Researchers find possible molecular explanation for caffeine reducing mood disorders

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(Medical Xpress)—An international team of researchers has found a possible molecular explanation for the stress reducing capabilities of caffeine. In their paper published in *Proceedings of the National Academy of Sciences*, the team describes experiments they conducted with caffeine and its impact on adenosine A2A receptors (A2AR) in

mouse brains and what they discovered through their efforts.

Most people who drink coffee or tea will claim that it helps reduce feelings of stress, despite the beverage containing caffeine, a known stimulant. Others have suggested that the calming that comes about from drinking caffeinated beverages helps reduce stress or mood related ailments, including depression, though some have also suggested the stress reduction from such beverages comes from the comfort of sitting calmly while drinking, or because it occurs while socializing. In this new effort, the researchers believe they have found a chemical and molecular explanation.

To better understand what happens in the brain when caffeine is introduced, the researchers conducted several experiments with mice—most of which consisted of giving the mice a beverage containing caffeine, putting them in a stressful environment and then measuring how they responded versus mice in the same situation sans caffeine imbibing. The researchers also measured A2AR in the mouse brains, which were previously known to be impacted by caffeine.

In analyzing their results the researchers found that in addition to changes in behavior by the mice, they also found a reduction in both synaptic plasticity and protein density, as compared to the mice that did not endure abnormal amounts of stress—they also found that giving the mice caffeine caused an increase in A2AR levels and that blocking A2AR activity via drugs or by removing the gene for A2AR, caused the same effect as giving the mice caffeine. Their findings also reveal, the researchers claim, the means by which chronic stress contributes to stress disorders.

The researchers acknowledge that the mouse brain and human brain differ to such a degree that their findings cannot be used to prove that caffeine reduces stress the same way in people, but it is their belief that

further research will show that to be the case nonetheless.

More information: Caffeine acts through neuronal adenosine A2A receptors to prevent mood and memory dysfunction triggered by chronic stress, Manuella P. Kaster, *PNAS*, DOI: 10.1073/pnas.1423088112

Abstract
The consumption of caffeine (an adenosine receptor antagonist) correlates inversely with depression and memory deterioration, and adenosine A2A receptor (A2AR) antagonists emerge as candidate therapeutic targets because they control aberrant synaptic plasticity and afford neuroprotection. Therefore we tested the ability of A2AR to control the behavioral, electrophysiological, and neurochemical modifications caused by chronic unpredictable stress (CUS), which alters hippocampal circuits, dampens mood and memory performance, and enhances susceptibility to depression. CUS for 3 wk in adult mice induced anxiogenic and helpless-like behavior and decreased memory performance. These behavioral changes were accompanied by synaptic alterations, typified by a decrease in synaptic plasticity and a reduced density of synaptic proteins (synaptosomal-associated protein 25, syntaxin, and vesicular glutamate transporter type 1), together with an increased density of A2AR in glutamatergic terminals in the hippocampus. Except for anxiety, for which results were mixed, CUS-induced behavioral and synaptic alterations were prevented by (i) caffeine (1 g/L in the drinking water, starting 3 wk before and continued throughout CUS); (ii) the selective A2AR antagonist KW6002 (3 mg/kg, p.o.); (iii) global A2AR deletion; and (iv) selective A2AR deletion in forebrain neurons. Notably, A2AR blockade was not only prophylactic but also therapeutically efficacious, because a 3-wk treatment with the A2AR antagonist SCH58261 (0.1 mg/kg, i.p.) reversed the mood and synaptic dysfunction caused by CUS. These results herald a key role for synaptic A2AR in the control of chronic stress-induced modifications and suggest A2AR as candidate targets to alleviate the consequences of

chronic stress on brain function.