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Role of Adenosine Signaling in Penile Erection and Erectile Disorders

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Abstract

Introduction—Penile erection is a hemodynamic process, which results from increased flow and retention of blood in the penile organ due to the relaxation of smooth muscle cells. Adenosine, a physiological vasorelaxant, has been shown to be a modulator of penile erection.

Aim—To summarize the research on the role of adenosine signaling in normal penile erection and erectile disorders.

Main Outcome Measures—Evidence in the literature on the association between adenosine signaling and normal and abnormal penile erection, i.e., erectile dysfunction (ED) and priapism.

Methods—The article reviews the literature on the role of endogenous and exogenous adenosine in normal penile erection, as well as in erectile disorders namely, ED and priapism.

Results—Adenosine has been shown to relax corpus cavernosum from various species including human in both in vivo and in vitro studies. Neuromodulatory role of adenosine in corpus cavernosum has also been demonstrated. Impaired adenosine signaling through A_{2B} receptor causes partial resistance of corpus cavernosum, from men with organic ED, to adenosine-mediated relaxation. Increased level of adenosine has been shown to be a causative factor for priapism.

Conclusion—Overall, the research reviewed here suggests a general role of exogenous and endogenous adenosine signaling in normal penile erection. From this perspective, it is not surprising that impaired adenosine signaling is associated with ED, and excessive adenosine signaling is

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associated with priapism. Adenosine signaling represents a potentially important diagnostic and therapeutic target for the treatment of ED and priapism.

Keywords

Adenosine; Penile Erection and Erectile Physiology; Erectile Disorders; Adenosine Receptor; Priapism; Erectile Dysfunction

Introduction

The tone of arterial and cavernous smooth muscle cells is a key regulator of penile erection, and is determined by the balance of relaxants and constrictors [1]. Nitric oxide (NO) is the principal mediator of penile erection [2], but that does not exclude a role of other signaling molecules, either released by neurons, and/or endothelial and smooth muscle cells in the regulation of the process.

One such mediator is adenosine. Adenosine triphosphate (ATP) and its metabolite, adenosine have long been of interest as modulators of penile erection [3]. Considerable work has been carried out to show that ATP and especially adenosine act as relaxants of corpus cavernosa in vitro [4–7]. Recent work has revealed novel roles of adenosine in penile function, such as a modulator of adrenergic neurotransmission, and a causative factor for erectile disorder called priapism [8,9]. In light of these interesting discoveries, it is necessary to critically look at the research on the role of adenosine signaling in erectile physiology. This review starts with a brief introduction of penile physiology and adenosine metabolism, followed by an extensive overview of adenosine signaling in penile erection and erectile disorders.

Physiological Control of Penile Erection and Flaccidity

Anatomy of Penile Organ

The penis contains three cylindrical tissues: the ventral corpus spongiosum and dorsally a pair of corpus cavernosum [10]. The corpus cavernosum (CC) contains open spaces called sinusoids, which are surrounded by smooth muscle cells [11,12]. Blood is supplied to the CC by cavernous arteries, which penetrate the tunica albuginea and enter the CC. Cavernosal arteries branch into resistant arteries called helicine arteries, which feed directly into sinusoidal spaces. The blood from the sinusoids is drained into subtunical venules that coalesce just beneath the tunica albuginea [12,13].

Penile flaccidity and erection are regulated by multiple cellular systems including neuronal, vascular, endothelial, and smooth muscle cells.

Regulation of Penile Flaccidity

Generally, for about 23 hours of the day, the penis in most men is in the flaccid state [14]. During this state, smooth muscle cells of penile arteries and CC are contracted. The flaccidity is mainly maintained by tonic release of noradrenaline through the rich sympathetic innervation of penile smooth muscles. Noradrenaline contracts smooth muscle cells in penile arteries and CC, thereby increasing vascular resistance and collapsing sinusoidal spaces, respectively [3].

Regulation of Penile Erection

During penile erection, vascular smooth muscle relaxation decreases vascular resistance, thereby increasing blood flow through cavernous and helicine arteries, filling sinusoids, which are expanded due to the relaxation of smooth muscle cells in the CC. This results in an increase in intracavernosal pressure and compression of subtunical veins against tunica albuginea,

thereby restricting outflow of blood from CC and entrapping pressurized blood in the CC [12].

Even though NO, released during nonadrenergic, noncholinergic (NANC) neurotransmission and from endothelium, is the principal relaxant of the penile smooth muscle cells, multiple other factors, either neuronal or vascular in origin, have also been shown to modulate penile erection [3,15–18]. Adenosine, like NO, is a potent vasodilator and has long been implicated in the regulation of penile erection.

Adenosine Metabolism

Adenosine is formed continuously by degradation of adenine nucleotides, intracellularly and extracellularly. Under normal physiological conditions, intra- and extracellular levels of adenosine are in nanomolar range, but they rise into millimolar concentrations under stressful conditions like hypoxia, ischemia, and cellular damage. Intracellularly, adenosine is formed predominantly by dephosphorylation of adenosine monophosphate (AMP), catalyzed by intracellular 5'-nucleotidase. Hydrolysis of s-adenosyl-homocysteine also contributes to intracellular adenosine formation [19]. Inside the cell, adenosine is catabolized by two enzymes, adenosine kinase (ADK) and adenosine deaminase (ADA). ADK phosphorylates adenosine to AMP, and is critical for regulating intracellular levels of adenosine and maintaining intracellular levels of nucleotides. ADA catalyses irreversible conversion of adenosine to inosine. Under normal conditions, ATP is degraded to adenosine, but under cellular stress ATP degradation increases. Intracellular adenosine homeostasis is also maintained by bi-directional equilibrative nucleoside transporters (ENT) in the plasma membrane, through facilitated diffusion of adenosine in the direction of concentration gradient [19]. Adenosine is also generated extracellularly by degradation of adenine nucleotides. ATP is released from neurons as neurotransmitters, and also released from cells through connexin hemichannels, and when the cell membrane is subjected to mechanical stress [20]. Intracellular ATP levels are in millimolar range; hence, when the cell membrane is damaged, extracellular ATP levels increase. Extracellular adenine nucleotides are dephosphorylated by ectonucleotidases. Ectonucleotidases such as CD39, hydrolyse ATP and ADP to AMP. Ecto-5'-nucleotidase (CD73) catalyses dephosphorylation of AMP to adenosine [21]. Extracellular adenosine is transported into the cells through ENT, depending upon concentration gradient, and is also degraded to inosine by extracellular ADA [19]. Adenosine metabolism is depicted in Figure 1.

Role of Adenosine in Penile Erection

Many studies, both in vivo and in vitro, implicating adenosine as a modulator of penile erection in multiple species, will be reviewed in this section and are summarized in Table 1.

In Vivo Studies

Studies in dog showed that intracavernous injection of adenosine (0.67–15 µg/kg B.W.) induced a full erection, which was independent of acetylcholine effect [25]. Consistently, Takahashi et al. [26] further investigated the hemodynamic effect of intracavernous injection of adenosine in dogs. They found that adenosine increased arterial blood flow and intracavernous pressure (ICP) thereby inducing penile erection in a dose dependent manner (10–100 µg) [26]. Adenosine-mediated increased ICP was potentiated by pretreatment with equilibrative nucleoside transporter inhibitor (dipyridamole at 100 µg) and was significantly decreased by nonselective adenosine receptor antagonist theophylline at 1 mg [26]. These studies indicate that adenosine is capable of inducing penile erection via its receptor. Subsequently, Takahashi et al. [26] further observed that upon intracavernous co-injection of adenosine (minimum dosage to increase ICP: 27.8 µg) and acetylcholine (minimum dosage to

increase ICP: 9.5 μ g) the erectile effects were synergistic but not additive. These findings imply that adenosine-mediated penile erection is likely via a different mechanism from that of acetylcholine. Noto et al. [27] also reported dose-dependent increase in ICP upon intracavernous adenosine injection (0.1–1 mM). This increase in ICP was abolished by pretreatment with 8-(p-sulphophenyl) theophylline (8-SPT; 0.1 mM), a nonspecific adenosine receptor antagonist. Overall, these studies demonstrate that adenosine is capable of inducing penile erection via adenosine receptor signaling.

In Vitro Studies

Wu et al. [4] reported adenosine induced relaxation of CC of rabbit, both under base-line tension and precontraction (0.1–1 mM). This observation was substantiated by multiple other studies in rabbit [6,22–24]. More importantly, Chiang et al. [24] observed inhibition of nerve stimulated contraction of corpus cavernous strips of rabbit by adenosine and its analogs (5'-N-ethyl-carboxamidoadenosine [NECA] or R-phenylisopropyl-adenosine) in a dosage-dependent way (from 10^{-5} to 10^{-2} M). In this study, the authors also reported inhibition of noradrenaline-induced contraction of corpus cavernosum by adenosine and its analogs. Thus, these studies indicate that adenosine, a potent vasodilator, induces CC relaxation under cavernosal nerve stimulation. Supporting this finding, Mantelli et al. [6] found adenosine (3 μ M–3 mM) to be more potent relaxant than acetylcholine in rabbit corpus cavernous strips as adenosine completely relaxed the precontracted corpus cavernous strips (CCS), while acetylcholine did not. In agreement with Mantelli et al. [6], Filippi et al. [7] observed that adenosine relaxed the precontracted human CCS in a dosage dependent manner and the highest concentration (3 mM) almost completely relaxed the tissue. Similarly, adenosine (100 μ M) and its analogs (such as NECA 10 μ M) have also been found to induce relaxation in CCS from humans and mice [7–9,28,29].

Taken together, both in vitro and in vivo studies demonstrate that adenosine is capable of inducing relaxation in CC and even erection in multiple species.

Role of Adenosine Receptors in Penile Erection

Extracellular adenosine affects physiological processes by signaling through four different receptors; A₁, A_{2A}, A_{2B}, and A₃. All four receptors are G-protein coupled. A₁ and A₃ couple to inhibitory G-protein, G_i, to inhibit adenylyl cyclase that results in decreased cyclic AMP [30] levels, intracellularly. A_{2A} and A_{2B} couple to stimulatory G-protein, G_s, to activate adenylyl cyclase that results in increased cyclic AMP (cAMP) levels intracellularly [19]. The expression of adenosine receptors in penile tissue and the role of adenosine signaling via its receptor in penile physiology will be thoroughly reviewed in this section.

Expression of Adenosine Receptors in Corpus Cavernosum

There are limited studies available to directly characterize adenosine receptor expression profile in CC. Filippi et al. [7] demonstrated the presence of the A₂ adenosine receptors in human CC by employing binding studies, which is by far the only attempt to characterize the adenosine receptors in penis using this method. Filippi et al. [7] used ¹²⁵I-labeled 2-[4-(2-[2-(4-aminophenyl)methyl carbonylamino]ethylaminocarbonyl)-ethyl) phenyl]ethylamino-5'-N-ethylcarboxamido adenosine ([¹²⁵I] PAPA-APEC), an A₂ selective agonist to characterize A₂ receptors in Human CC. They found a single class of high affinity, low capacity binding sites. In a competition binding experiment PAPA-APEC binding was completely displaced by adenosine and an A_{2a} selective agonist CGS21680. In this study, the author reported that CGS21680 shows higher affinity than adenosine. This binding profile fits the presence of A_{2a} receptors at a low density.

Employing real-time polymerase chain reaction technique, Mi et al. [9] showed A_{2B} to be the predominant receptor subtype, expressed in corpus cavernous smooth muscle cells of mice at an mRNA level. Relatively low-level expression of A_{2A} was detected, while mRNA of A₁ and A₃ were nondetectable. More work needs to be done employing techniques, such as immunohistochemistry and western-blot, to study the expression profile of receptor subtypes in constituent cells as well as in whole organ at a protein level, which is functionally more relevant.

Adenosine Receptors Involved in Adenosine Induced Relaxation of Corpus Cavernosum

There is a sizable amount of work employing pharmacological tools to identify, which adenosine receptor is involved in adenosine mediated relaxation of CC. For example, Mantelli et al. [6] reported that relaxant effect of exogenously added adenosine in rabbit CC is mediated by activation of A₂ receptors, which was further substantiated by numerous studies in multiple species [7–9,22,27–29]. Based on the potency of receptor subtype specific agonist and the effect of receptor subtype specific antagonists, Mantelli et al. [6] suggested involvement of A_{2A} receptor in adenosine induced relaxation of rabbit CC. Filippi et al. [29] and Noto et al. [27] also implicated a role of A_{2A} in adenosine induced relaxation in CC of rabbit and dog, respectively.

In human, Faria et al. [28] demonstrated involvement of A₂ receptors in adenosine induced relaxation of human CC, using A₂ subtype selective agonists and antagonists. An A_{2A} selective agonist (CGS21680c), at saturation concentration, could induce about 50% of the maximum relaxation induced by adenosine analog, NECA, a nonselective adenosine receptor agonist. The relaxation caused by NECA was significantly inhibited by pretreatment of human CCS with A_{2B} selective antagonist (MRS1706), but had no significant effect on the relaxation induced by A_{2A} selective agonist (CGS21680c). Pretreatment with an A_{2A} selective antagonist (ZM241385), with an appreciable affinity for A_{2B}, significantly inhibited relaxation caused by both, A_{2A} selective agonist (CGS21680c) and NECA. Based on these results, the authors suggested involvement of both, A_{2A} and A_{2B} receptors in adenosine induced relaxation of human CC [28]. This observation is very much in agreement with the one reported by Tostes et al. [8], who also observed adenosine induced relaxation in mouse CC to be mediated through activation of both, A_{2A} and A_{2B} receptors.

In addition to pharmacological approaches, genetic studies have recently been performed by Mi et al. [9]. In this study, using adenosine receptor deficient mice, Mi et al. [9] observed complete absence of adenosine mediated relaxation in CCS from A_{2B} receptor knockout mice, while CCS from A₁, A_{2A}, and A₃ knockout mice and wild type mice showed a dose-dependent increase in relaxation. Thus, both genetic and pharmacological studies provide strong evidence that adenosine induced relaxation of CC is mediated through A₂ receptors in multiple species.

Adenosine Receptors Involved in Adenosine Mediated Neuromodulation in Corpus Cavernosum

Adenosine modulates release of neurotransmitters as well as their effects, both in the central and peripheral nervous system [31]. This neuromodulatory role of adenosine has been demonstrated in CC of different species.

In an in vivo study in dogs, Takahashi et al. [25] found the cavernous nerve stimulation induced erectile response to be enhanced by pretreatment with ENT inhibitor, dipyridamole, and was reduced by pretreatment with nonselective adenosine receptor antagonist theophylline. This observation along with the finding that upon intracavernous co-injection of adenosine and acetylcholine, the pro-erectile effects were synergistic, but not additive, prompted Takahashi et al. [25] to propose that adenosine plays a cooperative role with acetylcholine, and that it has

a physiological role as a neuromodulator in canine penile erection. In agreement with the results of Takahashi et al. [25], Mi et al. [9] reported that reducing the adenosine levels in vivo by ADA injection, resulted in a significant decrease in electric field stimulation (EFS) induced relaxation of CCS of mice. The results reported by Chiang et al. [24] further supported the role of adenosine as a neuromodulator in a penile erection. In this study, adenosine and its analogs inhibited nerve stimulated contraction of CCS of rabbit. Based on the potency order, the authors suggested involvement of A₂ receptor signaling in the neuromodulation. In support of their conclusion, Chiang et al. [24] observed that A₂ receptor antagonist abolished EFS induced relaxation. Chiang et al. [24] also reported inhibition of noradrenaline induced contraction of CC by adenosine and its analogs. Based on these results, Chiang et al. [24] indicated that modulation of adrenergic effects by adenosine in CC is through post-junctional receptors. The rank order of potency of adenosine and its analogs in inhibiting noradrenaline- and EFS-induced contraction of CC, and the observation that A₂ receptor antagonist abolished EFS induced relaxation, but A_{2A} selective agonist, had no effect on noradrenaline induced contraction, led the authors to conclude that the adenosine receptor involved in neuromodulation of relaxation of rabbit CC is of A_{2B} type.

In contrast to Chiang et al. (1994), Tostes et al. [8] showed the involvement of A₁ receptor in the modulation of neuronally induced contraction by endogenous adenosine. Endogenously generated adenosine was found to inhibit EFS induced contraction, which was sympathetic in origin and adrenergic in nature, in mouse CCS. Both, A_{2A} and A_{2B} receptors were found to have no role in neuronal modulation. On the other hand, A₁ receptor selective antagonist abolished the inhibitory effect of endogenous adenosine. Adenosine is known to inhibit release of noradrenaline from sympathetic nerves through activation of presynaptic A₁ receptors [32,33]. A direct experimental evidence for adenosine-mediated inhibition of noradrenaline release in CC, will unequivocally establish neuromodulatory role of adenosine in penile erection.

Adenosine Mediated Intracellular Signaling in Corpus Cavernous Relaxation

Adenosine is a potent endogenous vasodilator. Adenosine induced vasodilation is considered to be mediated by increasing intracellular cyclic AMP [30] levels in vascular smooth muscle cells through A₂ receptor signaling [34]. The section below will review the intracellular signaling mechanisms involved in adenosine mediated smooth muscle relaxation and penile erection by focusing on two key intracellular second messengers, cAMP and cyclic guanosine monophosphate (cGMP). cAMP and cGMP activate their respective downstream protein kinases, protein kinase A (PKA) and protein kinase G (PKG), which in turn phosphorylate their downstream targets, resulting in a decrease in intracellular Ca⁺² concentration, leading to smooth muscle relaxation [35]. PKG also contributes to smooth muscle relaxation, by phosphorylating RhoA and inhibiting RhoA-Rho kinase signaling pathway, an important signaling mechanism involved in mediating smooth muscle contraction in penis [35,36]. Working model of adenosine mediated intracellular signaling in CC is shown in Figure 2.

Adenosine Induced cAMP in Corpus Cavernosum via Adenosine Receptor Activation—Using genetic approaches, Mi et al. [9] demonstrated that adenosine through A_{2B} receptor leads to cAMP induction in mouse CC. Consistent with genetic findings, the authors observed that EFS induced cAMP generation in mouse CC is completely blocked by A_{2B} receptor antagonist [9]. Finally, the authors demonstrated that adenosine-mediated cAMP induction was completely abolished in the corpus cavernosal smooth muscle cells (CCSMCs) purified from A_{2B} receptor deficient mice. Pharmacological studies further supported the genetic finding that adenosine-mediated cAMP induction is via A_{2B} receptor signaling in CCSMCs [9].

Role of NO and cGMP in Adenosine Induced Relaxation of Corpus Cavernosum

—Adenosine induced vasodilation is considered to be endothelium independent. However, accumulating evidence indicates a role of endothelium derived NO in adenosine induced vasodilation [37–39]. Adenosine induces NO synthesis in endothelial cells through A₂ receptor signaling [40–43]. Few studies have demonstrated the role of NO signaling in adenosine mediated CCS relaxation. For example, in human CC, Faria et al. [28] reported that adenosine-mediated CC relaxation is partially dependent on endothelial derived NO, and induction of NO synthesis is most likely mediated through A_{2B} receptor signaling. In rabbit, Chiang et al. [24] also indicated that adenosine induced relaxation in CCS is partly endothelium dependent. In addition to these studies, we have recently provided both, genetic and pharmacological evidence for adenosine induced generation of cGMP, the down-stream second messenger of NO signaling, via A_{2B} receptor in mouse CCS. However, adenosine does not stimulate cGMP generation in CCSMCs, suggesting that in the CC of mice adenosine may induce NO synthesis in non muscle cells, and the possible cellular target may be the endothelial cells [9]. Using EFS to mimic normal, physiological penile erection, the authors further found that EFS-induced cGMP generation in mouse CCS is also partially dependent upon A_{2B} receptor signaling in a NO dependent manner [9]. This observation suggests that endogenous adenosine may play a part in facilitating mouse penile erection. Based on the above information, adenosine induced relaxation of CC may partly depend upon NO synthesis, most probably mediated through A_{2B} receptors on the endothelial cells.

Thus, exogenous and endogenous adenosine through A_{2B} receptor mediates induction of both, cAMP and cGMP synthesis in mouse CC, but the cellular targets are different. It is important to determine how much each signaling cascade, cAMP and cGMP, triggered by adenosine, contributes to smooth muscle relaxation and eventually penile erection.

Role of Adenosine in ATP Induced Corpus Cavernous Relaxation

After the suggestion that NANC neurotransmission plays a role in penile erection [44], and before it was established that NO was the major NANC neurotransmitter [45], a lot of interest was generated in ATP, as a potential candidate for NANC neurotransmitter in penile tissue, in the early 90s. ATP was described earlier, as a potential NANC neurotransmitter [46,47]. A sizeable amount of work has been carried out to evaluate the modulatory role of ATP in penile erection [4,5,22,23,27,29,48–52]. In many studies, relaxant effects of ATP on CC were found to be attributable to its metabolite, adenosine. For example, Ragazzi et al. [23] observed the ATP induced relaxation in rabbit CC to be independent of P2Y receptor signaling, which is known to mediate vasorelaxation by ATP [53,54]. This observation, along with the fact that in the same study adenosine concentration dependently induced relaxation of precontracted CC, prompted the authors to hypothesize that the effects of ATP were mediated by adenosine, derived from ATP metabolism, acting through adenosine receptors. Similarly, Filippi et al. [29] also reported that the smooth muscle relaxant effect of ATP in rabbit CC is partly mediated by adenosine acting through A_{2A} receptors. The role of adenosine in ATP induced relaxation of penile tissue is supported by yet another study [27]. The work was carried out in vivo in dogs. Tumescence upon intracavernous injection of ATP was abolished by pretreatment with 8-SPT, a nonspecific adenosine receptor antagonist, indicating that adenosine derived from metabolic breakdown of ATP was responsible for the relaxing effect of ATP [27]. Overall, evidence from multiple studies demonstrates that part of the relaxant effect of ATP in CC is mediated by its metabolite adenosine.

Role of Adenosine Signaling in Erectile Disorders

Along with normal penile erection, adenosine signaling has also been found to be critical in erectile disorders, viz. erectile dysfunction (ED) and priapism. Studies evaluating role of adenosine signaling in erectile disorders are summarized in Table 2.

ED

ED is characterized by the inability to develop or maintain an erection sufficient to permit satisfactory sexual intercourse [17]. Based on the causes, ED is classified into psychogenic and organic. Causes of organic ED could be neurogenic, hormonal, or vasculogenic in nature. Organic ED could also be a result of aging or other systemic disease such as diabetes and chronic renal failure [17].

Response of ED Corpus Cavernosum to Adenosine—Few studies have been carried out to evaluate the response of CC, from men with organic ED and CC from animal models for diseases, which lead to ED, to adenosine [28,55–58]. Gur and Ozturk [56] studied the response of CC from diabetic and non-diabetic impotent men. They observed enhanced sensitivity of CC from diabetic men to adenosine-induced relaxation compared to CC from non-diabetic men. An enhanced response, but not sensitivity to adenosine was noted in diabetic rats compared to nondiabetic rats. The extent of relaxation induced by adenosine in CC from men with and without diabetes was greater than in rats with and without diabetes [56]. The authors suggest a greater role as a modulator for adenosine in human CC than in the corporeal tissue of rats [56]. Carneiro et al. [57] reported preservation of adenosine induced relaxation in CC from an obese and type II diabetic mouse compared to control, but did not observe any enhancement. Their results are in agreement with Ayan et al. [55], who observed similar results in CC from diabetic rabbits and controls. This group [57], in agreement with their earlier report on the neuromodulatory role of adenosine in CC of mouse [8], further observed inhibition of contractile response in CC, induced by electric stimulation of adrenergic nerves, by endogenous adenosine through A₁ receptor in the obese and diabetic mouse. The results reported by Carneiro et al. [57] are also in agreement with Kilicarslan et al. [58], who also observed adenosine induced relaxation of CC of rabbit to be unchanged by chronic renal failure. Similar results were also reported in CC of hypothyroid rabbits with significantly reduced levels of testosterone [60]. It is interesting to note that additional testosterone therapy shows no effect on the response of CC to adenosine in rabbit [62]. In all these conditions, diabetes, chronic renal failure, and hypothyroidism, impairment of nonadrenergic noncholinergic neurotransmission and endothelial dysfunction seem to contribute toward ED [57,58,60], but adenosine induced relaxation of CC is preserved, indicating a potential therapeutic role for adenosine.

In contrast to the above studies, Faria et al. [28] observed partial resistance of CC from men with vasculogenic impotence to adenosine induced relaxation and showed that dysfunctional A_{2B} receptors, supposedly on the endothelium, are the cause for the signaling impairment. They suggested targeting A_{2A} receptors, supposedly on the smooth muscle cells, as a treatment for vasculogenic ED.

Adenosine as a Treatment for ED—Adenosine, due to its vasorelaxant properties, has always been looked upon as a potential treatment for ED. Chiang et al. [24] evaluated potential of adenosine as a treatment for ED. They observed that intracorporeal injection of adenosine in impotent men caused increased cavernosal arterial flow and resulted in tumescence or suboptimal erection, but failed to cause full erection, while intracorporeal injection of prostaglandin E1 (PGE1) was able to do so. These results are partly in agreement with Kilic et al. [59], who evaluated the potential of adenosine as an agent in the diagnosis of vasculogenic

impotence. Kilic et al. [59] did not even observe any changes in cavernosal arterial blood flow at low to moderate dosage of intracavernous adenosine, and had to administer a very high dose of adenosine to elicit a full erection. Both the studies detected no side effect upon adenosine injection, and Kilic et al. [59] reported absence of fibrosis and curvature 6 months after the injections. Chiang et al. [24] attributed the lack of erection upon adenosine injection to the rapid degradation of adenosine, which was also the reason put forth by Kilic et al. [59] for the short duration of erection caused by adenosine injection. Adenosine has a short half-life [63] due to rapid degradation of extracellular adenosine by ADA [19]. Inhibition of ADA has been shown to enhance adenosine-induced relaxation of mouse CCS [9]. Co-injection of an ADA inhibitor with adenosine might improve its therapeutic potential. A different explanation was provided by Filippi et al. [7] for the lack of effect of adenosine on penile erection. They observed similar results as that of Chiang et al. [24]. Filippi et al. [7] experimentally demonstrated that along with precontracted human CCS adenosine could also completely relax noradrenaline contracted penile venous strips, while the effect of PGE1 on venous strips was limited. The authors [7] suggest that the ability of adenosine to relax both penile arteries and veins might impair the initial buildup of intracavernous pressure, thereby preventing venoocclusion and ultimately erection.

Priapism

Priapism is characterized by a condition of persistent penile erection in the absence of sexual stimulation and interest [64]. It is caused by disturbance of hemodynamic mechanisms in the penis, which leads to the trapping of blood inside the organ [65]. About 40% of sickle cell disease (SCD) patients display priapism, and SCD transgenic (Tg) mouse is an established animal model to study the disorder [9,66–68]. Priapism is a painful pathological condition that requires urgent medical attention as it carries a risk of fibrosis leading to permanent structural damage to the penis and ultimately ED. Treatment options are limited due to the lack of understanding of molecular mechanisms underlying the phenotype [69].

Excess Adenosine Contributes to Priapism—A serendipitous observation in our lab revealed the role of adenosine signaling in priapism. Unexpected priapic phenotype in ADA knock-out ($ADA^{-/-}$) mice led to further investigation, which showed that priapism could be corrected by ADA injections, thereby implying that higher level of adenosine caused prolonged penile erection [9,61]. CCS from $ADA^{-/-}$ mice was more sensitive to EFS than CCS from wild type mice with significantly more pronounced relaxation [9]. To identify, which adenosine receptor is essential for adenosine mediated penile vascular relaxation, CCS relaxation in adenosine receptor deficient mice in response to adenosine was measured. Adenosine induced relaxation was completely absent in CCS from $A_{2B}^{-/-}$ mice, but was not affected in other adenosine receptor subtype deficient mice thus providing strong genetic evidence for the role of A_{2B} receptor [9]. To assess the general significance of high adenosine levels in the pathophysiology of priapism, the potential contribution of excess adenosine to the priapism associated with SCD was investigated. Like $ADA^{-/-}$ mice, the penis of SCD Tg mice also had higher levels of adenosine than those of controls and CCS from SCD Tg mice were more sensitive to EFS than those of controls. Treatment with ADA and A_{2B} receptor antagonist, individually, significantly reduced the force and duration of relaxation of CCS from SCD Tg mice, thereby suggesting a general contributory role of elevated adenosine in priapism through activation of A_{2B} receptors and novel therapeutic possibility [9].

Polyethylene Glycol Modified ADA as a Potential Treatment for Priapism—To establish the cause and effect relationship between enhanced level of adenosine and development of priapism in $ADA^{-/-}$ mice, we regulated adenosine levels in $ADA^{-/-}$ mice by injecting them intraperitoneally with different doses of polyethylene glycol modified ADA (PEG-ADA). The mice on low dosage of PEG-ADA developed prolonged penile erection,

which was quickly corrected by injection of a high dose of PEG-ADA [9,61]. This finding provides an evidence for the first time that PEG-ADA, a safe drug, which has been used successfully to treat both, human and mouse, with ADA deficiency [70,71], is likely a novel effective therapeutic treatment for priapism.

Conclusion and Significance

Early studies hinted at a potential role for adenosine signaling in penile erection [8,24,25]. Attention has recently returned back to adenosine signaling with reports indicating that impaired A_{2B}R signaling is associated with ED in men [28] and excess adenosine contributes to priapism via A_{2B}R signaling in both, ADA^{-/-} mice and SCD Tg mice [9]. Substantial evidence suggests a general role for adenosine signaling in normal penile erection as vasorelaxant and neuromodulator. From this perspective, it is not surprising that impaired adenosine signaling is associated with ED [28] and excessive adenosine signaling is associated with priapism [9]. Thus, adenosine signaling represents a potentially important therapeutic target for the treatment of priapism and ED. Notably, the discovery of excess adenosine as the causative factor for priapism in mice opens up the possibility of treating this painful disorder with PEG-ADA enzyme therapy. In contrast, preservation of adenosine-induced relaxation in CC of men with organic ED holds a great promise to evaluate adenosine as a potential therapeutic treatment.

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Figure 1.

Adenosine metabolism. Adenosine is formed by degradation of adenine nucleotides, intracellularly and extracellularly. Intracellularly, adenosine is formed predominantly by dephosphorylation of adenosine monophosphate (AMP) by intracellular 5'-nucleotidase (cyto 5'NT), but hydrolysis of s-adenosyl-homocysteine (AdoHcy) by s-adenosyl-homocysteine hydrolase (SAHH) also contributes. Inside the cell, adenosine is catabolized by two enzymes, adenosine kinase (ADK) and adenosine deaminase (ADA). ADK phosphorylates adenosine to AMP. ADA catalyses irreversible conversion of adenosine to inosine. Adenosine is also generated extracellularly by degradation of adenine nucleotides. Ectonucleotidases such as CD39 hydrolyse ATP and ADP to AMP. Ecto-5'-nucleotidase (CD73) catalyses dephosphorylation of AMP to adenosine. Extracellular adenosine is degraded to inosine by extracellular ADA. Adenosine homeostasis is maintained by bi-directional transport through equilibrative nucleoside transporters (ENT) in the plasma membranes in the direction of concentration gradient. Extracellular adenosine mediates signals through membrane anchored G-protein coupled receptors (AR).

Figure 2.

Working model of adenosine mediated intracellular signaling in corpus cavernosum. Adenosine induces synthesis of both, cGMP and cAMP, in corpus cavernosum. cAMP induction is mediated through A_{2B} receptor on smooth muscle cells. Induction of cGMP by adenosine is most possibly mediated by activation of nitric oxide (NO) synthesis in endothelial cells through A_{2B} receptor signaling. NO upon diffusing into smooth muscle cells may induce cGMP. Both, cAMP and cGMP, activate their downstream kinases, PKA and PKG, respectively, which in turn phosphorylate their downstream targets resulting in a decrease in intracellular Ca⁺² concentration that leads to smooth muscle relaxation. PKG also phosphorylates RhoA and inhibits RhoA-Rho kinase signaling pathway, thereby contributing to smooth muscle relaxation.

Table 1

In-vivo and in-vitro studies evaluating the effect of adenosine on corpus cavernosum

Species	In vitro/in vivo study	Findings	Reference
Mouse	In vitro	<ul style="list-style-type: none"> • Exogenously added adenosine relaxed precontracted corpus cavernosum (10^{-8}–3×10^{-4} M) • Endogenous adenosine signaling inhibited electric field stimulated contraction of corpus cavernosum (dypyrrole: 10^{-7}–10^{-4} M; MRS1706: 10^{-7} M) 	[8]
Mouse	In vitro	Exogenously added adenosine relaxed corpus cavernosum (10^{-8} – 10^{-2} M) <ul style="list-style-type: none"> • Reduction in endogenous level of adenosine with adenosine deaminase injection inhibited electric field stimulated relaxation of precontracted corpus cavernosum (DCF: 5–100 mM) 	[9]
Rabbit	In vitro	Exogenously added adenosine relaxed precontracted corpus cavernosum (3 mM–3 mM)	[4,6,22,23]
Rabbit	In vitro	<ul style="list-style-type: none"> • Exogenously added adenosine relaxed precontracted corpus cavernosum (10^{-5}–10^{-2} M) • Exogenously added adenosine inhibited electric field stimulated contraction of corpus cavernosum (10^{-5}–10^{-2} M) 	[24]
Dog	In vivo	Intracavernous injection of adenosine induced a full erection (0.67–15 mg/kg body weight)	[25]
Dog	In vivo	<ul style="list-style-type: none"> • Intracavernous injection of adenosine induced an increase in arterial blood flow (27.8 mg minimum dose) • Intracavernous injection of adenosine induced a full erection (27.8 mg minimum dose) 	[26]
Dog	In vivo	Intracavernous injection of adenosine induced an increase in intracavernous pressure (1 mM)	[27]
Human	In vitro	Exogenously added adenosine relaxed precontracted corpus cavernosum ($IC_{50} = 2.38 \pm 0.17$ mM)	[7,28,29]
Human	In vivo	Intracavernous injection of adenosine induced an increase in blood flow velocity but failed to induce erection (6–600 μ g)	[7]

Table 2

Role of adenosine signaling in erectile disorders (including erectile dysfunction and priapism)

Description of model	Findings	Reference
Type I diabetic rabbit	Preservation of the relaxant effect of adenosine in the corpus cavernosum of diabetic rabbit	[55]
Type I diabetic rat	Enhanced relaxant response to adenosine in the corpus cavernosum of diabetic rats compared to the corpus cavernosum of control rat	[56]
Diabetic and non-diabetic impotent men	Enhanced sensitivity of corpus cavernosum from diabetic men to adenosine induced relaxation compared to corpus cavernosum from non-diabetic men	[56]
Obese and Type II diabetic (db/db) mouse	Preservation of the relaxant effect of adenosine in the corpus cavernosum of db/db mouse	[57]
Rabbit with Chronic renal failure (CRF)	Preservation of the relaxant effect of adenosine in the corpus cavernosum of CRF rabbit	[58]
Men with impotence	Increased cavernosal arterial flow and induce partial penile erection upon intracorporeal injection of adenosine (30–40 mg)	[24]
Men with impotence	No change in cavernosal arterial blood flow at low doses of intracavernous injection of adenosine (25–25- μ g) and induction of penile erection only upon relatively very high doses of intracavernous injection of adenosine (500–1000 μ g or infusion at 120 μ g/kg/minute for 10 minutes)	[59]
Men with vasculogenic impotence	Partial resistance of corpus cavernosum to adenosine induced relaxation due to dysfunctional A _{2B} receptor	[28]
Hyperthyroid rabbit	Preservation of the relaxant effect of adenosine in the corpus cavernosum of hyperthyroid rabbit	[60]
Adenosine deaminase deficient mouse (ADA ^{-/-})	ADA-enzyme therapy correct spontaneously prolonged penile erection quickly (5 u PEG-ADA injection); Both PEG-ADA (2–20 u) and A _{2B} R antagonist, MRS1706 (1–10 μ M) inhibit cavernosal relaxation induced by electrical field stimulation	[9,61]
Sickle cell disease transgenic mouse	Both PEG-ADA (2–20 u) and A _{2B} R antagonist, MRS1706 (1–10 μ M) inhibit cavernosal relaxation induced by electrical field stimulation	[9,61]