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Research report

The effects of anandamide and oleamide on cognition depend on diurnal variations

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ABSTRACT

Cannabinergic receptor 1 (CB1r) is highly expressed in almost the entire brain; hence, its activation affects diverse functions, including cognitive processes such as learning and memory. On the other hand, it has been demonstrated that CB1r expression fluctuates along the light-dark cycle. In this context, the objective of this work was to characterize the cannabinergic influence over cognitive processes and its relationship with the light-dark cycle. To this aim we studied the effects of two endogenous cannabinoids, anandamide (AEA) and oleamide (ODA), on the consolidation of memory and event-related potentials (ERPs) depending on the light-dark cycle. Our results indicate that AEA and ODA impair the consolidation of spatial and emotional memories and reduce the amplitude of several components of the ERP complex, depending on the phase of the light-dark cycle. This study further supports the notion that endocannabinoids participate in the regulation of cognitive processes with strong influence of environmental variables such as the light-dark cycle.

1. Introduction

The cannabinergic system has been implicated in many physiological processes, such as movement control (Ameri, 1999; Fernández-Ruiz and Gonzáles, 2005), food intake (Hao et al., 2000; Martinez-Gonzalez et al., 2004; Soria-Gómez et al., 2007), sexual behavior (Martinez-Gonzalez et al., 2004), and sleep (Prospéro-García et al., 2016). One of the reasons for these widespread cannabinergic functions is that the cannabinoid receptor 1 (CB1r) is highly expressed in almost all of the central nervous system (Tsuo et al., 1998; Pettit et al., 1998; Egertova and Elphik, 2000). The relationship between the cannabinergic system and cognitive processes such as learning and memory has been extensively explored in different models including rodents (for reviews, Goodman and Packard, 2015; Busquets-Garcia et al., 2015). For example, we know that systemic and intracerebral administrations of CB1r agonists impair the consolidation of spatial (Hampson and Deadwyler, 1998; Rueda-Orozco et al., 2008; Abush and Akirav, 2010; Wise et al., 2011; Galanopoulos et al., 2014) and fear memories (Murillo-Rodriguez et al., 1998, 2001; Maćkowiak et al., 2009; Kruk-Slomka et al., 2016). On the other hand, previous studies in our laboratory have shown that the CB1r receptor (mRNA and protein) fluctuates in the hippocampus of rats following the light-dark cycle, and it exhibits the highest concentration during the light hours (Rueda-Orozco et al., 2008). Furthermore, it has been shown that the levels of endogenous cannabinoids, such as anandamide (AEA) or 2-arachidonoyl-glycerol (2-AG), in the nucleus accumbens, prefrontal cortex, hippocampus, hypothalamus, and striatum of rats also fluctuate according to the light-dark cycle (Valenti et al., 2004; Murillo-Rodriguez et al., 2006). These variations in the concentration of endocannabinoids and in the expression of CB1r suggest that the impact of the cannabinergic modulation on different brain functions could vary depending on time of day. In support of this possibility, we have previously reported that in rats, the circadian levels of CB1r in the hippocampus are closely related to the navigation strategy used by animals to solve a spatial memory test (Rueda-Orozco et al., 2008). In addition, we have shown that intrahippocampal administrations of endocannabinoids modify sleep patterns depending on the phase of the light-dark cycle (Rueda-Orozco et al., 2010).

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On the other hand, extensive literature suggests that event-related potentials (ERPs) are reliable bioindicators of normal and abnormal cognitive processing in humans (Blokland et al., 2015; Lascano et al., 2017), and that several areas of the limbic system, importantly the hippocampus, generate at least the P3 component (Soltani and Knight 2000; Polich 2004; Ludowing et al., 2010; Modi and Sahin, 2017). It has also been reported that most ERP components in rodents are similar to those recorded in humans (Sambeth et al., 2003; Modi and Sahin, 2017), making these bioindicators a useful tool to evaluate pharmacological effects of target compounds such as cannabinoids (Featherstone et al., 2015). Despite the large body of evidence and the importance of fully understanding the mechanisms by which the cannabinergic system modulates cognitive processes like learning and memory, we are still far from understanding the different factors that may contribute to the final behavioral outcome of systemic and local administrations of cannabinergic compounds. In this context, the main objective of this work is to further characterize the differential influence of the cannabinergic system on cognitive processes depending on the light-dark cycle. To this aim we decided to evaluate, in two points of the cycle corresponding to the highest (light, 13:00 h) and lowest (dark, 01:00 h) expression of CB1r in the hippocampus (Rueda-Orozco et al., 2008), the effect of systemic and local administrations of the endocannabinoids oleamide (ODA) and AEA in two behavioral protocols to assess spatial and fear memories and in ERPs evoked by an acoustic paradigm.

2. Results

2.1. Barnes maze

To evaluate the effects of systemic administrations of endocannabinoids on the consolidation of spatial memory, we trained animals in the Barnes maze (BM; Barnes, 1979) and administered AEA or ODA at the end of each training session in two points of the light-dark cycle corresponding to the highest (13:00 h; light phase) and lowest (01:00 h; dark phase) concentrations of CB1r in the hippocampus (Rueda-Orozco et al., 2008). Drug injections were performed immediately after each training session; this way, memory acquisition and recall were spared from locomotion effects known to be induced by these cannabinoids (see Methods). Training was conducted in an illuminated room regardless of the phase of the cycle; hence, all animals had access to spatial cues (see Methods). It has been previously shown that the BM can be solved by using at least two strategies, spatial or serial (Barnes, 1979; Harrison et al., 2006), and consistent with our previous report (Rueda-Orozco et al., 2008), control animals showed a significantly higher expression of the spatial strategy during the light phase of the cycle (Kruskal–Wallis/Chi-sq = 134.94; $p < 0.001^{**}$; Fig. 1b; VEH-light vs. VEH-dark $p < 0.001$). No significant differences between light and dark phases were observed in the times to solve the task (ANOVA $F = 6.14$; $p < 0.001^{***}$; Fig. 2a VEH-light vs. VEH-dark $p = 1.0$). However, according to the use of serial strategy in subjects trained during the dark phase, a significant increase was observed both in the number of errors (ANOVA $F = 2.33$; $p = 0.043^{*}$; Fig. 2b; VEH-light vs. VEH-dark $p = 0.048$) and in the distance (Kruskal–Wallis/Chi-sq = 38.41; $p < 0.001^{**}$; Fig. 2c; VEH-light vs. VEH-dark $p = 0.004$). Systemic administration of AEA significantly increased random behavior at expense of spatial and serial strategies during the light and dark phases of the cycle, respectively (Fig. 1b). During the light phase, we also observed a significant increase in the times, number of errors, and distance (Fig. 2a-c). Differences between these execution variables during the dark phase did not reach statistical significance. Interestingly, systemic administration of ODA produced similar effects to those of AEA, but they were less potent during the light phase, when

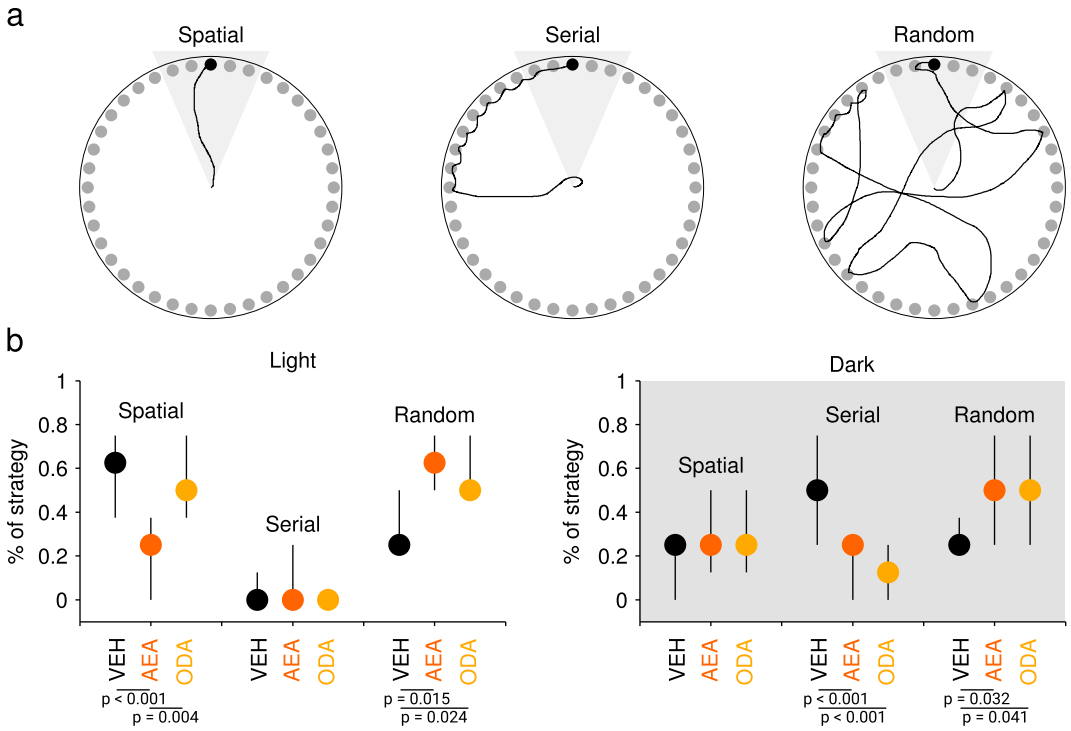

Fig. 1. Effects of systemic injections of endocannabinoids on the navigation strategies in the BM. (**a**) Schematic representation of the navigation strategies in the BM; the maze has 40 holes on its periphery, one of which leads to the escape box (black hole). Hypothetical trajectories are presented for each strategy; shaded triangles indicate the target zone where animals would exclusively explore for a strategy to be considered spatial, refer to text for full description. (**b**) Comparison of the percentage of strategies (median, 25th and 75th percentiles; data collected during the last 3 days of training) used by the control and experimental groups during the light (left panel) and dark (right shaded panel) phases of the cycle. Significant differences and p values are indicated by lines connecting experimental groups under each plot.