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Review

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.

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

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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, 2005b, 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_1Rs (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, 2012b, 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 A_1R (Li et al., 2007a; Shen et al., 2014). Reduced A_1R activation promotes excitatory neurotransmitter release and decreases the postsynaptic membrane potential (Fredholm, 1995, 2010). Indeed, deficiency of A_1Rs 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, 2008; Shen et al., 2014). New data sets from our laboratory show that astrogliosis (Fig. 1) and overexpression of ADK (Figs. 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, 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