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Differential treatment regimen-related effects of cannabinoids on D1 and D2 receptors in adolescent and adult rat brain

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ABSTRACT

Animal studies suggest differential effects of cannabinoids on dopamine-related behaviours in adolescence and adulthood however few studies have investigated the underlying neurochemical effects of cannabinoids during adolescence. The aim of the present study was to compare the effects of treatment with the synthetic cannabinoid, HU210, on dopamine receptor density in adolescent and adult rats. Adolescent (postnatal day (PND) 35) and adult (PND 70) rats received a single dose of 100 μg/kg HU210 or 25, 50 or 100 μg/kg HU210 for 4 or 14 days. Dopamine D1 receptor (D1R) or D2 receptor (D2R) density was measured in the medial and lateral (CPUL) caudate putamen, nucleus accumbens, olfactory tubercle (TU) and substantia nigra (D1R only) using in vitro autoradiography. D1R and D2R densities were 1.6–1.7- and 1.1–1.4-fold higher respectively in adolescent control rats compared to adults. In adult rats, D1R density was increased by 1.2- and 1.3-fold ($p < 0.05$) in CPUL and TU respectively compared to controls, after 14 days of HU210 treatment. A significant overall effect of treatment ($p < 0.05$) on D2R density was also observed in adults after the single dose and 4 and 14 days administration of HU210. In adolescents, an overall effect of treatment on D1R density after a single exposure to HU210 was seen ($p = 0.0026$) but no changes in D1R or D2R densities were observed in other treatment groups. These results suggest that the adolescent rat brain does not display the same compensatory mechanisms activated in the adult brain following cannabinoid treatment.

1. Introduction

The endocannabinoid system modulates the release of both excitatory and inhibitory neurotransmitters in many regions in the postnatal brain (Wilson and Nicoll, 2002). Direct modulation is achieved when endocannabinoids such as anandamide are released from postsynaptic terminals. They then act as retrograde messengers mainly activating the presynaptically located CB1 receptor and suppress the release of neurotransmitters such as glutamate, GABA (Wilson and Nicoll, 2002; Marsicano et al., 2003; Howlett et al., 2004; Monory et al., 2006) and dopamine (Ong and Mackie, 1999; Rodríguez de Fonseca et al., 2001). Indirect modulation of dopamine release also takes place through a trans-synaptic mechanism involving GABAergic or glutamatergic synapses (van der Stelt and Di Marzo, 2003). The endocannabinoid system is believed to be involved processes such as control of movement, cognition and attention that are also controlled by dopamine (Breivogel and Childers, 1998; Wilson and Nicoll, 2002; Romero et al., 2002; Viggiano et al., 2003; Cropley et al., 2006; Pattij et al., 2008).

Like other drugs of abuse, exogenous cannabinoids are thought to elicit their pharmacological effects in part through the activation of dopaminergic neurons in the brain (French et al., 1997; Gardner and Vorel, 1998; Rodríguez de Fonseca et al., 2001; Parolaro et al., 2005; Bossong et al., 2009). It has been shown that acute exposure to cannabis increases dopamine release in the brain in rodents and humans (Sakurai-Yamashita et al., 1989; Voruganti et al., 2001; Cheer et al., 2004; Fadda et al., 2006; Bossong et al., 2009; Polissidis et al., 2009). In behavioural experiments in rodents, turning induced by striatal injections of cannabinoids can be blocked by D1 and D2 receptor antagonists (Souilhac et al., 1995). Electrophysiological studies in rats have also shown that acute cannabinoid administration leads to excitation of dopamine neurons in the nucleus accumbens, ventral tegmentum and substantia nigra (French et al., 1997; Gessa et al., 1998). These studies clearly indicate significant interactions between the endocannabinoid and dopaminergic systems.

Adolescence is an important period for neuronal maturation (Spear, 2000; Andersen, 2003). During this time, alterations take

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Table 1
Comparison of behavioural and neurochemical effects of cannabinoid treatment during adolescence and adulthood in rats.

Drug	Adolescent treatment	Adult treatment	Behavioural alterations Adolescent vs. adult	Neurochemical correlates Adolescent vs. adult	Reference
THC 0.5–5 mg/kg (single dose)	PND 28	PND 65	Adolescents find THC less aversive than adults in place and taste aversive tests Acute locomotor-reducing effect of THC greater in adults than adolescents	N/A	Schramm-Sapyta et al. (2007)
THC 10 mg/kg twice daily	PND 29–39	PND 68–78	Adolescents less sensitive than adults to hypolocomotor and hypothermic effects of THC following sub-chronic dosing	N/A	Wiley et al. (2007)
WIN 55,212-2 1.2 mg/kg	PND 40–65	>PND 70 (20 injections over 25 days)	Adolescent-treated rats showed deficits in prepulse inhibition (which could be reversed by administration haloperidol), deficits in object recognition and lower break points in a progressive ratio task compared to adults Treatment during adulthood had no effect on behaviours tested	N/A	Schneider and Koch (2003)
WIN 55,212-2 1.2 mg/kg	PND 40–65	>PND 80 (20 injections over 25 days)	Adolescent-treated rats showed d eficits in object and social recognition, social behaviour, play and self-grooming Treatment during adulthood had no effect on behaviours tested	N/A	Schneider et al. (2008)
THC 1–5 mg/kg	PND 32–50	PND 64–82	Adolescents find THC less aversive than adults in place aversive tests Adolescents display greater residual cognitive deficits than adults	Differential expression of 27 hippocampal proteins in adolescents and 10 in adults	Quinn et al. (2008)
CP55940 0.15–0.30 mg/kg	PND 30–51	PND 56–77	Significantly poorer working memory in adolescent but not adult treated rats	N/A	O'Shea et al. (2004)
THC 2.5–10 mg/kg	PND 35–45	N/A	Increase in depressive-like behaviour in male rats when tested in adulthood	↓ CB1R density and functionality	Rubino et al. (2008)
HU210 0.025–0.1 mg/kg	PND 35–49	PND 70–84	Adolescents developed more rapid tolerance than adults to the weight loss inducing effects of HU210	Dose-dependent ↓ CB1R density less marked in adolescents than in adults ↑ 5HT1AR density and mRNA in hippocampus of adult but not adolescent-treated rats	Dalton and Zavitsanou (2010) and Zavitsanou et al. (2010)

5HT1AR: 5HT1A serotonin receptor; CB1R: CB1 cannabinoid receptor; N/A: not applicable; PND: postnatal day; THC: delta-9-tetrahydrocannabinol; vs.: versus.

place in the brain such as neuronal myelination and synaptic remodelling and pruning. Changes in levels of neurotransmitters and their receptors also occur (Spear, 2000). In the rat brain for example, dopamine receptor numbers peak during adolescence, which ranges from approximately postnatal day (PND) 28–42 in the rat (Spear, 2000), and then decline in adulthood (Teicher et al., 1995; Andersen et al., 1997; Tarazi and Baldessarini, 2000). A similar pattern of developmental overproduction in the dopamine system followed by synaptic elimination during late adolescence appears to occur in humans (reviewed by Spear, 2000; Weickert et al., 2007).

Despite a range of behavioural studies comparing the effects of cannabinoid exposure in adolescence and adulthood or the long-term effects of cannabinoids in adult rats treated as adolescents (summarised in Table 1), to date, few studies have examined the underlying neurochemical changes that take place in the adolescent brain following cannabinoid exposure (Table 1). We have previously shown that CB1 receptor downregulation in response to treatment with the synthetic cannabinoid HU210 is smaller in the brain of adolescent rats compared to adults (Dalton et al., 2009; Dalton and Zavitsanou, 2010). In light of these results, we hypothesise that the same treatment regimen may have differential effects on the downstream effectors of CB1 receptor activation, such as the dopaminergic system (van der Stelt and Di Marzo, 2003), in adolescence and adulthood. Therefore, in the present study, we compare the effects of a single, sub-chronic and chronic treatment with the synthetic cannabinoid, HU210, on dopamine D1 and D2 receptor density in dopamine projecting regions in adolescent and adult rat brain.

2. Materials and methods

2.1. Animals

Adolescent and adult male Wistar rats were obtained from the Animal Resource Centre Pty Ltd. (Perth, Australia) and were housed in polyethylene boxes with wire lids (489 mm × 343 mm × 240 mm) in groups of 3–4 per cage. All handling of rats and procedures were carried out in accordance with the guidelines established by