Depression: A new enzyme AT Play

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Depression: A new enzyme AT Play

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Neuronal activity is the main contributor to the high-energy demand of the human brain. ATP is needed for the maintenance of ionic gradients, neurotransmitter transport and release, as well as the signaling pathways that follow activation of post-synaptic receptors. The inability to maintain a high supply of ATP through tight regulatory mechanisms can, therefore, have severe consequences for brain function. In this issue of *EMBO Reports*, Cui et al. [1] show that pharmacological inhibition or genetic inactivation of CD39, an ectonucleotide tri(di)phosphohydrolase responsible for converting ATP into AMP, has antidepressant-like effects by maintaining high extracellular ATP levels in the presence of stress.

Major Depressive Disorder (MDD) is a severe psychiatric disorder that drives millions of individuals worldwide to lose interest or joy in day-to-day life activities. Despite causing overwhelming disabilities, current treatments are mostly symptomatic due to the poor understanding of its molecular mechanism. The historical notion of MDD as a monoamine deficiency has in recent years been replaced by a more expanded view of the neurobiology of depression. We now consider MDD as a highly complex and heterogeneous disorder, with alterations in synapse formation and plasticity, neurogenesis and inflammation being involved in its pathophysiology [2].

Recently, insufficient release of ATP by astrocytes was linked to chronic stress-induced depressive-like behaviors of mice [3]. Further work on the regulation of extracellular ATP established Calhm2 (Calcium Homeostasis Modulator Family Member 2) as an ATP-releasing channel in astrocytes. Loss of Calhm2 in the hippocampus of mice was sufficient to produce depression-related behaviors, accompanied by reduced spine density and neuronal activity [4]. In both studies, restoring physiological ATP levels had a rapid antidepressant-like effect. The essential role of ATP in maintaining neuronal activity and dynamically regulating astrocyte-neuron communication [5] could therefore provide a mechanistic link between ATP dysregulation and MDD. However, the specific underlying molecular pathways have not been elucidated until now.

In this issue, Cui et al. [1] describe a novel mechanism responsible for ATP dysregulation in MDD. Mice susceptible to 10 days of Chronic Social Defeat Stress (CSDS), a well-established chronic stress model that causes MDD-associated symptoms, showed higher inorganic phosphate (Pi) release from hippocampal slices than controls. The higher levels of Pi likely originate from the

hydrolysis of ATP into ADP/AMP and Pi and therefore served as a proxy for higher extracellular ATPase activity. Through screening several candidate ATPases, the authors focused on CD39, since both mRNA and protein levels of CD39 were higher in the hippocampus of stress-susceptible compared with stress–resilient mice. Apyrase, a functional analog of CD39, infused in both the lateral cerebral ventricle and hippocampus produced deficits in social interaction and sucrose preference tests, suggesting that reducing extracellular ATP levels is sufficient to induce social avoidance and anhedonia, core symptoms of MDD. On the other hand, restoring physiological ATP levels in the hippocampus of apyrase-treated mice reversed social avoidance.

Cui et al. [1] went on to show that pharmacological inhibition and genetic silencing of CD39 could partially rescue depressive-like behaviors in defeated mice. Injection of either a CD39 antagonist or a lentivirus expressing a CD39-targeting siRNA into the hippocampus of susceptible mice could successfully rescue social avoidance and despair, as measured by tail suspension and forced swim tests. Importantly, inhibition and knockdown of CD39 replenished the levels of extracellular ATP by attenuating ATPase activity, suggesting that the antidepressant action of CD39 inhibition was due to the modulation of extracellular ATP levels. At the cellular level, Cui et al. [1] showed that socially defeated mice produced fewer neurons than control mice as observed by a reduction in the number of BrdU-positive cells. Additionally, dentate granule neurons of susceptible mice had less dendritic spines, providing a possible cellular basis for the observed behavioral impairments. Strikingly, both phenotypes were ameliorated by pharmacological inhibition and genetic knockdown of CD39, raising the possibility that disturbances in extracellular ATP levels directly impact on neuro- and spinogenesis in the hippocampus.

In conclusion, an impressive array of results provided by Cui et al. [1] point to a potential role of CD39 in promoting stress susceptibility by decreasing extracellular ATP followed by impaired neuro- and spinogenesis (Fig. 1). Given that CD39 has already been considered as therapeutic target in cancer [6], these findings have undoubtedly far-reaching implications not only for our mechanistic understanding of MDD, but also possibly for the development of novel therapeutics in stress-related diseases. Moreover, this study raises a number of important questions that need to be addressed in future experiments. For example, although the authors nicely showed that overexpression of a functional analog of CD39 induces depressive-like behaviors, anhedonia as measured by a deficit in sucrose preference displayed by susceptible mice, could not be rescued by either ATP infusion or inhibition of CD39 in the hippocampus. It would therefore be important to corroborate these findings with additional behavioral tests to measure deficits in the response to reward, such as the conditioned place preference (CPP) test. Comparing the antidepressant

action of CD39 inhibition to known antidepressants, like fluoxetine, would also be informative. In addition, it should be investigated whether CD39 might be relevant in other brain regions important for mood regulation, such as the Nucleus accumbens or amygdala. In contrast to anhedonia, social avoidance was very consistently rescued by CD39 inhibition. Social avoidance is observed not only in MDD, but is also a core symptom of autism-spectrum disorders, anxiety and schizophrenia [7]. It would be highly interesting to more specifically address the role of CD39 in the regulation of social behavior.

One important aspect that warrants further investigation is the actual source of CD39. In addition to astrocytes and neurons, CD39 is also highly expressed in microglia [8]. Since it is well known that neuroinflammation is induced by chronic stress in rodent models of depression [9], higher levels of CD39 upon CDSD could, at least in part, result from heightened CD39-release from activated microglia. In the future, cell-type specific knockouts of CD39 in microglia and astrocytes could shed light on the contribution of the different cell types to the observed stress-induced CD39 hyperactivity.

Another interesting finding by Cui et al. is that CD39 inhibition increased the number of newly produced neurons as well as the number of dendritic spines in the hippocampus of defeated mice. What is currently missing is a mechanistic link between CD39 and these cellular phenotypes. Does CD39 promote neurogenesis and/or synaptogenesis solely by modulating the levels of extracellular ATP or might it even directly bind to post-synaptic receptors? It could also be speculated that adenosine, the final product of ATP breakdown, could mediate at least some of the effects of CD39 in chronically stressed mice through the activation of purinergic signaling [10]. A more in-depth biochemical analysis of this pathway could help to better understand the mechanism of CD39 action in the brain. Overall, the current study adds to the growing list of publications that support an important role for ATP as a protective factor in neuropsychiatric conditions. The development of drugs that boost extracellular ATP levels, possibly in combination with the elevation of mitochondrial ATP production, might therefore be a promising strategy for these devastating diseases.

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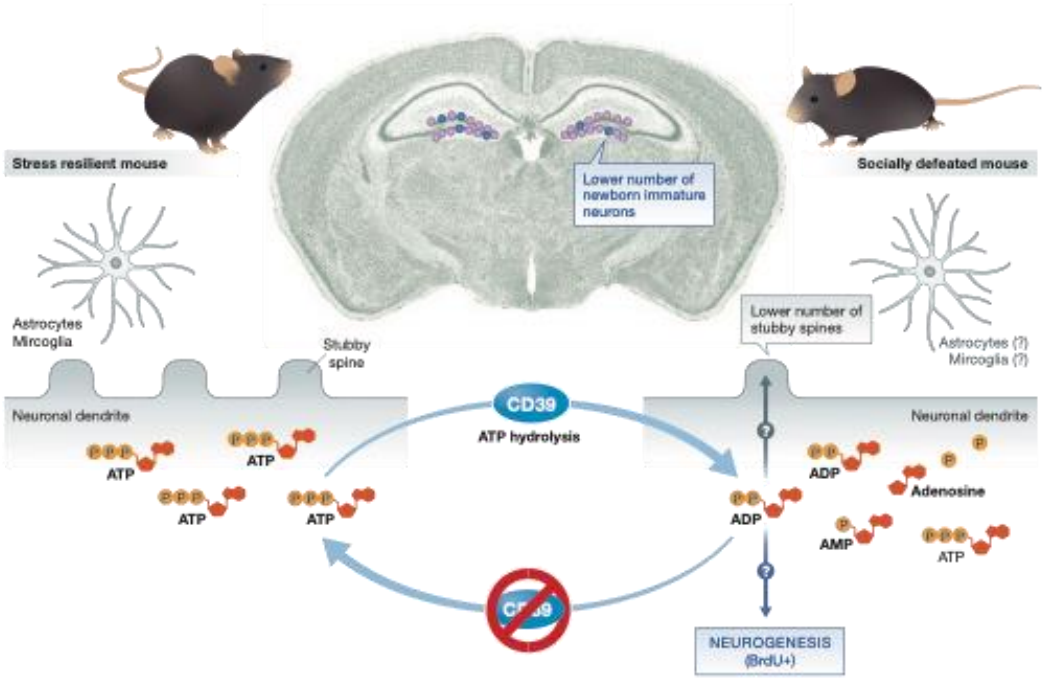
Figure1: Proposed model for the role of excessive CD39-mediated ATP hydrolysis in the hippocampus of socially defeated mice. Cui et. al showed that after chronic social defeat stress, susceptible mice (right) show increased hydrolysis of extracellular ATP by the enzyme CD39 compared with control mice (left). Infusion of a functional analog of CD39 into the hippocampus produced depressive-like behaviors, such as social avoidance, anhedonia and despair. On the other hand, both inhibition and genetic silencing of CD39 abolished the excessive ATPase activity and restored ATP levels in susceptible mice. Socially defeated mice also showed less newborn immature neurons (light blue, upper panel) and stubby spines (dark blue, lower panel). Suppressing CD39 activity attenuated both of the cellular and behavioral phenotypes.


Stress resilient mouse
Socially defeated mouse
Lower number of newborn immature neurons
Astrocytes
Mircoglia
Stubby spine
Lower number of stubby spines
Astrocytes (?)
Mircoglia (?)
Neuronal dendrite
Neuronal dendrite
CD39
ATP hydrolysis
ATP
ATP
ATP
ATP
ADP
ADP
Adenosine
AMP
ATP
NEUROGENESIS
(BrdU+)