

Sirtuin 1 and Adenosine in Brain Disorder Therapy

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The neuromodulatory role of adenosine and regulation of brain disorders by Adenosine Receptors (AR) has become critical to brain disorder therapy in different neurodegenerative conditions such as epilepsy, Parkinson's or Alzheimer's disease. Adenosine as a neuromodulator [1] Activates A1 Receptors (A1R) and facilitatory A2A Receptors (A2AR). Disruption of adenosine homeostasis results in seizures with adenosine induction of epigenetic changes by hypomethylation of DNA and inhibition of DNA methylation (epileptogenesis) [2,3]. Brain inflammation and induction of various neurodegenerative diseases now involve adenosine with its therapy [2] relevant to epilepsy and prevention of bacterial Lipopolysaccharide (LPS) induced neuroinflammation through the AR receptors [4,5]. Connections between the anti-aging gene Sirtuin 1 (Sirt 1) [6,7] and AR receptors [1] are relevant to epigenetics (DNA methylation), glucose and lipid metabolism in chronic diseases such as NAFLD, cardiovascular disease and neurodegeneration [8,9]. Diet, LPS and the Sirt 1 have become important to epilepsy with mitochondrial function essential to the prevention of oxidative stress induced by seizures [8,10]. LPS is a critical repressor of Sirt 1 and a competitive inhibitor of many cell functions such as glucose, cholesterol and mitochondrial biogenesis [8,11]. Adenosine treatment with relevance to epileptogenesis [2,3] requires intact cell Sirt 1

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activity to maintain epigenetic changes, synaptic plasticity [12-14] and neuron survival. Sirt 1 and its regulation of NO [15] in the brain is primary to epilepsy/epigenetics [16,17] with effects of adenosine secondary with relevance to NO cell homeostasis [18,19], epilepsy [2,3] and brain disorder therapy.

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