Adenosine’s Autacoid Function in the Central Nervous System and the Behavioral State of Conservation- Withdrawal

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Abstract
The purine nucleoside adenosine has the critical autacoid function of directly linking cellular excitability to energy availability. The mechanism is activated whenever the rate of adenosine triphosphate (ATP) utilization exceeds the rate of synthesis. In CNS neurons, adenosine is produced by the rapid intracellular hydrolysis of purine nucleotides during neural excitation and then is extruded into extracellular space. The nucleoside is also produced by the extracellular hydrolysis of ATP by ectonucleotidases. Extracellular adenosine interacts with G-protein linked stereospecific receptors to reestablish metabolic homeostasis by exerting extraordinarily potent inhibition of neural excitation via a number of mechanisms. This autacoid mechanism is directly linked to the production of a depression-like behavioral state termed conservation-withdrawal during times of physical stress or severe emotional distress. We review evidence here that adenosine produces a transition to conservation-withdrawal by activation of A2A receptors in the ventral-medial striatum.

Keywords: Adenosine; A2A receptor; Autacoid; Behavioral depression; Conservation-withdrawal; Learned helplessness; Striatum

Introduction
Adenosine as an autacoid
The purine nucleoside adenosine functions as an autacoid that links cellular excitability to energy availability in most forms of excitable tissue [1-2]. Adenosine signaling meets all of the criteria of an autocrine mechanism: the nucleoside is produced at the synapse to regulate signal transduction; its production and release are highly regulated; and there are multiple mechanisms of reuptake, deactivation, and degradation to limit its action to a discrete region (Figure 1).

Adenosine plays a crucial homeostatic role in regulating neural excitability in the central nervous system. Figure 1 shows a generic synapse in the CNS to summarize adenosine pharmacology and function. Brain adenosine concentrations normally are about 10,000 fold lower than those of ATP (adenosine triphosphate) [3]. Extracellular adenosine is increased by one of two mechanisms. Adenosine’s autacoid function is engaged whenever the rate of ATP utilization exceeds the rate of synthesis. In brain neurons, this type of imbalance in the energy supply/demand ratio can result from excessive neural activation or from a shortage in brain glucose or oxygen. The nucleoside is produced in nanomolar concentrations as cellular work increases via S-adenosyl-L-homocysteine (SAH) metabolism and is extruded into extracellular space via bidirectional transporters [4-5]. Adenosine is also produced by the rapid hydrolysis of extracellular ATP [6]. Adenine nucleotides are actively transported into and co-localized with neurotransmitter in synaptic vesicles. ATP is co-released with neurotransmitter from the presynaptic terminal at the time of synaptic activation. Carbon dioxide [CO2] concentrations increase in the synaptic cleft during the course neural excitation and cellular respiration. Extracellular pH decreases as a consequence. Acidification of the cleft activates membranebound ectonucleotidases, which convert ATP into adenosine.

Extracellular adenosine exerts its homeostatic and regulatory actions by interacting with four G-protein coupled stereospecific receptors: A1, A2A, A2B, and A3 [7,8]. A1 receptors are widely distributed in the brain and mediate adenosine’s inhibitory actions by coupling with a Gi protein that inhibits adenyl cyclase [9]. A2 receptors...
receptors mediate adenosine’s excitatory actions by coupling a Gs protein that excites adenylyl cyclase [10-11]. The A2B subtype is a low-affinity receptor that is widely distributed in most brain regions. The high-affinity A2A subtype has a much more limited distribution, being localized primarily on enkephalin-containing GABAergic neurons in the striatopallidal tract of the striatum [12-13]. Limited concentrations of A2A receptors also are found in the thalamus [14-16], nucleus tractus solitarius [17-18], and cholinergic neurons of the pontine reticular formation [19-20]. A3 receptors are found primarily in the periphery, with high concentrations in testes and mast cells, and are not heavily expressed in the brain. These receptors play an important role in regulating inflammatory reactions [21-22].

The primary mechanism by which adenosine reestablishes metabolic homeostasis is to produce profound and prolonged inhibition of neural excitation. A number of highly selective receptor agonists that mimic the effects of adenosine at each receptor subtype are now available. By contrast, caffeine and theophylline are widely used to elevate mood, combat fatigue, and reverse the effects of sleep. These methylxanthine stimulants derive their stimulant properties by acting as nonselective antagonists at brain adenosine receptors [1-2].

Extracellular adenosine is regulated by two mechanisms. The nucleoside is rapidly transported into the presynaptic terminal by a bidirectional transporter and converted into 5’AMP by adenosine kinase [4]. The reuptake transporter is blocked by nitrobenzyltheoinosine (NBTI). Blockade of the adenosine reuptake also is at least partially responsible for the anxiolytic and anticonvulsant actions of the benzodiazepine diazepam [2]. The second regulatory mechanism is a degradation pathway involving adenosine deaminase, which converts the nucleoside into inactive inosine that is then degraded into stable uric acid [24]. The degradation pathway is blocked by erythro-9-(2-hydroxy-3-nonyl)adenine (EHNA).

### Adenosine and the behavioral state of conservation-withdrawal

This molecular regulatory mechanism has the unusual effect of directly mediating the transition to a depression-like state under highly aversive circumstances. We borrowed a term from the psychiatric literature (conservation-withdrawal) to characterize this reaction [25].

Engel and Schmale [26] originally coined this term in describing an exaggerated withdrawal response of a psychiatric patient to emotional challenges. The reaction unconditionally follows periods of intense catabolic output. The sensory unresponsiveness, cognitive dullness, and behavioral depression that characterize this state serve as adaptive mechanisms for husbanding limited resources and facilitating the recovery of metabolic homeostasis. The term is used more broadly in modern parlance to refer to enervated states associated with physical or psychological stress.

Conservation-withdrawal is an integral component of major depression and related mood disorders [26-28]. The state most closely corresponds to the affect-less, fatigue components of depression, rather than subsuming the entirety of the behavioral, cognitive, emotional, and motivational symptoms that comprise the disorder. It also represents the aspects of affective disorders that are most accurately modeled in animals. Conservation-withdrawal is also a key component of the after-reaction to physical and psychological stress. Symptoms of conservation-withdrawal are seen after a patient leaves the intensive care unit following a serious injury and are often confused with major depression [28-30]. These same symptoms also are the hallmark of the after-reaction to traumatic uncontrollable stress that has been variously termed learned helplessness [31], behavioral despair [32], behavioral depression [33], and the distress syndrome [34]. Finally, conservation-withdrawal is a critical component of sickness behavior—the lethargy, hypoactivity, decreased libido, anorexia, anhedonia, and increased sleep that accompanies infectious disease [35-37]. This dramatic shift in ongoing activity, along with the induction of fever, is a highly adaptive strategy for fighting infection [35]. The overlap among mood disorders, the after-reaction to traumatic stress, recuperation from injury, and sickness behavior [38-40] suggests a common biological mechanism underlying these enervated states. We have argued that the overlap is well accommodated by the concept of conservation-withdrawal [41-44]. Here we review recent data, from Plumb et al. indicating that adenosine mediates the behavioral depression component of a conservation-withdrawal reaction via purine receptors in the ventral-medial striatum. Previous research implicated adenosine signaling at A2A receptor in the production of conservation-withdrawal in a number of animal models of depression [45]. Most adenosine receptor subtypes have a wide distribution in the CNS. However, A2A receptors are primarily located in the striatum, with a dense population in the nucleus accumbens. These receptors interact with dopamine signaling to influence the motivational regulation of ongoing behavior. Thus, we hypothesized that adenosine signaling increases in the N. accumbens during times of extreme catabolic output and emotional distress to uncouple the dopaminergic signal from ongoing behavior. Normal commerce with the environment transitions to a state of conservation-withdrawal. If so, then we should be able to prevent the transition to a state of conservation-withdrawal via pharmacological blockade of N. accumbens A2A receptors.

Rats were surgically implanted with bilateral cannula in either the shell or core of nucleus accumbens. Following recovery from surgery, we exposed rats to traumatic shock stress (S: shock) or simple apparatus restraint (R: restraint) in the learned helplessness procedure. This is an animal model of post-traumatic stress disorder (PTSD) and comorbid depression. The behavioral syndrome induced by this procedure was considered to be a prototype for conservation-withdrawal by [26]. All rats were tested for shuttle-escape performance, the traditional measure of helplessness in rats [46], 24 hours later. Rats from each pretreatment condition received either bilateral microinfusion of the highly selective A2A receptor antagonist CSC (8-(3-chlorostyryl)caffeine) (S-CSC; R-CSC) or vehicle (S-Veh; R-Veh) 15 minutes before testing. Test data from experiments in the core (left panel) and shell (right panel) or N. accumbens shown in Figure 2. A profound difference in escapable latencies occurred in vehicle-treated shocked (S-Veh) and restrained (R-Veh) groups in both experiments. The difference between these groups defines the learned helplessness effect and is our measure of the behavioral depression component of a conservation-withdrawal reaction. Treatment of the shocked group with the A2A receptor antagonist CSC shortly before testing (S-CSC) completely eliminated the performance deficits in both experiments (Figure 2).

These data clearly implicate adenosine signaling the production of the learned helplessness effect and more generally a conservation-withdrawal reaction. Adenosine is acting at A2A receptors in the indirect pathway in the ventral-medial striatum to produce these effects. Adenosine regulates the motivational influence of mesolimbic dopamine signaling at these receptors. Activation of A2A receptors functionally uncouples dopamine from its receptor, undercutting the motivation for ongoing behavior. Conservation-withdrawal ensues.
Conclusion

Adenosine serves as an autacoid to regulated metabolic homeostasis in most forms of excitatory tissue. The nucleoside is produced in CNS neurons during periods of excessive or unregulated excitation. The autacoid acts to reestablish metabolic homeostasis under these circumstances by exerting profound and prolonged inhibition of neural excitation [26] elaboration of a conservation-withdrawal reaction anticipates exactly this type of molecular mechanism. The sensory unresponsiveness, cognitive dullness, and behavioral depression that characterize this state were seen as unconditional reaction to unresponsiveness, cognitive dullness, and behavioral depression that engenders exactly this type of reaction. Considerable evidence now suggests that activation of adenosine A2A receptors engenders exactly this type of reaction.

References


