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Physiology and Biochemistry of Erections

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The physiology of erection has received intense clinical and basic research scrutiny over the past two decades. This massive effort has led to a much clearer understanding of the macroscopic aspects of erection as well as identification of the prominent features of the etiology of erectile dysfunction (ED). However, it is clear that the devil is in the details of the erectile process. Therefore, to truly understand the precise mechanistic basis for erection and ED, much more still must be learned about how the biochemical cascades in the corporal smooth muscle cells are integrated to produce a normal erection, or how they are altered to result in ED. The ultimate goal of these basic research and clinical efforts will be to provide a rational scientific basis for mechanism-based, patient-specific therapies for ED. This article reviews fundamental aspects of the physiology of erection and summarizes the most recent information available concerning the putative biochemical correlates of these physiologic events.

Key Words: Erection; corporal smooth muscle; biochemistry; erectile dysfunction.

Introduction

Erectile dysfunction (ED) is defined as the inability to achieve and maintain an erection sufficient to permit satisfactory sexual intercourse *(1)*. The incidence of ED has been estimated at 20–30 million cases in the United States *(2,3)*. Altered function or impairment of any number of factors, alone or in combination, is sufficient to elicit ED. Among the most prevalent contributors are psychologic, neurologic, hormonal, arterial, and cavernosal (i.e., corporal smooth muscle cell [SMC]) factors. The emphasis in this article is on the latter. The rationale for this is related to the fact that incomplete relaxation of the corporal SMC network is both necessary and sufficient to elicit ED *(4–6)*. Moreover, a tremendous amount of information is available on the participation of this specialized vascular SMC type in erectile physiology and dysfunction. As such, this article provides a brief overview of the physiology of erection and the known biochemical events in the corporal SMC that are thought to underlie that process. From the presentation, it will be clear that many potential mechanisms can lead to erectile failure, and, therefore, numerous parallel lines of investigation exist for identifying novel therapeutics.

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Vascular and Neural Aspects of Penile Erection

Penile erection is a primarily a neurovascular event that is further modulated by the individual's psychologic and hormonal status. Briefly, sexual stimulation elicits nerve impulses that are carried to the penis to release neurotransmitters from the cavernous nerve terminals. Both autonomic and somatic nerves innervate the penis. Sympathetic nerves and parasympathetic nerves coalesce in the pelvis to form the cavernous nerves, which enter the corpora cavernosa, corpus spongiosum, and glans penis to regulate blood flow during erection and detumescence. The pudendal nerve, the somatic component, is responsible for penile sensation and the contraction and relaxation of the extracorporeal striated muscles (bulbocavernosus and ischiocavernosus).

On activation of proerectile neural pathways, neurotransmitters are released into the vascular tissues of the penis, where they interact with relaxing factors derived from the endothelial cells. The end result of these concurrent events is relaxation of the SMCs in the arteries and arterioles supplying the erectile tissue, producing a dramatic increase in penile blood flow. Relaxation of the trabecular smooth muscle, in turn, increases the compliance of the sinusoids and facilitates rapid filling and expansion of the sinusoidal system against the tunica albuginea (Fig. 1). The ensuing compression of the subtunical venular plexuses between the trabeculae and the tunica albuginea is referred to as the venoocclusive mechanism, and it effectively prevents venous outflow *(7,8)*. The trapped blood within the corpora cavernosa produces the erect state of the penis, which is associated with an intracavernous pressure of approx 100 mmHg (the full erection phase). During heightened sexual activity, the bulbocavernosus reflex is activated and the ischiocavernosus muscles contract to forcefully compress the base of the blood-filled corpora cavernosa and the penis

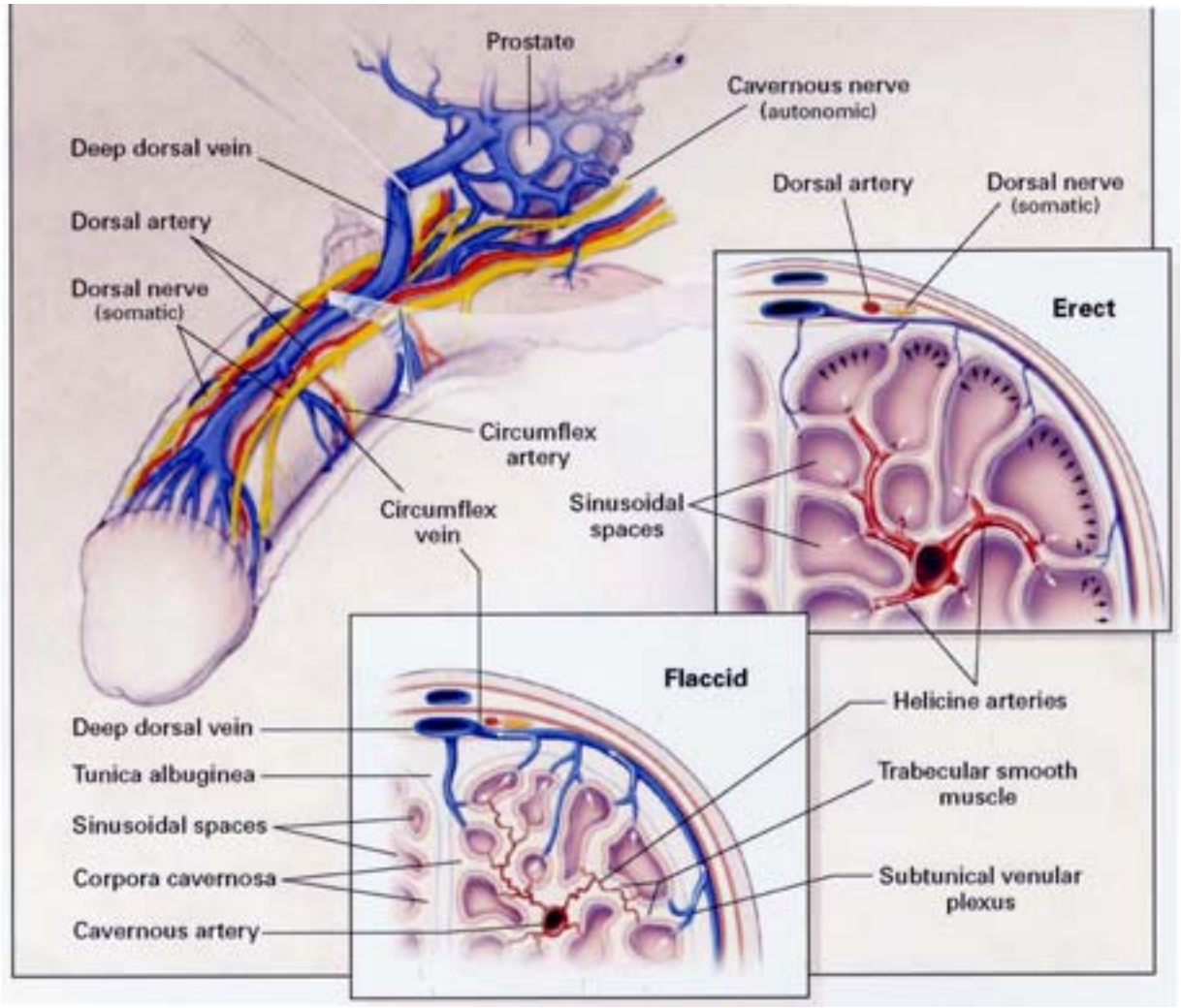

Fig. 1. Anatomy and mechanism of penile erection. The cavernous nerves (autonomic), which travel posterolaterally to the prostate, enter the corpora cavernosa and corpus spongiosum to regulate penile blood flow during erection and detumescence. The dorsal nerves (somatic), which are branches of the pudendal nerves, are primarily responsible for penile sensation. The mechanisms of erection and flaccidity are shown in the upper and lower inserts, respectively. During erection, relaxation of the trabecular smooth muscle and vasodilatation of the arterioles result in a severalfold increase in blood flow, which expands the sinusoidal spaces to lengthen and enlarge the penis. The expansion of the sinusoids compresses the subtunical venular plexus against the tunica albuginea. In addition, stretching of the tunica compresses the emissary veins, thus reducing the outflow of blood to a minimum. In the flaccid state, inflow through the constricted and tortuous helicine arteries is minimal, and there is free outflow via the subtunical venular plexus. (Reproduced with permission from ref. *10*.)

becomes even more rigid, with characteristic intracavernous pressures up to several hundred millimeters of mercury (the rigid erection phase). It is during this phase that both blood inflow and outflow temporarily cease *(9)*.

Detumescence ensues promptly on cessation of the proerectile neural stimulus and is further accelerated by the metabolism of second messengers (i.e., cyclic adenosine monophosphate [cAMP], cyclic guanosine 5'-monophosphate [cGMP]) by phosphodiesterases (PDEs), as well as the uptake, extrusion, and sequestration of other metabolites and ions (i.e., calcium). In addition, detumescence can be further augmented from sympathetic discharge during ejaculation. The primary impact is the recontraction of the trabecular smooth muscle, which eliminates the capacitive function of the penile vascular spaces and results in reopening of the venous channel and egress of the stored blood, and, therefore, flaccidity returns.

Macroscopic Physiology of Penile Flaccidity and Erection

Penile Flaccidity: Corporal Smooth Muscle Contraction

The corporal SMC exists in a partially constricted state the vast majority of the time in vivo. The degree of contraction at any point in time is the product of several factors, most notably intrinsic myogenic activity *(11)*, adrenergic neurotransmission *(12)*, and the activity of endothelium-derived contracting factors such as prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$)

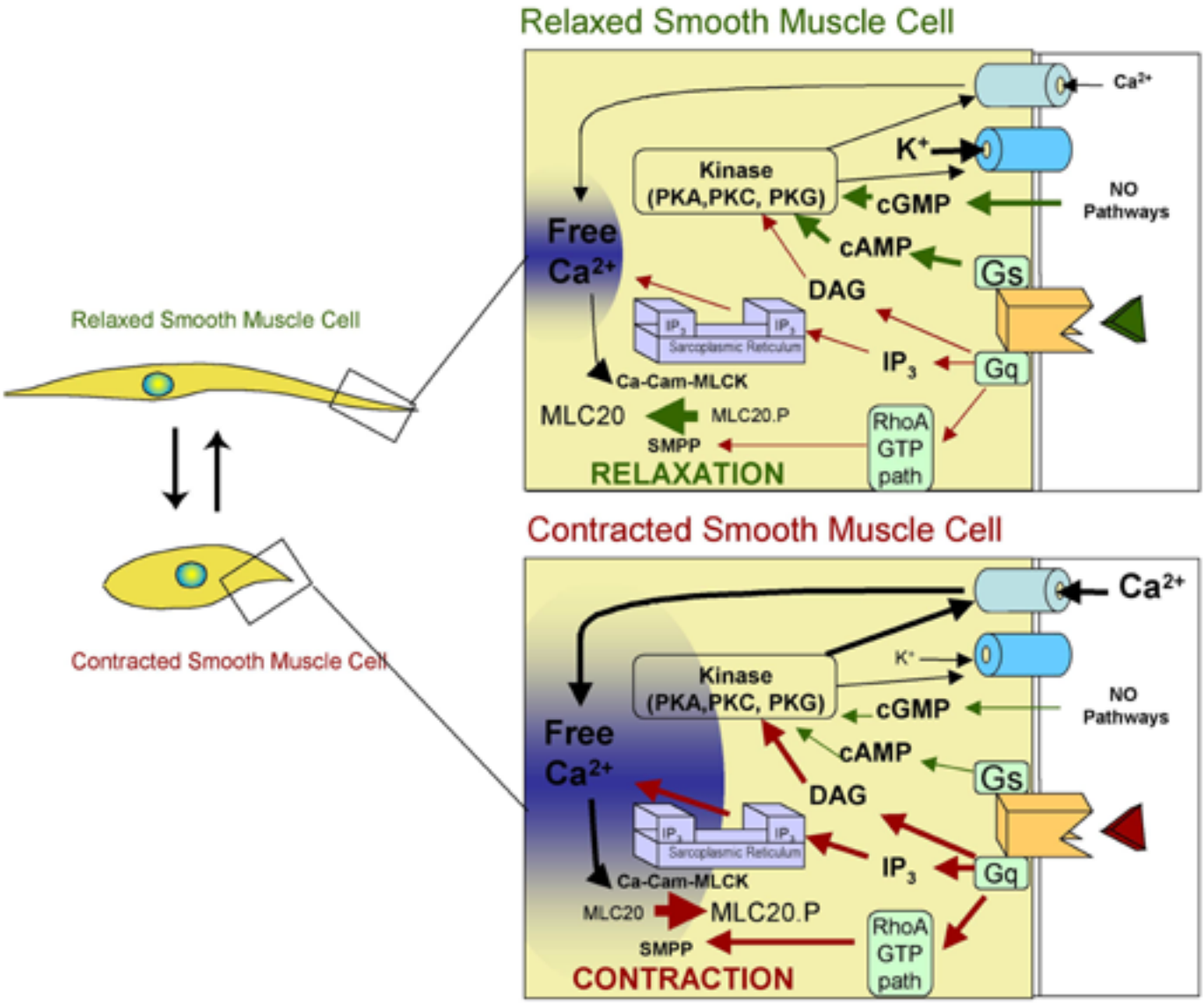

Fig. 2. Schematic depiction of mechanistic basis for control of corporal SMC tone. Shown on the left is a fully relaxed (top) and fully contracted (bottom) corporal SMC. On the right is shown the impact of cellular activation on the various second-messenger pathways, and, furthermore, their impact on the kinases and ion channels present in corporal SMCs. For clarity, those biochemical pathways whose activation or increased activity is involved in relaxation are shown in green, and those pathways whose activation or increased activity is involved in contraction are shown in red. In all cases, the thickness of the arrow is indicative of the relative level of activity of that particular pathway. For example, note that in the upper-right panel, the potassium efflux arrow is thick, and the calcium influx arrow is thin, indicating that K efflux is great compared with calcium influx during corporal smooth muscle relaxation. The shaded blue regions in both cells indicate the relative changes in the free intracellular calcium levels in the cytosol. PKA, PKC, and PKG: kinase A, C, and G, respectively; DAG: diacylglycerol; MLC20: myosin light chain 20; SMPP: smooth muscle myosin phosphatase; Cam: calmodulin; MLCK: myosin light chain kinase; Rho A: Rho A kinase; G_q and G_s: G-protein coupled to activation of phospholipase C (PLC) and adenylate cyclase enzymes, respectively; GTP, guanosine 5'-triphosphate.

or endothelins (ETs) *(6,13–17)*. The mechanistic basis for these effects is diagrammed in Fig. 2.

Penile Erection: Corporal Smooth Muscle Relaxation

Nitric oxide (NO) released from nonadrenergic-noncholinergic neurotransmission and the endothelium is probably the principal neurotransmitter for penile erection *(18,19)*. Within the myocyte, NO activates a soluble guanylyl cyclase raising intracellular concentrations of cGMP. cGMP in turn activates a specific protein kinase (i.e., protein kinase G [PKG]), which phosphorylates certain proteins and ion channels, resulting in opening of the potassium channels and hyperpolarization; sequestration of intracellular calcium by the endoplasmic reticulum; and inhibition of calcium channels, diminishing calcium influx. The consequence is a drop in the free cytosolic calcium concentration and smooth muscle relaxation (Fig. 2). Of note, during the return to the flaccid state, cGMP is hydrolyzed to guanosine

monophosphate by PDE type 5. Other PDEs are also found in the corpus cavernosum, but they do not appear to play an important role in erections.

Regulation of Corporal SMC Tone

When a neural or humoral signal has activated the corporal or arterial SMC, another series of intracellular signal transduction events is activated (see Fig. 2). The cascade of events elicited by these divergent, yet somewhat overlapping intracellular signaling pathways depends on intercellular communication through gap junctions to ensure that signal spread is sufficiently coordinated to ensure the rapid and syncytial contraction and relaxation responses required for penile erection and detumescence, respectively.

The next section focuses on the more specific physiologic and biochemical factors and mechanisms that modulate corporal SMC tone to achieve these end points.

Physiologic and Biochemical Modulation of Corporal SMC Tone

Contraction and relaxation of myocytes represent opposite, or functionally antagonistic, sides of similar, if not identical, biochemical and physiologic cascades. The relevant neurotransmitters, hormones, or neuromodulators that elicit the contractile or relaxation response all exert their impact on the corporal SMC via a series of fairly well described intracellular biochemical cascades. These cascades can be generally subdivided into three major categories: (1) ionic mechanisms, (2) intracellular calcium mobilizing mechanisms, and (3) calcium sensitization mechanisms. A brief review of each of these major components is provided next, and a schematic summary of their contributions to contraction and relaxation of the corporal SMC is shown in Fig. 2.

Ionic Mechanisms

Ion channels are important modulators of the erectile process by virtue of their ability to modulate the excitability of corporal SMCs. They do so in large part by leveraging the existing electrochemical gradients in SMCs. The standing ionic gradients for the major ionic species relevant to myocyte tone—calcium ($[Ca^{2+}]_I = 80$ n*M*; $[Ca^{2+}]_o = 2$ m*M*), potassium ($[K^+]_I = 155$ m*M*; $[K^+]_o = 5$ m*M*), chloride ($[Cl^-]_I = 40$ m*M*; $[Cl^-]_o = 100$ m*M*) and sodium ($[Na^+]_I = 15$ m*M*; $[Na^+]_o = 145$ m*M*)—are maintained by a host of pumps, transporters, and cotransporters, a discussion of which is beyond the scope of this article, but which has been briefly reviewed in urogenital myocytes *(20)*. Let us now turn our attention to the relevance of ion channel activity in corporal smooth muscle to erectile physiology, function, and capacity.

K^+ (Potassium) Channels in Corporal Smooth Muscle

Of all the ion channels present in corporal smooth muscle, K channels are undoubtedly the best characterized and most heterogeneous *(20–22)*. At least four distinct K channel subtypes have been identified in corporal smooth muscle, and some of these (i.e., the maxi-K channel *[22]*) exhibit isoform diversity as well. K channel subtypes identified to date include (1) large-conductance calcium-sensitive K channels (i.e., maxi-K or *Slo*), (2) metabolically regulated K channels (K_{ATP}), (3) voltage-regulated K channels (K_{DR}; delayed rectifiers), and (4) A-type K current. The characteristics of the first two are still the best elucidated in human corporal smooth muscle *(21–31)*. However, in all cases, the physiologic relevance and effects of these channels is related to the hyperpolarizing currents that they mediate via the outward flux of K^+ down their electrochemical gradient. It is conceivable that differential tissue expression and disease-related alterations in K channel isoform expression may be of both diagnostic and therapeutic value. Not surprisingly, K channels are the only ion channels that have thus far been explored as potential therapeutic targets for the treatment of ED *(24,31,32)*.

Ca^{2+} (Calcium) Channels in Corporal Smooth Muscle

The L-type voltage-dependent calcium channel (VDCC) is apparently the most physiologically relevant Ca channel subtype present in corporal smooth muscle. Experimental evidence for the contribution of transmembrane calcium flux through these channels to the control of corporal SMC tone derives largely from pharmacologic experiments on isolated corporal tissue strips and Fura-2-based digital imaging microscopy on cultured and freshly isolated myocytes *(33–37)*. These studies have clearly shown that continuous transmembrane calcium flux through L-type VDCC is required for sustained contraction of human corporal smooth muscle. In addition, the expected unitary L-type Ca^{2+} currents in corporal myocytes have been identified using patch-clamp techniques *(20)*. Consistent with these observations, molecular studies have also provided evidence for the presence of the expected α_{1c}-subunit of the VDCC (i.e., L-type VDCC; M. Salman and G. J. Christ, unpublished observations). The physiologic significance of these channels is by virtue of the inward depolarizing Ca^{2+} currents that they mediate. Without question, then, continuous transmembrane calcium influx through these Ca channels is an absolute prerequisite to the initiation, maintenance, and modulation of corporal SMC tone.

Chloride Channels in Corporal Smooth Muscle

Previous studies have documented the presence of a stretch-activated/sensitive chloride channel, as well as a large calcium-sensitive chloride channel *(33,38)* and, moreover, proposed a potentially important role for depolarizing chloride currents in corporal SMC function (i.e., detumescence and flaccidity; see next section). A very recent investigation *(39)* provides perhaps the most detailed and compelling evidence for the presence and physiologic relevance of depolarizing chloride currents to the modulation of corporal SMC tone. This study provided both in vivo and in vitro evidence that calcium-sensitive chloride channels (Cl_{Ca}) play a potentially physiologically relevant role in the modu-

Table 1
Summary of Significant Modulators of Corporal SMC Tone

Contraction	Relaxation[a]
Noradrenaline	NO
ET-1	*Vasoactive intestinal polypeptide*
Neuropeptide Y	*Prostanoids (PGE_1/PGE_2)*
$PGF_{2\alpha}$	*Calcitonin gene-related peptide*
Angiotensin II	

[a]Italicized factors are those that utilize the cAMP/PKA pathway.

lation of both rat and human corporal smooth muscle. Thus, while a role for calcium and potassium channels in modulating corporal SMC tone is both better understood and currently more convincing, a role for chloride channels in modulating corporal SMC tone in response to both stretch (i.e., cellular deformation in response to alterations in intracavernous pressure or blood flow) and increases in the intracellular calcium level also seems plausible.

Coordination of Ion Channel Activity to Achieve Penile Erection and Detumescence

Figure 2 illustrates the mechanistic basis for the contribution of ion channels to the regulation of corporal SMC tone. The role of ion channels in modulating corporal SMC tone can be conceptualized in terms of their impact on the functionally antagonistic *calcium/potassium system.* Furthermore, the important link between K and Ca channel activity is ultimately mediated by their impact on the free intracellular calcium levels in the cytosol of the corporal myocyte. That is, on either receptor- (i.e., catecholamines) or nonreceptor- (i.e., membrane depolarization) mediated activation of the contractile portion of the intracellular biochemical cascade (Fig. 2), there is a transient three to fivefold elevation in the free intracellular calcium level, the peak of which occurs within ≈20–30 s. After this transient peak, the mean resting intracellular calcium level returns to near resting levels in ≈1 to 2 min *(34,35)*. These findings have been confirmed on cultured cells as well as freshly isolated myocytes (G. Lagaud, G. J. Christ, and W. Zhao, unpublished observations), in response to activation of both the ET_A (ET-1 receptor) and α_1-adrenergic receptors (i.e., phenylephrine-induced activation). Approximately 50% of the peak intracelluar calcium transient is a consequence of transmembrane calcium flux through L-type VDCCs. The remaining portion of the response presumably reflects calcium release from inositol triphosphate (IP_3)-sensitive intracellular calcium stores in the sarcoplasmic reticulum (discussed later). The magnitude of the transmembrane calcium flux, and thus its contribution to the peak intracellular calcium transient, is modulated by both K and Ca channel activity (and presumably Cl as well; see above). In short, any stimulus that increases corporal SMC tone does so, at least in part, by increasing the activity of L-type VDCCs, while simultaneously decreasing the activity of K channels. The algebraic sum of these two inversely correlated effects is that positively charged ions are moving into the corporal SMC (via Ca ions) and, therefore, depolarizing the cellular membrane potential and further increasing transmembrane Ca flux.

Conversely, during an appropriate sexual stimulus, the reverse process is initiated. That is, K channel activity is increased, the cellular membrane potential becomes more negative (as positive charge is moving out of the cell), and the activity of L-type VDCCs is decreased. This series of intracellular events leads to a decrease in transmembrane calcium flux; a reduction in the free intracellular calcium level; relaxation of corporal and arterial smooth muscle; and, thus, penile erection.

These facts account for the important role of ion channels in the modulation of corporal SMC tone and, thus, erectile capacity.

Calcium Mobilization

As mentioned earlier, corporal myocytes reside in a partially constricted state the vast majority of the time (i.e., flaccidity), from which they can be either further contracted (i.e., predisposing to erectile failure) or, conversely, further relaxed (i.e., normal erection). The degree of tone in smooth muscle is affected by the free intracellular calcium concentration. The critical importance of understanding calcium mobilization in corporal smooth muscle is related to the fact that activation of myocytes, either contraction or relaxation, is generally preceded by a rise and fall, respectively, in the free intracellular calcium levels. While there is more than one potential source of intracellular calcium store (i.e., IP_3 and ryanodine-sensitive sarcoplasmic reticulum calcium stores) as well as transmembrane calcium flux (i.e., calcium channels), the most well-described pathway in the corpora is attributable to intracellular calcium mobilization through the IP_3 receptor.

Intracellular Calcium Mobilization From Sarcoplasmic Reticulum: IP_3

Continuous transmembrane calcium flux through L-type VDCCs plays a critical role in the sustained contraction of many, if not all, SMCs, including corporal smooth muscle *(20)*. However, it is increases in intracellular calcium levels that provide the trigger for SMC contraction. These requisite increases in intracellular calcium levels are mediated both by the aforementioned transmembrane calcium flux and by liberation of intracellular calcium stores. While the endoplasmic (sarcoplasmic) reticulum provides the main storage site for agonist-induced changes in intracellular calcium levels, it still needs to be accessed by a intracellular signal transduction pathway. In the case of corporal smooth muscle, there is clear evidence for an important contribution of IP_3 receptor–mediated sarcoplasmic reticulum calcium stores *(33–35,40)*. As shown in Fig. 2, a major metabolic product of PLC activation is IP_3, which, in turn, via stereospecific receptor activation of channels on the

sarcoplasmic reticulum, liberates intracellular calcium from these stores and, thus, provides a major source of intracellular calcium for SMC contractility *(41)*.

Calcium Sensitization: Role of Calcium Sensitization and Erectile Physiology, Function, and Capacity

Certainly ion channels are not the only modulators of corporal SMC contractility. In fact, it has been well documented that following contraction, intracellular calcium levels return to near resting levels within 1 to 2 min in many SMC types, including corporal smooth muscle *(33–36)*, despite the fact that contractile responses are sustained. This phenomenon has been referred to as calcium sensitization, and the putative mechanism is outlined in Fig. 2. The initial observation was that the intracavernous injection of a Rho kinase inhibitor (Y-27632) elicited an increase in intracavernous pressure in the rat model in vivo, apparently independent of the NO pathway *(42)*. Recent in vitro studies indicate that a similar pathway may be relevant to the human and rabbit corpus cavernosum as well *(43,44)* and, moreover, that this pathway may be a physiologically relevant target of the endogenous NO cascade that is thought to be the primary stimulus for relaxation of corporal smooth muscle and penile erection *(45)*. Consistent with such a possibility, the expression of Rho A was shown to be approx 17-fold greater in the corpora than in physiologically distinct smooth muscles such as ileum, portal vein, femoral artery, or bladder *(44)*. In addition, two isoforms of Rho kinase, the myosin phosphatase regulatory subunit (MYPT-1), the myosin phosphatase catalytic subunit (PP1∂), and the phosphatase inhibitor CPI-17 have all been identified in human and rabbit corpus cavernosum *(44)*. Rho A and Rho kinase have also been demonstrated in rat corporal tissue *(46)*. The main physiologic implication of these observations is that during flaccidity, Rho kinase activity is at a relatively high level in the corpora, and, therefore, inhibition of this level of activity *per se* is a prerequisite to the erectile process. Other recent publications have discussed the physiologic, pathophysiologic, and therapeutic possibilities of this recently discovered pathway to erectile capacity *(47,48)*; however, this is not further discussed herein.

Recently, compelling evidence has been uncovered for the presence of an additional novel pathway to the control of penile erection—the guanylyl cyclase B pathway—as well as the potential involvement of the β_3-adrenergic receptor. Not much is yet known about these pathways, but some mention of their potential importance to the erectile process is relevant to this article.

Guanylyl Cyclase B Pathway

The importance of the NO/guanylate cyclase/cGMP/PKG pathway to erection is unequivocal. However, in addition to soluble guanylate cyclase, recent publications also indicate that corporal tissue expresses a particulate or membrane-bound form of guanylate cyclase as well *(49)*. Of the known isoforms of particulate guanylate cyclase, the most prominent in corporal tissue appears to be guanylate cyclase B (GC-B). The GC-B isoform is linked to cellular activation via C-type natriuretic peptide (i.e., CNP). CNP, in turn, is coupled to the intracellularly located GC-B in the corpora by virtue of activation of the extracellularly located natriuretic peptide receptor (NPR) 2 or B. As recently pointed out *(50)*, there is now evidence in rat, rabbit, and human corporal tissue that CNP elicits increases in cGMP levels via occupancy of the putative NPR 2 or B receptor and, thus, stimulation of the GC-B. These exciting initial observations further highlight the biochemical complexity of penile erection and may provide yet another useful strategy for the development of improved therapies for ED.

β_3-Adrenergic Receptor Pathway

In another recent article, Cirino et al. *(51)* emphasized the potential importance of the β_3-adrenergic receptor to the erectile process. In fact, as they pointed out, the β_3-adrenergic receptor subtype in the sympathetic nervous system has been well characterized and, furthermore, is known to play a major role in lipolysis. In this initial report, the investigators provided evidence that the β_3-adrenergic receptors present in human corpus cavernosum are able to relax corporal smooth muscle via a cGMP-dependent, but NO-independent phosphorylation pathway that apparently involves inhibition of the Rho kinase pathway.

Biochemical Mechanisms of Corporal Smooth Muscle Contraction and Relaxation: Summary and Conclusions

Despite the plethora of mechanisms available for cellular activation and the corresponding intracellular biochemical and physiologic cascade that they initiate, there are still some obvious common denominators involved in contraction and relaxation and, thus, modulation of the erectile process. For example, activation of the G_q/PLC/IP_3/DAG/PKC pathway can occur via the α_1-adrenergic or ET_A receptor subtypes. However, in both instances, cellular activation leads to increased corporal smooth muscle contraction via the physiologic sum of the impact of these intracellular messengers on transmembrane calcium flux (i.e., phosphorylation of L-type VDCCs and increased activity), liberation of intracellular calcium stores (via activation of the IP_3 receptor), alterations in ion channel activity (again, increases in Ca channel activity and decreases in K channel activity), and their corresponding effects on the Rho A/Rho kinase pathway (i.e., calcium sensitization). By contrast, activation of the G_s/adenylate cyclase/cAMP/PKA pathway, or the NO/guanylate cyclase/cGMP/PKG pathway, leads to decreased corporal SMC contraction via a combination of effects on these same targets, but in the exact opposite direction, and with physiologically antagonistic effects (see Fig. 2).

One final consideration with respect to the biochemistry and physiology of erection is the absolute importance of

syncytial corporal smooth muscle responses to erection, detumescence, and flaccidity. Therefore, we next review the mechanistic basis for intercellular communication among corporal SMCs, and its absolute importance to the erectile process.

Importance of Intercellular Communication Through Gap Junctions to Coordination of Erectile Response

Normal erection and detumescence require the rapid coordination of corporal SMC responses to activation by a limited source of neuronal effectors. Therefore, some mechanism must exist to ensure that the corporal SMCs behave as a functional, syncytial cellular network. Over the past decade, a series of publications *(52–61)* has outlined how intercellular communication through gap junction channels appears to provide the requisite anatomic substrate for this purpose. In fact, gap junctions are aqueous intercellular channels that provide partial cytoplasmic continuity between adjacent corporal SMCs. Each cell of a pair expresses a hexamer of presumably identical connexin proteins (i.e., a gap junction hemichannel or connexon), and the union of two connexons across the extracellular space serves as the gap junction channel. At the electron microscopic level, gap junction plaques are the recognizable hallmark of the concentration of hundreds to thousands of closely packed gap junction channels between two cells. Small junctional plaques (i.e., generally ≤0.25 μ*M*) are typically observed in human corporal tissue *(54)*. The constituent connexins comprise a rather large gene family, of which there are more than 16 known members, and all of the connexins are commonly named according to their putative molecular weights, ranging from as little as 26 to 57 kDa. Of the various connexin isoforms, Connexin43 (Cx43) is the primary one present and relevant to the function of corporal smooth muscle. Cx43 is relatively freely permeable to all of the second-messenger molecules/ions that regulate corporal SMC tone and, furthermore, has a mean open time of ≈0.5–1.0 s, a corresponding open probability of ≈85%, and a unitary conductance of ≈100 pS *(53–57)*. As such, Cx43-derived gap junction channels provide a relatively nonselective conduit that is quite well suited for its role in modulating the intercellular diffusion of physiologically relevant second-messenger molecules and ions. Certainly, gap junctions provide an important mechanism for coordinating corporal SMC responses and, thus, ensuring penile erection and detumescence.

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References

1. NIH Consensus Development Panel on Impotence. (1993). *JAMA* **270,** 83–90.
2. Benet, A. E. and Melman, A. (1995). *Urol. Clin. North Am.* **22,** 699–709.
3. Feldman, H. A., Goldstein, I., Hatzichristou, D. G., Krane, R. J., and McKinlay, J. B. (1994). *J. Urol.* **151,** 54–61.
4. Christ, G. J. (1995). *Urol. Clin. North Am.* **22,** 727–745.
5. Moreland, R. B., Hsieh, G., Nakane, M., and Brioni, J. D. (2001). *J. Pharmacol. Exp. Ther.* **296(2),** 225–234.
6. Andersson, K.-E. (2001). *Pharmacol. Rev.* **53(3),** P417–P450.
7. Fournier, G. R. Jr., Juenemann, K. P., Lue, T. F., and Tanagho, E. A. (1987). *J. Urol.* **137,** 163–167.
8. Banya, Y., Ushiki, T., Takagane, H., et al. (1989). *J. Urol.* **142,** 879–883.
9. Lue, T. F. and Tanagho, E. A. In: *Contemporary management of impotence and infertility.* Tanagho, E. A., Lue, T. F., and McClure, R. D. (eds.). Williams & Wilkins: Baltimore.
10. Lue, T. F. (2000). *N. Engl. J. Med.* **342,** 1802–1813.
11. Andersson, K. E. and Wagner, G. (1995). *Physiol. Rev.* **75,** 191–236.
12. Saenz de Tejada, I., Kim, N., Lagan, I., Krane, R. J., and Goldstein, I. (1989). *J. Urol.* **142,** 1117–1121.
13. Italiano, G., Calabrò, A., Spini, S., Ragazzi, E., and Pagano, F. (1998). *Urol. Res.* **26,** 39–44.
14. Christ, G. J., Lerner, S. E., Kim, D., and Melman, A. (1995). *J. Urol.* **153,** 1998–2003.
15. Mills, T. M., Pollock, D. M., Lewis, R. W., Branam, H. S., and Wingard, C. J. (2001). *Am. J. Physiol.* **281,** R476–R483.
16. Saenz de Tejeda, I., Carson, M. P., de las Morenas, A., Goldstein, I., and Traish, A. M. (1991). *Am. J. Physiol.* **261,** H1078–H1085.
17. Kim, D. C., Gondre, C. M., and Christ, G. J. (1996). *Int. J. Impot. Res.* **8,** 17–24.
18. Saenz de Tejada, I., Goldstein, I., Azadzoi, K., Krane, R. J., and Cohen, R. A. (1989). *N. Engl. J. Med.* **320,** 1025–1030.
19. Ignarro, L. J., Bush, P. A., Buga, G. M., Wood, K. S., Fukuto, J. M., and Rajfer, J. (1990). *Biochem. Biophys. Res. Commun.* **170,** 843–850.
20. Karicheti, V. and Christ, G. J. (2001). *Curr. Drug Targets* **2,** 1–20.
21. Noack, T. and Noack, P. (1997). *World J. Urol.* **15(1),** 45–49.
22. Malysz, J., Gibbons, S. J., Miller, S. M., et al. (2001). *J. Urol.* **166(3),** 1167–1177.
23. Davies, K. P., Desai, P., Day, N., Melman, A., and Christ, G. J. (2002). *J. Urol.* **167(4), (Suppl.),** 236.
24. Christ, G. J. (2002). *J. Androl.* **23(5),** S10–S19.
25. Christ, G. J., Spray, D. C., and Brink, P. R. (1993). *J. Androl.* **14,** 319–328.
26. Fan, S.-F., Brink, P. R., Melman, A., and Christ, G. J. (1995). *J. Urol.* **153,** 818–825.
27. Lee, S. W., Wang, H.-Z., Zhao, W., Ney, P., Brink, P. R., and Christ, G. J. (1999). *Int. J. Impot. Res.* **11,** 179–188.
28. Lee, S. W., Wang, H.-Z., and Christ, G. J. (1999). *Int. J. Impot. Res.* **11,** 189–199.
29. Wang, H.-Z., Lee, S. W., and Christ, G. J. (2000). *Int. J. Impot. Res.* **12,** 9–18.
30. Spektor, M., Rodriguez, R., Rosenbaum, R. S., Wang, H.-Z., Melman, A., and Christ, G. J. (2002). *J. Urol.* **167,** 2628–2635.
31. Venkateswarlu, K., Giraldi, A., Zhao, W., et al. (2002). *J. Urol.* **168,** 355–361.
32. Lawson, K. and Dunne, M. J. (2001). *Expert Opin. Invest. Drugs* **10(7),** 1345–1359.
33. Christ, G. J., Brink, P. R., Melman, A., and Spray, D. C. (1993). *Int. J. Impot. Res.* **5,** 77–96.
34. Christ, G. J., Moreno, A. P., Melman, A. P., and Spray, D. C. (1992). *Am. J. Physiol.* **263,** C373–C383.
35. Zhao, W. and Christ, G. J. (1995). *J. Urol.* **154,** 1571–1579.
36. Christ, G. J. and Melman, A. (1997). *Mol. Urol.* **1,** 45–54.
37. Christ, G. J., Maayani, S., and Melman, A. (1990). *Br. J. Pharmacol.* **101,** 375–381.

38 Fan, S.-F., Christ, G. J., Melman, A., and Brink, P. R. (1999). *Int. J. Impot. Res.* **11,** 1–7.
39 Karkanis, T., DeYoung, L., Brock, G. B., and Sims, S. (2003). *J. Appl. Physiol.* **94,** 301–313.
40 Krall, J. F., Fittingoff, M., and Raifer, J. (1988). *Biol. Reprod.* **39(4),** 913–922.
41 Sanders, K. M. (2001). *J. Appl. Physiol.* **91,** 1438–1449.
42 Chitaley, K., Wingard, C. J., Webb, R. C., et al. (2001). *Nat. Med.* **7,** 119–122.
43 Rees, R. W., Ralph, D. J., Royle, M., Moncada, S., and Cellek, S. (2001). *Br. J. Pharmacol.* **133,** 455–458.
44 Wang, H., Eto, M., Steers, W. D., Somlyo, A. P., and Somlyo, A. V. (2002). *J. Biol. Chem.* **277,** 30614–30621.
45 Mills, T. M., Chitaley, K., Lewis, R. W., and Webb, R. C. (2002). *Eur. J. Pharmacol.* **439,** 173, 174.
46 Mills, T. M., Chitaley, K., Wingard, C. J., Lewis, R. W., and Webb, R. C. (2001). *J. Appl. Physiol.* **91,** 1269–1273.
47. Andersson, K.-E. (2003). *J. Urol.* **170 P,** S6–S14.
48 Jin, L., Linder, A. E., Mills, T. M., and Webb, R. C. (2003). *Expert Opin. Ther. Targets* **2,** 265–276.
49 Kuthe, A., Reinecke, M., Uckert, S., et al. (2003). *J. Urol.* **169,** 1918–1922.
50 Christ, G. J. (2003). *J. Urol.* **169,** 1923.
51 Cirino, G., Sorrentino, R., d'Emmanuelr di Villa Bianca, R., et al. (2003). *PNAS* **100,** 5531–5536.
52. Christ, G. J., Moreno, A. P., Gondre, C. M., et al. In: *Progress in cell research,* vol. 3. Hall, J. E., Zampighi, G. A., and Davis, R. M. (eds.). Elsevier: Amsterdam.
53 Moreno, A. P., Campos de Carvalho, A. C., Christ, G. J., Melman, A., and Spray, D. C. (1993). *Am. J. Physiol.* **264,** C80–C92.
54 Campos de Carvalho, A. C., Moreno, A. P., Christ, G. J., et al. (1993). *J. Urol.* **149,** 1568–1575.
55 Christ, G. J., Brink, P. R., and Ramanan, S. V. (1994). *Biophys. J.* **67,** 1335–1344.
56. Christ, G. J., Spray, D. C., El-Sabban, M., Moore, L. K., and Brink, P. R. (1994). *Sci. Today (Braz.)* **18,** 80–86.
57 Brink, P. R., Ramanan, S. V., and Christ, G. J. (1996). *Am. J. Physiol.* **271,** C321–C331.
58 Lagaud, G., Davies, K. P., Venkateswarlu, K., and Christ, G. J. (2002). *Curr. Drug Targets* **3,** 427–440.
59 Serels, S., Day, N. S., Wen, Y. P., et al. (1998). *Int. J. Impot. Res.* **10,** 1–9.
60 Ramanan, S. V., Brink, P. R., and Christ, G. J. (1998). *J. Theor. Biol.* **193,** 69–84.
61. Melman, A. and Christ, G. J. (2002). *Heart Dis.* **4(4),** 252–264.