Pharmacology, Biochemistry and Behavior 158 (2017) 14–21

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

journal homepage: www.elsevier.com/locate/pharmbiochembeh

Effects of anandamide administration on components of reward processing during free choice

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ARTICLE INFO

Keywords:
Anandamide
Endocannabinoids
Motivation
Decision-making
Incentive contrast

ABSTRACT

Previous research has implicated the positive modulation of anandamide, an endocannabinoid neurotransmitter, on feeding behavior. Anandamide is particularly noteworthy as it acts as an endogenous ligand of the CB1 receptor, the same receptor that is activated by tetrahydrocannabinol, the primary psychoactive component in *Cannabis sativa*. Cannabis legalization in North America has presented with a need to study endocannabinoid agonists and their effects on behavior. Much has yet to be determined in terms of the role of the endocannabinoid system in decision-making scenarios. The research presented here tested the hypothesis that anandamide would augment motivation and reward processing via appetitive and consummatory measures during an operant, foraging task. A three-box design was used in order to provide the animals with a free choice, exploratory foraging environment. Discrimination, preference, and incentive contrast were analyzed as discrete measures of decision-making in the three-box paradigm. Anandamide administration (1 mg/kg) was found to significantly increase motivation for the optimal foraging outcome and alter basic processing of reward information involved in discrimination and relative valuation. The positive effects of anandamide on eating behavior and motivation have implications toward possible treatment modalities for patient populations presenting with disorders of motivation. These findings suggest the need for continued investigation of the endocannabinoid system as a central component of motivated behavior.

1. Introduction

Cannabis is the most widely used illegal drug in the world (Weinstein et al., 2016). Stereotypically, cannabis users are perceived as lazy and lacking in motivation. Indeed, research depicting a perceived lack of motivation in cannabis users has been described for many decades. Mcglothlin & West (1968) published an article outlining an amotivational syndrome induced by regular use of cannabis that is characterized by reduced achievement-based behavior and increased passivity. A subset of heavy cannabis users reported low energy and lack of motivation as a negative of long-term cannabis use (Reilly et al., 1998). Recently, Silveira et al. (2016) demonstrated Δ9-tetrahydrocannabinol (THC) dependent decreases in high effort/high reward trials without affecting ability to perform an attention challenge in Long-Evans rats. Specifically, their experimental design was able to separate measurements of motivation from measurements of trial accuracy, latency to recover reward, and latency to make a low or high effort choice. These factors did not significantly differ between controls and rats that received THC.

While this amotivational stereotype has persisted for decades, there has been an increase in evidence pointing to the contrary. Research investigating the effects of cannabinoids on cognition-related behavior found no difference in performance of a progressive ratio task between control squirrel monkeys (*Saimiri sciureus*) and squirrel monkeys given 0.03, 0.1, and 0.32 mg/kg doses of THC respectively (Kangas et al., 2016). The progressive ratio task was used as a measure of motivation; however, THC administration was correlated with dose-related decreases in the performance of discriminatory and attention tasks. Taken together, this research indicates that a dose-dependent decrease of performance in non-human primates given THC is due to cognitive impairment, rather than a decrease in motivation (Kangas et al., 2016). In 1980, an experiment investigating the effect of cannabis on work performance was published. The experimental group self-administered an average of 16.5 mg of THC smoked per day, an amount known to produce a reliable psychoactive effect. While the experimental group displayed greater increases in output per hour compared to the control group, there was no difference between control and experimental groups in regards to total output or total hours worked (Kagel et al.,

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http://dx.doi.org/10.1016/j.pbb.2017.05.008
Received 3 March 2017; Received in revised form 16 May 2017; Accepted 17 May 2017
Available online 18 May 2017
0091-3057/

1980). In addition to these findings, research investigating the relationship between depression, motivation, and cannabis use found that depression was a necessary factor in those who smoke either heavy or light amounts of cannabis to display amotivation (Musty and Kaback, 1995).

It is almost impossible to discuss THC without also mentioning cannabidiol (CBD), another phytocannabinoid present in cannabis, though in comparatively lower amounts (Swift et al., 2013). Recently, CBD has been indicated to attenuate motivational dysfunction by elevating anandamide (N-arachidonoylethanolamine; AEA) levels and activation of the 5-HT1a receptor (Zlebnik and Cheer, 2016). More specifically, CBD may reduce depressive symptoms such as anhedonia and associated amotivation by simulating anandamide-dependent neurogenesis in the hippocampus of mice (Campos et al., 2013). Additionally, serum anandamide levels have been found to negatively correlate with anxiety in female patients with major depression (Hill et al., 2008).

This series of evidence suggests anandamide may be a key compound involved in motivation (Zlebnik and Cheer, 2016). Anandamide is a neurotransmitter/neuromodulator that functions as an endogenous ligand of CB1 receptors. Synthesized via multiple pathways involving hydrolysis of phospholipid precursors, anandamide is a hydrophobic molecule which diffuses from the postsynaptic membrane to affect its presynaptic targets without the need for vesicular secretion (Freund et al., 2003). Anandamide functions as a partial agonist of the CB1 receptor, which is a g-protein coupled receptor most prevalent in the nucleus accumbens (NAcc), cerebellum, hippocampus, and prefrontal cortex (Howlett et al., 2002; Mahler et al., 2007; Solinas et al., 2008; Karimi et al., 2013). The distribution of CB1 receptors and anandamide's effect on them suggests that it is involved in the regulation of a large suite of motivated behaviors.

Indeed, microinjections of anandamide into the dorsal medial shell of the NAcc have been found to significantly increase hedonic reactions to sucrose solutions and greatly extend time spent eating in Sprague-Dawley rats (Mahler et al., 2007). Anandamide has also been found to significantly reduce anticipatory errors during an attention task (Panlilio et al., 2008) and improve cognitive performance during a radial arm maze (Hao et al., 2000). Interestingly, these effects cannot be attributed to depressed ambulatory effect even at the high dose of 10 mg/kg as significantly decreased latency to respond was noted at the same time (Panlilio et al., 2008). Others have looked at anandamide's effect on appetitive behavior and found that even at the low dose of 0.001 mg/kg, food intake was significantly increased (Hao et al., 2000).

The recent trend toward cannabis legalization has made it imperative to understand the effects of the endocannabinoid system, particularly its role in motivated behavior and decision-making (Di Marzo and Matias, 2005). Worth noting, THC, the primary psychoactive component in cannabis, acts as a partial agonist for the CB1 receptor. Cannabinoid research holds implications for therapeutic use of exogenous administration of endocannabinoids, medical cannabis usage, as well as cannabinoid abuse and addiction models.

While studies have revealed anandamide's influence on the motivation to feed, a majority have used an ad libitum consumption design (Williams and Kirkham, 1999; Hao et al., 2000; Kirkham et al., 2002). What has not been studied thus far is anandamide's effect on appetitive and consummatory behavior in a free choice, reward optimization-based operant task. That is to say, there has been no experimental work on anandamide and motivation using choice tasks in an animal model to date. There is a need to understand how this compound could alter choice and decision-making in order to examine possible benefits or harmful outcomes from exposure to anandamide (or anandamide-like compounds) in real-world situations with complex decisions and multiple outcomes.

To investigate this line of inquiry, our study used a novel, 3-box paradigm operant task with weekly shifting reward magnitudes (Fig. 2). The 3-box paradigm was designed to measure various aspects of decision making including discrimination, incentive contrast, and preference in a free-choice environment (Ricker et al., 2016a, 2016b). Discrimination is investigated by analyzing test subjects' ability to recognize choices that change in reward magnitude over time. Incentive contrast is measured by comparing rat behavior in the constant fixed ratio box to the shifting outcome box across weeks. Lastly, preference is analyzed by monitoring how rats choose between box outcomes within a single session. The paradigm combines aspects of decision making in order to elucidate these aspects of decision-making. We hypothesized that anandamide's hedonic impact on reward liking (Mahler et al., 2007) would motivate the rats to choose a high effort box when outcomes shifted above a small reward despite the disparity in effort required to attain.

2. Materials and methods

2.1. Animals

15 outbred, male Sprague-Dawley rats averaging 284 g in weight (*SD* = 42) were individually housed in 65 cm × 24 cm × 15 cm cages with corncob bedding. Water was available ad libitum in their home cages as well as throughout testing. Animals were food restricted to no < 87% of their free-feeding, baseline weight (Harlan Teklad Rat Chow #8604). During testing, animals fluctuated between 1.3% and 5.7% above their restriction weight. The rats were maintained on a 12-h reverse light/dark cycle (lights off at 9:00 a.m.). The colony room was maintained at 70 °F and approximately 56% humidity. All procedures were approved by the Bowling Green State University Institutional Animal Care and Use Committee (protocol 821,222). All efforts were made to keep animal suffering to a minimum.

2.2. Drugs

Anandamide ([*N*-(2hydroxyethyl)-5,8,11,14-eicosatetraenamide]; Tocris Cookson Inc.), supplied in a 1:4 soya oil/water emulsion was dissolved in 0.9% saline solution and administered at 1 mg/kg. This dosage was selected based on previous research indicating the greatest impact on consummatory behavior when compared with both higher and lower dosages (Williams and Kirkham, 1999; Higgs et al., 2003). Fresh drug solutions or saline control solutions were prepared on each test day and administered subcutaneously (SC) at a volume of 1 ml/kg.

2.3. Apparatus

The three-box reward-seeking paradigm consists of three 25.40 cm × 30.48 cm × 40.64 cm cast acrylic boxes (Fig. 1). A door is located on the front of the middle “decision” box. To the left and right of the center box (117 cm either way) are additional boxes with identical dimensions. Cast acrylic tunnels (9 cm diameter) connect the peripheral boxes on either side to the center box. Each outer box is

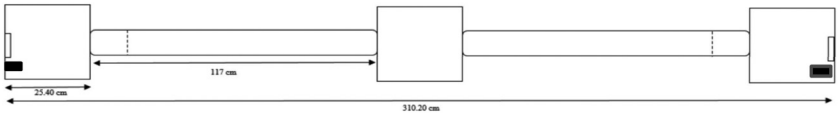

Fig. 1. Apparatus used to examine free choice. The environment has three boxes with the total length of ~8 ft between the to goal boxes on either end. A middle box separates the two option locations with tubing linking all three environments.