Chronic caffeine intake alters glutamate signaling and glial reactivity profile in hippocampus of juvenile rats

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The central nervous system is an extremely complex system and depends on the formation of correct connectivity for its proper functioning. The environment is capable of modifying the neural circuit that guides our behavior in a process called neural plasticity. The hippocampus, a structure related to learning and memory, has been used to study the mechanisms underlying neural reorganization. Caffeine, a psychoactive drug consumed worldwide, is known to modulate neuroplasticity, primarily by blocking adenosine receptors, and its consumption has already been linked to preventing cognitive decline in many animal models of neurodegenerative diseases. It is widely known that both neurons and hippocampal glial cells present both A1 and A2A adenosine receptors, and recent studies have shown that glial cells can play an important role in cognition by regulating neuronal functioning. The aim of this work was to investigate the mechanisms by which caffeine can modulate hippocampal plasticity and altering animal behavior. Lister Hooded male rats underwent oral caffeine treatment (1 mg / mL) from postnatal day 21 (PND21) to postnatal day 40(PND40). Control animals received water *ad libithum*. After treatment, a group of animals underwent behavioral testing, and the hippocampal tissue was processed for immunofluorescence, Western Blot, D-aspartate uptake, and cAMP accumulation assays. Our results demonstrated that chronic caffeine treatment induces an improvement in memory performance, but also an increase in anxiety-like behavior. The treatment induced an increase in the A1R expression and also in the content of cAMP. Treated group showed an increased expression of NMDA subunit GluN1 in the hippocampus, accompanied by a change in the ratio of subunits GluN2A and GLUN2B when compared to their control groups. The consumption of caffeine also increased the content of excitatory amino acids transporters 1 and 2, and AMPA receptors. These data were along with an increased D-Aspartate uptake associated with the PKA pathway that was blocked by A1R e A2AR agonists, suggesting that both receptors might be coupled. Astrocytic and microglial reactivity are also decreased in the caffeine treated groups. Together, these results suggest that caffeine is capable of modulating the glutamatergic system in the hippocampus of adolescent rats.