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Δ9-tetrahydrocannabinol attenuated methamphetamine-induced increase of neuronal nitric oxide synthase expression and Glial Fibrillary Acidic Protein immunoreactivity

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Methamphetamine (METH) is an illicit potent psychostimulant with neurotoxic properties (Maxwell and Brecht 2011). Its heavy use increases the activation of neuronal nitric oxide synthase (nNOS), production of peroxynitrites, microglia stimulation, and induces hyperthermia and anorectic effects. Most METH recreational users also consume cannabis. Preclinical studies have shown that natural (Δ9-tetrahydrocannabinol, Δ9-THC) and synthetic cannabinoid CB1 receptor agonists exert neuroprotective effects in different models of cerebral damage (Krasnova and Cadet 2009; LaVoie et al. 2004). Here, we investigated the neuroprotective effect of Δ9-THC on METH-induced neurotoxicity by examining its ability to prevent anorectic and hyperthermic effects and reduce astrocyte activation and nNOS overexpression in selected brain areas. Rats exposed to a METH (4x10 mg/kg, 2 hours apart) neurotoxic regimen were pre- or post-treated with Δ9-THC (1 or 3 mg/kg) and killed 3 days after the last METH administration. Body weight and core body temperature were monitored and semi-quantitative immunohistochemistry was performed using antibodies against nNOS and Glial Fibrillary Acidic Protein (GFAP). Compared to controls, METH-induced nNOS overexpression was significantly attenuated by post-treatment with 1 mg/kg Δ9-THC (-16 %), while GFAP-immunoreactivity was reduced in the caudate-putamen (CPu) by post-treatment with 1 and 3 mg/kg Δ9-THC1 (-40 and -37%, respectively) and by pre-treatment with Δ9-THC (3 mg/kg, -56%). The cannabinoid CB1 receptor antagonist SR141716A completely blocked METH-induced nNOS overexpression in the CPu, and partially reverted the Δ9-THC-mediated decrease of METH-induced GFAP-immunoreactivity in the prefrontal cortex, but failed to counteract Δ9-THC effects in the CPu. Our results indicate that Δ9-THC reduces METH-induced brain damage via inhibition of nNOS expression and astrocyte activation mediated by CB1-dependent and independent mechanisms.

References

[1] Maxwell JC and Brecht ML (2011) Methamphetamine: here we go again? Addict Behav 36: 1168-1173.
[2] Krasnova IN and Cadet JL (2009) Methamphetamine toxicity and messengers of death. Brain Res Rev 60: 379-407.
[3] LaVoie MJ, Card JP, Hastings TG (2004) Microglial activation precedes dopamine terminal pathology in methamphetamine-induced neurotoxicity. Exp Neurol 187: 47-57.

Key words

Δ9-tetrahydrocannabinol, GFAP, methamphetamine, neurotoxicity, neuroprotection, nNOS.