Biochemical and Anatomical Substrates of Depression and Sickness Behavior

Thomas C. Hanff, MD, Stephanie J. Furst, and Thomas R. Minor, PhD

Departments of Psychology and Neuroscience, University of California, Los Angeles, California, U.S.A.

ABSTRACT

This paper reviews recent research on the contribution of the proinflammatory cytokine interleukin-1β (IL-1β) and the purine nucleoside adenosine in mediating behavioral depression and related symptoms of conservation-withdrawal in animal models of both major depression and illness. Activation of brain IL-1β receptors appears to contribute to conservation-withdrawal symptoms in animals treated with reserpine or lipopolysaccharide, suggesting a common underlying mechanism. Moreover, brain cytokine signaling is capable of recruiting adenosine signaling at adenosine A_{2A} receptors, which directly mediate symptoms of behavioral depression. The adenosine receptors densely populate spiny GABAergic neurons in the striopallidal tract in the striatum and form part of an A_{2A}/D_2/mGLU receptor complex. Activation of these A_{2A} receptors functionally uncouples dopamine's excitatory motivation influence from ongoing behavior, leading to a state of conservation-withdrawal, and antagonism of the ventral medial striatum A_{2A} receptors in reserpinated rats relieves symptoms of behavioral depression.

INTRODUCTION

Sickness behavior – the lethargy, hypoactivity, decreased libido, anorexia, anhedonia, and increased sleep that accompanies infectious disease (1, 2) was once thought to be a maladaptive consequence of an animal's immune response, damaging the animal's ability to successfully interact with its environment. However, two decades of research into the biological mechanism of sickness behavior have modified this view, demonstrating that sickness behavior is an adaptive central motivational state necessitated by the metabolic constraints for mounting a fever (3).

The characterization of sickness behavior as a motivational state underscores similarities among mood disorders, the reaction to traumatic stress and recuperation from injury (4). Each of these conditions is associated with intense catabolic output (5) and is automatically and unconditionally followed by a compensatory shift to a behavioral state termed *conservation-withdrawal* (6). The sensory unresponsiveness, cognitive dullness and behavioral depression that characterize this state are adaptive mechanisms for husbanding limited resources and facilitating the recovery of energy homeostasis.

Conservation-withdrawal is an integral component of major depression and related mood disorders (7). This reaction 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 (8). Conservation-withdrawal also is a key component of the after-reaction to physical and psychological stress. Thus 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 (9). These same symptoms also are the hallmark of the after-reaction to traumatic psychological stress that has been variously termed learned helplessness (10), behavioral depression (11) and the distress syndrome (12), and they comprise a critical component of sickness behavior.

This paper reviews research from our laboratory on conservation-withdrawal reactions in two animal paradigms that have been used to model symptoms of major depression: induction of sickness behavior with endotoxin or interleukin-1β (IL-1β), and systemic injection

Address for Correspondence: ✉ Thomas R. Minor, Departments of Psychology and Neuroscience, University of California, Los Angeles, CA 90095-1563, U.S.A. minor@psych.ucla.edu

of reserpine. We have examined the potential contribution of two signaling pathways – one involving the purine nucleoside adenosine, and the other involving the proinflammatory cytokine IL-1β – to the induction of conservation-withdrawal in each of these paradigms. Both of these molecules modulate excitable tissue in the periphery (13, 14). They also produce global organized responses by binding to receptors in the central nervous system to alter neural signaling (15, 16). More important, both of these pathways are capable of producing the symptoms of conservation-withdrawal. A brief review of cytokine and adenosine signaling are presented below.

I. MODULATORS OF CONSERVATION-WITHDRAWAL

A. Brain Adenosine Signaling. Adenosine participates in a purine feedback pathway that regulates excitable tissue with respect to available energy.

The purine nucleotide adenosine triphosphate (ATP) and the nucleoside adenosine (ADO) serve as endpoints in intracellular metabolism, with expendable energy represented in the number of high-energy phosphate bonds (17). These molecules also are liberated into extracellular space to convey information concerning intracellular energy state. Adenosine signaling is actively engaged by challenges to metabolic homeostasis (18). The nucleoside exerts very potent inhibition on excitatory transmission in brain as a compensatory reaction to neural energy failure (19).

Adenosine is extruded into extracellular space or hydrolyzed from extracellular nucleotides whenever the rate of adenosine triphosphate (ATP) hydrolysis exceeds the synthesis rate (20). Such an imbalance of the energy supply/demand ratio can result from excessive neural activation or from a shortage in brain glucose or oxygen. The extracellular nucleoside binds to specific G-protein linked adenosine receptors (A_1, A_{2A}, A_{2B}, & A_3), which are widely distributed on pre- and post-synaptic membranes and in the microvascular bed (21). Adenosine interacts with a number of cellular effector systems via these receptors to decrease membrane excitability and inhibit transmitter release, thereby decreasing metabolic demand in the target neuron (22). Adenosine also acts at the system level to produce a number of changes that protect neural tissue from the potentially excitotoxic effects of activation in the absence of sufficient energy (23).

Extracellular adenosine concentrations normally are controlled by high- and low-affinity nucleoside uptake transporters (24). Adenosine is rapidly converted to 5'AMP by adenosine kinase once inside the cell, which decreases subsequent extrusion via gradient transport.

The receptor-mediated effects of the ligand also are regulated by a degradation pathway located on glia, which converts extracellular adenosine to inactive inosine and eventually to uric acid (25).

The features of adenosine signaling that are most relevant to conservation-withdrawal, and particularly the aspects of the syndrome related to behavioral depression, involve activation of A_{2A} receptors in the striatum. The striatum (caudate-putamen, nucleus accumbens and olfactory tubercle) is the major component of the basal ganglia in which excitatory glutamatergic inputs from the cortex, thalamus, and limbic areas are integrated with dopaminergic inputs from the mesencephalon. These processes converge primarily on medium-sized spiny (GABAergic) neurons that project either to the substantia nigra (via the direct or strionigral/entopeduncular paths) or to the globus pallidus (via the indirect or striopallidal path) (26). The striatum plays a critical role in integrating sensory, emotional, motivational and motor components of ongoing action (27). As such, the striatum is a plausible center for the uncoupling of motivation and action during behavioral depression. Moreover, activation of striopallidal A_{2A} receptors is precisely the type of molecular mechanisms that is anticipated by the concept of conservation-withdrawal.

Adenosine modulates dopaminergic functions in the dorsal and ventral striatum where the nigrostriatal, mesostriatal, and mesolimbic neuronal pathways terminate. Strong evidence now implies the existence of an adenosine A_{2A}/D_2 heteromeric complex coupled in an antagonistic relationship. Hillion et al. (28) 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 heteromeric complex result in conformational changes in the D_2 receptor, but it also decreases D_2 activated coupling to its G_i-protein (29). Recent evidence suggests that A_{2A} receptors modulate glutamatergic afferents to the region via an antagonistic coupling to dopamine D_2 receptors (30), and a synergistic coupling to metabotropic glutamate (mGLU5) receptors (31). The functional consequences of this arrangement are that activation of D_2 receptors augments ongoing action. By contrast, activation of A_{2A} or mGLU5 receptors antagonizes dopamine's effect on ongoing action to produce behavioral depression.

B. Bidirectional Immune-to-Brain Signaling. Systemic administration of lipopolysaccharide (LPS), the active fragment of endotoxin from gram-negative bacteria, induces the synthesis of proinflammatory cytokines in peripheral macrophages – interleukin-1β (IL-1β), IL-6, and tumor necrosis factor (TNFα) (32). Kupffer cells in the liver also express IL-1β as a consequence of LPS administration and may serve as the primary immune-to-brain communication pathway. This signal is transferred via the vagal nerve complex to the brain nucleus tractus solitarius (NTS) where IL-1β is then expressed. The cytokine also is expressed relatively quickly thereafter in a variety of other brain nuclei, particularly in the hypothalamus (33).

IL-1β binds to specific receptors distributed throughout the brain to induce *sickness behavior* – lethargy, hypoactivity, decreased libido, anorexia, anhedonia and increased sleep (32). This dramatic shift in ongoing activity, along with the induction of fever, is assumed to be a highly adaptive strategy to fight infection.

Symptoms of sickness behavior and major depression overlap considerably (33).

Plasma cytokine concentrations are elevated in depressed patients and normalize with electroconvulsive therapy and a return of normal affect (34). In animal models, systemic administration of endotoxin not only increases brain concentrations of IL-1β, but also produces swim deficits (35), as well as other experimental indexes of depression (36). These LPS-induced ailments are reversed by chronic (but not acute) treatment with tricyclic antidepressants (36).

Important for the present purpose is the recent finding that LPS-induced swim deficits is reversed by systemic administration of an A_{2A} receptor antagonist (37). These data support an important interaction between purine (adenosine) and cytokine (IL-1β) signaling in one model of behavioral depression and suggest that the interaction may occur in the central nervous system as well as in the periphery. We provide additional support for this hypothesis in the following review.

II. RESERPINE-INDUCED DEPRESSION.

We have conducted a considerable number of studies on the ability of reserpine to induce behavioral depression or conservation-withdrawal in rats (38, 39). Unlike the data from the learned helplessness paradigm, the reserpine data provide very clear support for a role of both adenosine signaling and cytokine signaling in conservation-withdrawal.

Reserpine was introduced in the United States in the early 1950s as a treatment for hypertension (40). The extract reduces both cardiac output and peripheral vascular resistance by depleting stores of biogenic amines in the central and autonomic nervous systems. Reserpine binds irreversibly to storage vesicles in monoaminergic neurons (41). The vesicles become "leaky," resulting in seepage of transmitter into the cytoplasm, where it is either destroyed by intraneuronal monoamine oxidase or diffuses into the synaptic cleft. The end result is that little or no active transmitter is released at the synapse following depolarization. Recovery from the effects of reserpine requires synthesis of new storage vesicles, which can take several days to accomplish after discontinuing drug treatment (42).

The historic significance of reserpine is more related to unwanted side-effects than its efficacy as an antihypertensive or tranquilizing agent. Unfortunately, a significant portion of the population undergoing reserpine treatment for hypertension developed severe symptoms of major depression. These inconsistencies led us to revisit the animal literature on reserpine to ask whether behavioral depression is due to depletion of brain monoamines or some secondary consequence of drug treatment. Below we review the major findings from a lengthy series of experiments that implicate brain adenosine A_{2A} and IL-1β signaling in reserpine-induced depression in rats.

A. IL-1β Signaling. One of the main problems in making a convincing case for a direct role of the biogenic amines in reserpine-induced depression is that the time course for their depletion does not fit the time course for behavioral impairment. For instance, Bean et al. (43) reported that dopamine (DA) depletion in striatum, n. accumbens, and frontal cortex occur rapidly and reach a maximum about 6 hours after an ip injection of 6 mg/kg of reserpine. DA levels remained at floor levels until the 18-hour point and then increases thereafter, such that DA baselines recover within 48 hours.

As shown below, a behavioral deficit is evident before maximum DA depletion occurs and persists after DA levels recover.

We determined the time course for reserpine's effect by injecting groups of rats with a single, 6 mg/kg, ip dose of reserpine or DMSO vehicle. Rats were tested in a forced swim task 1, 24, 48, 72 or 168 hours after drug treatment. Reserpine, in vehicle controls, resulted in large deficit in swim performance with close to a two-fold increase in floating times.

Peroxide radicals are produced as a byproduct of the degradation of biogenic amines by monamine oxidase (44). The concentration of these radicals may be sufficient to damage tissue when monoamines are rapidly depleted with a large reserpine dose. Activation of brain IL-1β receptors in the hypothalamus and elsewhere would produce the symptoms of sickness behavior and conservation-withdrawal. Because behavioral depression is a major component of these reactions, IL-1β is a plausible mediator of swim deficits following reserpine treatment.

We tested this possibility by stereotaxically implanting groups of rats with guide cannulae in the right lateral ventricle. Groups either received an ip injection of 6 mg/kg of reserpine or injected with DMSO vehicle. DMSO-treated groups received a 6 μg infusion of the IL-1 receptor antagonist (IL-1ra). All groups were tested for swim performance 15 minutes later.

Reserpine-treated rats showed a large swim deficit relative to the DMSO control 1 hour and also 24 hours after the injection. Icv injection of the IL-1ra had no untoward effect on swim performance and also failed to improve swim performance in reserpine-treated rats. We then assessed IL-1β potential contribution at 48 hours post-injection.

It seemed possible that IL-1β is induced at longer post-injection times to mediate swim deficits following reserpine treatment.

To test this possibility rats were implanted with a guide cannula in the right lateral ventricle. Groups received an ip injection of DMSO vehicle or an ip injection of 6 mg/kg reserpine. All rats were tested for swim performance 48 hours later. One reserpine group received icv infusion of saline vehicle and one reserpine group received icv infusion of the IL-1ra. Results revealed reserpine treatment produced a large increase in floating time 48 hours later. These data provide clear evidence for a long-term deficit that is mediated by IL-1β. Thus, reserpine-induced depression consists of multiple deficits, depending on whether or not a proinflammatory cytokine is induced.

If the above is correct, temporal variations in brain IL-1β should parallel the behavioral results for the IL-1ra. Rats were injected with 6 mg/kg of reserpine or DMSO vehicle. Sacrifice occurred at 0, 1, 24, 48, 72, or 168 hours post drug treatment. Brains were dissected into hypothalamus and hippocampus because these regions are implicated in sickness behaviors.

Reserpine produced a large rise in the concentration of IL-1β in the hypothalamus, and to a lesser degree in the hippocampus, 48 and 72 hours after the injection, but not at earlier times. IL-1β concentrations returned to baseline within 168 hours of reserpine treatment. These data suggest that there are two temporally distinct components to reserpine-induced depression. An *early component* is evident 1 hour after reserpine treatment and persists for 24 hours. This deficit is not occasioned by a rise in brain IL-1β concentrations and is not reversed by the IL-1ra.

Some other mechanism must mediate this initial component of reserpine-induced depression. A second, *late component* is evident 48 hours after reserpine treatment, persists for at least 72 hours, and recovers within 168 hours. Brain IL-1β concentrations rise substantially at these times, particularly in the hypothalamus (45). Moreover, the IL-1ra completely reversed swim deficits at the 48 and 72-hours points. Overall, these data indicate that a rise in brain IL-1β is a sufficient, but not a necessary condition for behavioral depression or conservation-withdrawal in this paradigm.

B. Adenosine A_{2A} Signaling. One condition under which adenosine exerts potent compensatory inhibition is during excessive neural activation (46). Large amounts of monoamine transmitter are likely to diffuse into the synaptic cleft with the destruction of storage vesicles upon initial reserpine treatment. The resulting neuronal excitation might be sufficient to compromise metabolic homeostasis and provoke adenosine-mediated inhibition as a compensatory mechanism. If so, then the early component of the reserpine swim deficit, in particular, is likely to involve adenosine signaling. A potential contribution of this mechanism to the late-component deficit is less clear, but certainly possible. Thus, the present experiments assessed the ability of nonselective (A_1/A_2), or highly selective A_1, A_2, A_{2A}, or A_{2B}, adenosine receptor antagonists to reverse deficits in forced swim performance occurring 1 or 48 hours after an injection of 6 mg/kg of reserpine.

Swim deficits 1 and 48 hours after reserpine treatment were reversed by the nonselective adenosine receptor antagonist caffeine and by the moderately selective A_2 antagonist 3,7-Dimethyl-1-propargylxanthine (DMPX) in a dose-dependent manner. However, no benefit was afforded by any dose of an A_1 antagonist 8-Phenyltheophylline (8-PT), or the A_{2B} antagonist alloxazine (AX) at either time point.

Data displayed evidence that swim deficits 1 hour after reserpine treatment are mediated at adenosine A_{2A} receptors. Groups of rats received an ip injection

of 6 mg/kg reserpine or DMSO vehicle. Forty-five minutes later, one DMSO-treated group was injected with 1.0 mg/kg of the selective A_{2A} antagonist CSC. Reserpine-treated groups received an ip injection of 0, 0.01, 0.1, or 1.0 mg/kg of CSC. All rats were tested for swim performance 15 minutes later. As evident in the figure, CSC alone had no effect on swim performance relative to the DMSO control. Pretreatment with reserpine produced a large swim deficit 1 hour later and this effect was completely reversed by CSC in a dose-dependent manner.

The A_{2A} antagonist is equally effective at reversing the late component of the reserpine-induced deficit, whereas other types of adenosine receptor antagonists are not. The moderately selective A_2 antagonist DMPX reversed swim deficits 48 hours after reserpine treatment, however, no benefit was afforded by any dose of the A_1 antagonist 8-PT, or the A_{2B} antagonist AX. The beneficial effects of DMPX were due to its action at A_{2A} receptors, at a dose of 1.0 mg/kg of CSC, which completely reversed swim deficits 48 hours after reserpine treatment.

The evidence linking behavioral depression in several paradigms to adenosine signaling at A_{2A} receptors provides significant insight as to where this response is organized in the brain. Given the limited distribution of A_{2A} receptors in brain, the critical role of A_{2A} receptor activation in behavioral depression as reviewed above, and the role of the striatum in linking motivation and action, this brain region would seem to be an excellent candidate to mediate conservation-withdrawal reactions following reserpine treatment.

Figure 1. *Effects of bilateral microinfusion of CSC on reserpine-induced swim deficits. Rats received an ip injection of reserpine or DMSO vehicle 24 hours before forced swim testing. CSC or vehicle was directly infused into the ventral medial striatum 10 minutes before swim testing.*

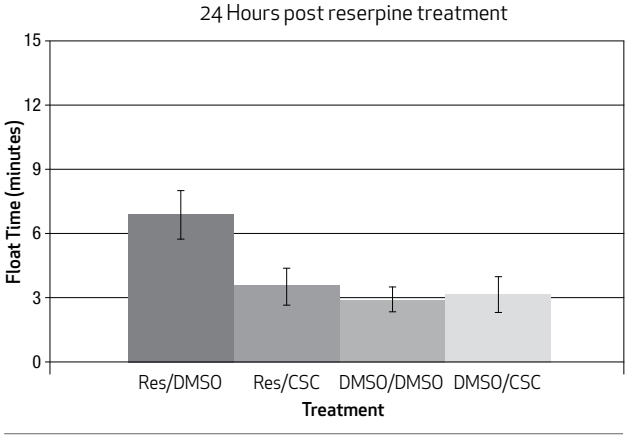

Figure 1 provides preliminary evidence activation of A_{2A} receptors in the ventral medial striatum are critical mediators of reserpine-induced depression. Rats were implanted with bilateral guide cannulae in the ventral medial striatum. After recovery, groups either received an ip injection of 6 mg/kg reserpine or DMSO vehicle. To activate A_{2A} receptors, 30 nM of CSC or vehicle was infused in to the ventral medial striatum twenty-four hours later. Reserpine again produced a large deficit in swim performance relative to the vehicle control. These data provide preliminary evidence that A_{2A} receptors in striatum mediate swim deficits following reserpine treatment, and more generally, the behavioral depression component of conservation-withdrawal.

III. SICKNESS BEHAVIOR

Enhanced synthesis of IL-1β in the brain parenchyma is evident as early as 2 hours after systemic treatment with LPS, with substantially higher concentrations of the proinflammatory cytokine being expressed 6 hours later in the NTS and the PVN and arcuate nuclei of the hypothalamus (47). Activation of hypothalamic IL-1β receptors is thought to mediate sickness behavior and related symptoms of conservation-withdrawal (48).

The foregoing experiments on reserpine-induced depression suggest that brain adenosine signaling might contribute importantly to sickness behavior as well. Treatment with reserpine in the previous studies presumably produced some condition – e.g., cell damage in the periphery or brain – that resulted in the induction of brain IL-1ß. The symptoms of behavioral depression occurring with the induction of the brain cytokine appear to depend on concomitant activation of striatum A_{2A} receptors, which ultimately impairs swim performance in reserpine-treated rats. As noted earlier, adenosine A_{2A} signaling provides inhibitory feedback on proinflammatory cytokine signaling in peripheral immune cells (49). Evolution may have capitalized on this primitive cytokine-purine interaction to produce a more complicated brain interaction that regulates overt behavior at times of illness. The suppression of ongoing behavior is certainly an important aspect of sickness as a means of conserving resources and regulating fever. Although the precise nature of the interaction between brain IL-1β and adenosine is not clear, activation of A_{2A} receptors in the striatum is precisely the type of mechanism to accomplish this outcome.

A preliminary test of this potential interaction was assessed by inducing sickness behavior with a system injection of LPS. All rats initially had a guide cannula

inserted in the right lateral ventricle during stereotaxic surgery. Following recovery, groups were injected with saline or LPS. Twenty-four hours later, one LPS-treated group received icv infusion of the IL-1ra and an ip injection of DMSO. Another LPS-treated group received icv infusion of saline and an ip injection of CSC.

Groups Vehicle and LPS received icv infusion of saline and an ip injection of DMSO. All rats were tested in the forced swim task 15 minutes later.

A comparison of groups Vehicle and LPS indicate that treatment with endotoxin produced a large deficit in swim performance 24 hours later. This increase in floating time was completely reversed by either icv infusion of the IL-1ra or peripheral injection of the A_{2A} receptor antagonist CSC.

Additional evidence for a purine-cytokine interaction in sickness behavior was obtained by infusing IL-1β directly into the right lateral ventricle 1 hour before swim testing. The ensuing deficit in performance was completely reversed by icv infusion of the IL-1ra or ip injection of CSC.

These data are in good agreement with recent findings in other animal models of depression. Yirmiya (38) initially reported that peripheral injection of endotoxin produced symptoms of major depression, including evidence of conservation-withdrawal within 24 hours of the injection. El Yacoubi et al. (50) demonstrated that endotoxin-induced swim deficits are reversed by systemic administration of A_{2A} receptor antagonists.

The most plausible explanation for these data, in conjunction with those already discussed, is that behavioral depression or conservation-withdrawal is a "downstream" consequence of brain cytokine signaling. In this context, activation of brain IL-1β receptors is a sufficient, but not a necessary condition for impaired test performance. Because the A_{2A} receptor antagonist CSC universally reverses evidence of impaired test performance (51), it seemed likely that activation of brain IL-1β receptors recruits adenosine signaling at A_{2A} to produce symptoms of behavioral depression.

Although data are still lacking, the likely site of adenosine's action is the spiny GABAergic neurons of the striatum.

OVERVIEW

This article has reviewed the evidence concerning the contribution of the proinflammatory cytokine IL-1β and the purine nucleoside adenosine to the symptoms of conservation-withdrawal in two different paradigms (injection with reserpine and injection of endotoxin). Symptoms of conservation-withdrawal are observed in both of these paradigms and are assumed to be an after reaction to intense catabolic output. The sensory unresponsiveness, cognitive dullness, and behavioral depression that characterize this state are assumed to be adaptive mechanisms for husbanding limited resources and facilitating the recovery of metabolic homeostasis.

IL-1β contributes directly to conservation-withdrawal following systemic treatment with reserpine or LPS. The cytokine's contribution is delayed for 48 hours after reserpine treatment. At this point, IL-1β concentration rise substantially in the hypothalamus and hippocampus. The IL-1ra also is effective in reversing swim deficits at this time, but not earlier. We suspect that this rise in brain IL-1β may be related to tissue damage and the consequent activation of cytokine-producing microglia in the brain following reserpine treatment. Systemic LPS has a more immediately effect on brain IL-1β concentrations (52) and behavioral depression. The mechanism of the increase in this instance is likely to be immune-to-brain communication via the vagus (53).

The most direct mechanism of behavioral depression in these paradigms is activation of brain adenosine A_{2A} receptors. Although more research is needed for stronger conclusions, the likely locus of these receptors is the spiny GABAergic neurons of the striopallidal (or indirect) path in the striatum.

Activation of these receptors appears to be necessary and sufficient for evidence of conservation-withdrawal in the learned helplessness, reserpine-induced depression, and LPS-induced sickness behavior paradigms. Moreover, behavioral deficits resulting from IL-1β receptor activation are reversed by antagonists of the A_{2A} receptor, although the reverse is not true. This pattern of data may suggest that Il-1β receptor activation may recruit adenosine signaling in striatum A_{2A} receptors to uncouple motivational influences from ongoing behavior.

There are a number of potentially important implications to these data. First, cytokine signaling appears to exacerbate and prolong the conservation-withdrawal reactions in major depression and illness. Down-regulating this form of signaling should hasten recovery. More important, the affect-less, fatigue components of stress, depression, and illness should be directly alleviated by manipulating the A_{2A}/D_2/mGLU heteromeric receptor complex. The present data clearly suggest that

blockade of the A_{2A} receptor produces direct benefit. If the conceptualization of this receptor complex is correct, additional benefit should be derived from a combination of A_{2A} antagonists, D_2 agonists, and mGLU, antagonists. Such a combination should minimize fatigue and recouple motivation influences on ongoing behavior.

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