Annals of Depression and Anxiety

Austin Publishing Group

Open Access Full Text Article

Review Article

# Animal Models of Depression: A Focus on Adenosine Signaling at $A_{2A}$ Receptors

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**Received:** August 11, 2014; **Accepted:** August 29, 2014; **Published:** September 02, 2014

**Abstract**

This review focuses on the role of the purine nucleoside adenosine in animal models of depression. There is evidence provided that adenosine $A_{2A}$ receptors are involved in several animal models of depression: learned helplessness, behavioral despair, reserpine-induced depression, and effort-related choice. In these models, adenosine $A_{2A}$ antagonists reverse behavioral deficits and exhibit a profile similar to that of classical antidepressants, suggesting that adenosine $A_{2A}$ antagonists could be useful in the treatment of depression.

## Current Theories of Depression

Major depressive disorder is one of the most common and debilitating psychiatric illnesses in the United States; each year 6.7% of adults experience a depressive episode [1]. The neurobiology of depression has been well studied and debated, with early evidence suggesting a "monoamine theory of depression". A cornerstone of the monoamine theory of depression is the observation that many patients being treated with reserpine, an alkaloid extract from the root of the climbing shrub *Rauwolfia Serpentina* that inhibits vesicular monoamine transporters and depletes monoamine levels, developed symptoms of major depression [2]. Similarly, it was later found that monoamine oxidizes inhibitors and tricyclic antidepressants, which are used to treat depression, enhance brain monoamine neurotransmission. These observations led to the development of the catecholamine [3,4] and monoamine [5] theories of depression. Other evidence in support of the monoamine theory of depression comes from the findings that depletion of monoamine stores mitigates the efficacy of antidepressants [6,7], and drugs which deplete monoamine stores can induce depression [8,9].The early monoamine theory of depression has been revised and expanded upon (see Harro and Oreland 2001 [10] for a review), and various versions have been formed. Other theories of depression include neuro genesis (See Ogłodek et al 2014 [11] for a review) and inflammation (see Dantzer 2006 [12] for a review). These theories will not be discussed in detail, as they are beyond the scope of this review.

There is considerable evidence supporting the previously mentioned theories of depression; however, there are likely other mechanisms contributing to the symptoms of depression, and novel pharmacological targets should be investigated. Thus, in the present review, we focus on the contributions of a brain-signaling pathway involving purine nucleoside adenosine to animal models of depression. Adenosine signaling at $A_2A$ receptors is implicated in several animal models of depression, including learned helplessness [13,14], behavioral despair [15,16], cytokine-induced depression [17,18], and effort-related choice [19-23]. We will review these animal models and the behavioral effects of adenosine signaling in these procedures.

## Adenosine

The discovery of the adenosine receptor, and its eventual link to the action of methylxanthine stimulants [24,25], foreshadowed a significant role of this signaling mechanism in behavior, particularly in fatigue-like processes. Caffeine and theophylline, the active ingredients in coffee and tea, respectively, are widely used to elevate mood, combat fatigue, and avoid sleepiness. These compounds derive their stimulant properties by acting as nonselective antagonists at brain adenosine receptors.

Adenosine signaling is closely linked to cellular energy homeostasis [26-31]. The process is engaged whenever the rate of ATP (adenosine triphosphate) utilization exceeds the rate of synthesis. In 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 [32,33]. Adenosine also can be rapidly hydrolyzed from extracellular nucleotides by a family of ectonucleotidases [34]. Extracellular adenosine acts as a modulator of several functions in the brain, including neuronal viability, neuronal membrane potential, propagation of action potentials, astrocytes function, microglia reactivity, primary metabolism in both neurons and astrocytes, and regulation of blood flow [35,36]. Adenosine exerts its homeostatic and regulatory actions by interacting with four G-protein-coupled stereo specific receptors: $A_1$, $A_{2A}$, $A_{2B}$, and $A_3$ [37,38]. $A_1$receptors are widely distributed in the brain and mediate adenosine's inhibitory actions by coupling with $G_i$ proteins, which inhibit adenylyl cyclase. $A_2$ receptors mediate adenosine's excitatory actions by coupling to $G_s$ proteins, which stimulate adenylyl cyclase [39,40]. The $A_{2B}$ subtype is a low-affinity receptor that is widely distributed in most brain regions. The high-affinity $A_{2A}$ subtype has a much more limited distribution, being localized primarily on enkephalin-containing GABA ergic neurons in the striatopallidal tract of the striatum [41,42]. Limited concentrations of $A_{2A}$ receptors also are found in the thalamus [42-44], nucleus tractus solitaries [45,46] and cholinergic neurons of the pontine reticular formation [47]. $A_3$ receptors are found primarily in the periphery, with high concentrations in the testes and mast cells, and are not heavily expressed in the brain. These receptors play an important role in regulating inflammatory reactions [48,49].

Adenosine modulates dopaminergic functions in the dorsal and ventral striatum where the nigrostriatal, mesostriatal, and mesolimbic




**Citation:** Hart EE, Conoscenti MA and Minor TR. Animal Models of Depression: A Focus on Adenosine Signaling at $A_2A$ Receptors. Ann Depress Anxiety. 2014;1(3): 1011.

neuronal pathways terminate. Strong evidence now implies the existence of adenosine $A_{2A}/D_2$ heterogenic complexes coupled in an antagonistic relationship. Hillion *et al* [50] showed that when cells stably transfected with $D_2$ receptors were transiently cotransfected with a tagged$A_{2A}$ receptor, they formed receptor complexes in the absence of exogenous agonists for either receptor. Not only does binding of the $A_{2A}$ receptor in the heterogenic complex result in conformational changes in the $D_2$ receptor, but it also decreases $D_2$ activated coupling to its $G_i$-protein [51]. Activation of the $D_2$ receptor in the heterogenic complex results in $G_i$-mediated inhibition of the activation of adenylyl cyclase by the $A_{2A}$ linked $G_{olf}$-protein [52]. In this conception, $A_{2A}$ receptors modulate glutamatergic afferents to the region *via* an antagonistic coupling to dopamine $D_2$ receptors [53,54]. The functional consequences of this arrangement are that activation of $D_2$ receptors augments ongoing action [55,56]. By contrast, activation of $A_{2A}$receptors produces behavioral depression [19].

Given that both reserpine [2] and tetrabenazine [8,57,58], induce depressive symptoms in humans, that $A_{2A}$ antagonists reverse the behavioral effects of these drugs in animals [16,20], and that both drugs deplete extracellular dopamine [20,59], we propose that the aforementioned antagonistic interactions between $D_2$ and $A_{2A}$ receptors modulate the potential antidepressant effects of $A_{2A}$ antagonists. Figure 1 summarizes the opposing effects on signal transduction of $A_{2A}$ and $D_2$ receptors.

To date, there are no published clinical trials investigating the antidepressant efficacy of $A_2A$ antagonists or any studies investigating adenosine synthesis, metabolism, or receptor distribution in post-mortem tissue from depressed patients. Based on the animal data presented here, we believe this is an area of research that should be expanded upon Figure 1.

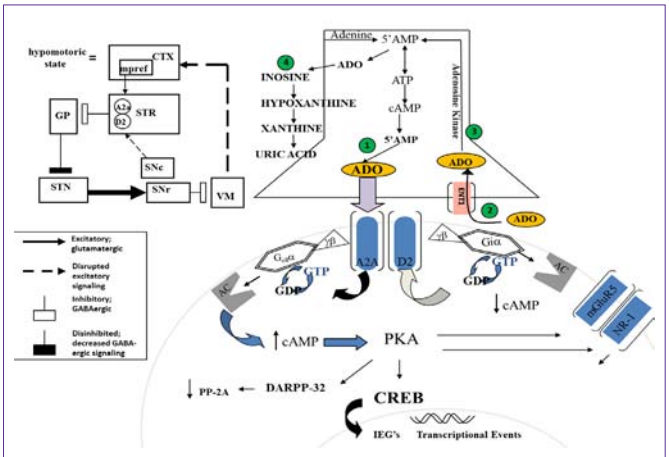


**Figure 1:** Adenosine signaling in the A2A/D2/m GLU receptor complex in the striatum. Activation of the A2A receptor results in increased GABA ergic signaling from the striatopallidal cells which project to the external globus pallid us. The tonic inhibitory projections are attenuated by the increase in the GABA ergic signal arriving from the striatum. This disinherits the sub thalamic nucleus, which sends an increased excitatory projection to the substantia nigra pars reticulate, where heightened inhibitory signal disrupt normal motor output from the ventro medial thalamus, resulting in hypo motility. (1) 5'Nucleotidases convert 5'AMP to ADO, which is extruded into extracellular space via Ca++ dependent release. High- and low-affinity nucleoside uptake transporters are responsible for extracellular ADO concentration. (2) Blocking the ENT1 transporter with NBT1 (an ADO transport inhibitor) is one suggested mechanism for extracellular increase in ADO. Once inside the cell, (3) ADO is converted to 5'AMP via adenosine kinase, thereby increasing expendable energy (represented in the number of high-energy phosphate bonds). (4) The ADO degradation pathway, located on glia, converts ADO to the inactive insane and eventually to uric acid. The A2A linked $G_{olf}$ protein results in an accumulation of c AMP. The c AMP accumulation leads to activation of PKA, which facilitates the phosphorylation of certain dopaminergic and glutamatergic-modulating genes (e.g. DARPP-32), along with CREB, which results in further transcriptional events, most notably c-fos and other immediate early genes.

## Learned Helplessness and Adenosine Signaling

The learned helplessness paradigm is an animal model of depression. The experiment is a simple two-phase procedure. Sets of three rats are restrained in wheel-turn chambers in the pretreatment phase. The first rat in each triad is exposed to a series of controllable shock escape trials. The rat must complete a 360° turn of the wheel with its paws following shock onset in order to terminate the aversive event on each trial. A second rat receives yoked inescapable (uncontrollable) shock on each trial. Shock comes on at the same time for both rats on a trial and terminates when the first rat completes the escape response. Wheel-turn responses by the yoked rats are ineffective in altering shock. Thus, both rats receive the same intensity pattern and duration of shock on each trial, but differ in the extent to which they can exert behavioral control over the stressor. These rats receive 100 such trials over a period of 2 h. A third rat is simply restrained in the chamber for the same period of time and receives no shock. The restrained rat provides a behavioral and physiological baseline from which any differential effects of stressor controllability can be assessed during later testing. Although the nature of the test varies with the interests of the experimenter, the traditional measure of helplessness has been a performance in a shuttle-escape task conducted 24 h after stress pretreatment [60]. The shuttle-escape task consists of five fixed ratio-1 (FR-1) trials during which a single shuttle crossing is required to terminate shock. This is followed by 25 trials (or FR-2 trials) during which a rat must run from one side of the shuttle box to the other, and then return, to terminate shock. Both trial types are presented with an average inter trial interval of 60s; however, 3 minutes intervene between trial types, which maximizes escape deficits in inescapably shocked rats without adversely affecting control subjects [61]. Trials terminate automatically if the appropriate response requirement is not met within 40 seconds of shock onset. Groups typically do not differ in mean escape latencies during FR-1 trials. However, large performance differences occur when the response requirement is made more difficult (FR-2 trials). Rats preexposed to escapable shock in the pretreatment phase perform as efficiently as restrained controls during escape testing. By contrast, rats preexposed to yoked inescapable shock show severe impairment, with near-maximum escape latencies during the FR-2 trials. This general pattern among groups holds for a wide variety of behavioral and biological stress indices. Moreover, because escapable and inescapably shocked rats receive the same pattern, intensity, and durations of shock during pretreatment, the differential performance of these two groups in the test phase provides unequivocal evidence that some psychological variable related to behavioral control, or lack thereof, modulates the impact of the shock stressor [62]. It is important to note that not all rats display helpless behavior after exposure to shock. Research investigating the nature of individual differences in helplessness

suggests that susceptibility is associated with abnormalities in HPA axis activation [63], reduced reward sensitivity [64], increased novelty seeking [64], and synaptic potentiation in the medial prefrontal cortex [65]. Resilience has been linked to synaptic weakening in the medial prefrontal cortex [65] and altered sensitivity to the behavioral effects of GABA-A receptor antagonists [66]. The helpless phenotype has been validated in other tests. Helpless rats show motor disturbances akin to the psychomotor retardation seen in depressed patients [67-69], alterations in REM sleep [70], decreased saccharin consumption [71], and congenitally helpless rats show impaired work output for sucrose solution [72].

A simpler version of this procedure is often used when testing the efficacy of experimental compounds at alleviating stress-induced pathology. Because rats exposed to escapable shock do not show behavioral or physiological impairment, this condition adds an unnecessary expense to basic pharmaceutical research. Thus, much of the research discussed here compares rats exposed to variable-duration inescapable shocks during the pretreatment phase with the restrained control. Research over the past decade has yielded a consensus on a number of critical issues concerning the psychological and neurobiological determinants of helplessness. Behavioral disturbances following inescapable shock are a consequence of the induction and prolonged maintenance of fear during exposure to the uncontrollable stressor [73-75]. Controllable stress is less debilitating because it is less fear provoking (see and Hunter 2002 [76] for a review). The consequence of maintaining an intense catabolic reaction during inescapable shock is that a number of neural systems associated with fear and stress are rendered hyper responsive and highly vulnerable to subsequent stress for 24–72 h. Inescapably shocked rats enter the test phase of the helplessness experiment in an anxious, agitated state. Exposure to comparatively mild stress during the first few shuttle escape trials provokes exaggerated behavioral activation to the shock and excessive fear during the interval between trials [77,78]. This behavioral reaction is correlated with sustained Glucocorticoid secretion [79], rapid turnover of brain biogenic amines [80], depletion of forebrain nor epinephrine [81-83], dopamine [84,85] and γ-amino butyric acid (GABA) [86], and excessive release of excitatory amino acid transmitters [87] and N-methyl-D-aspartate (NMDA) receptor activation [88]. The initial response is short-lived and the animal rapidly transitions from a highly catabolic state to one of behavioral quiescence, dissociation, or conservation-withdrawal. This general pattern of excessive neural activation is reminiscent of the conditions that compromise brain metabolic homeostasis and result in potent compensatory inhibition by adenosine. Although little was known about the behavioral effects of adenosine at the time we started this research, there was evidence that adenosine analogs suppress spontaneous motor activity and can produce a semi-hypnotic state [89-91]. These properties of receptor agonists suggest adenosine signaling may be a plausible mechanism for the behavioral depression and cognitive dysfunction associated with conservation-withdrawal and helplessness. Thus, we hypothesized that the excessive and unregulated neural activation that characterizes inescapably shocked rats during the first few minutes of escape testing rapidly compromises neural energy homeostasis, resulting in potent compensatory adenosine regulation.

The least intuitive prediction of this hypothesis, at least from a psychological perspective, is that treatment with methylxanthine stimulants just prior to testing in inescapably shocked rats should dramatically improve escape performance. The conceptual difficulty here is that methylxanthine have rather potent angiogenic effects, particularly at high doses. Thus the prediction is that a condition that stems from too much fear [74,92] will be improved by a treatment that induces anxiety. Despite this conundrum, the straightforward prediction is well substantiated. Figure 2 (left panel) shows the effects of pretest treatment with various drugs on shuttle-escape performance in rats previously exposed to inescapable shock. Each point represents the mean FR-2 escape latencies for groups of eight rats. The nonselective adenosine receptor antagonist's caffeine and theophylline reversed the effects of inescapable shock on later escape performance in a dose-dependent manner, relative to the vehicle control. Amphetamine, a nonxanthine psychomotor stimulant, had no beneficial effect at any dose under study. The ability of the methylxanthine to reverse the helplessness effect was not due to drug state dependency and these drugs had no effect on the performance of non-shocked restrained controls Figure 2.

Adenosine analogs have the opposite effect on escape performance. Figure 2 (right panel) shows the FR-2 shuttle escape latencies of groups of rats receiving a pretest injection of various adenosine analogs. One group of rats was exposed to Inescapable Shock (IS) and one group was restrained (REST) during the pretreatment phase of the experiment. Twenty-four hours later, these groups received vehicle (V) 15 min before escape testing and defined the boundaries of the helplessness effect. Other restrained groups were injected with various doses of either: (a) 5'-N-Ethylcarboxamidoadenosine (NECA), a high affinity, but nonselective adenosine receptor agonist; (b) R (−) Phenylethyladenosine (R (−)PIA), a high-affinity, highly selective agonist of the $A_1$ receptor; or (c) S(+)-Phenylethyladenosine (S(+)PIA), the relatively inactive enantiomer of R-PIA. Later escape

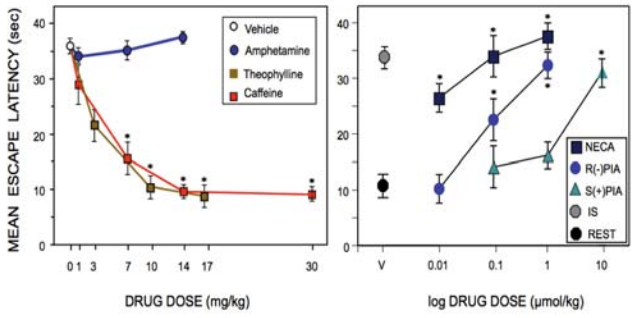


**Figure 2:** (Left Panel) Grand mean FR-2 shuttle-escape latencies as a function of drug type and dose. All rats were exposed to un signaled inescapable shock on day 1. Shuttle-escape testing occurred 24 h later. Groups of rats received an i.p. injection of vehicle or various doses of amphetamine, caffeine or theophylline 15 min before testing. Each point in the figure is the mean for a group of eight rats. *$p$<.05, different from vehicle. (Right Panel) Grand mean FR-2 shuttle-escape latencies as a function of drug type and dose. One group of rats was exposed to Inescapable Shock (IS) and one group was restrained (REST) in tubes 24 h prior to shuttle escape testing. These groups were treated with vehicle 15 min before testing and their performance sets the boundaries for the learned helplessness effect. All other groups were restrained in tubes 24 h before receiving an i.p. injection of the nonselective adenosine agonist NECA, the highly selective $A_1$ receptor agonist R(−)PIA, or its enantiomer S(+)PIA. Escape testing occurred 15 min later. *$p$<.05, different from restraint-vehicle group. Figures taken from Minor et al 1994 [13,14].

testing of these groups clearly indicated that the effects of inescapable shock are mimicked by activation of adenosine receptors. The comparison of NECA and R (–) PIA provided the first evidence that this effect may be mediated at the $A_2$receptor. Moreover, the deleterious effects of pretreatment with inescapable shock or pretest treatment with NECA on escape performance is not reversed by peripheral treatment with the polarized methylxanthine stimulant 8-(p-Sulfopenyl)-theophylline (8-SPT), which does not cross the blood–brain barrier [93], but is completely reversed by theophylline, which acts both centrally and peripherally [13,14]. These data suggest that the effects of adenosine signaling on shuttle escape latencies are occurring within the Central Nervous System (CNS).

NECA and inescapable shock also interact synergistically. Exposure to an ineffective number of inescapable shocks during pretreatment combines with the administration of sub threshold doses of NECA just prior to testing to produce performance deficits in the shuttle-escape task. The contribution of adenosine to the helplessness effect appears to be related to neural over activation and subsequent metabolic failure. Over activation of glutamate neurons in prefrontal cortex substantially impairs later escape performance [94]. The deficit is completely reversed by adenosine receptor antagonists, suggesting that over activation lead to compensatory adenosine signaling, which then impairs performance [87]. Escape performance is also impaired by systemic treatment with the glycolytic inhibitor 2-deoxy-D-glucose (2-DG) in a dose-dependent manner [95]. This effect of 2-DG is not a direct consequence of glucoprivation or metabolic inhibition per se. Escape deficits are completely eliminated by peripheral and central administration of caffeine and theophylline, but are not reversed by the peripherally acting receptor antagonist 8-SPT. These data suggest that 2-DG compromises brain energy metabolism, resulting in compensatory adenosine regulation. Potent inhibition of brain substrates responsible for escape performance ultimately impairs performance.

Endogenous extracellular adenosine concentrations are regulated by two mechanisms. The nucleoside is converted to inactive insane and eventually to uric acid via a degradation pathway involving adenosine delaminate [32,96,97]. The nucleoside also is removed from the synaptic cleft via equilibrate nucleoside transporters (ENT1 and ENT2), as well as an active transport system involving Na+ [98]. Adenosine is rapidly converted to 5' AMP via adenosine kinase once inside the cell, which stops active gradient transport of the nucleoside. Disabling either of these regulatory mechanisms functionally increases synaptic adenosine concentrations and its action at extracellular receptors. Thus, if brain adenosine signaling mediates the escape deficits produced by initial exposure to inescapable shock, then enhancing the small and otherwise non-debilitating endogenous concentrations produced by prior restraint stress by either blocking degradation or uptake transport should disrupt test performance. Woodson et al [99] demonstrated that inhibiting adenosine delaminate, using erythro-9-(2-hydroxy-3-nonyl) adenine (EHNA), mimics the effects of inescapable shock on shuttle-escape performance in rats. Micro infusion of EHNA into the brain ventricles of previously restrained rats impaired test escape performance in a dose-dependent manner. This effect of EHNA, as well as the effect of earlier exposure to inescapable shock, was reversed by pretest treatment with adenosine receptor antagonist caffeine. A sub threshold dose of EHNA also interacted in synergy with preexposure to an ineffective number of inescapable shocks to maximally impair shuttle-escape performance at the time of testing. Increasing endogenous adenosine concentrations by blocking the uptake transporter yields a similar pattern of results [100]. Micro infusion of the nucleoside transport blocker S-(4-nitrobenzyl)-6-theoinosine (NBTI) into the right lateral ventricle of rats that underwent restraint stress 24 hours earlier produces a large deficit in shuttle-escape performance, which is comparable to that produced by prior exposure to inescapable shock. NBTI impairs escape performance in a dose-dependent manner. Moreover, a sub threshold dose of the adenosine uptake inhibitor NBTI acts synergistically with an ineffective number of inescapable preshocks to maximize deficits in test escape performance, suggesting that NBTI and inescapable shock are acting on the same neural mechanism. Analysis of the receptor mediating shock-induced and NBTI-induced escape deficits, using highly selective receptor antagonists, supported earlier evidence for an $A_2$ receptor. Both types of deficits were reversed by the nonselective adenosine receptor antagonist caffeine and the highly selective A2A receptor antagonist CSC (8-(3-chloro-styrl) caffeine in a dose-dependent manner. The highly selective $A_1$ (DPCPX: 8-Cyclopentyl-1,3-Dipropylxanthine) receptor antagonist failed to improve performance in rats preexposed to inescapable shock or receiving intra cerebral ventricular (i.c.v.) infusion of NBTI shortly before escape testing. These data strongly suggest that activation of $A_{2A}$ receptors mediates deficits in escape performance, regardless of whether those deficits occur because of prior stress or by enhancing endogenous adenosine signaling through pharmacological means. As discussed in detail later, $A_{2A}$ receptors have a limited and unique distribution in the CNS. Thus, these data have important implications for the anatomical locus and mechanism by which adenosine signaling mediates behavioral depression.

## Adenosine Signaling in Screens of Antidepressant Activity

Two widely used screens for antidepressant activity include the forced swim test [101] and tail suspension test [102]. The forced swim test is conducted in mice or rats and involves subjecting the animal to an inescapable chamber for a given length of time. During testing, time spent struggling or swimming and time spent floating (immobile) are recorded. Increased time floating is interpreted as despair-like behavior. Established antidepressants increase time spent swimming, decreasing time spent floating. The tail suspension test is conducted in mice, and involves suspending the animal by its tail and recording time struggling versus time spent immobile. Interpretations are the same as those of the forced swim test, and antidepressants also decrease immobility time in this test.

Vangelis and his colleagues have accumulated considerable evidence for a role of $A_{2A}$ receptor signaling in the forced swim and tail suspension tests (see El Yacoubi et al. 2003 [103] for a review). They argue on the basis of these data that $A_{2A}$ receptor antagonists may have potent antidepressant properties. Much of the evidence for the role of adenosine signaling in behavioral despair comes from studying $A_{2A}$ receptor knockout mice [15]. These mice showed increased mobility relative to wild types in both forced swim and tail suspension test [15,35,103]. Immobility scores in the forced swim task in CD1 mice (wild-type controls) are reduced in a dose-dependent

manner by caffeine and the highly selective $A_{2A}$ receptor antagonist SCH 58216. Similar results are obtained in the tail-suspension test. Moreover, the benefits of treatment with the $A_{2A}$ receptor antagonist in mice genetically selected for spontaneous helplessness were only slightly less than the benefits of the antidepressant imipramine. The benefits of an $A_{2A}$ receptor antagonist in these procedures are likely to result from an interaction with striatal dopamine. The dopamine $D_2$ antagonist haloperidol increases immobility in both forced swim and tail-suspension tests [15,103]. Moreover, co treatment with haloperidol mitigates the behavioral activating effects of caffeine in these procedures. Interestingly, co treatment with haloperidol and SCH 58216 decreased the activating effect of the $A_{2A}$ receptor antagonist on spontaneous activity, but did not alter its benefits in behavioral despair paradigms.

## Adenosine Signaling in Reserpine-Induced Forced Swim Test Deficits

Huang and Minor [17,87,104] treated rats with an i.p. injection of 6 mg/kg of reserpine and then tested independent groups in a forced swim task for symptoms of conservation-withdrawal at various times thereafter. Large deficits in swim performance, as characterized by a large increase in floating time, were evident as early as 1 h post drug treatment, persisted for at least 72 h, and recovered within a week. The determinants of reserpine-induced depression are complex and change over time. Moreover, the impairment is likely to be a "downstream" consequence of reserpine effect on the monoamines rather than a direct result of their depletion per se. Adenosine plays a critical role in swim deficits as early as 1 h post drug treatment and continues to be a critical mediator at all time points thereafter. Caffeine and the highly selective $A_{2A}$receptor antagonist CSC reverse swim deficits at all time points under study [16]. $A_1$ and $A_{2B}$receptor antagonists have no such effect [16]. Figure 3 show the effect of $A_{2A}$ receptor antagonist CSC on reserpine-induced swim deficits Figure 3.

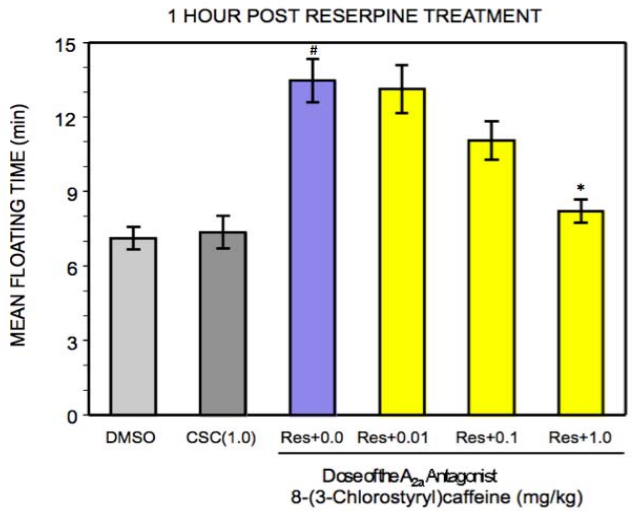


**Figure 3:** The $A_{2A}$ antagonist CSC (1.0 mg/kg i.p.) reverses the depressive effects of reserpine (6.0 mg/kg i.p.) in forced swim testing. CSC (1.0 mg/kg) by itself has no effect on swim performance. Figure taken from Minor and Hanff 2014 [16] #$p$<.05, different from DMSO (reserpine vehicle). *$p$<.05, different from 6.0 mg/kg reserpine (single factor ANOVA with Newman-Keuls post-hoc test).

The proinflammatory cytokine interleukin-1β (IL-1β) increases dramatically in the hypothalamus and to a lesser extent in the hippocampus 48–72 h after reserpine treatment and then returns to normal levels in the brain within 168 h. In this context, the IL-1β receptor antagonist has no effect on swim deficits 1 h after reserpine treatment, but substantially improves performance 48 h later. Although there is only a small literature on the potential interactions between adenosine and IL-1β, it is clear that these pathways interact. For instance, application of endotoxins or IL-1β on PC12 or THP-1 cells up regulates the density of $A_{2A}$ receptors and increases extracellular concentrations of adenosine [105,106]. Furthermore, the $A_{2A}$antagonist CSC reverses forced swim test deficits induced by IL-1β (Figure 4).

## Effort-Related Choice and Adenosine Signaling

Major depressive disorder is characterized by profound motivational deficits [68,69] that have been described as anergia [20], fatigue [20], and motivational anhedonia [107]. Depressed patients show impairments in effort-related decision making and prefer low effort/low reward options to high effort/high reward options [108]. This effort-related choice has been well characterized as an animal model of the motivational symptoms of depression [20,22,23]. Salam one and colleagues have used a task to assess effort-related choice extensively. In this procedure, animals are given a choice between a high effort, high reward option (lever pressing for sugar pellets) and a low effort, low reward option (freely available lab chow with no work requirement). This task has been dubbed the concurrent operant/chow feeding choice procedure. In this task, shifts in effort-related choice (decreases in lever pressing with concurrent increases in chow consumption) are proposed to be analogous to anergia or fatigue commonly seen in depression [18,20,23]. Another task that measures effort-related choice used by the Salam one lab is the T-maze barrier choice task. In this paradigm, animals are also given a choice between

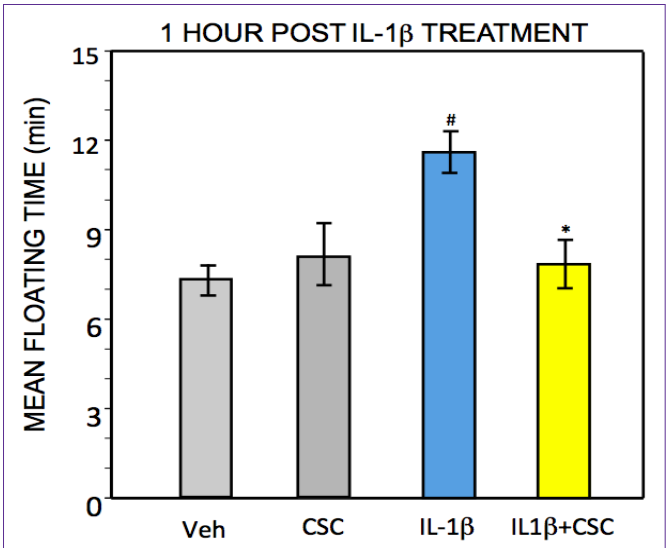


**Figure 4:** The $A_{2A}$ antagonist CSC (1.0 mg/kg i.p.) reverses the depressive effects of Interleukin 1-β (2 ng uni lateral i.c.v.) in forced swim testing. CSC by itself has no effect on swim performance. Figure taken from [113] #$p$<.05, different from vehicle. *$p$ <.05, different from IL1-β (single factor ANOVA with Newman-Keuls post-hoc test).

a high effort/high reward option and a low effort/low reward option. In one arm of the T, animals can approach and consume 2 sugar pellets. In the other arm, animals can earn 4 sugar pellets, but they must climb over a 44 cm barrier to get to them. In both of these tests of effort, adenosine signaling has shown a clear contribution.

$D_1$ antagonism [109], $D_2$ antagonism [109,110], as well as dopamine depletions [20] were all shown to produce impairments in effort, shifting behavior away from high effort choices. In all three cases, concurrent administration of an adenosine $A_{2A}$ antagonist reverses these impairments, restoring lever presses to baseline and decreasing consumption of freely available lab chow. Moreover, administration of A2A antagonists alone has very little effect on fixed-ratio responding [111]. In line with data from Minor and colleagues [16] demonstrating $A_1$ receptor antagonists do not reverse impairments in the forced swim test, $A_1$ receptor antagonists also do not reverse impairments in exertion of effort induced by $D_1$ or $D_2$ antagonism in the operant/ concurrent chow feeding choice procedure [23].

In the operant/concurrent chow feeding choice procedure, adenosine $A_{2A}$ receptor stimulation with micro infusions of CGS21680 into the nucleus accumbency was shown to produce impairments in effort [19], decreasing lever pressing and increasing chow intake. These data directly demonstrate a role of adenosine signaling at $A_{2A}$ receptors in fatigue-like processes.

Data from the Salam one lab has shown the same pattern of results in the T-maze barrier choice task. Adenosine $A_{2A}$ antagonists reverse impairments in effort induced by $D_2$ antagonism [21,112]. Furthermore, $A_{2A}$ receptor knockout mice do not show haloperidol-induced impairments in effort [21], suggesting that $A_{2A}$ receptor activation is necessary for $D_2$ antagonist-induced impairments in effort.

In line with data collected by Minor and colleagues [17], the pro-inflammatory cytokine IL-1β has effects on effort-related choice [18], producing behavioral effects that resemble those of dopamine antagonism. Just as swim deficits induced by IL-1β are reversed by $A_{2A}$ antagonism [17], effects on effort-related choice are also reversed by $A_{2A}$ antagonism [18].

## Conclusion

Adenosine signaling plays a role in several animal models of depression. Learned helplessness, forced swim, tail suspension, and effort-related choice are all affected by manipulations of adenosine neurotransmission. Blockade of $A_{2A}$ receptors reverses impairments in these behaviors; and$A_{2A}$ antagonists have behavioral effects that resemble those of antidepressants. Moreover, stimulation of $A_{2A}$ receptors and manipulations that increase adenosine neurotransmission produce deficits in these behaviors. Taken together, evidence suggests adenosine $A_{2A}$ receptors could prove to be a useful target for treating depression, and future research should address this.

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Ann Depress Anxiety - Volume 1 Issue 3 - 2014
**ISSN : 2381-8883** | www.austinpublishinggroup.com


**Citation:** Hart EE, Conoscenti MA and Minor TR. Animal Models of Depression: A Focus on Adenosine Signaling at $A_2A$ Receptors. Ann Depress Anxiety. 2014;1(3): 1011.