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Cannabinoids induce apathetic and impulsive patterns of choice through CB1 receptors and TRPV1 channels

Zahra Fatahi [a], Zahra Reisi [a], Gregor Rainer [b], Abbas Haghparast [a, c, **], Abbas Khani [d, *]

[a] Neuroscience Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Visual Cognition Laboratory, Department of Medicine, University of Fribourg, 1700 Fribourg, Switzerland
[c] Iran National Science Foundation, Tehran, Iran
[d] Functional Brain Mapping Laboratory, Department of Basic Neurosciences, University of Geneva, 1211 Geneva, Switzerland

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ABSTRACT

Despite evidence from psychiatry and psychology clinics pointing to altered cognition and decision making following the consumption of cannabis, the effects of cannabis derivatives are still under dispute and the mechanisms of cannabinoid effects on cognition are not known. In this study, we used effort-based and delay-based decision tasks and showed that ACEA, a potent cannabinoid agonist induced apathetic and impulsive patterns of choice in rats in a dose-dependent manner when locally injected into the anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), respectively. Pre-treatment with AM251, a selective cannabinoid type 1 (CB1) receptor antagonist, reversed ACEA-induced impulsive and apathetic patterns of choice in doses higher than a minimally effective dose. Unlike CB1 receptor antagonist, pretreatment with capsazepine, a transient receptor potential vanilloid type 1 (TRPV1) channel antagonist, was effective only at an intermediary dose. Furthermore, capsazepine per se induced impulsivity and apathy at a high dose suggesting a basal tonic activation of TRPV1 channels that exist in the ACC and OFC to support cost-benefit decision making and to help avoid apathetic and impulsive patterns of decision making. Taken together, unlike previous reports supporting opposing roles for the CB1 receptors and TRPV1 channels in anxiety and panic behavior, our findings demonstrate a different sort of interaction between endocannabinoid and endovanilloid systems and suggest that both systems contribute to the cognitive disrupting effects of cannabinoids. Given prevalent occurrence of apathy and particularly impulsivity in psychiatric disorders, these results have significant implications for pharmacotherapy research targeting these receptors.

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1. Introduction

Several lines of studies have linked cannabis consumption to altered cognition and decision making. Most of these studies have been conducted in human participants who are cannabis abusers or recreational consumers. They generally point to more impulsive and risky decision making among recreational (Griffith-Lendering et al., 2012; Moreno et al., 2012) and chronic (Fridberg et al., 2010; Leppink et al., 2014; Solowij et al., 2012) users of cannabis compared to healthy participants. Additionally, it has also been shown that the pattern of decision making and reward processing can predict the future changes in cannabis use (Cousijn et al., 2013) such that participants biased towards immediate rewards were more likely to increase drug use. At the structural level, Szeszko et al. (2007) demonstrated that first-episode schizophrenic patients who consume cannabis have smaller gray matter anterior cingulate cortex (ACC), a key brain region in processing decision making, compared to healthy volunteers and patients who did not use cannabis. At the functional level, it has been shown that cannabis users exhibited orbitofrontal cortex (OFC), another key brain area in processing decision making, hypoactivations in response to rewarded outcomes compared to control participants (De Bellis et al., 2013). Despite controversial evidence on the effects of cannabis consumption on cognitive functions in general and decision making patterns in particular (Dougherty et al., 2013;

* Corresponding author. Functional Brain Mapping Laboratory, Department of Basic Neurosciences, University of Geneva, Rue Michel Servet 1, CH-1211 Geneva, Switzerland.
** Corresponding author. Neuroscience Research Center, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
E-mail address: abbas.khani@unige.ch (A. Khani).

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Egerton et al., 2005; Grant et al., 2012; Hermann et al., 2009; Lane et al., 2005; Moreno et al., 2012; Solowij et al., 2012; Whitlow et al., 2004), mechanistic investigation of consequences of cannabinoid system activation has been scarce and the mechanisms of cannabinoid system involvement in frontal cortical circuits of decision making are poorly understood.

We have recently demonstrated (Khani et al., 2015) that the activation of cannabinoid system in the ACC, but not the OFC, makes animals effort aversive such that they are less willing to expend physical effort to acquire higher amount of reward. On the other hand, the activation of cannabinoid system in the OFC, but not the ACC, induced impulsive patterns of choice such that the animals preferred small immediate reward to large delayed reward. Similar to lesion studies (Rudebeck et al., 2006), these effects were double-dissociable with the cannabinoid system involvement in effort-based and delay-based decision making in the ACC and OFC, respectively.

Endocannabinoid and endovanilloid systems are closely related and, indeed, several endogenous as well as synthetic cannabinoids act not only as cannabinoid type 1 (CB1) receptor agonists but also activate transient receptor potential vanilloid type 1 (TRPV1) channels (Toth et al., 2009). Both receptors are abundant in the prefrontal cortical areas (Eggan and Lewis, 2007; Madasu et al., 2015; Mailleux and Vanderhaeghen, 1992; Roberts et al., 2004) and show overlapping localization in these areas (Micale et al., 2009). Electrophysiological studies have shown that the function of these two receptors relies on different cellular mechanisms: Whereas CB1 receptor activation leads to the inhibition of calcium influx and therefore reduction of the neurotransmitter release (Vaughan et al., 2000), TRPV1 activation facilitates calcium influx and neurotransmitter release (Starowicz et al., 2007). At the behavioral level, it has been demonstrated that CB1 and TRPV1 receptors mediate opposing functions (Casarotto et al., 2012) in different brain areas particularly in emotion-related behaviors such as anxiety and defensive behavior (Fogaca et al., 2012; Terzian et al., 2009). Indeed, it has been suggested that the biphasic response profile (Fogaca et al., 2012; Moreira and Lutz, 2008) following the administration of some of the cannabinoid agents is due to the activation of the TRPV1 receptors in addition to the activation of the CB1 receptors. The contribution of each of CB1 receptors and TRPV1 channels in frontal areas in cognitive functions such as altering decision making patterns are not known. Given above mentioned lines of evidence, it is possible that the effects of the cannabinoid agonists in the frontal areas are mediated by either CB1 or TRPV1 receptors or by interaction of both receptors.

To address differential contribution of the CB1 and TRPV1 receptors in modulating cost-benefit decision making, we first microinjected different doses of a potent cannabinoid agonist into the ACC or OFC during different versions of cost-benefit decision making tasks to determine whether the response profile is biphasic or not. Then we studied the effects of CB1 and TRPV1 receptor antagonists in conjunction to a potent cannabinoid agonist during decision making to disentangle the contribution of each receptor type. Our results suggest a more complex interplay of cannabinoid/vanilloid systems that establishes a cognitive homeostasis supporting optimal decision making.

2. Materials and methods

2.1. Subjects

Male Wistar rats (Pasteur institute, Iran) were used as subjects in all experiments. The rats were eight weeks old at their arrival and were housed in groups of three per cage under standard temperature and light/dark conditions with free access to water and food. After the habituation to the facility, handling and behavioral training started. At this stage the food was restricted for an initial body weight of about 90% of the free feeding weight (240-270 g) followed by a controlled weight gain of about 6–12 g per week. The animals were naïve to any behavioral experiment. All experiments were executed in compliance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80-23, revised 1996) and were approved by the Research and Ethics Committee of Shahid Beheshti University of Medical Sciences.

2.2. Apparatus and behavioral training

T-mazes (PVC) with three arms of 60 cm long each, 10 cm wide and 40 cm high were used for the experiments (Fig. 1). The apparatus specifications, surgery and behavioral procedures have been detailed elsewhere (Khani et al., 2015). Briefly, the mazes had food wells at the end of goal arms. During effort-based decision making training, triangular barriers with different heights (10-30 cm) were placed in the midpoint of the high-reward goal arm. In delay-based decision making task, four retractable doors were used in the goal

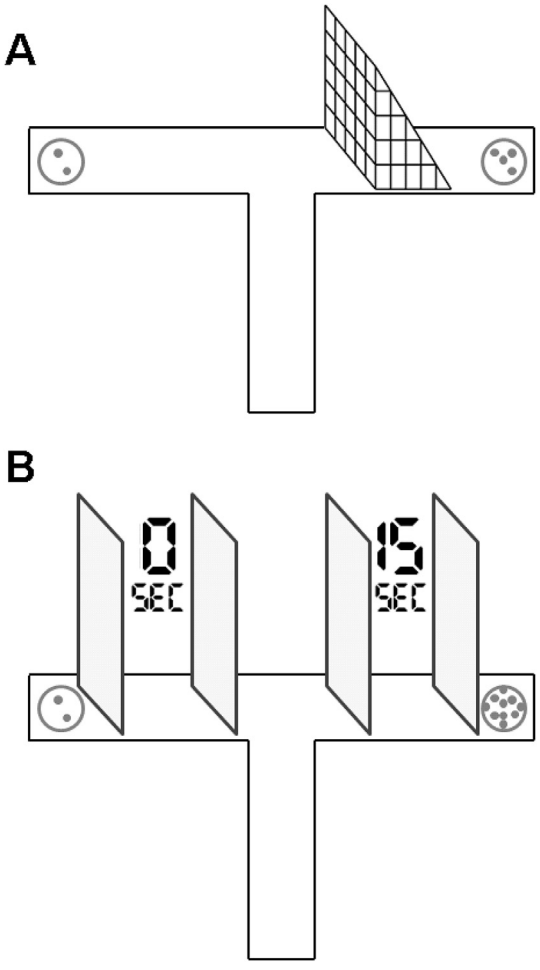

Fig. 1. Schematic illustration of the cost-benefit T-maze decision making tasks used in this study. **A**) During effort-based decision making, the rats could choose between 4 pellets at the cost of expending physical effort to climb a 30 cm barrier or 2 pellets at no physical effort cost in terms of climbing a barrier. **B**) During delay-based decision making, the animals could choose between 2 pellets that were immediately available or 10 pellets that required a waiting time of 15 s. During the control tasks, a same-sized barrier (equal effort) or a same-long delay (equal delay) was introduced to the low reward arm as well.

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