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Cannabinoid type-1 receptor ligands, alone or in combination with cocaine, affect vigilance-related behaviors of marmoset monkeys

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ABSTRACT

Endocannabinoids (eCB) have been functionally linked to cocaine's rewarding effects. However, results differ at the behavioral level, with few reports in nonhuman primates (NHPs). Here we analyzed whether repeatedly administered cannabinoid type-1 receptor (CB1r) agonist WIN 55-212,2 (WIN) or antagonist AM 251 (AM) induce effects per se and if concurrent pre-treatments affect cocaine-induced changes in marmoset behavior. Six groups were tested: WIN-saline; WIN-cocaine; AM-saline; AM-cocaine; vehicle-cocaine; and vehicle-saline. Subjects were pre-treated with either WIN (1 mg/kg), AM (2 mg/kg) or vehicle and then injected with cocaine (5 mg/kg) or saline. Six exposures were held at 48 h intervals. Behaviors were scored during 15-min in an open-field on days 1 and 6, as well as a withdrawal (WD) trial. Marmosets became hypervigilant during cocaine exposures, which did not condition to the injection context. CB1r activation induced an equivalent response, whereas AM had no effect on its own. However, when given as a pre-treatment to cocaine, CB1r blockade enhanced the former's hypervigilance effect and potentially conditioned this response to the exposure context. Enhancement may have resulted from AM's inhibition of eCB-potentiated cocaine-induced anxiogenesis and/or its action independent of the eCB system, or even CB1r-mediated changes in synaptic plasticity involved in cocaine reward-learning. All effects were independent of motor function. Thus, changes in CB1r function – alone and in combination with cocaine – affected stereotyped vigilance-related behaviors in this NHP, further implicating the eCB system in the neurobiological mechanisms of cocaine addiction.

1. Introduction

In nonhuman primates (NHPs), exposure to psychostimulants such as cocaine typically induces a hypervigilance effect, although stereotyped oral movements, grooming and manipulation of objects have also been reported, as well as the tracking and/or grasping of nonexistent stimuli (Cagni et al., 2012; Castner and Goldman-Rakic, 1999, 2003; Castner et al., 2000; Farfel et al., 1992; Kleven and Woolverton, 1990; Melamed et al., 2013; Post et al., 1976; Ridley et al., 1982). These stereotyped pyschotomimetic or hallucinatory-like behaviors may escalate following repeated exposure (Cagni et al.,

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2012; Melamed et al., 2013) and persist for weeks or even months after treatment discontinuation (Castner and Goldman-Rakic, 1999). This would involve functional adaptations in neuromodulatory systems, which in NHPs may not be solely related to the typical enhancement of dopamine release in the nucleus accumbens (NAc) (Bradberry, 2007). Other neurochemical mechanisms seem to co-participate in cocaine-induced behavioral events observed in NHPs.

One recently implicated mechanism is that of the endocannabinoid system. Endocannabinoids (eCB) are important retrograde messengers that, in the brain, act mainly on the cannabinoid type-1 receptor (CB1r). This receptor was initially characterized as the binding site of the main psychoactive constituents of the marijuana plant (*Cannabis sativa*) and is highly conserved among vertebrates (Elphick, 2012). It is mostly located pre-synaptically coupled to $G_{i/o}$-proteins where it inhibits the release of different neurotransmitters (Katona and Freund, 2008).

Several lines of evidence have functionally linked eCBs transmission, via CB1r, with different mechanisms underlining cocaine addiction. For instance, CB1r are not only highly expressed in reward-related neural structures (Herkenham et al., 1990), but were specifically targeted during cocaine exposure and influenced the functional output of these areas (Winters et al., 2012). At these locations, its mRNA is co-expressed with that of dopamine receptors (Hermann et al., 2002), suggestive of an interaction at the signal transduction level (Meschler and Howlett, 2001). Besides, cocaine enhances eCB release in reward-related loci (Centonze et al., 2004), with both eCBs and plant/synthetic CB1r analogs promoting mesolimbic dopamine release and neuronal firing (reviewed in Gardner, 2005). This contrasts with studies that found no specific neuromodulatory interaction (Caille et al., 2007; Castañeda et al., 1991; Gifford et al., 1997; Gonzalez et al., 2002). At the behavioral level, pre-clinical results also differ considerably, inasmuch as both CB1r activation (Arnold et al., 1998; Fattore et al., 1999; Ferrari et al., 1999; Przegalinski et al., 2005; Vlachou et al., 2003, 2008) and its genetic/pharmacological blockade attenuated cocaine's primary rewarding effects in different animal models and procedures (Chaperon et al., 1998; Corbillé et al., 2007; Li et al., 2009; Orio et al., 2009; Soria et al., 2005; Xi et al., 2008). A lack of effect has also been a frequent outcome (Adamczyk et al., 2012; Arnold et al., 1998; Corbillé et al., 2007; Cossu et al., 2001; Ferrari et al., 1999; Filip et al., 2006; Gerdeman et al., 2008; Panlilio et al., 2007; Tanda et al., 2000). Thus, eCB modulation of cocaine-induced behavioral events requires further characterization, even if a more consistent role has been indicated for its secondary effects, such as reinstatement and relapse (reviewed in Sidhpura and Parsons, 2011).

When aiming for a more translational approach to the human condition, NHPs are highly suitable to study reward-associated behaviors (Maior et al., 2011; Weerts et al., 2007), including those related to the eCB system. Compared to rodents, NHPs will readily self-administer CB1r agonists (Justinova et al., 2003, 2005; Tanda et al., 1999), have a distinct motor response (Meschler et al., 2001) and display higher CB1r densities in learning/memory-related areas (Ong and Mackie, 1999), an aspect putatively related to drug addiction. However, few studies have been carried out in NHPs. So, here we analyzed whether repeatedly administered CB1r ligands induce behavioral effects on their own and if concurrent pre-treatments affect cocaine-induced changes in locomotion and/or vigilance-related behaviors in marmoset monkeys.

2. Results

When cocaine and the CB1r agonist WIN 55-212,2 (WIN; 1 mg/kg) were administered (Fig. 1), scanning behavior differed significantly between groups (duration: $F_{3,48}=13.46$, $p<0.001$;

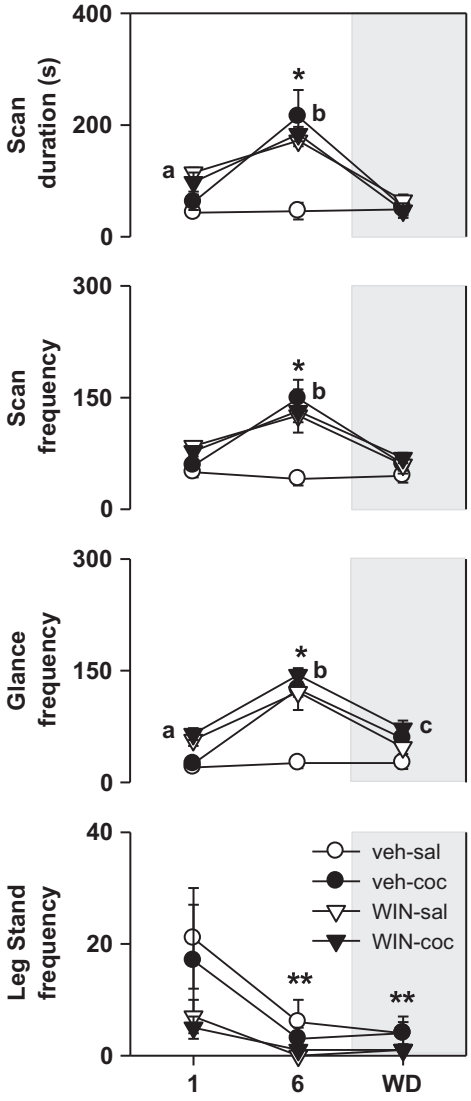

Fig. 1 – Mean (±SEM) scan duration (in seconds), as well as the number of scans, glances and leg stands made by the vehicle-saline (veh-sal), vehicle-cocaine (veh-coc), WIN 55-212,2-saline (WIN-sal) and WIN 55-212,2-cocaine (WIN-coc) treated marmosets ($n=5$/group) during the first (1) and last (6) exposure trials and the withdrawal trial (WD). Within-group differences: $^{*}p<0.05$ trial 6 vs. trials 1 and WD in the veh-coc, WIN-sal and WIN-coc groups; $^{**}p<0.05$ vs. trial 1 (for all groups); between-group differences: (a) $p<0.05$ WIN-sal vs. veh-sal group (only for scan duration and glance frequency); (b) $p<0.05$ veh-sal vs. remaining three groups; (c) $p<0.05$ WIN-coc vs. veh-sal group (only for glance frequency).