

β -lactams modulate astroglial glutamate transporters and attenuate dependence to CP 55,940, a CB1 receptor agonist, in rat model

Abstract

Studies on cannabinoids have reported contradictory findings, showing both aversion and rewarding outcomes in conditioned place preference (CPP). Various possibilities have been suggested to explain the aversive properties of cannabinoids, including the pharmacokinetics profile and dose selection. In this study, we have established a CPP method to investigate the effects of modulating astroglial glutamate transporters in cannabinoid dependence using a cannabinoid receptor 1 (CB1R) agonist, CP 55,940 (CP). Previous reports using CPP paradigm demonstrated the involvement of glutamatergic system in seeking behavior of several drugs of abuse such as cocaine, heroin and nicotine. Glutamate homeostasis is maintained by several astroglial glutamate transporters, such as glutamate transporter 1 (GLT-1), cystine/glutamate transporter (xCT) and glutamate aspartate transporter (GLAST). In this study, we investigated the effects of Ampicillin/Sulbactam, β -lactam compounds known to upregulate GLT-1 and xCT, on cannabinoid seeking behavior using CP. We found first that one prime dose of CP induced CP reinstatement; this effect was associated, in part, with significant downregulation of xCT expression in the nucleus accumbens, dorsomedial prefrontal cortex and amygdala. Moreover, GLT-1 expression was downregulated in the amygdala. Importantly, Ampicillin/Sulbactam treatment during the extinction phase attenuated CP-induced reinstatement and restored the expression of GLT-1 and xCT in mesocorticolimbic brain regions. These findings suggest that β -lactams may play a potential therapeutic role in attenuating dependence to cannabinoids, in part, through upregulation of GLT-1 and xCT.