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Adenosine Receptors and Epilepsy: Current Evidence and Future Potential

Susan A. Masino^{*,1}, Masahito Kawamura Jr[†], and David N. Ruskin^{*}

^{*}Department of Psychology and Neuroscience Program, Trinity College, Hartford, Connecticut, USA

[†]Department of Pharmacology, Jikei University School of Medicine, Minato-ku, Tokyo, Japan

Abstract

Adenosine receptors are a powerful therapeutic target for regulating epileptic seizures. As a homeostatic bioenergetic network regulator, adenosine is perfectly suited to establish or restore an ongoing balance between excitation and inhibition, and its anticonvulsant efficacy is well established. There is evidence for the involvement of multiple adenosine receptor subtypes in epilepsy, but in particular the adenosine A₁ receptor subtype can powerfully and bidirectionally regulate seizure activity. Mechanisms that regulate adenosine itself are increasingly appreciated as targets to thus influence receptor activity and seizure propensity. Taken together, established evidence for the powerful potential of adenosine-based epilepsy therapies and new strategies to influence receptor activity can combine to capitalize on this endogenous homeostatic neuromodulator.

1. INTRODUCTION

Adenosine is a ubiquitous and powerful homeostatic bioenergetic network regulator (Boison, Masino, & Geiger, 2011). It exerts these effects through receptor-dependent and -independent effects, and has the powerful potential to restore homeostasis irrespective of the specific mechanism of upstream disruption of network function. Chronic neurological disorders are characterized by an assortment of metabolic and neuronal changes, and adenosine is in a unique position to address metabolic and neuronal dysfunction broadly. Overall, influencing adenosine receptor function can modulate neuronal activity directly and shift seizure threshold, regardless of whether the seizure's etiology is metabolic, genetic, environmental, or unknown.

Epilepsy is a prevalent neurological disorder that affects about 50 million people worldwide (World Health Organization, 2005). The prevalence of epilepsy is 3–14 per 1000 people in children (Hauser, Annegers, & Kurland, 1991; Medina et al., 2005; Oka et al., 2006; Olafsson & Hauser, 1999; Rwiza et al., 1992) and 5–19 per 1000 people in adults (Hauser et al., 1991; Medina et al., 2005; Olafsson & Hauser, 1999; Rwiza et al., 1992; Tellez-Zenteno, Matijevec, & Wiebe, 2005), indicating that epilepsy is one of the most common disorders of

¹Corresponding author: susan.masino@trincoll.edu.

the brain. Epilepsy is defined as “a chronic brain disorder of various etiologies characterized by recurrent seizures due to excessive discharge of cerebral neurones (epileptic seizures), associated with a variety of clinical and laboratory manifestations” in Dictionary of Epilepsy (Gastaut, 1973). It is a (1) chronic disorder of (2) the central nervous system, and involves (3) repetitive seizure events with (4) various causes. It is increasingly appreciated that seizures are comorbid with a primary diagnosis of other common disorders in adults and children, such as Alzheimer’s disease and autism (Devinsky, 2003; Gaitatzis, Sisodiya, & Sander, 2012; Gleichmann, Chow, & Mattson, 2011).

One of the hallmarks of epilepsy is its diverse etiology. The underlying causes are categorized as (1) genetic, (2) structural/metabolic (due to injury, environmental triggers, etc.), and (3) unknown. These three terms are intended to replace the traditional terms idiopathic, symptomatic, and cryptogenic (Berg et al., 2010). Genetic epilepsy is caused by known or presumed genetic defects that directly link to seizures (e.g., childhood absence epilepsy, autosomal dominant nocturnal frontal lobe epilepsy, and Dravet syndrome). Structural/metabolic epilepsies include brain injury, stroke, tumor, and infection; some genetic epilepsies cause seizures due to clear structural or metabolic defects. Unfortunately, nearly half of childhood epilepsies have an unknown cause (Wirrell, Grossardt, Wong-Kissel, & Nickels, 2011).

Epilepsy is frequently associated with a psychiatric disorder and/or cognitive dysfunction. It has been reported that psychiatric comorbidity occurs in 20–50% of epilepsy patients (Akanuma, Hara, Adachi, Hara, & Koutroumanidis, 2008; Cutting, Lauchheimer, Barr, & Devinsky, 2001; Filho, Mazetto, da Silva, Caboclo, & Yacubian, 2011; Trinka et al., 2006). Depression is one of the psychiatric comorbidities with the highest prevalence among patients with epilepsy (Hauser & Hesdorffer, 2001), and anxiety disorder is also a common psychiatric comorbidity (Devinsky, 2003). Autism spectrum disorder, Asperger syndrome, and attention-deficit/ hyperactivity disorder are also frequently comorbid with epilepsy (Devinsky, 2003). Interestingly, epilepsy patients with psychiatric comorbidity diagnoses are more likely to be refractory to medication compared to patients without (Akanuma et al., 2008), and psychiatric comorbidities are associated with poor outcomes (Devinsky, 2003). Sleep disruption is also common with an epilepsy diagnosis (Malow, 2005).

Because epilepsy has various underlying causes, and because most often the cause(s) are unknown, it is difficult to treat all epilepsies similarly or even successfully. The most common treatment for epilepsy is therapeutic management of seizures with antiepileptic drugs (AEDs), and about 70% of epileptic patients benefit from AEDs. However ~30% of patients remain medically refractory to AEDs because of inefficacy in controlling seizures or significant adverse events and side effects (St. Louis, 2009; Vajda, 2007). Based on multiple lines of evidence, adenosine remains one of the most promising targets for medically refractory epilepsy as well as epilepsy in general. Here, we describe the involvement of adenosine receptors in control of seizures; where possible, we focus on research within the last decade. We outline adenosine-based antiepileptic and potentially antiepileptogenic effects through receptors, novel adenosine augmentation therapies, and metabolic diet-based therapy.

2. ADENOSINE REGULATES ONGOING NEUROTRANSMISSION

Adenosine is not a classically packaged and released neurotransmitter, yet acts like a transmitter by influencing neuronal activity, primarily via pre- and postsynaptic adenosine A₁ (A₁R) and A₂ (A₂R) receptor subtypes. With this modulatory role on neurotransmission, adenosine is in a unique position to influence the balance of excitation and inhibition without interfering directly with postsynaptic GABA or glutamate receptors. Strong neuronal activity in the nervous system leads directly to elevated extracellular levels of the neuromodulator adenosine. At the same time, A₁Rs inhibit synaptic transmission; thus, adenosine is an inhibitory neuromodulator (Newby, 1984) and so is a target of opportunity in conditions involving neural overactivity such as epilepsy. This activity-induced increase in adenosine serves to increase adenosine “tone” directly in the zone where there is increased neuronal activity. This conceptual framework demonstrates that adenosine is positioned as a homeostatic network modulator: an epilepsy therapy enhances this modulatory role could deliver seizure control and network stability exactly where it is needed most.

Among adenosine receptor subtypes (reviewed by Chen, Lee, & Chern, 2014), direct inhibition of neurotransmission is mediated mostly by the A₁R subtype. Well-established effects on excitatory glutamatergic transmission have been reported for some regions such that overall activity is reduced, but transmission via GABA and other neurotransmitters can also be affected (Sperlágh & Vizi, 2011). Sufficiently high levels of adenosine shut down neurotransmission completely at some synapses (Canals, Larrosa, Pintor, Mena, & Herreras, 2008; Coelho et al., 2006; Kukley, Schwan, Fredholm, & Dietrich, 2005; Martín et al., 2007; Pearson, Damian, Lynas, & Frenguelli, 2006). In addition, adenosine can diffuse away from the site of activation to inhibit neighboring synapses and neurons thus exerting network-level effects (Andersson, Blomstrand, & Hanse, 2007; Chen et al., 2013; Lovatt et al., 2012; Pascual et al., 2005; Serrano, Haddjeri, Lacaille, & Robitaille, 2006).

3. ADENOSINE RECEPTOR SUBTYPES AND EPILEPSY

As noted above, adenosine release is particularly prominent after the excessive neuronal activity of seizures or *in vitro* seizure-like activity (Dulla, Frenguelli, Staley, & Masino, 2009; Etherington et al., 2009; Ilie, Raimondo, & Akerman, 2012; Kaku, Jiang, Hada, Morimoto, & Hayashi, 2001; Lovatt et al., 2012; Van Gompel et al., 2014), and tissue content of adenosine rises rapidly after seizure initiation (Winn, Welsh, Rubio, & Berne, 1980). These seizure-related adenosine elevations are believed to be a feedback mechanism that limits seizure intensity or duration (Ilie et al., 2012; Lovatt et al., 2012; Van Gompel et al., 2014). As with neurotransmission *per se*, much evidence from animal research shows that this effect is A₁R-mediated. Systemic injection of A₁R-selective agonists limits seizures and convulsions in numerous types of experimental seizures and epilepsies (Girardi, Auzmendi, Charo, Gori, & Castro, 2010; Girardi, Canitrot, Antonelli, Gonzalez, & Coirini, 2007; Gouder, Fritschy, & Boison, 2003; Li, Kang, Shi, Liu, & Zhang, 2013; Li & Zhang, 2011; Luszczyk, Kozicka, Swiader, & Czuczwar, 2005; Mares, 2010; Moezi, Akbarian, Niknahad, & Shafaroodi, 2013; Muzzi, Coppi, Pugliese, & Chiarugi, 2013; Pometlova, Kubova, & Mares, 2010; Tosh et al., 2012; Vianna, Ferreira, Doná, Cavalheiro, & da Silva Fernandes, 2005; Zuchora, Wielosz, & Urbanska, 2005). In addition, A₁R activation

augments the effects of standard AEDs (Borowicz, Łuszczki, & Czuczwar, 2002; Łuszczki et al., 2005). Focal intracranial activation of A₁Rs in various brain regions is also anticonvulsant (Guttinger, Padrun, Pralong, & Boison, 2005; Heidarianpour, Sadeghian, Mirnajafi-Zadeh, Fathollahi, & Mohammad-Zadeh, 2006; Hosseinmardi, Mirnajafi-Zadeh, Fathollahi, & Shahabi, 2007; Rezvani, Mirnajafi-Zadeh, Fathollahi, & Palizvan, 2007a, 2007b; Zeraati, Mirnajafi-Zadeh, Fathollahi, Namvar, & Rezvani, 2006). Drug development efforts have long been focused on developing central-acting therapeutics and limiting peripheral side effects, particularly cardiac side effects. Recent research suggests targeting highly specific regions of the A₁R may offer an advance in direct A₁R-based antiseizure therapies (Tosh et al., 2012).

Conversely, and further confirming antiseizure effects of A₁Rs, systemic injection of A₁R-selective antagonists worsens seizures (Fukuda et al., 2010) and blunts the beneficial effects of standard AEDs (Chwalczuk, Rubaj, Swiader, & Czuczwar, 2008; Zuchora et al., 2005) and experimental anticonvulsant compounds (Akula & Kulkarni, 2014; Rezvani, Roohbakhsh, Allahtavakoli, & Shamsizadeh, 2010; Uzbay, Kayir, & Ceyhan, 2007). Strikingly, systemic genetic inactivation of this receptor subtype leads to spontaneous electrographic seizures in cerebral cortex, allows focal seizure activity to generalize, and promotes status epilepticus after traumatic brain injury (Fedele, Li, Lan, Fredholm, & Boison, 2006; Kochanek et al., 2006; Masino, Li, et al., 2011).

In brain slices and cultures, seizure-like or epileptiform electrical patterns (repetitive bursts of action potentials, oscillatory field potentials, etc.) can be induced by elevating excitability or limiting inhibition. As expected, adenosine release is prominent during this type of epileptiform activity, and is auto-inhibitory via A₁Rs (demonstrated by A₁R-selective antagonist application and use of tissue from A₁R knock-out (KO) mice) (Avsar & Empson, 2004; Dulla et al., 2005, 2009; Etherington & Frenguelli, 2004; Etherington et al., 2009; Gu, Hazra, Aulakh, & Ziburkus, 2014; Hargus, Jennings, Perez-Reyes, Bertram, & Patel, 2012; Kluft et al., 2012; Muzzi et al., 2013; Salmani, Fathollahi, Mirnajafizadeh, & Semnanian, 2011; Wang et al., 2013; Wu, Wong, Wu, Sheppy, & Zhang, 2009; Zhou et al., 2011).

A₁Rs have long been strongly associated with antiseizure effects due to their clear effects on neuronal activity, high affinity, and widespread distribution. They are concentrated and influence ongoing transmission in seizure-prone areas (neocortex and hippocampus). Yet, other adenosine receptors may also play a role and offer therapeutic targets for epilepsy. For example, A_{2A}Rs are excitatory in most brain regions; therefore, A_{2A}Rs antagonists would be more likely to have antiseizure effects. A_{2A}Rs have a strikingly restricted anatomical distribution compared to A₁Rs (for review see Chen et al., 2014; Mishina & Ishikawa, 2014). Thus, it is perhaps not surprising that a number of paradigms have shown it was not involved in convulsions (Akula & Kulkarni, 2014; Hargus et al., 2012; Li & Zhang, 2011; Rezvani et al., 2007a; Uzbay et al., 2007; Wang et al., 2013; Young & Dragunow, 1994), and one study showed that A_{2A}R modulation of convulsions was selective to the basal ganglia (Rosen & Berman, 1987). When significant effects are found, pharmacological evidence from *in vivo* and *in vitro* studies mostly shows that A_{2A}Rs are proconvulsant and proseizure (D'Alimonte et al., 2009; Etherington & Frenguelli, 2004; Li et al., 2012; Mares, 2010; Vianna et al., 2005; Zeraati et al., 2006), though some studies have evidence for

anticonvulsant or anatomically specific effects (Hosseinmardi et al., 2007; Moschovos, Kostopoulos, & Papatheodoropoulos, 2012). Regardless of valence, some of these effects were found in regions with few receptors, which could suggest a nonspecificity of drug dose or concentration, although A_{2A}Rs may have functional actions even if expressed at quite low levels (Cunha et al., 1994). Mice with genetic inactivation of A_{2A}Rs are seizure-resistant in several models, further supporting a proconvulsant receptor action (El Yacoubi, Ledent, Parmentier, Costentin, & Vaugeois, 2008, 2009; El Yacoubi et al., 2001).

Regarding other adenosine receptor, though central expression is low, pharmacological evidence for effects of the adenosine A₃ receptor (A₃R) has been reported in a few studies, but results are mixed. Notably, A₃R activation promotes seizure-like activity in hippocampal slices (Etherington & Frenguelli, 2004; Laudadio & Psarropoulou, 2004), whereas an anticonvulsant effect of this receptor was suggested in studies measuring convulsions and using systemic administration (Borowicz, Œwi der, Wielosz, & Czuczwar, 2004; Vianna et al., 2005). Thus, there may be region-specific A₃R effects. There are essentially no data on seizure involvement of A_{2B}Rs, which are also expressed only at a low level in the brain.

In sum, pharmacological manipulations of ARs have long been targeted in treating epilepsy, with A₁R activation being the most effective. A₁R agonists as a whole, however, have a number of peripheral side effects (most dangerously involving the heart) such that they have not been pursued clinically – though some recent compounds lack cardiac effects in animal models (Luongo et al., 2012) – and new strategies may produce central nervous system-dominant compounds. Conversely, existing anticonvulsant drugs do not have substantial affinities for ARs (Macdonald & Kelly, 1995) but there may be AEDs with some A₁R activity. A gentler means of promoting adenosinergic transmission to reduce seizures might be to reduce metabolism of adenosine. Allopurinol is an inhibitor of xanthine oxidase that elevates levels of compounds “upstream” of this enzyme in the degradative pathway from adenosine to uric acid (Schmidt et al., 2009). Allopurinol enhances A₁R activity (Essawy & Elbaz, 2013; Schmidt et al., 2009). This drug is very well tolerated in patients, and two out of three double-blind and placebo-controlled studies concluded that it helped with seizure control (Coppola & Pascotto, 1996; Togha, Akhondzadeh, Motamedi, Ahmadi, & Razeghi, 2007; Zagnoni et al., 1994).

4. CHRONIC CHANGES IN ADENOSINE RECEPTOR ACTIVATION

One of the most widely consumed psychoactive drugs, caffeine, blocks adenosine receptors (except A₃R). Caffeine can, on its own, induce seizures, but only at acute doses far above what humans self-administer. At more reasonable doses, caffeine reduces the anticonvulsant activity of some AEDs in animal models and apparently humans as well (Chro ci ska-Krawczyk, Jargiełło-Baszk, Wałek, Tylus, & Czuczwar, 2011), and epileptic patients who are not habitual caffeine users should therefore avoid a large acute intake of caffeine. This is particularly true if there is a circadian pattern to their seizures: a large acute dose of caffeine should be avoided around the time when they are most vulnerable to a seizure.

In contrast, for habitual caffeine users, the situation is more complex due to chronic changes in adenosine receptors. Most metabotropic neurotransmitter receptors respond to chronic

antagonism by increased expression, an apparently homeostatic response. ARs are not exceptions to this principle: central A₁R and A_{2A}R levels in experimental animals are augmented after chronic caffeine (Daval, Deckert, Weiss, Post, & Marangos, 1989; Fredholm, 1982; Johansson, Georgiev, Lindström, & Fredholm, 1997; Kaplan, Greenblatt, Kent, & Cotreau-Bibbo, 1993; Li, Dai, et al., 2008; Marangos, Boulenger, & Patel, 1984; Rudolphi, Keil, Fastbom, & Fredholm, 1989; Tsutsui et al., 2004) and after or chronic theophylline (a closely related drug) treatment (Lupica, Berman, & Jarvis, 1991; Murray, 1982; Szot, Sanders, & Murray, 1987). Adenosinergic transmission should be improved with higher receptor expression, and indeed, in some studies, seizures in experimental animals are moderated by prior chronic (>1 week) caffeine (El Yacoubi et al., 2008, 2001). Unsurprisingly, chronic caffeine is also neuroprotective (Cognato et al., 2010; Li, Dai, et al., 2008; Rudolphi et al., 1989; Tsutsui et al., 2004). The ideal situation for a seizure-inducing event might therefore be in a habitual coffee drinker with no or low circulating caffeine; such events are not predictable, unfortunately. One recent study concluded that seizures in epileptic patients were unrelated to either habitual or acute caffeine intake (Samsonsen, Braathen, Reimers, Helde, & Brodtkorb, 2013).

5. GLIOSIS, ADENOSINE KINASE, AND EPILEPTOGENESIS

Not only does the adenosinergic system modulate seizures, but the reverse is also true. One particularly relevant target of seizure activity is the astrocytic enzyme adenosine kinase (ADK), the major intracellular enzyme for adenosine regulation and rephosphorylation. This enzyme is acutely downregulated after seizures, which is likely to aid in adenosinergic protection against excessive neuronal activity. However, gliosis is prominently involved in some types of epilepsy (traumatic brain injury-related; tumor-related; temporal lobe) and consequently ADK becomes over-expressed (Aronica et al., 2011; de Groot et al., 2012; Luan et al., 2013; Masino, Li, et al., 2011). Transgenic overexpression of ADK in forebrain causes spontaneous seizures which can be ameliorated by adenosine delivery (Li, Ren, et al., 2008). In fact, gliosis-related seizures are specifically caused by ADK overexpression (Li, Lan, & Boison, 2008; Li, Ren, et al., 2008). Such a nonhomeostatic positive feedback among seizures, gliosis, elevated ADK, and depleted adenosine has been posited to underlie epileptogenesis itself (Boison, 2008). Careful pharmacological inhibition of ADK might therefore be useful in preventing epileptic progression and restoring normal network excitability.

6. HUMAN ADENOSINE RECEPTOR POLYMORPHISMS

In humans, some adenosine receptor gene variants have been associated with seizure disorders. An A_{2A}R polymorphism associated with encephalopathy with febrile status epilepticus is related to increased receptor expression and second messenger output (Shinohara et al., 2013), in accordance with the apparent proconvulsant effect of this receptor subtype. Some polymorphisms in A₁Rs are associated with traumatic brain injury-related seizures, particularly late-onset seizures (Wagner et al., 2010), underscoring the experimental association between this receptor subtype and injury-related seizures. Notably, adenosine-related genes that are not receptors (but would be expected to influence adenosine levels) also have seizure-related polymorphisms. Duplications of a chromosomal region

containing the gene for adenosine deaminase (an extracellular enzyme metabolizing adenosine to inosine) are associated with childhood epilepsy in some individuals (Chen et al., 2011; Muhle et al., 2010). A polymorphism in the gene for an equilibrative nucleoside transporter-1 (a major means of removal of adenosine from the extracellular space) is associated with withdrawal-associated seizures in alcoholics (Kim et al., 2011).

7. ADENOSINE AND NEUROINFLAMMATION

Evidence indicates that at least some epileptogenic mechanisms involve an important inflammatory component (Vezzani et al., 2000; Vitaliti, Pavone, Mahmood, Nunnari, & Falsaperla, 2014). Inflammation in the brain is associated with a number of seizure-related conditions (central infection, cancer, physical injury, and ischemia) and the inverse is also true in that seizure activity elevates brain inflammation (Riazi, Galic, & Pittman, 2010). Many types of cells involved in inflammation express adenosine receptors, and so adenosine influences immune cell activity in a receptor subtype- and cell type-dependent manner, and adenosine receptors on non-immune cells (such as neurons) also influence inflammation (Blackburn, Vance, Morschl, & Wilson, 2009; Kumar & Sharma, 2009; Linden, 2001). Furthermore, adenosine receptor subtypes differ in desensitization after prolonged activation (Blackburn et al., 2009), such that subtype involvement might change during the course of events. Thus, general statements about a particular subtype being pro- or anti-inflammatory are essentially impossible. As an illustration of the complexity, brain A_{2A}Rs have been concluded to be either proinflammatory or anti-inflammatory in recent studies (Golembiowska, Wardas, Noworyta-Sokolowska, Kaminska, & Gorska, 2013; Gyoneva et al., 2014; Kermanian, Soleimani, Ebrahimzadeh, Haghiri, & Mehdizadeh, 2013; Loram et al., 2013; Mecha et al., 2013; Mohamed, Agha, & Nassar, 2012; Simoes et al., 2012; Yao et al., 2012). Much of this pattern is explainable by A_{2A}R location: using elegant combinations of transplantation and genetic KO, it has been shown in several models that A_{2A}Rs expressed by bone marrow-derived cells (particularly white blood cells) and by native brain cells have opposing effects on central inflammatory insults (Huang et al., 2006; Mills, Kim, Krenz, Chen, & Bynoe, 2012; Yu et al., 2004).

8. ADENOSINE-BASED MECHANISMS UNDERLYING ANTICONVULSANT DIET THERAPY

Fasting is well known to decrease the incidence of seizures. From these historical observations, a ketogenic diet (KD, a low-carbohydrate high-fat protocol) was designed in the 1920s to mimic the metabolic state of fasting and thus reduce epileptic seizures (Wilder, 1921). During the next two decades, development of AEDs gradually replaced fasting and KD as the first choice for an antiepileptic therapy. However, in recent decades, as it nears its hundredth anniversary, KD has increasingly been noted as a useful therapy for epilepsy because it has been demonstrated repeatedly that patients with medically refractory epilepsy benefit from KD therapy (Hallböök, Köhler, Rosén, & Lundgren, 2007). KD is reported to reduce seizure activity both in humans (Freeman, Kossoff, & Hartman, 2007; Henderson, Filloux, Alder, Lyon, & Caplin, 2006; Neal et al., 2008; Wiznitzer, 2008) and rodents (Bough et al., 2006; Hartman, Lyle, Rogawski, & Gasior, 2008; Rho, Kim, Robbins,

Anderson, & Schwartzkroin, 1999; Uhlemann & Neims, 1972). Despite nearly 100 years from the advent of KD therapy, the key mechanisms underlying the anticonvulsant effect of KD is still undetermined and an active research topic (Bough & Rho, 2007; Nylen, Likhodii, & Burnham, 2009).

Some of the proposed mechanisms of a KD's antiseizure effects include increased GABA production (Melø, Nehlig, & Sonnewald, 2006; Yudkoff, Daikhin, Nissim, & Lazarow, 2001) (note that these GABA mechanisms are similar to AED mechanisms and cannot explain KD's success in medically refractory seizures), inhibition of glutamate release through reducing glutamate uptake via vesicular glutamate transporters by direct action of ketone bodies (Juge et al., 2010), direct opening of metabolic ATP-sensitive potassium (K_{ATP}) channels with increasing ketone levels (Ma, Berg, & Yellen, 2007), increase of mitochondrial gene expression (Noh et al., 2004; Nylen, Velazquez, et al., 2009), and decreased IL-1 β cytokine expression (Vezzani et al., 2000). Alongside these mechanisms, growing lines of evidence support adenosine and adenosine receptors as one of the key mechanisms underlying the anticonvulsant effect of KDs (Masino & Geiger, 2008). Thus far, the most compelling evidence was reported by using ADK-transgenic (ADK-Tg) mice, heterozygous A₁R-KO mice and homozygous A₁R-KO mice. During control diet feeding, these three lines of transgenic mice demonstrated spontaneous electrographic hippocampal seizures via reduction of extracellular adenosine levels (with ADK overexpression) or lacking activation of A₁Rs (in heterozygous A₁R-KO mice, seizures events were smaller and fewer than in homozygous A₁R-KO mice, but in both models spontaneous seizures occurred significantly). KD reduced seizures in ADK-Tg mice and heterozygous A₁R-KO mice, but did not decrease spontaneous seizures in homozygous A₁R-KO mice. The selective A₁R inhibitor 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) reversed this KD effect in ADK-Tg mice and heterozygous A₁R-KO mice. In the presence of DPCPX, spontaneous electric seizures in homozygous A₁R-KO mice were unchanged. This report strongly argues that the reduction of seizures with KD is caused by the activation of A₁R (Masino, Li, et al., 2011).

More detailed mechanisms of a KD's effect through activation of A₁R were investigated by using a brain slice preparation which mimicked a KD *in vitro*. Increased ketone body levels with a KD might accelerate intra-cellular ATP production and decrease blood glucose levels (Masino & Rho, 2012), and it has been reported that a KD increases brain concentrations of ATP in rodents (DeVivo, Leckie, Ferrendelli, & McDougal, 1978; Nakazawa, Kodama, & Matsuo, 1983; Nylen, Velazquez, et al., 2009) and humans (Pan, Bebin, Chu, & Hetherington, 1999) and decreases blood glucose levels in both (Bough et al., 2006; Huttenlocher, 1976). Interestingly, reduction of blood glucose is also known to decrease the influence of seizures in both rodents (Greene, Todorova, McGowan, & Seyfried, 2001; Mantis, Centeno, Todorova, McGowan, & Seyfried, 2004) and humans (Muzykewicz et al., 2009). Based on this evidence, and using a whole-cell patch clamp technique, neuronal intracellular ATP concentration was increased and extracellular glucose concentration was reduced in order to mimic a KD. This *in vitro* condition which mimicked a KD caused hyperpolarization through autocrine activation of A₁R. Reduced glucose caused opening of pannexin-1 channels which are known to be ATP-releasing sites. Opening of pannexin channels released ATP from the intracellular to the extracellular space, and release of ATP increases extracellular adenosine levels after rapid breakdown with ectonucleotidases

(Cunha, Sebastiao, & Ribeiro, 1998; Dunwiddie, Diao, & Proctor, 1997). The resulting A₁R activation opened K_{ATP} channels and hyperpolarized the neuron (Kawamura, Ruskin, & Masino, 2010).

Hyperpolarization with this adenosinergic autocrine modulation described above causes homeostatic reduction of neuronal activity and could exert a strong antiseizure effect. Taken together, these data show that adenosine receptor-based seizure suppression might be one of the main mechanisms of KD-induced anticonvulsant effects. For example, activation of A₁Rs is known to prevent GABA_A receptor blocker-induced seizure-like activity (Thompson, Haas, & Gähwiler, 1992) because adenosine receptors decrease excitatory synaptic transmission by inhibiting voltage-gated calcium channels and hyperpolarize neurons by opening of potassium channels (Schulte & Fredholm, 2003). Therefore, by activating adenosine/A₁R-based mechanisms, KDs act on different pathways than AEDs and might explain why KDs are highly effective in treating medically refractory epilepsies.

9. CONCLUSIONS

Epilepsy has been documented as an ongoing part of human civilization from 2000 BC to present (Magiorkinis, Sidiropoulou, & Diamantis, 2010). Therefore, epilepsy has always coexisted with us, and it remains a perennial and prevalent problem. Today, AEDs and surgical therapies can successfully manage many epilepsy patients. However, 30% of patients are medically refractory, and we need strategies for reversing epilepsy and for treating the millions of people in this patient population.

Adenosine has been recognized as an anticonvulsant for several decades, and it is a perennial therapeutic target. This seemingly permanent place for adenosine receptors on the landscape of epilepsy treatments acknowledges their capacity to treat all types of seizures—metabolic, genetic, environmental, or unknown origin—and to treat seizures for which no other therapies are effective. Improved adenosine-based options may be better tolerated than some of the current AEDs, and could help some patients avoid surgery. This is particularly true if adenosine can exert a combination of receptor-based antiseizure effects and receptor-independent antiepileptic effects. For example, local adenosine augmentation therapies and adenosine-based anticonvulsant diets might be new strategies for medically refractory epilepsy.

One of the issues of present AEDs is that AEDs often control seizures but may exacerbate psychiatric comorbidities (Devinsky, 2003). The potential of a KD (perhaps through adenosine-based mechanisms) is that it can improve not only epilepsy as well as various types of neurological disorders (Masino, Kawamura, Wasser, Pomeroy, & Ruskin, 2009), including autism which is often comorbidity with epilepsy (Evangelidou et al., 2003; Ruskin et al., 2013). Furthermore adenosine is reported to improve autism spectrum disorders (Masino, Kawamura, Cote, Williams, & Ruskin, 2013; Masino, Kawamura, et al., 2011, Masino, Li, et al., 2011). Also, local adenosine augmentation therapies ameliorate the cognitive symptoms and psychomotor-related symptoms in schizophrenia (Shen et al., 2012). These adenosine-based strategies might shed light on desired therapies that reduce seizures and improve psychiatric comorbidity simultaneously.

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