Adenosine Signaling
Good or Bad in Erectile Function?

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Abstract—The erectile status of penile tissue is governed largely by the tone of cavernosal smooth muscle cells, which is determined by the balance of vascular relaxants and constrictors. Vascular relaxants play a key role in regulating the tone of cavernosal smooth muscle and thus the initiation and maintenance of penile erection. Early studies drew attention to the potential role of adenosine signaling in this process. However, the serendipitous discovery of the effect of sildenafil on erectile physiology drew more attention toward nitric oxide (NO) as a vasodilator in the process of penile erection, and a recently discovered, unexpected erectile phenotype of adenosine deaminase–deficient mice reemphasizes the importance of adenosine as a key regulatory of erectile status. Adenosine, like NO, is a potent and short-lived vasorelaxant that functions via cyclic nucleotide second messenger signaling to promote smooth muscle relaxation. Recent studies reviewed here show that adenosine functions to relax the corpus cavernosum and promote penile erection. Excess adenosine in penile tissue contributes to the disorder called priapism, and impaired adenosine signaling is associated with erectile dysfunction. More recent research summarized in this review reveals that adenosine functions as a key endogenous vasodilator in the initiation and maintenance of normal penile erection. This new insight highlights adenosine signaling pathways operating in penile tissue as significant therapeutic targets for the treatment of erectile disorders. (Arterioscler Thromb Vasc Biol. 2012;32:845-850.)

Key Words: adenosine signaling ■ erectile dysfunction ■ penile erection ■ priapism

Penile erection is a neurovascular event modulated by psychological factors and hormonal status. The erectile status of penile tissue is governed largely by the tone of cavernosal smooth muscle cells, which is determined by the balance of vascular relaxants and constrictors. The flaccid state is maintained by chronic release of noradrenaline from cavernosal nerves that keep the cavernosal smooth muscle cells contracted, collapsing the sinusoidal spaces and preventing blood flow into the tissue. On sexual stimulation, the release of specific neurotransmitters from the cavernous nerves and of relaxing factors from the endothelial cells leads to cavernosal smooth muscle relaxation and the flow of blood into the sinusoidal spaces, which become expanded. This results in an increase in intracavernosal pressure and compression of subeutinal veins against the tunica albuginea, thereby restricting outflow of blood from corpus cavernosum with consequent tissue engorgement. Thus, penile erection is largely a hemodynamic process based on regulated entry of blood into the sinusoidal spaces of the corpus cavernosum.

Introduction to Adenosine Signaling
Adenosine is a pleiotrophic signaling nucleoside that elicits a multitude of effects on target cells by engaging specific G protein–coupled receptors. Four such receptors have been described, ADORA1, ADORA2A, ADORA2B, and ADORA3. Each receptor has a unique affinity for adenosine and a distinct cellular and tissue distribution. In most cases, ADORA1 and ADORA3 are coupled to the inhibitory G protein subunit (Goi) and hence serve to lower intracellular levels of the second messenger cAMP. ADORA2A and ADORA2B are commonly coupled to adenylyl cyclase by the stimulatory G protein subunit (Gos) and serve to increase intracellular cAMP (Figure 1). Adenosine is generated intracellularly and extracellularly by degradation of adenine nucleotides. Under normal physiological conditions, intra- and extracellular levels of adenosine are in the nanomolar range, but they rise into millimolar concentrations under stressful conditions such as hypoxia, ischemia, and cellular damage. Intrapcellularly, adenosine is formed predominantly by dephosphorylation of adenosine monophosphate (AMP), catalyzed by intracellular cytosolic enzyme 5'-nucleotidase. Hydrolysis of S-adenosyl-homocysteine also contributes to intracellular adenosine formation. Inside the cell, adenosine is further metabolized by 2 enzymes, adenosine kinase (ADK) and adenosine deaminase (ADA). ADK phosphorylates adenosine to AMP, whereas ADA catalyzes the
Adenosine-mediated increased intracavernous pressure thereby inducing penile erection in a dose-dependent manner.\textsuperscript{21} These studies indicate that adenosine is capable of inducing penile erection via adenosine receptor signaling. Wu et al\textsuperscript{22} reported that adenosine induced relaxation of the corpus cavernosum of rabbits, under both baseline tension and precontraction. More importantly, Chiang et al\textsuperscript{23} observed dose-dependent inhibition of nerve stimulated contraction of corpus cavernosal strips (CCSs) of rabbits by adenosine and its analogs (5'-N-ethyl-carboxamidoadenosine or R-phenylisopropyl adenosine). Filippi et al\textsuperscript{24} observed that adenosine relaxed the precontracted human corpus cavernous strips in a dose-dependent manner and at high concentrations almost completely relaxed the tissue. Similarly, adenosine and its analogs induce relaxation in corpus cavernous strips from mice.\textsuperscript{24–28} Taken together, both in vitro and in vivo studies demonstrate that adenosine is capable of inducing corpus cavernosal relaxation and penile erection in multiple species.

**The Importance of Adenosine Receptor Signaling**

To identify which adenosine receptor mediated cavernosal smooth muscle relaxation, Mi et al measured CCS relaxation in each of the 4 adenosine receptor–deficient mice in response to different dosages of adenosine.\textsuperscript{27} The results show that Adora\textsubscript{1}\textsuperscript{−/−}, Adora\textsubscript{2a}\textsuperscript{−/−}, Adora\textsubscript{3}\textsuperscript{−/−}, and wild-type mice displayed a dose-dependent increase in relaxation in response to increasing concentrations of adenosine. In contrast, the adenosine-dependent relaxation was almost completely absent in CCSs from Adora\textsubscript{2b}\textsuperscript{−/−} mice. In earlier work, Chiang et al\textsuperscript{23} provided pharmacological evidence that the ADORA2B contributed to cavernosal smooth muscle relaxation in the rabbit. Overall, these results provide strong evidence that the ADORA2B receptor is required for CCS relaxation in response to adenosine.

**Downstream Signaling in Cavernosal Smooth Muscle Cells**

To determine the signaling components functioning downstream of ADORA2B, Mi et al measured cAMP levels in response to adenosine in the cultured isolated CCSs of both wild-type and ADORA2B receptor-deficient mice. The results showed that adenosine induced cAMP levels in a dose-dependent manner in wild-type cells but not in Adora\textsubscript{2b} receptor-deficient CCSs. Similarly, they found that the adenosine-mediated induction of cAMP in wild-type CCSs was inhibited by an ADORA2B antagonist. Thus, both genetic and pharmacological evidence indicates that adenosine acts via ADORA2B signaling to induce cAMP levels in CCSs to induce relaxation.\textsuperscript{27}

To determine the cell types involved with ADORA2B signaling in the penis, Mi et al purified and cultured corpus cavernosal smooth muscle cells (CCSMCs) from wild-type and Adora\textsubscript{2b}-deficient mice.\textsuperscript{27} Analysis of CCSMC RNA from wild-type mice showed that Adora\textsubscript{2b} RNA was the most abundant adenosine receptor RNA in these cells. Additional experiments showed that adenosine mediated induction of cAMP in CCSMCs was blocked by an ADORA2B antagonist and was absent in CCSMCs of Adora\textsubscript{2b}-deficient mice. Overall, these results provide additional pharmacological and genetic evidence that ADORA2B signaling is required for adenosine-mediated stimulation of cAMP production in CCSMCs.\textsuperscript{27}

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**Adenosine Signaling and Penile Erection**

**Exogenous Adenosine Induces Cavernosal Smooth Muscle Relaxation**

Adenosine, like nitric oxide (NO), is a potent vasodilator and has long been implicated in the regulation of penile erection.\textsuperscript{2,16–19} Early studies in dogs showed that intracavernous injection of adenosine induced a full erection, which was independent of acetylcholine.\textsuperscript{20} Takahashi et al\textsuperscript{21} further investigated the hemodynamic effects of intracavernous injection of adenosine in dogs. They found that adenosine increased arterial blood flow and intracavernous pressure, thereby inducing penile erection in a dose-dependent manner.\textsuperscript{21} Adenosine-mediated increased intracavernous pressure was potentiated by pretreatment with an equilibrative nucleoside transporter inhibitor and was significantly decreased by irreversible deamination of adenosine to inosine. Adenosine is also generated extracellularly by degradation of adenine nucleotides. ATP is released from neurons as neurotransmitters and when the cell membrane is subjected to mechanical stress. Extracellular adenine nucleotides are initially dephosphorylated by the ectonucleotidase CD39, which hydrolyzes ATP to ADP and ADP to AMP. Ecto-5'-nucleotidase (CD73) catalyzes the dephosphorylation of AMP to adenosine and is generally the rate-limiting step in the formation of adenosine from extracellular adenine nucleotides. Adenosine is a pleiotrophic signaling nucleoside that elicits a multitude of effects on target cells by engaging specific G protein–coupled receptors. Four such receptors have been described: ADORA1, ADORA2A, ADORA2B, and ADORA3.

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**Figure 1.** Adenosine is generated intracellularly and extracellularly by degradation of adenine nucleotides. Intracellularly, adenosine is formed predominantly by dephosphorylation of adenosine monophosphate (AMP), catalyzed by intracellular cytosolic enzyme 5'-nucleotidase. Hydrolysis of S-adenosyl-homocysteine (AdoHcy) by S-adenosyl-homocysteine hydrolase (SAHH) also contributes to intracellular adenosine formation. Inside the cell, adenosine is further metabolized by 2 enzymes, adenosine kinase (ADK) and adenosine deaminase (ADA). ADK phosphorylates adenosine to AMP, whereas ADA catalyzes the irreversible deamination of adenosine to inosine. Adenosine is also generated extracellularly by degradation of adenine nucleotides. ATP is released from neurons as neurotransmitters and when the cell membrane is subjected to mechanical stress. Extracellular adenine nucleotides are initially dephosphorylated by the ectonucleotidase CD39, which hydrolyzes ATP to ADP and ADP to AMP. Ecto-5'-nucleotidase (CD73) catalyzes the dephosphorylation of AMP to adenosine and is generally the rate-limiting step in the formation of adenosine from extracellular adenine nucleotides. Adenosine is a pleiotrophic signaling nucleoside that elicits a multitude of effects on target cells by engaging specific G protein–coupled receptors. Four such receptors have been described: ADORA1, ADORA2A, ADORA2B, and ADORA3.
Increased Endogenous Adenosine Production in Penile Tissues in Response to Cavernosal Nerve Stimulation

The experiments described above involved either the injection of adenosine into penile tissue or the addition of adenosine to tissue explants or primary cell cultures. In each of these cases, adenosine (or adenosine analogs such as 5′-N-ethylcarboxamidoadenosine) are added exogenously. In an effort to determine whether the regulated production of endogenous adenosine plays a direct role in penile erection, Wen et al.29,30 used a well-established method to mimic normal physiological erection by electric stimulation of the cavernous nerve to induce an erectile response.31–33 Flacid penile tissue was obtained as a control from sham-operated unstimulated mice. Tissue extracts from flaccid and erected penile tissue were fractionated by high-pressure liquid chromatography to measure endogenous adenosine levels. The results show that the concentration of adenosine in penile tissue doubled as a result of cavernous nerve stimulation. The functional importance of the adenosine production within penile tissues in response to cavernous nerve stimulation in vivo. Additional genetic and pharmacological studies showed that CD73-mediated adenosine production contributed to increased extracellular adenosine production by shear-stressed endothelial cells. Additional studies showed that shear stress-mediated elevated adenosine functions through the ADORA2B to activate the phosphatidylinositol 3-kinase–AKT signaling cascade, resulting in increased eNOS phosphorylation and NO production. Subsequent in vivo studies showed that adenosine is induced during sustained penile erection and contributes to phosphatidylinositol 3-kinase–AKT activation and subsequent eNOS phosphorylation via ADORA2B signaling. Overall, these findings identified a previously unrecognized role of adenosine signaling in penile erection and revealed the underlying mechanisms accounting for adenosine production and signaling pathways involved in the process. These findings also reveal novel therapeutic possibilities for the treatment of disorders of erectile function.

Priapism: A Condition Resulting From Excessive Adenosine Signaling

Priapism is a condition of persistent penile erection lasting more than 4 hours in the absence of sexual excitation. Although uncommon in the general population, it was recognized as a serious complication of sickle cell disease (SCD) as early as 1934.34 Priapism is a dangerous and urgent condition because of its major complication, penile fibrosis. Because priapism is poorly understood, there are no mechanism-specific treatment options for the disorder except evacuation of blood and draining of the corpus cavernosum to relieve engorgement, coupled with intracavernosal injection of an α-adrenergic receptor agonist to stimulate cavernosal smooth muscle contraction. Some researchers used red blood cell exchange pheresis to treat priapism associated with SCD. However, no randomized clinical trials have been performed to determine its clinical efficacy.35

An Unexpected Phenotype of Adenosine Deaminase–Deficient Mice

Priapism is known to be associated with hypoxic and ischemic conditions. Although adenosine is known to be induced under hypoxic and ischemic conditions,3,36 the pathological role of adenosine in priapism was not recognized until an unexpected priapism phenotype in adenosine deaminase (ADA)–deficient mice was observed.27 ADA is a purine metabolic enzyme that catalyzes the conversion of adenosine to inosine. As a result of ADA deficiency, these mice exhibit a marked increase in adenosine concentrations, particularly in the penis, which has the highest level of adenosine among all the tissues examined. These mice display features of priapism seen in humans, including spontaneous and prolonged penile erection, increased vascular relaxation in response to neurostimulation, and penile fibrosis. The spontaneously occurring priapism observed with ADA-deficient mice was quickly relieved by intraperitoneal injection of polyethylene glycol modified (PEG)-ADA. This observation provided the initial clue that elevated adenosine in the penes of Ada−/− mice was responsible for the spontaneous prolonged penile erection. These findings indicate that ADA-deficient mice represent a novel and important animal model to study the role of adenosine signaling in priapism.
Molecular Mechanisms of Adenosine-Induced Priapism

ADA-deficient mice are a well-accepted animal model to study the contribution of excessive adenosine signaling to various pathological conditions. SCD transgenic (Tg) mice are a well-accepted animal model of priapism. To further evaluate the role of adenosine signaling in priapism, we tested the effect of PEG-ADA on electric field stimulation–induced relaxation of CCS for both ADA-deficient mice and SCD mice. The results show that 60 seconds of electric field stimulation at 5 V and 30 Hz evoked a substantial and prolonged relaxation of CCS from ADA-deficient mice and SCD Tg mice in comparison with CCS from control mice. Consistently, treatment of CCS in ADA-deficient mice and SCD Tg mice with PEG-ADA inhibited the increased CCS vascular relaxation. Thus, these results indicate that elevated adenosine contributes to the prolonged penile erection and substantial penile vascular relaxation with ADA-deficient mice. The analysis of 4 adenosine receptor–deficient mice revealed that the ADORA2B is essential for adenosine-dependent penile vascular smooth muscle relaxation and erection and that upregulated ADORA2B signaling contributes to priapic activity in ADA/−/− mice. Additional studies showed that priapic activity in SCD Tg mice was also due to elevated adenosine signaling via ADORA2B signaling, suggesting a general contributory role of adenosine and ADORA2B signaling in priapism. This signaling pathway represents a potentially important therapeutic target for the treatment of priapism.

PEG-ADA May Be Useful in the Prevention and Treatment of Priapism

To address the role of adenosine in priapism seen in ADA-deficient mice, we regulated adenosine levels in ADA-deficient mice with different amounts of PEG-ADA enzyme therapy. The ADA-deficient mice were maintained on high dose enzyme therapy at 5 U per week for at least 8 weeks to allow for normal penile development. At 8 weeks of age, the dose of PEG-ADA was gradually tapered down to a low dosage at 0.625 U per week. After 2 weeks at the low dosage of PEG-ADA treatment, we found that ~25% mice displayed spontaneously prolonged penile erection lasting for 12 to 72 hours. Strikingly, the prolonged penile erections observed in these ADA-deficient mice were quickly corrected (around 6–7 minutes) by intraperitoneal injection of a high dose of PEG-ADA. This data indicated that PEG-ADA enzyme therapy quickly corrects the priapism observed in ADA deficient mice.

To confirm this in vivo finding, we treated ADA-deficient mice and SCD Tg mice with different dosage of PEG-ADA to adjust adenosine to different levels in vivo. At the end of each experiment, adenosine levels in penile tissue were determined by high-pressure liquid chromatography. Erectile function was determined by CCS relaxation in response to electric field stimulation. The results showed a high dosage regimen of PEG-ADA enzyme therapy from birth in ADA-deficient mice prevented the increased electric field stimulation–induced CCS relaxation by lowering penile adenosine levels to normal. The significance and general utility of PEG-ADA enzyme therapy in priapism was confirmed and extended by showing that PEG-ADA treatment normalized penile adenosine levels in SCD Tg mice and relieved the priapic features in these. Taken together, our preclinical studies with 2 mouse models of priapism have identified a novel application of PEG-ADA as a safe and mechanism-based drug in prevention and treatment of priapism. Additional therapeutic approaches for the treatment of priapism may include the use of ADORA2B antagonists. These findings provide a strong justification for clinical trials in men experiencing priapism.

The Role of Adenosine Signaling in Penile Fibrosis Associated With Priapism

Penile fibrosis is dangerous and urgent complication of priapism because it eventually results in erectile dysfunction (ED). The pathogenesis of penile fibrosis associated with priapism likely results from a combination of prolonged penile erection, ischemic-mediated inflammatory response, vascular damage and attempted tissue repair. Multiple factors are released from locally insulted penile tissue and responding cells. Previous studies have demonstrated the role of extracellular nucleotide release in acute inflammatory conditions. In contrast, chronically persistently elevated adenosine is known to induce fibrosis in the lung and kidneys. Recently, Wen et al have demonstrated that elevated adenosine levels in penile tissue contribute to vascular damage and penile fibrosis associated with priapism, and further studies have shown that chronic reduction of adenosine by PEG-ADA enzyme therapy prevented and attenuated the progression of vascular damage and the increased profibrotic gene expression associated with penile fibrosis in both ADA-deficient mice and SCD Tg mice. Mechanistically, using both pharmacological and genetic tools, we determined that transforming growth factor-β functions downstream of the ADORA2B and is responsible for excess adenosine-mediated penile fibrosis seen in both lines of mice. Overall, these preclinical studies have identified a previously unrecognized novel application of PEG-ADA as a safe, effective, and mechanism-based drug to treat and prevent priapism and penile fibrosis in animals and provide a strong justification for clinical trials in men experiencing priapism.

Adenosine Signaling in SCD and Adenosine-Based Therapy

The functional role of adenosine signaling in SCD disease is not limited to priapism. For example, earlier studies by Wallace et al have demonstrated that activation of ADORA2A is capable of inhibition of invariant natural killer T cells in the lung and subsequent decreases pulmonary dysfunction in the NY1DD mouse model of SCD. More recently, our laboratory has demonstrated that elevated adenosine is detrimental to induce erythrocyte sickling, a central pathogenesis of SCD, in both Berkley SCD mice and in cultured human sickle erythrocytes. We further demonstrated that excessive adenosine signaling through the ADORA2B triggers sickling by induction of 2,3-diphosphoglycerate, an erythroid specific metabolite that induces O2 release from hemoglobin in both SCD mice and humans. These findings show that adenosine has dual roles in the pathogenesis of SCD by working on different adenosine receptors on different
cell types: (1) ADORA2A activation on invariant natural killer T cell leads to inhibition of lung dysfunction in SCD mice; and (2) ADORA2B activation on erythrocytes induces sickling by increasing 2,3-diphosphoglycerate production and subsequently promoting deoxygenation and polymerization. These findings pointed out novel adenosine-based therapeutic implications for SCD. In view of the potentially beneficial effects of adenosine-mediated ADORA2A activation on invariant natural killer T cells, an ADORA2B antagonist may be a better choice than PEG-ADA because it will specifically block only 1 of the 4 adenosine receptors without the loss of potentially beneficial effects resulting from the activation of other adenosine receptors on different cell types.

**Defective Adenosine Signaling and ED**

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

The etiology of vasculogenic ED has been associated with reduced NO formation either from nerve fibers or from endothelial cells of the corpus cavernosum. Early work by Chiang et al indicated that the relaxing effect of adenosine in rabbit cavernosal tissue is partially endothelium dependent and involves the release of endothelium-derived relaxing factors, presumably NO. Pharmacological evidence provided by Chiang et al indicated that the adenosine receptors involved in this response were of the A2B subtype. More recent data by Faria et al also showed that adenosine-induced relaxation of human CCS was stimulated by endothelial cells of the corpus cavernosum. Early work by Chiang et al indicated that the relaxing effect of adenosine in rabbit cavernosal tissue is partially endothelium dependent and involves the release of endothelium-derived relaxing factors, presumably NO. Pharmacological evidence provided by Chiang et al indicated that the adenosine receptors involved in this response were of the A2B subtype. More recent data by Faria et al also showed that adenosine-induced relaxation of human CCS was stimulated by endothelial derived NO produced as a result of ADORA2B activation. These findings are consistent with our data showing that in mice penile smooth muscle relaxation produced by adenosine is mediated in large part by the synthesis and release of NO following the activation of NO synthase secondary to intracellular signaling cascades resulting from ADORA2B activation, presumably on endothelial cells.

A potential role for impaired adenosine signaling in ED was reported by Faria et al, who observed partial resistance of corpus cavernosum from men with vasculogenic impotence to adenosine-induced relaxation and showed that dysfunctional ADORA2B, supposedly on the endothelium, are the cause for the signaling impairment.

Adenosine, because of its vasorelaxant properties, has always been looked on as a potential treatment for ED. Chiang et al evaluated the 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, whereas intracorporeal injection of prostaglandin E1 was able to induce full erection signaling via its receptor. PEG1 receptor activation leads to subsequent activation of adenyl cyclase, induction of cAMP levels, and eventually relaxation of vascular smooth muscle cells in corpus cavernosum. These results are partly in agreement with those of Kilic et al, who evaluated the potential of adenosine as an agent in the diagnosis of vasculogenic impotence. Chiang et al attributed the lack of erection on adenosine injection to the rapid degradation of adenosine, which was also the reason put forth by Kilic et al for the short duration of erection caused by adenosine injection. In view of our findings, and those of others, showing the importance of ADORA2B activation on penile erection, it is possible that ADORA2B agonists could serve a useful therapeutic role in vasculogenic ED. Recently a novel specific ADORA2B agonist, BAY 60-6583, has been shown to have a therapeutic role in myocardial ischemia by activation of ADORA2B, suggesting that it may also have a potential therapeutic role in ED.

**Concluding Remarks**

An unexpected erectile side effect of sildenafil on erectile physiology drew more attention toward NO as a vasodilator in the process of penile erection, and a recently discovered, unexpected priapic phenotype of adenosine deaminase–deficient mice enhances the importance of adenosine as a key regulatory of erectile status. Adenosine and NO share multiple features, making them excellent contributors to erectile physiology. First, both are well-known potent vasodilators and neurotransmitters. Second, both have a very short half life. Third, both induce the synthesis of cyclic nucleotide second messengers and penile erection. Specifically, adenosine functions through G protein–coupled receptors to modulate adenylyl cyclase and the synthesis of cAMP. NO functions through guanylyl cyclase to induce the synthesis of cGMP. Finally, adenosine-mediated cAMP induction and NO-mediated cGMP induction are capable of inducing protein kinase A and protein kinase G, respectively, resulting in decreased calcium/calmodulin-dependent myosin light chain phosphorylation and enhanced smooth muscle relaxation. In conclusion, neuronal activation–mediated ATP release, leading to increased adenosine and neuronal nitric oxide synthases.
activation-mediated NO release, independently contributes to the initiation of penile erection. Subsequently, shear stress-mediated ATP release, resulting in increased adenosine, contributes to maintenance of penile relaxation. Eventually, continuous production of adenosine mediated by shear stress leads to sustained and potent penile erection via direct effect on vascular smooth muscle cells by induction of cAMP and indirect activation of eNOS via phosphatidylinositol 3-kinases-AKT in endothelial cells. A model depicting the actions of adenosine and NO in erectile physiology is presented in Figure 2.

Disclosures

None.

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