

Preface



For many years the “retaliatory metabolite” and neuromodulator adenosine has been recognized as an endogenous anticonvulsant and neuroprotective molecule. As the core molecule of ATP and of nucleic acids, adenosine forms a unique link among cell energy, gene regulation, and neuronal excitability. Adenosine has long been a highly coveted therapeutic target, and its actions at the A_1 receptor subtype hold well-established and profound therapeutic potential for conditions such as stroke, brain injury, pain, and epilepsy, among others. To date, receptor-based strategies to augment the therapeutic influence of adenosine have been unable to harness its clinical potential, primarily due to side effects at identical peripheral adenosine receptors.

Emerging evidence ignites new hope for adenosine-based therapies in the central nervous system. Parallel and converging lines of research include studies on the ongoing regulation of adenosine by nonpathological, physiologically relevant

stimuli, by metabolism and astrocytes and also by exciting new cell-based approaches. All of these modes of regulation have detailed associated mechanisms established by basic research and, accordingly, proven or predicted clinical implications.

In this book we assemble diverse recent research on regulating the influence of adenosine in the central nervous system. We outline clinical implications and highlight emerging adenosine-based therapies. For example, the relationship between adenosine and the highly altered metabolic state during hibernation has important predictions for neuroprotection. As part of a major paradigm shift, we now understand that the regulation of extracellular adenosine by astrocytes is critical for normal sleep and could be pivotal for the prevention and treatment of epilepsy. In addition, there is an established functional relationship where adenosine and dopamine receptors form receptor heteromers and extend the clinical reach of the regulation of adenosine directly into the realm of dopaminergic disorders and neuropsychiatry. Finally, a ketogenic (high-fat, low-carbohydrate) diet is a metabolic therapy used to treat pediatric and medically refractory epilepsy for nearly 100 years. Although its efficacy is well established, the key neural mechanisms underlying its success remained unclear, hindering development of analogous pharmacological solutions. Converging evidence points to a critical link between ketogenic metabolism and increased adenosine.

Given its ubiquitous presence in the extracellular fluid, and the central role of adenosine as both a metabolic sensor and an effector, it is not surprising that adenosine function and dysfunction in the central nervous system appears to be a common link between diverse neurological and neuropsychiatric conditions. The broad therapeutic implications of understanding the regulation of adenosine extend to acute and chronic neurological disorders as diverse as brain injury, epilepsy, pain, neurodegenerative disorders, and dopamine-related disorders. Here we combine cellular and clinical evidence in an attempt to strengthen the conceptual underpinnings of this important research area and foster a broad and interdisciplinary perspective regarding the therapeutic potential and mechanisms associated with adenosine in the central nervous system.

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