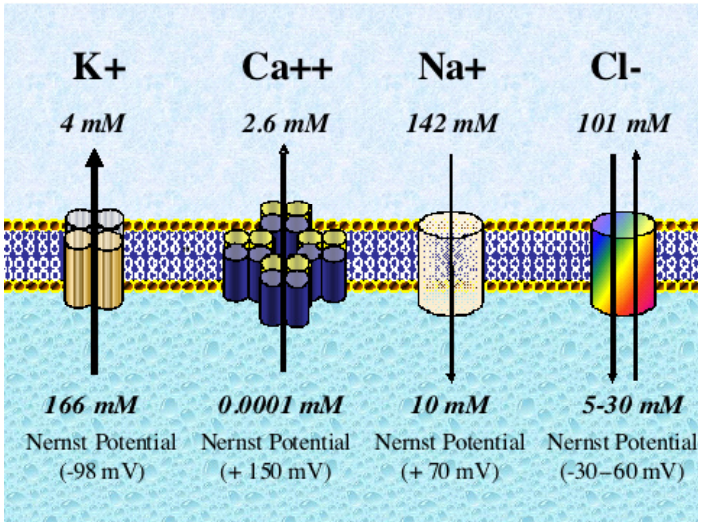

Figure 2
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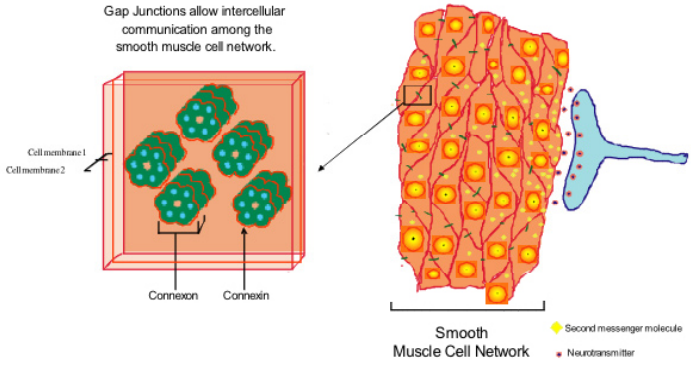

Figure 3
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The gap junctions allow a signal that occurs at one location in the penis to be rapidly transmitted along the entire smooth muscle framework of the penile corpora.

The next observation was that potassium channels, which are ubiquitous in nature and in all cells throughout the body, are present in the smooth muscle of the urogenital system. There are four major channels present: (1) the maxi-K or BK channel that is activated by calcium ions and cell voltage, (2) the K_{ATP} channel that is sensitive to activation by ATP, (3) the K_{IR} which is an inward rectifier channel, and (4) a K_V or voltage-dependant channel. It is of interest that for animals to protect themselves from predators or to obtain food they often use defensive mechanism toxins that interfere with potassium channel function. For example the scorpion produces several such toxins that block the most prevalent potassium channel, the Maxi-K or the BK channel.

The honeybee, several kinds of spiders, scorpions (fig. 4), and the green mamba all produce K channel blockers. These toxins or potential channel blockers are actively used in research today to study the various potassium channels.

Figure 4
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A primary take-home message is that when potassium channels are open in response to intracellular signals, such as increased intracellular calcium ion concentration or nitric oxide induced protein kinase, then the membrane potential becomes more negative and causes the cell to relax [13].

In recent years, another pathway has been recognized to be important in the sustained contraction of the smooth muscle cells that is not dependent on intracellular calcium levels. That pathway includes RhoA and Rho kinase (fig. 5). Rho-kinase is an enzyme activated by RhoA at the level of the cell membrane by a contractile agonist such as endothelin that binds to the ET_A receptor [14]. Rho kinase exerts its effect by inhibiting the smooth muscle myosin phosphatase (by phosphorylating it) and the cell stays contracted. That is because the balance between smooth muscle myosin phosphatase (the enzyme that would ordinarily inhibit smooth muscle contraction by dephosphorylating the regulatory light chain 20 (MLC20) of smooth muscle myosin) and the smooth muscle myosin light chain kinase (that induces contraction via phosphorylating the MLC20) is tipped in favor of smooth muscle contraction.

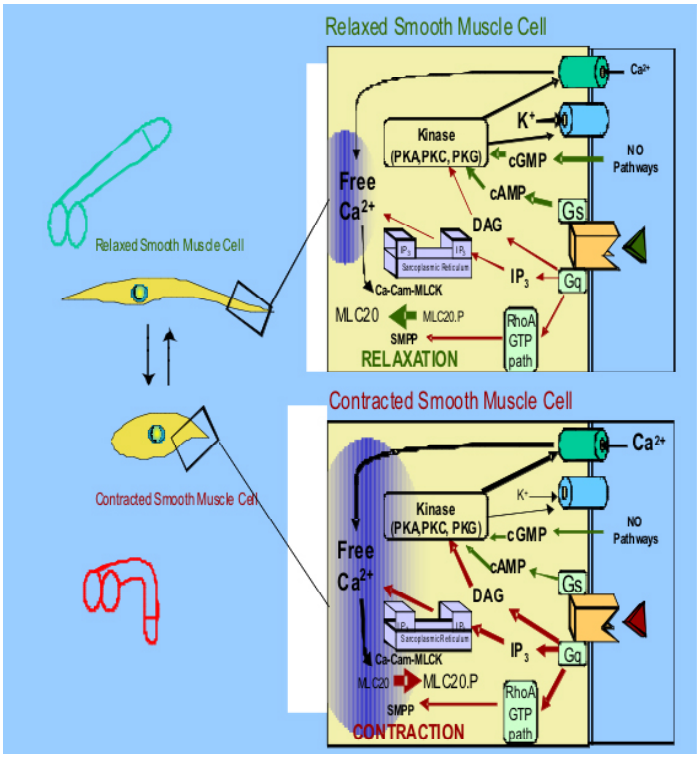

Figure 5
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This action of Rho kinase is called calcium-sensitization under which the cell can remain contracted even at a lower level of intracellular calcium concentration when this enzyme is activated.

HOW DOES MAXI-K CHANNEL GENE TRANSFER WORK?

As noted above, the rationale for the usefulness of K channel gene therapy is related to the important contributions that ion channels make to the contraction and relaxation of smooth muscle cells (i.e., myocytes). Ion channels are membrane proteins that provide a selective permeability barrier to the movement of ions across the cell membrane (influx and efflux of ions; i.e. K^+ and Ca^{2+}). In short, these membrane proteins provide a selective channel through which ions can flow (K^+ flows through K channels, and Ca^{2+} flows through Ca channels, but not vice versa). The opening and closing of these channels is regulated by numerous cellular processes (Figure 6). However, anything that increases the extent that they are open will increase the amount of ions that can move through the channel over any given period. The idea behind Maxi-K channel gene transfer is to increase the number of Maxi-K channels in the

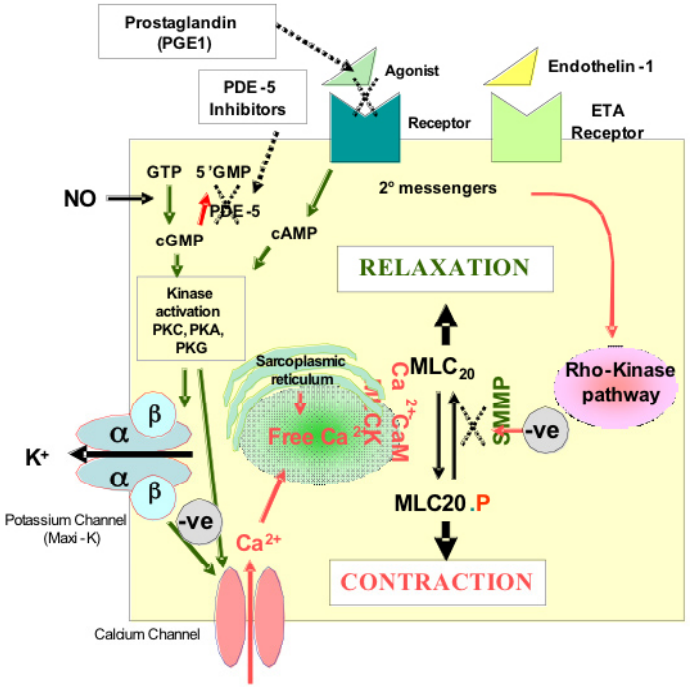

Figure 6
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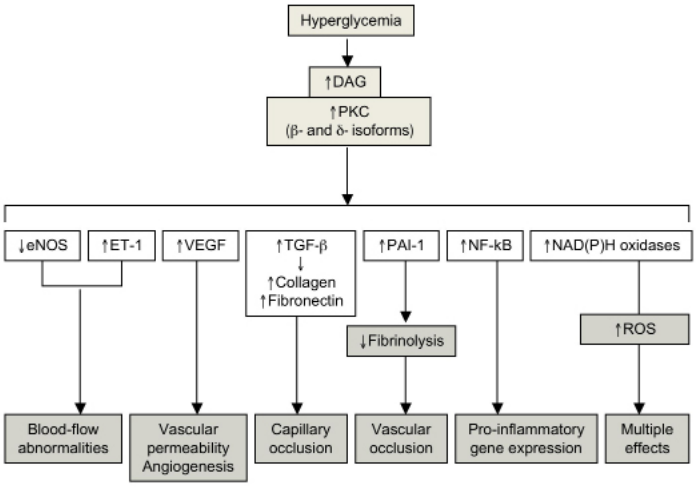
cell membrane that are diminished by aging and disease so that when the cells are activated by the normal erectile stimuli (i.e. nitric oxide released from nerves), there will be an increase in the efflux of K^+ from the cell [15].

DIABETES AND ED

Many of the patients that we take care of with ED have hyperglycemia and diabetes. The effect of hyperglycemia is manifold (fig. 7), but two of the effects in particular can specifically alter erectile mechanism. One is the decreased production of nitric oxide synthase by endothelial cells as a consequence of increased release of the potent vasoconstrictor at ET-1 that causes blood flow abnormalities in the penis. Secondly, there is also an increased production of reactive oxygen species that can adversely affect the smooth muscle cells which results in ED [16].

Y Tong and K Davies in our lab have recently discovered that the genes hSMR3 or ProL 1 expressed in the prostate, corpora cavernosal smooth muscle cells, and submandibular gland, which encode a family of peptides called opiorphins (members of the opiorphin gene family), act as biomarkers for ED [17]. Expression is decreased in the corpora of patients with age and diabetes-related ED resulting from several etiologies. The level of expression of ProL 1 and hSMR3 is 5-10x higher in normal patients without ED.

The action of the ProL 1 or hSMR3 products (known as opiorphins in humans, and sialorphin in rats) is to inhibit the enzyme known as neutral endopetidase (NEP) or neprilysin (fig. 8). NEP breaks down a peptide agonist bound at a receptor complex at the cell membrane, limiting its effect. Thus, as diagrammed below, breakdown of the opiorphins (by inhibition of the NEP) allows a prolonged action of the agonist on the cell membrane. Potentially lowered levels of opiorphins that occurs with diabetes may allow the prolonged action of a contractile agonist on the cell and therefore promotes cell contraction (i.e. ED).



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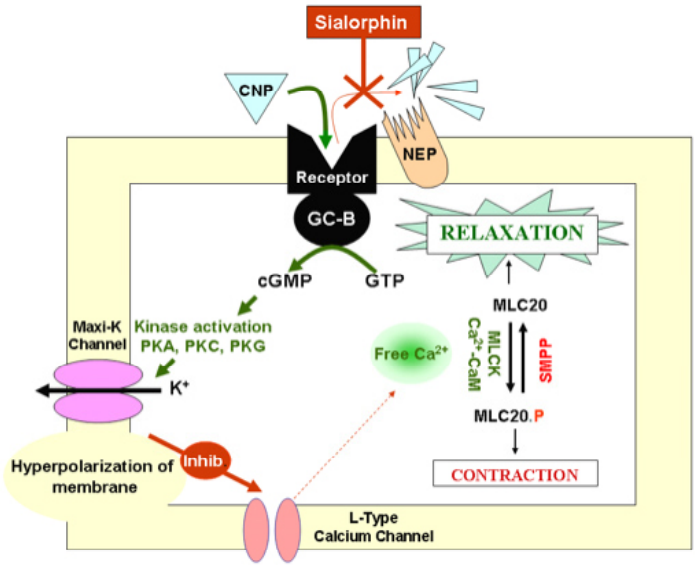

Figure 8
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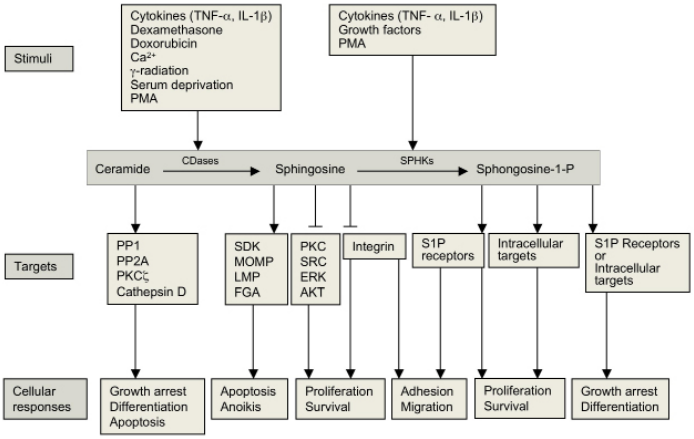
ME DiSanto in our lab is now working on a potential new mechanism of regulating smooth muscle contractility by sphingolipids (fig. 9), fat containing molecules present on the cell membrane that have many functions, one of them being cell contraction. Individual members of this family of sphingolipids have distinct effects on a wide range of cellular signaling pathways as shown in the figure below. ME DiSanto's initial work has focused on the balance between ceramide and sphingosine-1-phosphate (S1P) and the metabolic enzymes that regulate the interconversion of these molecules. S1P can activate any of five different G-coupled protein receptors, but only three (S1P1, S1P2 and S1P3) are predominant in SM cells. Both the S1P2 and S1P3 seem to enhance smooth muscle contraction, and again, when cell contraction is present so is ED. It appears that patients who have diabetes have a higher activity of S1P3 and are more easily contracted, and they all have higher levels of serum S1P.

One of the objectives of our laboratory is to create a molecular profile for erectile dysfunction by measuring the serum levels of S1P, ET-1, and opiorphins (fig. 10). In diabetic patients, only 50% will develop the symptoms of ED. Using S1P, ET-1, and opiorphins as biomarkers, we hope to be able to predict which diabetic patients have a predilection for ED or other vascular diseases. It has also been recognized in recent years that men with ED have a higher rate of cardiovascular disease. It is anticipated that these predicted biomarkers will lead men to earlier diagnosis and treatment.



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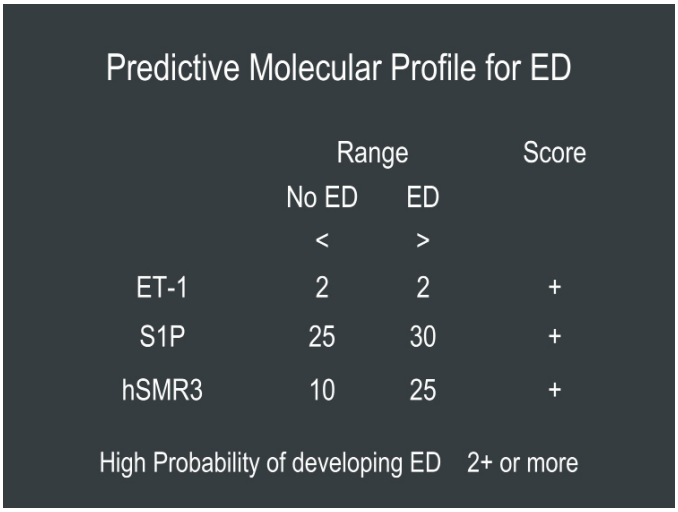

Figure 10
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CONFLICT OF INTEREST

Arnold Melman is a directing member and co-founder of Ion Channel Innovations, LLC.

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