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Comorbidities in Neurology: Is Adenosine the Common Link?

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Abstract

Comorbidities in Neurology represent a major conceptual and therapeutic challenge. For example, temporal lobe epilepsy (TLE) is a syndrome comprised of epileptic seizures and comorbid symptoms including memory and psychiatric impairment, depression, and sleep dysfunction. Similarly, Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS) are accompanied by various degrees of memory dysfunction. Patients with AD have an increased likelihood for seizures, whereas all four conditions share certain aspects of psychosis, depression, and sleep dysfunction. This remarkable overlap suggests common pathophysiological mechanisms, which include synaptic dysfunction and synaptotoxicity, as well as glial activation and astrogliosis. Astrogliosis is linked to synapse function via the tripartite synapse, but astrocytes also control the availability of gliotransmitters and adenosine. Here we will specifically focus on the 'adenosine hypothesis of comorbidities' implying that astrocyte activation, via overexpression of adenosine kinase (ADK), induces a deficiency in the homeostatic tone of adenosine. We present evidence from patient-derived samples showing astrogliosis and overexpression of ADK as common pathological hallmark of epilepsy, AD, PD, and ALS. We discuss a transgenic 'comorbidity model', in which brain-wide overexpression of ADK and resulting adenosine deficiency produces a comorbid spectrum of seizures, altered dopaminergic function, attentional impairment, and deficits in cognitive domains and sleep regulation. We conclude that dysfunction of adenosine signaling is common in neurological conditions, that adenosine dysfunction can explain comorbid phenotypes, and that therapeutic adenosine augmentation might be effective for the treatment of comorbid symptoms in multiple neurological conditions.

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Author contributions

D.B. and E.A. co-wrote the manuscript. E.A. contributed to the histopathological data.

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Keywords

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1. Introduction

Temporal lobe epilepsy (TLE), Alzheimer's disease (AD), Parkinson's disease (PD), and Amyotrophic Lateral Sclerosis (ALS) share a wide range of comorbid symptoms, which involve increased neuronal excitability and a wide range of cognitive and psychiatric symptoms. This remarkable overlap suggests the existence of common pathogenic mechanisms, which include synaptic dysfunction and synaptotoxicity (Jensen, 2011; Noebels, 2011; Swann and Rho, 2014; Zhou and Roper, 2012), inflammatory processes (Kobow et al., 2012; Miller and Spencer, 2014; Perry, 2012), and glial activation (Ravizza et al., 2013; Stanimirovic and Friedman, 2012; Suvisaari and Mantere, 2013). Although several mechanisms might contribute to the development of comorbid symptomatology, we will here address and focus on the 'adenosine hypothesis of comorbidities', which suggests that adenosine deficiency *per se* can be a sufficient cause for the generation of a wide spectrum of symptoms shared among seemingly distinct neurological conditions. The purine ribonucleoside adenosine is an endogenous modulator of brain activity (Boison, 2007a; Dunwiddie, 1980; Etherington and Frenguelli, 2004; Fredholm et al., 2005b; Ribeiro and Sebastiao, 2010) that acts as endogenous ligand of four types of G protein coupled adenosine receptors (A_1 , A_{2A} , A_{2B} , and A_3) (Chen et al., 2013). As component of ATP, adenosine has maintained an evolutionary ancient role to adapt metabolic activity to available energy supplies (Newby, 1984). Whereas ATP degradation is a major source for adenosine, physiological adenosine levels are kept low by efficient metabolic clearance. Because physiological adenosine levels are about 100,000 times lower than ATP levels, fluctuations in adenosine tone will not affect the availability of ATP, which is primarily derived from the *de novo* biosynthetic pathway leading to the formation of IMP (Boison, 2013; Fredholm et al., 2005a; Fredholm et al., 2005b; Fredholm et al., 1984).

In the brain adenosine fulfills two very different, seemingly opposing roles. As a homeostatic regulator and retaliatory metabolite adenosine sets the inhibitory and general neuroprotective 'tone' via activation of widespread inhibitory A_1 Rs (Meghji and Newby, 1990). On the synaptic level however, adenosine facilitates synaptic function via activation of stimulatory A_{2A} Rs (Cunha, 2001, 2008). Whereas the tonic inhibitory pool of adenosine is thought to be largely under the control of astrocytes, the stimulatory pool of adenosine acting at the synapse level is likely derived from neurons to allow a highly localized modulation of individual synapses (Cunha, 2001, 2008; Lovatt et al., 2012; Meghji and Newby, 1990). These two parallel, but different functions of adenosine have likely evolved to increase salience of synaptic transmission in a tonically inhibited network, a mechanistic strategy to enhance the signal to noise ratio (Cunha, 2001). The ability of neuron-derived adenosine to facilitate synaptic function via A_{2A} R activation contributes to synaptotoxicity and is a rational explanation for the neuroprotective effects of caffeine and A_{2A} R antagonists (Cunha, 2005).

In addition to the adenosine receptor dependent effects described above, adenosine provides biochemical feedback inhibition of DNA methylation and thereby assumes a role as modulator of epigenetic functions (Williams-Karnesky et al., 2013). Through a combination of adenosine receptor dependent and independent functions, adenosine assumes the role of homeostatic network regulator capable to affect several different signaling pathways and biochemical enzyme reactions in a synergistic manner (Arch and Newsholme, 1978; Boison et al., 2013; Cunha, 2001; Newby, 1984). Adenosine homeostasis in the brain is largely under the control of metabolic clearance through adenosine kinase (ADK) expression in astrocytes (Boison, 2013). Here we propose that maladaptive changes in adenosine homeostasis occur during the pathogenesis of temporal lobe epilepsy (TLE) and likewise in neurodegenerative conditions such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS).

Synaptotoxicity, immune activation, inflammatory processes, and glial activation play a major role in the pathogenesis of all four conditions (Aronica et al., 2012; Jensen et al., 2013; Lucin and Wyss-Coray, 2009), leading ultimately to astrogliosis, overexpression of ADK, and a deficiency in the availability of adenosine – a sequence, which has been identified as characteristic pathological hallmark of human TLE (Aronica et al., 2013). Through the tripartite synapse astrocytes interact with neurons (Araque et al., 1999; Halassa and Haydon, 2010) and adenosine itself affects synaptic function (Duarte et al., 2012; Matos et al., 2012a; Silva et al., 2007) with a gain of function of synaptic A_2A Rs contributing to synaptotoxicity and adaptive processes of astrocytes affecting glutamate homeostasis and thereby synaptic function (Matos et al., 2012a; Matos et al., 2012b; Matos et al., 2015). Thus, a self-reinforcing triad of astrocyte activation, adenosine dysfunction, and synaptotoxicity may contribute to the development of comorbid symptomatology. Here we will focus here on astrogliosis and adenosine deficiency as common pathological hallmarks in Neurology.

Because data on cause-effect relationships of adenosine dysfunction and disease pathogenesis are sparse we will present largely correlative and conceptual advances in support of our hypothesis. The development of an adenosine deficient 'comorbidity model' (see below) however suggests that adenosine deficiency *per se* might be sufficient to trigger a wide range of comorbid symptoms. The apparent common overlap of maladaptive changes in adenosine homeostasis suggests common pathogenic mechanisms, which might be tied to common triggers of disease initiation. For example, the ADK hypothesis of epileptogenesis suggests that a precipitating injury triggers an acute surge in adenosine, which facilitates inflammatory processes and glial activation, resulting in astrogliosis, overexpression of ADK and adenosine deficiency, which in turn drives hypermethylation of DNA (Boison, 2008; Li et al., 2008; Williams-Karnesky et al., 2013). Similar mechanisms might also play a role in neurodegenerative conditions. If adenosine deficiency is a common pathological hallmark in a wider range of neurological conditions, then therapeutic adenosine augmentation might have the potential to treat comorbid conditions, such as those discussed here, in a holistic manner.

2. Glial activation – a common histopathological finding in Neurology

Clinical neurological findings show a remarkable overlap in symptom presentation across seemingly unrelated neurological conditions. In the search for common substrates and mechanisms for comorbidities in Neurology, we will focus primarily on histopathological findings and astroglial pathology. Those descriptive data sets conceptually support our hypothesis that certain histopathological changes (e.g. glial activation) might provide a substrate for comorbid symptom genesis. We will first discuss clinical and histopathological data in an attempt to find common pathological substrates for comorbid symptoms found in epilepsy, AD, PD, and ALS, and then discuss the role of astrogliosis and adenosine dysregulation in more detail.

In the adult brain adenosine levels are largely under the control of metabolic clearance through astrocytes (Boison et al., 2010) and the astrocyte-based enzyme ADK, which in conjunction with equilibrative nucleoside transporters provides an efficient metabolic reuptake system for adenosine (Boison, 2013; Studer et al., 2006). Genetic disruption of the *Adk* gene in glial, but not in neuronal cells, induces the release of adenosine (Fedele et al., 2004). Conversely, the genetic overexpression of *Adk* in astrocytes is sufficient to induce epileptic seizures by reducing the tissue tone of homeostatic adenosine, which results in reduced activation of the inhibitory A₁R (Li et al., 2007a; Shen et al., 2014). Reduced A₁R activation promotes excitatory neurotransmitter release and decreases the postsynaptic membrane potential (Fredholm, 1995, 2010). Indeed, deficiency of A₁Rs increases neuronal excitability and can be a direct cause for electrographic seizure activity (Boison, 2007b; Li et al., 2007a; Masino et al., 2011). If intracellular ADK expression levels are low, astrocytes can release adenosine directly through equilibrative nucleoside transporters; conversely, overexpression of ADK in conjunction with astrogliosis causes adenosine deficiency and spontaneous recurrent seizures (Aronica et al., 2011; Li et al., 2012; Li et al., 2008; Shen et al., 2014). New data sets from our laboratory show that astrogliosis (Fig. 1) and overexpression of ADK (Fig. 2–5) are found in human brain specimen from patients with epilepsy, AD, PD, and ALS. Although the findings presented in this section are correlative and descriptive, they suggest the existence of common pathophysiological mechanisms.

2.1. Temporal lobe epilepsy

Several clinical studies indicate that patients with epilepsy have a high prevalence of both psychiatric and somatic comorbidities, which may precede, co-occur with, or follow the diagnosis of epilepsy [for reviews see (Gaitatzis et al., 2004; Gaitatzis et al., 2012; LaFrance et al., 2008)]. Psychiatric disorders, including cognitive changes, attention deficits, psychosis, and personality changes, as well as depression, anxiety, and migraine occur more frequently in people with epilepsy than in the general population, particularly in patients with refractory epilepsy. Importantly, neurodegenerative conditions such as dementias and Alzheimer' disease (prevalence ratio 6.3 and 8, respectively) and Parkinson' disease (prevalence ratio, 3.2) appear more frequently in people with epilepsy (Gaitatzis et al., 2004; Gaitatzis et al., 2012). A recent study supports a structural basis for psychiatric comorbidities in patients with TLE, pointing to synaptic dysfunction, as well as to aberrant plasticity within hippocampal networks (Kandratavicius et al., 2012). Several studies

revealed an association of dentate gyrus (DG) pathological changes with long-term seizure histories and cognitive dysfunction suggesting a compromised regenerative capacity of the DG in a subpopulation of TLE patients (Blumcke et al., 2009; Coras et al., 2010). Further evidence suggests similar mechanisms underlying cellular aging and neurodegeneration are also widespread in other forms of epilepsy such as in developmental lesions associated with chronic intractable epilepsy (Iyer et al., 2014; Prabowo et al., 2014).

Hippocampal sclerosis (HS) is the most common neuropathological finding in patients undergoing surgery for intractable TLE. Histopathologically, HS is defined by specific features, including a characteristic pattern of neuronal cell loss associated with astrogliosis (Fig. 1 A–B). The neuronal cell loss involves mainly the CA1, CA4, and CA3 subfields, whereas the CA2 subfield is often spared. As described several years ago, another characteristic feature of HS is represented by the sharp interface of neuronal loss between CA1 and the subiculum, which is preserved (Thom et al., 2009); Fig. 1 A). The criteria for the diagnosis of HS are summarized in the International League Against Epilepsy (ILAE) report, which classifies HS into 3 subtypes, based on the histological patterns of subfield neuronal loss and gliosis (Blumcke et al., 2013). Other alterations in HS include dispersion of the granule cell layer of the dentate gyrus, alterations of interneuronal populations and mossy fiber sprouting (Thom, 2014). These features may represent a useful diagnostic to distinguish HS associated with chronic epilepsy from other causes of HS [e.g. HS with dementia/neurodegeneration; (Bandopadhyay et al., 2014)]. Because the reorganization of excitatory and inhibitory networks in the dentate gyrus appears to be a characteristic of HS associated with chronic epilepsy, subtle alterations of the dentate gyrus may also occur in HS with dementia (Bandopadhyay et al., 2014).

Astrogliosis is a pathological hallmark of various types of medically refractory focal epilepsy, including TLE associated with HS (Sofroniew and Vinters, 2010; Thom et al., 2009). Activation of astrocytes is also observed in focal malformations of cortical development, such as focal cortical dysplasia (FCD) and cortical tubers in patients with tuberous sclerosis complex (TSC), which are among the most common causes of pharmacologically intractable epilepsies in children and young adults [for reviews see (Aronica and Crino, 2014; Aronica et al., 2012)]. The presence of astrogliosis in epilepsy-associated pathologies has stimulated extensive research focused on the role of reactive astrocytes in the pathophysiological processes that underlie the development of epilepsy. In both experimental and human epileptic tissues astrocytes undergo complex changes in their physiological properties (including dysregulation of astroglial Kir channels and gap junction proteins), which can alter glio-neuronal communication, contributing to seizure precipitation and recurrence and suggesting an astrocytic basis for epilepsy (Seifert et al., 2010; Seifert et al., 2006; Seifert and Steinhauser, 2013; Steinhauser et al., 2012). Astrocytes initiate, regulate and amplify immune-mediated mechanisms involved in different neurological disorders, including epilepsy (Aronica et al., 2012; Devinsky et al., 2013; Farina et al., 2007; Vezzani et al., 2008). Astrocytes also release the gliotransmitters glutamate, D-serine, and ATP, which all influence neuronal networks, and dysregulation of gliotransmitter release has been implicated in epilepsy pathophysiology (Halassa et al., 2007; Vezzani et al., 2011; Zorec et al., 2012). In addition, astrocytes can influence network excitability in epilepsy through dysfunctional adenosine homeostasis, resulting from changes in ADK expression

levels (Aronica et al., 2013; Boison, 2008). Overexpression of ADK has been reported in specimens of patients undergoing surgery for pharmacologically refractory TLE with HS [(Aronica et al., 2013; Aronica et al., 2011; Masino et al., 2011); Fig. 2 B–C]. Higher expression of ADK has been detected in the peritumoral infiltrated tissue of patients with epileptogenic astroglial brain tumors (de Groot et al., 2012). Increased ADK expression has likewise been observed in reactive astrocytes and balloon/giant cells of FCD and TSC specimens (Fig. 2 F–G). Increased ADK in epilepsy is expected to lower the tissue tone of adenosine and thereby to increase neuronal excitability and to precipitate seizures (Li et al., 2007a; Li et al., 2012; Li et al., 2008).

2.2. Alzheimer's disease

Both psychiatric and somatic comorbidities have been reported in AD and may influence AD progression, accelerating cognitive decline (Amore et al., 2007; Cechetto et al., 2008; Craft, 2009; Perez-Madrinan et al., 2004; Schmidt et al., 2011). Neuropsychiatric symptoms, (including depression, apathy, agitation, or psychosis) are a key disabling component of AD and understanding their neurobiological substrates represents a crucial challenge for AD research (Geda et al., 2013). Recently, there has been growing interest in the comorbidity between AD and epilepsy (Larner, 2010). Unprovoked seizures, such as complex partial seizures, occur in AD more frequently than in the general population and it is estimated that at least 10% to 20% of all AD patients have at least one unprovoked seizure (Mendez and Lim, 2003; Rao et al., 2009; Scarmeas et al., 2009). Seizures usually are observed in later stages of the disease and may be unrecorded or interpreted as confusion or delirium [for review see (Larner, 2010, 2011)]. Early-onset AD increases the relative risk of seizure development up to 80-fold (Amatniek et al., 2006; Mendez and Lim, 2003; Rao et al., 2009; Scarmeas et al., 2009). An attractive hypothesis is that the pathogenic mechanisms underlying seizure development and cognitive impairment may overlap, suggesting a bidirectional link and possible common disease mechanisms, which include remodeling of GABAergic circuits, aberrant integration and sprouting of newborn neurons, and the ability of beta-amyloid to deregulate synaptic plasticity (Palop and Mucke, 2009).

The neuropathological hallmarks of the AD brain are represented by parenchymal deposits of A β peptide (extracellular accumulation as diffuse or focal deposits) and intracellular accumulation of tau protein (as neurofibrillary tangles, neuropil threads and degenerating neurites in the corona of neuritic plaques/senile plaques), associated with progressive synaptic and neuronal loss, as well as reactive processes involving activation of astrocytes and microglial cells [(Duyckaerts, 2011); Fig. 1 C–D]. The combination, density and distribution of A β deposits, neurofibrillary tangles, and neuritic plaques allows the neuropathological diagnosis. Recently, the National Institute on Aging-Alzheimer's Association has published a new guideline for the neuropathologic assessment of Alzheimer's disease, which recognizes the existence of a pre-clinical stage of AD and recommends the evaluation of the severity of A β deposits in addition to neurofibrillary degeneration and neuritic plaque formation according to an "ABC" score (Hyman et al., 2012; Kovacs and Gelpi, 2012).

The contribution of glial activation in the onset and progress of neurodegenerative processes in AD is becoming increasingly recognized (Agostinho et al., 2010; Sofroniew and Vinters, 2010). Activated microglia and astrocytes release pro-inflammatory cytokines, chemokines, and reactive oxygen and nitrogen species, which all can disrupt nerve terminal activity and cause synaptotoxicity, which correlates with memory decline (Agostinho et al., 2010). In a seminal review article on this topic it was suggested that these phenomena precede the neuronal death associated with late stages of AD; thus, therapeutic strategies designed to control the activation of microglia and astrocytes and thereby curb the excessive production of pro-inflammatory and pro-oxidant factors hold promise for the control of neurodegeneration in dementia (Agostinho et al., 2010). Reactive astrocytes are often associated with amyloid plaques (Fig. 1 C–D) and astrogliosis increases in parallel with the progression of AD pathology (Simpson et al., 2010; Sofroniew and Vinters, 2010). Accordingly, A β plays a role in activating astrocytes, but particularly in the context of the more complex environment of the neuritic plaque (Nagele et al., 2004; Simpson et al., 2010). Particular attention has focused on the ability of reactive astrocytes to degrade extracellular deposits of A β (Pihlaja et al., 2008; Wyss-Coray et al., 2003), as well as on their involvement in the mechanisms of immune regulation in AD (Cornejo and Hetz, 2013; Fernandez et al., 2013; Mrak and Griffin, 2005; Salmina, 2009). Reactive astrocytes may increase neuronal vulnerability to excitotoxicity and oxidative stress, through different mechanisms, including uptake of glucose and release of lactate, as well as by the uptake of glutamate and the release of glutamine (Fuller et al., 2009; Steele and Robinson, 2012). Recent studies ascribe a specific role of astrocytic A_{2A}Rs in the ability of A β -induced impairment of glutamate uptake, which may provide an astrocyte-dependent mechanistic basis for glutamatergic synaptic dysfunction and synaptotoxicity in AD (Matos et al., 2012a). Importantly, astrocytic A_{2A}Rs were found to be upregulated in human AD (Orr et al., 2015). Since the genetic deletion of A_{2A}Rs in astrocytes and neural progenitor cells during brain development enhanced memory (Orr et al., 2015) the authors of this study concluded that AD-linked increases in astrocytic A_{2A} receptor levels contribute to memory loss. These findings contrast with a recent study, in which the selective deletion of A_{2A}Rs in postnatal astrocytes, triggered decreased working memory through a mechanism involving the disruption of glutamate homeostasis via aberrant GLT-I activity, increased presynaptic glutamate release, NMDA-R 2B subunit upregulation, and increased internalization of AMPA-R (Matos et al., 2015). Accordingly, selective GLT-I inhibition or blockade of GluR1/2 endocytosis prevented impaired working memory in the mutant animals (Matos et al., 2015). These findings demonstrate that astroglial A_{2A}Rs critically influence synaptic function and cognitive performance. Focal dysregulation of ADK expression/function in reactive astrocytes may represent an additional mechanism potentially contributing to the pathogenesis of the disease. Interestingly, we observed an increased expression of ADK in astrocytes surrounding amyloid deposits and tangle-containing neurons in patients with AD (Fig. 3 A–D), including also patients with Down syndrome (not shown). Increased ADK is expected to generate a local deficiency in homeostatic adenosine, an endogenous neuroprotectant of the brain (Cunha, 2005; Ribeiro, 2005; Stone et al., 2009), and thereby increase the likelihood for neurodegeneration via decreased activation of neuronal A₁Rs and astroglial A_{2A}Rs.

2.3. Parkinson's disease

Apart from the impairment of motor functions, the quality of life in PD is further complicated by higher rates of cognitive and psychiatric comorbidities, in particular depression (Dobkin et al., 2011; Marsh, 2013; Menza et al., 1993; Reijnders et al., 2008) which have been related to underlying neuropathological lesions (Paulus and Jellinger, 1991), however the underlying mechanisms of comorbidities in PD remain still unknown (Marsh, 2013). Association with epilepsy has been evaluated only in a minority of population studies, although cognitive impairment and depression are also common comorbid disorders in TLE (Gaitatzis et al., 2012; Szot, 2012).

The pathological hallmarks of the PD brain are represented by α -synuclein immunoreactive deposits in both neurons (intraneuronal cytoplasmic inclusion; Lewy body, LB; Fig. 1E), as well as in dystrophic neurites, associated with progressive neuronal loss in several subcortical nuclei [i.e. substantia nigra pars compacta, locus coeruleus, nucleus basalis of Meynert; (Duyckaerts, 2011)]. The neuropathological changes may be extended supratentorially to cortical regions and α -synuclein pathology often involves the peripheral autonomic system. Recent studies suggest that neuron to neuron or a trans-synaptic spread of α -synuclein pathology underlies the disease progression (Desplats et al., 2009) and may represent a unifying pathogenetic mechanism in different neurodegenerative disorders (Hallbeck et al., 2013; Jellinger, 2010; Polymenidou and Cleveland, 2012).

The neuronal cell loss is accompanied by mild to moderate astrogliosis (Fig. 1F) and microglia upregulation (Duyckaerts, 2011; Forno et al., 1992). The neuronal cell loss in PD is accompanied by astrogliosis, and the extent of reactivity correlates with progression of neurodegeneration and disease stage in Parkinsonian syndromes (Duyckaerts, 2011; Song et al., 2009). Several studies point to the role of reactive astrocytes in mediating the effects of both genetic and environmental factors contributing to dopaminergic neurodegeneration, although neuroprotective activities have been also reported (L'Episcopo et al., 2010; McGeer and McGeer, 2008; Nam et al., 2012; Rappold and Tieu, 2010; Vila et al., 2001). Astrocytes are also a target of PD pathology, since subpopulations of astrocytes accumulate abnormal proteins such as α -synuclein, parkin, and phospho-tau (Song et al., 2009). Early dysfunction of astrocytes, associated with α -synuclein accumulation, might contribute to the recruitment of microglia and amplification of the inflammatory response, leading to neurodegeneration in restricted brain regions (Halliday and Stevens, 2011). Several studies highlight the key role of astrocytes in inflammatory and oxidative stress mechanisms, which contribute to disease progression [for review see (Niranjan, 2014)]. Moreover, increased expression of ADK is observed in reactive astrocytes in both substantia nigra and neocortex of PD patients (Fig. 4 C–F). Increased ADK and resulting adenosine deficiency is expected to promote neurodegeneration and to affect motor function through altered adenosine/dopamine receptor interactions (Franco et al., 2007; Fuxe et al., 2007a; Fuxe et al., 2007b).

2.4. Amyotrophic lateral sclerosis

Dementia is relatively frequent in ALS and may be a consequence of either frontotemporal lobar degeneration or result from co-existing Alzheimer's disease (Rusina et al., 2010). Frontotemporal dementia frequently co-occurs with ALS and common cellular mechanisms

between ALS and frontotemporal dementia, as well as with other neurodegenerative diseases have been suggested (Robberecht and Philips, 2013). Similarly to other neurodegenerative diseases, psychiatric comorbidities, including depressive symptoms with a prevalence of mild and severe depression of 29% and 6%, respectively, have been reported in patients with ALS (Atassi et al., 2011; Ferentinos et al., 2011; Woolley et al., 2011). A recent study reveals that the prevalence of dementia, parkinsonism, and depressive symptoms was significantly higher in the ALS cohort compared to the general population (Korner et al., 2013). In the same cohort the rate of patients with epilepsy was slightly higher in patients with ALS compared with the general population (Korner et al., 2013).

Histopathologically, amyotrophic lateral sclerosis (ALS) is characterized by degeneration of both upper and lower motoneurons associated with prominent astrogliosis (Fig. 1G–H) and microglia activation (Duyckaerts, 2011). Atrophy of the anterior horn and pallor of the white matter of the lateral and anterior corticospinal tracts is often detected and, particularly in patients with long-term survival, a more wide spread pathology with extramotor involvement can be observed. The presence of a large variety of intraneuronal inclusions is a key to diagnosis, representing the hallmark of ALS. Recently TDP-43 has been identified as major ubiquitinated protein present in the large majority of ALS cases (Duyckaerts, 2011).

Experimental and clinical observations have suggested a role for non-neuronal cells, in particular astrocytes, in ALS pathogenesis (Hall et al., 1998; Lasiene and Yamanaka, 2011; Levine et al., 1999; Neusch et al., 2007). Mechanisms contributing to the loss of astrocyte-mediated neuroprotective functions, as well as to astrocyte-mediated neurotoxicity have been reported in ALS (Lepore et al., 2008; Martorana et al., 2012a). Accordingly, a subpopulation of spinal cord astrocytes has been shown to degenerate in ALS and impaired astrocytic functions, such as clearance of extracellular glutamate have been described (Lasiene and Yamanaka, 2011; Martorana et al., 2012b; Neusch et al., 2007). Moreover, accumulating evidence supports the involvement of astrocyte-mediated inflammatory responses in ALS pathogenesis (Lasiene and Yamanaka, 2011; McGeer and McGeer, 2002; Rizzo et al., 2014; Sta et al., 2011). Similarly to the above discussed pathologies, also in ALS we observed an upregulation of ADK expression in reactive astrocytes, compared to controls (Fig. 5 A–D). As discussed in the sections above, increased ADK and decreased tissue adenosine would promote neurodegenerative processes.

3. Epigenetic changes in epilepsy and neurodegenerative diseases

Increasing evidence suggests that epigenetic mechanisms contribute to the pathogenesis of epilepsy and neurodegenerative conditions (Kobow and Blumcke, 2011; Lubin, 2012; Millan, 2012; Qureshi and Mehler, 2010; Restrepo et al., 2011; Williams-Karnesky et al., 2013). Epigenetic changes do not affect the DNA sequence itself but affect DNA methylation or histone tail modifications, resulting in long-lasting alterations in chromatin structure and gene expression. Epigenetic mechanisms play key roles in fundamental regulatory processes in brain development, synaptic plasticity, and memory, but also play a role in neurologic disorders such as epilepsy and neurodegenerative disorders. The methylation hypothesis of epileptogenesis suggests that seizures by themselves can induce epigenetic chromatin modifications, thereby aggravating the epileptogenic condition

(Kobow and Blumcke, 2011). Importantly, DNA within epileptogenic brain areas is hypermethylated, both in human specimen from resective surgeries as well as in rodent models of TLE (Kobow et al., 2009; Kobow et al., 2013; Williams-Karnesky et al., 2013; Zhu et al., 2012). Although hypermethylation of DNA in the brain has been associated with epilepsy, there has been a lack of direct evidence demonstrating a causative role for increased DNA methylation in epilepsy progression. In a recent study we therefore explored the role of adenosine in reversing epigenetic changes associated with epilepsy (Williams-Karnesky et al., 2013). We found that induction of epilepsy in a rat model led to increased hippocampal DNA methylation that was associated with increased expression of ADK and increased metabolic clearance of adenosine, which is a negative feedback inhibitor of transmethylation reactions (Boison et al., 2002b; Williams-Karnesky et al., 2013). Importantly, the transient focal therapeutic delivery of adenosine to the epileptogenic hippocampus corrected epilepsy-associated changes in DNA methylation and prevented disease progression. These findings indicate that changes in DNA methylation are tightly linked to the status of adenosine homeostasis and constitute a key determinant of the progression of epilepsy; consequently, treatments that augment adenosine may reverse DNA hypermethylation and break the cycle of increasing seizure severity (Williams-Karnesky et al., 2013). In conclusion, overexpression of ADK in epilepsy might drive DNA methylation by providing enhanced metabolic clearance of the transmethylation inhibitor adenosine, thereby inducing a status of hypermethylated DNA in the epileptic brain.

As in epilepsy, hypermethylation of DNA might also play a role in the pathophysiology of neurodegenerative diseases. In a recent study of AD patients, 5-methylcytidine (5mC) as well as 5-hydroxymethylcytidine (5hmC) immunoreactivity was significantly increased in middle frontal gyrus and middle temporal gyrus compared with age-matched controls (Coppieters et al., 2014). Global levels of 5mC and 5hmC positively correlated with each other and with markers of AD including amyloid beta, tau, and ubiquitin loads. Importantly, these findings demonstrate global hypermethylation in the AD brain (Coppieters et al., 2014). DNA methylation profiles of human hippocampus from AD patients, revealed promoter hypermethylation of the dual-specificity phosphatase 22 (DUSP22) gene, which is a likely candidate gene for the pathogenesis of AD since it determines tau phosphorylation status and CREB signaling (Sanchez-Mut et al., 2014). Distinct changes in DNA methylation patterns have also been observed in patients with PD and ALS (Martin and Wong, 2013; Masliah et al., 2013) and increased global DNA methylation has been suggested as a biomarker for ALS (Tremolizzo et al., 2014). Together, these findings suggest that epilepsy and neurodegenerative conditions may share global changes in the methylome as a consequence of altered adenosine homeostasis.

4. Evidence from adenosine-deficient comorbidity model

Although the examples from the preceding sections are based on correlative and conceptual reasoning, they suggest that a deficiency in adenosine – as might be expected as a consequence of astroglial activation and overexpression of ADK – can mechanistically explain the generation of a wide spectrum of symptoms commonly seen as comorbidities shared across several neurological conditions. To experimentally test the hypothesis that adenosine deficiency may cause a spectrum of comorbid conditions we generated a

‘comorbidity model’ in mice by ubiquitous overexpression of the cytoplasmic isoform of ADK using a human ubiquitin promoter driven transgene of mouse *Adk* cDNA (Fedele et al., 2005). As a result, these Adk-tg mice were characterized by constitutive overexpression of transgenic ADK throughout the brain, with particularly high levels in hippocampal pyramidal neurons. Expression of the ADK transgene resulted in a >2-fold increase in global brain ADK activity and lack of modification of the EPSC response following the pharmacological blockade of A₁Rs in mossy fiber CA3 synapses demonstrating a reduction in hippocampal adenosine levels (Fedele et al., 2005). Overexpression of ADK resulted in a 50% reduction of tissue levels of adenosine (Shen et al., 2011). With a set of biosensor and electrophysiological studies we demonstrated that transgenic manipulation of ADK (*i*) critically influences the basal tone of adenosine, (*ii*) determines the degree of tonic adenosine dependent synaptic inhibition, which correlates with differential plasticity at hippocampal synapses with low release probability, (*iii*) modulates age-dependent effects of BDNF on hippocampal synaptic transmission, an action dependent upon co-activation of adenosine A_{2A} receptors, and (*iv*) influences GABA_A receptor-mediated currents in CA3 pyramidal neurons (Diógenes et al., 2014). These examples demonstrate that disruption of adenosine homeostasis affects several different downstream signaling pathways of adenosine simultaneously.

Phenotypically, Adk-tg mice are characterized by (*i*) spontaneous recurrent electrographic hippocampal seizures at a rate of around 4 seizures per hour with each seizure lasting around 20 seconds (Li et al., 2007a; Li et al., 2008); (*ii*) severe learning deficits in the Morris water maze task and in Pavlovian conditioning (Yee et al., 2007) and attentional impairment as demonstrated in the latent inhibition paradigm (Shen et al., 2012); (*iii*) altered locomotor control as evidenced by reduced A_{2A}R activation and lack of responsiveness to amphetamine (Shen et al., 2012); (*iv*) altered sleep physiology as shown by a remarkable reduction of EEG power in low frequencies in all vigilance states, by increased wake time and a 20% reduction in rapid eye movement (REM) sleep time, and by attenuation of the physiological effects of sleep deprivation.

Together, these findings represent the first – and to the best of our knowledge – only direct causal data sets demonstrating that overexpression of ADK in the brain and resulting adenosine deficiency are sufficient to precipitate a wide range of symptoms commonly found in the comorbid conditions discussed in this review. More specific work will be needed to address spatial, temporal, and cell-type specific requirements of ADK to modulate the symptomatology discussed here. New animal models and viral expression vectors have already been created, which will be used to address those questions in future studies.

5. Adenosine-dependent mechanisms and therapeutic applications

Clinical as well as experimental data suggest that a triad of synaptotoxicity, astrogliosis, and overexpression of ADK, resulting in a deficiency of homeostatic adenosine can directly cause a wide spectrum of comorbid symptoms shared across several neurological conditions (Figure 6). If adenosine deficiency is sufficient to precipitate comorbidities, then therapeutic adenosine augmentation should ameliorate those symptoms. New research data indeed suggest that therapeutic adenosine augmentation may provide benefit for a wide range of

conditions in addition to seizure control. In the following we will provide conceptual advances that might provide reasonable mechanistic explanations how adenosine deficiency might functionally be linked to the development of distinct neurological symptoms. In support of our hypotheses we provide direct experimental evidence for the therapeutic benefits of adenosine augmentation therapies.

5.1. Seizures

Adenosine is an endogenous anticonvulsant of the brain and responsible for seizure arrest and postictal refractoriness (Boison, 2012b; Dragunow, 1991; Dunwiddie, 1980; During and Spencer, 1992). The anticonvulsant effects of adenosine are mediated largely via activation of pre- and postsynaptic adenosine A₁ receptors, which mediate presynaptic inhibition and stabilize the postsynaptic membrane potential, respectively (Boison et al., 2010; Chen et al., 2013; Fredholm et al., 2005b; Fredholm and Dunwiddie, 1988). Consequently, therapeutic adenosine augmentation is a powerful therapeutic strategy to suppress epileptic seizures, even those that are refractory to conventional antiepileptic drugs (Boison, 2012a; Gouder et al., 2003; Huber et al., 2001). Several lines of evidence suggest that endogenous adenosine-based control mechanisms fail in chronic epilepsy. Histopathological and biochemical analyses from specimen surgically resected from patients with intractable epilepsy show decreased expression levels of A₁ receptors (Glass et al., 1996) and increased expression levels of ADK (Aronica et al., 2011; Masino et al., 2011). Likewise in rodent models of temporal lobe epilepsy reduced expression of A₁Rs and a general failure of adenosine-dependent endogenous anticonvulsant mechanisms has been demonstrated (Rebola et al., 2003). In line with these findings, overexpression of astroglial ADK and resulting adenosine deficiency has consistently been associated with the expression of spontaneous recurrent seizures in a wide range of clinically relevant rodent models of epilepsy (Aronica et al., 2011; Gouder et al., 2004; Li et al., 2012; Li et al., 2008). Importantly, overexpression of ADK during epileptogenesis correlated both spatially, as well as temporally with the onset of spontaneous recurrent seizures (Li et al., 2007a; Li et al., 2012), whereas spread and generalization of seizures from the ADK-overexpressing ictogenic brain area was prevented by endogenous A₁R dependent control mechanisms (Fedele et al., 2006; Li et al., 2012). The most direct evidence that overexpression of ADK can trigger recurrent seizures was achieved by local overexpression of the enzyme via an adeno associated virus (AAV) based vector engineered to selectively overexpress ADK in astrocytes. AAV-based overexpression of ADK in astrocytes of hippocampus or cortex triggered recurrent seizures at a rate of 1 to 4 electrographic seizures per hour (Shen et al., 2014; Theofilas et al., 2011). These findings demonstrate that the failure of endogenous adenosine-based control mechanisms can be a direct cause for epileptic seizures.

Therapeutic adenosine augmentation (as opposed to receptor agonists that still suffer from major systemic side effects) is now a well validated strategy for the suppression of epileptic seizures in a wide range of rodent models of epilepsy (Boison, 2012a). Focal implant- or cell-based adenosine augmentation prevented seizures in two species (mice and rats), and three different models of TLE (mouse intrahippocampal kainic acid; rat systemic kainic acid; rat hippocampal kindling) (Boison et al., 2002a; Boison et al., 1999; Gouder et al., 2003; Gouder et al., 2004; Güttinger et al., 2005a; Güttinger et al., 2005b; Huber et al.,

2001; Li et al., 2009; Li et al., 2008; Li et al., 2007b; Ren et al., 2007; Szybala et al., 2009; Theofilas et al., 2011; Williams-Karnesky et al., 2013; Wilz et al., 2008). Importantly, therapeutic adenosine augmentation suppressed carbamazepine-resistant seizures in the intrahippocampal kainic acid model of TLE (Gouder et al., 2003; Gouder et al., 2004). To date, the therapeutic efficacy of focal adenosine augmentation has been demonstrated in a combined total of >300 epileptic rodents. Dose response studies have shown that intraventricular doses of 50–500 ng adenosine / kg body weight / d provide effective seizure suppression in rodents, whereas doses of up to 5 mg ADO / kg / d were without sedative side effects (Güttinger et al., 2005b; Huber et al., 2001; Li et al., 2008; Li et al., 2007b; Wilz et al., 2008). The therapeutic efficacy of intracranial adenosine has independently been reproduced by Robert Fisher in a study to prevent bicuculline-induced ictal and epileptiform discharges (Anschel et al., 2004). In a recent study from Paul Boon's group adenosine has been infused with osmotic pumps into epileptic rats in which TLE was induced by systemic KA-induced SE (Van Dycke et al., 2010). In this independent validation in a TLE model, a 33% reduction in seizure rate was reported in the adenosine-treated animals. Together, our (Gouder et al., 2003; Güttinger et al., 2005a; Huber et al., 2001; Li et al., 2007b; Szybala et al., 2009; Williams-Karnesky et al., 2013; Wilz et al., 2008) and independent data sets (Van Dycke et al., 2010) demonstrate that adenosine effectively suppresses seizures in at least 3 rodent models of mTLE.

5.2. Cognition

Adenosine affects cognitive processes on several mechanistic levels through locally refined neuronal and astroglial A_{2A}R signaling effects and modulation of glutamatergic, dopaminergic, GABAergic, and BDNF-dependent mechanisms. Hippocampal A_{2A}Rs provide essential roles for LTP at mossy fiber-CA3 and at CA3-CA1 synapses (Costenla et al., 2011). Activation of the A_{2A}R leads to transactivation of the TrkA and TrkB receptors for BDNF, even in the absence of neurotrophins (Lee and Chao, 2001). Whereas A_{2A}R activation facilitates BDNF release and BDNF-induced potentiation of synaptic transmission (Diogenes et al., 2004; Tebano et al., 2008), genetic or pharmacological interference with A_{2A}R function leads to decreases in BDNF levels (Tebano et al., 2008; Wei et al., 2014), reduced TrkB expression and activation in the hippocampus, and impairment of BDNF-dependent LTP (Assaife-Lopes et al., 2010; Jeronimo-Santos et al., 2014; Lee and Chao, 2001). In line with those findings pharmacological or genetic disruption of A_{2A}R signaling reduced LTP in hippocampal and cortico-accumbal (Costenla et al., 2011; d'Alcantara et al., 2001; Rebola et al., 2008) and cortico-striatal (Flajolet et al., 2008) synapses.

Although the convergence of epidemiological and experimental data support a role of A_{2A}Rs in neurodegenerative processes the relative (and possibly opposing) roles of neuronal vs. astroglial A_{2A}Rs are currently unknown. New findings suggest that the astroglial A_{2A}R affects cognitive function through a novel mechanism involving astrocyte-driven neuronal adaptation processes (Matos et al., 2015). We identified a novel molecular mechanism linking astrocytic A_{2A}R-driven control of astrocytic GLT-1 activity and dynamic adaptation processes of glutamatergic synapses to neurodegeneration, cognitive impairment, and altered motor responses (Matos et al., 2015). This mechanism might play a previously unrecognized role in the regulation of cognitive performance and suggest that deficient activation of

astroglial A_{2A}Rs might compromise cognitive function. In line with this notion, a recent cell transplantation study has shown that local suprahypocampal implants of baby hamster kidney fibroblasts engineered to release therapeutic amounts of adenosine (Huber et al., 2001) reversed working memory deficits in Adk-tg mice in a delayed alternation task in the T-maze (Shen et al., 2012). Wild-type implants or implants of the adenosine releasing cells into the striatum did not affect cognition in these animals. These findings show that adenosine augmentation to the hippocampus can improve cognitive performance.

5.3. Psychosis

Psychosis, as seen in several of the comorbidities discussed here, as well as in schizophrenia, is tightly linked to hyperdopaminergic function (Tost et al., 2010), which in turn is at least partly under the control of adenosine: Reduced activation of presynaptic A₁Rs can trigger increased availability of dopamine (Borycz et al., 2007) leading to increased basal activity of the dopamine D₂ receptor, thus promoting psychosis (Seeman and Kapur, 2000). In addition, in the basal ganglia adenosine directly modulates dopaminergic signaling through complexes formed between adenosine and dopamine receptors (Fuxe et al., 2003; Fuxe et al., 2007a; Fuxe et al., 2007b; Fuxe et al., 2010). Although D₂R-A_{2A}R complexes remain to be documented in the prefrontal cortex, they have been suggested to be of particular relevance for the psychotic endophenotypes of schizophrenia (Rial et al., 2014). Postsynaptic D₂Rs in turn form heterodimers with A_{2A}Rs and this interaction is antagonistic, whereby reduced activation of the A_{2A}R enhances D₂R function (Fredholm and Svenningsson, 2003; Fuxe et al., 2003; Trifileff et al., 2011). Thereby, hypofunction of adenosine not only leads to increased dopamine, but also promotes the D₂R mediated responses, whereby decreased activation of A_{2A}Rs would increase D₂R signaling through the A_{2A}R-D₂R complexes, thus promoting the dopaminergic hyperfunction in psychosis (Ferre, 1997; Ferre et al., 1994). A link between ADO hypofunction and SZ is supported by clinical evidence demonstrating increased enzymatic degradation of adenosine in SZ patients (Brunstein et al., 2007; Dutra et al., 2010). Most recently, reduced striatal ectonucleotidase (adenosine producing enzyme) activity was found in schizophrenia patients (Aliagas et al., 2013). A meta-analysis of six randomized controlled trials comparing adenosine modulators with placebo as adjuvant therapy in patients with schizophrenia demonstrated benefits in overall psychopathology (especially positive symptoms) in schizophrenia (Hirota and Kishi, 2013). In particular, the adenosine reuptake inhibitor dipyrindole used as an adjuvant with the antipsychotic haloperidol significantly decreased psychotic symptoms in schizophrenia patients (Akhondzadeh et al., 2005; Akhondzadeh et al., 2000). In addition, the acute use of the competitive adenosine receptor antagonist caffeine affects dopaminergic neurotransmission and is known to worsen psychosis in persons with schizophrenia; further, an acute dose of caffeine may cause psychosis in susceptible persons (Cerimele et al., 2010; Hedges et al., 2009; Tibrewal and Dhillon, 2011; Williams and Gandhi, 2008). Together these data suggest that adenosine dysfunction might be implicated in human psychosis and that therapeutic adenosine augmentation might be a rational approach for intervention. This hypothesis was recently tested in a pre-pulse inhibition paradigm in mice that taxes gating functions commonly disrupted in schizophrenia. The ADK inhibitor ABT-702 improved pre-pulse inhibition both in normal mice, as well as in mice, in which pre-pulse inhibition was disrupted by apomorphine (Shen

et al., 2012). These seminal findings strongly support a novel anti-psychotic like role of therapeutic adenosine augmentation a finding that is not necessarily in contradiction to previous findings suggesting a mood stabilizing role of chronic caffeine and A_{2A}R antagonists (Cunha et al., 2008; Gomes et al., 2011; Lucas et al., 2011). Effects of adenosine homeostasis and signaling on psychiatric parameters likely depend on different sources of adenosine (astroglial vs. neuronal) and the fine-tuning of opposing signaling-effects orchestrated by astroglial vs. synaptic adenosine receptors and regional differences within the brain.

5.4. Depression

Although adenosine deficiency in depressive disorders has not directly been demonstrated, accumulating evidence suggests that augmentation of adenosine has potent anti-depressive like effects. One night of total sleep deprivation, known to augment adenosine signaling in the brain (Basheer et al., 2001; Benington et al., 1995; Mackiewicz et al., 2003), is one of the most effective treatments for the treatment of major depression (Hemmeter et al., 1998; Hemmeter et al., 2010). S-adenosylhomocysteine, a precursor of adenosine, is widely used for the treatment of major depression and several studies suggest therapeutic benefits (Carpenter, 2011; De Berardis et al., 2013). Likewise, complementary and alternative approaches known to increase adenosine such as sleep deprivation (Benington et al., 1995), exercise (Dworak et al., 2007), or acupuncture (Goldman et al., 2010) have demonstrated antidepressive effects (Hines and Haydon, 2014; Nahas and Sheikh, 2011). Both sleep deprivation as well as electroconvulsive therapy lead to upregulation of A₁Rs (van Calker and Biber, 2005). The most conclusive direct experimental evidence for a role of adenosine in major depression has recently been provided by Phil Haydon's group (Hines et al., 2013). Using an elegant approach combining dnSNARE mice, which are impaired in gliotransmission, with sleep deprivation and an A₁R agonist, Phil Haydon's group recently demonstrated that astrocytic signaling to A₁Rs was required for the robust reduction of depressive-like behaviors in mice following 12 hours of sleep deprivation (Hines et al., 2013). These findings suggest that therapeutic adenosine augmentation might constitute a promising approach for the treatment of comorbid depression in a wide range of neurological and neuropsychiatric disorders.

5.5. Motor control

Psychomotor activity is strongly regulated and fine-tuned by A_{2A}Rs in the striatum. Whereas A_{2A}Rs on striatopallidal neurons mediate the motor-stimulant effects of caffeine (Yu et al., 2008), A_{2A}Rs on striatopallidal medium spiny neurons antagonize D₂R function and potentiate psychomotor activity (Schiffmann et al., 2007). In contrast, the A_{2A}R located on striatal glutamatergic terminals modulates glutamate release and corticostriatal synaptic transmission (Ciruela et al., 2006; Martire et al., 2011; Quiroz et al., 2009; Rosin et al., 2003; Tozzi et al., 2007). Reduced activation of A_{2A}Rs in extrastriatal forebrain neurons therefore attenuates behavioral responses to psychostimulants such as cocaine, amphetamine, or L-DOPA (Bastia et al., 2005; Fredduzzi et al., 2002; Shen et al., 2008; Xiao et al., 2006). Together, these findings suggest that any disruption in adenosine homeostasis will affect psychomotor activity. As outlined in a preceding section, Adk-tg mice have lost responsiveness to amphetamine. If adenosine deficiency is responsible for the

lack of dopaminergic stimulation of psychomotor responses, then therapeutic adenosine augmentation should restore locomotor responses to amphetamine. Indeed, the transplantation of adenosine releasing BHK cells into the striatum, but not the transplantation of wild-type cells into striatum, or of adenosine releasing cells into the hippocampus, restored responsiveness to amphetamine (Shen et al., 2012). These findings suggest that adenosine augmentation to the striatum may augment dopaminergic function in neurodegenerative conditions.

5.6. Sleep

Adenosine is a key regulator of sleep homeostasis and sleep-associated cognitive performance (Basheer et al., 2004; Bjorness et al., 2009; Blutstein and Haydon, 2012; Halassa et al., 2009; Porkka-Heiskanen et al., 1997). A₁R agonists and antagonists induce and suppress sleep, respectively, via basal forebrain-mediated mechanisms (Benington et al., 1995; Ticho and Radulovacki, 1991; Virus et al., 1990). Likewise, the intracerebroventricular infusion of an A_{2A}R agonist increased sleep, whereas the same drug had no effects in A_{2A}R knockout mice (Satoh et al., 1998; Satoh et al., 1999; Scammell et al., 2001; Urade et al., 2003). It is now widely accepted that the arousal effects of caffeine are largely based on blockade of the A_{2A}R in the shell of the nucleus accumbens (Huang et al., 2005; Lazarus et al., 2011). In line with those findings any disruption in adenosine homeostasis is likely to result in a pathologically altered sleep phenotype. Since lower levels of adenosine promote and increase in wakefulness and since higher levels of adenosine have sleep promoting properties, therapeutic adenosine augmentation may improve overall sleep quantity and quality and thereby promote cognitive performance.

7. Outlook and Conclusions

Based on the pathophysiological and mechanistic findings and related therapeutic opportunities described in the preceding sections it is tempting to conclude that at least a subset of the epilepsies and neurodegenerative conditions discussed here are acquired syndromes that share common inflammatory processes, glial activation and resulting disruption of adenosine homeostasis. We propose that apparently distinct syndromes share common etiologies and that the nature, timing, and spatial configuration of a precipitating event (e.g. an injury or hypoxic event) determines whether those common pathogenetic mechanisms lead to the development of ‘epilepsy’ with a predominant seizure phenotype or the development of a neurodegenerative condition such as Alzheimer’s Parkinson’s, or ALS. In support of this hypothesis conditions exist that display remarkable overlapping pathologies between ALS, Parkinson’s and Alzheimer’s disease. ‘*Western Pacific Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia Complex*’ is a neurodegenerative condition, which is precipitated by the exposure to cycad plant toxins; importantly, the resulting neuropathology is a tauopathy, which is remarkably similar to that found in Alzheimer’s disease (Kisby and Spencer, 2011; Spencer et al., 2012; Spencer et al., 2010). Interestingly, the pathophysiological course of the disease appears to depend on the dose of the precipitating toxin: those exposed to the highest dose of the toxin develop fatal ALS (with sub-clinical nigrostriatal damage) relatively shortly after exposure; those exposed to intermediate doses survive with amyotrophy long enough to develop atypical

parkinsonism; those exposed to low doses reach old age and display dementia, while others with the lowest exposure levels have subclinical neurofibrillary disease reminiscent of early aging (Spencer et al., 2012; Spencer et al., 2010).

Although several pathophysiological mechanisms are likely to contribute to the development of comorbid symptomatology in Neurology, we conclude from the correlative, conceptual, and causal evidence presented here that dysfunction of adenosine signaling is common in neurological conditions, that adenosine dysfunction may explain comorbid phenotypes shared among seemingly unrelated neurological conditions, and that therapeutic adenosine augmentation might be an highly effective approach for the treatment of a comorbid spectrum of symptoms in multiple neurological conditions. Therapeutic augmentation of adenosine signaling can be achieved pharmacologically with receptor agonists, with inhibitors of adenosine metabolism, or with inhibitors of transport (Boison, 2012a; Boison et al., 2010). However, due to the ubiquitous distribution of those drug targets, wide-spread systemic side effects currently limit therapeutic implementation (Boison, 2012a). Adenosine kinase inhibitors represent some of the most promising adenosine elevating agents (Boison, 2013; Kowaluk and Jarvis, 2000; McGaraughty et al., 2005). Although the long-term use of those agents might be limited by hepatotoxicity (Boison et al., 2002b) recent findings suggest that short term adenosine augmentation provides long-term benefit via lasting adenosine-induced epigenetic changes (Williams-Karnesky et al., 2013). These findings may provide a new clinical perspective for the use of ADK inhibitors (Boison, 2013). Alternatively, dietary interventions such as therapy with a high-fat low-carbohydrate 'ketogenic diet' (KD) or lifestyle choices such as exercise are known to increase adenosine in the brain (Dworak et al., 2007; Masino et al., 2011). KD therapy is remarkably effective in preventing seizures in epilepsy while providing additional benefits to cognitive function and overall well-being (Freeman, 2009; Kossoff and Rho, 2009; Lutas and Yellen, 2013; Masino and Rho, 2012). Currently KD therapy is considered for the treatment of Alzheimer's disease (Aso et al., 2013; Van der Auwera et al., 2005), Parkinson's disease (Cheng et al., 2009), and amyotrophic lateral sclerosis (Zhao et al., 2006). It may well be that a therapeutic intervention known to increase adenosine signaling in the brain has therapeutic promise for a wide range of neurological and neuropsychiatric disorders.

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References

- Agostinho P, Cunha RA, Oliveira C. Neuroinflammation, oxidative stress and the pathogenesis of Alzheimer's disease. *Curr Pharm Des.* 2010; 16:2766–2778. [PubMed: 20698820]
- Akhondzadeh S, Safarcherati A, Amini H. Beneficial antipsychotic effects of allopurinol as add-on therapy for schizophrenia: a double blind, randomized and placebo controlled trial. *Prog Neuropsychopharmacol Biol Psychiatry.* 2005; 29:253–259. [PubMed: 15694232]

- Akhondzadeh S, Shasavand E, Jamilian H, Shabestari O, Kamalipour A. Dipyridamole in the treatment of schizophrenia: adenosine-dopamine receptor interactions. *J Clin Pharm Ther.* 2000; 25:131–137. [PubMed: 10849191]
- Aliagas E, Villar-Menendez I, Sevigny J, Roca M, Romeu M, Ferrer I, Martin-Satue M, Barrachina M. Reduced striatal ecto-nucleotidase activity in schizophrenia patients supports the "adenosine hypothesis". *Purinergic Signal.* 2013
- Amatniek JC, Hauser WA, DelCastillo-Castaneda C, Jacobs DM, Marder K, Bell K, Albert M, Brandt J, Stern Y. Incidence and predictors of seizures in patients with Alzheimer's disease. *Epilepsia.* 2006; 47:867–872. [PubMed: 16686651]
- Amore M, Tagariello P, Laterza C, Savoia EM. Subtypes of depression in dementia. *Arch Gerontol Geriatr.* 2007; 44(Suppl 1):23–33. [PubMed: 17317430]
- Anschel DJ, Ortega EL, Kraus AC, Fisher RS. Focally injected adenosine prevents seizures in the rat. *Exp Neurol.* 2004; 190:544–547. [PubMed: 15530893]
- Araque A, Parpura V, Sanzgiri RP, Haydon PG. Tripartite synapses: glia, the unacknowledged partner. *Trends Neurosci.* 1999; 22:208–215. [PubMed: 10322493]
- Arch JR, Newsholme EA. Activities and some properties of 5'-nucleotidase, adenosine kinase and adenosine deaminase in tissues from vertebrates and invertebrates in relation to the control of the concentration and the physiological role of adenosine. *Biochem J.* 1978; 174:965–977. [PubMed: 215126]
- Aronica E, Crino PB. Epilepsy related to developmental tumors and malformations of cortical development. *Neurotherapeutics.* 2014; 11:251–268. [PubMed: 24481729]
- Aronica E, Ravizza T, Zurolo E, Vezzani A. Astrocyte immune responses and epilepsy. *Glia.* 2012; 60:1258–1268. [PubMed: 22331574]
- Aronica E, Sandau US, Iyer A, Boison D. Glial adenosine kinase - A neuropathological marker of the epileptic brain. *Neurochem Int.* 2013; 63:688–695. [PubMed: 23385089]
- Aronica E, Zurolo E, Iyer A, de Groot M, Anink J, Carbonell C, van Vliet EA, Baayen JC, Boison D, Gorter JA. Upregulation of adenosine kinase in astrocytes in experimental and human temporal lobe epilepsy. *Epilepsia.* 2011; 52:1645–1655. [PubMed: 21635241]
- Aso E, Semakova J, Joda L, Semak V, Halbaut L, Calpena A, Escolano C, Perales JC, Ferrer I. Triheptanoin supplementation to ketogenic diet curbs cognitive impairment in APP/PS1 mice used as a model of familial Alzheimer's disease. *Curr Alzheimer Res.* 2013; 10:290–297. [PubMed: 23131121]
- Assaife-Lopes N, Sousa VC, Pereira DB, Ribeiro JA, Chao MV, Sebastiao AM. Activation of adenosine A2A receptors induces TrkB translocation and increases BDNF-mediated phospho-TrkB localization in lipid rafts: implications for neuromodulation. *J Neurosci.* 2010; 30:8468–8480. [PubMed: 20573894]
- Atassi N, Cook A, Pineda CM, Yerramilli-Rao P, Pulley D, Cudkowicz M. Depression in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler.* 2011; 12:109–112. [PubMed: 21091399]
- Bandopadhyay R, Liu JY, Sisodiya SM, Thom M. A comparative study of the dentate gyrus in hippocampal sclerosis in epilepsy and dementia. *Neuropathol Appl Neurobiol.* 2014; 40:177–190. [PubMed: 24028428]
- Basheer R, Halldner L, Alanko L, McCarley RW, Fredholm BB, Porkka-Heiskanen T. Opposite changes in adenosine A1 and A2A receptor mRNA in the rat following sleep deprivation. *Neuroreport.* 2001; 12:1577–1580. [PubMed: 11409719]
- Basheer R, Strecker RE, Thakkar MM, McCarley RW. Adenosine and sleep-wake regulation. *Prog Neurobiol.* 2004; 73:379–396. [PubMed: 15313333]
- Bastia E, Xu YH, Scibelli AC, Day YJ, Linden J, Chen JF, Schwarzschild MA. A crucial role for forebrain adenosine A(2A) receptors in amphetamine sensitization. *Neuropsychopharmacology.* 2005; 30:891–900. [PubMed: 15602504]
- Benington JH, Kodali SK, Heller HC. Stimulation of A1 adenosine receptors mimics the electroencephalographic effects of sleep deprivation. *Brain Res.* 1995; 692:79–85. [PubMed: 8548323]
- Bjorness TE, Kelly CL, Gao T, Poffenberger V, Greene RW. Control and function of the homeostatic sleep response by adenosine A1 receptors. *J Neurosci.* 2009; 29:1267–1276. [PubMed: 19193874]

- Blumcke I, Kistner I, Clusmann H, Schramm J, Becker AJ, Elger CE, Bien CG, Merschhemke M, Meencke HJ, Lehmann T, Buchfelder M, Weigel D, Buslei R, Stefan H, Pauli E, Hildebrandt M. Towards a clinico-pathological classification of granule cell dispersion in human mesial temporal lobe epilepsies. *Acta Neuropathol.* 2009; 117:535–544. [PubMed: 19277686]
- Blumcke I, Thom M, Aronica E, Armstrong DD, Bartolomei F, Bernasconi A, Bernasconi N, Bien CG, Cendes F, Coras R, Cross JH, Jacques TS, Kahane P, Mathern GW, Miyata H, Moshe SL, Oz B, Ozkara C, Perucca E, Sisodiya S, Wiebe S, Spreafico R. International consensus classification of hippocampal sclerosis in temporal lobe epilepsy: a Task Force report from the ILAE Commission on Diagnostic Methods. *Epilepsia.* 2013; 54:1315–1329. [PubMed: 23692496]
- Blutstein T, Haydon PG. The Importance of astrocyte-derived purines in the modulation of sleep. *Glia.* 2012
- Boison D. Adenosine as a modulator of brain activity. *Drug News Persp.* 2007a; 20:607–611.
- Boison D. Adenosine, astrogliosis and seizures: a new perspective of epileptogenesis. *Neuron Glia Biology.* 2007b; 2:S9–S9.
- Boison D. The adenosine kinase hypothesis of epileptogenesis. *Progress in Neurobiology.* 2008; 84:249–262. [PubMed: 18249058]
- Boison, D., et al. Adenosine augmentation therapy for epilepsy. In: Noebels, JL.; Avoli, M.; Rogawski, MA.; Olsen, RW.; Delgado-Escueta, AV., editors. *Jasper's Basic Mechanisms of the Epilepsies.* Oxford: Oxford University Press; 2012a. p. 1150-1160.
- Boison D. Adenosine dysfunction in epilepsy. *Glia.* 2012b; 60:1234–1243. [PubMed: 22700220]
- Boison D. Adenosine kinase: exploitation for therapeutic gain. *Pharmacological Reviews.* 2013; 65:906–943. [PubMed: 23592612]
- Boison D, Chen JF, Fredholm BB. Adenosine signalling and function in glial cells. *Cell Death Differ.* 2010; 17:1071–1082. [PubMed: 19763139]
- Boison D, Huber A, Padrun V, Deglon N, Aebischer P, Mohler H, et al. Seizure suppression by adenosine-releasing cells is independent of seizure frequency. *Epilepsia.* 2002a; 43:788–796. [PubMed: 12180995]
- Boison D, Sandau US, Ruskin DN, Kawamura M Jr, Masino SA. Homeostatic control of brain function - new approaches to understand epileptogenesis. *Front Cell Neurosci.* 2013; 7:109. [PubMed: 23882181]
- Boison D, Scheurer L, Tseng JL, Aebischer P, Mohler H. Seizure suppression in kindled rats by intraventricular grafting of an adenosine releasing synthetic polymer. *Exp Neurol.* 1999; 160:164–174. [PubMed: 10630201]
- Boison D, Scheurer L, Zumsteg V, Rülcke T, Litynski P, Fowler B, Brandner S, Mohler H, et al. Neonatal hepatic steatosis by disruption of the adenosine kinase gene. *Proc Natl Acad Sci USA.* 2002b; 99:6985–6990. [PubMed: 11997462]
- Borycz J, Pereira MF, Melani A, Rodrigues RJ, Kofalvi A, Panlilio L, Pedata F, Goldberg SR, Cunha RA, Ferre S. Differential glutamate-dependent and glutamate-independent adenosine A1 receptor-mediated modulation of dopamine release in different striatal compartments. *J Neurochem.* 2007; 101:355–363. [PubMed: 17254024]
- Brunstein MG, Silveira EM Jr, Chaves LS, Machado H, Schenkel O, Belmonte-de-Abreu P, Souza DO, Lara DR. Increased serum adenosine deaminase activity in schizophrenic receiving antipsychotic treatment. *Neurosci Lett.* 2007; 414:61–64. [PubMed: 17289263]
- Carpenter DJ. St John's wort and S-adenosyl methionine as "natural" alternatives to conventional antidepressants in the era of the suicidality boxed warning: what is the evidence for clinically relevant benefit? *Altern Med Rev.* 2011; 16:17–39. [PubMed: 21438644]
- Cechetto DF, Hachinski V, Whitehead SN. Vascular risk factors and Alzheimer's disease. *Expert Rev Neurother.* 2008; 8:743–750. [PubMed: 18457531]
- Cerimele JM, Stern AP, Jutras-Aswad D. Psychosis following excessive ingestion of energy drinks in a patient with schizophrenia. *Am J Psychiatry.* 2010; 167:353. [PubMed: 20194494]
- Chen JF, Eltzschig HK, Fredholm BB. Adenosine receptors as drug targets--what are the challenges? *Nat Rev Drug Discov.* 2013; 12:265–286. [PubMed: 23535933]

- Cheng B, Yang X, An L, Gao B, Liu X, Liu S. Ketogenic diet protects dopaminergic neurons against 6-OHDA neurotoxicity via up-regulating glutathione in a rat model of Parkinson's disease. *Brain Res.* 2009; 1286:25–31. [PubMed: 19559687]
- Ciruela F, Casado V, Rodrigues RJ, Lujan R, Burgueno J, Canals M, Borycz J, Rebola N, Goldberg SR, Mallol J, Cortes A, Canela EI, Lopez-Gimenez JF, Milligan G, Lluís C, Cunha RA, Ferre S, Franco R. Presynaptic control of striatal glutamatergic neurotransmission by adenosine A1-A2A receptor heteromers. *J Neurosci.* 2006; 26:2080–2087. [PubMed: 16481441]
- Coppieters N, Dieriks BV, Lill C, Faull RL, Curtis MA, Dragunow M. Global changes in DNA methylation and hydroxymethylation in Alzheimer's disease human brain. *Neurobiol Aging.* 2014; 35:1334–1344. [PubMed: 24387984]
- Coras R, Siebzehnrbul FA, Pauli E, Huttner HB, Njunting M, Kobow K, Villmann C, Hahnen E, Neuhuber W, Weigel D, Buchfelder M, Stefan H, Beck H, Steindler DA, Blumcke I. Low proliferation and differentiation capacities of adult hippocampal stem cells correlate with memory dysfunction in humans. *Brain.* 2010; 133:3359–3372. [PubMed: 20719879]
- Cornejo VH, Hetz C. The unfolded protein response in Alzheimer's disease. *Semin Immunopathol.* 2013; 35:277–292. [PubMed: 23609500]
- Costenla AR, Diogenes MJ, Canas PM, Rodrigues RJ, Nogueira C, Maroco J, Agostinho PM, Ribeiro JA, Cunha RA, de Mendonça A. Enhanced role of adenosine A(2A) receptors in the modulation of LTP in the rat hippocampus upon ageing. *Eur J Neurosci.* 2011; 34:12–21. [PubMed: 21615561]
- Craft S. The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged. *Arch Neurol.* 2009; 66:300–305. [PubMed: 19273747]
- Cunha RA. Adenosine as a neuromodulator and as a homeostatic regulator in the nervous system: different roles, different sources and different receptors. *Neurochem Int.* 2001; 38:107–125. [PubMed: 11137880]
- Cunha RA. Neuroprotection by adenosine in the brain: from A1 receptor activation to A2A receptor blockade. *Purinergic Signaling.* 2005; 1:111–134.
- Cunha RA. Different cellular sources and different roles of adenosine: A(1) receptor-mediated inhibition through astrocytic-driven volume transmission and synapse-restricted A(2A) receptor-mediated facilitation of plasticity. *Neurochemistry International.* 2008; 52:65–72. [PubMed: 17664029]
- Cunha RA, Ferre S, Vaugeois JM, Chen JF. Potential therapeutic interest of adenosine A(2A) receptors in psychiatric disorders. *Current Pharmaceutical Design.* 2008; 14:1512–1524. [PubMed: 18537674]
- d'Alcantara P, Ledent C, Swillens S, Schiffmann SN. Inactivation of adenosine A2A receptor impairs long term potentiation in the accumbens nucleus without altering basal synaptic transmission. *Neuroscience.* 2001; 107:455–464. [PubMed: 11719000]
- De Berardis D, Marini S, Serroni N, Rapini G, Iasevoli F, Valchera A, Signorelli M, Aguglia E, Perna G, Salone A, Di Iorio G, Martinotti G, Di Giannantonio M. S-Adenosyl-L-Methionine augmentation in patients with stage II treatment-resistant major depressive disorder: an open label, fixed dose, single-blind study. *ScientificWorldJournal.* 2013; 2013:204–649.
- de Groot M, Iyer A, Zurolo E, Anink J, Heimans JJ, Boison D, Reijneveld CJ, Aronica E. Overexpression of ADK in human astrocytic tumors and peritumoral tissue is related to tumor-associated epilepsy. *Epilepsia.* 2012; 53:58–66. [PubMed: 22092111]
- Desplats P, Lee HJ, Bae EJ, Patrick C, Rockenstein E, Crews L, Spencer B, Masliah E, Lee SJ. Inclusion formation and neuronal cell death through neuron-to-neuron transmission of alpha-synuclein. *Proc Natl Acad Sci U S A.* 2009; 106:13010–13015. [PubMed: 19651612]
- Devinsky O, Vezzani A, Najjar S, De Lanerolle NC, Rogawski MA. Glia and epilepsy: excitability and inflammation. *Trends Neurosci.* 2013; 36:174–184. [PubMed: 23298414]
- Diogenes MJ, Fernandes CC, Sebastiao AM, Ribeiro JA. Activation of adenosine A2A receptor facilitates brain-derived neurotrophic factor modulation of synaptic transmission in hippocampal slices. *J Neurosci.* 2004; 24:2905–2913. [PubMed: 15044529]
- Diógenes MJ, Neves-Tomé R, Fucile S, Martinello K, Scianni M, Theofilas P, Lopatá J, Ribeiro JA, Maggi L, Frenguelli BG, Limatola C, Boison D, Sebastião AM. Homeostatic control of synaptic

activity by endogenous adenosine is mediated by adenosine kinase. *Cerebral Cortex*. 2014; 24:67–80. [PubMed: 22997174]

- Dobkin RD, Menza M, Allen LA, Gara MA, Mark MH, Tiu J, Bienfait KL, Friedman J. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. *Am J Psychiatry*. 2011; 168:1066–1074. [PubMed: 21676990]
- Dragunow M. Adenosine and seizure termination. *Ann Neurol*. 1991; 29:575. [PubMed: 1859190]
- Duarte JM, Agostinho PM, Carvalho RA, Cunha RA. Caffeine consumption prevents diabetes-induced memory impairment and synaptotoxicity in the hippocampus of NONcZNO10/LTJ mice. *PLoS One*. 2012; 7:e21899. [PubMed: 22514596]
- Dunwiddie TV. Endogenously released adenosine regulates excitability in the in vitro hippocampus. *Epilepsia*. 1980; 21:541–548. [PubMed: 7418669]
- During MJ, Spencer DD. Adenosine: a potential mediator of seizure arrest and postictal refractoriness. *Ann Neurol*. 1992; 32:618–624. [PubMed: 1449242]
- Dutra GP, Ottoni GL, Lara DR, Bogo MR. Lower frequency of the low activity adenosine deaminase allelic variant (ADA1*2) in schizophrenic patients. *Rev Bras Psiquiatr*. 2010; 32:275–278. [PubMed: 20414589]
- Duyckaerts C. Disentangling Alzheimer's disease. *Lancet Neurol*. 2011; 10:774–775. [PubMed: 21802368]
- Dworak M, Diel P, Voss S, Hollmann W, Struder HK. Intense exercise increases adenosine concentrations in rat brain: implications for a homeostatic sleep drive. *Neuroscience*. 2007; 150:789–795. [PubMed: 18031936]
- Etherington LA, Frenguelli BG. Endogenous adenosine modulates epileptiform activity in rat hippocampus in a receptor subtype-dependent manner. *Eur J Neurosci*. 2004; 19:2539–2550. [PubMed: 15128407]
- Farina C, Aloisi F, Meinl E. Astrocytes are active players in cerebral innate immunity. *Trends Immunol*. 2007; 28:138–145. [PubMed: 17276138]
- Fedele DE, Gouder N, Güttinger M, Gabernet L, Scheurer L, Rulicke T, Crestani F, Boison D. Astroglialosis in epilepsy leads to overexpression of adenosine kinase resulting in seizure aggravation. *Brain*. 2005; 128:2383–2395. [PubMed: 15930047]
- Fedele DE, Koch P, Brüstle O, Scheurer L, Simpson EM, Mohler H, Boison D. Engineering embryonic stem cell derived glia for adenosine delivery. *Neurosci Lett*. 2004; 370:160–165. [PubMed: 15488315]
- Fedele DE, Li T, Lan JQ, Fredholm BB, Boison D. Adenosine A1 receptors are crucial in keeping an epileptic focus localized. *Exp Neurol*. 2006; 200:184–190. [PubMed: 16750195]
- Ferentinos P, Paparrigopoulos T, Rentzos M, Zouvelou V, Alexakis T, Evdokimidis I. Prevalence of major depression in ALS: comparison of a semi-structured interview and four self-report measures. *Amyotroph Lateral Scler*. 2011; 12:297–302. [PubMed: 21428731]
- Fernandez G, Mandolesi P, Rotstein NP, Colombo O, Agamennoni O, Politi LE. Eye movement alterations during reading in patients with early Alzheimer disease. *Invest Ophthalmol Vis Sci*. 2013; 54:8345–8352. [PubMed: 24282223]
- Ferre S. Adenosine-dopamine interactions in the ventral striatum. Implications for the treatment of schizophrenia. *Psychopharmacology (Berl)*. 1997; 133:107–120. [PubMed: 9342776]
- Ferre S, O'Connor WT, Snarud P, Ungerstedt U, Fuxe K. Antagonistic interaction between adenosine A2A receptors and dopamine D2 receptors in the ventral striopallidal system. Implications for the treatment of schizophrenia. *Neuroscience*. 1994; 63:765–773. [PubMed: 7898676]
- Flajolet M, Wang Z, Futter M, Shen W, Nuangchamnon N, Bendor J, Wallach I, Nairn AC, Surmeier DJ, Greengard P. FGF acts as a co-transmitter through adenosine A(2A) receptor to regulate synaptic plasticity. *Nat Neurosci*. 2008; 11:1402–1409. [PubMed: 18953346]
- Forno LS, DeLanney LE, Irwin I, Di Monte D, Langston JW. Astrocytes and Parkinson's disease. *Prog Brain Res*. 1992; 94:429–436. [PubMed: 1287728]
- Franco R, Lluís C, Canela EI, Mallol J, Agnati L, Casado V, Ciruela F, Ferre S, Fuxe K. Receptor-receptor interactions involving adenosine A1 or dopamine D1 receptors and accessory proteins. *J Neural Transm*. 2007; 114:93–104. [PubMed: 17024327]

- Fredduzzi S, Moratalla R, Monopoli A, Cuellar B, Xu K, Ongini E, Impagnatiello F, Schwarzschild MA, Chen JF. Persistent behavioral sensitization to chronic L-DOPA requires A2A adenosine receptors. *J Neurosci*. 2002; 22:1054–1062. [PubMed: 11826134]
- Fredholm BB. Adenosine receptors in the central nervous system. *NIPS*. 1995; 10:122–128.
- Fredholm BB. Adenosine receptors as drug targets. *Exp Cell Res*. 2010; 316:1284–1288. [PubMed: 20153317]
- Fredholm BB, Chen JF, Cunha RA, Svenningsson P, Vaugeois JM, et al. Adenosine and brain function. *Int Rev Neurobiol*. 2005a; 63:191–270. [PubMed: 15797469]
- Fredholm BB, Chen JF, Masino SA, Vaugeois JM, et al. Actions of adenosine at its receptors in the CNS: Insights from knockouts and drugs. *Annu Rev Pharmacol Toxicol*. 2005b; 45:385–412. [PubMed: 15822182]
- Fredholm BB, Dunwiddie TV. How does adenosine inhibit transmitter release? *Trends Pharmacol Sci*. 1988; 9:130–134. [PubMed: 2907698]
- Fredholm BB, Dunwiddie TV, Bergman B, Lindstrom K. Levels of adenosine and adenine nucleotides in slices of rat hippocampus. *Brain Res*. 1984; 295:127–136. [PubMed: 6324948]
- Fredholm BB, Svenningsson P. Adenosine-dopamine interactions: development of a concept and some comments on therapeutic possibilities. *Neurology*. 2003; 61:S5–S9. [PubMed: 14663001]
- Freeman JM. Seizures, EEG events, and the ketogenic diet. *Epilepsia*. 2009; 50:329–330. [PubMed: 19215282]
- Fuller S, Munch G, Steele M. Activated astrocytes: a therapeutic target in Alzheimer's disease? *Expert Rev Neurother*. 2009; 9:1585–1594. [PubMed: 19903019]
- Fuxe K, Agnati LF, Jacobsen K, Hillion J, Canals M, Torvinen M, Tinner-Staines B, Staines W, Rosin D, Terasmaa A, Popoli P, Leo G, Vergoni V, Lluís C, Ciruela F, Franco R, Ferre S. Receptor heteromerization in adenosine A2A receptor signaling: relevance for striatal function and Parkinson's disease. *Neurology*. 2003; 61:S19–S23. [PubMed: 14663004]
- Fuxe K, Ferre S, Genedani S, Franco R, Agnati LF. Adenosine receptor-dopamine receptor interactions in the basal ganglia and their relevance for brain function. *Physiol Behav*. 2007a
- Fuxe K, Marcellino D, Genedani S, Agnati L. Adenosine A(2A) receptors, dopamine D(2) receptors and their interactions in Parkinson's disease. *Mov Disord*. 2007b
- Fuxe K, Marcellino D, Leo G, Agnati LF. Molecular integration via allosteric interactions in receptor heteromers. A working hypothesis. *Curr Opin Pharmacol*. 2010; 10:14–22. [PubMed: 19942481]
- Gaitatzis A, Carroll K, Majeed A, J WS. The epidemiology of the comorbidity of epilepsy in the general population. *Epilepsia*. 2004; 45:1613–1622. [PubMed: 15571520]
- Gaitatzis A, Sisodiya SM, Sander JW. The somatic comorbidity of epilepsy: a weighty but often unrecognized burden. *Epilepsia*. 2012; 53:1282–1293. [PubMed: 22691064]
- Geda YE, Schneider LS, Gitlin LN, Miller DS, Smith GS, Bell J, Evans J, Lee M, Porsteinsson A, Lancot KL, Rosenberg PB, Sultzer DL, Francis PT, Brodaty H, Padala PP, Onyike CU, Ortiz LA, Ancoli-Israel S, Bliwise DL, Martin JL, Vitiello MV, Yaffe K, Zee PC, Herrmann N, Sweet RA, Ballard C, Khin NA, Alfaro C, Murray PS, Schultz S, Lyketsos CG. Neuropsychiatric Syndromes Professional Interest Area of, I. Neuropsychiatric symptoms in Alzheimer's disease: past progress and anticipation of the future. *Alzheimers Dement*. 2013; 9:602–608. [PubMed: 23562430]
- Glass M, Faull RL, Bullock JY, Jansen K, Mee EW, Walker EB, Synek BJ, Dragunow M. Loss of A1 adenosine receptors in human temporal lobe epilepsy. *Brain Res*. 1996; 710:56–68. [PubMed: 8963679]
- Goldman N, Chen M, Fujita T, Xu Q, Peng W, Liu W, Jensen TK, Pei Y, Wang F, Han X, Chen JF, Schnermann J, Takano T, Bekar L, Tieu K, Nedergaard M. Adenosine A1 receptors mediate local anti-nociceptive effects of acupuncture. *Nat Neurosci*. 2010; 13:883–888. [PubMed: 20512135]
- Gomes CV, Kaster MP, Tome AR, Agostinho PM, Cunha RA. Adenosine receptors and brain diseases: neuroprotection and neurodegeneration. *Biochim Biophys Acta*. 2011; 1808:1380–1399. [PubMed: 21145878]
- Gouder N, Fritschy JM, Boison D. Seizure suppression by adenosine A1 receptor activation in a mouse model of pharmacoresistant epilepsy. *Epilepsia*. 2003; 44:877–885. [PubMed: 12823569]
- Gouder N, Scheurer L, Fritschy J-M, Boison D. Overexpression of adenosine kinase in epileptic hippocampus contributes to epileptogenesis. *J Neurosci*. 2004; 24:692–701. [PubMed: 14736855]

- Güttinger M, Fedele DE, Koch P, Padrun V, Pralong W, Brüstle O, Boison D. Suppression of kindled seizures by paracrine adenosine release from stem cell derived brain implants. *Epilepsia*. 2005a; 46:1–8.
- Güttinger M, Padrun V, Pralong W, Boison D. Seizure suppression and lack of adenosine A1 receptor desensitization after focal long-term delivery of adenosine by encapsulated myoblasts. *Exp Neurol*. 2005b; 193:53–64. [PubMed: 15817264]
- Halassa MM, Fellin T, Haydon PG. The tripartite synapse: roles for gliotransmission in health and disease. *Trends Mol Med*. 2007; 13:54–63. [PubMed: 17207662]
- Halassa MM, Florian C, Fellin T, Munoz JR, Lee SY, Abel T, Haydon PG, Frank MG. Astrocytic modulation of sleep homeostasis and cognitive consequences of sleep loss. *Neuron*. 2009; 61:213–219. [PubMed: 19186164]
- Halassa MM, Haydon PG. Integrated brain circuits: astrocytic networks modulate neuronal activity and behavior. *Annu Rev Physiol*. 2010; 72:335–355. [PubMed: 20148679]
- Hall ED, Oostveen JA, Gurney ME. Relationship of microglial and astrocytic activation to disease onset and progression in a transgenic model of familial ALS. *Glia*. 1998; 23:249–256. [PubMed: 9633809]
- Hallbeck M, Nath S, Marcusson J. Neuron-to-neuron transmission of neurodegenerative pathology. *Neuroscientist*. 2013; 19:560–566. [PubMed: 23831598]
- Halliday GM, Stevens CH. Glia: initiators and progressors of pathology in Parkinson's disease. *Mov Disord*. 2011; 26:6–17. [PubMed: 21322014]
- Hedges DW, Woon FL, Hoopes SP. Caffeine-induced psychosis. *CNS Spectr*. 2009; 14:127–129. [PubMed: 19407709]
- Hemmeter U, Bischof R, Hatzinger M, Seifritz E, Holsboer-Trachsler E. Microsleep during partial sleep deprivation in depression. *Biol Psychiatry*. 1998; 43:829–839. [PubMed: 9611673]
- Hemmeter UM, Hemmeter-Spernal J, Krieg JC. Sleep deprivation in depression. *Expert Rev Neurother*. 2010; 10:1101–1115. [PubMed: 20586691]
- Hines DJ, Haydon PG. Astrocytic adenosine: from synapses to psychiatric disorders. *Philos Trans R Soc Lond B Biol Sci*. 2014; 369:20130594. [PubMed: 25225088]
- Hines DJ, Schmitt LI, Hines RM, Moss SJ, Haydon PG. Antidepressant effects of sleep deprivation require astrocyte-dependent adenosine mediated signaling. *Transl Psychiatry*. 2013; 3:e212. [PubMed: 23321809]
- Hirota T, Kishi T. Adenosine hypothesis in schizophrenia and bipolar disorder: a systematic review and meta-analysis of randomized controlled trial of adjuvant purinergic modulators. *Schizophr Res*. 2013; 149:88–95. [PubMed: 23870805]
- Huang ZL, Qu WM, Eguchi N, Chen JF, Schwarzschild MA, Fredholm BB, Urade Y, Hayaishi O. Adenosine A2A, but not A1, receptors mediate the arousal effect of caffeine. *Nat Neurosci*. 2005; 8:858–859. [PubMed: 15965471]
- Huber A, Padrun V, Deglon N, Aebischer P, Mohler H, Boison D. Grafts of adenosine-releasing cells suppress seizures in kindling epilepsy. *Proc. Natl. Acad. Sci. USA*. 2001; 98:7611–7616. [PubMed: 11404469]
- Hyman BT, Phelps CH, Beach TG, Bigio EH, Cairns NJ, Carrillo MC, Dickson DW, Duyckaerts C, Frosch MP, Masliah E, Mirra SS, Nelson PT, Schneider JA, Thal DR, Thies B, Trojanowski JQ, Vinters HV, Montine TJ. National Institute on Aging-Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease. *Alzheimers Dement*. 2012; 8:1–13. [PubMed: 22265587]
- Iyer A, Prabowo A, Anink J, Spliet WG, van Rijen PC, Aronica E. Cell injury and premature neurodegeneration in focal malformations of cortical development. *Brain Pathol*. 2014; 24:1–17. [PubMed: 23586324]
- Jellinger KA. Neuropathology in Parkinson's disease with mild cognitive impairment. *Acta Neuropathol*. 2010; 120:829–830. author reply 831. [PubMed: 20922398]
- Jensen CJ, Massie A, De Keyser J. Immune players in the CNS: the astrocyte. *J Neuroimmune Pharmacol*. 2013; 8:824–839. [PubMed: 23821340]
- Jensen FE. Epilepsy as a spectrum disorder: Implications from novel clinical and basic neuroscience. *Epilepsia*. 2011; 52(Suppl 1):1–6. [PubMed: 21214533]

- Jeronimo-Santos A, Batalha VL, Muller CE, Baqi Y, Sebastiao AM, Lopes LV, Diogenes MJ. Impact of in vivo chronic blockade of adenosine A2A receptors on the BDNF-mediated facilitation of LTP. *Neuropharmacology*. 2014; 83:99–106. [PubMed: 24747180]
- Kandratavicius L, Lopes-Aguiar C, Bueno-Junior LS, Romcy-Pereira RN, Hallak JE, Leite JP. Psychiatric comorbidities in temporal lobe epilepsy: possible relationships between psychotic disorders and involvement of limbic circuits. *Rev Bras Psiquiatr*. 2012; 34:454–466. [PubMed: 23429818]
- Kisby GE, Spencer PS. Is neurodegenerative disease a long-latency response to early-life genotoxin exposure? *Int J Environ Res Public Health*. 2011; 8:3889–3921. [PubMed: 22073019]
- Kobow K, Auvin S, Jensen F, Loscher W, Mody I, Potschka H, Prince D, Sierra A, Simonato M, Pitkanen A, Nehlig A, Rho JM. Finding a better drug for epilepsy: antiepileptogenesis targets. *Epilepsia*. 2012; 53:1868–1876. [PubMed: 23061663]
- Kobow K, Blumcke I. The methylation hypothesis: do epigenetic chromatin modifications play a role in epileptogenesis? *Epilepsia*. 2011; 52(Suppl 4):15–19. [PubMed: 21732935]
- Kobow K, Jeske I, Hildebrandt M, Hauke J, Hahnen E, Buslei R, Buchfelder M, Weigel D, Stefan H, Kasper B, Pauli E, Blumcke I. Increased reelin promoter methylation is associated with granule cell dispersion in human temporal lobe epilepsy. *J Neuropathol Exp Neurol*. 2009; 68:356–364. [PubMed: 19287316]
- Kobow K, Kaspi A, Hari Krishnan KN, Kiese K, Ziemann M, Khurana I, Fritzsche I, Hauke J, Hahnen E, Coras R, Muhlechner A, El-Osta A, Blumcke I. Deep sequencing reveals increased DNA methylation in chronic rat epilepsy. *Acta Neuropathol*. 2013; 126:741–756. [PubMed: 24005891]
- Korner S, Kollwe K, Ilseemann J, Muller-Heine A, Dengler R, Krampfl K, Petri S. Prevalence and prognostic impact of comorbidities in amyotrophic lateral sclerosis. *Eur J Neurol*. 2013; 20:647–654. [PubMed: 23094606]
- Kossoff EH, Rho JM. Ketogenic diets: evidence for short- and long-term efficacy. *Neurotherapeutics*. 2009; 6:406–414. [PubMed: 19332337]
- Kovacs GG, Gelpi E. Clinical neuropathology practice news 3–2012: the "ABC" in AD-revised and updated guideline for the neuropathologic assessment of Alzheimer's disease. *Clin Neuropathol*. 2012; 31:116–118. [PubMed: 22551914]
- Kowaluk EA, Jarvis MF. Therapeutic potential of adenosine kinase inhibitors. *Expert Opin Investig Drugs*. 2000; 9:551–564.
- L'Episcopo F, Tirolo C, Testa N, Caniglia S, Morale MC, Marchetti B. Glia as a turning point in the therapeutic strategy of Parkinson's disease. *CNS Neurol Disord Drug Targets*. 2010; 9:349–372. [PubMed: 20438439]
- LaFrance WC Jr, Kanner AM, Hermann B. Psychiatric comorbidities in epilepsy. *Int Rev Neurobiol*. 2008; 83:347–383. [PubMed: 18929092]
- Larner AJ. Epileptic seizures in AD patients. *Neuromolecular Med*. 2010; 12:71–77. [PubMed: 19557550]
- Larner AJ. Presenilin-1 mutation Alzheimer's disease: a genetic epilepsy syndrome? *Epilepsy Behav*. 2011; 21:20–22. [PubMed: 21501974]
- Lasiene J, Yamanaka K. Glial cells in amyotrophic lateral sclerosis. *Neurol Res Int*. 2011; 2011:718–987.
- Lazarus M, Shen HY, Cherasse Y, Qu WM, Huang ZL, Bass C, Winsky-Sommerer R, Semba K, Fredholm B, Boison D, Hayaishi O, Urade Y, Chen JF. Arousal effect of caffeine depends on adenosine A2A receptors in the shell of the nucleus accumbens. *J Neurosci*. 2011; 31:10067–10075. [PubMed: 21734299]
- Lee FS, Chao MV. Activation of Trk neurotrophin receptors in the absence of neurotrophins. *Proc Natl Acad Sci U S A*. 2001; 98:3555–3560. [PubMed: 11248116]
- Lepore AC, Dejea C, Carmen J, Rauck B, Kerr DA, Sofroniew MV, Maragakis NJ. Selective ablation of proliferating astrocytes does not affect disease outcome in either acute or chronic models of motor neuron degeneration. *Exp Neurol*. 2008; 211:423–432. [PubMed: 18410928]
- Levine JB, Kong J, Nadler M, Xu Z. Astrocytes interact intimately with degenerating motor neurons in mouse amyotrophic lateral sclerosis (ALS). *Glia*. 1999; 28:215–224. [PubMed: 10559780]

- Li T, Lan JQ, Fredholm BB, Simon RP, Boison D. Adenosine dysfunction in astrogliosis: cause for seizure generation? *Neuron Glia Biology*. 2007a; 3:353–366. [PubMed: 18634566]
- Li T, Lytle N, Lan J-Q, Sandau US, Boison D. Local disruption of glial adenosine homeostasis in mice associates with focal electrographic seizures: a first step in epileptogenesis? *Glia*. 2012; 60:83–95. [PubMed: 21964979]
- Li T, Ren G, Kaplan DL, Boison D. Human mesenchymal stem cell grafts engineered to release adenosine reduce chronic seizures in a mouse model of CA3-selective epileptogenesis. *Epilepsy Res*. 2009; 84:238–241. [PubMed: 19217263]
- Li T, Ren G, Lusardi T, Wilz A, Lan JQ, Iwasato T, Itoharu S, Simon RP, Boison D. Adenosine kinase is a target for the prediction and prevention of epileptogenesis in mice. *J Clin Inv*. 2008; 118:571–582. PMID: PMC2157568.
- Li T, Steinbeck JA, Lusardi T, Koch P, Lan JQ, Wilz A, Segschneider M, Simon RP, Brustle O, Boison D. Suppression of kindling epileptogenesis by adenosine releasing stem cell-derived brain implants. *Brain*. 2007b; 130:1276–1288. [PubMed: 17472985]
- Lovatt D, Xu Q, Liu W, Takano T, Smith NA, Schnermann J, Tieu K, Nedergaard M. Neuronal adenosine release, and not astrocytic ATP release, mediates feedback inhibition of excitatory activity. *Proc Natl Acad Sci U S A*. 2012; 109:6265–6270. [PubMed: 22421436]
- Lubin FD. Epileptogenesis: can the science of epigenetics give us answers? *Epilepsy Curr*. 2012; 12:105–110. [PubMed: 22690136]
- Lucas M, Mirzaei F, Pan A, Okereke OI, Willett WC, O'Reilly EJ, Koenen K, Ascherio A. Coffee, caffeine, and risk of depression among women. *Arch Intern Med*. 2011; 171:1571–1578. [PubMed: 21949167]
- Lucin KM, Wyss-Coray T. Immune activation in brain aging and neurodegeneration: too much or too little? *Neuron*. 2009; 64:110–122. [PubMed: 19840553]
- Lutas A, Yellen G. The ketogenic diet: metabolic influences on brain excitability and epilepsy. *Trends Neurosci*. 2013; 36:32–40. [PubMed: 23228828]
- Mackiewicz M, Nikonova EV, Zimmerman JE, Galante RJ, Zhang L, Cater JR, Geiger JD, Pack AI. Enzymes of adenosine metabolism in the brain: diurnal rhythm and the effect of sleep deprivation. *J Neurochem*. 2003; 85:348–357. [PubMed: 12675911]
- Marsh L. Depression and Parkinson's disease: current knowledge. *Curr Neurol Neurosci Rep*. 2013; 13:409. [PubMed: 24190780]
- Martin LJ, Wong M. Aberrant regulation of DNA methylation in amyotrophic lateral sclerosis: a new target of disease mechanisms. *Neurotherapeutics*. 2013; 10:722–733. [PubMed: 23900692]
- Martire A, Tebano MT, Chiodi V, Ferreira SG, Cunha RA, Kofalvi A, Popoli P. Pre-synaptic adenosine A2A receptors control cannabinoid CB1 receptor-mediated inhibition of striatal glutamatergic neurotransmission. *J Neurochem*. 2011; 116:273–280. [PubMed: 21062287]
- Martorana A, Bulati M, Buffa S, Pellicano M, Caruso C, Candore G, Colonna-Romano G. Immunosenescence, inflammation and Alzheimer's disease. *Longev Healthspan*. 2012a; 1:8. [PubMed: 24764513]
- Martorana F, Brambilla L, Valori CF, Bergamaschi C, Roncoroni C, Aronica E, Volterra A, Bezzi P, Rossi D. The BH4 domain of Bcl-X(L) rescues astrocyte degeneration in amyotrophic lateral sclerosis by modulating intracellular calcium signals. *Hum Mol Genet*. 2012b; 21:826–840. [PubMed: 22072391]
- Masino SA, Li T, Theofilas P, Sandau US, Ruskin DN, Fredholm BB, Geiger JD, Aronica E, Boison D. A ketogenic diet suppresses seizures in mice through adenosine A1 receptors. *J Clin Inv*. 2011; 121:2679–2683.
- Masino, SA.; Rho, JM. Mechanisms of Ketogenic Diet Action. In: Noebels, JL.; Avoli, M.; Rogawski, MA.; Olsen, RW.; Delgado-Escueta, AV., editors. *Jasper's Basic Mechanisms of the Epilepsies*. Bethesda (MD): 2012.
- Masliah E, Dumaop W, Galasko D, Desplats P. Distinctive patterns of DNA methylation associated with Parkinson disease: identification of concordant epigenetic changes in brain and peripheral blood leukocytes. *Epigenetics*. 2013; 8:1030–1038. [PubMed: 23907097]

- Matos M, Augusto E, Machado NJ, dos Santos-Rodrigues A, Cunha RA, Agostinho P. Astrocytic adenosine A2A receptors control the amyloid-beta peptide-induced decrease of glutamate uptake. *J Alzheimers Dis.* 2012a; 31:555–567. [PubMed: 22647260]
- Matos M, Augusto E, Santos-Rodrigues AD, Schwarzschild MA, Chen JF, Cunha RA, Agostinho P. Adenosine A2A receptors modulate glutamate uptake in cultured astrocytes and gliosomes. *Glia.* 2012b; 60:702–716. [PubMed: 22298379]
- Matos M, Shen H-Y, Augusto E, Wang Y, Wei CJ, Wang YT, Agostinho P, Boison D, Cunha RA, Chen J-F. Deletion of adenosine A2A receptors from astrocytes disrupts glutamate homeostasis leading to psychomotor and cognitive impairment: relevance to schizophrenia. *Biol Psychiatry.* 2015 *in press.*
- McGaraughty S, Cowart M, Jarvis MF, Berman RF. Anticonvulsant and antinociceptive actions of novel adenosine kinase inhibitors. *Curr Top Med Chem.* 2005; 5:43–58. [PubMed: 15638777]
- McGeer PL, McGeer EG. Inflammatory processes in amyotrophic lateral sclerosis. *Muscle Nerve.* 2002; 26:459–470. [PubMed: 12362410]
- McGeer PL, McGeer EG. Glial reactions in Parkinson's disease. *Mov Disord.* 2008; 23:474–483. [PubMed: 18044695]
- Meghji P, Newby AC. Sites of adenosine formation, action and inactivation in the brain. *Neurochem Int.* 1990; 16:227–232. [PubMed: 20504561]
- Mendez M, Lim G. Seizures in elderly patients with dementia: epidemiology and management. *Drugs Aging.* 2003; 20:791–803. [PubMed: 12964886]
- Menza M, Forman N, Sage J, Cody R. Psychiatric symptoms in Parkinson's disease: a comparison between patients with and without "on-off" symptoms. *Biol Psychiatry.* 1993; 33:682–684. [PubMed: 8329503]
- Millan MJ. An epigenetic framework for neurodevelopmental disorders: From pathogenesis to potential therapy. *Neuropharmacology.* 2012
- Miller AA, Spencer SJ. Obesity and neuroinflammation: a pathway to cognitive impairment. *Brain Behav Immun.* 2014; 42:10–21. [PubMed: 24727365]
- Mrak RE, Griffin WS. Potential inflammatory biomarkers in Alzheimer's disease. *J Alzheimers Dis.* 2005; 8:369–375. [PubMed: 16556968]
- Nagele RG, Wegiel J, Venkataraman V, Imaki H, Wang KC, Wegiel J. Contribution of glial cells to the development of amyloid plaques in Alzheimer's disease. *Neurobiol Aging.* 2004; 25:663–674. [PubMed: 15172746]
- Nahas R, Sheikh O. Complementary and alternative medicine for the treatment of major depressive disorder. *Can Fam Physician.* 2011; 57:659–663. [PubMed: 21673208]
- Nam HW, McIver SR, Hinton DJ, Thakkar MM, Sari Y, Parkinson FE, Haydon PG, Choi DS. Adenosine and glutamate signaling in neuron-glia interactions: implications in alcoholism and sleep disorders. *Alcohol Clin Exp Res.* 2012; 36:1117–1125. [PubMed: 22309182]
- Neusch C, Bahr M, Schneider-Gold C. Glia cells in amyotrophic lateral sclerosis: new clues to understanding an old disease? *Muscle Nerve.* 2007; 35:712–724. [PubMed: 17373702]
- Newby AC. Adenosine and the concept of 'retaliatory metabolites'. *Trends Biochem Sci.* 1984; 9:42–44.
- Niranjan R. The role of inflammatory and oxidative stress mechanisms in the pathogenesis of Parkinson's disease: focus on astrocytes. *Mol Neurobiol.* 2014; 49:28–38. [PubMed: 23783559]
- Noebels J. A perfect storm: Converging paths of epilepsy and Alzheimer's dementia intersect in the hippocampal formation. *Epilepsia.* 2011; 52(Suppl 1):39–46. [PubMed: 21214538]
- Orr AG, Hsiao EC, Wang MM, Ho K, Kim DH, Wang X, Guo W, Kang J, Yu GQ, Adame A, Devidze N, Dubal DB, Masliah E, Conklin BR, Mucke L. Astrocytic adenosine receptor A2A and Gs-coupled signaling regulate memory. *Nat Neurosci.* 2015; 18:423–434. [PubMed: 25622143]
- Palop JJ, Mucke L. Epilepsy and cognitive impairments in Alzheimer disease. *Arch Neurol.* 2009; 66:435–440. [PubMed: 19204149]
- Paulus W, Jellinger K. The neuropathologic basis of different clinical subgroups of Parkinson's disease. *J Neuropathol Exp Neurol.* 1991; 50:743–755. [PubMed: 1748881]

- Perez-Madrinan G, Cook SE, Saxton JA, Miyahara S, Lopez OL, Kaufer DI, Aizenstein HJ, DeKosky ST, Sweet RA. Alzheimer disease with psychosis: excess cognitive impairment is restricted to the misidentification subtype. *Am J Geriatr Psychiatry*. 2004; 12:449–456. [PubMed: 15353383]
- Perry VH. Innate inflammation in Parkinson's disease. *Cold Spring Harb Perspect Med*. 2012; 2:a009373. [PubMed: 22951445]
- Pihlaja R, Koistinaho J, Malm T, Sikkilä H, Vainio S, Koistinaho M. Transplanted astrocytes internalize deposited beta-amyloid peptides in a transgenic mouse model of Alzheimer's disease. *Glia*. 2008; 56:154–163. [PubMed: 18004725]
- Polymenidou M, Cleveland DW. Prion-like spread of protein aggregates in neurodegeneration. *J Exp Med*. 2012; 209:889–893. [PubMed: 22566400]
- Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjørkum AA, Greene RW, McCarley RW. Adenosine: A mediator of the sleep-inducing effects of prolonged wakefulness. *Science*. 1997; 276:1265–1268. [PubMed: 9157887]
- Prabowo AS, Iyer AM, Veersema TJ, Anink JJ, Schouten-van Meeteren AY, Spliet WG, van Rijen PC, Ferrier CH, Thom M, Aronica E. Expression of neurodegenerative disease-related proteins and caspase-3 in glioneuronal tumours. *Neuropathol Appl Neurobiol*. 2014
- Quiroz C, Lujan R, Uchigashima M, Simoes AP, Lerner TN, Borycz J, Kachroo A, Canas PM, Orru M, Schwarzschild MA, Rosin DL, Kreitzer AC, Cunha RA, Watanabe M, Ferre S. Key modulatory role of presynaptic adenosine A2A receptors in cortical neurotransmission to the striatal direct pathway. *ScientificWorldJournal*. 2009; 9:1321–1344. [PubMed: 19936569]
- Qureshi IA, Mehler MF. Epigenetic mechanisms underlying human epileptic disorders and the process of epileptogenesis. *Neurobiol Dis*. 2010; 39:53–60. [PubMed: 20188170]
- Rao SC, Dove G, Cascino GD, Petersen RC. Recurrent seizures in patients with dementia: frequency, seizure types, and treatment outcome. *Epilepsy Behav*. 2009; 14:118–120. [PubMed: 18782632]
- Rappold PM, Tieu K. Astrocytes and therapeutics for Parkinson's disease. *Neurotherapeutics*. 2010; 7:413–423. [PubMed: 20880505]
- Ravizza T, Kostoula C, Vezzani A. Immunity activation in brain cells in epilepsy: mechanistic insights and pathological consequences. *Neuropediatrics*. 2013; 44:330–335. [PubMed: 24166145]
- Rebola N, Coelho JE, Costenla AR, Lopes LV, Parada A, Oliveira CR, Soares-da-Silva P, de Mendonça A, Cunha RA. Decrease of adenosine A1 receptor density and of adenosine neuromodulation in the hippocampus of kindled rats. *Eur J Neurosci*. 2003; 18:820–828. [PubMed: 12925008]
- Rebola N, Lujan R, Cunha RA, Mulle C. Adenosine A2A receptors are essential for long-term potentiation of NMDA-EPSCs at hippocampal mossy fiber synapses. *Neuron*. 2008; 57:121–134. [PubMed: 18184569]
- Reijnders JS, Ehrt U, Weber WE, Aarsland D, Leentjens AF. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov Disord*. 2008; 23:183–189. quiz 313. [PubMed: 17987654]
- Ren G, Li T, Lan JQ, Wilz A, Simon RP, Boison D. Lentiviral RNAi-induced downregulation of adenosine kinase in human mesenchymal stem cell grafts: a novel perspective for seizure control. *Exp Neurol*. 2007; 208:26–37. [PubMed: 17716659]
- Restrepo A, Smith CA, Agnihotri S, Shekarforoush M, Kongkham PN, Seol HJ, Northcott P, Rutka JT. Epigenetic regulation of glial fibrillary acidic protein by DNA methylation in human malignant gliomas. *Neuro Oncol*. 2011; 13:42–50. [PubMed: 21075782]
- Rial D, Lara DR, Cunha RA. The adenosine neuromodulation system in schizophrenia. *Int Rev Neurobiol*. 2014; 119:395–449. [PubMed: 25175974]
- Ribeiro JA. What can adenosine neuromodulation do for neuroprotection? *Curr Drug Targets CNS Neurol Disord*. 2005; 4:325–329. [PubMed: 16101552]
- Ribeiro JA, Sebastiao AM. Modulation and metamodulation of synapses by adenosine. *Acta Physiol (Oxf)*. 2010; 199:161–169. [PubMed: 20345418]
- Rizzo F, Riboldi G, Salani S, Nizzardo M, Simone C, Corti S, Hedlund E. Cellular therapy to target neuroinflammation in amyotrophic lateral sclerosis. *Cell Mol Life Sci*. 2014; 71:999–1015. [PubMed: 24100629]

- Robberecht W, Philips T. The changing scene of amyotrophic lateral sclerosis. *Nat Rev Neurosci*. 2013; 14:248–264. [PubMed: 23463272]
- Rosin DL, Hettinger BD, Lee A, Linden J. Anatomy of adenosine A2A receptors in brain: morphological substrates for integration of striatal function. *Neurology*. 2003; 61:S12–S18. [PubMed: 14663003]
- Rusina R, Ridzon P, Kulist'ak P, Keller O, Bartos A, Buncova M, Fialova L, Koukolik F, Matej R. Relationship between ALS and the degree of cognitive impairment, markers of neurodegeneration and predictors for poor outcome. A prospective study. *Eur J Neurol*. 2010; 17:23–30. [PubMed: 19572947]
- Salmina AB. Neuron-glia interactions as therapeutic targets in neurodegeneration. *J Alzheimers Dis*. 2009; 16:485–502. [PubMed: 19276541]
- Sanchez-Mut JV, Aso E, Heyn H, Matsuda T, Bock C, Ferrer I, Esteller M. Promoter hypermethylation of the phosphatase DUSP22 mediates PKA-dependent TAU phosphorylation and CREB activation in Alzheimer's disease. *Hippocampus*. 2014; 24:363–368. [PubMed: 24436131]
- Satoh S, Matsumura H, Hayaishi O. Involvement of adenosine A2A receptor in sleep promotion. *Eur J Pharmacol*. 1998; 351:155–162. [PubMed: 9686998]
- Satoh S, Matsumura H, Koike N, Tokunaga Y, Maeda T, Hayaishi O. Region-dependent difference in the sleep-promoting potency of an adenosine A2A receptor agonist. *Eur J Neurosci*. 1999; 11:1587–1597. [PubMed: 10215911]
- Scammell TE, Gerashchenko DY, Mochizuki T, McCarthy MT, Estabrooke IV, Sears CA, Saper CB, Urade Y, Hayaishi O. An adenosine A2a agonist increases sleep and induces Fos in ventrolateral preoptic neurons. *Neuroscience*. 2001; 107:653–663. [PubMed: 11720788]
- Scarmeas N, Honig LS, Choi H, Cantero J, Brandt J, Blacker D, Albert M, Amatniek JC, Marder K, Bell K, Hauser WA, Stern Y. Seizures in Alzheimer disease: who, when, and how common? *Arch Neurol*. 2009; 66:992–997. [PubMed: 19667221]
- Schiffmann SN, Fisone G, Moresco R, Cunha RA, Ferre S. Adenosine A(2A) receptors and basal ganglia physiology. *Prog Neurobiol*. 2007
- Schmidt C, Wolff M, Weitz M, Bartlau T, Korth C, Zerr I. Rapidly progressive Alzheimer disease. *Arch Neurol*. 2011; 68:1124–1130. [PubMed: 21911694]
- Seeman P, Kapur S. Schizophrenia: more dopamine, more D2 receptors. *Proc Natl Acad Sci U S A*. 2000; 97:7673–7675. [PubMed: 10884398]
- Seifert G, Carmignoto G, Steinhauser C. Astrocyte dysfunction in epilepsy. *Brain Res Rev*. 2010; 63:212–221. [PubMed: 19883685]
- Seifert G, Schilling K, Steinhauser C. Astrocyte dysfunction in neurological disorders: a molecular perspective. *Nat Rev Neurosci*. 2006; 7:194–206. [PubMed: 16495941]
- Seifert G, Steinhauser C. Neuron-astrocyte signaling and epilepsy. *Exp Neurol*. 2013; 244:4–10. [PubMed: 21925173]
- Shen H-Y, Coelho JE, Ohtsuka N, Canas PM, Day Y-J, Huang Q-Y, Rebola N, Yu L, Boison D, Cunha RA, Linden J, Tsien JZ, Chen JF. A critical role of the adenosine A2A receptor in extra-striatal neurons in modulating psychomotor activity as revealed by opposite phenotypes of striatum- and forebrain-A2A receptor knockouts. *J Neurosci*. 2008; 28:2970–2975. [PubMed: 18354001]
- Shen H-Y, Sun H, Hanthorn MM, Zhi Z, Lan J-Q, Poulsen DJ, Wang R, Boison D. Overexpression of adenosine kinase in cortical astrocytes generates focal neocortical epilepsy in mice. *J Neurosurg*. 2014; 120:628–638. [PubMed: 24266544]
- Shen HY, Lusardi TA, Williams-Karnesky RL, Lan JQ, Poulsen DJ, Boison D. Adenosine kinase determines the degree of brain injury after ischemic stroke in mice. *J Cereb Blood Flow Metab*. 2011; 31:1648–1659. PMID: PMC3137468. [PubMed: 21427729]
- Shen HY, Singer P, Lytle N, Wei CJ, Lan JQ, Williams-Karnesky RL, Chen JF, Yee BK, Boison D. Adenosine augmentation ameliorates psychotic and cognitive endophenotypes of schizophrenia. *J Clin Invest*. 2012; 122:2567–2577. [PubMed: 22706302]

- Silva CG, Porciuncula LO, Canas PM, Oliveira CR, Cunha RA. Blockade of adenosine A(2A) receptors prevents staurosporine-induced apoptosis of rat hippocampal neurons. *Neurobiol Dis.* 2007
- Simpson JE, Ince PG, Lace G, Forster G, Shaw PJ, Matthews F, Savva G, Brayne C, Wharton SB, Function MRCC, Ageing Neuropathology Study, G. Astrocyte phenotype in relation to Alzheimer-type pathology in the ageing brain. *Neurobiol Aging.* 2010; 31:578–590. [PubMed: 18586353]
- Sofroniew MV, Vinters HV. Astrocytes: biology and pathology. *Acta Neuropathol.* 2010; 119:7–35. [PubMed: 20012068]
- Song W, Patel A, Qureshi HY, Han D, Schipper HM, Paudel HK. The Parkinson disease-associated A30P mutation stabilizes alpha-synuclein against proteasomal degradation triggered by heme oxygenase-1 over-expression in human neuroblastoma cells. *J Neurochem.* 2009; 110:719–733. [PubMed: 19457084]
- Spencer PS, Fry RC, Palmer VS, Kisby GE. Western Pacific ALS-PDC: a prototypical neurodegenerative disorder linked to DNA damage and aberrant proteogenesis? *Front Neurol.* 2012; 3:180. [PubMed: 23267344]
- Spencer PS, Lasarev MR, Palmer VS, Kisby GE. Neurotoxic cycad components and Western Pacific ALS/PDC. *Ann Neurol.* 2010; 68:975–976. author reply 976. [PubMed: 21194164]
- Sta M, Sylva-Steenland RM, Casula M, de Jong JM, Troost D, Aronica E, Baas F. Innate and adaptive immunity in amyotrophic lateral sclerosis: evidence of complement activation. *Neurobiol Dis.* 2011; 42:211–220. [PubMed: 21220013]
- Stanimirovic DB, Friedman A. Pathophysiology of the neurovascular unit: disease cause or consequence? *J Cereb Blood Flow Metab.* 2012; 32:1207–1221. [PubMed: 22395208]
- Steele ML, Robinson SR. Reactive astrocytes give neurons less support: implications for Alzheimer's disease. *Neurobiol Aging.* 2012; 33:423 e421–423 e413. [PubMed: 21051108]
- Steinhauser C, Seifert G, Bedner P. Astrocyte dysfunction in temporal lobe epilepsy: K⁺ channels and gap junction coupling. *Glia.* 2012 *in press.*
- Stone TW, Ceruti S, Abbracchio MP. Adenosine receptors and neurological disease: neuroprotection and neurodegeneration. *Handb Exp Pharmacol.* 2009; 193:535–587. [PubMed: 19639293]
- Studer FE, Fedele DE, Marowsky A, Schwerdel C, Wernli K, Vogt K, Fritschy JM, Boison D. Shift of adenosine kinase expression from neurons to astrocytes during postnatal development suggests dual functionality of the enzyme. *Neuroscience.* 2006; 142:125–137. [PubMed: 16859834]
- Suvisaari J, Mantere O. Inflammation theories in psychotic disorders: a critical review. *Infect Disord Drug Targets.* 2013; 13:59–70. [PubMed: 23713669]
- Swann JW, Rho JM. How is homeostatic plasticity important in epilepsy? *Adv Exp Med Biol.* 2014; 813:123–131. [PubMed: 25012372]
- Szot P. Common factors among Alzheimer's disease, Parkinson's disease, and epilepsy: possible role of the noradrenergic nervous system. *Epilepsia.* 2012; 53(Suppl 1):61–66. [PubMed: 22612810]
- Szybala C, Pritchard EM, Wilz A, Kaplan DL, Boison D. Antiepileptic effects of silk-polymer based adenosine release in kindled rats. *Exp Neurol.* 2009; 219:126–135. [PubMed: 19460372]
- Tebano MT, Martire A, Potenza RL, Gro C, Pepponi R, Armida M, Domenici MR, Schwarzschild MA, Chen JF, Popoli P. Adenosine A(2A) receptors are required for normal BDNF levels and BDNF-induced potentiation of synaptic transmission in the mouse hippocampus. *J Neurochem.* 2008; 104:279–286. [PubMed: 18005343]
- Theofilas P, Brar S, Stewart K-A, Shen H-Y, Sandau US, Poulsen DJ, Boison D. Adenosine kinase as a target for therapeutic antisense strategies in epilepsy. *Epilepsia.* 2011; 52:589–601. PMID: PMC3075862. [PubMed: 21275977]
- Thom M. Review: Hippocampal sclerosis in epilepsy: a neuropathology review. *Neuropathol Appl Neurobiol.* 2014; 40:520–543. [PubMed: 24762203]
- Thom M, Eriksson S, Martinian L, Caboclo LO, McEvoy AW, Duncan JS, Sisodiya SM. Temporal lobe sclerosis associated with hippocampal sclerosis in temporal lobe epilepsy: neuropathological features. *J Neuropathol Exp Neurol.* 2009; 68:928–938. [PubMed: 19606061]
- Tibrewal P, Dhillon R. Caffeine induced psychotic exacerbation. *Aust N Z J Psychiatry.* 2011; 45:179–180. [PubMed: 21070185]

- Ticho SR, Radulovacki M. Role of adenosine in sleep and temperature regulation in the preoptic area of rats. *Pharmacol Biochem Behav.* 1991; 40:33–40. [PubMed: 1780343]
- Tost H, Alam T, Meyer-Lindenberg A. Dopamine and psychosis: theory, pathomechanisms and intermediate phenotypes. *Neurosci Biobehav Rev.* 2010; 34:689–700. [PubMed: 19559045]
- Tozzi A, Tscherter A, Belcastro V, Tantucci M, Costa C, Picconi B, Centonze D, Calabresi P, Borsini F. Interaction of A2A adenosine and D2 dopamine receptors modulates corticostriatal glutamatergic transmission. *Neuropharmacology.* 2007; 53:783–789. [PubMed: 17889039]
- Tremolizzo L, Messina P, Conti E, Sala G, Cecchi M, Airolidi L, Pastorelli R, Pupillo E, Bandettini Di Poggio M, Filosto M, Lunetta C, Agliardi C, Guerini F, Mandrioli J, Calvo A, Beghi E, Ferrarese C, Consortium E. Whole-blood global DNA methylation is increased in amyotrophic lateral sclerosis independently of age of onset. *Amyotroph Lateral Scler Frontotemporal Degener.* 2014; 15:98–105. [PubMed: 24224837]
- Trifileff P, Rives ML, Urizar E, Piskrowski RA, Vishwasrao HD, Castrillon J, Schmauss C, Slattman M, Gullberg M, Javitch JA. Detection of antigen interactions ex vivo by proximity ligation assay: endogenous dopamine D2-adenosine A2A receptor complexes in the striatum. *Biotechniques.* 2011; 51:111–118. [PubMed: 21806555]
- Urade Y, Eguchi N, Qu WM, Sakata M, Huang ZL, Chen JF, Schwarzschild MA, Fink JS, Hayaishi O. Sleep regulation in adenosine A2A receptor-deficient mice. *Neurology.* 2003; 61:S94–S96. [PubMed: 14663019]
- van Calker D, Biber K. The role of glial adenosine receptors in neural resilience and the neurobiology of mood disorders. *Neurochem Res.* 2005; 30:1205–1217. [PubMed: 16341582]
- Van der Auwera I, Wera S, Van Leuven F, Henderson ST. A ketogenic diet reduces amyloid beta 40 and 42 in a mouse model of Alzheimer's disease. *Nutr Metab (Lond).* 2005; 2:28. [PubMed: 16229744]
- Van Dycke A, Raedt R, Dauwe I, Sante T, Wyckhuys T, Meurs A, Vonck K, Wadman W, Boon P. Continuous local intrahippocampal delivery of adenosine reduces seizure frequency in rats with spontaneous seizures. *Epilepsia.* 2010; 51:1721–1728. [PubMed: 20726873]
- Vezzani A, Aronica E, Mazarati A, Pittman QJ. Epilepsy and brain inflammation. *Exp Neurol.* 2011
- Vezzani A, Ravizza T, Balosso S, Aronica E. Glia as a source of cytokines: implications for neuronal excitability and survival. *Epilepsia.* 2008; 49(Suppl 2):24–32. [PubMed: 18226169]
- Vila M, Jackson-Lewis V, Guegan C, Wu DC, Teismann P, Choi DK, Tieu K, Przedborski S. The role of glial cells in Parkinson's disease. *Curr Opin Neurol.* 2001; 14:483–489. [PubMed: 11470965]
- Virus RM, Ticho S, Pilditch M, Radulovacki M. A comparison of the effects of caffeine, 8-cyclopentyltheophylline, and alloxazine on sleep in rats. Possible roles of central nervous system adenosine receptors. *Neuropsychopharmacology.* 1990; 3:243–249. [PubMed: 2400543]
- Wei CJ, Augusto E, Gomes CA, Singer P, Wang Y, Boison D, Cunha RA, Yee BK, Chen JF. Regulation of Fear Responses by Striatal and Extrastriatal Adenosine A Receptors in Forebrain. *Biol Psychiatry.* 2014; 75:855–863. [PubMed: 23820821]
- Williams-Karnesky RL, Sandau US, Lusardi TA, Lytle NK, Farrell JM, Pritchard EM, Kaplan DL, Boison D. Epigenetic changes induced by adenosine augmentation therapy prevent epileptogenesis. *J Clin Inv.* 2013; 123:3552–3563.
- Williams JM, Gandhi KK. Use of caffeine and nicotine in people with schizophrenia. *Curr Drug Abuse Rev.* 2008; 1:155–161. [PubMed: 19630714]
- Wilz A, Pritchard EM, Li T, Lan JQ, Kaplan DL, Boison D. Silk polymer-based adenosine release: Therapeutic potential for epilepsy. *Biomaterials.* 2008; 29:3609–3616. [PubMed: 18514814]
- Woolley SC, Zhang Y, Schuff N, Weiner MW, Katz JS. Neuroanatomical correlates of apathy in ALS using 4 Tesla diffusion tensor MRI. *Amyotroph Lateral Scler.* 2011; 12:52–58. [PubMed: 21271791]
- Wyss-Coray T, Loike JD, Brionne TC, Lu E, Anankov R, Yan F, Silverstein SC, Husemann J. Adult mouse astrocytes degrade amyloid-beta in vitro and in situ. *Nat Med.* 2003; 9:453–457. [PubMed: 12612547]
- Xiao D, Bastia E, Xu YH, Benn CL, Cha JH, Peterson TS, Chen JF, Schwarzschild MA. Forebrain adenosine A2A receptors contribute to L-3,4-dihydroxyphenylalanine-induced dyskinesia in hemiparkinsonian mice. *J Neurosci.* 2006; 26:13548–13555. [PubMed: 17192438]

- Yee BK, Singer P, Chen JF, Feldon J, Boison D. Transgenic overexpression of adenosine kinase in brain leads to multiple learning impairments and altered sensitivity to psychomimetic drugs. *Eur J Neurosci.* 2007; 26:3237–3252. [PubMed: 18005073]
- Yu L, Shen HY, Coelho JE, Araujo IM, Huang QY, Day YJ, Rebola N, Canas PM, Rapp EK, Ferrara J, Taylor D, Muller CE, Linden J, Cunha RA, Chen JF. Adenosine A2A receptor antagonists exert motor and neuroprotective effects by distinct cellular mechanisms. *Ann Neurol.* 2008; 63:338–346. [PubMed: 18300283]
- Zhao Z, Lange DJ, Voustianouk A, MacGrogan D, Ho L, Suh J, Humala N, Thiagarajan M, Wang J, Pasinetti GM. A ketogenic diet as a potential novel therapeutic intervention in amyotrophic lateral sclerosis. *BMC Neurosci.* 2006; 7:29. [PubMed: 16584562]
- Zhou FW, Roper SN. Impaired hippocampal memory function and synaptic plasticity in experimental cortical dysplasia. *Epilepsia.* 2012; 53:850–859. [PubMed: 22417090]
- Zhu Q, Wang L, Zhang Y, Zhao FH, Luo J, Xiao Z, Chen GJ, Wang XF. Increased expression of DNA methyltransferase 1 and 3a in human temporal lobe epilepsy. *J Mol Neurosci.* 2012; 46:420–426. [PubMed: 21826395]
- Zorec R, Araque A, Carmignoto G, Haydon PG, Verkhratsky A, Parpura V. Astroglial excitability and gliotransmission: an appraisal of Ca²⁺ as a signalling route. *ASN Neuro.* 2012; 4

Highlights

- Dysfunction of adenosine signaling is common in neurological conditions.
- Adenosine dysfunction can explain co-morbid phenotypes shared among seemingly unrelated neurological conditions.
- Therapeutic adenosine augmentation is an effective strategy for the treatment of comorbid symptoms in multiple neurological conditions.

Figure 1. Histopathological findings: astrogliosis

Panels A and B: hippocampal sclerosis (HS). A, NeuN showing a typical pattern of neuronal cell loss in HS (ILAE Type 1) associated with prominent astrogliosis (B, GFAP). Panels C and D: Alzheimer's disease (AD), CA1 region with an amyloid plaque (asterisk in C) surrounded by reactive astrocytes (arrows in D). Panels E and F: Parkinson's disease (PD), substantia nigra; asterisk in E and F indicate neurons containing Lewy bodies surrounded by glial cells (arrows). Panels G and H: amyotrophic lateral sclerosis (ALS) spinal cord showing strong vimentin (Vim) expression in reactive astrocytes in both ventral horn (G)

and white matter (H). Sections are counterstained with hematoxylin. A and B: scale bar in A: 500 μm . C–D: scale bar in G; C–D: 80 μm ; E–H: 40 μm .

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Figure 2. ADK immunoreactivity in epilepsy associated pathologies: hippocampal sclerosis (HS), focal cortical dysplasia (FCD) and cortical tubers in patients with tuberous sclerosis complex (TSC)

Panels A, D and E: control hippocampus (CA1) and cortex (CTX, D) and white matter (WM, E) without detectable ADK immunoreactivity (IR) in glial cells. Panels B and C: hippocampal sclerosis (B, CA1; C, hilus), showing increased ADK expression in reactive astrocytes (arrows and insert in B); insert in C: merged confocal image, showing expression of ADK (red) in astrocytes (GFAP positive, green). Panels F–G: FCDIIb (F) and TSC (G) specimens showing increased ADK expression in astroglial cells (arrows) and balloons/giant

cells (asterisks). ADK is visualized using DAB (diaminobenzidine). Sections are counterstained with hematoxylin. Scale bar in H: A-B, D-E, F: 80 μ m; C and G: 40 μ m.

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Figure 3. ADK immunoreactivity in hippocampus in Alzheimer's disease (AD)

Panels A–D: AD hippocampus (CA1) showing strong ADK expression in reactive astrocytes surrounding pyramidal neurons (arrows in A and B) and amyloid plaques (arrows in C and D; asterisks in C and D: amyloid deposits. Insert in B shows positive astrocytes in the vicinity of amyloid deposit (asterisk) and a tangle-containing neuron (arrow-head). ADK is visualized using DAB (diaminobenzidine). Sections are counterstained with hematoxylin. Scale bar in D: A- 80 μ m; B and C: 40 μ m; D: 20 μ m.

Figure 4. ADK immunoreactivity in substantia nigra (SN) and cortex (CTX) in Parkinson's disease (PD)

Panels A–B: control SN (CA1) without weak or not detectable ADK immunoreactivity (IR) in glial cells (arrows in B). Panels C–D: PD SN showing strong ADK expression in reactive astrocytes surrounding remaining neurons (arrows). Panels E–F: ADK expression in reactive astrocytes in frontal cortex of PD patients (arrows). ADK is visualized in red using Fast Red. Sections are counterstained with hematoxylin. Inserts in D and F: merged confocal images, showing expression of ADK (red) in astrocytes (GFAP positive, green). Scale bar in F: A, E: 80 μ m; C, D, F: 40 μ m; B: 20 μ m.

Figure 5. ADK immunoreactivity in the cervical spinal cord of control and amyotrophic lateral sclerosis (ALS) spinal cord

Panels A–B: control cervical spinal cord showing weak or no detectable expression in the large majority of glial cells in both ventral horn (VH, A) and white matter (Wm, B); inserts in A and B: high magnification photomicrograph (arrows indicate glial cells). Panels C–D: ALS cervical spinal cord showing strong ADK expression in reactive astrocytes in both VH (C) and WM (D); insert in C and insert (a) in D: high magnification photomicrograph (arrows indicate glial cells). ADK is visualized using DAB (diaminobenzidine). Sections are counterstained with hematoxylin. Insert (b) in D: merged confocal image, showing expression of ADK (red) in astrocytes (GFAP positive, green). Scale bar in D: A–D: 140 μ m.

Chronic disruption of network homeostasis

Figure 6. Comorbidities in Neurology

Illustration of a possibly self-reinforcing triad of synaptotoxicity, astrogliosis, and adenosine deficiency, as common pathogenetic pathways which might provide a rational explanation for common comorbid symptoms (bottom) shared across several neurological conditions (top).