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Possible involvement of endocannabinoids in the increase of morphine consumption in maternally deprived rat

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ABSTRACT

Whether adolescent exposure to chronic delta-9-tetrahydrocannabinol (THC) facilitates progression to opioid consumption is still controversial. In a maternal deprivation model (3 h daily from postnatal day 1–14), we previously reported that adolescent exposure to chronic THC blocks morphine dependence in maternally deprived (D) rats. Owing to the existence of a functional cross-interaction between the opioid and cannabinoid systems in reward, we evaluated if the vulnerability to opiate reward in D rats, may involve an alteration of the endocannabinoid system. Anandamide and 2-arachidonoylglycerol (2-AG), were quantified in the striatum and mesencephalon of adolescent and adult D and non-deprived (animal facility rearing, AFR) rats by isotope dilution liquid chromatography–mass spectrometry. Oral morphine self-administration behavior was analyzed for 14 weeks, 24 days after chronic injection of the cannabinoid CB1 receptor antagonist/inverse agonist, SR141716A (3 mg/kg) for 2 weeks during adolescence (PND 35-48).

Adolescent D rats exhibited higher basal levels of anandamide than adolescent AFR rats in the nucleus accumbens (38%), the caudate–putamen nucleus (62%) and the mesencephalon (320%), whereas adult D rats showed an increase of anandamide and 2-AG levels in the nucleus accumbens (50% and 24%, respectively) and of 2-AG in the caudate–putamen nucleus (48%), compared to adult AFR rats. Chronic administration of SR141716A to adolescent D rats blocked the escalation behavior in the morphine consumption test. Our data suggest that altered brain endocannabinoid levels may contribute to the escalation behavior in the morphine consumption test in a maternal deprivation model.

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1. Introduction

Controversial results have been reported regarding the possible additive effects of brain cannabinoid and opiate systems at facilitating progression to consumption of opioids and the role of cannabis intake in this context. Most of the studies have been performed after chronic cannabinoid treatment in adult animals and only few data have been obtained after chronic cannabinoid exposure during adolescence, which is an important neurodevelopmental period. Adolescence may be a stage of particular vulnerability to the effects of delta-9-tetrahydrocannabinol (THC), the main psychoactive ingredient of marijuana, since receptors for this compound, the cannabinoid type-1 (CB1) receptors, were shown to mature slowly with maximal levels during adolescence, and may therefore undergo post-adolescent pruning (Belue et al., 1995; Rodriguez de Fonseca et al., 1993). Rat adolescent exposure to the cannabinoid agonist, WIN55212.2, was shown to induce tolerance to morphine (Pistis et al., 2004), whereas an increase of heroin intake was described after THC pre-exposure of rats during adolescence (Ellgren et al., 2007) and heroin-induced conditioned place preference was enhanced following exposure to the

Abbreviations: AEA, N-arachidonoylethanolamine; AFR, animal facility rearing; AM404, inhibitor of endocannabinoid membrane transporter; CB1, cannabinoid type-1 receptor; CB2, cannabinoid type-2 receptor; CP-55940, cannabinoid type-1 agonist; CPu, caudate–putamen nucleus; D, maternally deprived rat; 2-AG, 2-arachidonoylglycerol; JZL184, inhibitor of 2-AG hydrolysis; N.Acc., nucleus accumbens; PF-3845, inhibitor of AEA hydrolysis; SR141716A, CB1 receptor antagonist/inverse agonist; THC, delta-9-tetrahydrocannabinol.

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cannabinoid receptor agonist CP-55940 either post-natally (Singh et al., 2006) or during adolescence (Biscaia et al., 2008). We reported that exposing neonatal male rats to an episode of 3 h per day of maternal deprivation (deprivation of new born pups from their mothers as well as littermates from each other) from postnatal days 1–14 induces long-term behavioral and biochemical alterations that resemble opiate dependence, with an escalation behavior in morphine consumption test and an increase of weight gain after morphine removal (Vazquez et al., 2005a, 2006). Interestingly, adolescent exposure (PND 35-48) to chronic THC blocks morphine dependence in maternally deprived (D) rats (Morel et al., 2009).

Owing to the existence of a functional cross-interaction between the opioid and cannabinoid systems in reward (Ledent et al., 1999; Navarro et al., 2001; Tanda and Goldberg, 2003), we evaluated if the vulnerability to opiate dependence in D rats, may involve an alteration of the endocannabinoid system. We, therefore, analyzed the concentrations of the two major endocannabinoids, anandamide (*N*-arachidonoylethanolamine, AEA) and 2-arachidonoylglycerol (2-AG) (Devane et al., 1992; Mechoulam et al., 1995) in the caudate–putamen nucleus (CPu), nucleus accumbens (N.Acc.) and in mesencephalon of adolescent and adult non-deprived (Animal Facility Rearing = AFR) and D rats. Indeed, AEA and 2-AG acting at CB1 receptors in these brain areas are known to play an important role in reward signaling (for review, see Solinas et al. (2008)). Furthermore, we chronically administered to AFR and D rats during adolescence (PND 35-48) the selective CB1 receptor antagonist/inverse agonist, SR141716A and analyzed the responses to morphine consumption in adulthood.

2. Materials and methods

2.1. Animals

The experimental procedure and care of the animals were in accordance with local committee guidelines and the European Communities Council Directive of November 24, 1986 (86/609/EEC). All efforts were made to minimize animal suffering, to reduce the number of animals, and alternative to in vivo techniques (in vitro release experiments) have been used.

Two series of 20 Long–Evans rats (Janvier, Le Genest St. Isle, France) on day 14 of gestation were used. The dams gave birth 1 week after inclusion. Litters were housed in plastic cages in a well ventilated, temperature controlled (22 ± 1 °C) environment on a 12 h light/dark cycle (lights on from 8:00 am to 8:00 pm). Dams received rat chow and water ad libitum.

2.2. Drugs

Morphine (25 mg/l) was a gift from Francopia (Gentilly, France) and was dissolved in tap water for the oral self-administration test. The CB1 receptor antagonist SR141716A or rimonabant [(Npiperidin-1-yl)-5-(4-chlorophenyl)-1(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxy amide] was a gift from Sanofi-Aventis (Paris, France), it was dissolved in ethanol, cremophore, sterile water (1/1/18). SR141716A was i.p. administered in a volume of 1 ml/kg.

2.3. Maternal deprivation procedure

Maternal deprivation was performed as previously described (Vazquez et al., 2005a). On postnatal day 1, litters were cross-fostered and culled to 8 male pups. Neonates belonging to the maternal deprivation group were individually placed in temperature- (30–34 °C) and humidity-controlled cages divided into compartments. Pups were isolated for 3 h daily from days 1–14 (01:00–04:00 pm). D pups received no other handling except that required to change the bedding in their cages once weekly. Rat pups not subjected to maternal deprivation (AFR) remained with their mothers during this period and received no specific handling other than changing the bedding in their cages once a week.

From days 15–22, all pups remained with their mothers. On day 22, pups were weaned from their mothers and housed in groups of 3–4. One or two rats from each litter within the group were used in individual experiments in order to avoid any litter effect.

2.4. Basal endocannabinoid level quantification

AFR and D adolescent and adult rats (PND 34 and PND 90 respectively, $n = 8–10$) were killed by decapitation. The CPu, the N.Acc. and the mesencephalon were collected by manual dissection on dry-ice according to the atlas of Paxinos and Watson (1997), were frozen in isopentane at −30 °C and then stored at −80 °C until the dosage.

Tissues were homogenized in 5 volumes of chloroform/methanol/Tris HCl 50 mM (2:1:1) containing 5 pmol of d^8-AEA and d^5-2-AG. Homogenates were centrifuged at 13,000 3 g for 16 min (4 °C), the aqueous phase plus debris was collected and extracted again twice with 1 volume of chloroform. The organic phases from the 3 extractions were pooled and the organic solvents evaporated in a rotating evaporator. Lyophilized samples were then stored frozen at −80 °C under nitrogen atmosphere until analyzed.

Lyophilized extracts were re-suspended in chloroform/methanol 99:1 by volumes. The solutions were then purified by open bed chromatography on silica as described in Bisogno et al. (1997). Fractions eluted with chloroform/methanol 9:1 by volume (containing AEA, 2-AG) were collected, the excess solvent was evaporated with a rotating evaporator, and aliquots were analyzed by isotope dilution-liquid chromatography/atmospheric pressure chemical ionization/mass spectrometry carried out under conditions described previously (Marsicano et al., 2002) and allowing the separation of 2-AG and AEA. Mass spectrometric detection was carried out in the selected ion monitoring mode using m/z values of 356 and 348 (molecular ions +1 for deuterated and undeuterated AEA) and 384 and 379 (molecular ions +1 for deuterated and undeuterated 2-AG). For 2-AG, the areas of the peaks corresponding to 1(3)-and 2-isomers were added together. The amounts of the compounds were expressed as picomoles/gram (AEA) or milligram (2-AG) of wet tissue weight.

2.5. Chronic SR141716A treatment

Another series of rats were daily injected with SR141716A (3 mg/kg) or vehicle (ethanol, cremophore, sterile water (1/1/18)) during postnatal days 35–48. The behavioral experiments were carried out 24 days after the last injection of SR141716A (Fig. 1).

2.6. Morphine intake

The measurement of morphine solution consumption was performed during 14 weeks using a two-bottle choice paradigm as described (Vazquez et al., 2005a, 2006). The rats ($n = 11–13$ per group) were first trained to consume water for 5 days to habituate the rats to the free choice. One of the bottles of water was then replaced by a bottle of morphine solution (25 mg/l) during 14 weeks. No sucrose was added to morphine solution. The consumption in ml was measured twice a week.

2.7. Statistical analysis

The data of endocannabinoid levels were analyzed using two-way analysis of variance (ANOVA: between-subject for the independent variables deprivation and age) followed by one-way ANOVA and Newman–Keuls for multiple comparisons. The results of the oral self-administration experiment and of body weights were analyzed using two-way repeated-measures analysis of variance (ANOVA: between-subject for the independent variables deprivation and treatment and within subject for the independent variable time) followed by one-way ANOVA and Newman–Keuls for multiple comparisons. All data were analyzed with Statview software (SAS, Cary NC, USA) for Macintosh. The level chosen for statistical significance was 5%.

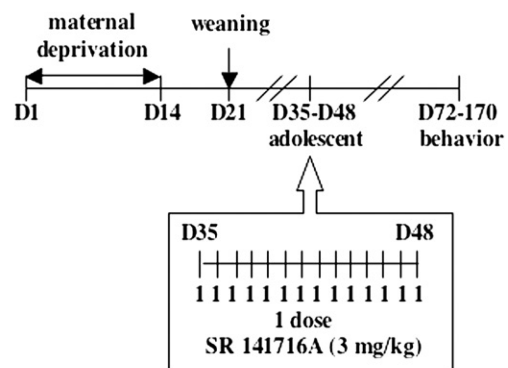

Fig. 1. Experimental procedure for chronic SR141716A treatment. Maternal deprivation started one day after birth (D1) 3 h daily for 14 days (D14). Weaning occurred at days 22. The chronic i.p. injection of SR141716A started at day 35. The administration was performed daily at the dose of 3 mg/kg for 14 days. Morphine oral self-administration test was performed 24 days after the last injection of SR141716A.

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