Chapter 13
Role of Adenosine Receptors in Epileptic Seizures

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Abstract Epileptic seizures are caused by an electrical disturbance of brain activity that results in abnormal and excessive synchronization of neurons. Adenosine is a long-known anticonvulsant endogenous substance, exerting its actions through diverse mechanisms of action at different cellular targets. In this review we discuss the main actions of adenosine during acute and chronic phases of epileptic seizure progression and the mechanisms involved. There should be considered three main levels of adenosine actions: (1) neuronal level, where adenosine, mostly through its receptors A_1, A_{2A} and A_3, alters intrinsic neuronal properties and excitatory/inhibitory network balance; (2) non-neuronal level, by affecting astrocytic function; and (3) homeostatic control level, through epigenetic regulatory mechanisms. Together, these actions make adenosine as a sort of "universal modulator or maestro" of desynchronization of epileptic focus, with great therapeutic potential in the treatment of resistant forms of epileptic seizures. Indeed, adenosine augmentation therapies are being considered to tackle epilepsy, which include gene therapy strategies and dietary interventions. Further research on new drugs that specifically target the mechanisms of actions involved in the pathological process of the disease are needed to take full advantage of adenosine anticonvulsant actions in the control of epileptic seizures.

Keywords Epilepsy · Seizure models · Neuroprotection · Adenosine-control mechanisms · Adenosine-based therapies · GABAergic transmission.

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13.1 Introduction

This chapter aims to provide an overview on how adenosine, through its receptors, acts as an anticonvulsant substance to control seizure activity. We will focus our attention on the main modulatory targets of adenosine which include the control of intrinsic neuronal properties, excitatory and inhibitory network balance and the homeostatic and epigenetic regulation. The mechanisms involved in these actions will be addressed, and its impact on in vitro and in vivo models of epilepsy will be analysed. Lastly, we will highlight the most recent and innovative adenosine-based strategies developed for therapeutic intervention in the control of epileptic seizures.

13.2 Epilepsy and Epileptic Seizures

Epilepsy is a brain disease with an heterogenous prevalence among different countries but estimated to be of around 1% worldwide (Sander and Shorvon 1996; Beghi and Hesdorffer 2014; Bell et al. 2014). The disease is predominantly characterized by the recurrent and unpredictable interruption of normal brain function by epileptic seizures, and it comprises all the neurobiological, cognitive, psychological and social consequences that this condition may have on people's lives (Fisher et al. 2005). For practical and clinical purposes, it was recently included in the definition of epilepsy the requirement of having at least two epileptic seizures occurring >24h apart or one epileptic seizure and a very high risk of recurrence over the next 10 years (Fisher et al. 2014). This definition, elaborated by the International League Against Epilepsy (ILAE), points out two important aspects that should be emphasized: first, that epilepsy exists when recurrent epileptic seizures occur, but epileptic seizures may occur without implying the diagnose of epilepsy; second, that epilepsy is not only characterized by its clinical neurological manifestations but also by all the repercussions that the disease may have on the patient and its family (including social implication).

Adenosine has been coined as a putative endogenous anticonvulsant a long time ago (Dunwiddie 1980; Dragunow et al. 1985). Since then, there was a great increase in our knowledge of the mechanisms of action of adenosine receptors that mediate its action and metabolic pathways involved in the homeostatic control of its intra- and extracellular concentration. The understanding of seizures also increased. In this chapter we will mostly focus our attention on adenosine actions that are related with seizure events. These include adenosine action on the mechanism underlying epileptic seizures per se, on the sequence of events that convert a normal neuronal network into a hyperexcitable network (epileptogenesis) and on the control of seizure activity in in vitro and in vivo experimental models of epilepsy. Although some of the epilepsy-associated comorbidities will be briefly addressed, we will leave all the other elements that define this disease out of our discussion.

It is important also to clarify the definition of epileptic seizures (or simply referred as seizures), which are described as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain (Fisher et al. 2005). Clinically, when an epileptic seizure is identified, it is crucial that the clinician classifies the seizure according to its type and aetiology. This is helpful not only for diagnostic purposes but also for the use and development of antiepileptic therapies, investigation of seizure mechanisms and facilitation of worldwide communication among pairs. Seizures are thus classified according to its type in (1) focal, when originated within a network limited to one hemisphere; (2) generalized, when originated in bilaterally distributed networks; or (3) unclassified, when the local of onset is unknown (Berg and Millichap 2013). Each category can be further classified according to the level of awareness (retained awareness seizure or impaired awareness seizure), motor behaviour (atonic, tonic, clonic, myoclonic, epileptic spasms or a combination of these) and nonmotor behaviour (e.g. absence seizures) (Fisher et al. 2017). A focal seizure can eventually generalize, being classified as focal to bilateral tonic-clonic seizure (Fisher et al. 2017).

The etiologic classification recognizes six groups that have also implications for treatment. These include structural, genetic, infectious, immune, metabolic or unknown aetiology (Scheffer et al. 2017). A structural aetiology implies the presence of neuroimaging abnormalities as the most likely cause of seizure. Such changes may be acquired by stroke, trauma or even infection or developmental malformations. Genetic aetiology is when the epileptic seizures directly result from a known or presumed genetic disorder. Infection is one of the most common aetiologies of epileptic seizures worldwide (Vezzani et al. 2016) and includes viral, bacterial, fungal and parasitic infections of the central nervous system that result in seizures. An immune-mediated seizure is mostly associated with auto-immune diseases affecting the central nervous system (such as anti-NMDA receptor encephalitis) and deserves an isolated category given its specific treatment implications (Lancaster and Dalmau 2012). Metabolic causes refer to well-stablished metabolic defects where seizures are the core symptom (examples include porphyria or pyridoxine-dependent seizure). Unknown cause is defined when the aetiology is not possible to stablish. Unknown aetiology accounts for about one-third of all seizures worldwide, but this number varies depending on the healthcare provider and country (Banerjee et al. 2009). In this classification, of course, the categories are not hierarchical nor mutually exclusive, and a seizure event can have more than one aetiology (e.g. tuberous sclerosis complex, which results from mutations in genes TSC1 and TSC2 causing central nervous system tumours, is considered to have a genetic and a structural cause).

Given the diversity of types and aetiologies of seizures, we cannot consider only one form of epilepsy but rather a group of epilepsy syndromes, each of which characterized by the occurrence of specific seizure properties. Such differences need to be considered when planning and carrying experimental research on epilepsy, namely, in the devise of animal models in vitro and in vivo. These models serve a variety of purposes that include the screening of new antiepileptic compounds for their anticonvulsant or antiepileptogenic properties (in acute or chronic models of

epilepsy), their efficacy against different types of epilepsy and the study of the mechanisms involved in drug resistance in epilepsy or associated comorbid features, such as cognitive and psychiatric comorbidities (Löscher 2011). Animal models are usually grouped in "acute seizure models" and "chronic epilepsy models". The term "acute" refers to models in which seizures are induced by electrical or chemical stimulation in otherwise naïve and healthy (non-epileptic) animals; the term "chronic" is used to refer to models in which animals have been made epileptic by electrical, chemical or genetic means (Löscher 2011) (Table 13.1). Other mechanisms can be used to induce acute or chronic seizures, depending on the epilepsy aetiology to be studied (e.g. traumatic brain injury, hyperthermia, hypoxia, systemic/focal infection, among others).

The in vitro seizure models include neuronal cultures, brain slice cultures (organotypic) or acute slice models (Raimondo et al. 2017). These are particularly important for the study of basic physiology, pharmacology and molecular biology of seizures and epileptogenesis. Acute slices can be obtained from "normal" animals, in which in vitro manipulations are used to generate epileptiform activity or obtained from chronically epileptic animals or even human patients. To induce epileptiform activity in otherwise naïve slices, many different strategies can be used depending on what type of seizure activity is intended to be measured. These include high-frequency electrical stimulation, GABAergic inhibition, glutamatergic (kainic acid) or muscarinic (pilocarpine) activation, potassium channel blockers (4-aminopyridine), low extracellular calcium, low extracellular magnesium or high extracellular potassium models (Ivanov and Bernard 2017).

A plethora of >20 antiepileptic drugs (AEDs) are currently available to use in clinical practice. In fact, up to 70% of newly diagnosed people with epilepsy can be successfully treated with the drugs currently available (Kwan and Brodie 2001). The mechanism of action of most drugs reflects what we know about the underlying abnormalities occurring in seizure generation and propagation. These include targeting hyper-excitation or hypo-inhibition by preventing activation of depolarizing sodium or calcium channels, enhancing the inactivation of sodium channels, facilitating hyperpolarizing potassium channels or affecting neurotransmission by blocking glutamate-mediated actions or promoting GABA-induced inhibition (Bialer and White 2010; Rogawski et al. 2016) (Fig. 13.1). Nonetheless, one-third of patients with epilepsy cannot be controlled with these tools (Granata et al. 2009). Resistance to pharmacotherapy may be already present when the treatment is initiated, as occurs in some infant seizure syndromes (e.g. include Ohtahara syndrome, Dravet syndrome and others), or it may evolve during the course of chronic epilepsy or status epilepticus, after a positive initial response to the drug (Heinemann et al. 2006). When medication fails to control seizures, other options are considered and may include neurosurgical treatment (Engel 1996a), vagus nerve stimulation (Uthman 2000) or dietary therapy (e.g. ketogenic diet) (Bough and Rho 2007). Apart from surgery, where the rational is to isolate or resect the epileptogenic tissue (i.e., the focus of the disease), vagus nerve stimulation and ketogenic diet are alternative neuromodulatory approaches aimed to influence several neuronal targets simultaneously and achieve a greater control of the disease. Identical reasoning can

Table 13.1 Acute and chronic models of epilepsy

Model	Induction	Model of human epilepsy	Seizure type	Use
Acute models				
Electrical stimulation				
Maximal electroshock model (MES)	Whole-brain stimulation via the cornea or ear	Model of tonic-clonic generalized seizure	Generalized onset: clonic, tonic, tonic-clonic seizures	Antiepileptic drug screening Electrophysiological and behavioural changes caused by focal seizures Molecular and physiological changes related to acute epileptiform activity
6 Hz psychomotor seizure	Low-frequency stimulation via the cornea	Model of partial limbic seizure	Motor onset: automatisms; Nonmotor onset: behavioural arrest; Generalized onset: myoclonic seizures	
Local electrical stimulation	Cortical stimulation via implanted electrodes	Model of focal motor type of frontal lobe seizures Model of status epilepticus	Motor onset: automatisms, falls, clonic seizures; Nonmotor onset: behavioural arrest	
Chemical stimulation				
GABA-related drugs	Systemic or intracranial injection of PTZ, bicuculline, picrotoxin, 3-MPA, GAD synthesis inhibitors	Model of generalized myoclonic, tonic-clonic and absence seizures Depend on the drug and dose used	Motor onset: clonic, hyperkinetic and myoclonic seizures; Nonmotor onset: absence seizures; generalized onset, clonic, tonic, tonic-clonic seizures	Antiepileptic drug screening Study of antiepileptic drugs for status epilepticus Molecular and physiological changes related to acute epileptiform activity Electrophysiological and behavioural changes caused by focal seizures
Excitatory amino acid-related drugs	Systemic or intracranial injection of kainic acid, AMPA, NMDA, homocysteine	Model of focal motor seizure with automatisms Model of focal to bilateral tonic-clonic seizures Model of status epilepticus Depend on the drug and dose used	Motor onset: automatisms, falls, clonic, hyperkinetic and myoclonic seizures Nonmotor onset: behavioural arrest, autonomic Focal to bilateral tonic-clonic	

(continued)

Table 13.1 (continued)

Model	Induction	Model of human epilepsy	Seizure type	Use
Acetylcholine-related drugs	Systemic or intracranial injection of pilocarpine, organophosphorus compounds	Model of focal impaired awareness seizures Model of human poisoning Model of status epilepticus Depend on the drug and dose used	Motor onset: automatisms, falls clonic and tonic seizures Nonmotor onset: autonomic Focal to bilateral tonic-clonic	
Other drugs	Systemic of intracranial injection of strychnine, aminophylline, insulin-induced hypoglycaemia, antibiotics (penicillin), tetanus toxin	Models of focal epilepsy Depend on the drug and dose used	Motor onset: automatisms (tetanus toxin), clonic seizures (tetanus toxin, hypoglycaemia), myoclonic seizures (penicillin) Nonmotor onset: behavioural arrest (tetanus toxin) Focal to bilateral tonic-clonic (hypoglycaemia) Generalized onset: clonic and tonic seizures (penicillin), tonic-clonic (penicillin, hypoglycaemia)	

Chronic models				
Acquired epilepsy				
Electrical kindling	Repeated and intermittent intracerebral stimulation via implanted electrodes in specific brain regions	Model of focal impaired awareness seizures Model of focal to bilateral tonic-clonic seizures Chronic models of temporal lobe epilepsy Depend on induction, drug and dose used	Motor onset: automatisms, falls, hyperkinetic, clonic and tonic seizures Nonmotor onset: behavioural arrest Focal to bilateral tonic-clonic seizures Generalized onset	Study of epileptogenesis and long-term consequences of epilepsy Study comorbidities associated with epilepsy Antiepileptic drug screening and pharmacoresistant epilepsies
Chemical kindling	Repeated and intermittent systemic or intracerebral administration of convulsant agents in specific brain region: Excitatory amino acids (glutamate, NMDA, AMPA) GABAergic modulators (PTZ, picrotoxin, bicuculline) Cholinergic agents (carbachol, pilocarpine) Others			
Brain pathology models	Hyperthermia seizures Hypoxia model Posttraumatic epilepsy	Model of febrile seizures Models of stroke and brain injury	Motor onset: automatisms, clonic, myoclonic and tonic-clonic seizures Nonmotor onset: behavioural arrest Generalized onset: tonic-clonic seizures	Study of epileptogenesis, mechanisms and long-term consequences of epilepsy Antiepileptic drug screening
Genetic animal models of epilepsy				
Generalized absence epilepsy rats of Strasbourg (GAERS)	Genetic animals	Models of spontaneous recurrent seizures Models of absence seizures Model of idiopathic epilepsies	Generalized nonmotor onset: absence	Study of epileptogenesis and long-term consequences of epilepsy Study comorbidities associated with epilepsy Electrophysiological and behavioural changes caused by absence seizures Antiepileptic drug screening
Genetic epilepsy prone rats (GEPRs)	Genetic animals	Model of reflex seizures	Generalized onset: tonic and tonic-clonic seizures	
Audiogenic models	Acoustic stimulation in genetically prone animals	Model of reflex epilepsy Model of temporal lobe epilepsy	Generalized motor onset: automatisms, hyperkinetic, tonic-conic seizures	

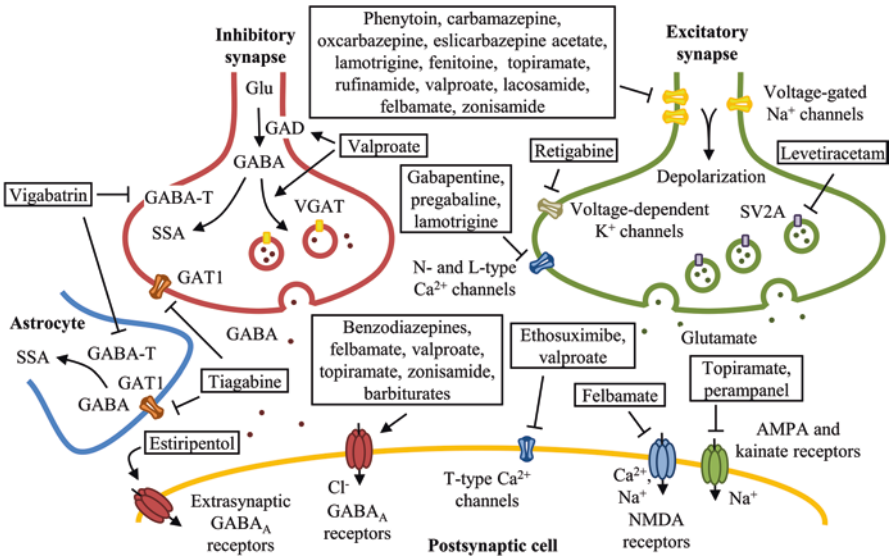

Fig. 13.1 Mechanisms of action of antiepileptic drugs at inhibitory and excitatory synapses and astrocytes. The targets include block activation of sodium channels (phenytoin, carbamazepine, oxcarbazepine, eslicarbazepine acetate, lamotrigine, topiramate, rufinamide, felbamate, zonisamide, valproate) or enhance inactivation of sodium channels (lacosamide, rufinamide), block calcium channels (gabapentin, pregabalin, lamotrigine, ethosuximide, valproate) and open potassium channels (retigabine); enhance $GABA_AR$ actions (benzodiazepines, felbamate, valproate, topiramate, zonisamide, barbiturates) or extrasynaptic $GABA_ARs$ (stiripentol); increase GABA turnover by increasing its synthesis – via GAD – and/or release (valproate), inhibiting GABA reuptake through GABA transporters type 1 (GAT1) (tiagabine) or inhibiting GABA transaminase (GABA-T) (vigabatrin); block AMPA and kainate receptors (topiramate, perampanel) or NMDA receptors (felbamate); and inhibit synaptic vesicle glycoprotein 2 (SV2A) (levetiracetam)

be applied to the use of adenosine-based strategies in the control of seizures and epilepsy. In fact, most of the targets of AEDs mentioned above are, indeed, also targets of adenosine modulation (Sebastião and Ribeiro 2009). Ketogenic diet also involves adenosine-dependent mechanism (Masino and Geiger 2008). Thus, it is not surprising that, apart from all difficulties with the implementation of adenosine in clinical practice (mostly due to the well-known peripheral side effects), adenosine is still highly and enthusiastically studied as an important and promising approach to fight drug-resistant epilepsies.

13.3 Grounds for Anticonvulsant Actions of Adenosine

Since Phillis' first observations that adenosine has a depressive action in the central nervous system (Phillis et al. 1974), many studies have followed showing that adenosine is capable of influencing not only neuronal firing (Kostopoulos et al. 1975;

Phillis and Kostopoulos 1975) but also to directly alter excitatory synaptic responses (Kuroda and Kobayashi 1975; Scholfield 1978; Schubert and Mitzdorf 1979; Dunwiddie and Hoffer 1980). The first evidence relating adenosine and epileptic seizures came from studies showing that right after seizure initiation there was a rapid and dramatic increase in adenosine levels (Pull and McIlwain 1972; Schultz and Lowenstein 1978; Schrader et al. 1980; Winn et al. 1980). Later, adenosine was shown to act as an endogenous anticonvulsant in vitro, in a rat hippocampal preparation of epileptiform discharges (Dunwiddie 1980), and also in vivo, in a rat drug-induced seizure model (Dunwiddie and Worth 1982). These and other findings (Albertson et al. 1983; Barraco et al. 1984; Dragunow et al. 1985; Chin 1989) paved the way for comprehensive studies about the use of adenosine and adenosine-related compounds as putative therapeutic strategies in epilepsy. Today, it is largely accepted that adenosine indeed has a role as an anticonvulsant substance. There are, however, several aspects that should be considered when discussing the influence of adenosine on seizures and epilepsy.

First is that the capacity of adenosine to shape neuronal excitability and arrest seizures depends on the stage of disease progress. This is of particular interest since the adenosinergic system not only influences neuronal excitability during a seizure event but is also dramatically affected by the epileptogenic process per se. This means that adenosine-mediated actions may vary depending on whether they are directed to neuronal circuits that are experiencing a seizure event for the first time (i.e. acute seizures) or circuits suffering from neurobiological modifications after a first neuronal insult (that may also affect the adenosinergic system) as occurs during epileptogenesis and stablished epilepsy (i.e. chronic seizures). This has also important clinical and therapeutic implications. Acute actions of endogenous adenosine in an inaugural seizure event may have significant neuroprotective value but little application for clinical intervention. On the other hand, subsequent adaptive changes that contribute to the development of recurrent seizure events and the establishment of epilepsy, as well as the emergence of resistance to classical EADs, may potentially benefit from adenosine-based therapies.

Another aspect to consider is the targets of adenosine actions. Indeed, adenosine is known to affect excitability far beyond its synaptic effects (Cunha 2001). Thus, in a tentative dissection of the mechanism by which adenosine exerts its anticonvulsant actions, it is relevant to separate the actions occurring at the (1) neuronal level, which include changes in neuronal excitability and synaptic transmission; (2) non-neuronal level, mostly related to regulation of glial function; and (3) homeostatic control level, corresponding to variations in adenosine metabolism and epigenetic control. Nevertheless, all mechanisms are mutually dependent and operate together to generate an orchestrated action to influence network activity and seizures. It is noteworthy to mention that this chapter does not intend exhaustively describe all mechanisms by which adenosine exerts its actions upon excitability. We will only focus on studies where there is direct evidence for the interference of adenosine or adenosine receptors on seizure activity.

13.4 Adenosine as a Seizure Control Substance

13.4.1 A_1Rs in Acute Models of Seizure

As mentioned above, the capacity of adenosine to control seizure events has been proposed a long time ago (Dunwiddie 1980; Dunwiddie and Worth 1982). Studies that followed have confirmed and broaden the actions of adenosine on many different seizure models in vitro and in vivo. We should start by looking to adenosine action on acute seizure models of epilepsy. As first observed by Dunwiddie and Worth, adenosine actions in these models are mostly associated with A_1 receptors (A_1Rs) (Dunwiddie and Worth 1982). When adenosine analogues or selective A_1R agonists were systemically injected in electrical- or chemical-induced seizure models, an anticonvulsant action and arrest of epileptic seizures were observed (Dragunow and Goddard 1984; Turski et al. 1985; Morrisett et al. 1987; Whitcomb et al. 1990; Von Lubitz et al. 1993; Young and Dragunow 1994; Adami et al. 1995; Pourgholami et al. 1997a; Malhotra and Gupta 1997; Sarro et al. 1999; Zgodziński et al. 2001; Huber et al. 2002; Girardi et al. 2007; Li et al. 2013). These actions were observed also in immature animals, suggesting that the A_1R-mediated anticonvulsant effects also occur early in the developing brain (Mareš 2010; Pometlová et al. 2010). Repeated activation of A_1Rs, however, tends to develop tolerance and a gradual loss of their anticonvulsant capacities (Adami et al. 1995). Importantly, there is an endogenous role of adenosine in the suppression of seizures since blocking A_1R activation aggravates epileptic activity (Dragunow and Goddard 1984; Dragunow and Robertson 1987; Morrisett et al. 1987; Whitcomb et al. 1990; Zhang et al. 1993; Von Lubitz et al. 1993; Fukuda et al. 2010) and converts recurrent seizure patterns into status epilepticus (Young and Dragunow 1994). Significant seizure suppression can also be achieved by increasing adenosine levels through inhibitors of adenosine kinase, adenosine deaminase or adenosine transporters blockers (Eldridge et al. 1989; Zhang et al. 1993). Together, these studies highlight three main aspects: first, that adenosine is not only capable of preventing seizure occurrence when administered before the trigger insult but also stop an already stablished seizure event (working as a true anticonvulsant substance); second, adenosine-mediated endogenous mechanisms are crucial to restrain ongoing seizure events, but further anticonvulsant effect is still possible through exogenous activation of A_1R; and, finally, adenosine actions occur in different acute models of epileptic seizures, regardless the mechanism of induction is electrical stimulation (Dragunow and Robertson 1987; Whitcomb et al. 1990; Young and Dragunow 1994; Pometlová et al. 2010) or by manipulation of GABAergic system (Zhang et al. 1993; Adami et al. 1995; Malhotra and Gupta 1997; Girardi et al. 2007; Mareš 2010; Li et al. 2013), of the glutamatergic system (Von Lubitz et al. 1993; Li et al. 2013), or by other chemical manipulation (Turski et al. 1985; Eldridge et al. 1989; Li et al. 2013).

All mentioned studies have in common the control by A_1R via intraperitoneal injections of selective drugs. However, their low permeability through the blood-brain barrier (Brodie et al. 1987) and peripheral actions, mostly related to cardiovas-

cular side effects (Stella et al. 1993; Schindler et al. 2005), has hampered the use of A_1R agonists for the treatment of central nervous system (CNS) diseases. To minimize these effects and potentiate adenosine actions in the brain, other approaches include intracranial activation of A_1R in specific brain regions known to be responsible for the epileptic seizure initiation and/or spreading. In fact, intracranial perfusion of A_1R agonists conferred protection against 3-nitropropionic acid (a mitochondrial toxin) (Zuchora et al. 2001), bicuculline-induced (Franklin et al. 1989) and pilocarpine-induced seizures through changes in glutamate, GABA and dopamine levels at the epileptic focus (Khan et al. 2000, 2001). An alternative, non-invasive possibility is the development of tissue selective adenosine receptor agonists. An A_1R agonist with anticonvulsant activity without causing motor behaviour alterations usually occurring as a consequence of sedation and bradycardia has been identified (Tosh et al. 2012), but the mechanisms subserving such tissue selectivity remain to be identified.

13.4.2 A_1Rs in Chronic Models of Epilepsy

Regarding actions of A_1Rs in chronic models of epilepsy, they are described for the kindling model of limbic seizure propagation, which mostly involves connections between piriform cortex, amygdala, hippocampus and entorhinal cortex (Lopes da Silva et al. 1990). The kindling model is one of the most commonly used chronic models of epilepsy, particularly for the study of temporal lobe (limbic) epilepsy (TLE) (Goddard 1967; Goddard et al. 1969). In kindling animals, seizures initiate and are confined to the focal area of stimulation and progressively propagate through other brain structures that serve as pathways for generalization of subsequent seizures (Sato et al. 1990). Thus, seizure progression may be hypothetically interrupted not only in the original focus of the seizure but also in parts of the brain, other than the epileptic focus, that are responsible for its propagation. This is, indeed, what happens with adenosinergic control of limbic seizures. Intra-hippocampal and intra-amygdala injections of A_1R agonists have, as expected, inhibitory actions on hippocampal- and amygdala-kindling parameters, respectively (Rosen and Berman 1987; Pourgholami et al. 1997b). Importantly, however, activation of A_1Rs in the hippocampus (Pourgholami et al. 1997a; Alasvand Zarasvand et al. 2001), entorhinal cortex (Mohammad-Zadeh et al. 2005), piriform cortex (Rezvani et al. 2007a, b) or perirhinal cortex (Mirnajafi-Zadeh et al. 1999) reduced seizure duration and afterdischarges specifically in amygdala. These effects are pathway dependent, since intra-amygdala A_1R activity had no significant anticonvulsant action neither on hippocampal-kindled seizures (except for secondary afterdischarges) (Mirnajafi-Zadeh et al. 2000), entorhinal cortex-kindled seizures (Mohammad-Zadeh et al. 2005) nor piriform cortex-kindling animals (Shahabi et al. 2006), despite the influence of amygdala in its propagation (Sato et al. 1990). Hippocampal and entorhinal cortex A_1Rs are also involved in supressing entorhinal cortex- and piriform cortex-kindling, respectively (Heidarianpour et al. 2006;

Zeraati et al. 2006; Hosseinmardi et al. 2007). Importantly, blockade of A_1R actions in these models aggravates seizure activity and generalization, pointing to an endogenous action of adenosine, through A_1Rs, in restraining limbic epilepsy. Together, these results indicate that the anticonvulsant actions of A_1Rs (1) are not only relevant in acute seizure control but also in chronic models of epilepsy, (2) are region and pathway specific and (3) are capable of restraining seizure exacerbation not only in the brain region where seizure emerges but also in the surrounding areas responsible for propagation and consequent generalization of seizures.

The translational potential of invasive approaches as intracranial injections of A_1R agonists can only be envisaged for very serious disease conditions. Another potential approach for intracranial activation of A_1Rs is to provide a local and sustained source of adenosine. This was first achieved by intraventricular implantation of an adenosine-releasing synthetic polymer, which led to a reduction of seizure activity in the rat kindling model of partial epilepsy (Boison et al. 1999). Also, ex vivo gene therapy approaches in kindled rats showed profound but transient reduction in seizure activity (Huber et al. 2001; Boison et al. 2002; Güttinger et al. 2005a). Long-term anticonvulsive effects were obtained with local release of adenosine through encapsulated myoblasts implanted in the vicinity of the epileptic focus (Güttinger et al. 2005b). Protection from convulsive seizures lasted for 3 to 8 weeks and caused no desensitization of A_1Rs and no side effects as sedation or changes in locomotor behaviour (Güttinger et al. 2005b).

The capacity of adenosine to keep the epileptic focus localized was also demonstrated in a status epilepticus model using A_1R-knock out (A_1R-KO) mice (Fedele et al. 2006). In fact, A_1R-KO animals submitted to unilateral intra-hippocampal kainic acid injections not only showed severe convulsions and increased mortality when compared to control animals but also displayed greater extend of neuronal loss both in the ipsi- and contralateral hippocampus. Similar results were obtained with A_1R-KO mice subjected to traumatic brain injury-induced seizures (Kochanek et al. 2006).

Despite the neuroprotective and anticonvulsant actions of adenosine A_1Rs in acute and chronic stages of epilepsy, adenosine release and A_1R (but also $A_{2A}R$) activation during seizures have been associated with sudden unexpected death in epilepsy (SUDEP) (Shen et al. 2010; Faingold et al. 2016). Postictal hypoventilation is considered as a major contributor to the cause of death in SUDEP, particularly during the sleeping period (Massey et al. 2014; Richerson et al. 2016). Thus, given the known depressant actions of adenosine on brainstem respiratory network (Vandam et al. 2008; Zwicker et al. 2011) and its sedative effects (Porkka-Heiskanen et al. 1997), seizure-induced elevation of adenosine levels may further contribute to respiratory distress associated with SUDEP. Importantly, caffeine treatment after seizure onset might be beneficial (Shen et al. 2010).

Altogether, data from chronic models of epilepsy reveal that even after the establishment of recurrent seizure events, and besides all the consequent neuronal adaptations that may occur in neuronal circuitry, adenosine A_1Rs are still able to restrain and cease further progression of the disease in a tentative action to re-establish normal network communication. Risk of SUDEP may however be increased.

13.4.3 Adenosine A_{2A}Rs and A_3Rs in Seizure Control

Although the major interest about adenosine control of epileptic activity has been the inhibitory A_1R system, an increasing number of studies are now focusing on facilitatory adenosine A_{2A} receptors (A_{2A}Rs).

The majority of results point to a pro-excitatory role of A_{2A}Rs, although some data is still conflicting. Some studies have shown that A_2R or A_{2A}Rs are not involved in convulsions (Rosen and Berman 1987; Janusz and Berman 1992; Young and Dragunow 1994; Malhotra and Gupta 1997; Uzbay et al. 2007; Rezvani et al. 2007a; Akula and Kulkarni 2014). Surprisingly, studies using acute models of chemical-induced seizures and audiogenic-susceptible seizures show that activation of A_2R or even A_{2A}Rs agonists contribute to seizure suppression (Adami et al. 1995; Jones et al. 1998a, b; Sarro et al. 1999; Boison et al. 2002) and that its blockade has pro-convulsant actions (Vianna et al. 2005). In a kindling model of chronic epilepsy, the effects of NECA (an agonist with slightly more potency to A_2R than A_1R) was compared with that of a prototype A_1R agonist, and data obtained allowed to suggest an A_2R-mediated seizure suppression in the caudate nucleus (Rosen and Berman 1987), but not in the amygdala (Janusz and Berman 1992). Focal injection of CGS21680 (an adenosine A_{2A}R agonist) leads to a reduction in the severity of bicuculline-induced seizures, but these actions were attributed to A_1Rs (Zhang et al. 1994), which highlights the need of careful pharmacological controls before concluding on the action of adenosine receptors, in particular of those expressed at low levels in relevant brain areas, in seizures.

Apart from these initial studies, some of them performed before development of selective adenosine receptor ligands, more recent studies have consistently been showing proconvulsive effects of A_{2A}Rs in chronic models of amygdala (Li et al. 2012b) and piriform cortex (Zeraati et al. 2006; Hosseinmardi et al. 2007) kindling. Genetic ablation of A_{2A}Rs confirms these proconvulsant actions since A_{2A}R-KO animals show attenuated intensity of pentylenetetrazol-induced (El Yacoubi et al. 2008) or ethanol withdrawal-induced (El Yacoubi et al. 2001) seizures. Protection is not only evident during the acute convulsive period but also in preventing proconvulsive epileptogenic changes during evolution of kindling (El Yacoubi et al. 2009). An A_{2A}R antagonist was also shown to reduce synchronous pyramidal cell firing in acute hippocampal slices under hyperexcitable conditions (Rombo et al. 2015).

In a genetic model of absence epilepsy (WAG/Rij), in vivo A_{2A}R activation increases spontaneous discharges and aggravates epileptiform activity of hippocampal slices recorded 1–5 h post-injections (D'Alimonte et al. 2009). It was recently shown that a genetic variation in human adenosine A_{2A}R gene (ADORA2A) associated with increased expression of A_{2A}R and higher levels of cAMP production is a predisposing factor for childhood encephalopathy following severe febrile seizures (Shinohara et al. 2013), a finding that also favours the idea of a proconvulsant action of A_{2A}Rs.

Progressive development of stress-induced seizures and deficits in learning and memory have been reported to occur in mice with genetic deletion of adenosine

kinase (ADK-KO) in the brain (Sandau et al. 2016). This somehow mimics a rare disease in humans, ADK deficiency, which have psychomotor delay and convulsive seizures commencing between the first and third year of life (Bjursell et al. 2011). Intracellular ADK is known to regulate extracellular levels of adenosine, with low ADK activity being associated with protection against seizures (Gouder 2004). Thus, the finding that ADK-KO leads to progressive seizure development was unexpected. A study designed to find out possible mechanisms underlying these findings allowed to conclude that chronically enhanced levels of extracellular adenosine, caused by absence of adenosine kinase in the forebrain, favour $A_{2A}R$ activity, which thus enhances the action of brain-derived neurotrophic factor (BDNF) upon synaptic plasticity (Sandau et al. 2016), which most probably leads to maladaptative circuitry formation. Indeed, blocking $A_{2A}R$ activity in ADK-KO mice, as well as blocking BDNF receptors, attenuated seizure risk and restored cognitive performance. Interestingly, A_1R blockade exacerbates seizure phenotype in this mice model, thus indicating that extracellular adenosine, through A_1R, maintains its anticonvulsant activity (Sandau et al. 2016). This study, together with other studies showing the proconvulsant action of $A_{2A}R$, highlights the need to attenuate the overactivation of $A_{2A}R$ while testing the action of adenosine augmentation therapies against pharmacoresistant forms of epilepsy.

In conclusion, the presently available evidence points towards a proconvulsant action of $A_{2A}R$. Some discrepancies that have been reported may be ascribed to several reasons including pharmacological tools to identify the receptors, the mode of administration and concentrations used (receptor selectivity *vs* access of drugs to the epileptic tissue), differences in the seizure model used (that underlie different mechanisms of seizure induction) and the brain region and the neuronal circuits involved in seizure initiation and propagation (brain region and pathway specificity of $A_{2A}R$ actions). Maladaptive changes of $A_{2A}Rs$ levels in acute and chronic models of epilepsy may also explain part of the inconsistencies (see Chapter 13.5 below).

Regarding A_3Rs, much less information is known, and again, some discrepancies are reported. In an audiogenic seizure model of epilepsy, A_3Rs were ineffective in controlling seizures (Sarro et al. 1999). However, the A_3R-selective agonists, Cl-IB-MECA, were reported to facilitate epileptiform discharges in the CA3 area of the immature hippocampus (Laudadio and Psarropoulou 2004), whereas A_3R antagonists increased the GABAergic current stability in different epileptic tissues (Roseti et al. 2008), in line with the possibility of a proconvulsant action of A_3Rs. In contrast, in acute chemical-induced seizure models, activation of A_3R seemed to be anticonvulsant (Von Lubitz et al. 1995a), and its blockade was proconvulsant (Vianna et al. 2005). In an electroshock seizure model, A_3Rs raised the threshold for electro-convulsions and reduced the severity of seizures, in line with the idea of the anticonvulsant actions of this receptor (Borowicz et al. 2004). The relatively low affinity of adenosine to A_3R (Von Lubitz et al. 1994a; Dunwiddie et al. 1997) makes their activation possible only when relatively high concentrations of extracellular adenosine are reached, as occurs during high-frequency neuronal discharge. Furthermore, the expression of A_3R is much more restricted to some tissues and brain areas than that of A_1R. These two characteristics of A_3R can turn into an advantage and raise the interest to develop A_3R-selective ligands, which may have

less side effects than A_1R agonists to control pharmacoresistant seizures. However, it becomes clear that further steps in this direction require further studies to clarify the role of A_3R in epilepsy.

Overall, it becomes evident that the actions of adenosine in acute and chronic phases of the epileptogenic process are valuable to hamper the progression of epileptic seizures. The long-known strategy of activating A_1Rs as therapeutic approach to suppress seizures may profit from concomitant modulation of $A_{2A}Rs$ and A_3Rs to further promote the anticonvulsant effects of adenosine.

13.4.4 Adenosine and AEDs

Since the early findings that adenosine acts as an anticonvulsant substance, there is interest in the study of its interaction with conventional AED. In fact, there is evidence that some AEDs influence the purinergic transmission and that purine ligands affect AED actions. Early reports suggested that alterations in extracellular levels of adenosine or in the degree of activation of adenosine receptors may be an important component of the anticonvulsant actions of carbamazepine (Lewin and Bleck 1977; Skeritt et al. 1982). The interaction seems much stronger at A_1Rs then $A_{2A}Rs$ (Marangos et al. 1983; Skerritt et al. 1983; Weir et al. 1984; Dodd et al. 1986; Fujiwara et al. 1986). Prolonged treatment with carbamazepine, however, causes a marked upregulation of adenosine receptors in the brain (Marangos et al. 1985). Benzodiazepines such as diazepam and midazolam, as well as diphenylhydantoin, act as potent adenosine uptake inhibitors at therapeutic doses (Hammond et al. 1981; Phillis and Wu 1982; Phillis 1984; Bender and Hertz 1986; Narimatsu and Aoki 1999) causing an accumulation of extracellular endogenously released adenosine and potentiating their anticonvulsant actions (Kaplan et al. 1992; Narimatsu and Aoki 1999).

Conversely, adenosine receptor ligands also interfere with AED actions. Aminophylline and theophylline (non-selective $A_1R/A_{2A}R$ antagonists) have been shown to diminish the efficacy of diazepam and valproate against electrical- and chemical-induced seizures (Czuczwar et al. 1985; Kulkarni et al. 1991; Malhotra et al. 1996; Zuchora et al. 2005), in line with the possibility that some of the anticonvulsant actions of those AEDs are due to enhanced extracellular adenosine levels. This may also apply to the sedative actions of benzodiazepines, since both aminophylline and theophylline showed to reverse the sedative effects of diazepam in postoperative animal models (Arvidsson et al. 1982; Niemand et al. 1984, 1986; Malhotra et al. 1996). Also, adenosine receptor activation potentiated the anticonvulsant actions of diazepam and valproate via A_1Rs (Czuczwar et al. 1990) and phenobarbital, diphenylhydantoin, valproate and carbamazepine via both A_1Rs and A_3Rs (Borowicz et al. 1997, 2000, 2002) in electrical models of epilepsy. Together, these studies show a close interaction between AEDs and adenosine receptors in the control of seizures and highlight the potential concomitant use of conventional and adenosine-based strategies to potentiate their anticonvulsant actions.

13.5 Adenosine Control Mechanisms in Epileptic Seizures

Before discussing the specific mechanisms by which adenosine acts as an anticonvulsant and antiepileptogenic substance, a discussion about how the adenosinergic system per se is affected by acute and chronic seizures should be made (Table 13.2).

Anticonvulsant actions of adenosine result from a rapid increase in its extracellular concentration after seizures initiation, both in animal models (Schrader et al. 1980; Winn et al. 1980; Lewin and Bleck 1981; Berman et al. 2000; Kaku et al. 2001) and humans (During and Spencer 1992; Van Gompel et al. 2014). Adenosine levels increase 6- to 31-folds its basal levels, reaching ~2–3 μM concentration few seconds after the onset of epileptic activity (During and Spencer 1992) and remain high up to seizure termination (Van Gompel et al. 2014). Released adenosine is generated in the cytosol of spiking neurons as a consequence of metabolic exhaustion, reaching extra-

Table 13.2 Acute and long-term adaptive changes of adenosinergic system to epileptic seizures

Adenosine system	Acute adaptations	Long-term adaptations
Adenosine levels	**Increase in adenosine levels**[1–6]	**Moderate increase in adenosine levels**[7] during recurrent seizure events **Low basal levels of adenosine**[7]
A_1Rs	**Increase in A_1R density**[8–13] (hippocampus, cortex and cerebellum) No change in A_1R density (striatum)[9, 10];	**Decrease in A_1R density**[7, 14–18] (rodent and humans) Increase in A_1R protein and mRNA levels[19–23]
A_{2A}Rs	**Increase in A_{2A}R density**[17, 24, 25] (neurons and glia) Decrease in A_{2A}R protein and mRNA level[19]	
ATP and AMP levels	**Increase in ATP and AMP levels**[26, 27]	**Decrease in ATP levels**[7]
Ectonucleotidases	**Increase in density and activity of Ecto-5′-nucleotidase**[7,28, 29] **Decrease in activity of ATPases**[30–32]	
Equilibrative nucleoside transporter (ENT)	**Decrease in density and efficiency of ENT**[7, 33]	
Adenosine kinase (ADK)	**Decrease in ADK expression**[34]	**Increase in ADK expression**[34–37]

In bold are considered the main adaptations. References: (1) Schrader et al. (1980), (2) Winn et al. (1980), (3) Lewin and Bleck (1981), (4) During and Spencer (1992), (5) Kaku et al. (2001), (6) Van Gompel et al. (2014), (7) Rebola et al. (2003), (8) Daval and Sarfati (1987), (9) Angelatou et al. (1990), (10) Angelatou et al. (1991), (11) Daval and Werck (1991), (12) Pagonopoulou et al. (1993), (13) Vanore et al. (2001), (14) Ekonomou et al. (1998), (15) Ekonomou et al. (2000), (16) Ochiishi et al. (1999), (17) Rebola et al. (2005), (18) Glass et al. (1996), (19) Adén et al. (2004), (20) Tchekalarova et al. (2005), (21) Hargus et al. (2012), (22) Angelatou et al. (1993), (23) Luan et al. (2017), (24) Saura et al. (2005), (25) Orr et al. (2015), (26) Wieraszko and Seyfried (1989), (27) Muzzi et al. (2013), (28) Schoen et al. (1999), (29) Lie et al. (1999), (30) Nagy et al. (1990), (31) Bonan et al. (2000a), (32) Bonan et al. (2000b), (33) Pagonopoulou and Angelatou (1998), (34) Gouder (2004), (35) Li et al. (2008), (36) de Groot et al. (2012), (37) Aronica et al. (2011)

cellular space directly through equilibrate nucleoside transporters (ENTs) (Lovatt et al. 2012). Extracellular levels are controlled by the activity of intracellular adenosine kinase (ADK), an enzyme that in the hippocampus, from P14 onwards, is mostly expressed in astrocytes (Studer et al. 2006; Etherington et al. 2009; Kiese et al. 2016). During a seizure event induced by chemical agents, the density of A_1R, or their G-protein coupling, increases after the first minutes to hours after the convulsion (Daval and Sarfati 1987; Angelatou et al. 1990, 1991; Daval and Werck 1991; Pagonopoulou et al. 1993; Psarropoulou et al. 1994; Vanore et al. 2001). An exception to this overall increase seems to be the striatum where no change or a slight decrease in A_1R density was detected, as compared with other brain areas where the expected increase was found (Angelatou et al. 1990, 1991). In electrically evoked seizure models induced with single electroconvulsive shock, no changes were observed in expression of A_1Rs (Newman et al. 1984; Gleiter et al. 1989). However, this may be related with the intensity of stimulus used to induce seizures, since stronger multi-shock stimulation does lead to an increase in A_1R density (Gleiter et al. 1989). It is clear from this set of data that the first adaptation of the adenosinergic system after initiation of seizures is to restrain the abnormal convulsive activity and try to re-establish normal network function. This is mostly achieved by potentiating the neuroprotective actions of adenosine through increase of its extracellular levels and A_1R expression.

On the other hand, long-term adaptations of adenosine and adenosine receptors to recurrent seizures differ from those observed in acute models (Table 13.2). When evaluating adenosine levels and adenosine receptor density in chronic models of seizures, several aspects can be pointed out: (1) the rising concentrations of adenosine during a recurrent convulsion in chronic models do not reach the same values as in an inaugural seizure event (Rebola et al. 2003); (2) outside the convulsive periods, the extracellular concentration of adenosine drops to levels lower then basal concentrations observed in non-epileptic tissue (Rebola et al. 2003); and (3) A_1R density decreases progressively along the epileptogenesis process (Ekonomou et al. 1998, 2000) and remains low several weeks after the first convulsion (Ochiishi et al. 1999; Rebola et al. 2003, 2005). These observations are also supported by a loss of hippocampal A_1Rs in patients suffering from temporal lobe epilepsy (Glass et al. 1996) and are in agreement with the requirement of higher doses of A_1R agonists necessary to produce anticonvulsant effects along status epilepticus progression (Young and Dragunow 1994; Adami et al. 1995). However, part of the reduction in A_1R density may be influenced by significant neuronal loss observed after recurrent seizures events (Engel 1996b). This may explain some of the contrasting results showing increased A_1R protein and mRNA levels in chronic models of seizure (Adén et al. 2004; Tchekalarova et al. 2005; Hargus et al. 2012). Also, in tissue from human temporal lobe epilepsy (Angelatou et al. 1993) and human Rasmussen encephalitis (Luan et al. 2017), it was found an increase in the density of A_1R. The exact reason for discrepancies compared to Glass observations (Glass et al. 1996) is unclear, but one possible explanation may be the differences in control tissue (biopsy *vs* autopsy of non-epileptic brain controls).

Regarding $A_{2A}Rs$, most studies report long-term changes in receptor protein levels. In opposite to A_1Rs, $A_{2A}Rs$ protein levels are increased several weeks after the

establishment of epilepsy (Rebola et al. 2005). Upregulation of A_{2A}Rs does not only occur in neurons but also in glia (Saura et al. 2005; Orr et al. 2015). One study, though, describes a decrease in A_{2A}R protein and mRNA levels using a kindled seizure model of epilepsy (Adén et al. 2004). Curiously, using a genetic model of absence epilepsy, where it is thus possible to evaluate receptor levels before and after seizures onset, it was shown that A_{2A}R levels are only high after the first symptoms appear and not during the presymptomatic period, where A_{2A}R density is even lower than in control animals (D'Alimonte et al. 2009). This increase may thus be a consequence, and not a direct cause, of recurrent seizure activity, although it may contribute to the progression and aggravation of convulsions. Alternatively, one may think that the increase in A_{2A}R levels is itself a gate of the disease, coinciding with the very first event. Pharmacological treatment of these animals with an A_{2A}R antagonist before disease onset would help to clarify this issue.

In parallel with changes in receptor levels, other long-term changes in the adenosinergic system also occur. These include decrease in ATP levels (Rebola et al. 2003) and suppression of recurrent epileptiform discharges through activation of A_1Rs (Avsar and Empson 2004; Klaft et al. 2012; Muzzi et al. 2013); increase in ecto-5´-nucleotidase activity (Schoen et al. 1999; Lie et al. 1999; Rebola et al. 2003), the enzyme responsible for hydrolysing AMP into adenosine (Zimmermann et al. 2012); decrease in ecto-ATPase activity (Nagy et al. 1990; Bonan et al. 2000a, b); decrease in density and efficiency of equilibrative nucleoside transporter (ENT) (Pagonopoulou and Angelatou 1998; Rebola et al. 2003); and upregulation of ADK in rodents and human epileptic tissue (Aronica et al. 2011). Together, these long-term changes will contribute to low, but mostly ATP-derived, extracellular levels of adenosine that will lead to activation of A_{2A}Rs (Cunha et al. 1996) and contribute to propagation of seizure activity (for a resume of the changes, see Table 13.2).

13.5.1 Neuronal Mechanisms of A_1Rs

The in vivo models of seizure are extremely useful to address the consequences of adenosine manipulation for the control of seizures and epileptogenesis, as discussed in the previous section. Nonetheless, when trying to further explore and detail the specific mechanisms by which adenosine and adenosine receptors exert its effects, the use of in vitro models of seizures may prove extremely helpful. Indeed, how A_1Rs exert its anticonvulsant effects was first advanced by Lee and co-workers in vitro by demonstrating that A_1R-mediated suppression of epileptiform activity was chemical synapse independent (Lee et al. 1984). The authors proposed that a hyperpolarizing effect of A_1Rs, through blockage of outward K^+ currents, might be involved in the process. Indeed, some years later, adenosine A_1Rs were shown to change K^+ channels not by inhibiting outward K^+ currents but instead by facilitating G-proteins coupled inwardly rectifying K^+ channels (GIRKs) (Trussell and Jackson 1987), ATP-sensitive K^+ channels (K_{ATP}) (Li and Henry 1992) and small conductance Ca^{2+}-activate K^+ channels (SK) (Clark et al. 2009) and in this way regulate

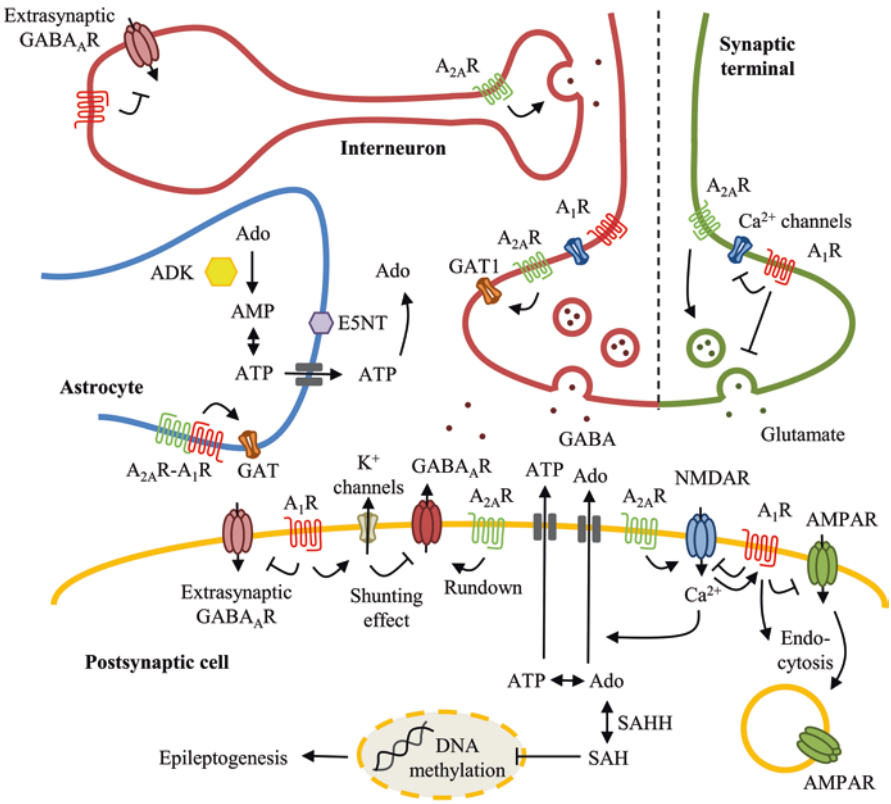

Fig. 13.2 Actions of adenosine during epileptic seizures. The mechanism by which adenosinergic system exerts its anticonvulsant actions is shown. These can be separated in neuronal mechanisms, which include A_1R and $A_{2A}R$ presynaptic actions (on glutamate and GABA release) and postsynaptic actions (through potassium channels, AMPAR, NMDAR and $GABA_AR$s); non-neuronal mechanisms, involving astrocytes and regulation of adenosine levels (through changes in density and activity of ADK, E5NT, GAT or ENT); and homeostatic and epigenetic control, by modulating DNA methylation status and epileptogenesis. See text for further details and references. A_1R, A_1 receptor; $A_{2A}R$, A_{2A} receptor; Ado, adenosine; ADK, adenosine kinase; AMP, adenosine 5'-monophosphate; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ATP, adenosine 5'-triphosphate; E5NT, ecto-5'-nucleotidase; ENT, equilibrative nucleoside transporter, GABA, gamma-aminobutyric acid; $GABA_AR$, GABA type A receptor; GAT, GABA transporter; NMDAR, N-methyl-D-aspartate receptor

local depolarization of neurons through hyperpolarization (Ehrengruber et al. 1997). This is still considered one of the main mechanisms that contribute to A_1R-dependent suppression of seizures.

Many other alternatives and complementary mechanisms have been proposed to explain adenosine actions on the different forms of epileptic seizures (Fig. 13.2). As discussed before, seizures have traditionally been viewed as caused by an imbalance between excitation (too much) and inhibition (too little) that compromise normal network functioning. Hyper-excitation may be caused by ionic (inward sodium or

calcium current) changes or excitatory neurotransmission dysfunction (mostly glutamate); hypo-inhibition may result from dysregulation of potassium or chloride currents or disturbances in GABA-mediated neurotransmission. Most of these systems are also targets of adenosine receptors. In fact, in parallel with the postsynaptic hyperpolarizing effect already mentioned, A_1Rs also control epileptiform activity by altering glutamatergic and GABAergic transmission.

Considering glutamatergic transmission, we can distinguish pre- and postsynaptic actions of adenosine. Presynaptically, A_1Rs reduce the release probability of glutamate through inhibition of voltage-dependent Ca^{2+} channels (VDCCs) (MacDonald et al. 1986; Schubert et al. 1986; Wu and Saggau 1994) or reduction of Ca^{2+}-independent spontaneous release (Scholz and Miller 1992; Scanziani et al. 1992), with demonstrated anticonvulsant consequences in kainic acid-induced and picrotoxin-induced models of seizures (Arvin et al. 1989; Wang et al. 2013). Postsynaptically, actions are mostly related with interactions with AMPARs and NMDARs. Increased neuronal excitability during seizures leads to increased glutamate release and activation of glutamate receptors. Both AMPARs and NMDARs have been implicated in the initiation and establishment of epileptic seizures (Rice and Delorenzo 1998; Kharazia and Prince 2001; Kohl and Dannhardt 2001; Zhang et al. 2003). Suppression of A_1R tonus in vitro causes a sustained synaptic-mediated epileptiform activity that has an AMPAR-dependent (Alzheimer et al. 1993; Moschovos et al. 2012) and NMDAR-dependent component (Thümmler and Dunwiddie 2000). Antiepileptogenic actions through AMPARs may be explained by a recent finding showing that A_1Rs mediate a persistent synaptic depression of glutamatergic transmission through AMPAR endocytosis (Chen et al. 2014). Through NMDARs, A_1R modulation involves the control of synaptic transmission and synaptic plasticity phenomena (de Mendonça et al. 1995; De Mendonça and Ribeiro 2000) that have implications during intense neuronal activity. For example, hampering A_1R activation during burst activity will result in overactivation of NMDARs and consequent induction of maladaptive NMDAR-dependent plasticity phenomena responsible for maintaining and exacerbating disruptive circuits and seizures (Thümmler and Dunwiddie 2000). In a Mg^{2+}-free in vitro model of seizures, the epileptiform activity gated by NMDAR activation (Nowak et al. 1984) is reduced after activation of A_1R (O'Shaughnessy et al. 1988). Also, in a 3-MP model of seizures, A_1Rs prevent the adaptive changes of NMDAR system (decrease in NR2B subunit expression) that occur as a consequence of seizures (Giraldez and Girardi 1998; Girardi et al. 2010). Together, these studies support the idea of a protective role of endogenous adenosine A_1R activation through NMDARs by keeping excessive excitability, thus checking and preventing epileptogenesis, which has been observed both ex vivo (Alzheimer et al. 1989; Hamil et al. 2012) and in vivo (Hamil et al. 2012). Reciprocal modulation has also been observed between A_1Rs and NMDARs. In fact, NMDAR activation during synchronized neuronal activity is another mechanism that explains the rising levels of adenosine during seizures (Hoehn and White 1990a, b; Manzoni et al. 1994). Also, chronic activation of NMDARs (in doses insufficient to cause behaviourally effects) promote a shift in A_1R function towards a high-affinity state (Von Lubitz et al. 1995b) that results in increased potency of protective effects of A_1Rs following a new and intensive insult (Von Lubitz et al. 1994b). The interplay

between A_1R and NMDAR contributes in this way to explain part of the neuroprotective actions of A_1Rs during stablished epileptic activity.

In the case of inhibitory transmission, adenosine A_1Rs have proven to directly influence GABA function in several brain areas (Sebastião et al. 2015). At the hippocampus, however, strong evidence exists about the lack of A_1R effects on phasic GABAergic transmission (Yoon and Rothman 1991; Lambert and Teyler 1991; Prince and Stevens 1992). Alternative mechanisms (Rombo et al. 2016b) include direct influence on GABA type A receptor ($GABA_AR$), the ionotropic receptor for GABA (Petersen 1991; Concas et al. 1993) and control of tonic inhibition (Rombo et al. 2016a). While evaluating control of GABAergic function at the hippocampus, it is important to distinguish between control of GABAergic inputs to inhibitory neurons and control of GABAergic inputs to excitatory neurons. A_1R-mediated decrease in tonic inhibition seems to be less relevant in pyramidal neurons than in interneurons (Rombo et al. 2016a), thus most probably contributing to an overall decrease in pyramidal neuron excitability. Whether the A_1R-mediated inhibition of $GABA_AR$ function reported by Concas et al. (1993) also predominates in interneurons rather than in pyramidal neurons is not known.

A complex interaction seems to exist between adenosine and $GABA_AR$ recognition sites, including sites for allosteric ligands (such as benzodiazepine). There is nevertheless evidence that A_1R-mediated influence over GABA-dependent transmission contributes to the anticonvulsant actions of adenosine (Klitgaard et al. 1993). Some authors document an interference of adenosine analogues on $GABA_AR$ number (Skolnick et al. 1980; Davies 1985) and binding properties (Davies 1985). Others show no effects of adenosine and adenosine receptors on $GABA_AR$ affinity (Williams et al. 1981). Another mechanistic explanation for these actions is that A_1R activation would exert a shunting effect over $GABA_AR$-mediated chloride conductance through facilitation of K^+ channels (Ilie et al. 2012). This effect is particularly relevant during intense neuronal activity, when $GABA_AR$ responses transiently switch from hyperpolarizing to depolarizing and excitatory (Thompson and Gähwiler 1989; Staley et al. 1995; Kaila et al. 1997). In such conditions of increased GABA and adenosine concentrations, inhibition of tonic GABA responses in principal neurons would further suppress network excitability (Ortiz and Gutiérrez 2015; Rombo et al. 2016a). Control of GABA levels by regulating GABA transporter (GAT) function in nerve terminals and astrocytes, in an activity-dependent manner, may also contribute to these actions (Cristóvão-Ferreira et al. 2009, 2013). To our knowledge, besides A_1R-GABA interplay to refrain epileptiform activity during ongoing seizures, there are no studies relating these two systems in the prevention of epileptogenesis and control of mechanisms that lead to stablished epilepsy.

Together, the above-mentioned studies provide experimental evidence to support the general consensus that neuronal anticonvulsant and antiepileptogenic mechanisms of adenosine A_1Rs are mostly mediated by changes in excitatory transmission and hyperpolarization of principal neurons. Other complementary mechanisms affecting GABA-mediated transmission may interfere to further potentiate endogenous A_1R-mediated antiseizure actions and reestablishment of normal network functioning.

13.5.2 Neuronal Mechanisms of A_{2A}Rs and A_3Rs

In opposition to A_1R actions, both A_{2A}Rs and A_3Rs are mostly considered excitatory and proconvulsant. This is supported by in vitro studies where these receptors contribute to the progression of seizures (Fig. 13.2).

Ex vivo, antagonists of A_{2A}Rs restrain epileptiform activity (Etherington and Frenguelli 2004; Rombo et al. 2015), and A_{2A}R agonists show a proconvulsant action (Klitgaard et al. 1993; Longo et al. 1995). The exact mechanisms by which A_{2A}R blockade confers neuroprotection in epilepsy are not completely understood, since most of what is known is from models of brain damage after ischemia (Cunha 2005). It is, however, reasonable to think that similar mechanisms may also be present during excessive neuronal activation generated from seizure events. This would include control of glutamate release, where A_{2A}R blockade protects neurons from excitotoxic glutamate outflow induced by ischemic stimuli (Popoli et al. 2002; Melani et al. 2003; Marcoli et al. 2003). Other possible mechanisms include prevention of neurotoxicity induced by AMPARs (Dias et al. 2012, 2013) and NMDARs (Robledo et al. 1999; Wirkner et al. 2004). However, ex vivo models of seizures show complex modulatory actions of A_{2A}Rs, since while facilitating NMDAR-independent induction of persistent epileptiform activity, A_{2A}Rs also suppress NMDAR-dependent progression of neuronal discharges (Moschovos et al. 2012). A novel mechanism by which brain-wide ADK deficiency (with significantly increased brain adenosine levels) leads to epileptic phenotype includes increased activation of A_{2A}Rs and disruption of synaptic plasticity phenomena, through a mechanism that involves A_{2A}R-mediated exacerbation of BDNF functioning (Sandau et al. 2016). Despite the evidence of direct effect of A_{2A}R activation on excitatory glutamatergic synapses, this may not completely explain the proconvulsive actions of these receptors. In fact, facilitation of epileptiform activity through A_{2A}Rs can also be explained by synergistic disinhibition of pyramidal cells through GABAergic communication between interneurons (Rombo et al. 2015). Direct actions of A_{2A}Rs on GABA function are also observed in human epileptic tissue, where endogenous A_{2A}R activity was shown to increase $GABA_A$R instability and consequent rundown of GABAergic responses (Roseti et al. 2008, 2009). Precluding these actions by preventing A_{2A}R activation during epileptiform activity has significant anticonvulsant effects (Roseti et al. 2008; Rombo et al. 2015).

Much less is known about A_3Rs, and as discussed above there is evidence for anti- as well as proconvulsive actions of A_3R agonists. Their endogenous contribution to the promotion of epileptiform activity is limited, although its blockade is still capable of attenuating seizure intensity (Etherington and Frenguelli 2004). The effects may be direct or indirect, through A_1Rs, influencing presynaptically glutamatergic transmission or postsynaptically K^+ channels function (Dunwiddie et al. 1997) and desensitization of $GABA_A$Rs (Roseti et al. 2009).

Despite scarce information about the operating mechanisms exerted by A_{2A}Rs and A_3Rs during epileptiform activity, it is evident that blockade of A_{2A}R, and most probably also of A_3R, would prevent their synaptic neurotoxic effects responsible for aggravating neuronal excitability and epileptiform activity.

13.5.3 Non-neuronal Mechanisms of Adenosine

Astrocytes play a pivotal role in the generation and propagation of epileptic seizures by controlling synchronization of neuronal firing, ion homeostasis, reuptake of neurotransmitters and neuromodulators and release of gliotransmitters (Seifert et al. 2010). In what concerns adenosine metabolism, astrocytes have been implicated in regulating the levels of endogenous extracellular adenosine by directly participating in the adenosine cycle (Fig. 13.2). This involves (1) neuronal and astrocyte release of ATP (Pascual et al. 2005; Fields and Burnstock 2006), (2) extracellular formation of adenosine via a cascade of ecto-nucleotidases (Zimmermann 2000) and (3) uptake of adenosine back to neurons and astrocytes through ENT (King et al. 2006). The extracellular levels of adenosine are primarily controlled by actions of the astroglial enzyme ADK (Boison 2006). Perturbation of astrocyte homeostasis can affect the adenosinergic system and disrupt its neuroprotective effects. In fact, astrogliosis occurring in the epileptic brain is associated with increased expression of ADK and consequent depletion of adenosine levels, further exacerbating seizures (Gouder 2004; Li et al. 2008; de Groot et al. 2012). This evidence led to the proposal of an "ADK hypothesis of epileptogenesis" (Boison 2008, 2016a) based on biphasic changes in adenosine homeostasis during disease progression. A dysregulation of the normal brain functioning (due to structural, genetic, infectious, immune or metabolic causes) may result in an imbalance between excitatory and inhibitory mechanisms, thus leading to a seizure event. The immediate response to the insult consists of an acute surge in adenosine levels that is potentiated by acute downregulation of ADK (Gouder 2004), resulting in the termination of seizure. However, these seizure control actions may come with a price. Besides neuroprotective A_1R activation, seizure event and adenosine rise will also contribute to adaptive changes that occur in the adenosinergic system including (1) downregulation of inhibitory A_1Rs; (2) upregulation and overactivation of excitatory A_{2A}Rs; (3) switch in ADK expression, from decreased levels to sustained ADK overexpression (Gouder 2004); and (4) exacerbation of astrogliosis (Fiebich et al. 1996; Gebicke-Haerter et al. 1996; Bouilleret et al. 1999). All these adaptive changes contribute for the progression of the epileptogenic process (Li et al. 2007a). In fact, once astrogliosis and ADK overexpression are stablished, recurrent seizure onset is more likely (Li et al. 2007a, 2008, 2012a). Therefore, dysregulation of astrocyte and ADK functioning plays a significant role in the process that turns a normal brain into an epileptic brain (Boison 2016a).

13.5.4 Homeostatic and Epigenetic Mechanisms

One of the main actions of adenosine in mammalian cells is to control cell metabolism. Adenosine is in a privileged position to do this since minor changes in intracellular ATP concentrations as a result of metabolic challenges will result in disproportional larger changes in extracellular concentrations of adenosine (Cunha 2001). Besides the adenosine receptor-dependent actions discussed in the previous sections, adenosine exerts a more global biochemical regulation of cell function by means of epigenetic control, through DNA methylation (Williams-Karnesky et al. 2013) (Fig. 13.2). The classical source of adenosine is from a hydrolysing cascade reaction from ATP to ADP and to AMP by ectonucleotidases. However, another important source of adenosine is the hydrolysis of S-adenosyl-L-homocysteine (SAH) by SAH hydrolase (SAHH) (Schrader et al. 1981). SAH is involved in the transmethylation pathway responsible for methylation of DNA (James et al. 2002). Alterations in adenosine levels will thus influence SAH levels and DNA methylation. These epigenetic modifications are responsible for altering gene transcription without modifying the underlying DNA sequence. Methylation of the DNA has already been described in cells from the CNS (Ma et al. 2009), and it is responsible for some of the pathological changes observed during epileptogenic process (Henshall and Kobow 2015). When adenosine levels rise (e.g. during a seizure event), there is a shift in the equilibrium of the SAHH reaction towards the formation of SAH. Rises in SAH levels block DNA methyltransferase activity and decrease global DNA methylation levels (Williams-Karnesky et al. 2013). In this phase, adenosine-induced epigenetic mechanisms may be responsible for transcription and expression of epileptogenesis initiating genes (Boison 2016a). In later stages of epileptogenesis, increased ADK expression leads to a decrease in adenosine levels and consequent establishment of an hypermethylated DNA status that will further aggravate the epileptogenic condition (Miller-Delaney et al. 2015; Boison 2016b). These studies highlight a novel modulatory mechanism of adenosine in the control of epileptogenesis involving DNA methylation and epigenetic control.

13.6 Adenosine-Based Therapies

The experimental evidence discussed above about the anticonvulsant, neuroprotective and antiepileptogenic properties of adenosine provides the rational for the use of adenosine augmentation therapies in the treatment of epileptic seizures and epilepsy. This section intends to briefly discuss the most prominent approaches to increase adenosine levels in brain and holt synchronized neuronal activity and seizure progression.

13.6.1 Focal Adenosine Augmentation

One of the main reasons to prefer focal adenosine delivery approaches instead of systemic drug use is to avoid the considerable peripheral side effects of adenosine (mostly cardiovascular). Focal approaches are considered safe and feasible alternatives given the focal nature of many forms of epilepsy (Nilsen and Cock 2004). Tools for focal delivery include polymeric brain implant (Wilz et al. 2008), cell-based therapy and gene therapy (Löscher et al. 2008). To increase the concentrations of adenosine in the epileptic focus and supress seizure, the most effective strategy is by disrupting metabolic adenosine clearance through manipulation of ADK activity.

Starting with gene therapy approaches, two strategies have been used to augment adenosine levels: (1) antisense cDNA to disrupt the endogenous *Adk* gene (Theofilas et al. 2011) and (2) RNA interference (RNAi) to knock down ADK expression (Ren et al. 2007; Boison 2010). Both strategies can effectively be used to engineer focal release of adenosine, but additional studies are needed to evaluate its effectiveness in clinically relevant models of epilepsy (Boison 2016a).

Cell therapy approaches consist of injecting into the brain cell-derived implants that will exert its anticonvulsant actions via paracrine release of adenosine (Nilsen and Cock 2004). This method proved to be extremely efficient in supressing seizures and epileptogenesis (Huber et al. 2001; Li et al. 2007b, 2008, 2009).

Silk-based adenosine delivery strategies have unique therapeutic properties that bring them closer to clinical implementation. These properties include high biocompatibility and slow degradation kinetics (Horan et al. 2005). As occurred with cell-based therapies, polymeric brain implants were effective either when implanted before seizure induction (Wilz et al. 2008) or after full establishment of epilepsy (Szybala et al. 2009).

Together, data briefly discussed above suggests that focal adenosine augmentation therapies are promising strategies for preventing seizure occurrence and hamper epileptogenesis progression.

13.6.2 Dietary Therapies

Dietary therapies are effective, safe, non-pharmacologic treatments for intractable epilepsy, especially in children (Payne et al. 2011). The most used type of diet is the ketogenic diet (KD). This is a high-fat, low-carbohydrate, adequate-protein diet that has been used since the 1920s but resurged in popularity over the past 15 years (Wheless 2008). Despite its long clinical use, the mechanism by which KD suppresses seizure is not completely clarified (Rogawski et al. 2016). The hallmark of KD is the production of ketone bodies by the liver and its use as primary energy source. The anticonvulsant mechanisms include (1) ketone body-mediated inhibition of glutamate release and activation of K_{ATP}; (2) increased GABA synthesis; (3)

increased mitochondrial function and biogenesis (with consequent rise in ATP production); (4) decreased production of reactive oxygen species; and (5) increased adenosine concentration, among others. The adenosine and adenosine receptor-mediated actions are indeed one of the key mechanisms underlying the anticonvulsant actions of KD (Masino et al. 2014). It was shown that reduction of seizure with KD is caused by increased adenosine signalling in the brain (Masino and Geiger 2008, 2009, Masino et al. 2011, 2012), mostly through activation of A_1Rs (Masino et al. 2011). It is now clear the beneficial effects of the KD in the treatment of several forms of epilepsy (Neal et al. 2008; Lambrechts et al. 2017). The success of this strategy probably relies on its strong multifactorial mechanisms, and adenosine A_1R-mediated anticonvulsant actions significantly contribute for this.

13.7 Conclusions and Future Perspectives

Accumulated evidence from the past 50 years of research on adenosine actions to control the initiation and progression of seizure events and epilepsy were briefly reviewed in this chapter. There are three main conclusions we can take from this data:

1. Endogenous adenosine has a true anticonvulsant capacity and antiepileptogenic potential, mostly through A_1R activation. However, recent data have been demonstrating the benefits of concomitantly modulating A_{2A}R and even A_3R to further potentiate its actions. The therapeutic use of adenosine depends on the stage of disease progression (acute *vs* chronic) and the targeting receptor and should always take into consideration its peripheral side effects (mostly cardiovascular-related).
2. There are considerable adaptations of the adenosinergic system during the epileptogenic process that influences the mechanisms of action and disease progression. The anticonvulsant actions are exerted (I) at the synaptic level, mostly through A_1R activation of potassium channels but also by A_1R and A_{2A}R control of glutamate and GABA function at pre-, post- and peri-synaptic compartments; (II) at non-neuronal level, by changing adenosine concentration through ADK expression in astrocytes; and (III) at homeostatic control level, by affecting DNA methylation status and consequently, the epileptogenic process.
3. Several strategies are being developed to take advantage of all the potential of adenosinergic manipulation in the control and treatment of seizure events and prevent epileptogenesis. These include therapeutic adenosine augmentation strategies ranging from gene therapy to dietary intervention (such as ketogenic diet). The concomitant use of adenosine strategies together with conventional AED therapies currently available may potentiate and expand the efficacy of the intervention.

The diversity of adenosine effects and mechanisms of action are, indeed, an advantage for its use in epilepsy. However, this capacity of adenosine to act as a

"universal modulator or maestro" of network functioning may come with a price. In fact, attention should be given to clearly differentiate the anti- and proconvulsant actions of adenosine that result from activation of different receptors at different neuronal and non-neuronal compartments. The mechanisms by which adenosine exerts its influence to regulate excitability in physiological, but mostly during pathophysiological situations, should thus be further understood. The challenge will be to take advantage of the homeostatic role of adenosine without never losing sight on the highly selective and sometimes opposing effects that are exerted by adenosine through its different receptors. Attention should thus be given not only to further develop strategies for increasing adenosine levels in the brain with the least peripheral side effects possible but also in the development of innovative adenosine ligands specifically directed to affect relevant neuronal targets, leaving untouched the ones not involved in the pathology.

As a final remark, and considering epileptogenesis itself, where too little is known on the influence of adenosine, inflammatory pathways have been highlighted as crucial in the underlying molecular mechanisms of epilepsy (van Vliet et al. 2018). Adenosine receptors, in particular $A_{2A}R$ (Chen and Pedata 2008; Dai and Zhou 2011) and A_3R (Jacobson et al. 2017), interfere with the inflammatory cascade in a multiplicity of ways. There is thus time to also explore this avenue to better predict the influence of adenosine-based therapies in epilepsy.

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