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Sex differences in the cannabinoid regulation of energy homeostasis

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Summary This review highlights the progress made thus far in characterizing the behavioral and cellular mechanisms through which cannabinoids regulate energy homeostasis. We performed microstructural analysis of feeding behavior in gonadectomized guinea pigs and gonadally intact, transgenic CB1 receptor knockout mice to determine how cannabinoids affect circadian rhythms in food intake and meal pattern. We also implanted data loggers into the abdominal cavity to correlate the appetite-modulating properties of cannabinoids with changes in core body temperature. We then coupled the effects on feeding behavior and temperature regulation with synaptic changes in the hypothalamic feeding circuitry via whole-cell patch clamp electrophysiological recording from neurons in the arcuate nucleus (ARC), in order to gain a more global perspective on the cannabinoid modulation of energy homeostasis. We observed marked sex differences in cannabinoid effects on food intake and core body temperature — with male guinea pigs exhibiting a comparatively greater sensitivity to the hyperphagia and hypophagia, as well as the hypothermia and hyperthermia, produced by CB1 receptor agonists and antagonists, respectively. In addition, male but not female CB1 receptor knockout mice show a diminished nocturnal food intake and average daily body weight relative to their wildtype littermate controls. The disparity in the CB1 receptor-mediated hyperphagia is paralleled by sex differences in the cellular effects of cannabinoids at anorexigenic, guinea pig proopiomelanocortin (POMC) synapses. Postsynaptically, cannabinoids potentiate an A-type K^+ current (I_A) in POMC neurons from female guinea pigs, whereas in males the activation of an inwardly rectifying K^+ current is observed. Presynaptically, while cannabinoids inhibit glutamatergic input onto POMC neurons in males and females to similar degrees, males are more refractory to the cannabinoid-induced inhibition of convergent GABAergic input than females. These data reveal pervasive sex differences in the cannabinoid regulation of energy homeostasis that are consistent with changes in the excitability of POMC neurons.

1. Introduction

Over the past 30 years the literature is marked by a number of reports demonstrating sex differences in the biological

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activity and metabolism of cannabinoids. Males consume marijuana in greater amounts, at higher rates, and report a greater subjective psychotropic effect of Δ^9-tetrahydrocannabinol (THC) than do females (Paton and Kandel, 1978; Perez-Reyes et al., 1981; Penetar et al., 2005). Men also exhibit higher circulating levels of THC, and are much more likely to be arrested for driving under the influence of cannabis (Jones et al., 2008). On the other hand, female rodents express greater amounts of hepatic cytochrome P-450 isozymes and aldehyde oxygenase activity that may facilitate conversion of THC to potent bioactive metabolites such as 11-hydroxy-THC (Narimatsu et al., 1991; Watanabe et al., 1992; Narimatsu et al., 1992). In addition, self-administration of the CB1 receptor agonist WIN 55,212-2 in female Long Evans and Lister Hooded rats is more rapidly acquired, and more robustly maintained, than in their male counterparts (Fattore et al., 2007). These reported inequities in cannabinoid ingestion or self-administration, coupled with disparate metabolism, xenobiotic transformation and expression of cannabinoid receptors (Rodríguez de Fonseca et al., 1994), would differentially alter cannabinoid availability and signal strength in the target tissues and brain regions, and thus the biological effects of cannabinoids, in males and females. Indeed, cannabinoids elicit a comparatively greater antinociception and locomotor effects in female rodents (Tseng and Craft, 2001; Wiley, 2003; Tseng et al., 2004), and women are more susceptible to cannabinoid-induced hemodynamic changes and visuospatial memory impairment than men (Pope et al., 1997; Mathew et al., 2003). Cannabinoids also regulate the transcription of proopiomelanocortin (POMC) and preprocorticotropin-releasing hormone (CRH) genes in a sexually differentiated manner; with the THC-induced increases in CRH expression in males dependent upon the presence of dihydrotestosterone, and the increases in POMC expression in females dependent upon the presence of estrogen (Corchero et al., 2001). In addition, they interact with other drugs of abuse such as nicotine to modulate anxiety in a sex-specific fashion (Marco et al., 2006). Given the burgeoning wealth of evidence for sex differences in cannabinoid regulated biology, we focus here on those pertaining to the behavioral and cellular mechanisms through which cannabinoids modulate energy homeostasis.

2. Sex differences in the cannabinoid regulation of feeding and core body temperature

Both naturally occurring and synthetic cannabinoids stimulate hyperphagia (Cota et al., 2003; Fride et al., 2005) and hypothermia (Fitton and Pertwee, 1982; Hillard et al., 1999). Microstructural analyses of the effects of the CB1 receptor agonist WIN 55,212-2 on food intake and meal pattern in gonadectomized guinea pigs show a considerably more robust stimulation of intake in males than in females. This is characterized by a more prolonged, acute increase in hourly intake that peaks 2 h after administration, and a more extensive, latent nocturnal increase in hourly intake (Fig. 1), that collectively translates into a more substantial, cumulative daily intake measured 24 h after administration (Fig. 2). In males, the hyperphagia produced by WIN 55,212-2 is associated with increased meal size and duration, and a latent increase in meal frequency, whereas in females it is coupled with both acute and latent increases in meal frequency (Diaz et al., in press). Conversely, the CB1 receptor antagonist AM251 produced a modest decrease in hourly food intake that overall was greater in males than in females. AM251 acutely reduced intake 2 h after administration, and blocked the peak intake that occurred 1 h after lights off (19:00 h), to equivalent degrees in male and female animals (Fig. 1). However, the antagonist produced a prolonged and pronounced decrease in hourly intake during the latter part of the nocturnal period that was observed exclusively in males (Fig. 1). This disparate anorectic effect of AM251 is associated with both acute and latent nocturnal decreases in meal frequency in male but not female guinea pigs (Diaz et al., in press). Interestingly, the circadian hourly intake pattern observed in AM251-treated

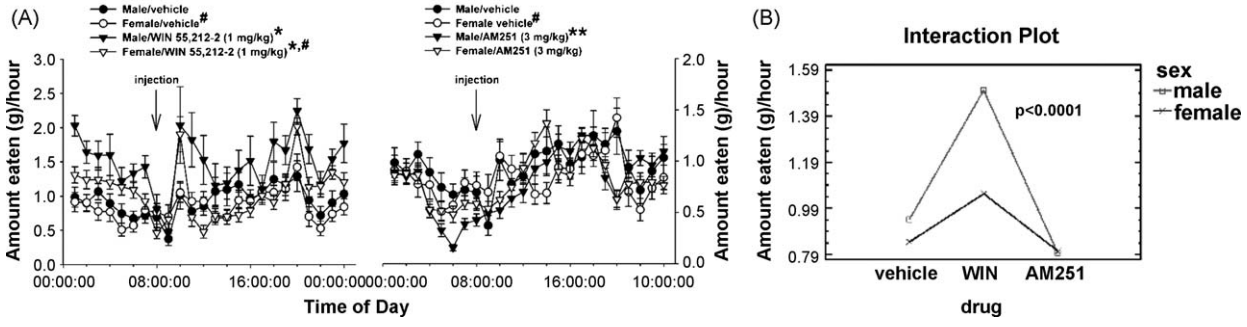

Figure 1 Sex differences in cannabinoid-induced alterations in hourly food intake. (A) Gonadectomized male and female animals were injected with WIN 55,212-2 (1 mg/kg; s.c.), AM251 (3 mg/kg; s.c.) or their cremephor/ethanol/saline vehicle at 08:00 and immediately placed back into their respective feeding chambers. The symbols represent means and vertical lines 2 S.E.M. ($n = 4$) of the total amount of food consumed every hour over a 24-h period. The data to the left of the injection arrow represent the average cumulative intake measured at hourly intervals from 1:00 to 8:00 a.m. across the 7 days of exposure. *Values from animals treated with WIN 55,212-2 that are significantly different (multi-factorial ANOVA/LSD; $p < 0.05$) than those observed in vehicle-treated controls. #Values from females that are significantly different (multi-factorial ANOVA/LSD; $p < 0.05$) than those from their male counterparts. **Values from animals treated with AM251 that are significantly different (multi-factorial ANOVA/LSD; $p < 0.05$) than those observed in vehicle- or agonist-treated animals. (B) An interaction plot that illustrates the significant interaction between sex and drug, and the significant changes in hourly intake in agonist- and antagonist-treated animals. Printed with permission from Diaz et al. (in press) (S. Karger AG, Basel).