Available online at www.sciencedirect.com

SCIENCE DIRECT

European Journal of Pharmacology 495 (2004) 1–16

www.elsevier.com/locate/ejphar

Review

Adenosine uptake inhibitors

Tohru Noji*, Akira Karasawa, Hideaki Kusaka

Pharmaceutical Research Institute, Kyowa Hakko Kogyo Co., Ltd., 1188 Shimotogari, Nagaizumi, Sunto, Shizuoka 411-8731, Japan

Received 29 January 2004; received in revised form 30 April 2004; accepted 10 May 2004

Abstract

Adenosine is a purine nucleoside and modulates a variety of physiological functions by interacting with cell-surface adenosine receptors. Under several adverse conditions, including ischemia, trauma, stress, seizures and inflammation, extracellular levels of adenosine are increased due to increased energy demands and ATP metabolism. Increased adenosine could protect against excessive cellular damage and organ dysfunction. Indeed, several protective effects of adenosine have been widely reported (e.g., amelioration of ischemic heart and brain injury, seizures and inflammation). However, the effects of adenosine itself are insufficient because extracellular adenosine is rapidly taken up into adjacent cells and subsequently metabolized. Adenosine uptake inhibitors (nucleoside transport inhibitors) could retard the disappearance of adenosine from the extracellular space by blocking adenosine uptake into cells. Therefore, it is expected that adenosine uptake inhibitors will have protective effects in various diseases, by elevating extracellular adenosine levels. Protective or ameliorating effects of adenosine uptake inhibitors in ischemic cardiac and cerebral injury, organ transplantation, seizures, thrombosis, insomnia, pain, and inflammatory diseases have been reported. Preclinical and clinical results indicate the possibility of therapeutic application of adenosine uptake inhibitors.

Keywords: Adenosine; Adenosine uptake inhibitor (nucleoside transport inhibitor); Protective effect; Therapeutic application

1. Introduction

Adenosine is an endogenous purine nucleoside released from various tissues and organs. Adenosine controls the supply and demand of energy and modulates a variety of physiological responses by interacting with specific cell-surface G-protein-coupled receptors (Collis and Hourani, 1993; Stiles, 1997; Fredholm et al., 2001). Under several adverse conditions, including ischemia, hypoxia, trauma, stress, seizures, pain, and inflammation, adenosine production is increased due to an increased demand for the energy supplied by ATP, which is metabolized to AMP and adenosine (Cronstein, 1995; Latini and Pedata, 2001). Indeed, the activity of 5′ -nucleotidase, which metabolizes AMP to adenosine, is reported to be elevated in adverse conditions (Kitakaze et al., 1993b; Johnson et al., 1999). The increased extracellular adenosine protects against excessive tissue damage or organ dysfunction by interacting with adenosine receptors (Ralevic and Burnstock, 1998; Linden, 2001). However, the elevation of endogenous adenosine levels is insufficient to exert pharmacological effects because extracellular adenosine usually disappears quickly due to its rapid uptake into adjacent cells (e.g., erythrocytes and endothelial cells) and subsequent metabolism (Plagemann et al., 1985; Moser et al., 1989). In fact, adenosine added to whole blood is taken up with a half-life of less than 30 s and disappears within 1 min (Dawicki et al., 1986; Yeung et al., 1991). In addition, exogenous adenosine and its agonists attenuate ischemic cardiac and cerebral injury (Von Lubitz et al., 1988; Toombs et al., 1992), seizures (Murray et al., 1985), pain (Sawynok et al., 1986), and inflammation (Schrier et al., 1990) in several animal models. However, their therapeutic application has been limited by side effects (e.g., hypotension, renal diuresis, bradycardia, and sedation) resulting from the systemic pharmacological effects of adenosine (Jacobson et al., 1992; Williams, 2000).

Adenosine uptake inhibition is an approach to enhance the pharmacological effects of adenosine in pathophysiological conditions since adenosine uptake is one of the key events regulating extracellular adenosine concentrations (Linden, 1997; IJzerman and van der Wenden, 1997).

* Corresponding author. Licensing and Business Development, Kyowa Hakko Kogyo Co., Ltd., 1-6-1 Ohtemachi, Chiyoda, Tokyo 100-8185, Japan. Tel.: +81-3-3282-0917; fax: +81-3-3282-0107.

E-mail address: tohru.noji@mx6.ttcn.ne.jp (T. Noji).

0014-2999/$ - see front matter © 2004 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejphar.2004.05.003

Adenosine is taken up from the extracellular space into adjacent cells through specific transport proteins (nucleoside transporters) on the plasma membrane (Thorn and Jarvis, 1996). Therefore, adenosine uptake inhibitors (nucleoside transport inhibitors) could retard the disappearance of extracellular adenosine, elevate extracellular concentrations of adenosine, and enhance the protective effects of endogenous adenosine in tissues and organs undergoing accelerated adenosine production under adverse conditions (Van Belle, 1993; Baldwin et al., 1999). As a result, adenosine uptake inhibitors are expected to exhibit ameliorating effects in various types of disease. In this review, the potential therapeutic applications of adenosine uptake inhibitors for various diseases are highlighted.

2. Adenosine receptors, formation and disposition of adenosine and nucleoside transporters

2.1. Adenosine receptors and their functions

The receptors activated by adenosine are termed purine P_1 receptors and are different from the receptors activated by adenine nucleotides (purine P_2 receptors; Filtz et al., 1997; Khakh and Kennedy, 1998; Burnstock and Williams, 2000). Purine P_1 receptors have been further subdivided into four adenosine receptor subtypes (A_1, A_{2A}, A_{2B} and A_3; Poulsen and Quinn, 1998; Olah and Stiles, 2000; Fredholm et al., 2001). Adenosine A_1 receptors are coupled to $G_{i/o}$ proteins and inhibit adenylyl cyclase (intracellular cAMP is decreased). It has also been reported that adenosine A_1 receptors interact with phospholipase C and potassium channels (Fredholm et al., 2000). Adenosine A_{2A} and A_{2B} receptors are coupled to G_s proteins and stimulate adenylyl cyclase (intracellular cAMP is increased). Adenosine A_{2A} and A_{2B} receptors have a high and a low affinity for adenosine, respectively. Adenosine A_3 receptors have been documented to be $G_{i/q}$ coupled and appear to inhibit adenylyl cyclase and to activate phospholipase C (inositol triphosphate and diacylglycerol are increased; Fredholm et al., 2000). Unlike adenosine A_1 and A_{2A} receptors, activation of adenosine A_3 receptors requires relatively high concentrations of adenosine.

Adenosine receptors are distributed throughout the body and control a variety of physiological functions (Collis and Hourani, 1993). Adenosine A_1 receptors induce cardiac depression (e.g., bradycardia and negative cardiac inotropy), vasoconstriction, bronchoconstriction, renal effects (e.g., renin release inhibition, glomerular filtration rate attenuation and antidiuresis), and central nervous system (CNS) effects (e.g., neurotransmitter release attenuation and sedation). In contrast, adenosine A_2 receptors mediate vasodilatation, bronchodilation, immunosuppression, and inhibition of platelet aggregation and neutrophil activation.

Several selective agonists and antagonists for adenosine A_1, A_{2A} and A_3 receptor subtypes are now available (Jacobson and van Rhee, 1997; Van Muijlwijk-Koezen et al., 2001; De Ligt and IJzerman, 2002; Cristalli et al., 2003).

2.2. Formation and disposition of adenosine in normal and adverse conditions

Under physiological conditions, adenosine is mainly formed intracellularly from *S*-adenosylhomocysteine by *S*-adenosylhomocysteine hydrolase and phosphorylated to AMP by adenosine kinase (Fig. 1A; Geiger et al., 1997; Latini and Pedata, 2001). In these circumstances, intracellular adenosine concentrations are under enzymatic control and kept low.

In several adverse situations, including ischemia, hypoxia, trauma, stress, seizures, pain, and inflammation, adenosine is mainly produced by the breakdown of ATP and extracellular concentrations of adenosine are increased (Fig. 1B; Kowaluk et al., 1998; Latini and Pedata, 2001). Under adverse conditions, 5′-nucleotidase activity is elevated (Kitakaze et al., 1993b; Johnson et al., 1999), and the increase in extracellular adenosine concentrations can be attenuated by a 5′-nucleotidase inhibitor (Headrick et al., 1992; Minamino et al., 1995). This route for adenosine production appears to be especially active during periods when cellular energy demands are high and the oxygen

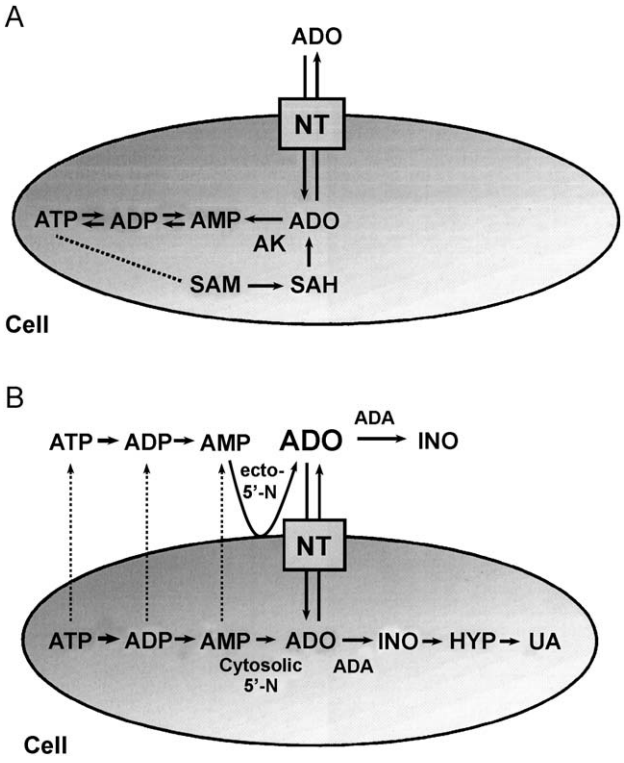

Fig. 1. Production and metabolism of adenosine under normal (A) and adverse (B) conditions. ADA: adenosine deaminase, ADO: adenosine, ADP: adenosine diphosphate, AK: adenosine kinase, AMP: adenosine monophosphate, ATP: adenosine triphosphate, HYP: hypoxanthine, INO: inosine, 5′-N: 5′-nucleotidase, NT: nucleoside transporter, SAH: *S*-adenosylhomocysteine, SAM: *S*-adenosylmethionine, UA: uric acid.

supply is low. Increased adenosine readjusts the energy supply-to-demand ratio, increases organ blood flow by vasodilatation, and exerts various kinds of protective effects (Ralevic and Burnstock, 1998; Linden, 2001). However, the increased extracellular adenosine is rapidly taken up into cells by nucleoside transporters and predominantly metabolized to inosine by adenosine deaminase (Plagemann et al., 1985; Geiger et al., 1997).

2.3. Nucleoside transporters

Adenosine is transported across cell membranes by nucleoside transporters (Cass et al., 1999; Cabrita et al., 2002), and these transporters play a key role in the regulation of extracellular adenosine concentrations. Nucleoside transporters are subdivided into two main categories based on their functional characteristics and molecular structure (Cass et al., 1998; Casado et al., 2002): (i) equilibrative (passive, facilitated diffusion) nucleoside transporters (termed ENTs) that transport nucleosides across cell membranes in either direction depending on intra- and extracellular nucleoside concentrations, and (ii) concentrative (active, sodium ion-dependent) nucleoside transporters (termed CNTs) that promote the influx of nucleosides into cells against their concentration gradient, using energy derived from the sodium ion gradient that exists across plasma membranes. The equilibrative nucleoside transporters are found throughout the body. In contrast, the concentrative nucleoside transporters are found in specialized tissues or organs (e.g., small intestine epithelium, choroids plexus, macrophages, splenocytes, the kidneys, the liver, and the brain; Griffith and Jarvis, 1996; Cass et al., 1998).

Equilibrative nucleoside transporters are further subdivided into two subtypes (Yao et al., 1997; Hyde et al., 2001), *e*quilibrative-*s*ensitive (*es*) nucleoside transporters (equilibrative nucleoside transporter 1: ENT1) and *e*quilibrative-*i*nsensitive (*ei*) nucleoside transporters (equilibrative nucleoside transporter 2: ENT2), based on their differential sensitivity to inhibition by the nucleoside analogue, *S*6-(4-nitrobenzyl)mercaptopurine riboside (NBMPR, nitrobenzylthioinosine). The *es* nucleoside transporters are potently inhibited by NBMPR at low nanomolar concentrations, whereas the *ei* nucleoside transporters are inhibited only by micromolar concentrations. Many cell types express both *es* and *ei* nucleoside transporters simultaneously, but the *es* nucleoside transporters are far more abundant (Buolamwini, 1997). Although equilibrative nucleoside transporters have been divided into just two subtypes as shown above (ENT1 and ENT2), variations in their kinetic and sequential properties suggest the possible presence of an additional transporter isoform (ENT3; Hyde et al., 2001).

Concentrative, sodium ion-dependent nucleoside transporters can be subdivided into five subtypes based on their substrate selectivity and inhibitor sensitivity (Wang et al., 1997; Ritzel et al., 2001): N1/*cif* (*c*oncentrative, inhibitor-*i*nsensitive, accepting *f*ormycin B as a substrate but not thymidine), N2/*cit* (*c*oncentrative, inhibitor-*i*nsensitive, accepting *t*hymidine as a substrate but not formycin B), N3/*cib* (*c*oncentrative, inhibitor-*i*nsensitive, with *b*road substrate specificity), N4/*cit* (like N2 but it also accepts guanosine as a substrate), and N5/*cs* (*c*oncentrative, inhibitor-*s*ensitive).

Among these transporters, most studies have focused on the role of *es* nucleoside transporters because these transporters are widely expressed throughout the body and have functions in many cells (Griffith and Jarvis, 1996; Buolamwini, 1997).

3. Adenosine uptake inhibitors (nucleoside transport inhibitors)

3.1. Mechanism of action

Since equilibrative nucleoside transporters are predominant in many cells, either influx or efflux of adenosine can occur depending on the direction of its existing concentration gradient (Griffith and Jarvis, 1996; Buolamwini, 1997). Under various adverse conditions, adenosine could be taken up from the extracellular space into cells because of the increase in extracellular adenosine formation by ATP degradation and the increase in extracellular adenosine concentrations (Headrick et al., 1992; Kitakaze et al., 1993b). Under these conditions, adenosine uptake inhibitors are expected to retard the disappearance of extracellular adenosine by blocking nucleoside transporters and to enhance the pharmacological effects of adenosine interacting with cell-surface adenosine receptors (Fig. 2). As a consequence of the increase in extracellular adenosine, adenosine uptake inhibitors would amplify the protective

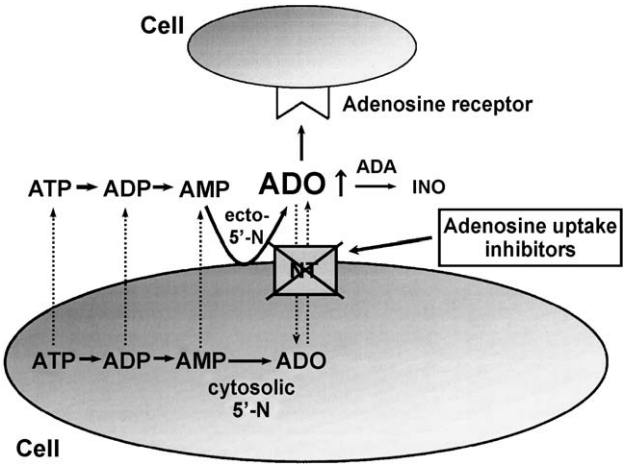

Fig. 2. Effects of adenosine uptake inhibitors on the action and metabolism of adenosine under adverse conditions. ADA: adenosine deaminase, ADO: adenosine, ADP: adenosine diphosphate, AMP: adenosine monophosphate, ATP: adenosine triphosphate, INO: inosine, 5′ -N: 5′ -nucleotidase, NT: nucleoside transporter.

effects of adenosine against several diseases. Adenosine uptake inhibitors may have fewer side effects than adenosine and adenosine receptor agonists since endogenous adenosine levels are selectively elevated by adenosine uptake inhibitors in tissues or organs undergoing accelerated adenosine formation (Van Belle, 1993; Linden, 1997). Therefore, it is expected that adenosine uptake inhibitors present a novel therapeutic approach to the treatment of various diseases.

3.2. Representative adenosine uptake inhibitors

Many of the currently available adenosine uptake inhibitors (Fig. 3) are highly selective for *es* nucleoside transporters. Interference by adenosine uptake inhibitors with nucleoside transporters can be studied in displacement studies of [^{3}H]NBMPR binding to membranes or cells harvested from tissues and organs (Table 1). The adenosine uptake inhibitory activity of compounds has been evaluated by measuring the disappearance of adenosine added to a cell suspension (e.g., erythrocytes and cardiomyocytes) or whole blood in vitro (Table 1). In addition, for some compounds, ex vivo inhibition of adenosine uptake is determined by measuring the disappearance of adenosine added to blood taken after systemic administration of compounds.

3.2.1. NBMPR

NBMPR, a nucleoside analogue, is one of the most potent and specific inhibitors of *es* nucleoside transporters ([^{3}H]NBMPR binding inhibition $K_i = 10^{-9}$ M level; Verma and Marangos, 1985; Conant and Jarvis, 1994) and inhibits adenosine uptake in washed erythrocytes with IC_{50} values of 10^{-9}–10^{-8} M (Baer et al., 1990). The introduction of [^{3}H]NBMPR has greatly facilitated the characterization of *es* nucleoside transporters, and NBMPR is an important tool for the study and characterization of nucleoside transporters (Shi et al., 1984; Castillo-Melendez et al., 1996).

3.2.2. Dipyridamole

Dipyridamole, a pyrimidopyrimidine derivative, is used clinically as a coronary vasodilator and a platelet aggregation inhibitor (Picano and Michelassi, 1997; De Schryver et al., 2003). Dipyridamole inhibits both *es* and *ei* nucleoside transporters (Dunwiddie and Diao, 2000; Ward et al., 2000). It has been reported that dipyridamole inhibits [^{3}H]NBMPR binding to membranes or cells with K_i values of 10^{-9}–

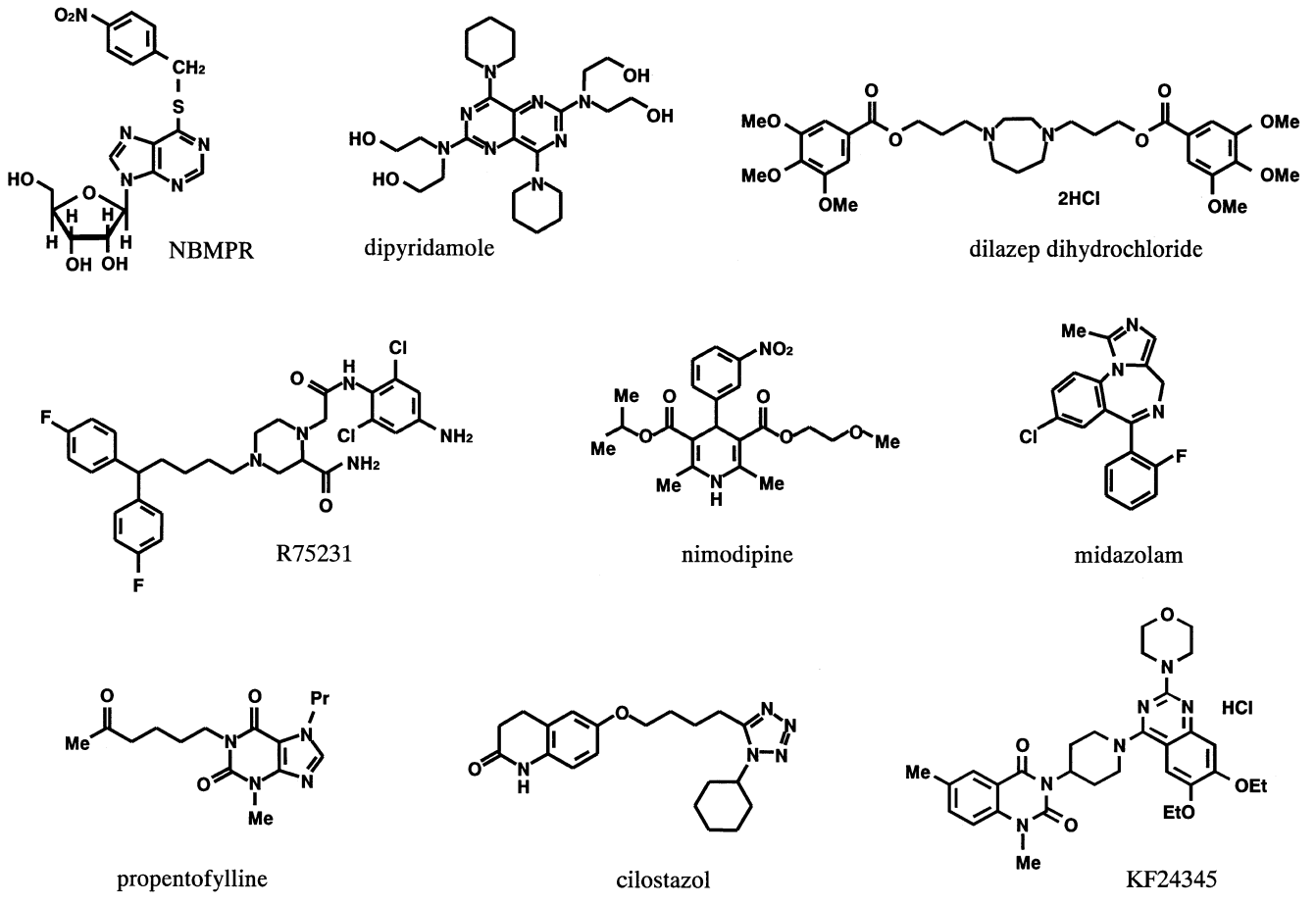

Fig. 3. Chemical structures of representative adenosine uptake inhibitors. NBMPR: *S*6-(4-nitrobenzyl)mercaptopurine riboside.

Table 1
Characteristics of representative adenosine uptake inhibitors

Inhibitors	[^{3}H]NBMPR binding inhibition K_i (membranes or cells)	Adenosine uptake inhibition IC_{50} (cells[a])	Comments or remarks
NBMPR	10^{-9} M	10^{-9}–10^{-8} M	[^{3}H]NBMPR is widely used.
Dipyridamole	10^{-9}–10^{-7} M (rat 10^{-6} M)	10^{-7} M	Clinically used. High doses are required for adenosine uptake inhibitory activity after oral administration.
Dilazep	10^{-10}–10^{-9} M (rat 10^{-7} M)	10^{-9} M	Clinically used. Oral adenosine uptake inhibitory activity is weak.
Lidoflazine	10^{-7} M	10^{-7} M	A prototype.
Mioflazine	10^{-8} M	10^{-8}–10^{-6} M	
Soluflazine	10^{-8} M	10^{-8}–10^{-6} M	A water-soluble mioflazine analogue.
R75231	10^{-10} M	–	Orally active.
Draflazine	10^{-10} M	–	The (−)-enantiomer of R75231.
Nimodipine	10^{-7}–10^{-6} M	10^{-7}–10^{-6} M	Clinically used. Calcium channel antagonistic activity seems to be predominant for its clinical effects.
Diazepam	10^{-5}–10^{-4} M	–	
Clonazepam	10^{-4} M	–	
Midazolam	10^{-6} M	–	
Iodotubercidin	10^{-6} M	–	An adenosine kinase inhibitor.
Propentofylline	10^{-5}–10^{-4} M	10^{-6}–10^{-4} M	An adenosine A_1 receptor antagonist.
Cilostazol	(IC_{50} = 10^{-5} M)	10^{-6} M	Clinically used. A dual inhibitor of adenosine uptake and phosphodiesterase type 3.
KF24345	10^{-10}–10^{-9} M	10^{-8}–10^{-7} M	Orally active.

NBMPR: *S*6-(4-nitrobenzyl)mercaptopurine riboside.
Referenced from Marangos et al. (1982), Patel et al. (1982), Verma and Marangos (1984), Williams et al. (1984), Heaton and Clanachan (1987), Parkinson and Fredholm (1991), Fredholm et al. (1992), IJzerman et al. (1992), Deckert et al. (1993), Conant and Jarvis (1994), Parkinson and Geiger (1996), Liu et al. (2000), Seubert et al. (2000) and Noji et al. (2002b) for [^{3}H]NBMPR binding inhibition studies, Striessnig et al. (1985), Van Belle et al. (1986), Baer et al. (1990), Yeung et al. (1991), Parkinson et al. (1993), Noji et al. (2002b) and Sun et al. (2002) for adenosine uptake inhibition studies.
[a] Expressing nucleoside transporters.

10^{-7} M (Marangos et al., 1982; Verma and Marangos, 1985; Heaton and Clanachan, 1987) and inhibits adenosine uptake in whole blood with IC_{50} values of 10^{-7} M (Yeung et al., 1991). Because of its short-lasting action and poor oral bioavailability, a high dosage of dipyridamole is required for effective inhibition of nucleoside transport in vivo (Van Belle and Janssen, 1991). Although one of its principal pharmacological mechanisms is adenosine uptake inhibition, dipyridamole also has other pharmacological actions including phosphodiesterase inhibition (Harker and Kadatz, 1983; Dogne et al., 2002).

3.2.3. Dilazep

Dilazep is a symmetrical alkyl- and cycloalkyldiamine aromatic ester (Qian et al., 1984; IJzerman and van der Wenden, 1997). It is equipotent with NBMPR as an *es* nucleoside transport inhibitor ([^{3}H]NBMPR binding inhibition K_i = 10^{-10}–10^{-9} M; Verma and Marangos, 1985; Conant and Jarvis, 1994) and inhibits adenosine uptake into erythrocytes with IC_{50} values in the 10^{-9} M range (Baer et al., 1990). Although dilazep also inhibits adenosine uptake ex vivo (by intravenous or intraperitoneal administration), its inhibitory activity on adenosine uptake following oral administration is weak (Baer et al., 1991; Van Belle and Janssen, 1991). The symmetry of the molecule is important for adenosine uptake inhibition since "half" molecules are not active (IJzerman and van der Wenden, 1997). When the effects of dilazep on the CNS are examined, it has to be injected into the brain because of its poor CNS activity following systemic administration (Dar, 1989). Like dipyridamole, dilazep is also clinically used as a coronary vasodilator and a platelet aggregation inhibitor (Marzilli et al., 1984; Nakamura et al., 2000).

3.2.4. Lidoflazine and its derivatives

This group includes the classical calcium channel antagonists, lidoflazine (the lead compound), and its analogues, mioflazine, soluflazine (a fully water-soluble mioflazine analogue), 2-(aminocarbonyl)-*N*-(4-amino-2,6-dichlorophenyl)-4-[5,5-bis(4-fluorophenyl)pentyl]-1-piperazineacetamide (R75231) and its enantiomer, draflazine (the (−)-enantiomer of R75231). They inhibit [^{3}H]NBMPR binding to membranes or cells with K_i values of 10^{-10}–10^{-7} M (Conant and Jarvis, 1994; IJzerman et al., 1992) and also inhibit adenosine uptake into erythrocytes from various species (IC_{50} = 10^{-8}–10^{-6} M; Van Belle et al., 1986; Baer et al., 1990). In addition, R75231 inhibits ex vivo adenosine uptake in animals, and the oral activity of R75231 seems to be good compared with that of dipyridamole and dilazep (Baer et al., 1991; Van Belle and Janssen, 1991). Cardioprotective effects of R75231 have been widely reported.

3.2.5. Dihydropyridines

Several dihydropyridine calcium channel antagonists have been shown to inhibit *es* nucleoside transporters. Nimodipine, which is clinically used in subarachnoid hemorrhage to prevent vasospasm and subsequent ischemic

damage (Koos et al., 1985), inhibits site-specific [^{3}H]NBMPR binding to human brain membranes with K_i values of 10^{-7}–10^{-6} M (Deckert et al., 1993). Nimodipine also inhibits adenosine transport in human erythrocytes with IC_{50} values of 10^{-7}–10^{-6} M (Striessnig et al., 1985). It is widely believed that the clinical effects of nimodipine are mediated by an inhibitory action on calcium influx through voltage-gated L-type channels (Scriabine et al., 1989); however, adenosine uptake inhibition may be also a relevant mechanism for the clinical effects of nimodipine, at least in part (Deckert and Gleiter, 1994). Non-dihydropyridine calcium antagonists (e.g., verapamil and diltiazem) do not inhibit nucleoside transport (Striessnig et al., 1985).

3.2.6. Benzodiazepines

Benzodiazepines (e.g., diazepam, clonazepam and midazolam) have been shown to be relatively weak nucleoside transport inhibitors ([^{3}H]NBMPR binding inhibition $K_i = 10^{-6}$–10^{-4} M; Patel et al., 1982; Williams et al., 1984; Seubert et al., 2000).

3.2.7. Iodotubercidin

Iodotubercidin, an adenosine kinase inhibitor, is reported to inhibit [^{3}H]NBMPR binding to cells ($K_i = 10^{-6}$ M level; Parkinson and Geiger, 1996).

3.2.8. Propentofylline

Propentofylline, a xanthine derivative and an adenosine A_1 receptor antagonist, has been shown to be a relatively weak nucleoside transport inhibitor ([^{3}H]NBMPR binding inhibition $K_i = 10^{-5}$–10^{-4} M; Parkinson and Fredholm, 1991; Fredholm et al., 1992). In addition, propentofylline inhibits adenosine uptake into cultured cells expressing equilibrative nucleoside transporters with IC_{50} values of 10^{-6}–10^{-4} M (Parkinson et al., 1993). Since propentofylline can cross the blood–brain barrier, its neuroprotective effects in cerebral ischemia have been examined (Parkinson et al., 1994; Sweeney, 1997). Adenosine uptake inhibition is thought to contribute in part to the neuroprotective effects of propentofylline.

3.2.9. Cilostazol

The quinolinone derivative cilostazol, which is in clinical use, is a dual inhibitor of phosphodiesterase type 3 and adenosine uptake (Elam et al., 1998; Liu et al., 2001). Cilostazol inhibits [^{3}H]NBMPR binding to membranes ($IC_{50} = 10^{-5}$ M level; Liu et al., 2000) and also inhibits adenosine uptake into cells ($IC_{50} = 10^{-6}$ M level; Sun et al., 2002).

3.2.10. KF24345

The quinazoline derivative 3-[1-(6,7-diethoxy-2-morpholinoquinazolin-4-yl)piperidin-4-yl]-1,6-dimethyl-2,4(1*H*,3*H*)-quinazolinedione hydrochloride (KF24345) is a recently identified adenosine uptake inhibitor. KF24345 inhibits [^{3}H]NBMPR binding to membranes or cells with K_i values of 10^{-10}–10^{-9} M (Hammond and Archer, 2004) and also inhibits adenosine uptake into cells with IC_{50} values of 10^{-8}–10^{-7} M (Noji et al., 2002b). In addition, KF24345 causes a long-lasting inhibition of adenosine uptake following oral administration in mice (Noji et al., 2002b).

4. Potential therapeutic applications of adenosine uptake inhibitors

4.1. Ischemic injury

Under ischemic (hypoxic) conditions, adenosine production is markedly increased and extracellular adenosine concentrations are elevated in ischemic areas (Kitakaze et al., 1993b; Sweeney, 1997). Adenosine uptake inhibitors block adenosine uptake from the extracellular space, increasing local concentrations of extracellular adenosine and thereby amplifying the protective effects of endogenous adenosine in ischemic organs (Wardas, 2002).

4.1.1. Ischemic cardiac injury

Adenosine exerts protective effects in the ischemic and reperfused myocardium by several mechanisms (Ely and Berne, 1992; Kitakaze et al., 1993a; Bullough et al., 1995; Mullane and Bullough, 1995). (1) Adenosine minimizes the workload of the heart and its oxygen demand during ischemia by decreasing the heart rate, depressing sinoatrial node activity, and attenuating atrioventricular nodal conduction through adenosine A_1 receptor pathways and subsequent activation of ATP-sensitive potassium channels. (2) Adenosine causes coronary vasodilatation and increases myocardial oxygen supply through the activation of adenosine A_{2A} receptors on vascular smooth muscle and endothelial cells. (3) Adenosine inhibits neutrophil activation (e.g., oxygen radical production and adhesion to endothelial cells) and platelet aggregation, preserving endothelial cell integrity and limiting the vascular injury. These mechanisms help to restore the balance between oxygen supply and demand, and so adenosine ultimately decreases reperfused myocardial damage, attenuates reversible post-ischemic ventricular dysfunction, and reduces myocardial infarct size. It has also been demonstrated that adenosine contributes to preconditioning, a process by which transient ischemia protects tissues or organs from damage during subsequent prolonged ischemia (Liang and Jacobson, 1999; Baxter, 2002). This protective action is mediated by adenosine A_1 and A_3 receptor pathways, and ATP-sensitive potassium channels seem to contribute to preconditioning as an end-effector (de Jong et al., 2000; Mubagwa and Flameng, 2001).

NBMPR (intracoronary infusion in the 10^{-5} M concentration range), administered with the adenosine deaminase inhibitor erythro-9-(2-hydroxy-3-nonyl)-adenine, augments myocardial adenosine levels during ischemia and improves

postischemic recovery of hemodynamic function in dog hearts (Zughaib et al., 1993). Perfused hearts from guinea pigs treated with dipyridamole (oral intake at 4 mg/kg/day) show a sustained protection against ischemia–reperfusion injury (Figueredo et al., 1999). Dilazep (intravenous infusion at 0.2 mg/kg) prolongs the size-limiting effects of ischemic preconditioning on infarcts in rabbit hearts (Yamasaki et al., 2000).

Effects of lidoflazine derivatives on ischemic cardiac injury have been widely reported. Lidoflazine (intravenous administration at 1 mg/kg) increases myocardial adenosine concentrations and protects the heart against ischemia–reperfusion injury in dogs (Chang-Chun et al., 1992). The effects of lidoflazine are attenuated by aminophylline, an adenosine receptor antagonist, suggesting that the protective effects of lidoflazine are mediated by adenosine receptors. The possibility that lidoflazine may be beneficial as a cardioprotective agent during coronary artery surgery has also been reported in humans (De Hert et al., 1997). Soluflazine (in the 10^{-7} M concentration range) induces adenosine accumulation during ischemia and improves functional recovery after ischemia in isolated cat hearts (Van Belle et al., 1989). R75231 (intracoronary infusion at 0.6–1.4 mg or intravenous administration at 0.1 mg/kg) increases the tissue adenosine content, coronary blood flow, and hyperemia after coronary artery occlusion, improves functional recovery after ischemia, and decreases myocardial infarct size in several animal models of ischemia and reperfusion (Kirkeboen et al., 1992; Galinanes et al., 1993; Kirkeboen et al., 1994; Martin et al., 1997). The in vivo dosage of R75231 used in these studies is one that completely inhibits adenosine uptake ex vivo (Van Belle and Janssen, 1991; Galinanes et al., 1993; Martin et al., 1997). In addition, R75231 (intravenous administration at 0.05 mg/kg) enhances the infarct size-limiting effects of ischemic preconditioning in rabbits (Itoya et al., 1994). Although the effects of R75231 are thought to be mediated predominantly by the action of endogenous adenosine, there are some reports showing that the cardioprotective effects of R 75231 are mediated by its action as a calcium antagonist (Grover and Sleph, 1994). Draflazine (in the perfusate to the heart in micromolar concentrations) protects the heart (e.g., functional recovery and creatine kinase release reduction) against ischemia–reperfusion injury in pigs (Sommerschild et al., 1997).

4.1.2. Ischemic cerebral injury

As is the case with ischemic cardiac injury, adenosine also exhibits protective effects against cerebral ischemia. It has been reported that stimulation of adenosine A_1 receptor decreases the morbidity and mortality associated with focal or global brain ischemia (Von Lubitz, 1999; Phillis and Goshgarian, 2001). Inhibition of transmitter release and neuronal excitability, hyperpolarization of neurons, and blockade of sodium ion channels are thought to contribute to the protective effects of adenosine (Von Lubitz, 2001; Dalpiaz and Manfredini, 2002). These actions could attenuate excitotoxic damage by limiting sodium ion entry and by reducing metabolic demand, which would help to preserve ATP stores. In addition, by acting through adenosine A_{2A} receptor pathways, adenosine ameliorates post-ischemic cerebral blood flow, inhibits platelet aggregation and neutrophil adhesion, and decreases post-ischemic cerebral damage (Pedata et al., 2001; Von Lubitz, 2001). Although it has been reported that adenosine A_{2A} receptor antagonists protect against cerebral ischemic damage, this effect seems to be only expressed temporally in the acute phase of cerebral ischemia and with topical application of adenosine A_{2A} receptor antagonists. This effect is in addition to the protective effects of peripheral adenosine A_{2A} receptor activation against reperfusion injury (Pedata et al., 2001).

NBMPR (intracortical infusion at 10^{-4} M level) increases cortical interstitial adenosine levels during ischemia and reperfusion and ameliorates the effects of postischemic hypoperfusion in pigs (Gidday et al., 1996). Dipyridamole (perfusion into the frontal cortex in concentrations in the 10^{-4} M range) increases cerebral extracellular adenosine levels following ischemia and is suggested to protect the brain against ischemic insult (Park and Gidday, 1990; Seif-El-Nasr and Khattab, 2002). Since dipyridamole does not appear to cross the blood–brain barrier, its possible CNS activity following its systemic administration may be mediated by the inhibition of adenosine permeation through the blood–brain barrier (Sinclair et al., 2001).

The protective effects of propentofylline have been widely reported in ischemic cerebral injury. Propentofylline (administration into the hippocampus at 10^{-5}–10^{-2} M or intraperitoneal administration at 10–20 mg/kg) enhances the ischemia-evoked increase in adenosine levels in the hippocampus, decreases glutamate release in the hippocampus following ischemia, and attenuates cerebral injury caused by ischemia in several animal models (Andine et al., 1990; Dux et al., 1990; Miyashita et al., 1992; Kano et al., 1994; Gidday et al., 1995). Propentofylline (intraperitoneal administration at 20 mg/kg) also potentiates the protective effect of preconditioning against ischemia in gerbil brains (Kawahara et al., 1998). The protective effects of propentofylline are abolished by theophylline, an adenosine receptor antagonist.

4.2. Organ transplantation

Adenosine has been reported to be beneficial in organ transplantation, acting by mechanisms similar to those for its action against ischemia and reperfusion injury (Southard and Belzer, 1995; Lemasters and Thurman, 1997). Adenosine improves postischemic functional recovery and preserves transplanted organs. These usages have been extensively studied in cardiac muscle, and it has been reported that exogenously supplemented adenosine in cardioplegic solutions improves the recovery of cardiac function after ischemia and long-term cardiac preservation

(Petsikas et al., 1990; Galinanes and Hearse, 1992). In addition, adenosine has been shown to be necessary for better performance of University of Wisconsin and St. Thomas' Hospital solutions in preserving the heart (de Jong et al., 1990; Lasley and Mentzer, 1994).

NBMPR (in cardioplegic solution at 10^{-9}–10^{-6} M) increases the adenosine content at the end of storage, increases coronary blood flow, and improves functional recovery of cold-stored human and rat hearts (Yang et al., 1994; Fremes et al., 1995). An adenosine A_1 receptor antagonist, 1,3-dipropyl-8-cyclopentylxanthine, blocks the effects of NBMPR, suggesting that the protective effects of NBMPR are mediated by adenosine A_1 receptor pathways. R75231 (in cardioplegic solution in concentrations in the 10^{-6} M range) prevents ATP depletion, adenosine breakdown, and hypoxanthine accumulation during cold storage of dog hearts, and is effective in their long-term preservation (Flameng et al., 1991; Masuda et al., 1992; Mollhoff et al., 1992). It has also been suggested that R75231 could be beneficial for the preservation of liver and kidney transplants (Booster et al., 1995; Todo et al., 1997).

4.3. Seizures

Adenosine is an endogenous homeostatic neuroprotective agent (Fredholm, 1997; Ribeiro et al., 2003). Consistent with its role as an inhibitory neuromodulator, adenosine exhibits anticonvulsant effects (Foster et al., 1994; Dunwiddie, 1999). In addition, exogenously administered adenosine receptor agonists decrease seizure activity (Dunwiddie and Masino, 2001). The anticonvulsant effects of adenosine appear to be mediated primarily by adenosine A_1 receptors. Adenosine stabilizes the membrane potential and attenuates synaptic transmission in the CNS without itself acting as a neurotransmitter (Knutsen and Murray, 1997). These actions of adenosine, mediated mainly by adenosine A_1 receptors, inhibit neurotransmitter release, especially the release of excitatory amino acids such as glutamate. Therefore, adenosine could attenuate neuronal excitability and ultimately decrease neuronal cell death.

Dipyridamole (at 10^{-6}–10^{-5} M) decreases excitatory synaptic transmission and epileptiform activity in the rat hippocampus (Mitchell et al., 1993; Tancredi et al., 1998; Narimatsu and Aoki, 2000). The depressive activity of dipyridamole is antagonized by caffeine (a nonselective adenosine receptor antagonist) or 1,3-dipropyl-8-cyclopentylxanthine (an adenosine A_1 receptor antagonist), suggesting that dipyridamole exerts its effects through adenosine A_1 receptor pathways. Soluflazine (at 10^{-6} M level) depresses electrophysiological activity and epileptogenetic events in guinea pig hippocampal slices by increasing endogenous adenosine levels (Ashton et al., 1987, 1988). In addition, midazolam (at 10^{-6} M level) depresses excitatory synaptic transmission in rat hippocampal slices, and it is suggested that the effects of midazolam could contribute to the therapeutic applications, including those for epilepsy, of benzodiazepines (Narimatsu and Aoki, 1999). The effects of midazolam are reversed by aminophylline (an adenosine receptor antagonist).

4.4. Thrombosis

Adenosine inhibits platelet aggregation and attenuates tissue factor expression on endothelial cells induced by various stimuli (e.g., tumor necrosis factor-α, thrombin and phorbol 12-myristate 13-acetate), acting mainly through adenosine A_{2A} receptor pathways (Anfossi et al., 1995; Deguchi et al., 1998; Pasini et al., 2000). Since platelet activation and tissue factor expression on endothelial cells play a pivotal role as initiating events in arterial thrombosis (Leff et al., 1997; Deguchi et al., 1998), the inhibitory effects of adenosine on platelet and endothelial cell activation are thought to be beneficial for the treatment of thrombosis.

Anti-thrombotic effects of dipyridamole and dilazep, which are clinically used as anti-platelet drugs, have been reported. Dipyridamole inhibits platelet aggregation in human whole blood in vitro (at 10^{-5} M level; Gresele et al., 1986) and exhibits anti-thrombotic effect in rats (intravenous administration at 1 mg/kg; Takiguchi et al., 1992). The anti-platelet action of dipyridamole is reversed by adenosine deaminase. Dilazep (at 10^{-5}–10^{-4} M) inhibits tissue factor activity and its expression induced by stimuli in human umbilical vein endothelial cells and monocytes (Deguchi et al., 1997). 8-(*p*-Sulfophenyl) theophylline, an adenosine receptor antagonist, partially counteracts the inhibitory effects of dilazep, which suggests that the effects of dilazep are mediated by endogenous adenosine, at least in part. Cilostazol has been reported to inhibit platelet aggregation elicited by chemical or physical stimuli in vitro ($IC_{50} = 10^{-6}$–10^{-5} M; Minami et al., 1997; Sun et al., 2002) and exhibits anti-thrombotic effects in vivo (by oral intake at 30 mg/kg × 2/day; Kohda et al., 1999). Cilostazol is clinically used for the treatment of intermittent claudication or lower extremity peripheral arterial occlusive disease (Liu et al., 2000, 2001). The vasodilatation and inhibition of platelet aggregation caused by cilostazol are thought to contribute to its beneficial clinical effects (Schror, 2002).

4.5. Arrhythmia

Adenosine slows the heart rate (negative chronotropic effect on cardiac pacemakers) and atrioventricular nodal conduction (negative dromotropic effect on myocardium) through adenosine A_1 receptor pathways (Pelleg, 1993). Potassium ion channel activation, outward potassium ion current induction, and hyperpolarization in the sinus node and atrioventricular node are thought to contribute to the negative chronotropic and dromotropic effects of adenosine (Wilbur and Marchlinski, 1997). In addition, it has been reported that adenosine antagonizes the stimulatory effects

of β-adrenoceptor agonists (Belardinelli et al., 1997). From these observations, adenosine is expected to exhibit anti-arrhythmic effects such as termination of paroxysmal supraventricular tachycardia and catecholamine-dependent ventricular tachycardia (Belardinelli et al., 1997). Indeed, adenosine was introduced into the clinical setting as an anti-arrhythmic drug for the acute management of re-entrant supraventricular tachycardia. However, adenosine causes bradyarrhythmia and atrial fibrillation (Belardinelli et al., 1997; Pelleg et al., 2002).

R75231 (intravenous administration at 0.1 mg/kg) decreases the incidence of ventricular fibrillation after coronary artery occlusion in open-chest pigs (Wainwright et al., 1993). Draflazine (infused in isolated guinea pig hearts at 10^{-7} M level) depresses atrioventricular nodal conduction, and its effects are reversed by 8-cyclopentyltheophylline (an adenosine A_1 receptor antagonist), which suggests the involvement of endogenous adenosine acting at adenosine A_1 receptors (Kollias-Baker et al., 1994; Dennis et al., 1996). In addition, dipyridamole (300 mg/day for 2 to 4 weeks) increases serum adenosine concentrations and suppresses catecholamine- and calcium ion influx-sensitive ventricular arrhythmia without changing the heart rate in humans (Kobayashi et al., 1996).

4.6. Insomnia

The idea that adenosine plays a role in sleep is a natural extension of the observation that adenosine receptor antagonists such as caffeine promote wakefulness and disrupt normal sleep. Endogenous adenosine levels in the basal forebrain are increased during prolonged wakefulness and adenosine receptor agonists generally promote sleep, whereas adenosine receptor antagonists reduce sleep (Dunwiddie and Masino, 2001). Adenosine decreases the activity of the wakefulness-promoting cell group, especially the cholinergic cells in the basal forebrain, through adenosine A_1 receptor pathways (Basheer et al., 2000). This action of adenosine is thought to contribute to its sleep-promoting effects. Prolonged wakefulness induces local energy depletion in the cholinergic basal forebrain, which increases extracellular adenosine concentrations (Porkka-Heiskanen et al., 2002). Increased extracellular adenosine concentrations promote sleep and then are decreased during sleep. Attenuation of the inhibition of the wakeful-active cell group by the decrease in adenosine levels leads to the initiation of a new period of wakefulness (Porkka-Heiskanen, 1999).

NBMPR (topical application to the cholinergic basal forebrain at 10^{-6}–10^{-5} M) increases adenosine concentrations in the basal forebrain, decreases the discharge rate of the basal forebrain neurons, and promotes sleep in animals (Porkka-Heiskanen et al., 1997; Alam et al., 1999). Soluflazine (intracerebroventricular administration in concentrations in the 10^{-8} M range) increases sleep in rats (O'Connor et al., 1991). Mioflazine (oral administration at 2.5 mg/kg) decreases wakefulness and increases slow-wave sleep in dogs (Wauquier et al., 1987). The sleep-improving effects of mioflazine are antagonized by caffeine.

4.7. Pain

Adenosine exerts multiple effects on pain transmission both at spinal and peripheral sites (Dickenson et al., 2000). In the spinal cord, adenosine provides pain relief through adenosine A_1 receptor pathways in acute nociceptive, inflammatory, and neuropathic pain tests (Sawynok, 1998). Adenosine attenuates both presynaptic and postsynaptic activities through the activation of ATP-sensitive potassium ion channels, hyperpolarization, and inhibition of calcium ion conductance (Sawynok, 1997). As a result, the release and activity of substance P, calcitonin gene-related peptides and glutamate at nerve terminals are attenuated, and these inhibitory activities of adenosine are thought to contribute to its anti-nociceptive effects (Sollevi, 1997; Sawynok and Liu, 2003). In addition, it has been reported that spinally released adenosine acts as a mediator of anti-nociception by opioid and 5-hydroxytryptamine (Sawynok, 1997; Sollevi, 1997), whereas peripheral adenosine exhibits pro-nociceptive effects (Burnstock and Wood, 1996). Therefore, systemically administered adenosine and its agonists have the potential to exhibit both anti-nociceptive and pro-nociceptive effects based on the route of administration. If these agents relieve pain when systemically administered, this probably reflects a spinal site of action (Sawynok, 1997).

Dilazep (intrathecal administration at 10^{-8} nmol) induces anti-nociception in mice (Keil and Delander, 1995). Dilazep is thought to inhibit spinal adenosine uptake and thus increases the extracellular adenosine concentrations, inducing anti-nociception.

4.8. Inflammatory diseases

Adenosine is released at sites of inflammation and acts as an endogenous anti-inflammatory agent (Cronstein, 1994, 1995). Adenosine A_{2A} receptor pathways have an important role in the anti-inflammatory effects of adenosine (Ohta and Sitkovsky, 2001; Sitkovsky, 2003). Adenosine inhibits neutrophil functions (e.g., oxygen radical production, rolling, adhesion to vascular endothelium, injury to endothelial cells, phagocytosis, and arachidonic acid release; Cronstein et al., 1986; Revan et al., 1996; Cronstein, 1997; Krump and Borgeat, 1999), macrophage functions (e.g., production of pro-inflammatory cytokines including tumor necrosis factor-α; Parmely et al., 1993; Bouma et al., 1994; Rosengren and Firestein, 1997), and endothelial cell activation (e.g., cytokine release and adhesion molecule expression; Bouma et al., 1996). In addition, it has been reported that adenosine agonists exert anti-inflammatory effects in vivo (Schrier et al., 1990; Le Vraux et al., 1993). Furthermore, adenosine mediates the anti-inflammatory effects of methotrexate and

sulfasalazine, which are clinically used for the treatment of inflammatory diseases (Cronstein et al., 1993; Gadangi et al., 1996).

It has been reported that dipyridamole and KF24345 inhibit inflammatory events both in vitro and in vivo (Le Vraux et al., 1993; Noji et al., 2002b). In addition, dipyridamole and KF24345 exert protective effects in models of inflammatory disease, as shown below.

4.8.1. Glomerulonephritis

Glomerulonephritis is an inflammatory disease of the kidneys, characterized by the accumulation of extracellular matrix within the damaged glomeruli, impaired filtration, and proteinuria (Bruijn et al., 1988; Stratta et al., 1999). The formation of immune complexes within the glomerulus is a key initiating pathophysiological event, and leukocytes are involved in the glomerular injury (O'Meara and Brady, 1997). The complement system, platelet-activating factor, chemokines, and cytokines are also involved in the pathogenesis of glomerulonephritis (Camussi, 1994; O'Meara and Brady, 1997). In addition, the initial insult-induced loss of nephron units may lead to an increase in glomerular pressure and to hyperfiltration in the remaining nephrons. These events can aggravate glomerulosclerosis and result in a further loss of nephron units (Jackson, 1997). The anti-inflammatory effects and the renal hemodynamic effects of adenosine (e.g., preglomerular vessel constriction, postglomerular vessel relaxation, tubuloglomerular feedback system mediation, renal renin release attenuation, and subsequent reduction of intraglomerular pressure) could ameliorate the severity of glomerulonephritis (Osswald et al., 1980; Murray and Churchill, 1985; Churchill and Bidani, 1987; Agmon et al., 1993). Indeed, 2chloro-adenosine, an adenosine receptor agonist, abolishes proteinuria in rats with glomerulonephritis (Poelstra et al., 1993).

Dipyridamole (intraperitoneal administration at 10 mg × 2/day to 140–160-g rats for 4 weeks) attenuates proteinuria in experimental glomerulonephritis (Izumino et al., 1986). In addition, KF24345 (oral administration at 10 mg/kg/day for 5 weeks) attenuates proteinuria and glomerular pathophysiological changes associated with glomerulonephritis in mice (Noji et al., 2002a).

4.8.2. Acute pancreatitis

Acute pancreatitis is a disease characterized by necrosis, vacuolization, and edema of the pancreas, and elevated activities of serum amylase and lipase (Steinberg and Tenner, 1994; Saluja and Steer, 1999). Several mediators, such as activated pancreatic enzymes (Leach et al., 1991), chemokines and cytokines (Denham et al., 1997; Grady et al., 1997), transcriptional factors (Steinle et al., 1999), platelet-activating factor (Konturek et al., 1992), and free radicals (Niederau et al., 1992), are assumed to be involved in the pathogenesis of acute pancreatitis; however, the mechanisms underlying the pathogenesis and progression of the disease are complex and not fully understood. In severe cases, the pancreatic damage may subsequently lead to serious complications (e.g., systemic inflammatory response syndrome and multiple organ dysfunction syndrome) with a high mortality (Banks, 1993; Steer, 1993).

The anti-inflammatory effects and the hemodynamic effects in the pancreas (e.g., the amelioration of pancreatic ischemia based on pancreas vasodilatation; Quere et al., 1997) of adenosine could protect against pancreatic damage. In addition, as shown above, adenosine directly inhibits the activation of neutrophils and macrophages, which play a key role in the development of serious systemic complications in acute pancreatitis (Niederau et al., 1991; Ogawa, 1998). Therefore, adenosine is thought to protect the pancreas against, and to inhibit the progression of, the serious complications of acute pancreatitis. Indeed, an adenosine-based therapeutic strategy in multiple organ failure has been reported (Hasko et al., 2002).

KF24345 (oral administration at 10 mg/kg) attenuates the pancreas injury of mild acute pancreatitis and decreases mortality in mice with severe acute pancreatitis (Noji et al., 2002c,d). The mortality-decreasing effects of KF24345 are blocked by 4-(2-[7-amino-2-(2-furyl)[1,2,4]triazolo[2,3-a][1,3,5]triazin-5-ylamino]ethyl)phenol, a selective adenosine A_{2A} receptor antagonist, suggesting that KF24345 inhibits the development of serious systemic complications in acute pancreatitis mainly through adenosine A_{2A} receptor pathways.

4.9. Others

In addition to regulating the transmembrane movements and physiological actions of adenosine, nucleoside transporters control the entry of other nucleosides and nucleoside analogues (Griffiths et al., 1997). Analogue drugs used for cancer chemotherapy (e.g., cladribine, fludarabine, cytarabine, and gemcitabine) are substrates for both equilibrative and concentrative nucleoside transporters (Baldwin et al., 1999).

Compounds that inhibit equilibrative nucleoside transporters are used together with chemotherapeutic nucleoside analogues. In cells that possess only equilibrative nucleoside transporters, intracellular concentrations of free nucleoside drugs will be less than or equal to the extracellular concentrations of the drugs. Even if equilibrative nucleoside transport inhibitors are applied to these types of cells, they would only inhibit the cellular uptake of nucleoside drugs, and intracellular concentrations of cytotoxic nucleoside drugs would not be higher than their extracellular concentrations. Concentrative nucleoside transporters might be most abundant in tumor cells. In cells that possess both equilibrative and concentrative nucleoside transporters, the intracellular free drug concentrations will represent a balance between concentrative uptake, metabolism, and equilibrative nucleoside transporter-mediated efflux. In these cells, equilibrative nucleoside transport inhibitors would

enhance the intracellular accumulation of cytotoxic nucleoside drugs, which are taken up into cells by concentrative nucleoside transporters. Therefore, it is expected that equilibrative nucleoside transport inhibitors (adenosine uptake inhibitors) could potentiate the cytotoxic effects of antimetabolite nucleoside analogues (anticancer chemotherapy agents) without affecting normal cells. It has been reported that dipyridamole enhances the cytotoxicity of thymidylate synthase inhibitors and antifolate agents (Chan and Howell, 1990; Curtin et al., 1999; Smith et al., 2001).

5. Conclusion

Various kinds of adenosine uptake inhibitors are currently available and have been used to characterize adenosine uptake sites in tissues or organs and to examine the role of adenosine in physiological functions or disease pathogenesis. In addition, abundant evidence has accumulated that adenosine uptake inhibitors may have therapeutic applications in various diseases. Adenosine uptake inhibitors are able to enhance the protective effects of endogenous adenosine released at sites of tissue or organ damage, potentially obviating the undesirable side effects associated with systemic administration of direct-acting adenosine receptor agonists. Protective or ameliorating effects of adenosine uptake inhibitors in ischemic cardiac and cerebral injury, organ transplantation, seizures, thrombosis, arrhythmia, insomnia, pain, and inflammatory diseases have been reported. Adenosine uptake inhibitors are expected to exhibit protective and ameliorating effects against various clinical diseases.

References

Agmon, Y., Dinour, D., Brezis, M., 1993. Disparate effects of adenosine A_1- and A_2-receptor agonists on intrarenal blood flow. Am. J. Physiol. 265, F802–F806.

Alam, M.N., Szymusiak, R., Gong, H., King, J., McGinty, D., 1999. Adenosinergic modulation of rat basal forebrain neurons during sleep and waking: neuronal recording with microdialysis. J. Physiol. 521, 679–690.

Andine, P., Rudolphi, K.A., Fredholm, B.B., Hagberg, H., 1990. Effect of propentofylline (HWA 285) on extracellular purines and excitatory amino acids in CA1 of rat hippocampus during transient ischaemia. Br. J. Pharmacol. 100, 814–818.

Anfossi, G., Massucco, P., Piretto, V., Mularoni, E., Cavalot, F., Mattiello, L., Trovati, M., 1995. Glyceryl trinitrate enhances the adenosine-induced inhibition of platelet responses: a mechanism potentially involved in the in vivo anti-aggregating effects of organic nitrates. Clin. Exp. Pharmacol. Physiol. 22, 803–811.

Ashton, D., Willems, R., De Prins, E., Van Belle, H., Wauquier, A., 1987. The nucleoside-transport inhibitor soluflazine (R 64 719) increases the effects of adenosine in the guinea-pig hippocampal slice and is antagonized by adenosine deaminase. Eur. J. Pharmacol. 142, 403–408.

Ashton, D., De Prins, E., Willems, R., Van Belle, H., Wauquier, A., 1988. Anticonvulsant action of the nucleoside transport inhibitor, soluflazine, on synaptic and non-synaptic epileptogenesis in the guinea-pig hippocampus. Epilepsy Res. 2, 65–71.

Baer, H.P., Haq, A., El-Soofi, A., Serignese, V., Paterson, A.R., 1990. Potencies of mioflazine and its derivatives as inhibitors of adenosine transport in isolated erythrocytes from different species. J. Pharm. Pharmacol. 42, 367–369.

Baer, H.P., Serignese, V., Moorji, A., Van Belle, H., 1991. In vivo effectiveness of several nucleoside transport inhibitors in mice and hamsters. Naunyn-Schmiedeberg's Arch. Pharmacol. 343, 365–369.

Baldwin, S.A., Mackey, J.R., Cass, C.E., Young, J.D., 1999. Nucleoside transporters: molecular biology and implications for therapeutic development. Mol. Med. Today 5, 216–224.

Banks, P.A., 1993. Medical management of acute pancreatitis and complications. In: Go, V.L., DiMagno, E.P., Gardner, J.D., Lebenthal, E., Reber, H.A., Scheele, G.A. (Eds.), The Pancreas: Biology, Pathobiology, and Disease. Raven Press, New York, NY, pp. 593–611.

Basheer, R., Porkka-Heiskanen, T., Strecker, R.E., Thakkar, M.M., McCarley, R.W., 2000. Adenosine as a biological signal mediating sleepiness following prolonged wakefulness. Biol. Signals Recept. 9, 319–327.

Baxter, G.F., 2002. Role of adenosine in delayed preconditioning of myocardium. Cardiovasc. Res. 55, 483–494.

Belardinelli, L., Curtis, A.B., Bertolet, B., 1997. Cardiac electrophysiology of adenosine: antiarrhythmic and proarrhythmic actions. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 185–202.

Booster, M.H., Yin, M., Maessen, J.G., Stubenitsky, B.M., Wijnen, R.M., Kootstra, G., 1995. Protection of canine renal grafts by renin–angiotensin inhibition through nucleoside transport blockade. Transpl. Int. 8, 207–213.

Bouma, M.G., Stad, R.K., van den Wildenberg, F.A., Buurman, W.A., 1994. Differential regulatory effects of adenosine on cytokine release by activated human monocytes. J. Immunol. 153, 4159–4168.

Bouma, M.G., van den Wildenberg, F.A., Buurman, W.A., 1996. Adenosine inhibits cytokine release and expression of adhesion molecules by activated human endothelial cells. Am. J. Physiol. 270, C522–C529.

Bruijn, J.A., Hogendoorn, P.C., Hoedemaeker, P.J., Fleuren, G.J., 1988. The extracellular matrix in pathology. J. Lab. Clin. Med. 111, 140–149.

Bullough, D.A., Magill, M.J., Firestein, G.S., Mullane, K.M., 1995. Adenosine activates A2 receptors to inhibit neutrophil adhesion and injury to isolated cardiac myocytes. J. Immunol. 155, 2579–2586.

Buolamwini, J.K., 1997. Nucleoside transport inhibitors: structure–activity relationships and potential therapeutic applications. Curr. Med. Chem. 4, 35–66.

Burnstock, G., Wood, J.N., 1996. Purinergic receptors: their role in nociception and primary afferent neurotransmission. Curr. Opin. Neurobiol. 6, 526–532.

Burnstock, G., Williams, M., 2000. P2 purinergic receptors: modulation of cell function and therapeutic potential. J. Pharmacol. Exp. Ther. 295, 862–869.

Cabrita, M.A., Baldwin, S.A., Young, J.D., Cass, C.E., 2002. Molecular biology and regulation of nucleoside and nucleobase transporter proteins in eukaryotes and prokaryotes. Biochem. Cell. Biol. 80, 623–638.

Camussi, G., 1994. Interactive effects of tumor necrosis factor and platelet-activating factor in the pathogenesis of glomerular injury. Lab. Invest. 70, 435–436.

Casado, F.J., Lostao, M.P., Aymerich, I., Larrayoz, I.M., Duflot, S., Rodriguez-Mulero, S., Pastor-Anglada, M., 2002. Nucleoside transporters in absorptive epithelia. J. Physiol. Biochem. 58, 207–216.

Cass, C.E., Young, J.D., Baldwin, S.A., 1998. Recent advances in the molecular biology of nucleoside transporters of mammalian cells. Biochem. Cell. Biol. 76, 761–770.

Cass, C.E., Young, J.D., Baldwin, S.A., Cabrita, M.A., Graham, K.A., Griffiths, M., Jennings, L.L., Mackey, J.R., Ng, A.M., Ritzel, M.W., Vickers, M.F., Yao, S.Y., 1999. Nucleoside transporters of mammalian cells. Pharm. Biotechnol. 12, 313–352.

Castillo-Melendez, M., Jarrott, B., Lawrence, A.J., 1996. Radioligand bind-

ing and autoradiographic visualization of adenosine transport sites in human inferior vagal ganglia and their axonal transport along rat vagal afferent neurons. J. Auton. Nerv. Syst. 57, 36–42.
Chan, T.C., Howell, S.B., 1990. Role of hypoxanthine and thymidine in determining methotrexate plus dipyridamole cytotoxicity. Eur. J. Cancer 26, 907–911.
Chang-Chun, C., Masuda, M., Szabo, Z., Szerafin, T., Szecsi, J., Van Belle, H., Flameng, W., 1992. Nucleoside transport inhibition mediates lidoflazine-induced cardioprotection during intermittent aortic crossclamping. J. Thorac. Cardiovasc. Surg. 104, 1602–1609.
Churchill, P.C., Bidani, A., 1987. Renal effects of selective adenosine receptor agonists in anesthetized rats. Am. J. Physiol. 252, F299–F303.
Collis, M.G., Hourani, S.M., 1993. Adenosine receptor subtypes. Trends Pharmacol. Sci. 14, 360–366.
Conant, A.R., Jarvis, S.M., 1994. Nucleoside influx and efflux in guinea-pig ventricular myocytes. Inhibition by analogues of lidoflazine. Biochem. Pharmacol. 48, 873–880.
Cristalli, G., Lambertucci, C., Taffi, S., Vittori, S., Volpini, R., 2003. Medicinal chemistry of adenosine A_{2A} receptor agonists. Curr. Topics Med. Chem. 3, 387–401.
Cronstein, B.N., 1994. Adenosine, an endogenous anti-inflammatory agent. J. Appl. Physiol. 76, 5–13.
Cronstein, B.N., 1995. A novel approach to the development of anti-inflammatory agents: adenosine release at inflamed sites. J. Investig. Med. 43, 50–57.
Cronstein, B.N., 1997. Adenosine regulation of neutrophil function and inhibition of inflammation via adenosine receptors. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 285–299.
Cronstein, B.N., Levin, R.I., Belanoff, J., Weissmann, G., Hirschhorn, R., 1986. Adenosine: an endogenous inhibitor of neutrophil-mediated injury to endothelial cells. J. Clin. Invest. 78, 760–770.
Cronstein, B.N., Naime, D., Ostad, E., 1993. The antiinflammatory mechanism of methotrexate. J. Clin. Invest. 92, 2675–2682.
Curtin, N.J., Bowman, K.J., Turner, R.N., Huang, B., Loughlin, P.J., Calvert, A.H., Golding, B.T., Griffin, R.J., Newell, D.R., 1999. Potentiation of the cytotoxicity of thymidylate synthase (TS) inhibitors by dipyridamole analogues with reduced (α_1-acid glycoprotein binding. Br. J. Cancer 80, 1738–1746.
Dalpiaz, A., Manfredini, S., 2002. Adenosine A_1 receptor: analysis of the potential therapeutic effects obtained by its activation in the central nervous system. Curr. Med. Chem. 9, 1923–1937.
Dar, M.S., 1989. Central nervous system effects and behavioral interactions with ethanol of centrally administered dilazep and its metabolites in mice. Eur. J. Pharmacol. 164, 303–313.
Dawicki, D.D., Agarwal, K.C. , Parks Jr., R.E. 1986. Potentiation of the antiplatelet action of adenosine in whole blood by dipyridamole or dilazep and the cAMP phosphodiesterase inhibitor, RA 233. Thromb. Res. 43, 161–175.
Deckert, J., Gleiter, C.H., 1994. Adenosine—an endogenous neuroprotective metabolite and neuromodulator. J. Neural Transm., Suppl. 43, 23–31.
Deckert, J., Bereznai, B., Hennemann, A., Gsell, W., Gotz, M., Fritze, J., Riederer, P., 1993. Nimodipine inhibits [^{3}H]nitrobenzylthioinosine binding to the adenosine transporter in human brain. Eur. J. Pharmacol. 238, 131–133.
Deguchi, H., Takeya, H., Wada, H., Gabazza, E.C., Hayashi, N., Urano, H., Suzuki, K., 1997. Dilazep, an antiplatelet agent, inhibits tissue factor expression in endothelial cells and monocytes. Blood 90, 2345–2356.
Deguchi, H., Takeya, H., Urano, H., Gabazza, E.C., Zhou, H., Suzuki, K., 1998. Adenosine regulates tissue factor expression on endothelial cells. Thromb. Res. 91, 57–64.
De Hert, S.G., Rodrigus, I.E., Haenen, L.R., Broecke, P.W., Boeckxstaens, C.J., Gillebert, T.C., 1997. Effects of lidoflazine on left ventricular function in patients. J. Cardiothorac. Vasc. Anesth. 1, 42–48.
de Jong, J.W., van der Meer, P., van Loon, H., Owen, P., Opie, L.H., 1990. Adenosine as adjunct to potassium cardioplegia: effect on function, energy metabolism, and electrophysiology. J. Thorac. Cardiovasc. Surg. 100, 445–454.
de Jong, J.W., de Jonge, R., Keijzer, E., Bradamante, S., 2000. The role of adenosine in preconditioning. Pharmacol. Ther. 87, 141–149.
de Ligt, R.A., IJzerman, A.P., 2002. Intrinsic activity at adenosine A_1 receptors: partial and inverse agonism. Curr. Pharm. Des. 8, 2333–2344.
Denham, W., Yang, J., Fink, G., Denham, D., Carter, G., Ward, K., Norman, J., 1997. Gene targeting demonstrates additive detrimental effects of interleukin 1 and tumor necrosis factor during pancreatitis. Gastroenterology 113, 1741–1746.
Dennis, D.M., Raatikainen, M.J., Martens, J.R., Belardinelli, L., 1996. Modulation of atrioventricular nodal function by metabolic and allosteric regulators of endogenous adenosine in guinea pig heart. Circulation 94, 2551–2559.
De Schryver, E.L., Algra, A., van Gijn, J., 2003. Cochrane review: dipyridamole for preventing major vascular events in patients with vascular disease. Stroke 34, 2072–2080.
Dickenson, A.H., Suzuki, R., Reeve, A.J., 2000. Adenosine as a potential analgesic target in inflammatory and neuropathic pains. CNS Drugs 13, 77–85.
Dogne, J., de Leval, X., Benoit, P., Delarge, J., Masereel, B., David, J., 2002. Recent advances in antiplatelet agents. Curr. Med. Chem. 9, 577–589.
Dunwiddie, T.V., 1999. Adenosine and suppression of seizures. Adv. Neurol. 79, 1001–1010.
Dunwiddie, T.V., Diao, L., 2000. Regulation of extracellular adenosine in rat hippocampal slices is temperature dependent: role of adenosine transporters. Neuroscience 95, 81–88.
Dunwiddie, T.V., Masino, S.A., 2001. The role and regulation of adenosine in the central nervous system. Annu. Rev. Neurosci. 24, 31–55.
Dux, E., Fastbom, J., Ungerstedt, U., Rudolphi, K., Fredholm, B.B., 1990. Protective effect of adenosine and a novel xanthine derivative propentofylline on the cell damage after bilateral carotid occlusion in the gerbil hippocampus. Brain Res. 516, 248–256.
Elam, M.B., Heckman, J., Crouse, J.R., Hunninghake, D.B., Herd, J.A., Davidson, M., Gordon, I.L., Bortey, E.B., Forbes, W.P., 1998. Effect of the novel antiplatelet agent cilostazol on plasma lipoproteins in patients with intermittent claudication. Arterioscler. Thromb. Vasc. Biol. 18, 1942–1947.
Ely, S.W., Berne, R.M., 1992. Protective effects of adenosine in myocardial ischemia. Circulation 85, 893–904.
Figueredo, V.M., Diamond, I., Zhou, H., Camacho, S.A., 1999. Chronic dipyridamole therapy produces sustained protection against cardiac ischemia–reperfusion injury. Am. J. Physiol. 77, H2091–H2097.
Filtz, T.M., Harden, T.K., Nicholas, R.A., 1997. Structure, pharmacological selectivity, and second messenger signaling properties of G protein-coupled P2-purinergic receptors. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 39–53.
Flameng, W., Sukehiro, S., Mollhoff, T., Van Belle, H., Janssen, P., 1991. A new concept of long-term donor heart preservation: nucleoside transport inhibition. J. Heart Lung Transplant. 10, 990–998.
Foster, A.C., Miller, L.P., Wiesner, J.B., 1994. Regulation of endogenous adenosine levels in the CNS: potential for therapy in stroke, epilepsy and pain. Adv. Exp. Med. Biol. 370, 427–430.
Fredholm, B.B., 1997. Adenosine and neuroprotection. Int. Rev. Neurobiol. 40, 259–280.
Fredholm, B.B., Fastbom, J., Kvanta, A., Gerwins, P., Parkinson, F., 1992. Further evidence that propentofylline (HWA 285) influences both adenosine receptors and adenosine transport. Fundam. Clin. Pharmacol. 6, 99–111.
Fredholm, B.B., Arslan, G., Halldner, L., Kull, B., Schulte, G., Wasserman, W., 2000. Structure and function of adenosine receptors and their genes. Naunyn-Schmiedeberg's Arch. Pharmacol. 362, 364–374.
Fredholm, B.B., IJzerman, A.P., Jacobson, K.A., Klotz, K., Linden, J., 2001. International union of pharmacology: XXV. Nomenclature and classification of adenosine receptors. Pharmacol. Rev. 53, 527–552.
Fremes, S.E., Furukawa, R.D., Zhang, J., Li, R., Tumiati, L.C., Weisel,

R.D., Mickle, D.A., 1995. Cardiac storage with University of Wisconsin solution and a nucleoside-transport blocker. Ann. Thorac. Surg. 59, 1127–1133.

Gadangi, P., Longaker, M., Naime, D., Levin, R.I., Recht, P.A., Montesinos, M.C., Buckley, M.T., Carlin, G., Cronstein, B.N., 1996. The anti-inflammatory mechanism of sulfasalazine is related to adenosine release at inflamed sites. J. Immunol. 156, 1937–1941.

Galinanes, M., Hearse, D.J., 1992. Exogenous adenosine accelerates recovery of cardiac function and improves coronary flow after long-term hypothermic storage and transplantation. J. Thorac. Cardiovasc. Surg. 104, 151–158.

Galinanes, M., Qiu, Y., Van Belle, H., Hearse, D.J., 1993. Metabolic and functional effects of the nucleoside transport inhibitor R75231 in the ischaemic and blood reperfused rabbit heart. Cardiovasc. Res. 27, 90–95.

Geiger, J.D., Parkinson, F.E., Kowaluk, E.A., 1997. Regulators of endogenous adenosine levels as therapeutic agents. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 55–84.

Gidday, J.M., Fitzgibbons, J.C., Shah, A.R., Kraujalis, M.J., Park, T.S., 1995. Reduction in cerebral ischemic injury in the newborn rat by potentiation of endogenous adenosine. Pediatr. Res. 38, 306–311.

Gidday, J.M., Kim, Y., Shah, A.R., Gonzales, E.R., Park, T.S., 1996. Adenosine transport inhibition ameliorates postischemic hypoperfusion in pigs. Brain Res. 734, 261–268.

Grady, T., Liang, P., Ernst, S.A., Logsdon, C.D., 1997. Chemokine gene expression in rat pancreatic acinar cells is an early event associated with acute pancreatitis. Gastroenterology 113, 1966–1975.

Gresele, P., Arnout, J., Deckmyn, H., Vermylen, J., 1986. Mechanism of the antiplatelet action of dipyridamole in whole blood: modulation of adenosine concentration and activity. Thromb. Haemost. 55, 12–18.

Griffith, D.A., Jarvis, S.M., 1996. Nucleoside and nucleobase transport systems of mammalian cells. Biochim. Biophys. Acta 1286, 153–181.

Griffiths, M., Beaumont, N., Yao, S.Y., Sundaram, M., Boumah, C.E., Davies, A., Kwong, F.Y., Coe, I., Cass, C.E., Young, J.D., Baldwin, S.A., 1997. Cloning of a human nucleoside transporter implicated in the cellular uptake of adenosine and chemotherapeutic drugs. Nat. Med. 3, 89–93.

Grover, G.J., Sleph, P.G., 1994. The cardioprotective effects of R 75231 and lidoflazine are not caused by adenosine A_1 receptor activation. J. Pharmacol. Exp. Ther. 268, 90–96.

Hammond, J.R., Archer, R.G., 2004. Interaction of the novel adenosine uptake inhibitor 3-[1-(6,7-diethoxy-2-morpholinoquinazolin-4-yl)piperidin-4-yl]-1,6-dimethyl-2,4(1*H*,3*H*)-quinazolinedione hydrochloride (KF24345) with the *es* and *ei* subtypes of equilibrative nucleoside transporters. J. Pharmacol. Exp. Ther. 308, 1083–1093.

Harker, L.A., Kadatz, R.A., 1983. Mechanism of action of dipyridamole. Thromb. Res. 4, 39–46.

Hasko, G., Deitch, E.A., Szabo, C., Nemeth, Z.H., Vizi, E.S., 2002. Adenosine: a potential mediator of immunosuppression in multiple organ failure. Curr. Opin. Pharmacol. 2, 440–444.

Headrick, J.P., Matherne, G.P., Berne, R.M., 1992. Myocardial adenosine formation during hypoxia: effects of ecto-5′-nucleotidase inhibition. J. Mol. Cell. Cardiol. 24, 295–303.

Heaton, T.P., Clanachan, A.S., 1987. Nucleoside transport in guinea pig myocytes. Comparison of the affinities and transport velocities for adenosine and 2-chloroadenosine. Biochem. Pharmacol. 36, 1275–1280.

Hyde, R.J., Cass, C.E., Young, J.D., Baldwin, S.A., 2001. The ENT family of eukaryote nucleoside and nucleobase transporters: recent advances in the investigation of structure/function relationships and the identification of novel isoforms. Mol. Membr. Biol. 18, 53–63.

IJzerman, A.P., van der Wenden, N.M., 1997. Modulators of adenosine uptake, release, and inactivation. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 129–148.

IJzerman, A.P., Kruidering, M., van Weert, A., van Belle, H., Janssen, C., 1992. [^{3}H]R75231—a new radioligand for the nitrobenzylthioinosine sensitive nucleoside transport proteins. Characterization of (±)-[^{3}H]R75231 binding to calf lung membranes, stereospecificity of its two stereoisomers, and comparison with [^{3}H]nitrobenzylthioinosine binding. Naunyn-Schmiedeberg's Arch. Pharmacol. 345, 558–563.

Itoya, M., Miura, T., Sakamoto, J., Urabe, K., Iimura, O., 1994. Nucleoside transport inhibitors enhance the infarct size-limiting effect of ischemic preconditioning. J. Cardiovasc. Pharmacol. 24, 846–852.

Izumino, K., Iida, H., Asaka, M., Mizumura, Y., Sasayama, S., 1986. Effect of the antiplatelet agents ticlopidine and dipyridamole on experimental immune complex glomerulonephritis in rats. Nephron 43, 56–61.

Jackson, E.K., 1997. Renal actions of purines. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 217–250.

Jacobson, K.A., van Rhee, A.M., 1997. Development of selective purinoceptor agonists and antagonists. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 101–128.

Jacobson, K.A., van Galen, P.J., Williams, M., 1992. Adenosine receptors: pharmacology, structure–activity relationships, and therapeutic potential. J. Med. Chem. 35, 407–422.

Johnson, S.M., Patel, S., Bruckner, F.E., Collins, D.A., 1999. 5′-Nucleotidase as a marker of both general and local inflammation in rheumatoid arthritis patients. Rheumatology (Oxf.) 38, 391–396.

Kano, T., Katayama, Y., Kawamata, T., Hirota, H., Tsubokawa, T., 1994. Propentofylline administered by microdialysis attenuates ischemia-induced hippocampal damage but not excitatory amino acid release in gerbils. Brain Res. 641, 149–154.

Kawahara, N., Ide, T., Saito, N., Kawai, K., Kirino, T., 1998. Propentofylline potentiates induced ischemic tolerance in gerbil hippocampal neurons via adenosine receptor. J. Cereb. Blood Flow Metab. 18, 472–475.

Keil II, G.J., Delander, G.E. 1995. Time-dependent antinociceptive interactions between opioids and nucleoside transport inhibitors. J. Pharmacol. Exp. Ther. 274, 1387–1392.

Khakh, B.S., Kennedy, C., 1998. Adenosine and ATP: progress in their receptors' structures and functions. Trends Pharmacol. Sci. 19, 39–41.

Kirkeboen, K.A., Aksnes, G., Lande, K., Ilebekk, A., 1992. Role of adenosine for reactive hyperemia in normal and stunned porcine myocardium. Am. J. Physiol. 263, H1119–H1127.

Kirkeboen, K.A., Ilebekk, A., Tonnessen, T., Leistad, E., Naess, P.A., Christensen, G., Aksnes, G., 1994. Cardiac contractile function following repetitive brief ischemia: effects of nucleoside transport inhibition. Am. J. Physiol. 267, H57–H65.

Kitakaze, M., Hori, M., Kamada, T., 1993a. Role of adenosine and its interaction with (adrenoceptor activity in ischaemic and reperfusion injury of the myocardium. Cardiovasc. Res. 27, 18–27.

Kitakaze, M., Hori, M., Takashima, S., Sato, H., Inoue, M., Kamada, T., 1993b. Ischemic preconditioning increases adenosine release and 5'-nucleotidase activity during myocardial ischemia and reperfusion in dogs: implications for myocardial salvage. Circulation 87, 208–215.

Knutsen, L.J., Murray, T.F., 1997. Adenosine and ATP in Epilepsy. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 423–447.

Kobayashi, Y., Miyata, A., Chiyoda, K., Nakagawa, H., Jinbo, Y., Tanno, K., Kikushima, S., Kurano, K., Baba, T., Katagiri, T., 1996. Dipyridamole suppresses catecholamine- and Ca^+ influx-sensitive ventricular arrhythmias. Jpn. Circ. J. 60, 629–640.

Kohda, N., Tani, T., Nakayama, S., Adachi, T., Marukawa, K., Ito, R., Ishida, K., Matsumoto, Y., Kimura, Y., 1999. Effect of cilostazol, a phosphodiesterase III inhibitor, on experimental thrombosis in the porcine carotid artery. Thromb. Res. 96, 261–268.

Kollias-Baker, C., Xu, J., Pelleg, A., Belardinelli, L., 1994. Novel approach for enhancing atrioventricular nodal conduction delay mediated by endogenous adenosine. Circ. Res. 75, 972–980.

Konturek, S.J., Dembinski, A., Konturek, P.J., Warzecha, Z., Jaworek, J., Gustaw, P., Tomaszewska, R., Stachura, J., 1992. Role of platelet activating factor in pathogenesis of acute pancreatitis in rats. Gut 33, 1268–1274.

Koos, W.T., Perneczky, A., Auer, L.M., Boker, D.K., Gaab, M., Jaksche, H., Kostron, H., Meinig, G., Muizelaar, J.P., van der Werf, A.J., Seibert, H.K., Ulrich, F., Sprung, C., 1985. Nimodipine treatment of ischemic neurological deficits due to cerebral vasospasm after subarachnoid hemorrhage. Neurochirurgia 28, 114–117.

Kowaluk, E.A., Bhagwat, S.S., Jarvis, M.F., 1998. Adenosine kinase inhibitors. Curr. Pharm. Des. 4, 403–416.

Krump, E., Borgeat, P., 1999. Adenosine. An endogenous inhibitor of arachidonic acid release and leukotriene biosynthesis in human neutrophils. Adv. Exp. Med. Biol. 447, 107–115.

Lasley, R.D., Mentzer Jr., R.M. 1994. The role of adenosine in extended myocardial preservation with the University of Wisconsin solution. J. Thorac. Cardiovasc. Surg. 107, 1356–1363.

Latini, S., Pedata, F., 2001. Adenosine in the central nervous system: release mechanisms and extracellular concentrations. J. Neurochem. 79, 463–484.

Leach, S.D., Modlin, I.M., Scheele, G.A., Gorelick, F.S., 1991. Intracellular activation of digestive zymogens in rat pancreatic acini. Stimulation by high doses of cholecystokinin. J. Clin. Invest. 87, 362–366.

Leff, P., Robertson, M.J., Humphries, R.G., 1997. The role of ADP in thrombosis and the therapeutic potential of P_{2T}-receptor antagonists as novel antithrombotic agents. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 203–216.

Lemasters, J.J., Thurman, R.G., 1997. Reperfusion injury after liver preservation for transplantation. Annu. Rev. Pharmacol. Toxicol. 37, 327–338.

Le Vraux, V., Chen, Y.L., Masson, I., De Sousa, M., Giroud, J.P., Florentin, I., Chauvelot-Moachon, L., 1993. Inhibition of human monocyte TNF production by adenosine receptor agonists. Life Sci. 52, 1917–1924.

Liang, B.T., Jacobson, K.A., 1999. Adenosine and ischemic preconditioning. Curr. Pharm. Des. 5, 1029–1041.

Linden, J., 1997. Allosteric enhancement of adenosine receptors. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 85–97.

Linden, J., 2001. Molecular approach to adenosine receptors: receptor-mediated mechanisms of tissue protection. Annu. Rev. Pharmacol. Toxicol. 41, 775–787.

Liu, Y., Fong, M., Cone, J., Wang, S., Yoshitake, M., Kambayashi, J., 2000. Inhibition of adenosine uptake and augmentation of ischemia-induced increase of interstitial adenosine by cilostazol, an agent to treat intermittent claudication. J. Cardiovasc. Pharmacol. 36, 351–360.

Liu, Y., Shakur, Y., Yoshitake, M., Kambayashi, J., 2001. Cilostazol (Pletal®): a dual inhibitor of cyclic nucleotide phosphodiesterase type 3 and adenosine uptake. Cardiovasc. Drug Rev. 19, 369–386.

Marangos, P.J., Patel, J., Clark-Rosenberg, R., Martino, A.M., 1982. [^{3}H]Nitrobenzylthioinosine binding as a probe for the study of adenosine uptake sites in brain. J. Neurochem. 39, 184–191.

Martin, B.J., Lasley, R.D. , Mentzer Jr., R.M. 1997. Infarct size reduction with the nucleoside transport inhibitor R-75231 in swine. Am. J. Physiol. 272, H1857–H1865.

Marzilli, M., Simonetti, I., Levantesi, D., Trivella, M.G., De Nes, M., Perissinotto, A., Puntoni, R., Buzzigoli, G., Boni, C., Michelassi, C., L'Abbate, A., 1984. Effects of dilazep on coronary and systemic hemodynamics in humans. Am. Heart J. 108, 276–285.

Masuda, M., Chang-Chun, C., Mollhoff, T., Van Belle, H., Flameng, W., 1992. Effects of nucleoside transport inhibition on long-term ex vivo preservation of canine hearts. J. Thorac. Cardiovasc. Surg. 104, 1610–1617.

Minami, N., Suzuki, Y., Yamamoto, M., Kihira, H., Imai, E., Wada, H., Kimura, Y., Ikeda, Y., Shiku, H., Nishikawa, M., 1997. Inhibition of shear stress-induced platelet aggregation by cilostazol, a specific inhibitor of cGMP-inhibited phosphodiesterase, in vitro and ex vivo. Life Sci. 61, PL 383–PL 389.

Minamino, T., Kitakaze, M., Komamura, K., Node, K., Takeda, H., Inoue, M., Hori, M., Kamada, T., 1995. Activation of protein kinase C increases adenosine production in the hypoxic canine coronary artery through the extracellular pathway. Arterioscler. Thromb. Vasc. Biol. 15, 2298–2304.

Mitchell, J.B., Lupica, C.R., Dunwiddie, T.V., 1993. Activity-dependent release of endogenous adenosine modulates synaptic responses in the rat hippocampus. J. Neurosci. 13, 3439–3447.

Miyashita, K., Nakajima, T., Ishikawa, A., Miyatake, T., 1992. An adenosine uptake blocker, propentofylline, reduces glutamate release in gerbil hippocampus following transient forebrain ischemia. Neurochem. Res. 17, 147–150.

Mollhoff, T., Sukehiro, S., Van Belle, H., Van Aken, H., Flameng, W., 1992. Successful transplantation after long-term preservation of dog hearts. Anesthesiology 77, 291–300.

Moser, G.H., Schrader, J., Deussen, A., 1989. Turnover of adenosine in plasma of human and dog blood. Am. J. Physiol. 256, C799–C806.

Mubagwa, K., Flameng, W., 2001. Adenosine, adenosine receptors and myocardial protection: an updated overview. Cardiovasc. Res. 52, 25–39.

Mullane, K., Bullough, D., 1995. Harnessing an endogenous cardioprotective mechanism: cellular sources and sites of action of adenosine. J. Mol. Cell. Cardiol. 27, 1041–1054.

Murray, R.D., Churchill, P.C., 1985. Concentration dependency of the renal vascular and renin secretory responses to adenosine receptor agonists. J. Pharmacol. Exp. Ther. 232, 189–193.

Murray, T.F., Sylvester, D., Schultz, C.S., Szot, P., 1985. Purinergic modulation of the seizure threshold for pentylenetetrazol in the rat. Neuropharmacology 24, 761–766.

Nakamura, T., Ushiyama, C., Shimada, N., Sekizuka, K., Ebihara, I., Hara, M., Koide, H., 2000. Effect of the antiplatelet drug dilazep dihydrochloride on urinary podocytes in patients in the early stage of diabetic nephropathy. Diabetes Care 23, 1168–1171.

Narimatsu, E., Aoki, M., 1999. Involvement of the adenosine neuromodulatory system in the benzodiazepine-induced depression of excitatory synaptic transmissions in rat hippocampal neurons in vitro. Neurosci. Res. 33, 57–64.

Narimatsu, E., Aoki, M., 2000. Transient depression of excitatory synaptic transmission induced by adenosine uptake inhibition in rat hippocampal slices. Brain Res. 862, 284–287.

Niederau, C., Ude, K., Niederau, M., Luthen, R., Strohmeyer, G., Ferrell, L.D., Grendell, J.H., 1991. Effects of the seleno-organic substance Ebselen in two different models of acute pancreatitis. Pancreas 6, 282–290.

Niederau, C., Niederau, M., Borchard, F., Ude, K., Luthen, R., Strohmeyer, G., Ferrell, L.D., Grendell, J.H., 1992. Effects of antioxidants and free radical scavengers in three different models of acute pancreatitis. Pancreas 7, 486–496.

Noji, T., Sato, H., Sano, J., Nishikawa, S., Kusaka, H., Karasawa, A., 2002a. Treatment with an adenosine uptake inhibitor attenuates glomerulonephritis in mice. Eur. J. Pharmacol. 449, 293–300.

Noji, T., Takayama, M., Mizutani, M., Okamura, Y., Takai, H., Karasawa, A., Kusaka, H., 2002b. KF24345, an adenosine uptake inhibitor, suppresses lipopolysaccharide-induced tumor necrosis factor-α production and leukopenia via endogenous adenosine in mice. J. Pharmacol. Exp. Ther. 300, 200–205.

Noji, T., Nan-ya, K., Katagiri, C., Mizutani, M., Sano, J., Nishikawa, S., Karasawa, A., Kusaka, H., 2002c. Adenosine uptake inhibition ameliorates cerulein-induced acute pancreatitis in mice. Pancreas 25, 387–392.

Noji, T., Nan-ya, K., Mizutani, M., Katagiri, C., Sano, J., Ttakada, C., Nishikawa, S., Karasawa, A., Kusaka, H., 2002d. KF24345, an adenosine uptake inhibitor, ameliorates the severity and mortality of lethal acute pancreatitis via endogenous adenosine in mice. Eur. J. Pharmacol. 454, 85–93.

O'Connor, S.D., Stojanovic, M., Radulovacki, M., 1991. The effect of soluflazine on sleep in rats. Neuropharmacology 30, 671–674.

Ogawa, M., 1998. Acute pancreatitis and cytokines: "second attack" by septic complication leads to organ failure. Pancreas 16, 312–315.

Ohta, A., Sitkovsky, M., 2001. Role of G-protein-coupled adenosine receptors in downregulation of inflammation and protection from tissue damage. Nature 414, 916–920.

Olah, M.E., Stiles, G.L., 2000. The role of receptor structure in determining adenosine receptor activity. Pharmacol. Ther. 85, 55–75.

O'Meara, Y.M., Brady, H.R., 1997. Lipoxins, leukocyte recruitment and the resolution phase of acute glomerulonephritis. Kidney Inter., Suppl. 58, S56–S61.

Osswald, H., Nabakowski, G., Hermes, H., 1980. Adenosine as a possible mediator of metabolic control of glomerular filtration rate. Int. J. Biochem. 12, 263–267.

Park, T.S., Gidday, J.M., 1990. Effect of dipyridamole on cerebral extracellular adenosine level in vivo. J. Cereb. Blood Flow Metab. 10, 424–427.

Parkinson, F.E., Fredholm, B.B., 1991. Effects of propentofylline on adenosine A_1 and A_2 receptors and nitrobenzylthioinosine-sensitive nucleoside transporters: quantitative autoradiographic analysis. Eur. J. Pharmacol. 202, 361–366.

Parkinson, F.E., Geiger, J.D., 1996. Effects of iodotubercidin on adenosine kinase activity and nucleoside transport in DDT_1 MF-2 smooth muscle cells. J. Pharmacol. Exp. Ther. 277, 1397–1401.

Parkinson, F.E., Paterson, A.R., Young, J.D., Cass, C.E., 1993. Inhibitory effects of propentofylline on [^{3}H]adenosine influx. A study of three nucleoside transport systems. Biochem. Pharmacol. 46, 891–896.

Parkinson, F.E., Rudolphi, K.A., Fredholm, B.B., 1994. Propentofylline: a nucleoside transport inhibitor with neuroprotective effects in cerebral ischemia. Gen. Pharmacol. 25, 1053–1058.

Parmely, M.J., Zhou, W. , Edwards III, C.K., Borcherding, D.R., Silverstein, R., Morrison, D.C. 1993. Adenosine and a related carbocyclic nucleoside analogue selectively inhibit tumor necrosis factor-α production and protect mice against endotoxin challenge. J. Immunol. 151, 389–396.

Pasini, F.L., Capecchi, P.L., Perri, T.D., 2000. Adenosine and chronic ischemia of the lower limbs. Vasc. Med. 5, 243–250.

Patel, J., Marangos, P.J., Skolnick, P., Paul, S.M., Martino, A.M., 1982. Benzodiazepines are weak inhibitors of [^{3}H]nitrobenzylthioinosine binding to adenosine uptake sites in brain. Neurosci. Lett. 29, 79–82.

Pedata, F., Corsi, C., Melani, A., Bordoni, F., Latini, S., 2001. Adenosine extracellular brain concentrations and role of A_{2A} receptors in ischemia. Ann. N.Y. Acad. Sci. 939, 74–84.

Pelleg, A., 1993. Mechanisms of action and therapeutic potential of adenosine and its analogues in the treatment of cardiac arrhythmias. Coron. Artery Dis. 4, 109–115.

Pelleg, A., Pennock, R.S., Kutalek, S.P., 2002. Proarrhythmic effects of adenosine: one decade of clinical data. Am. J. Ther. 9, 141–147.

Petsikas, D., Ricci, M.A., Baffour, R., de Varennes, B., Symes, J., Guerraty, A., 1990. Enhanced 24-hour in vitro heart preservation with adenosine and adenosine monophosphate. J. Heart Transplant. 9, 114–118.

Phillis, J.W., Goshgarian, H.G., 2001. Adenosine and neurotrauma: therapeutic perspectives. Neurol. Res. 23, 183–189.

Picano, E., Michelassi, C., 1997. Chronic oral dipyridamole as a 'novel' antianginal drug: the collateral hypothesis. Cardiovasc. Res. 33, 666–670.

Plagemann, P.G., Wohlhueter, R.M., Kraupp, M., 1985. Adenosine uptake, transport, and metabolism in human erythrocytes. J. Cell. Physiol. 125, 330–336.

Poelstra, K., Brouwer, E., Baller, J.F., Hardonk, M.J., Bakker, W.W., 1993. Attenuation of anti-Thy1 glomerulonephritis in the rat by anti-inflammatory platelet-inhibiting agents. Am. J. Pathol. 142, 441–450.

Porkka-Heiskanen, T., 1999. Adenosine in sleep and wakefulness. Ann. Med. 31, 125–129.

Porkka-Heiskanen, T., Strecker, R.E., Thakkar, M., Bjorkum, A.A., Greene, R.W., McCarley, R.W., 1997. Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. Science 276, 1265–1268.

Porkka-Heiskanen, T., Alanko, L., Kalinchuk, A., Stenberg, D., 2002. Adenosine and sleep. Sleep Med. Rev. 6, 321–332.

Poulsen, S.A., Quinn, R.J., 1998. Adenosine receptors: new opportunities for future drugs. Bioorg. Med. Chem. 6, 619–641.

Qian, J.Q., Batink, H.D., Timmermans, P.B., van Zwieten, P.A., 1984. Interaction between dilazep and α-adrenoceptors. Pharmacology 29, 198–203.

Quere, I., Hillaire-Buys, D., Brunschwig, C., Chapal, J., Janbon, C., Blayac, J.P., Petit, P., Loubatieres-Mariani, M.M., 1997. Effects of homocysteine on acetylcholine- and adenosine-induced vasodilatation of pancreatic vascular bed in rats. Br. J. Pharmacol. 122, 351–357.

Ralevic, V., Burnstock, G., 1998. Receptors for purines and pyrimidines. Pharmacol. Rev. 50, 413–492.

Revan, S., Montesinos, M.C., Naime, D., Landau, S., Cronstein, B.N., 1996. Adenosine A_2 receptor occupancy regulates stimulated neutrophil function via activation of a serine/threonine protein phosphatase. J. Biol. Chem. 271, 17114–17118.

Ribeiro, J.A., Sebastiao, A.M., de Mendonca, A., 2003. Participation of adenosine receptors in neuroprotection. Drug News Perspect. 16, 80–86.

Ritzel, M.W., Ng, A.M., Yao, S.Y., Graham, K., Loewen, S.K., Smith, K.M., Hyde, R.J., Karpinski, E., Cass, C.E., Baldwin, S.A., Young, J.D., 2001. Recent molecular advances in studies of the concentrative Na+-dependent nucleoside transporter (CNT) family: identification and characterization of novel human and mouse proteins (hCNT3 and mCNT3) broadly selective for purine and pyrimidine nucleosides (system cib). Mol. Membr. Biol. 18, 65–72.

Rosengren, S., Firestein, G.S., 1997. Purinergic modulation of septic shock and systemic inflammation response syndrome. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 301–313.

Saluja, A.K., Steer, M.L., 1999. Pathophysiology of pancreatitis. Role of cytokines and other mediators of inflammation. Digestion 60 (Suppl. 1), 27–33.

Sawynok, J., 1997. Purines and nociception. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 495–513.

Sawynok, J., 1998. Adenosine receptor activation and nociception. Eur. J. Pharmacol. 317, 1–11.

Sawynok, J., Liu, X.J., 2003. Adenosine in the spinal cord and periphery: release and regulation of pain. Prog. Neurobiol. 69, 313–340.

Sawynok, J., Sweeney, M.I., White, T.D., 1986. Classification of adenosine receptors mediating antinociception in the rat spinal cord. Br. J. Pharmacol. 88, 923–930.

Schrier, D.J., Lesch, M.E., Wright, C.D., Gilbertsen, R.B., 1990. The antiinflammatory effects of adenosine receptor agonists on the carrageenan-induced pleural inflammatory response in rats. J. Immunol. 145, 1874–1879.

Schror, K., 2002. The pharmacology of cilostazol. Diabetes Obes. Metab. 4, S14–S19.

Scriabine, A., Schuurman, T., Traber, J., 1989. Pharmacological basis for the use of nimodipine in central nervous system disorders. FASEB J. 3, 1799–1806.

Seif-El-Nasr, M., Khattab, M., 2002. Influence of inhibition of adenosine uptake on the γ-aminobutyric acid level of the ischemic rat brain. Arzneim.-Forsch./Drug Res. 52, 353–357.

Seubert, C.N., Morey, T.E., Martynyuk, A.E., Cucchiara, R.F., Dennis, D.M., 2000. Midazolam selectively potentiates the A_2A- but not A1-receptor-mediated effects of adenosine. Role of nucleoside transport inhibition and clinical implications. Anesthesiology 92, 567–577.

Shi, M.M., Wu, J.R., Lee, C., Young, J.D., 1984. Nucleoside transport. Photoaffinity labelling of high-affinity nitrobenzylthioinosine binding sites in rat and guinea pig lung. Biochem. Biophys. Res. Commun. 118, 594–600.

Sinclair, C.J., Krizanac-Bengez, L., Stanness, K.A., Janigro, D., Parkinson, F.E., 2001. Adenosine permeation of a dynamic in vitro blood–brain barrier inhibited by dipyridamole. Brain Res. 898, 122–125.

Sitkovsky, M.V., 2003. Use of the A_2A adenosine receptor as a physiological immunosuppressor and to engineer inflammation in vivo. Biochem. Pharmacol. 65, 493–501.

Smith, P.G., Thomas, H.D., Barlow, H.C., Griffin, R.J., Golding, B.T., Calvert, A.H., Newell, D.R., Curtin, N.J., 2001. In vitro and in vivo properties of novel nucleoside transport inhibitors with improved pharmacological properties that potentiate antifolate activity. Clin. Cancer Res. 7, 2105–2113.

Sollevi, A., 1997. Adenosine for pain control. Acta Anaesthesiol. Scand., Suppl. 110, 135–136.

Sommerschild, H.T., Grund, F., Offstad, J., Jynge, P., Ilebekk, A., Kirkeboen, K.A., 1997. Importance of endogenous adenosine during ischemia and reperfusion in neonatal porcine hearts. Circulation 96, 3094–3103.

Southard, J.H., Belzer, F.O., 1995. Organ preservation. Annu. Rev. Med. 46, 235–247.

Steer, M.L., 1993. Etiology and pathophysiology of acute pancreatitis. In: Go, V.L., DiMagno, E.P., Gardner, J.D., Lebenthal, E., Reber, H.A., Scheele, G.A. (Eds.), The Pancreas: Biology, Pathobiology, and Disease. Raven Press, New York, NY, pp. 581–592.

Steinberg, W., Tenner, S., 1994. Acute pancreatitis. N. Engl. J. Med. 330, 1198–1210.

Steinle, A.U., Weidenbach, H., Wagner, M., Adler, G., Schmid, R.M., 1999. NF-κB/Rel activation in cerulein pancreatitis. Gastroenterology 116, 420–430.

Stiles, G.L., 1997. Adenosine receptor subtypes: new insights from cloning and functional studies. In: Jacobson, K.A., Jarvis, M.F. (Eds.), Purinergic Approaches in Experimental Therapeutics. Wiley-Liss, New York, NY, pp. 29–37.

Stratta, P., Canavese, C., Sandri, L., Ciccone, G., Santi, S., Barolo, S., Messuerotti, A., Quaglia, M., Mazzucco, G., Fop, F., Segoloni, G.P., Piccoli, G., 1999. The concept of 'glomerulonephritis'. The fascinating history of evolution and emergence of a specialist's nosology focus on Italy and Trino. Am. J. Nephrol. 19, 83–91.

Striessnig, J., Zernig, G., Glossmann, H., 1985. Human red-blood-cell Ca^{2+} -antagonist binding sites. Evidence for an unusual receptor coupled to the nucleoside transporter. Eur. J. Biochem. 150, 67–77.

Sun, B., Le, S.N., Lin, S., Fong, M., Guertin, M., Liu, Y., Tandon, N.N., Yoshitake, M., Kambayashi, J., 2002. New mechanism of action for cilostazol: interplay between adenosine and cilostazol in inhibiting platelet activation. J. Cardiovasc. Pharmacol. 40, 577–585.

Sweeney, M.I., 1997. Neuroprotective effects of adenosine in cerebral ischemia: window of opportunity. Neurosci. Biobehav. Rev. 21, 207–217.

Takiguchi, Y., Wada, K., Nakashima, M., 1992. Comparison of the inhibitory effects of the TXA_2 receptor antagonist, vapiprost, and other antiplatelet drugs on arterial thrombosis in rats: possible role of TXA_2. Thromb. Haemost. 68, 460–463.

Tancredi, V., D'Antuono, M., Nehlig, A., Avoli, M., 1998. Modulation of epileptiform activity by adenosine A_1 receptor-mediated mechanisms in the juvenile rat hippocampus. J. Pharmacol. Exp. Ther. 286, 1412–1419.

Thorn, J.A., Jarvis, S.M., 1996. Adenosine transporters. Gen. Pharmacol. 27, 613–620.

Todo, S., Zhu, Y., Zhang, S., Jin, M.B., Ishizaki, N., Tanaka, H., Subbotin, V., Starzl, T.E., 1997. Attenuation of ischemic liver injury by augmentation of endogenous adenosine. Transplantation 63, 217–223.

Toombs, C.F., McGee, D.S., Johnston, W.E., Vinten-Johansen, J., 1992. Myocardial protective effects of adenosine. Infarct size reduction with pretreatment and continued receptor stimulation during ischemia. Circulation 86, 986–994.

Van Belle, H., 1993. Nucleoside transport inhibition: a therapeutic approach to cardioprotection via adenosine? Cardiovasc. Res. 27, 68–76.

Van Belle, H., Janssen, P.A., 1991. Comparative pharmacology of nucleoside transport inhibitors. Nucleosides Nucleotides 10, 975–982.

Van Belle, H., Wynants, J., Xhonneux, R., Flameng, W., 1986. Changes in creatine phosphate, inorganic phosphate, and the purine pattern in dog hearts with time of coronary artery occlusion and effect thereon of mioflazine, a nucleoside transport inhibitor. Cardiovasc. Res. 20, 658–664.

Van Belle, H., Goossens, F., Wynants, J., 1989. Biochemical and functional effects of nucleoside transport inhibition in the isolated cat heart. J. Mol. Cell. Cardiol. 21, 797–805.

van Muijlwijk-Koezen, J.E., Timmerman, H., IJzerman, A.P., 2001. The adenosine A_3 receptor and its ligands. Prog. Med. Chem. 38, 61–113.

Verma, A., Marangos, P.J., 1985. Nitrobenzylthioinosine binding in brain: an interspecies study. Life Sci. 36, 283–290.

von Lubitz, D.K., 1999. Adenosine and cerebral ischemia: therapeutic future or death of a brave concept? Eur. J. Pharmacol. 371, 85–102.

von Lubitz, D.K., 2001. Adenosine in the treatment of stroke: yes, maybe, or absolutely not? Expert Opin. Investig. Drugs 10, 619–632.

von Lubitz, D.K., Dambrosia, J.M., Kempski, O., Redmond, D.J., 1988. Cyclohexyl adenosine protects against neuronal death following ischemia in the CA1 region of gerbil hippocampus. Stroke 19, 1133–1139.

Wainwright, C.L., Parratt, J.R., Van Belle, H., 1993. The antiarrhythmic effects of the nucleoside transporter inhibitor. R75231, in anaesthetized pigs. Br. J. Pharmacol. 109, 592–599.

Wang, J., Schaner, M.E., Thomassen, S., Su, S.F., Piquette-Miller, M., Giacomini, K.M., 1997. Functional and molecular characteristics of Na(+)-dependent nucleoside transporters. Pharm. Res. 14, 1524–1532.

Ward, J.L., Sherali, A., Mo, Z.P., Tse, C.M., 2000. Kinetic and pharmacological properties of cloned human equilibrative nucleoside transporters, ENT1 and ENT2, stably expressed in nucleoside transporter-deficient PK15 cells. ENT2 exhibits a low affinity for guanosine and cytidine but a high affinity for inosine. J. Biol. Chem. 275, 8375–8381.

Wardas, J., 2002. Neuroprotective role of adenosine in the CNS. Pol. J. Pharmacol. 54, 313–326.

Wauquier, A., Van Belle, H., Van den Broeck, W.A., Janssen, P.A., 1987. Sleep improvement in dogs after oral administration of mioflazine, a nucleoside transport inhibitor. Psychopharmacology 91, 434–439.

Wilbur, S.L., Marchlinski, F.E., 1997. Adenosine as an antiarrhythmic agent. Am. J. Cardiol. 79, 30–37.

Williams, M., 2000. Purines: from premise to promise. J. Auton. Nerv. Syst. 81, 285–288.

Williams, E.F., Barker, P.H., Clanachan, A.S., 1984. Nucleoside transport in heart: species differences in nitrobenzylthioinosine binding, adenosine accumulation, and drug-induced potentiation of adenosine action. Can. J. Physiol. Pharm. 62, 31–37.

Yamasaki, K., Tanaka, M., Yokota, R., Fujiwara, H., Sasayama, S., 2000. Dilazep dihydrochloride prolongs the infarct size-limiting effect of ischemic preconditioning in rabbits. Heart Vessels 15, 227–232.

Yang, X., Zhu, Q., Claydon, M.A. , Hicks Jr., G.L., Wang, T. 1994. Enhanced functional preservation of cold-stored rat heart by a nucleoside transport inhibitor. Transplantation 58, 28–34.

Yao, S.Y., Ng, A.M., Muzyka, W.R., Griffiths, M., Cass, C.E., Baldwin, S.A., Young, J.D., 1997. Molecular cloning and functional characterization of nitrobenzylthioinosine (NBMPR)-sensitive (es) and NBMPR-insensitive (ei) equilibrative nucleoside transporter proteins (rENT1 and rENT2) from rat tissues. J. Biol. Chem. 272, 28423–28430.

Yeung, P.K., Mosher, S.J., Macrae, D.A., Klassen, G.A., 1991. Effect of diltiazem and its metabolites on the uptake of adenosine in blood: an in-vitro investigation. J. Pharm. Pharmacol. 43, 685–689.

Zughaib, M.E., Abd-Elfattah, A.S., Jeroudi, M.O., Sun, J., Sekili, S., Tang, X., Bolli, R., 1993. Augmentation of endogenous adenosine attenuates myocardial 'stunning' independently of coronary flow or hemodynamic effects. Circulation 88, 2359–2369.