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Research Report

Long-term consequences of URB597 administration during adolescence on cannabinoid CB1 receptor binding in brain areas

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ABSTRACT

Despite the alarming increment in the use and abuse of cannabis preparations among young people, little is known about possible long-term consequences of targeting the endocannabinoid system during the critical developmental period of adolescence. Therefore, we aimed to analyze possible long-lasting neurobiological consequences of enhancing endocannabinoid signalling during adolescence, by means of blocking anandamide (AEA) hydrolysis. Adolescent Wistar male rats were administered an inhibitor of AEA hydrolysis, i.e. URB597 (0, 0.1 or 0.5 mg/kg/day from postnatal days 38 to 43). The expression of brain cannabinoid receptor type 1 (CB1R) was then analyzed by [^{3}H]CP-55,940 auto-radiographic binding at adulthood. Repeated URB597 administration during adolescence persistently modified CB1R binding in a region-dependent manner. A long-lasting decrease of CB1R binding levels was found in caudate-putamen, nucleus accumbens, ventral tegmental area and hippocampus, while an opposite increment was observed in the locus coeruleus. Present results provide evidence for long-lasting effects of adolescent URB597 administration. Activation of endocannabinoid transmission during the still plastic phase of adolescence may have implications for the maturational end-point of the endocannabinoid system itself, which could lead to permanent alterations in neuronal brain circuits and behavioural responses. Insights into the developmental trajectories of this neuromodulatory system may help us to better understand and prevent outcomes of neonatal and adolescent cannabis exposure.

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Abbreviations: 2-AG, 2-arachidonylglycerol; AEA, Anandamide; BSA, bovine serum albumin; CB1R, Cannabinoid receptor type 1; CB2R, Cannabinoid receptor type 2; ECS, Endocannabinoid system; FAAH, Fatty-acid amide hydrolase; URB597, Cyclohexyl-carbamic acid 3′-carbamoyl-biphenyl-3-yl ester

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1. Introduction

The endocannabinoid system (ECS) consists of endogenous ligands called endocannabinoids, typically anandamide (AEA) and 2-arachidonylglycerol (2-AG), which act upon activation of cannabinoid receptors (types 1 and 2, CB1R and CB2R, respectively). Due to their lipophilic nature, endocannabinoids are not stored in vesicles, but they are synthesized and released locally 'on demand' in response to a variety of stimuli (Freund et al., 2003; Piomelli, 2003). CB1R is the predominant cannabinoid receptor within the central nervous system, and is highly expressed in brain regions involved in emotional processing, motivation, motor activation and cognitive function (Mackie, 2005). Endocannabinoids are inactivated by cellular uptake and subsequent enzymatic cleavage: AEA is metabolized by fatty acid amide hydrolase (FAAH) (McKinney and Cravatt, 2005), while 2-AG is mainly catalyzed by monoacylgliceride lipase (Dinh et al., 2002).

Endocannabinoids mainly act as retrograde messengers on presynaptic CB1Rs, transiently suppressing transmitter release. Therefore, they have been involved in a variety of synaptic-plasticity phenomena (Chevaleyre et al., 2006; Edwards et al., 2008; Freund et al., 2003; Vigh and von Gersdorff, 2007). Likewise, there is evidence for a role of the ECS in neural development. Both CB1R and endocannabinoid ligands can be detected in the brain during early developmental periods (Belue et al., 1995; Mato et al., 2003; Rodriguez de Fonseca et al., 1993; Romero et al., 1997). During the perinatal period, CB1Rs exhibit an atypical distribution possibly related to a specific role of the ECS in brain development. At early developmental stages, the ECS seems to influence the expression of key genes for neural development, to participate in axonal growth and fasciculation and in the establishment of correct neuronal connectivity (Fernandez-Ruiz

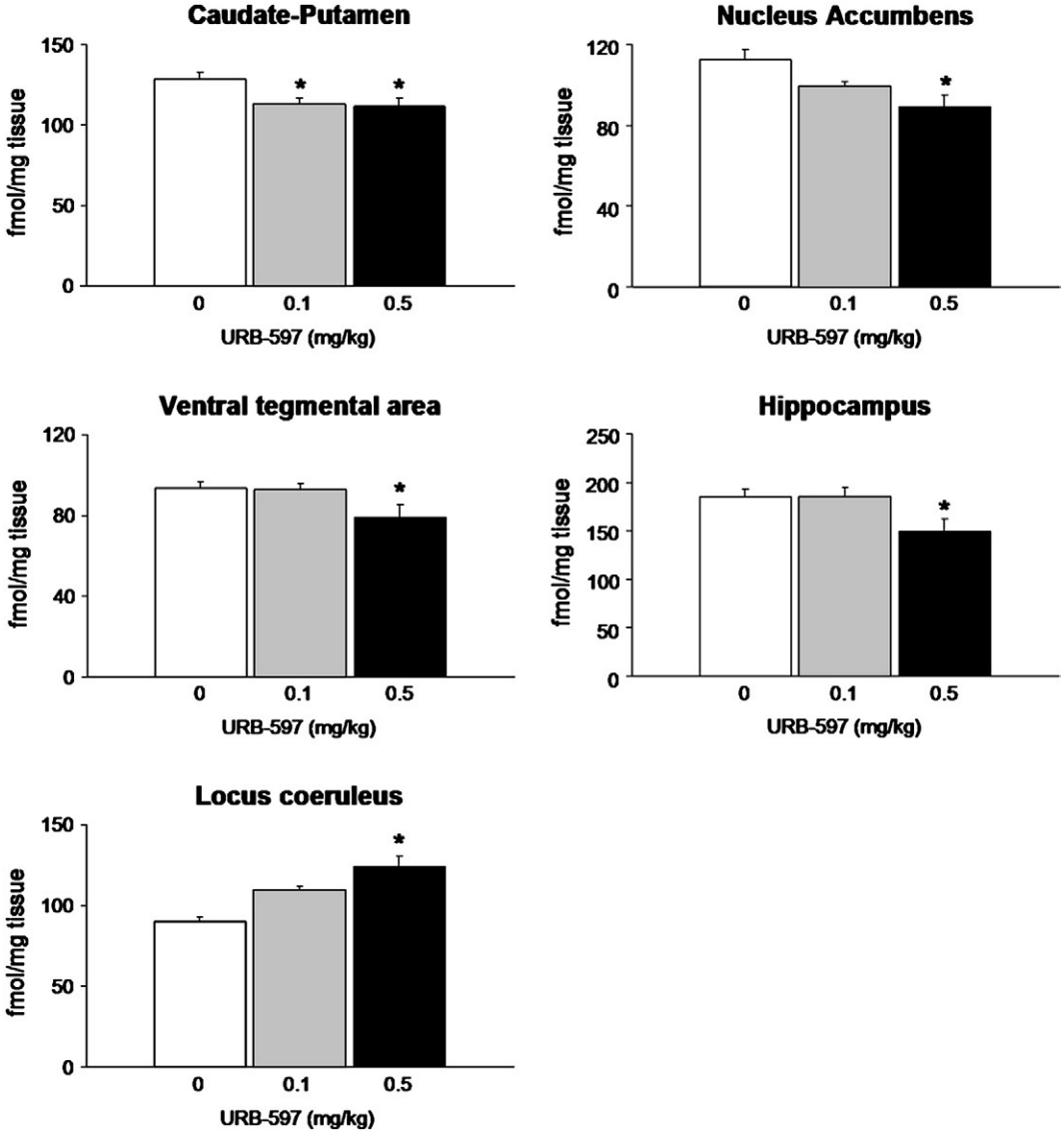

Fig. 1 – Enduring modifications of brain CB1R density following repeated URB597 administration during adolescence (0.1 and 0.5 mg/kg/day from postnatal days 38 to 43). Gray levels obtained with densitometric analysis were transformed in fmol/mg of tissue using ^{3}H-labeled standards. Data are mean ± SEM (bars) values. *P < 0.05 vs. vehicle-injected animals.