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Effects of co-administration of 2-arachidonylglycerol (2-AG) and a selective μ-opioid receptor agonist into the nucleus accumbens on high-fat feeding behaviors in the rat

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ABSTRACT

Previous research has demonstrated that the nucleus accumbens is a site where opioids and cannabinoids interact to alter feeding behavior. However, the influence of the endocannabinoid 2-arachidonylglycerol (2-AG) on the well-characterized model of intra-accumbens opioid driven high-fat feeding behavior has not been explored. The present experiments examined high-fat feeding associated behaviors produced by the interaction of 2-AG and the μ-opioid receptor agonist DAla[2],N,Me-Phe[4],Gly-ol[5]-enkaphalin (DAMGO) administered into the nucleus accumbens. Sprague-Dawley rats were implanted with bilateral cannulae aimed at the nucleus accumbens and were co-administered both a sub-threshold dose of 2-AG (0 or 0.25 μg/0.5 μl/side) and DAMGO (0, 0.025 μg or 0.25 μg/0.5 μl/side) in all dose combinations, and in a counterbalanced order. Animals were then immediately allowed a 2 h-unrestricted access period to a palatable high-fat diet. Consumption, number and duration of food hopper entries, and locomotor activity were all monitored. DAMGO treatment led to an increase in multiple behaviors, including consumption, duration of food hopper entry, and locomotor activity. However, combined intra-accumbens administration of DAMGO and a subthreshold dose of 2-AG led to a significant increase in number of food hopper entries and locomotor activity, compared to DAMGO by itself. The results confirm that intra-accumbens administration of subthreshold dose of the endogenous cannabinoid 2-AG increases the DAMGO-induced approach and locomotor behaviors associated with high-fat feeding.

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1. Introduction

The latest data indicate that 34.9% of the adult and 16.9% of the child U.S. population is obese (Ogden et al., 2014). Although obesity is certainly the result of a complex set of factors, including sedentary lifestyle, economic factors, genetic predisposition, and stressful life events, the over consumption of calorically dense palatable foods is involved. Research examining the nature of this critical behavior of overconsumption has revealed a distributed feeding network that includes many key regions of the brain and many neuromodulators that may contribute (Will et al., 2003; Berthoud, 2012, for review). The nucleus accumbens in particular, and its associated circuitry, is a critical region that mediates the response to palatable food, most notably the actions of opioids (Pecina and Berridge, 2000; Will et al., 2003). For example, administration of the selective μ-opioid agonist D-Ala^2, NMe-Phe^4, Glyol^5-enkephalin (DAMGO) into the nucleus accumbens produces a robust binge-like consumption of palatable diets such as those high in fat and/or sugar (Zhang and Kelley, 2000; Pecina and Berridge, 2000). Behavioral and pharmacological characterizations of intra-accumbens DAMGO suggest that it does not induce a state of negative energy balance (i.e. "hunger") (Hanlon et al., 2004; Will et al., 2009). Indeed, evidence suggests that the activation of the accumbens with DAMGO acts to increase the hedonic or rewarding nature of the food independent of negative energy balance, in turn producing increased consumption and associated food seeking behaviors (Kelley et al., 2002; Pecina and Berridge, 2000; Will et al., 2009).

Overlapping with the comparably longer period of research on opioids (Bodnar, 2013), research on endocannabinoids has led to promising targets that could lead to therapeutic advancements in the treatment of both obesity and drug addiction (Isoldi and Aronne, 2008; Bermudez-Silva et al., 2010). Systemic activation of the endocannabinoid system produces many of the same behavioral effects as the opioid system, including increased feeding behavior, and reinforcement of drug self-administration behavior (Maldonado and Rodriguez de Fonseca, 2002; Tanda and Goldberg, 2003; Silvestri and Di Marzo, 2013; Cristino et al., 2014; Jager and Witkamp, 2014). The endocannabinoids 2-arachidonoylglycerol (2-AG) (Mechoulam et al., 1995; Sugiura et al., 1995) and anandamide (Devane et al., 1992) have both been shown to increase feeding behavior when administered into the nucleus accumbens (Kirkham et al., 2002; Mahler et al., 2007). However, the combined influence of these endocannabinoids and opioid receptor agonists has not been explored in a palatable feeding model. It has been demonstrated that the behavioral effects of cannabinoids are partially dependent on co-activation of the opioid system (Williams and Kirkham, 2002; Maldonado and Rodriguez de Fonseca, 2002; Justinova et al., 2004; Skelly et al., 2010). For example, feeding increased by striatal infusions of cannabinoid and opioid agonists is blocked by prior administration of opioid and cannabinoid receptor antagonists, respectively (Williams and Kirkham, 2002; Skelly et al., 2010). Also, sub-threshold doses of opioid and cannabinoid antagonists that have little or no effect on feeding independently, demonstrate a potentiated effect when administered together (Kirkham and Williams, 2001; Chen et al., 2004; Tallett et al., 2009). Finally, intra-accumbens administration of a subthreshold dose of a selective CB1 agonist WIN55212-2 and DAMGO increased high-fat feeding above levels produced by DAMGO alone (Skelly et al., 2010).

The present study was designed to examine the potential interaction of the opioid and cannabinoid systems within the well-characterized model of intra-accumbens opioid-induced high-fat feeding. Specifically, a sub-threshold dose of 2-AG and multiple near-threshold doses of the μ-opioid agonist DAMGO were co-administered into the nucleus accumbens and multiple behaviors associated with high fat feeding were assessed, including food-directed approach (food hopper entries), consumption, and locomotor activity. Assessing approach, as well as consumption behaviors, has been shown to be critical in understanding the diverse effect of the interaction of opioids and cannabinoids (Tallett et al., 2009). Also, increased food-directed approach responses do not always predict a parallel increase in consumption measures (Will et al., 2009). Therefore, the current study investigated whether a sub-threshold dose of the endocannabinoid 2-AG alter the feeding behaviors driven by intra-accumbens DAMGO.

2. Results

2.1. Consumption

An ANOVA conducted on the food consumption during the total 2 h test session revealed no main effect of 2-AG pretreatment (Fig. 1) (vehicle or 0.25 μg) ($F(1,36)=1.99$, *ns*), a significant main effect of DAMGO treatment (saline, 0.025 μg, or 0.0025 μg) ($F(2,36)=14.85$, $p<0.0001$), and no interaction ($F(2,36)=1.20$, *ns*) (Fig. 2). As can be observed in the smaller inset in Fig. 2, there was a strong trend of decreasing consumption across time with the majority of consumption following all treatments occurring in the first 30 min. To further analyze this trend and treatment effects across time, an ANOVA examining 2-AG pretreatment *x* DAMGO treatment *x* time interval interaction was conducted. There was again no main effect of 2-AG pretreatment ($F(1,144)=1.58$, *ns*), yet a significant main effect of DAMGO treatment ($F(2,144)=12.22$, $p<0.0001$), and time interval ($F(3,144)=183.15$, $p<0.0001$). The only significant interaction observed was a DAMGO treatment *x* time interaction ($F(6,144)=12.91$, $p<0.0001$). Post-hoc comparisons of consumption during the first 30 min interval revealed that the highest dose of DAMGO, with or without 2-AG pretreatment, was significantly increased ($p<0.05$) compared to control treatment (vehicle pretreatment+saline treatment). No other treatment comparison reached significance ($p>0.05$).

2.2. Food hopper entries

An ANOVA conducted on the total number of food hopper entries during the 2 h test session revealed no main effect of 2-AG treatment ($F(1,36)=2.12$, *ns*), a significant main effect of DAMGO treatment ($F(2,36)=3.59$, $p<0.05$), and a significant 2-AG *x* DAMGO treatment interaction ($F(2,36)=3.60$, $p<0.05$). As displayed in Fig. 3, post-hoc comparisons revealed that intra-accumbens 2-AG and both DAMGO doses did not increase total hopper entries alone ($p>0.05$). However, the combined