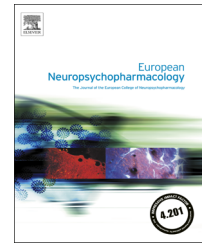




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Strain- and context-dependent effects of the anandamide hydrolysis inhibitor URB597 on social behavior in rats

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Received 24 February 2014; received in revised form 1 April 2014; accepted 7 May 2014

KEYWORDS

Endocannabinoids;
Social behavior;
Ultrasonic
vocalizations;
Strain;
URB597

Abstract

Genetic and environmental factors play an important role in the cannabinoid modulation of motivation and emotion. Therefore, the aim of the present study was to test whether anandamide modulation of social behavior is strain- and context-dependent. We tested the effects of the anandamide hydrolysis inhibitor URB597 on social behavior and 50-kHz ultrasonic vocalizations (USVs) in adolescent and adult Wistar and Sprague-Dawley rats tested in different emotionally arousing conditions (familiarity/unfamiliarity to the test cage, low/high light). Under all experimental conditions, adolescent and adult Sprague-Dawley rats displayed higher levels of social behavior and emitted more 50-kHz USVs than Wistar rats. URB597 enhanced social play behavior in adolescent Wistar rats under all experimental conditions. However, URB597 only increased social interaction in adult Wistar rats under unfamiliar/high light conditions. URB597 did not affect adolescent social play behavior and adult social interaction in Sprague-Dawley rats under any experimental condition. Moreover, URB597 increased the USVs emitted during social interaction by adolescent Wistar and adult Sprague-Dawley rats tested under familiar/high light and unfamiliar/high light, respectively. These results show that anandamide has distinct roles in adolescent and adult social behaviors. Anandamide modulation

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of adolescent social play behavior is strain- but not context-dependent. Conversely, anandamide modulation of adult social behavior and USV emission depends upon both strain and experimental context. Furthermore, these results confirm that profound behavioral differences exist between Wistar and Sprague-Dawley rats, which may explain the sometimes contradictory effects of cannabinoid drugs on emotionality in different strains of rodents.

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1. Introduction

It is known since ancient times that exposure to cannabis-derived drugs produces a wide range of effects on emotionality in humans (Zanettini et al., 2011). Upon discovery and characterization of the endocannabinoid system, it has become clear that these effects are related to the abundance of cannabinoid receptors in brain areas involved in emotional responses, where endocannabinoids influence the activity of neurotransmitter systems involved in emotion and motivation (Haller et al., 2004; Millan, 2003; Trezza et al., 2012a).

In the last 10 years, indirect stimulation of endocannabinoid signaling through inhibition of the enzymes responsible for endocannabinoid degradation has emerged as a useful approach to study the role of endocannabinoid neurotransmission in emotional and motivational states. Thus, drugs that inhibit endocannabinoid deactivation increase endocannabinoid neurotransmission only in active synapses, thus preserving the spatiotemporal specificity of endocannabinoid activity (Di Marzo, 2009). For instance, URB597 is a potent inhibitor of fatty acid amide hydrolase (FAAH, which catalyzes the intracellular hydrolysis of anandamide), but does not bind cannabinoid receptors and does not induce the well known effects of CB1 cannabinoid receptor agonists, such as catalepsy, hypothermia, or hyperphagia (Kathuria et al., 2003). However, it exerts analgesic-, anxiolytic-, and antidepressant-like effects in rodents (Gobbi et al., 2005; Hill et al., 2007; Kathuria et al., 2003; Naidu et al., 2007; Rademacher and Hillard, 2007; Realini et al., 2011). Furthermore, we have previously shown that URB597, administered either systemically (Trezza and Vanderschuren, 2008) or into limbic brain regions such as the nucleus accumbens and amygdala (Trezza et al., 2012b), enhances social play behavior in rats. Social play is a vigorous, characteristic form of social interaction in young mammals, thought to be crucial for proper social and cognitive development (Panksepp et al., 1984; Vanderschuren and Trezza, 2013). Altogether, these studies indicate that anandamide signaling maintains emotional homeostasis and regulates positive aspects of social interactions. However, it has also been shown that the behavioral consequences of pharmacological inhibition of FAAH largely depend on the environmental context (Naidu et al., 2007). For instance, URB597 administration did not affect behavior under non-stressful conditions but protected against the anxiogenic effects of stressful stimuli and circumstances in rats (Haller et al., 2009). The effects of URB597 on social behavior also appear to be context-dependent, since the increase in social play behavior induced by URB597 in adolescent rats was influenced by the level of social activity of the test partner (Trezza and Vanderschuren, 2008).

Strain differences in the effects of cannabinoid compounds on emotional and motivational processes in rodents

have also been reported (Arnold et al., 2010; Brand et al., 2012; Cadoni et al., in press; Deiana et al., 2007). The aim of the present study was therefore to investigate whether the effects of URB597 on social behavior in adolescent and adult rats are strain- and context-dependent. To address this aim, we tested the effects of systemic administration of URB597 on social behavior in adolescent and adult Wistar and Sprague-Dawley rats tested under different experimental conditions (i.e., low or high light, familiarity or unfamiliarity to the testing environment). We used Wistar and Sprague-Dawley rats because these outbred strains are widely used in behavioral pharmacology studies (Hedrich, 2006) and are known to differ in a wide range of emotional-related behaviors (Rex et al., 2004; Staples and McGregor, 2006; Walker et al., 2009), including adolescent (Manduca et al., 2014) and adult (Rex et al., 2004) social behavior.

In rodents, the emission of ultrasonic vocalizations (USVs) is considered a measure of affective states and a means of communication (Knutson et al., 2002). In rats, low frequency (around 18–30 kHz) USVs have been associated with negative social experiences (e.g., exposure to predator odor or inescapable foot shocks, inter-male fighting), while high frequency (around 50 kHz) USVs have been detected in social contexts involving potential reward (e.g., sexual approach, social play) (Burgdorf et al., 2011). Previous studies have shown that cannabinoid drugs, including URB597, modulate maternal separation-induced USVs in rat pups (Bortolato et al., 2006; Kathuria et al., 2003; McGregor et al., 1996) and adult low frequency USVs (Butler et al., 2012). Since strain differences in the effects of cannabinoid compounds on USV emission in adult rats have been reported (Arnold et al., 2010), we also investigated the effects of URB597 on USV emission during active social interactions in adolescent and adult Wistar and Sprague-Dawley rats tested in different environmental conditions.

2. Experimental procedures

2.1. Animals

Male Wistar and Sprague-Dawley rats (Charles River Laboratories, Calco, Italy) arrived in our animal facility at 21 days of age and were housed in groups of either 4 (adolescent rats) or 2 (adult rats) in $43 \times 26 \times 20 \text{ cm}^3$ ($l \times w \times h$) Macrolon cages under controlled conditions (i.e. temperature $21 \pm 1^\circ \text{C}$, $60 \pm 10\%$ relative humidity and 12/12-h light cycle with lights on at 7:00 AM). Food and water were available ad libitum. We used 148 couples of Wistar and 162 couples of Sprague-Dawley rats. All animals were experimentally naïve and were used only once (i.e., each animal received one injection only, with either drug or vehicle solution). All experiments were approved by the Italian Ministry of Health (Rome, Italy) and performed in agreement with the guidelines of the Italian Ministry

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