European Journal of Therapeutics
pISSN: 2564-7784
eISSN: 2564-7040

Eur J Ther. 2026;32(5):629–643.
https://doi.org/10.58600/eurjther3224

Review Article

Role of Adenosine in Testicular and Ovarian Ischemia/reperfusion Injury

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Received: 2026–07–01 **Accepted:** 2026–08–14 **Published Online:** 2026–09–07

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ABSTRACT

Objective: The purpose of this review is to comprehensively evaluate the potential role of adenosine in testicular and ovarian ischemia/reperfusion (I/R) injury. This review provides an overview of the current role of adenosine receptors in I/R injury due to testicular and ovarian torsion/detorsion (T/D). This review article presents an updated summary of the effects of adenosine receptor agonists and antagonists on testicular and ovarian tissues.

Methods: A comprehensive literature search was performed in PubMed, Web of Science, Cochrane Library, and ClinicalTrials.gov. The final search was conducted on June 15, 2026, covering the period from January 1, 2020. The search primarily focused on studies published within the last five years, but earlier significant studies were included where necessary to provide historical context or general information. Only original articles published in the English or Turkish language in peer-reviewed journals were included in the review. Narrative and systematic reviews, conference proceedings, expert opinions, and case reports were excluded from the review.

Results: Modulation of adenosine receptors may play an important role in the pathophysiology of testicular and ovarian ischemia. Among the receptor subtypes, A1 and A2A receptor agonists generally demonstrated protective effects in experimental models, whereas evidence regarding A2B and A3 receptors remains limited and, in some cases, inconsistent. The magnitude of these effects appears to depend on receptor subtype, pharmacological agent, dose, timing of administration, and experimental model. However, current evidence is derived predominantly from preclinical studies.

Conclusion: The use of adenosine receptor agonists may provide protective effects on testicular and ovarian damage induced by T/D or I/R. These agents may hold promise in the treatment of testicular and ovarian ischemia. However, the current evidence is predominantly preclinical, and more well-designed preclinical and clinical trials are needed before it can be implemented in clinical practice.

Keywords: adenosine receptor agonists, adenosine receptor antagonists, ischemia-reperfusion injury, ovarian torsion, testicular torsion

INTRODUCTION

Testicular torsion is a urological condition that requires urgent intervention, caused by the twisting of the spermatic cord, resulting in reduced blood flow to the affected testicle and potentially causing testicular atrophy [1]. Twisting of the testis along the spermatic cord causes venous congestion and reduced arterial blood flow to the testis, leading to ischemia [2]. The severity of ischemia depends on the duration of the torsion and the degree of cord rotation [1-4]. If the ischemia duration is prolonged, irreversible damage to the testis may occur. This damage typically occurs within a timeframe of 4 to 8 hours, depending on the degree of testicular rotation and the duration of the torsion. Therefore, in cases of testicular torsion causing testicular ischemia, rapid and accurate diagnosis along with urgent intervention is crucial. For this purpose, studies aimed at both developing effective new treatment strategies and better understanding the pathophysiology of torsion will make significant contributions to the literature.

The underlying etiology of testicular torsion is not fully understood. However, genetic factors, environmental factors, and a history of trauma may predispose a patient to torsion [4]. Testicular torsion typically presents with swelling in the scrotal area, and sudden-onset scrotal pain. Surgical intervention is essential to untwist the spermatic cord, correct the rotation of the twisted testicle, and facilitate tissue reperfusion [1]. Inducing detorsion, while beneficial, can also lead to several side effects. Reperfusion leads to the formation of free radicals, endothelial cell damage, microcirculation disorders, and germ cell loss [1–3].

Main Points

- Both testicular and ovarian torsion are pathologies that require immediate intervention and affect fertility.
- The ischemic damage caused by torsion and detorsion lead to numerous side effects.
- Four different receptors for adenosine (A_1, A_{2A}, A_{2B}, and A_3) have been identified. However, studies with adenosine agonists and antagonists in both ovarian and testicular tissue are very limited.
- A recent study indicates that the selective agonist of A_{2A} regadenoson can protect ovary against torsion/detorsion-induced injury.

Ovarian torsion, on the other hand, is a gynecological emergency in which complete or partial rotation of the ovary around its vascular pedicle interrupts venous and subsequently arterial blood supply, producing ischemia that progresses to infarction without prompt intervention [5]. It is an uncommon but important cause of acute pelvic pain and most often arises in association with an enlarged ovary or ovarian cyst [6,7]. It may affect females of all ages, including premenarchal and adolescent girls, in whom the diagnosis is often delayed [8,9]. Diagnosis is difficult because the symptoms are nonspecific, and Doppler ultrasonography is neither sensitive nor specific; normal Doppler flow has been reported in up to 60% of surgically confirmed cases [5,10].

Surgical management has progressively shifted from systematic oophorectomy toward ovarian-sparing detorsion over the past two decades, because the black-bluish, necrotic-appearing surface of a twisted ovary at surgery often reflects venous congestion rather than irreversible necrosis, and such ovaries frequently remain viable and recover follicular function after untwisting [5,11]. This shift has increased interest in pharmacological strategies to protect the ovary, because untwisting the ovary restores blood flow and also triggers a cascade of oxidative, inflammatory, and apoptotic events; in rat torsion/detorsion (T/D) models this cascade is accompanied by histopathological injury and oxidative and nitrosative stress [12]. No pharmacological adjunct to surgical detorsion has entered routine clinical practice so far.

Adenosine is an endogenous purine nucleoside formed by the linkage of the purine base adenine and ribofuranose through a glycosidic bond [13]. Adenosine accumulates rapidly in ischemic tissue as ATP is broken down, and through its receptors, it couples the metabolic state of the tissue to protective, anti-inflammatory, and vasoactive signalling; it is also pharmacologically tractable, with receptor agonists and antagonists already approved for human use [14,15]. Established use in an unrelated indication indicates only a known human safety and pharmacokinetic profile; it does not by itself imply efficacy or safety in gonadal ischemia/reperfusion (I/R) injury. This molecule plays a role in a wide range of functions in almost every system of the body. Four G protein-coupled receptor (GPCR) subtypes of adenosine have been identified: A_1, A_{2A}, A_{2B}, and A_3. These receptors are expressed and distributed in various cells and tissues, including the testis and ovary [14,16-18]. The adenosine system is both a useful framework for understanding testicular or ovarian

I/R injury and a candidate target for adjunctive therapy at the time of detorsion. Direct experimental evidence in the ovary, nevertheless, remains limited, so the case for adenosinergic intervention rests largely on adenosine biology and on evidence from other organs.

This review aimed to investigate the effects of adenosine agonists and antagonists on I/R injury due to testicular and ovarian T/D, to examine the contribution of adenosine receptor subtypes, and to evaluate potential new therapeutic targets.

MATERIALS AND METHODS

This review offers a detailed overview of existing and prospective pharmacotherapeutic options, along with their mechanisms of action. The online databases PubMed, Web of Science, Cochrane Library, and ClinicalTrials.gov were searched using a combination of keywords such as 'torsion,' 'detorsion,' 'ischemia,' 'reperfusion,' 'ovary,' 'ovarian,' 'testis,' and 'testicular,' along with their synonyms. Relevant keywords were searched individually and in various combinations using Boolean operators (AND, OR), with the search strategy adapted for each database. ClinicalTrials.gov was additionally searched to identify ongoing or unpublished studies relevant to the review topic. The final literature search was conducted on June 15, 2026. The search focused specifically on publications from the last five years. Studies published between January 1, 2020, and July 15, 2026, were primarily considered. However, earlier significant works were also included where necessary to provide historical background and essential information. Studies investigating adenosine or adenosine receptors in experimental or clinical models of testicular or ovarian T/D or I/R injury were eligible for inclusion. Only original articles published in the English or Turkish language in peer-reviewed journals were included. Reviews, conference abstracts, editorials, and case reports were excluded. Study selection was performed independently by all authors, with disagreements resolved by consensus. Titles and abstracts were screened independently by all reviewers, and potentially relevant articles were retrieved for full-text assessment. Any disagreements were resolved through discussion until consensus was reached. This review aims to examine the published literature and provide clinicians with a better understanding of the diagnosis and treatment of testicular or ovarian T/D or I/R injury. We supplemented the direct search results with relevant referenced articles within the full text of the papers identified from the search engines to ensure a more comprehensive appraisal of the subject.

RESULTS

Prevalence/incidence of testicular or ovarian torsion

The most common population affected by testicular torsion includes children in a bimodal distribution, with the most cases occurring in the first year of life and between 12 and 18 years, although cases do occur in adults [19]. The incidence of testicular torsion is approximately 1 in 4,000 in men under 25 years of age [20]. It has been reported that testicular torsion is diagnosed in 10–15% of patients presenting with acute scrotal pain, and orchiectomy is performed in 42% of patients undergoing scrotal exploration due to testicular torsion [4].

The incidence of pediatric ovarian torsion is estimated to be 4.9 cases per 100,000 girls per year [21]. Ovarian torsion occurs in around 2%–15% of patients who have surgical treatment of adnexal masses [22]. About 10%–22% of ovarian torsion occurs in pregnancy [23]. An older surgical series reported adnexal torsion in approximately 2.7% of emergency gynecologic operative procedures, corresponding to 102 of 3,772 procedures over a 10-year period [24].

Pathophysiology

Studies have shown that testicular torsion at 1, 2, and 4 hours negatively affects spermatogenesis and that germ cell loss occurs independently of Leydig and Sertoli cell loss, resulting in decreased sperm count and motility [25,26–28]. Testicular torsion often leads to infertility on the torsioned side, and surgical orchiectomy may be necessary. While fertility can be preserved with early intervention, prolonged torsion can compromise both testes, reducing blood flow to the contralateral testis and initiating tissue damage due to the production of reactive oxygen species (ROS) [29].

In rat testes, after 3 hours of ischemia and 3 hours of reperfusion, neutrophil recruitment, ROS formation, pro-inflammatory cytokines, adhesion molecules, lipid peroxidation, apoptosis, hypoxia, and alterations in microvascular blood flow occurred [26,1,28]. Furthermore, I/R damage leads to a decrease in total antioxidant capacity, superoxide dismutase (SOD), catalase, and glutathione peroxidase (GPx) levels, while malondialdehyde (MDA) levels increase. A low Johnsen score indicates impaired testicular spermatogenesis, while a high Cosentino score indicates damage to testicular tissue. Histopathologically, Johnsen and Cosentino scores become irregular in testicular torsion [27,31,6,30]. It has been suggested that germ cell apoptosis resulting from testicular torsion is linked to testicular lipid

peroxidation products, nitric oxide (NO), and myeloperoxidase (MPO) levels [25,31]. Therefore, the induced oxidative stress results not only from reduced oxygen supply but also from the suppression of the testicular antioxidant defense mechanism [6]. Following 2 hours of testicular I/R, proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1β (IL-1β), and IL-6 increase in rats [28]. This condition exhibits a significant increase in inflammatory markers [1,32]. Furthermore, as a result of I/R, the apoptosis pathway is activated by a time-dependent increase in p53, p21, and Bax proteins in DNA damage caused by oxidative stress. This, along with the activation of apoptotic genes, contributes to the failure of spermatogenesis [33]. Infertility following testicular torsion is influenced by the severity of ischemia and the extent of damage to the contralateral testis. The exact pathophysiology of torsion-related infertility is unclear [1]. However, one study in rats showed that even when blood flow returns to normal after 1 hour of torsion, testicular weight decreased on day 7 post-torsion and spermatogenesis was impaired after 30 days [29,34]. In addition to oxidative stress, decreased ATP production, reduced glycogen levels, and increased Ca+2 levels in the cell following I/R injury may also play a significant role in the pathology caused by testicular torsion [6]. As a result of ischemia, purines such as hypoxanthine and xanthine, which result from ATP catabolism, accumulate. These changes lead to damage in the testicular cell membrane [1].

The testis is a metabolic organ and therefore highly sensitive to hypoxia [30,35]. Hypoxia impairs the supply of oxygen and nutrients to the testicular tissue. This results in tissue acidosis, the failure of cellular ATP-dependent pumps, and the expulsion of cellular K+ due to anaerobic glycolysis, which limits ATP generation and creates lactic acid. During ischemia, a number of pro-inflammatory genes and transcription factors are activated. Hypoxia-induced increases in testicular Ca2+ largely cause testicular damage and decreases in ATP and glycogen levels. When ATP-dependent pumps dysfunction, K+ is excreted, and Ca2+ ions build up inside cells, impairing testicular metabolic function, cell lysis, and volume alterations. Additionally, testicular hypoxia also increases prostaglandin E1 (PGE1) production, which in turn suppresses tissue growth factor β1 (TGFβ1), leading to collagen deposition and vascular dysfunction. Furthermore, hypoxia inhibits the proliferation of germ cells by upregulating vascular endothelial growth factor (VEGF) [31,36]. Hypoxia initiates ROS formation, which in turn activates lipid peroxidation, DNA damage, and apoptosis in testicular and sperm cells [35]. Additionally, hypoxia damages mitochondria and triggers oxidative stress by activating inducible nitric oxide synthase (iNOS) and xanthine oxidase [37]. Edema is usually the first structural change seen in the cell during the ischemic phase. Macroscopically, it appears as pallor, increased testicular turgor, and weight. Microscopically, it is seen as small, clear cytoplasmic vacuoles characterized by vacuolar degeneration [36].

On reperfusion, restored oxygen delivery paradoxically generates ROS and reactive nitrogen species, which combine to form peroxynitrite and initiate endothelial and parenchymal cell death, adhesion-molecule expression, and neutrophil recruitment, reflected in increased myeloperoxidase activity [32]. Importantly, the same ATP catabolism that supplies the substrate for this oxidative burst also raises extracellular adenosine, linking the injury cascade directly to the receptor system discussed below [33,34].

While the exact time interval between the increase and decrease in testicular weight due to ischemia is unclear, studies have shown that I/R leads to a reduction in testicular weight [35,36] [39,40]. This decrease in testicular weight is due to severe post-reperfusion ROS release and a decrease in testicular metabolism. Additionally, I/R injury results in an increase in the Cosentino score, an accumulation of inflammatory cells, intratubular edema, and a decline in testicular histology. It also dramatically decreases the diameter and area of the seminiferous tubules as well as the diameter of the seminiferous lumen [36,40]. The primary endocrine function of the testis is the synthesis of testosterone by Leydig cells. Testicular I/R damage reduces circulating testosterone levels [41-43]. This decrease in serum testosterone lasted for more than a week [43]. Since Leydig cell mass is significantly reduced, the decrease in testosterone levels is associated with impaired Leydig cell function [37,40,43]. In addition, some studies report contralateral involvement after unilateral I/R injury, with a decrease in contralateral testicular volume and tubule diameter [38,44]. Studies have shown that in unilateral testicular torsion, oxidative stress and inflammation parameters are increased in both testes, p53 signalling is increased, and apoptosis is initiated through the downregulation of Bcl-2 [35,39,45,46].

The ovarian response to T/D follows the canonical I/R cascade [40]. This sequence is conserved across organs: a metabolic supply-demand imbalance with severe tissue

hypoxia and microvascular dysfunction during ischemia, followed by reperfusion-triggered innate immune activation and programmed cell death [33,34]. During the ischemic phase, depletion of oxygen and nutrients precipitates ATP exhaustion and its stepwise catabolism through ADP, AMP, and adenosine to hypoxanthine; on reperfusion, xanthine oxidase oxidizes the accumulated hypoxanthine with concomitant superoxide generation. Adenosine, therefore, has a central role in this process. The same purine breakdown that produces reperfusion oxidative stress also raises extracellular adenosine, which can then act through its receptors.

Both phases contribute to the final injury: ischemia itself causes ATP depletion and, if prolonged, irreversible necrosis, so its duration determines how much tissue can still be salvaged, while reperfusion adds the oxidative and inflammatory component described above for the testis. In rat ovarian T/D models, the reperfused ovary shows histopathological injury alongside marked oxidative and nitrosative stress, with 3-nitrotyrosine and disrupted thiol/disulfide homeostasis as the markers most consistently reported [12].

Two features specific to the ovary are relevant to adenosinergic intervention. One concerns the goal of treatment: preserving the primordial follicle pool, which determines reproductive lifespan, not ovarian structure as such; anti-Müllerian hormone (AMH) is the most accessible serum marker of ovarian reserve, but an indirect one, since it is produced by growing rather than primordial follicles [41]. Another concern is signalling the gonadotropin-driven cyclic adenosine monophosphate (cAMP) axis that governs steroidogenesis and folliculogenesis [42] is the same second-messenger pathway engaged by the Gs-coupled adenosine receptors (A_{2A}, A_{2B}), so adenosinergic stimulation acts on a signalling axis already central to ovarian physiology. This overlap is double-edged: although it offers a route to protection, strong or sustained cAMP elevation could, in principle, disturb normal folliculogenesis or steroidogenesis; this has not been examined.

DISCUSSION

Adenosine Receptors

Adenosine is a ubiquitous purine-based nucleoside that regulates various physiological processes through the activation of specific GPCRs known as adenosine receptors [43,52]. Adenosine-binding P1 purinergic receptors, also called adenosine receptors, are divided into four groups: A1, A2A, A2B, and A3. They belong to the class-A (rhodopsin-like) family of GPCR and have 7 transmembrane domains. They associate with G proteins to trigger intracellular modulations [52,53]. A1 and A3 receptors reduce adenyl cyclase and intracellular cAMP via inhibitory G protein (Gi), while A2A and A2B receptors activate adenyl cyclase and protein kinase A (PKA) signalling via stimulatory G protein (Gs)[53].

Physiologically, ATP is released from cells into the tissue environment in response to damage experienced during hypoxia [43,53]. When ATP is depleted, intracellular AMP and adenosine concentrations increase and function as metabolic stress signals. These stress signals trigger adenosine receptor activation by extracellular adenosine and activation of adenosine receptor-independent mechanisms. Extracellular adenosine can also be produced locally during an inflammatory response [44,54]. This response triggers a series of intracellular processes to restore physiological oxygen levels, reduce inflammatory responses, promote homeostasis, and prevent long-term tissue damage [53].

Given their importance in various systems of the body, understanding the mechanisms of adenosine and its receptors opens up new therapeutic perspectives for a wide range of pathologies and medical conditions. These receptors are distributed throughout the body, including the central nervous system, cardiovascular system, peripheral organs, and immune system [55].

Adenosine signalling in I/R operates at two levels: the ecto-enzymatic generation of extracellular adenosine and the four receptor subtypes through which it acts. During ischemia, adenosine accumulates extracellularly through ATP catabolism and CD39/CD73-mediated ectonucleotidase activity. It engages four GPCRs (A_1, A_{2A}, A_{2B}, and A_3) whose activation produces tissue protection through metabolic depression, anti-inflammatory immune modulation, vasodilation, and inhibition of mitochondrial permeability transition pore opening (Figure 1) [14,15,45]. The hypoxia-adenosine link is a recurring theme of I/R biology, with adenosine production transcriptionally amplified under low oxygen [45]. Upstream of the receptors, endothelial-targeted augmentation of CD39, the ecto-enzyme that initiates extracellular adenosine generation, reduces infarct volume and preserves blood-brain barrier integrity in murine global ischemia [46], identifying the ecto-enzymatic axis as a target distinct from receptor-level intervention.

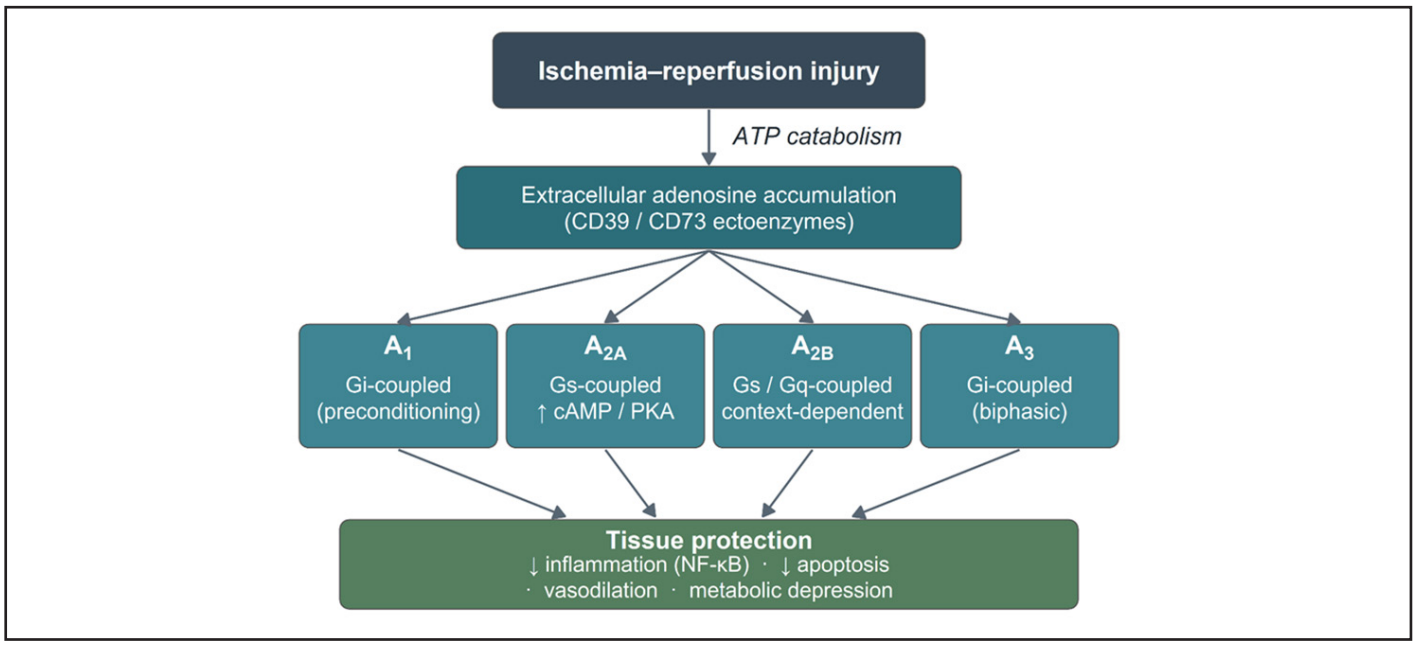

Figure 1. Adenosine generation and receptor signalling in I/R injury. During I/R, ATP is catabolized to adenosine, which accumulates extracellularly through CD39/CD73 ectoenzyme activity and engages four G protein-coupled receptors. A_1 and A_3 are Gi-coupled (A_1 acting largely through preconditioning, A_3 with biphasic, dose-dependent effects), whereas the Gs-coupled A_{2A} (raising cyclic AMP and engaging protein kinase A) and the Gs/Gq-coupled, context-dependent A2B are the subtypes most consistently associated with protection at reperfusion in non-gonadal organs. The pathways shown derive largely from non-gonadal models; their operation in the ovary has not been established. Downstream, this signalling attenuates NF-κB-driven inflammation and apoptosis and promotes vasodilation and metabolic depression, producing tissue protection. NF-κB, nuclear factor κB.

Adenosine Receptor Agonists and Antagonists

Specific adenosine receptor agonists and antagonists are being developed, and therapeutic applications benefiting both the peripheral and central nervous systems are being investigated. These receptors exert their effects via GPCR, thus making it possible to synthesize selective agonists and antagonists [47]. Adenosine is a naturally occurring purine nucleoside that non-selectively activates all four receptor subtypes. Due to their widespread expression throughout the body, adenosine receptors are involved in a number of pathological situations, such as inflammatory, neurological, cardiovascular, cancer, and sleep regulation [48]. For each adenosine receptor, there are direct-acting and potent agonists and antagonists available. Some of these agents are approved for use in humans. The non-selective agonist adenosine is approved for the treatment of supraventricular tachycardia; the selective agonist of A2A, regadenoson, is approved for clinical use in myocardial perfusion imaging. Adenosine A3 receptor agonists piclidenoson and namodenoson are in the clinical trial phase for autoimmune, inflammatory, and liver pathologies. Istradefylline, an adenosine A2A receptor antagonist, is used in the treatment of Parkinson's disease. AZD4,365 and PBF-509, A2A receptor antagonists, are currently in clinical trials for cancer treatment [44]. Table 1 summarizes various adenosine receptor agonists and antagonists used in preclinical and clinical studies.

A_{2A} and A_{2B} receptors, two Gs-coupled receptor subtypes, are thought to exert protective effects in some organs during reperfusion; however, their roles in testicular and ovarian I/R have not yet been fully elucidated. It has been shown that A_{2A} activation raises cAMP and engages PKA signalling, suppressing NF-κB-driven cytokine production [42], and regulates the autophagy-apoptosis balance [49]. A_{2B} couples to both Gs and Gq and has a low affinity for endogenous adenosine, so it is engaged only at the supraphysiological concentrations reached at reperfusion. Its effects are context-dependent: A_{2B} activation suppresses cytokine production by inhibiting the NF-κB pathway in hepatic injury [50] but can act as a pro-inflammatory mediator in other settings [14,15]. A_1 and A_3 are Gi-coupled. A_1 confers protection largely through preconditioning, before ischemia. A_3 agonism is cardioprotective and cerebroprotective in other organs but has biphasic, dose-dependent effects [14,15]; neither subtype has been studied in the ovary.

Table 1. Classification and mechanisms of action of adenosine receptors

Name	A_1AR	A_{2A}AR	A_{2B}AR	A_3AR
G protein coupling	**Gi/o**	**Gs**	**Gs/Gq**	**Gi/Gq**
Transduction mechanisms	↓Adenylyl cyclase ↑Phospholipase C	↑Adenylyl cyclase ↑MAP kinase	↑Adenylyl cyclase ↑Phospholipase C ↑MAP kinase	↓Adenylyl cyclase ↑Phospholipase C ↑PI 3-kinase ↑MAP kinase
Selective agonists	CCPA, CHA, CPA, ENBA, Trabodenoson	HENECA, CGS21680, CPCA, DPMA (CGS24012), Regadenoson, UK-432097	BAY60-6583	IB-MECA (CF-101), MRS5698, Namodenoson
Selective antagonists	DPCPX, DMPX, PSB36, Rolofylline (KW-3902)	Istradefylline, SCH442416, SCH58261, ZM241385	Enprofylline, MRS1754, PSB-1115, PSB-603	MRE3008F20, MRS1523, MRS-1191, PSB-10

BAY60–6583, 2-[[6-amino-3,5-dicyano-4-[4-(cyclopropylmethoxy)phenyl]-2-pyridinyl]thio]-acetamide; CCPA, 2-chloro-N-cyclopentyladenosine; CHA, N6-Cyclohexyladenosine; CPA, N6-Cyclopentyladenosine; CPCA, 5'-(N-Cyclopropyl)carboxamidoadenosine, DMPX, 3,7-Dimethyl-1-propargylxanthine; DPCPX, 8-cyclopentyl-1,3-dipropylxanthine; ENBA, (±)-5'-Chloro-5'-deoxy-ENBA; HENECA, 2-Hexynyl-5′-N-ethylcarboxamidoadenosine

Adenosine Receptors in Testicular I/R Injury

The A_1 receptor was the first adenosine receptor identified in the testis of rats [51]. In one study, the binding of cyclohexyladenosine (CHA), an adenosine A_1 receptor analogue, to testicular cell sections taken from immature rats was evaluated, demonstrating adenosine receptor expression in Sertoli cells [18]. In another study, mRNA transcripts encoding all adenosine receptors were observed in mouse testicular peritubular cells; however, only A_1, A_{2A}, and A_{2B} mRNAs were found in human testicular peritubular cells. Furthermore, A_{2B} has been found to localize in human Sertoli cells, germ cells, and peritubular cells. BAY60–6,583, a selective agonist of the adenosine A_{2B} receptor, has been reported to play a pro-inflammatory role in the testis by increasing IL-6 levels in human testicular peritubular cells [52]. The acidic pH of the epididymis is essential for sperm maturation and storage. This acidity is maintained by proton-pumping vacuolar H^+-ATPase present in the membranes and intracellular vesicles of epididymal clear cells. When luminal pH rises to alkaline levels, proton release by numerous vacuolar ATPases in the microvilli increases, causing the luminal pH to decrease. The apical accumulation of vacuolar ATPase, induced by alkaline pH in clear cells, is dependent on Ca^{2+} and cAMP elevation, but this relationship has not been clearly established [51]. When adenosine receptor expression in all epididymis and epididymal epithelial cells was examined in rats, all four adenosine receptors were highly expressed throughout the epididymis; however, A_1, A_{2B}, and A_3 were detected in epididymal epithelial cells. When rat epididymis was perfused *in vivo* with luminal adenosine, the length of vacuolar ATPase-labelled microvilli was increased; a PKA inhibitor significantly inhibited this effect. Accordingly, apical membrane accumulation of adenosine-dependent vacuolar ATPase is associated with PKA. These results demonstrate the involvement of the A_{2B} receptor, the only subtype that triggers cAMP increase in epididymal epithelial cells [53]. Adenosine is also an important mediator of smooth muscle contraction in the vas deferens and epididymis. Norepinephrine-induced vas deferens contractions were increased via A_1 receptor agonists, while in the prostate section, they were inhibited via both A_{2A} and A_{2B} receptors [54].

Studies investigating the role of adenosine receptors in testicular I/R are quite limited in the literature. When the effects of polydeoxyribonucleotide (PDRN), a heterogeneous polynucleotide preparation with adenosine A_{2A} receptor agonist activity rather than a single selective agonist, were examined in testicular I/R, it was shown to reduce histological damage, improve spermatogenic activity, and significantly increase VEGF mRNA and protein and eNOS mRNA. However, combination therapy with the antagonist 3.7-dimethyl-1-propargyxanthin (DMPX) reversed the positive effects. This VEGF response suggests that it may improve the tissue reperfusion process, including the regulation of testicular blood vessel vasodilation [55]. Another study demonstrated that PDRN increased testicular weight to the levels of healthy rats, raised testosterone levels, decreased tissue MDA levels, and increased glutathione levels in the testes after testicular I/R. These positive effects have been further enhanced with selenium-based combination therapy. The PDRN used in treatment has been shown to significantly reduce

phosphorylated extracellular signal-regulated kinases (ERK) 1/2 levels, thereby reducing testicular I/R-related inflammation, inhibiting apoptosis, and positively affecting spermatogenesis. Furthermore, increased hypoxia-inducible factor 1-alpha (HIF-1α) expression in Leydig cells during I/R was found to be associated with decreased serum testosterone levels; this decrease, paralleling the decrease in HIF-1α expression, was significantly reversed after PDRN administration [56].

The effects of PDRN have also been investigated in different testicular injury models. In cadmium-induced damage to the blood-testis barrier, PDRN similarly reduced phosphorylated ERK 1/2 levels and apoptosis, while increasing testosterone levels. In addition, in cases of blood-testis barrier damage, PDRN treatment reduced elevated levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) to near-control levels; histologically reduced testicular damage and macrophage migration; and also improved damage to the blood-testis barrier [57]. In testicular damage caused by varicocele, combined treatment with PDRN and selenium resulted in increased testosterone, glutathione, and GPx levels. They decreased mRNA expression of the nucleotide-binding oligomerization domain (NOD)-, leucine-rich repeat (LRR)-, and pyrin domain-containing protein 3 (NLRP3), caspase-1, and IL-1β levels [58].

Cordycepin, an adenosine analogue, has been shown to reduce TNF-α and MDA levels in testicular I/R injury, increase total antioxidant capacity, and decrease edema and inflammation [59].

Adenosine Receptors in Ovarian I/R Injury

In a rat ovarian I/R model, the A_{2A} agonist regadenoson, administered before ischemia, reduced nitrosative stress (3-nitrotyrosine) and preserved thiol/disulfide homeostasis. The A_{2A} antagonist istradefylline reversed this thiol protection, consistent with a receptor-mediated effect [60]. The findings were, however, mixed: the response was dose- and biomarker-dependent, serum MDA and histological injury scores were unchanged, and no reproductive endpoint (AMH or primordial follicle counts) was measured, leaving the net direction of ovarian A_{2A} signalling unresolved. The same study also formulated an istradefylline nanosuspension with antioxidant effects comparable to the free drug, a proof of principle for nanoformulation of a poorly water-soluble adenosine ligand.

Beyond this study, adenosinergic options in the ovary remain largely unexplored. The methylxanthine pentoxifylline has been tested: in a rat unilateral ovarian I/R model, it reduced MDA and nitric oxide, most clearly when combined with vitamin E, with bilateral effects suggesting a systemic, circulation-mediated component [61]. Pentoxifylline is, however, a non-selective phosphodiesterase inhibitor with only weak adenosine-receptor antagonist activity, so its benefit most plausibly reflects phosphodiesterase inhibition together with rheological and antioxidant effects, not adenosine-receptor signalling. Genuine indirect adenosinergic intervention, raising extracellular adenosine to engage the receptors, has not been evaluated. Dipyridamole, an equilibrative nucleoside transporter inhibitor that raises extracellular adenosine, would act through this route but has not been tested in the ovary. Selective A_1, $A_{2B,}$ and A_3 modulation has likewise not been reported in ovarian I/R. A_{2B} receptors may represent promising therapeutic targets. A_1 (preconditioning-dependent) and A_3 (biphasic), on the other hand, are less suited to the post-detorsion window, and none of these subtypes has been studied in the ovary. The adenosine system targets and their ovarian status are summarized in Table 2. A summary of experimental studies investigating pharmacological agents in testicular and ovarian T/D-induced I/R injury is presented in Table 3.

Future Directions

Three priorities follow. First, reproductive-endpoint standardization: future adenosinergic studies in the ovary should incorporate long-term AMH dynamics and primordial follicle counts measured at weeks-to-months follow-up, the endpoints absent from the only existing study, instead of relying on acute oxidative-stress markers and 24-hour histopathology alone. Long-term assessment should extend beyond AMH and follicle counts to functional outcomes: estrous cyclicity, hormone profiles, ovulation, pregnancy rates and offspring number. Second, receptor-by-subtype and upstream priorities: A_1, $A_{2B,}$ and A_3 modulation as primary ovarian interventions remain unexplored; the joint engagement of A_{2A} and A_{2B} at reperfusion in the heart [45] raises the open question of whether combined A_{2A}-plus-A_{2B} agonism would be protective or, given the variable and sometimes pro-inflammatory behavior of A_{2B}, potentially deleterious in the ovary, and the CD39/CD73 ecto-enzymatic axis that sets the rate of adenosine generation has produced protection in cardiac and cerebral I/R [46] but has not been examined in the ovary. Third, detorsion-timed dosing and organ-targeted delivery: efficacy must be re-established with agents given at reperfusion, not before ischemia, and

Table 2. Adenosine-system targets and their status in ovarian I/R

Target	Coupling / mechanism	Tested in ovarian I/R?	Key finding or status
Extracellular adenosine generation (CD39/CD73)	Ecto-enzymatic ATP → adenosine	No	Protective in cardiac and cerebral I/R; untested in the ovary [46]
A_{2A} receptor — agonist (regadenoson)	Gs → ↑cAMP; anti-inflammatory, antioxidant	Yes	↓ 3-nitrotyrosine, preserved thiol/disulfide homeostasis; histology and serum MDA unchanged; no reproductive endpoint [60]
A_{2A} receptor — antagonist (istradefylline)	A_{2A} receptor blockade	Yes	Reversed the agonist's thiol protection; dose- and biomarker-dependent response; nanosuspension comparable to free drug [60]
A_1 receptor	Gi; preconditioning	No	Protective only before ischemia; not feasible (torsion diagnosed after onset)
A_{2B} receptor	Gs and Gq; low affinity; context-dependent	No	Anti-inflammatory in hepatic injury but pro-inflammatory in other settings; untested in the ovary [50]
A_3 receptor	Gi; biphasic	No	Cardioprotective in other organs but biphasic; unexplored in the ovary
Pentoxifylline (methylxanthine)	Non-selective PDE inhibition; weak adenosine antagonism	Yes	↓ MDA, ↓ NO, greater with vitamin E; benefit not via adenosine agonism [61]
Dipyridamole	Raises extracellular adenosine (transporter inhibition)	No	Would engage receptors indirectly; untested

nanocarrier formulations of poorly soluble adenosine ligands should be advanced to limit off-target effects.

Limitations

Several factors explain the absence of clinical adoption of any pharmacological adjunct to ovarian detorsion, and they bear directly on adenosinergic translation. Because torsion is diagnosed only after the onset of ischemia [5], preconditioning strategies are excluded, and intervention is restricted to the reperfusion phase [14], which suits the Gs-coupled A_{2A} and A_{2B} receptors. The endpoint that ultimately matters clinically is preservation of ovarian reserve and fertility, not the acute biomarkers used in preclinical work, and ovarian torsion as a surgical emergency creates logistical and ethical challenges for randomized trials, including informed consent under time pressure and the disproportionate enrollment of pediatric and adolescent populations [5]. Against these barriers, some adenosinergic agents offer practical features: regadenoson, for example, is given intravenously, has a short half-life and a well-characterized hemodynamic profile, and is already FDA-approved as a pharmacological cardiac stress agent [62]. Whether such an agent could be given as a single dose at detorsion is, however, only a hypothesis: in the available ovarian model, the agonist was given before ischemia rather than at detorsion, and the supporting outcome data derive from cross-organ porcine cardiac-arrest models [63,64]. Regadenoson should therefore be regarded as a theoretical candidate for repurposing only: its established use in myocardial perfusion imaging says nothing about efficacy or safety in gonadal I/R, and any such use would face a high safety threshold, since torsion disproportionately affects children and gonadal protection is not a life-threatening indication. Two limitations affect adenosinergic translation specifically. The first is the off-target profile of systemic adenosinergic agents, which produce bradycardia, atrioventricular block, vasodilation, hypotension, and bronchoconstriction arising from the combined engagement of several receptor subtypes rather than any single one. The second is formulation: the limited water solubility of istradefylline [65] and similar ligands constrains delivery, and although the istradefylline nanosuspension developed in the ovarian model shows that nanoformulation is technically feasible, an antioxidant effect of an A_{2A} antagonist formulation does not establish that A_{2A} antagonism is beneficial in ovarian I/R. Nanoformulation should be evaluated not on solubility alone but on tissue targeting, release profile, pharmacokinetics and safety, particularly in pediatric populations. In our view, future studies should determine the most appropriate pharmacokinetic profile, specific half-life, the optimal dose, exposure duration, timing of administration, and targeted delivery strategy for evaluating adenosine receptor agonists as an alternative treatment to prevent infertility due to torsion.

Table 3. Summary of experimental studies investigating pharmacological agents in testicular and ovarian torsion/detorsion-induced ischemia/reperfusion injury.

Model	Ischemia duration	Reperfusion duration	Agent	Timing of administration	Main findings	Study
Sprague-Dawley rat testicular torsion I/R model	1 h	1, 7, and 30 days	PDRN (8 mg/kg) ± DMPX (0.1 mg/kg)	i.p., immediately after detorsion	T/D: histological injury↑, Johnsen score↓ PDRN: VEGF mRNA/protein↑, VEGFR1↑, eNOS↑, histological injury↓, Johnsen score and spermatogenesis↑ DMPX: markedly reduced the protective effects of PDRN.	Minutoli et al., 2012 [55]
Sprague-Dawley rat testicular torsion I/R model	1 h	30 days	PDRN (8 mg/kg) ± Selenium (3 mg/kg)	i.p., daily for 30 days during reperfusion	T/D: Leydig cells HIF-1α↑, MDA↑, pERK1/2↑, apoptosis↑, testicular weight↓, GSH↓, testosterone↓, Nrf2↓, structural injury↑ PDRN or selenium: MDA↓, apoptosis↓, Leydig-cell HIF-1α↓; testicular weight↑, GSH↑, testosterone↑, Nrf2↑, tissue organization improved.	Antonuccio et al., 2022 [56]
Wistar rat testicular I/R model	2 h	4 h	Cordycepin (10 mg/kg)	i.p., at detorsion	T/D: TNF-α↑, MDA↑, TOS↑, edema/inflammation↑, spermatozoa count↓ Cordycepin: TNF-α↓, MDA↓, TOS↓, TAS↑, edema/inflammation↓, spermatozoa count↑; histological injury↓.	Okur et al., 2018 [59]
Wistar rat, ovarian I/R model (ovarian artery ligation, not surgical torsion)	2 h	2 h	Regadenoson (3 and 30 μg/kg) ± Istradefylline (0.3 and 3 mg/kg)	i.p., 1 h before ischemia	I/R: serum MDA↑, serum and tissue 3-NT↑, serum disulfide↑, tissue Cu/Zn-SOD↓, serum native thiol↓, histopathological injury↑ Regadenoson: serum and tissue 3-NT↓, serum disulfide↓, serum native thiol↑ (30 μg/kg); tissue Cu/Zn-SOD↑ (3 μg/kg); no significant effect on serum MDA; histological appearance improved but scores not statistically significant Istradefylline: tissue Cu/Zn-SOD↑; pretreatment abolished the effects of regadenoson, indicating a receptor-mediated component; limited protective effect overall.	Mammadov et al., 2026 [60]

Abbreviations: 3-NT, 3-nitrotyrosine; **Cu/Zn-SOD**, copper/zinc superoxide dismutase; **DMPX**, 3,7-dimethyl-1-propargylxanthine; **eNOS**, endothelial nitric oxide synthase; **GSH**, reduced glutathione; **HIF-1α**, hypoxia-inducible factor-1 alpha; **MDA**, malondialdehyde; **NRF2**, nuclear factor erythroid 2-related factor 2; **pERK1/2**, phosphorylated extracellular signal-regulated kinase 1/2; **PDRN**, polydeoxyribonucleotide; **TAS**, total antioxidant status; **T/D**, torsion/detorsion; **TNF-α**, tumor necrosis factor-alpha; **TOS**, total oxidant status; **VEGF**, vascular endothelial growth factor; **VEGFR1**, vascular endothelial growth factor receptor 1.

One of the major limitations in the field of adenosine is the lack of direct measurements of tissue adenosine levels in the testis or ovary. This kind of measurement precludes the precise localization of endogenous adenosine, intracellular or extracellular, and also the understanding of its cellular origin. Therefore, further studies should be designed to determine adenosine concentrations in the testicular and ovarian tissues or fluids.

Since inflammation and oxidative/nitrosative stress are closely associated with the development of I/R injury, combined pharmacological treatment strategies may potentially generate additive or synergistic efficacy. However, before proceeding to this stage, the receptor specificity, dose-response, pharmacokinetics, and safety of each agent must be demonstrated in preclinical studies.

This review has several limitations. First, only studies published in English and Turkish are included. Second, the available evidence is based on experimental animal studies with significant heterogeneity in study design, I/R protocols, pharmacological applications, and outcomes. Furthermore, because this is designed as a narrative review, no formal methodological quality or risk of bias assessment has been conducted. Finally, direct evidence regarding ovarian I/R injury is limited compared to testicular studies.

CONCLUSION

Adenosine is closely tied to the I/R cascade: it accumulates as ATP is broken down during ischemia. I/R injury due to testicular and ovarian torsion is a serious pathology affecting fertility that requires immediate intervention. The search for pharmacological agents that can reduce or limit I/R injury due to torsion continues. Adenosine receptors, widely distributed throughout the body, are targeted in the treatment of many diseases. Agonists and antagonists of these receptors have been developed and investigated in various tissues. Clinically approved adenosinergic agents and feasible nanosuspension formulations make the system an attractive candidate, but their protective roles in the ovary and testis are not yet established. However, the tissue targeting, release profile, and pharmacokinetic properties of nanoformulations still need to be evaluated. Therefore, in the future, research into the effects of adenosine receptor ligands, particularly adenosine receptor agonists, on testicular and ovarian injury may provide a new perspective and influence the development of new treatment strategies. Standardized long-term reproductive-endpoint assessment, detorsion-timed dosing, and exploration of A_1, A_{2B}, A_{2A}, A_3, and CD39/CD73 targets are also required before it can advance to clinical investigation.

Acknowledgments: Author N. Igci gratefully acknowledges the financial support provided by TUBITAK Directorate of Science Fellowships and Grant Programmes (BIDEB) through the 2211-A National PhD Scholarship Program.

Funding: This work were supported by Gaziantep University Scientific Research Projects Coordination Unit (Project numbers: TF.DT.21.46 and TF.DT.25.17) and by the Scientific and Technological Research Council of Türkiye (TUBITAK, SBAG-124S442).

Conflict of Interest: The authors declare that there are no conflicts of interest.

Informed Consent: Not applicable.

Ethical Approval: Ethics committee approval was not required for this review article.

Author Contributions: Conception: Nazlıcan İğci; Şeniz Demiryürek - Design: Şeniz Demiryürek - Supervision: Şeniz Demiryürek - Data Collection and/or Processing: Nazlıcan İğci, Azad Mammadov - Analysis and/or Interpretation: Şeniz Demiryürek – Literature Review: Nazlıcan İğci, Azad Mammadov, Şeniz Demiryürek, Abdullah Tuncay Demiryürek - Writing: Nazlıcan İğci, Azad Mammadov, Şeniz Demiryürek, Abdullah Tuncay Demiryürek - Critical Review: Şeniz Demiryürek, Abdullah Tuncay Demiryürek.

REFERENCES

[1] Karaguzel E, Kadihasanoglu M, Kutlu O (2014) Mechanisms of testicular torsion and potential protective agents. Nat Rev Urol. 11(7):391–399. https://doi.org/10.1038/nrurol.2014.135

[2] Wenn J, Murray BP, Kynast RW, Zhen J (2024) An uncommon cause of testicular infarct: a case report and review of the literature of testicular infarcts from laparoscopic inguinal hernia repair. J Emerg Med. 67(4):e375-e378. https://doi.org/10.1016/j.jemermed.2024.05.006

[3] Jacobsen FM, Rudlang TM, Fode M, Østergren PB, Sønksen J, Ohl DA, Jensen CFS; CopMich Collaborative (2020) The impact of testicular torsion on testicular function. World J Mens Health. 38(3):298–307. https://doi.org/10.5534/wjmh.190037

[4] Laher A, Ragavan S, Mehta P, Adam A (2020) Testicular torsion in the emergency room: A review of detection and management strategies. Open Access Emerg Med. 12:237–246. https://doi.org/10.2147/oaem.S236767

[5] Tielli A, Scala A, Alison M, Vo Chieu VD, Farkas N, Titomanlio L, Lenglart L (2022) Ovarian torsion: diagnosis, surgery, and fertility preservation in the pediatric population. Eur J Pediatr. 181(4):1405–1411. https://doi.org/10.1007/s00431-021-04352-0

[6] Becker JH, de Graaff J, Vos MC (2009) Torsion of the ovary: A known but frequently missed diagnosis. Eur J Emerg Med. 16(3):124–126. https://doi.org/10.1097/MEJ.0b013e32831cbaf8

[7] Adeyemi-Fowode O, McCracken KA, Todd NJ (2018) Adnexal torsion. J Pediatr Adolesc Gynecol. 31(4):333–338. https://doi.org/10.1016/j.jpag.2018.03.010

[8] Ashwal E, Krissi H, Hiersch L, Less S, Eitan R, Peled Y (2015) Presentation, diagnosis, and treatment of ovarian torsion in premenarchal girls. J Pediatr Adolesc Gynecol. 28(6):526–529. https://doi.org/10.1016/j.jpag.2015.03.010

[9] Kives S, Gascon S, Dubuc É, Van Eyk N (2017) No. 341-Diagnosis and management of adnexal torsion in children, adolescents, and adults. J Obstet Gynaecol Can. 39(2):82–90. https://doi.org/10.1016/j.jogc.2016.10.001

[10] Sasaki KJ, Miller CE (2014) Adnexal torsion: review of the literature. J Minim Invasive Gynecol. 21(2):196–202. https://doi.org/10.1016/j.jmig.2013.09.010

[11] Oelsner G, Cohen SB, Soriano D, Admon D, Mashiach S, Carp H (2003) Minimal surgery for the twisted ischaemic adnexa can preserve ovarian function. Hum Reprod. 18(12): 2599-2602. https://doi.org/10.1093/humrep/deg498

[12] Demir M, Yilmaz B, Kalyoncu S, Tuncer M, Bozdag Z, Ince O, Bozdayi MA, Ulusal H, Taysi S (2021) Metformin reduces ovarian ischemia reperfusion injury in rats by improving oxidative/nitrosative stress. Taiwan J Obstet Gynecol. 60(1):45–50. https://doi.org/10.1016/j.tjog.2020.10.004

[13] Nuñez-Rios JD, Ulrich H, Díaz-Muñoz M, Lameu C, Vázquez-Cuevas FG (2025) Purinergic system in cancer stem cells. Purinergic Signal. 21(1):23–38. https://doi.org/10.1007/s11302-023-09976-5

[14] Borea PA, Gessi S, Merighi S, Vincenzi F, Varani K (2018) Pharmacology of adenosine receptors: the state of the art. Physiol Rev. 98(3):1591–1625. https://doi.org/10.1152/physrev.00049.2017

[15] IJzerman AP, Jacobson KA, Müller CE, Cronstein BN, Cunha RA (2022) International Union of Basic and Clinical Pharmacology. CXII: Adenosine receptors: a further update. Pharmacol Rev. 74(2):340–372. https://doi.org/10.1124/pharmrev.121.000445

[16] Sheth S, Brito R, Mukherjea D, Rybak LP, Ramkumar V (2014) Adenosine receptors: expression, function and regulation. Int J Mol Sci. 15(2):2024–2052. https://doi.org/10.3390/ijms15022024

[17] Bjelobaba I, Janjic MM, Stojilkovic SS (2015) Purinergic signaling pathways in endocrine system. Auton Neurosci. 191:102–116. https://doi.org/10.1016/j.autneu.2015.04.010

[18] Monaco L, Conti M (1986) Localization of adenosine receptors in rat testicular cells. Biol Reprod. 35(2):258–266. https://doi.org/10.1095/biolreprod35.2.258

[19] Kylat RI (2021) Perinatal testicular torsion. Arch Pediatr. 28(1):75–79. https://doi.org/10.1016/j.arcped.2020.10.006

[20] Huang WY, Chen YF, Chang HC, Yang TK, Hsieh JT, Huang KH (2013) The incidence rate and characteristics in patients with testicular torsion: A nationwide, population-based study. Acta Paediatr. 102(8):e363-e367. https://doi.org/10.1111/apa.12275

[21] Guthrie BD, Adler MD, Powell EC (2010) Incidence and trends of pediatric ovarian torsion hospitalizations in the United States, 2000-2006. Pediatrics. 125(3):532–538. https://doi.org/10.1542/peds.2009-1360

[22] Bridwell RE, Koyfman A, Long B (2022) High risk and low prevalence diseases: Ovarian torsion. Am J Emerg Med. 56:145–150. https://doi.org/10.1016/j.ajem.2022.03.046

[23] Huang C, Hong MK, Ding DC (2017) A review of ovary torsion. Tzu Chi Med J. 29(3):143–147. https://doi.org/10.4103/tcmj.tcmj_55_17

[24] Hibbard LT (1985) Adnexal Torsion. Am J Obstet

Gynecol. 152(4):456–461. https://doi.org/10.1016/s0002-9378(85)80157-5

[25] Ajike RA, Ajayi AF, Oyekunle OS, Saka WA, Hammed SO, Adedeji OJ, Ogunleye OD, Hezekiah OS, Olayinka-Akinpelu OV, Alabi BA, Ajao ID, Afolabi OA (2025) Potential therapeutic targets in the prevention of testicular ischemia-reperfusion injury. Front Reprod Health. 7:1706914. https://doi.org/10.3389/frph.2025.1706914

[26] Motamed Nia V, Rezaei N, Shokati Sayyad M, Seyedabadi M, Talebpour Amiri F, Shaki F (2024) The protective effects of citrulline on testicular injury induced by torsion and detorsion in adult male rats: An experimental study. J Reprod Infertil. 25(3):201–210. https://doi.org/10.18502/jri.v25i3.17014

[27] Minas A, Mahmoudabadi S, Gamchi NS, Antoniassi MP, Alizadeh A, Bertolla RP (2023) Testicular torsion in vivo models: Mechanisms and treatments. Andrology. 11(7):1267–1285. https://doi.org/10.1111/andr.13418

[28] Yakut S, Karabulut M, Koca RH, Erbaş E, Özkanlar S, Gençer BT, Kara A, Kumar KJS (2025) Protective effects of bromelain in testicular torsion-detorsion: Reducing inflammation, oxidative stress, and apoptosis while enhancing sperm quality. Biomolecules. 15(2):292. https://doi.org/10.3390/biom15020292

[29] Turner TT, Brown KJ (1993) Spermatic cord torsion: loss of spermatogenesis despite return of blood flow. Biol Reprod. 49(2):401–407. https://doi.org/10.1095/biolreprod49.2.401

[30] Oyedokun PA, Akhigbe RE, Ajayi LO, Ajayi AF (2023) Impact of hypoxia on male reproductive functions. Mol Cell Biochem. 478(4):875–885. https://doi.org/10.1007/s11010-022-04559-1

[31] Akhigbe RE, Odetayo AF, Akhigbe TM, Hamed MA, Ashonibare PJ (2024) Pathophysiology and management of testicular ischemia/reperfusion injury: Lessons from animal models. Heliyon. 10(9):e27760. https://doi.org/10.1016/j.heliyon.2024.e27760

[32] Vaos G, Zavras N (2017) Antioxidants in experimental ischemia-reperfusion injury of the testis: Where are we heading towards? World J Methodol. 7(2):37–45. https://doi.org/10.5662/wjm.v7.i2.37

[33] Eltzschig HK, Eckle T (2011) Ischemia and reperfusion—from mechanism to translation. Nat Med. 17(11):1391–1401. https://doi.org/10.1038/nm.2507

[34] Wu MY, Yiang GT, Liao WT, Tsai AP, Cheng YL, Cheng PW, Li CY, Li CJ (2018) Current mechanistic concepts in ischemia and reperfusion injury. Cell Physiol Biochem. 46(4):1650–1667. https://doi.org/10.1159/000489241

[35] Akhigbe RE, Hamed MA, Odetayo AF, Akhigbe TM, Ajayi AF, Ajibogun FAH (2021) Omega-3 fatty acid rescues ischaemia/perfusion-induced testicular and sperm damage via modulation of lactate transport and xanthine oxidase/uric acid signaling. Biomed Pharmacother. 142:111975. https://doi.org/10.1016/j.biopha.2021.111975

[36] Afolabi OA, Anyogu DC, Hamed MA, Odetayo AF, Adeyemi DH, Akhigbe RE (2022) Glutamine prevents upregulation of NF-kB signaling and caspase 3 activation in ischaemia/reperfusion-induced testicular damage: An animal model. Biomed Pharmacother. 150:113056. https://doi.org/10.1016/j.biopha.2022.113056

[37] Sangodele JO, Inuwa Z, Lawal B, Adebayo-Gege G, Okoli BJ, Mtunzi F (2021) Proxeed plus salvage rat testis from ischemia- reperfused injury by enhancing antioxidant's activities and inhibition of iNOS expression. Biomed Pharmacother. 133:111086. https://doi.org/10.1016/j.biopha.2020.111086

[38] Koşar A, Sarica K, Küpeli B, Alçiğir G, Süzer O, Küpeli S (1997) Testicular torsion: Evaluation of contralateral testicular histology. Int Urol Nephrol. 29(3):351–356. https://doi.org/10.1007/bf02550935

[39] Sarica K, Bakir K, Erbagci A, Yagci F, Uysal O, Uçak R (2001) Unilateral testicular torsion: evaluation of bcl-2, p-53 and PCNA expression in contralateral testes. Urol Int. 66(2):94–99. https://doi.org/10.1159/000056578

[40] Algoet M, Janssens S, Himmelreich U, Gsell W, Pusovnik M, Van den Eynde J, Oosterlinck W (2023) Myocardial ischemia-reperfusion injury and the influence of inflammation. Trends Cardiovasc Med. 33(6):357–366. https://doi.org/10.1016/j.tcm.2022.02.005

[41] Visser JA, de Jong FH, Laven JS, Themmen AP (2006) Anti-Müllerian hormone: a new marker for ovarian function. Reproduction. 131(1):1–9. https://doi.org/10.1530/rep.1.00529

[42] Hunzicker-Dunn M, Maizels ET (2006) FSH signaling pathways in immature granulosa cells that regulate target

gene expression: branching out from protein kinase A. Cell Signal. 18(9):1351–1359. https://doi.org/10.1016/j.cellsig.2006.02.011

[43] Cash E, Goodwin AT, Tatler AL (2023) Adenosine receptor signalling as a driver of pulmonary fibrosis. Pharmacol Ther. 249:108504. https://doi.org/10.1016/j.pharmthera.2023.108504

[44] Jacobson KA, Reitman ML (2020) Adenosine-related mechanisms in non-adenosine receptor drugs. Cells. 9(4):956. https://doi.org/10.3390/cells9040956

[45] Ruan W, Ma X, Bang IH, Liang Y, Muehlschlegel JD, Tsai KL, Mills TW, Yuan X, Eltzschig HK (2022) The hypoxia-adenosine link during myocardial ischemia-reperfusion injury. Biomedicines. 10(8):1939. https://doi.org/10.3390/biomedicines10081939

[46] Lee NT, Savvidou I, Selan C, Wright DK, Brkljaca R, Chia JSJ, Calvello I, Craenmehr DDD, Larsson P, Tarlac V, Vuong A, Carmichael I, Wang X, Peter K, Robson SC, Nandurkar HH, Sashindranath M (2025) Endothelial-targeted CD39 is protective in a mouse model of global forebrain ischaemia. J Neuroinflammation. 22(1):115. https://doi.org/10.1186/s12974-025-03394-7

[47] Solanki N, Dodiya R, Vejpara D, Azad S, Patel M, Patel S, Shah U, Soni A, Maheshwari R, Navale A, Patel A, Patel S, Sheth D, Tirgar P (2025) Adenosine receptor subtype modulators: Insight into molecular mechanisms and their therapeutic application. Am J Transl Res. 17(4):2376–2395. https://doi.org/10.62347/zyvy9443

[48] Jacobson KA, Müller CE (2016) Medicinal chemistry of adenosine, P2Y and P2X receptors. Neuropharmacology. 104:31–49. https://doi.org/10.1016/j.neuropharm.2015.12.001

[49] Xia Y, He F, Moukeila Yacouba MB, Zhou H, Li J, Xiong Y, Zhang J, Li H, Wang Y, Ke J (2022) Adenosine A_{2A} receptor regulates autophagy flux and apoptosis to alleviate ischemia-reperfusion injury via the cAMP/PKA signaling pathway. Front Cardiovasc Med. 9:755619. https://doi.org/10.3389/fcvm.2022.755619

[50] Zhao N, Xia G, Cai J, Li Z, Lv XW (2022) Adenosine receptor A2B mediates alcoholic hepatitis by regulating cAMP levels and the NF-kB pathway. Toxicol Lett. 359:84–95. https://doi.org/10.1016/j.toxlet.2022.01.012

[51] Belardin LB, Brochu K, Légaré C, Battistone MA, Breton S (2022) Purinergic signaling in the male reproductive tract. Front Endocrinol (Lausanne). 13:1049511. https://doi.org/10.3389/fendo.2022.1049511

[52] Missel A, Walenta L, Eubler K, Mundt N, Heikelä H, Pickl U, Trottmann M, Popper B, Poutanen M, Strauss L, Köhn FM, Kunz L, Spehr M, Mayerhofer A (2021) Testicular adenosine acts as a pro-inflammatory molecule: role of testicular peritubular cells. Mol Hum Reprod. 27(7):gaab037. https://doi.org/10.1093/molehr/gaab037

[53] Belleannée C, Da Silva N, Shum WW, Brown D, Breton S (2010) Role of purinergic signaling pathways in V-ATPase recruitment to apical membrane of acidifying epididymal clear cells. Am J Physiol Cell Physiol. 298(4):C817-C830. https://doi.org/10.1152/ajpcell.00460.2009

[54] Diniz C, Leal S, Gonçalves J (2003) Regional differences in the adenosine A2 receptor-mediated modulation of contractions in rat vas deferens. Eur J Pharmacol. 460(2-3):191–199. https://doi.org/10.1016/s0014-2999(02)02926-6

[55] Minutoli L, Antonuccio P, Squadrito F, Bitto A, Nicotina PA, Fazzari C, Polito F, Marini H, Bonvissuto G, Arena S, Morgia G, Romeo C, Caputi AP, Altavilla D (2012) Effects of polydeoxyribonucleotide on the histological damage and the altered spermatogenesis induced by testicular ischaemia and reperfusion in rats. Int J Androl. 35(2):133–144. https://doi.org/10.1111/j.1365-2605.2011.01194.x

[56] Antonuccio P, Pallio G, Marini HR, Irrera N, Romeo C, Puzzolo D, Freni J, Santoro G, Pirrotta I, Squadrito F, Minutoli L, Micali A (2022) Involvement of hypoxia-inducible factor 1-α in experimental testicular ischemia and reperfusion: Effects of polydeoxyribonucleotide and selenium. Int J Mol Sci. 23(21):13144. https://doi.org/10.3390/ijms232113144

[57] Squadrito F, Micali A, Rinaldi M, Irrera N, Marini H, Puzzolo D, Pisani A, Lorenzini C, Valenti A, Laurà R, Germanà A, Bitto A, Pizzino G, Pallio G, Altavilla D, Minutoli L (2016) Polydeoxyribonucleotide, an adenosine-A_{2A} receptor agonist, preserves blood testis barrier from cadmium-induced injury. Front Pharmacol. 7:537. https://doi.org/10.3389/fphar.2016.00537

[58] Antonuccio P, Micali AG, Romeo C, Freni J, Vermiglio G, Puzzolo D, Squadrito F, Irrera N, Marini HR, Rana RA, Pallio G, Minutoli L (2021) NLRP3 inflammasome: A new

pharmacological target for reducing testicular damage associated with varicocele. Int J Mol Sci. 22(3):1319. https://doi.org/10.3390/ijms22031319

[59] Okur MH, Arslan S, Aydogdu B, Zeytun H, Basuguy E, Arslan MS, Ibiloglu I, Kaplan I (2018) Protective effect of cordycepin on experimental testicular ischemia/reperfusion injury in rats. J Invest Surg. 31(1):1–8. https://doi.org/10.1080/08941939.2016.1246629

[60] Mammadov A, Demiryürek AT, Saracaloğlu A, Demirkıran C, Değim İT, Eronat Ö, Demiryürek Ş (2026) Contribution of adenosine A2A receptor agonist and antagonist on ovarian ischemia/reperfusion injury in rats. Turk J Med Sci. 56(1):364–376. https://doi.org/10.55730/1300-0144.6170

[61] Uguralp S, Bay Karabulut A, Mizrak B (2005) Effects of pentoxifylline and vitamin E on the bilateral ovary after experimental ovarian ischemia. Eur J Pediatr Surg. 15(2):107–113. https://doi.org/10.1055/s-2004-821256

[62] Lieu HD, Shryock JC, von Mering GO, Gordi T, Blackburn B, Olmsted AW, Belardinelli L, Kerensky RA (2007) Regadenoson, a selective A2A adenosine receptor agonist, causes dose-dependent increases in coronary blood flow velocity in humans. J Nucl Cardiol. 14(4):514–520. https://doi.org/10.1016/j.nuclcard.2007.02.016

[63] Wisniewski AM, Chancellor WZ, Young A, Money D, Beller JP, Charlton J, Lunardi N, Yang Z, Laubach VE, Mehaffey JH, Kron IL, Roeser ME (2024) Adenosine 2A receptor agonism improves survival in extracorporeal cardiopulmonary resuscitation. J Surg Res. 301:404–412. https://doi.org/10.1016/j.jss.2024.06.033

[64] Mehaffey JH, Money D, Charles EJ, Schubert S, Piñeros AF, Wu D, Bontha SV, Hawkins R, Teman NR, Laubach VE, Mas VR, Tribble CG, Maluf DG, Sharma AK, Yang Z, Kron IL, Roeser ME (2019) Adenosine 2A receptor activation attenuates ischemia reperfusion injury during extracorporeal cardiopulmonary resuscitation. Ann Surg. 269(6):1176–1183. https://doi.org/10.1097/SLA.0000000000002685

[65] Sivanandy P, Leey TC, Xiang TC, Ling TC, Wey Han SA, Semilan SLA, Hong PK (2021) Systematic review on Parkinson's disease medications, emphasizing on three recently approved drugs to control Parkinson's symptoms. Int J Environ Res Public Health. 19(1):364. https://doi.org/10.3390/ijerph19010364

How to Cite;

Igci N, Mammadov A, Demiryurek S, Demiryurek AT (2026) Role of Adenosine in Testicular and Ovarian Ischemia/reperfusion Injury. Eur J Ther. 32(5):629–643. https://doi.org/10.58600/eurjther3224