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*Review Article*

# Adenosine signaling: a potential therapeutic target for psychogenic erectile dysfunction

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**Abstract:** Therapeutic modalities for psychogenic erectile dysfunction (PED) are poorly targeted because of the lack of specific pathological features. The common symptoms of PED include psychological stress-related negative emotions and erectile dysfunction. Exploring their common therapeutic targets is helpful in the development of effective PED treatment strategies. Adenosine locally acts as a vasodilator or neuromodulator in the penis and promotes erection. Recent studies have demonstrated that adenosine (ADO) signaling is also involved in psychological stress. Herein, we review the pathogenesis of PED and the interaction between ADO and the erection regulator nitric oxide (NO) in brain and penile tissues. In addition, we summarize the regulatory role of ADO signal transduction in penile erection, psychological stress and negative emotions. Through our study, we found that ADO is involved in psychological stress and erectile events by combining adenosine $A_1$ receptors ($A_1R$) and adenosine $A_{2A}$ receptors ($A_{2A}R$). The application of $A_1R$ selective agonists may promote erection and improve psychological state.

**Keywords:** Psychogenic erectile dysfunction, psychological stress, purinergic signaling, adenosine

## Introduction

Erectile dysfunction (ED), which refers to the inability of men to maintain penile erection to achieve satisfactory sexual performance [1], is a global health problem. According to statistics, this condition affects approximately 150 million men worldwide, and its prevalence rate increases with age. It is predicted that by 2025, up to 322 million patients will have ED worldwide [2]. An epidemiological survey conducted on almost 100,000 people in 8 countries showed that Italy (48.6%) had the highest prevalence of ED, followed by China (41.6%) and then Brazil (37.2%) [3]. This condition not only negatively affects marriage and family harmony but may also be an early symptom and a risk factor for cardiovascular and peripheral vascular diseases [4]. Therefore, active early diagnosis and treatment are particularly important.

Clinically, ED can be categorized into three subtypes based on its etiology: organic, psychogenic, and mixed [5]. With the rapid pace of society, psychogenic ED (PED) has gradually become the focus of social attention owing to its high incidence and complex pathogenesis [6]. Unlike organic ED (OED), PED lacks specific pathological features and is generally associated with several factors such as psychological stress, spousal relationship, and lack of sexual knowledge. Most patients experience negative emotions such as anxiety, depression, and fear [7, 8]. PED has been found to account for 13%-85.2% of ED patients aged <40 years old [9, 10]. Since 2014, the number of adolescent patients with ED has increased by 31-fold, mostly owing to psychological factors [11]. Notably, OED can be used as a source of stress to enable the patient to simulate the aforementioned negative emotions to transform into mixed ED. Thus, psychological factors are considered to be involved in the pathogenesis of ED [12].

Penile erection is mainly regulated by the cyclic nucleotide pathway, of which the NO-cyclic gua-

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nosine monophosphate (cGMP) signaling pathway is the main regulatory pathway. NO regulates cGMP synthesis through guanylate cyclase and induces cavernous smooth muscle diastole to promote penile erection, whereas phosphodiesterase type 5 (PDE5) in penile tissues can hydrolyze cGMP and cause penile weakness [13, 14]. Phosphodiesterase type 5 inhibitors (PDE5I), such as tadalafil and sildenafil citrate, are the first-line treatment for ED owing to their ability to inhibit cGMP hydrolysis and improve erectile function [15]. Although PDE5I has been reported to rarely cause adverse reactions, such as headache, dyspepsia, and hypotension, its overall efficacy for patients with ED is satisfactory [16, 17]. Previous studies have confirmed that PDE5I has a therapeutic effect on PED [18]; however, psychological stressors and stress-related negative emotions cannot be alleviated and treated with oral PDE5I. Long-term use of PDE5I may overlook the psychological issues of patients with ED. In 2013, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [19], emphasized the importance of psychotherapy for ED treatment. Therefore, at this stage, the clinical treatment plan for PED mostly involves combination therapy with oral PDE5I and psychotherapy [18]. However, adherence to this therapy is significantly affected by the long duration of psychotherapy, high costs, and the fact that most patients with PED are not psychotherapeutically aware [20-22]. Therefore, it is necessary to identify drugs that can regulate psychological states and promote penile erection.

In addition to NO/cGMP signaling pathway-related molecules, other molecules released by neurons, endothelial cells, and smooth muscle cells are involved in penile erection. Purinergic signaling is an important extracellular signal that is involved in physiological and pathological processes and has recently gained extensive attention. Studies have demonstrated that adenosine (ADO) and adenosine receptors (ARs) are closely associated with penile erection, psychological stress, emotion regulation, and other processes [23-25] and can be used to treat PED. This review summarizes the role of ADO signaling transduction in the aforementioned processes to determine the candidate drugs for PED.

## Physiological mechanism of penile erection

Penile erection is a psychophysiological process that is initiated and dominated by the brain [26]. Previous studies have reported many brain regions related to penile erection, such as the prefrontal, parietal, and cingulate cortices; brain regions inhibiting erection, such as the caudate nucleus, amygdala, and hypothalamus; and brain regions that promote erection. The paraventricular nucleus of the hypothalamus is currently considered the control center of erection [27, 28]. The brain releases glutamate (Glu), dopamine (DA), 5-hydroxytryptamine (5-HT), gamma-amino-butyric acid (GABA), and other neurotransmitters to the spinal cord after processing and integrating the signals of visual, auditory, and tactile stimuli. Neurotransmitters form nerve impulses that inhibit the T10-L2 lateral horn sympathetic nerve centers and the hypogastric nerve, excite the S2-S4 lateral horn parasympathetic nerve centers and pelvic splanchnic nerve, and mediate the synthesis and release of NO by neuronal nitric oxide synthase in the nonadrenergic-noncholinergic (NANC) nerve endings of the corpus cavernosum (CC) and endothelial nitric oxide synthase (eNOS) in the endothelial cells of the vascular endothelium. NO activates guanylate cyclase to produce cGMP, which activates protein kinase G (PKG), inducing hyperpolarization of smooth muscle cell membranes and relaxation of CC smooth muscles to promote erection [16, 29, 30].

## Pathogenesis of PED

Previous studies have confirmed that patients with PED have anomalous brain structure and function [31, 32]. As shown in **Figure 1**, the brain exposed to psychological stress initiates a series of neuroendocrine responses to block sexual activity. Emotion-related brain regions, such as the prefrontal cortex, amygdala, and hippocampus, are involved in psychological stress sensing and the generation and transmission of nerve impulses to the paraventricular nucleus of the hypothalamus. The paraventricular nucleus triggers sequential stress responses mediated by the autonomic nervous system and hypothalamic-pituitary-adrenal (HPA) axis [33]. On the one hand, the tension of the sympathetic nervous system (SNS) rapidly increases under stress, resulting in the

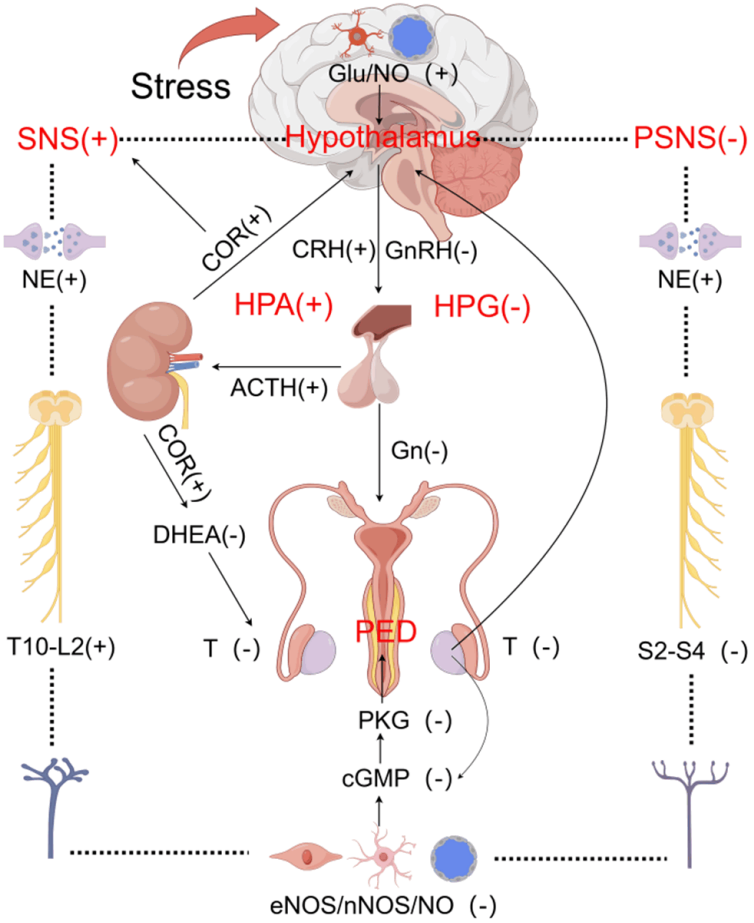


**Figure 1.** Pathogenesis of PED under psychological stress. "→" represent HPA/HPG axes, "..." represent ANS. When the body feels stress, the hypothalamus initiates a stress response, and the ANS is activated rapidly, which is manifested as SNS excitation and PSNS inhibition. HPA and HPG axes are activated slowly, which is manifested as HPA axis hyperexcitability and HPG axis inhibition, ultimately leading to ED and negative emotions. Abbreviations: ANS, Autonomic Nervous System; ATCH, adrenocor ticotropic hormore; CRH, corticotropin releasing hormone; Gn, gonadotropins; GnRH, gonadotropin-releasing hormone; HPG, hypothalamic-pituitary-gonadal; PSNS, parasympathetic nervous system.

release of a large amount of norepinephrine (NE). At this time, the expression of NO/nitric oxide synthase (NOS) is downregulated in the NANC and vascular endothelium, and cGMP production is reduced, resulting in penile weakness [34, 35]. However, the release of large amounts of Glu during stress causes the accumulation of NO in the brain and slow activation of the HPA axis, which is characterized by increased secretion of corticotropin-releasing and adrenocorticotropic hormones. Eventually, this results in the release of a large amount of cortisol (COR). COR exerts a strong negative effect on brain areas related to emotion regulation, which may be the basis of negative emotion. Abnormal secretion of COR causes circadian rhythm disorders, further promoting the tension of SNS and the release of NE, resulting in penile weakness [36]. Furthermore, the body preferentially synthesizes COR during stress, leading to a compensatory decrease in the metabolic levels of dehydroepiandrosterone (DHEA), a precursor of testosterone (T). T regulates the formation and degradation of cGMP; thus, the obstruction of T production can directly cause ED. A persistently low T expression leads to the suppression of hypothalamic-pituitary-testicular axis function, which is characterized by decreased release of gonadotropin-releasing hormone and gonadotropin. This eventually results in hypothalamic damage and the formation of a malignant stress circuit [37-39].

## Overview of ADO signaling

ADO is a precursor and metabolite of adenine nucleotides that is widely expressed in various systems of the body. It is mainly released by nerve endings and glial cells but is also generated by adenosine triphosphate (ATP) through the double hydrolysis of extracellular nucleosidases, such as ectonucleide triphosphate diphosphohydrolase-1 (CD39) and ecto-5'-nucleotidase (CD73). Simultaneously, intracellular ADO can also be transported outside the cell through nucleoside transporters on the cell membrane. **Figure 2** shows the source and metabolism of ADO. The physiological role of ADO was first described by Drury and Szent-Gyorgyi [40], and it has since been shown to be involved in multiple physiological and pathological processes *in vivo* by binding to its specific receptor [41]. ARs currently have four subtypes, $A_1R$, $A_{2A}R$, adenosine $A_{2B}$ receptors ($A_{2B}R$), and ade-

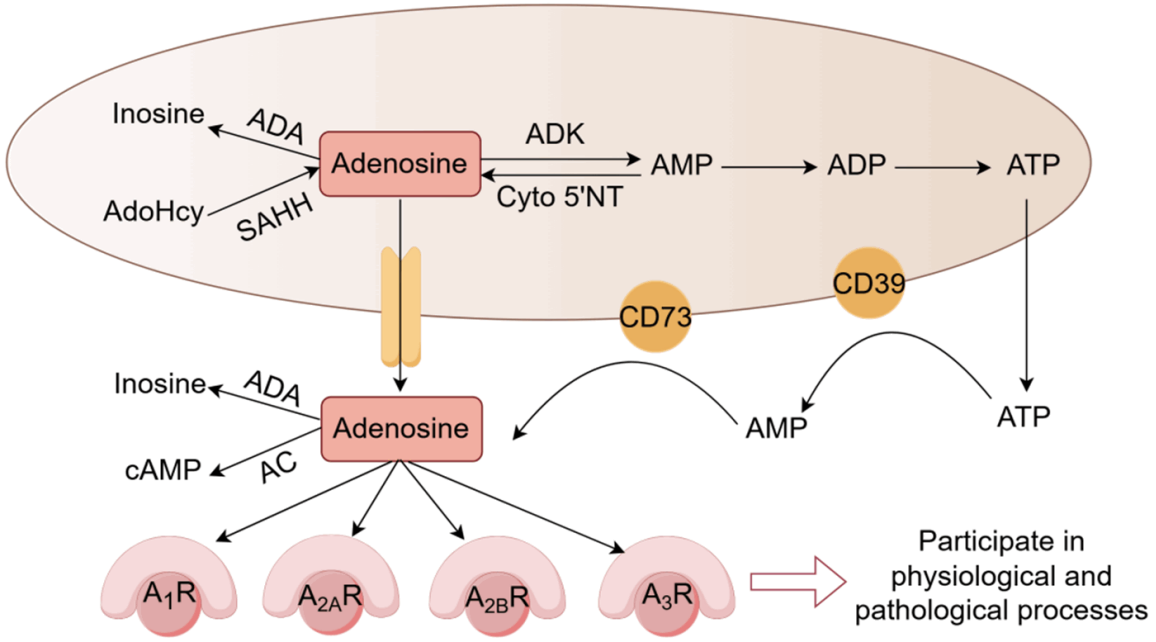


**Figure 2.** Overview of ADO Signaling. Intracellularly, ADO is mainly generated by AMP under the catalysis of Cyto 5'NT, and can also be produced by the hydrolysis of AdoHcy by SAHH. Most of the generated ADO is phosphorylated to AMP by ADK, thus participating in ATP synthesis and completing the recirculation of ADO, and a small portion of ADO is catalyzed by ADA to inosine, or transported to the extracellular space through nucleoside transport proteins on the cell membrane. Extracellularly, ATP becomes AMP after dephosphorylation catalyzed by CD39, and AMP becomes ADO after dephosphorylation catalyzed by CD73, which binds to specific receptors $A_1R$, $A_{2A}R$, $A_{2B}R$, and $A_3R$ to participate in the physiological and pathological processes of the organism. In addition, ADO regulates cAMP synthesis through AC. Abbreviations: AC, adenylate cyclase; ADA, adenosine deaminase; ADK, adenosine kinase; AdoHcy, S-adenosyl-homocysteine; AMP, adenosine monophosphate; Cyto 5'NT, cytosolic 5'-nucleotidase; SAHH, S-adenosyl-homocysteine hydrolase.

nosine $A_3$ receptors ($A_3R$), which belong to the G protein-coupled receptor superfamily and have different distributions, transduction mechanisms, and functions [42]. In the physiological state, the concentration of ADO is maintained at a low level (1-2 μmol/L), and it mainly binds to high-affinity $A_1R$ and $A_{2A}R$, whereas in pathological states, such as ischemia, inflammation, and stress, the extracellular concentration of ADO rapidly increases to 100-1,000 μmol/L, and it stimulates low-affinity $A_{2B}R$ and $A_3R$ [43].

### Distribution of ARs in brain and penile tissues

Four subtypes of ARs have different regions and density distributions in the brain. $A_1R$ has a high-density distribution in the cerebral cortex, hippocampus, cerebellum, thalamus, brain stem, and other regions and is concentrated in the synaptic part of neurons [44]. $A_{2A}R$ is mainly located in DA-enriched regions, including the striatum, nucleus ambiguus, pallidum, and olfactory bulb; its mRNAs are also distributed in the hippocampus, hypothalamus, amygdala, and choroid plexus epithelial cells, as detected via Reverse transcription-Polymerase chain reaction (RT-PCR) [45-47]. In addition, a previous study confirmed that $A_{2A}R$ exists in the whole nerve axis in rats via immunohistochemistry [48, 49]. Meanwhile, $A_{2B}R$ is mainly distributed in the Cornu ammonis 1 (CA1) and Cornu ammonis 3 (CA3) regions of the hippocampus, with a few in the thalamus, lateral ventricles, and striatum [43]. Finally, $A_3R$ has a high-density distribution in the striatum, olfactory bulb, auditory nerve, hippocampus, hypothalamus, thalamus, and cerebellum but a low-density distribution in the cortex and amygdala [44]. Furthermore, it is mainly expressed in the synaptic terminals of neurons, and its distribution in the presynaptic membrane of hippocampal neurons is more abundant than that in the postsynaptic membrane, suggesting that $A_3R$ plays a pivotal role in the release of presynaptic neurotransmitters [50-52]. Glial cells are higher in proportion than neuronal cells in the brain,

and the four AR subtypes have been detected in microglia and astrocytes [53, 54]. Compared with brain tissues, few studies have examined the expression profile of ARs in penile tissues. It is currently believed that $A_1R$ is mainly expressed in the cavernous and dorsal nerves of the penis. $A_{2B}R$ is the main subtype expressed in the smooth muscle cells of the cavernous body of the penis, whereas $A_{2A}R$ has low expression in these cells. Notably, the $A_3R$ expression in penile tissues is difficult to detect [55-57]. The aforementioned distribution of ARs provides a material basis for the biological role of ADO signaling in the pathological process of PED.

### Interaction between ADO and NO in brain and penile tissues

The production mechanism of NO is as follows: Glu in the synaptic gap binds to N-methyl-D-aspartate receptors in the postsynaptic membrane, resulting in the inward flow of $Ca^{2+}$. $Ca^{2+}$ and calmodulin activate NOS and catalyze the conversion of L-arginine to NO and citrulline [58]. Interestingly, ADO and NO share many similarities [59, 60], for example, 1) both are recognized as vasodilators and neurotransmitters, 2) both have extremely short half-lives (<10 s), and 3) both exert their physiological effects through nucleotide second messengers. Because both ADO and NO have broad and important biological importance and the latter is considered to be the major regulator of penile erection [13], it is imperative to focus on their interactions between them.

NO regulates cGMP synthesis through guanylate cyclase, ADO regulates cyclic adenosine monophosphate (cAMP) synthesis through adenylate cyclase, and cAMP and cGMP activate downstream protein kinase A (PKA) and PKG, respectively, and then phosphorylate downstream targets to jointly regulate ion channels [55]. Thus, the cascade signaling pathways of ADO/cAMP and NO/cGMP restrict each other, which is the basis of the interaction between ADO and NO [61, 62]. ADO and NO in the brain interact during neural and vascular regulations. During sustained stress, the brain releases large amounts of Glu, which results in NOS overactivation and a dramatic increase in NO synthesis [63, 64]. Moderate amounts of NO exert neuroprotective effects. However, an excessive amount of NO induces neurotoxicity, which can activate the HPA axis and increase the expression of COR, directly damaging the erectile center and emotion-related brain regions [65]. Therefore, the inhibition of NO accumulation in brain regions is expected to improve mental state and erectile function. The inhibitory and facilitatory effects of ADO on neurotransmission are mainly mediated by $A_1R$ and $A_{2A}R$ [66, 67]. Studies have found that the brain releases endogenous ADO during stress while reducing NO levels and eNOS activities [68-70]. NO in the basal ganglia, striatum, and hippocampus can promote ADO release and antagonize $A_1R$ activity, which may help counteract NO neurotoxicity [43]. In terms of vascular regulation, several dynamic exercise experiments have shown that NO and ADO exert common effects on vascular blood supply and oxygen delivery. When NO is sufficient, the vasodilatory effect of ADO is weakened; otherwise, the vasodilatory effect is enhanced [71-73].

ADO in penile tissues can also indirectly regulate cGMP synthesis by activating ARs to promote NO production [74]. Using genetic and pharmacological tools, it has been shown that ADO can induce cGMP production in mouse CC via $A_{2B}R$. However, it cannot promote cGMP production in CC smooth muscle cells, suggesting that ADO-induced NO originates from endothelial cells rather than muscle cells [55]. Electrophysiological experiments have shown that cGMP produced by electrically stimulated CC is partially dependent on the $A_{2B}R$-mediated NO pathway, suggesting that endogenous ADO is an important molecule in penile erection [56]. Further experiments have confirmed that blood flow shear stress induces endogenous ADO production in endothelial cells and increases eNOS phosphorylation via $A_{2B}R$ activation of the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway, which promotes NO production. The AKT and eNOS phosphorylation levels in the penises of $A_{2B}R$-knockout mice are both downregulated in wild-type mice, which exhibit impaired erectile function, suggesting that endogenous ADO induces NO production by activating $A_{2B}R$ [75]. Several *in vitro* experiments confirmed the aforementioned results indicating that the NO signaling pathway in endothelial cells is also involved in

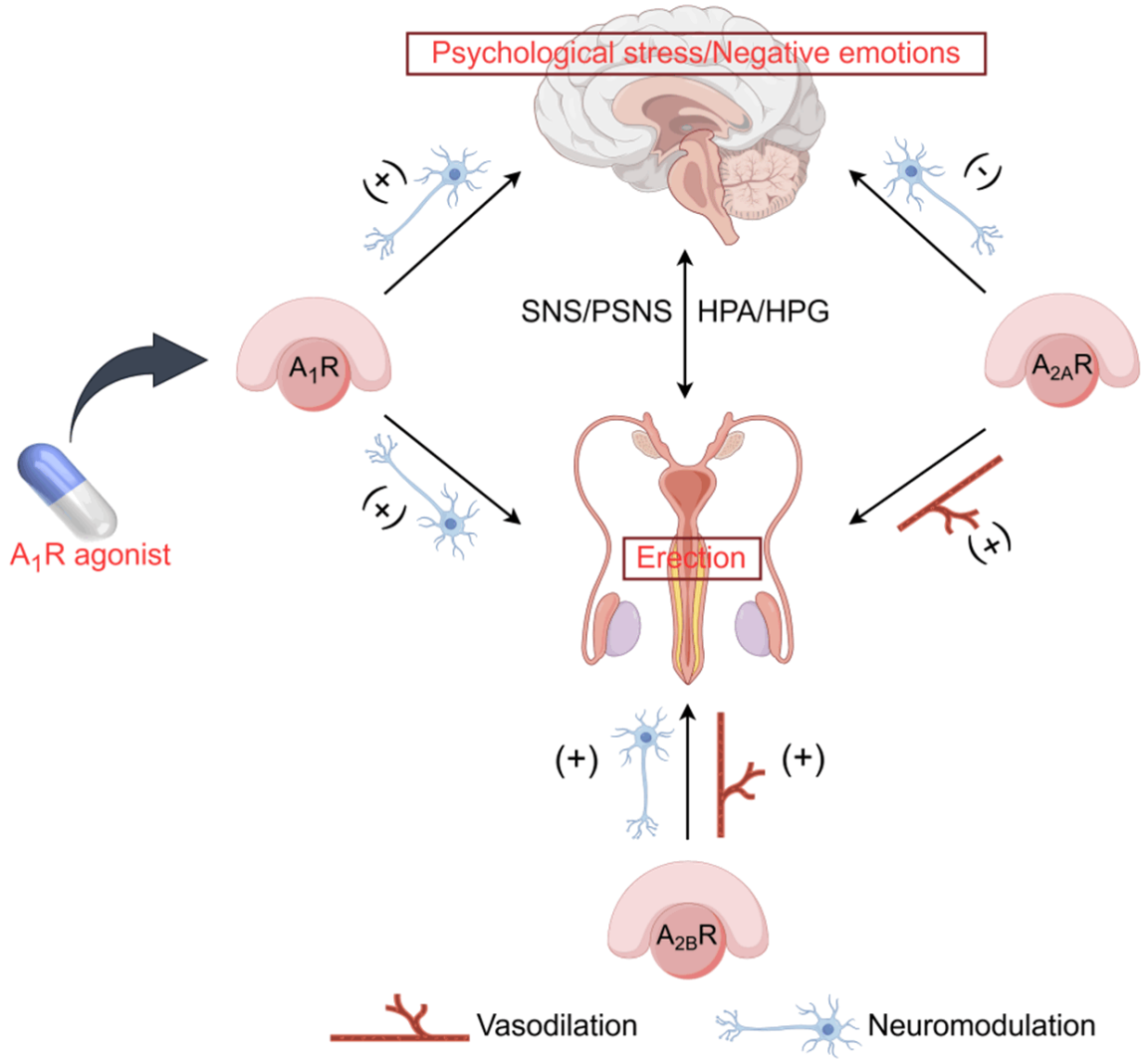


**Figure 3.** The role and mechanism of ARs in psychological stress and penile erection. +, relieve psychological stress and negative emotions or promote erection; -, promote psychological stress and negative emotions.

the exogenous ADO-mediated CC diastolic process [76-79].

### ADO signaling and CC diastole

Both endogenous and exogenous ADO can regulate cAMP synthesis and promote penile erection. CD73-deficient mice exhibit reduced endogenous ADO expression, leading to impaired erectile function [80]. Contrarily, ADA-deficient mice demonstrate excessive accumulation of endogenous ADO, inducing abnormal erections, defined as persistent erection lasting at least 4 h in the absence of sexual stimulation [81]. As a phosphodiesterase inhibitor (PDEI), caffeine intake can upregulate cGMP and cAMP levels in the CC and promote penile erection [82]. The diastolic effect of exogenous ADO on CC has been observed in humans, rats, dogs, and rabbits [83-85], with varying degrees of diastolic effect among individuals. After ADO treatment, the diastolic effect of CC in patients with ED and diabetes was better than that in patients with ED and no diabetes, and the erectile function of both groups were better than ED rats [84]. Furthermore, the diastolic effect of ADO on CC in 24-month-old rabbits was superior to that in 3- and 7-month-old rabbits [85].

As shown in **Figure 3**, ADO signaling promotes erection by acting as a vasodilator and neuromodulator [86]. ADO acts as a negative feedback regulator of sympathetic neurotransmitters through $A_1R$, which binds to $A_1R$ enriched

on neuronal cells and inhibits NE release dose-dependent manner. High expression of NE following SNS excitation elicits CC smooth muscle contraction, whereas $A_1R$ activation inhibits the NE-induced contractile response of CC smooth muscles in mice, which in turn promotes erection [55, 87]. Meanwhile, $A_{2A}R$ activation induces CC smooth muscle diastole, and it has been suggested that the CC diastolic effect exerted by ADO binding to $A_{2A}R$ is completely independent of the NO/cGMP pathway [88]. The ADO analog 5'-NN-ethylcarboxamide adenosine (NECA) is known to be a nonselective agonist of ARs, and drugs that excite $A_{2A}R$ can exert approximately 50% of the diastolic effect compared with NECA. Further *in vitro* experiments have confirmed that the diastolic effect exerted by NECA in preconstriction-treated human CC is significantly inhibited by the $A_{2B}R$ inhibitor, but this inhibitor does not significantly influence the diastolic effect exerted by drugs that previously excited $A_{2A}R$ [89]. Therefore, both $A_{2A}R$ and $A_{2B}R$ are involved in ADO-induced erections, which may be associated with the regulatory effect of ADO on penile arterial vascular tension after $A_{2A}R$ and $A_{2B}R$ activation [74].

$A_{2B}R$ plays a pivotal role in ADO-mediated erection [81, 90-94]. The NO/cGMP signaling pathway for erection is T-dependent. Low T levels inhibit the AKT/eNOS/cGMP signaling pathway and cAMP generation in rat CC by downregulating $A_{2B}R$ expression, ultimately leading to ED [95]. Excessive ADO in CC has also been suggested to induce abnormal penile erections via $A_{2B}R$ activation [56, 96, 97]. Therefore, strategies to promote or block $A_{2B}R$ activation may be beneficial for treating ED or abnormal erection. Furthermore, ADO combined with $A_{2B}R$ can exert a neuromodulatory effect similar to that of $A_1R$ (**Figure 3**). It can relax CC by inhibiting the nerve transmission of excitatory SNS to the rabbit penis. This effect is more pronounced in CC with intact endothelium [98]. Few studies have examined the involvement of $A_3R$ in erection, and the active site on $A_3R$ may not be involved in the ADO-induced erectile process. Notably, local or oral administration of $A_3R$ allosteric regulator has improved erectile function of ED rats [99]. A new ligand acting on the $A_3R$ allosteric regulatory site may exert special effects that differ from those of orthosteric ligands. Future studies focusing on this ligand are warranted.

### ADO signaling, psychological stress, and negative emotions

Previous studies established myocardial ischemia models in patients with heart failure induced by psychological stress and ADO administration. The results indicated that the biological indicators of the two groups were highly consistent, suggesting that ADO administration simulates psychological stress responses [100]. Early findings in rodents indicated that psychological stress responses induced abnormal ADO signaling and that acute and chronic psychological stress responses induced by restraints in rats contributed to increased ATP hydrolysis and elevated ADO levels [101-103]. To simulate changes in ADO during human stress, continued exploration was conducted using zebrafish, which are genetically highly similar to humans. A zebrafish model of acute psychological stress was constructed by restricting activities. It was observed that the changes in ATP hydrolysis and ADO levels in zebrafish were consistent with those in rodents [104]. The same result was obtained in a zebrafish model of chronic psychological stress [105]. Psychological stress can also affect AR activity. For example, the activity of astrocyte $A_1R$ in the prefrontal cortex and hippocampus of a mouse model of social pressure-induced chronic stress was significantly inhibited, and the mouse exhibited a depression-like behavior [106]. Mouse model of chronic stress established by exposing it to continuous unpredictable stress exhibited anxiety-like behaviors, accompanied by decreased synaptic plasticity and increased $A_{2A}R$ expression at the end of allergic neurons in the hippocampus [107]. In conclusion, psychological stress can cause high ADO and $A_{2A}R$ expressions and low $A_1R$ expression in brain regions. This change is considered to be a strategy for the body to rebuild balance after stress, but the specific mechanism remains unclear [104].

ADO, $A_1R$, and $A_{2A}R$ can also mediate psychological stress and stress-related negative emotions. Studies have found that $A_1R$-knockout mice exhibit aggravated anxiety- and depression-like behaviors and are resistant to the antidepressant effect of sleep deprivation [108]; however, these effects are relieved after $A_1R$ activation [109-111]. Astrocyte activation can upregulate the expression of extracellular

ADO and activate $A_1R$ to mediate the elimination of fear, which can be blocked by $A_1R$ antagonists [112]. Therefore, $A_1R$ activation can alleviate stress-related negative emotions, which may be associated with neural regulation. $A_1R$ can also inhibit the release of presynaptic Glu and increase the permeability of postsynaptic $K^+$ channels, thus inhibiting nerve excitation to regulate mental state [45, 113]. Furthermore, $A_1R$ activation can upregulate the expression of synaptophysin Homer1a in the prefrontal cortex and hippocampus, which is a common target of antidepressant therapy drugs, such as fluoxetine and ketamine [108, 114, 115]. $A_1R$ agonists are currently used to treat stress-related negative emotions; however, due to some complex reactions, the development of $A_1R$-positive allosteric modifiers as powerful anti-anxiety drugs is being considered [116].

Knockout or inhibition of $A_{2A}R$ in hippocampal neurons can prevent the recovery of fear memory following stress [117]. The $A_{2A}R$ antagonist reversed the depression-like behavior induced by chronic psychological stress [107] and was proven to be effective against stress injury caused by maternal separation [118]. As a non-specific AR antagonist, caffeine can reduce $A_{2A}R$ mRNA expression in caudate nucleus neurons and regulate stress-related anxiety-like behaviors [119]. Contrarily, the $A_{2A}R$ agonists can aggravate anxiety in mice [120], and an abnormally high $A_{2A}R$ expression in the lateral septum can lead to depression-like behaviors [121]. Therefore, inhibiting $A_{2A}R$ activity is another strategy to improve the mental state and relieve negative emotions, and its mechanism may be associated with the following neuroinflammation control and neuroendocrine regulation [122]. First, $A_{2A}R$ activation can upregulate the expression of cysteinyl aspartate-specific proteinase-1 (caspase-1) and interleukin-1β (IL-1β), leading to a neuroinflammatory response [123]. Second, $A_{2A}R$ induces neurotoxicity by promoting Glu release and inhibiting 5-HT release [124]. In addition, $A_{2A}R$ mediates the ADO and CD73 regulation of amygdala neuronal excitability and synaptic plasticity [125]. When the activity of $A_{2A}R$ is inhibited by caffeine, the expression of brain-driven neurotrophic factor in the hippocampus is upregulated, suggesting that inhibiting $A_{2A}R$ activity can exert a neuroprotective effect [119]. Furthermore, the inhibition of $A_{2A}R$ activity is associated with the recovery of HPA axis activity. Plasma corticosterone levels returned to the levels present in normal circadian rhythm after blocking $A_{2A}R$, indicating that $A_{2A}R$ is directly involved in the stress response [118].

## Conclusion

Although the previous two reviews [24, 126] have clearly reported that ADO signaling is an important target for the treatment of ED, only the local effects of ADO in penile tissues have been highlighted. Penile erection is a complex event initiated by the brain, and PED is caused by psychological stress. In summary, the role of ADO signaling transduction in brain and penile tissues is important for the treatment of PED.

Our review found that the ADO/cAMP signaling pathway interacts with the dominant pathway of erection, namely, NO/cGMP, in both brain and penile tissues. In the brain, ADO and $A_{2A}R$ are expressed at high levels under psychological stress, whereas $A_1R$ is expressed at low levels. $A_1R$ signaling activation improves negative emotions via neuromodulation, whereas $A_{2A}R$ signaling inhibition improves negative emotions via neuroendocrine regulation and neuroinflammatory control. In penile tissues, ADO, $A_1R$, $A_{2A}R$, and $A_{2B}R$ were expressed at low levels in the ED state, $A_1R$ and $A_{2B}R$ activation negatively regulated sympathetic neurotransmitters via feedback, and $A_{2A}R$ and $A_{2B}R$ activation relaxed CC vascular smooth muscle cells. ADO combined with $A_1R$ and $A_{2A}R$ participating in psychological stress and erectile events is expected to be a candidate target for PED activation. However, the expression levels of ADO and $A_{2A}R$ in the brain and penis tissues showed a reverse trend, and the specific mechanism needs to be further explored. There is a similar expression trend of $A_1R$ in brain and penile tissues, and the use of $A_1R$ selective agonists may improve both erectile function and psychological status. As a PDEI and $A_{2A}R$ antagonist, caffeine may be beneficial for PED treatment. Notably, caffeine can also antagonize $A_1R$ and $A_{2B}R$ activities, and further research is warranted to support this conclusion. The $A_1R$ and $A_3R$ allosteric regulatory sites also demonstrate the potential for PED treatment and are worthy of further research in the future.

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## Disclosure of conflict of interest

None.

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