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Sex Differences in Cannabinoid-Regulated Biology: A Focus on Energy Homeostasis

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Abstract

Considerable strides have been made over the past 20 years in our understanding of the ligands, receptor subtypes, signal transduction mechanisms and biological actions comprising the endocannabinoid system. From the ever-expanding number of studies that have been conducted during this time, it has become increasingly clear that sex differences are the cornerstone of cannabinoid-regulated biology. Available evidence has demonstrated that these sex differences endure in the absence of gonadal steroids, and are modulated by the acute, activational effects of these hormones. This review focuses on select aspects of sexually differentiated, cannabinoid-regulated biology, with a particular emphasis on the control of energy balance. It is anticipated that it will lend impactful insight into the pervasive and diverse disparities in how males and females respond to cannabinoids – from the organismal level down to the molecular level. Additionally, it will furnish a newfound appreciation for the need to recalibrate our thinking in terms of how cannabinoids are used as therapeutic adjuvants for a broad range of clinical disorders and associated comorbidities, including body wasting and obesity.

Keywords

cannabinoid; sex difference; estradiol; testosterone; AMP-activated protein kinase; glutamate; retrograde signaling; energy balance; cachexia; obesity

1. Introduction

The marijuana plant (i.e., *cannabis sativa*, *cannabis indica*) has played a diversified role in many cultures and societies over the millennia. It has been used for purposes ranging from the textile to the religious to the medicinal (Hamarneh, 1972; Mikuriya, 1969; Touw, 1981). The medicinal properties of *cannabis* have been leveraged through the ages by the Indians, Chinese, Greeks, Assyrians, Persians, Egyptians, Algerians, Moroccans, Hindus, Buddhists, Jews and Muslims as an analgesic, anesthetic, appetite stimulant and euphoriant (Brunner,

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1973; Hamarneh, 1972; Hindmarch, 1972; Mikuriya, 1969; Touw, 1981; Winek, 1977). *Cannabis* was introduced to Western medicine in the 19th century (Mikuriya, 1969), and various formulations could be found in the Materia Medica of the U.S. Pharmacopoeia up until 1941; removed only after Congress passed the Marihuana Tax Act in 1937 (Brunner, 1973; Mikuriya, 1969; Winek, 1977).

Of the 60 or so cannabinoid compounds found in *cannabis*, the primary psychotropic constituent is Δ^9-tetrahydrocannabinol (THC) (Mechoulam and Gaoni, 1965). THC binds two $G_{i/o}$-coupled receptors, each with seven transmembrane-spanning domains arranged in a serpentine fashion – namely, the cannabinoid CB1 and CB2 receptors (Gérard et al., 1991; Matsuda et al., 1990; Munro et al., 1993). More recently, it has been shown that THC activates a third G protein-coupled receptor, GPR55, that is apparently involved in the regulation of gastrointestinal motility, insulin secretion and adiposity (Lauckner et al., 2008; Lin et al., 2011; Moreno-Navarrete et al., 2012; Romero-Zerbo et al., 2011). Another major cannabinoid, cannabidiol (CBD), is found in relative abundance in *cannabis sativa* (Hillig and Mahlberg, 2004). It binds to CB1 and CB2 receptors with comparatively lower affinity than does THC, and is an antagonist at the GPR55 receptor (Matsuda et al., 1990; Munro et al., 1993; Ross, 2009). This pharmacological profile may help explain the ability of CBD to ameliorate encephalitis, enteritis and pancreatitis (Li et al., 2013; Lin et al., 2011). The two principle endogenous cannabinoids, anandamide and 2-arachidonoyl glycerol (2-AG), are derived from arachidonic acid and act as agonists at CB1 receptors (Devane et al., 1992; Ishac et al., 1996; Yoshida et al., 2006) and, in the case of the latter, CB2 receptors (Van Sickle et al., 2005). There is also evidence that L-α-lysophosphatidylinositol acts as an endogenous agonist at the GPR55 receptor (Moreno-Navarrete et al., 2012).

As can be inferred from the above two paragraphs, the array of biological processes regulated by the endocannbinoid system is quite diverse. It ranges from the regulation of pain processing to energy balance to inflammation, although this is by no means exhaustive. A striking feature about cannabinoid-regulated biology is the degree of sexual disparity between males and females. This review will cover recent advances in our understanding of sex differences in: 1) the metabolic disposition of cannabinoids, 2) cannabinoid abuse, 3) cannabinoid-induced antinociception, and 4) cannabinoid-induced changed in energy homeostasis, with a particular emphasis on the latter. It is anticipated that this review will impart new insights into the diversity of sex differences in, and gonadal steroid hormonal influences on, cannabinoid-regulated biology. Moreover, it should provide a newfound appreciation for how gender and endocrine status can guide decisions on whether or when to use cannabinoid ligands as therapeutic adjuncts for the treatment of conditions ranging from HIV/AIDS- or cancer-related cachexia to obesity.

2. Sex Differences in Cannabinoid Metabolism

Exogenous cannabinoids like THC are metabolized primarily by the liver. In male rats, THC is transformed *in vivo* either by hydroxylation at, in order of prevalence, the 11-, 8- and 3-carbon positions of the dibenzopyran backbone. However, 11-OH-THC is the predominant metabolite produced in female rats, followed by lesser amounts of THC-11-oic acid and 8α, 11-diOH-THC (Narimatsu et al., 1991). Liver microsomes prepared from female rats also

reveal the existence of a metabolite with an oxidized methyl group at the 9-carbon position, known as 9α, 10α-epoxyhexahydrocannabinol. This compound is second only to 11-OH-THC in abundance, but represents only a minor component of the metabolic profile for THC in males (Narimatsu et al., 1991). In addition, the ability of microsomal aldehyde oxygenase to convert substrates like 11-oxo-THC and 9-anthraldehyde to their corresponding carboxylic acids is sexually differentiated. Slightly lower activity is observed for the metabolism of 11-oxo-THC (per total amount of cytochrome P450), and more robust activity is seen for the metabolism of 9-anthraldehyde, in female mice than in their male counterparts (Watanabe et al., 1992). Moreover, the activity of alcohol oxygenase that converts 7-OH-THC to 7-oxo-THC is higher in female guinea pigs than in males (Matsunaga et al., 1997). The converse is true for rats, in which the activity of the microsomal alcohol oxygenase is ~3× higher in males than in females (Matsunaga et al., 2000). Finally, CBD is converted by guinea pig liver microsomes to 7-OH, 6-OH and 4-OH variants (Yamamoto et al., 1991). CBD also undergoes hepatic conversion to cannabielsoin in several rodent species, and the male rat microsomal production of this metabolite is over twice the rate as that observed in females (Yamamoto et al., 1991). A listing of the cannabinoid agonists, antagonists and metabolites discussed throughout this review can be found in Table 1.

With regard to endogenous cannabinoids, adolescent female rats exhibit higher levels of fatty acid amide hydrolase (FAAH; responsible for anandamide degradation) in the frontal cortex of the brain, and lower levels of monoglycerol lipase (MAGL; responsible for 2-AG degradation) in the ventral striatum and amygdala, than do their male counterparts (Marco et al., 2014). The levels of these enzymes are influenced by disruptive early life events in a sexually differentiated fashion. Indeed, maternal deprivation increased their expression in the frontal cortex of adolescent male rats, whereas it increased their expression in the hippocampus of adolescent female rats (Marco et al., 2014). The studies described above utilized gonadally intact animals, and so at this point the organizational and activational roles of gonadal steroid hormones in sexually disparate cannabinoid metabolism remain undefined.

3. Sex Differences in Cannabinoid Abuse

Data from early clinical studies in humans dating back to the 1970s indicated that men consume *cannabis* at a faster rate than women. Perez-Reyes and coworkers reported that they take more puffs per unit time, and exhibit a shorter interval between puffs (Perez-Reyes et al., 1981). This pattern of consumption resulted in higher THC levels in men than in women. Interestingly, the subjective, psychological effects reported by the male and female subjects were nearly identical, which the authors attributed to the men having a larger volume of distribution than the women (Perez-Reyes et al., 1981). On the other hand, Penetar and colleagues demonstrated that men were more sensitive to the cardiovascular effects of *cannabis* inhalation (i.e., increased heart rate), which was mirrored by subjective behavioral ratings of *cannabis* intoxication as assessed through visual analog scales and the Addiction Research Center Inventory (Penetar et al., 2005). These effects were further enhanced by nicotine pre-treatment (Penetar et al., 2005). In more contemporary studies in Europe, Swedish men were much more likely to be apprehended for driving under the

influence of *cannabis* than women, and had higher circulating levels of THC in samples taken at the time of arrest as well (Jones et al., 2008). Likewise, in France, more men presented to the emergency department over a two-year period ranging from 2009–2011 for mental and behavioral disturbances related to cannabinoid intoxication than did women (Le Querrec et al., 2015). Moreover, in the United States, males are more likely to use the emergently popular, synthetic cannabinoid formulation K2 (a.k.a., spice) than women (Hu et al., 2011). By contrast, no sex differences were reported for *cannabis*-induced impairment in simulated driving performance (Anderson et al., 2010). In addition, women appear to be more sensitive to cannabinoidinduced exacerbation of the postural syncope associated with the transition from the reclined to the standing position (Mathew et al., 2003). This is in keeping with recent trends observed with other drugs of abuse. Indeed, women currently exhibit a more rapid progression from first *cannabis* use to cannabinoid use disorder, and provide heightened, subjective behavioral ratings in response to *cannabis* that are associated with abuse liability (Cooper and Haney, 2014; Hernandez-Avila et al., 2004). The findings of Lundahl and Greenwald demonstrated that men self-report as feeling “down” when exposed to *cannabis*-associated cues, whereas women exhibit reduced compulsivity as assessed by the Marijuana Craving Questionaire following oral THC ingestion (Lundahl and Greenwald, 2015). Moreover, while men exhibit greater stability in the duration of the dependence episodes across their adult lifespan (Duncan et al., 2015), women are at greater risk for commencing *cannabis* use at younger ages and engaging in high-frequency alcohol and marijuana use that ultimately leads to a subsequent diagnosis of alcohol use disorder (Buu et al., 2014). These more recent findings are consistent with animal studies showing that female rats self-administer higher amounts of the cannabinoid receptor agonist WIN 55,212-2, and more rapidly acquire stable intake than do males (Fattore et al., 2007). Unfortunately, the clinical studies were not designed to assess the endocrine status of the participants, and thus there is no information on the potential organizational and/or activational effects of gonadal steroids in the sex differences described for cannabinoid abuse. However, estradiol reduces CB1 receptor binding in the prefrontal cortex and amygdala of ovariectomized rats; areas that are involved in the pathophysiologic sequelae of addiction (Castelli et al., 2014). It also increases locomotor activity and reduces prepulse inhibition of the startle reflex; behavioral effects suggestive of a greater vulnerability to cannabis addiction than that seen in males (Castelli et al., 2014).

4. Sex Differences in Cannabinoid-Induced Antinociception

Cannabinoid receptor agonists produce antinociception by altering neurotransmission within spinal and supraspinal pain-processing circuits (Hama and Sagen, 2011; Stein et al., 1996; Vaughan et al., 2000; Wallace et al., 2003). In addition, cannabinoid receptor agonists are effective and well tolerated when used to treat pain arising from a number of different etiologies (Lynch et al., 2006; Lynch and Ware, 2015; Toth et al., 2012; Woolridge et al., 2005). Interestingly, female rats are more sensitive to the cannabinoid receptor agonist-induced increase in the latency to withdraw the tail or paw in response to thermal or mechanical stimuli, respectively (Tseng and Craft, 2001). This sex difference involves the heightened conversion of THC in females to bioactive metabolites like the 11-OH-THC discussed earlier (Narimatsu et al., 1991; Tseng et al., 2004). Other contributing factors to

these sex differences include the activation of both CB1 and CB2 receptors in females, whereas in males only the CB1 receptors contribute (Craft et al., 2012). The enhanced responsiveness observed in females extends to the development of antinociceptive tolerance upon chronic treatment with THC (Wakley et al., 2014b). Similarly, females are more sensitive, via both CB1 and CB2 receptors, to the ability of THC to counter the allodynia and hyperalgesia observed after a week-long administration of Freund's adjuvant to the right hind paw than males are via activation of only CB1 receptors (Craft et al., 2013). On the other hand, Niu and coworkers showed using an orofacial myositis pain model that female rats required an ~30× higher dose of the CB1 receptor agonist arachidonylcyclopropylamide to produce the same reduction in mechanical hypersensitivity of the masseter muscle as seen in the male (Niu et al., 2012). Moreover, the antinociceptive efficacy of cannabinoids and other analgesic drugs is markedly attenuated in G protein-gated, inwardly-rectifying K^+ channel (GIRK)2-null mice, and this diminution is more prominent in males than in females (Blednov et al., 2003). The activation of GIRK channels produces a slow inhibitory postsynaptic potential that hyperpolarizes the postsynaptic cell membrane to cause a cessation in neuronal firing (Hille, 1992). CB1 receptors couple to GIRK channels in AtT20 cells, *Xenopus* oocytes, and in hypothalamic neurons of male but not female guinea pigs (Farhang et al., 2009; Henry and Chavkin, 1995; Mackie et al., 1995). Thus, the more prevalent coupling of CB1 receptors to GIRK channels in neurons within the pain-processing circuitry of males may help explain the disparities in the decline of antinociceptive efficacy observed between male and female GIRK2-null mice.

The sex difference in cannabinoid-induced antinociception persists after gonadectomy (Wakley et al., 2015), but is also susceptible to the activational effects of gonadal steroids. For example, estradiol potentiates the THC-induced increase in the latency to react to noxious mechanical stimuli, an effect mirrored when comparing the responses seen in diestrus vs. estrus (Craft and Leitl, 2008; Wakley et al., 2014a). Likewise, levels of pain-regulating endocannabinoids in the female rat have been shown to fluctuate over the course of the estrous cycle in several brain regions (e.g., hypothalamus, hippocampus) and the pituitary gland; with the biggest changes occurring around the time of ovulation and behavioral estrus (Bradshaw et al., 2006). On the other hand, data from the orofacial myositis pain model indicate that testosterone promotes cytokine-induced upregulation of CB1 receptor expression in the trigeminal ganglia of male rats (Niu et al., 2012). By contrast, ovariectomy enhances cannabinoid-induced antinociception in mice, which is completely reversed by estradiol replacement (Anaraki et al., 2008). This discrepancy is indicative of a species difference in the cannabinoid regulation of pain processing, which has implications as to whether or how these data pertain to the human condition. It is also reflective of an issue that will arise again when discussing cannabinoid effects on energy balance. Lastly, the development of antinociceptive tolerance is not dependent on the activational effects of gonadal steroids, as the blunted THC response seen in chronically treated, gonadally intact rats is indistinguishable from that seen in gonadectomized or gonadectomized, steroid-treated animals (Wakley et al., 2015).

5. Sex Differences in the Cannabinoid Regulation of Energy Homeostasis

It is well accepted that the cannabinoid regulation of energy balance involves coordinated interactions between the gut, liver, pancreas, adipose tissue and the brain (Borgquist and Wagner, 2013). Cannabinoids regulate gastrointestinal motility and secretion (Borgquist and Wagner, 2013), and in humans dronabinol reduces gastric emptying to a greater extent in women than it does in men (Esfandyari et al., 2006). Within the hypothalamus of the brain, there are a number of neuroanatomical substrates through which cannabinoids can influence the feeding circuitry. The hypothalamic feeding circuitry comprises orexigenic and anorexigenic components spread amongst several different hypothalamic nuclei (for review see (Viveros et al., 2011a). Orexigenic components can be found in the form of orexin- and melanin-concentrating hormone-containing somata in the lateral hypothalamic area, as well as neuropeptide Y (NPY)-/agouti-related peptide (AgRP)- and ghrelin-containing somata in the hypothalamic arcuate nucleus (ARC). Anorexigenic elements of the hypothalamic feeding circuitry include the ventromedial nucleus that, when lesioned, results in rampant hyperphagia and obesity (Stricker, 1978). The steroidogenic factor (SF)-1-containing neurons in the VMN provide a principal source of anorexigenic output from this region (Dhillon et al., 2006). The ARC contains another critical appetite-suppressing cell population known as the proopiomelanocortin (POMC) neurons. The POMC precursor peptide is posttranslationally modified to yield two neuropeptides involved in the regulation of energy balance – namely, α-melanocyte-stimulating hormone and β-endorphin. The vast majority of POMC neurons co-express another anorexigenic neuropeptide called cocaine- and amphetamine-regulated transcript. All of these afferent elements of the hypothalamic feeding circuitry project to, and make synaptic contact with, parvocellular corticotropin-releasing hormone (CRH) neurons in the hypothalamic paraventricular nucleus. This indicates that these CRH neurons represent a point of convergence and integration that is important for the generation of an efferent response (for review see (Viveros et al., 2011a). The focal administration of CB1 receptor agonists into hypothalamic nuclei such as the PVN and VMN increases energy intake (Jamshidi and Taylor, 2001; Verty et al., 2005). Along similar lines, the levels of hypothalamic endocannabinoids are influenced by peripheral appetite-regulating hormones. For example, anorexigenic leptin decreases the amounts of anandamide and 2-AG (Di Marzo et al., 2001), whereas orexigenic ghrelin increases them (Kola et al., 2008).

The first demonstration of sex differences in the cannabinoid regulation of energy intake came from Miller and coworkers, where they showed that fourth ventricular administration of the cannabinoid receptor agonist CP 55,940 stimulates the consumption of sweetened condensed milk in male rats at a 10× lower dose than that observed in females (Miller et al., 2004). This was corroborated several years later using our guinea pig animal model, when we showed the cannabinoid receptor agonist WIN 55,212-2 stimulated cumulative energy intake to a greater extent in orchidectomized males than it did in ovariectomized females (Diaz et al., 2009). This was associated with sexually disparate changes in meal pattern; with males exhibiting cannabinoid-induced increases in meal size, meal frequency and meal duration, and females exhibiting an increase in meal frequency only (Diaz et al., 2009). In addition, males are more sensitive to the hypothermic effects of cannabinoid receptor

agonists; exhibiting an ~0.5 °C greater reduction in core body temperature in response to WIN 55,212-2 than did females (Diaz et al., 2009). We have resolved these sex differences in the cannabinoid regulation of energy homeostasis down to the level of the hypothalamic feeding circuitry, where the pleiotropic actions of cannabinoids inhibit the excitability of anorexigenic POMC neurons in a sexually discrepant manner. In POMC neurons from orchidectomized male guinea pigs, CB1 receptor agonists activate postsynaptic GIRK channels that cause an outward current and hyperpolarization that, in turn, cause a cessation in neuronal firing (Ho et al., 2007). In POMC neurons from ovariectomized female guinea pigs, CB1 receptors couple to postsynaptic Kv4.2 channels underlying A-type K^+ currents (I_A). This coupling augments the I_A by causing a rightward shift in the inactivation curve, which lessens the magnitude of the hyperpolarization necessary to transition the Kv4.2 channels from the inactivated to the closed state, and increases the number of channels available to oppose a subsequent depolarizing stimulus (Tang et al., 2005). This, in turn, slows the rate of rise of the ramp-like depolarization toward threshold, increases the interspike interval, and reduces firing rate.

Cannabinoids also exert presynaptic effects on excitatory and inhibitory inputs impinging on POMC neurons. CB1 receptor agonists are equipotent in their ability to presynaptically inhibit glutamatergic input onto POMC neurons from gonadectomized male and female guinea pigs (Diaz et al., 2009). However, they presynaptically inhibit GABAergic input with a ~6× lower potency in POMC neurons from orchidectomized male guinea pigs than they do in those from ovariectomized female guinea pigs (Diaz et al., 2009). It therefore stands to reason that cannabinoids acutely enhance inhibitory tone onto POMC neurons to a greater extent in males than they do in females. This would be consistent with the findings of Corchero and co-workers, who demonstrated that chronically administered THC increased POMC gene expression more robustly in male rats than in female rats (Corchero et al., 2001).

Sex differences in the cannabinoid regulation of energy balance persist in the absence of gonadal steroids, and are forged by organizational effects of these hormones. However, we have compelling evidence that activational effects also play an important role in this process. Both estradiol in the female and testosterone in the male are ideally suited to influence various neuroanatomical substrates comprising the hypothalamic feeding circuitry. For example, estradiol increases POMC gene expression and β-endorphin secretion in rodents and primates (Cheung and Hammer, 1995; Ferin et al., 1984; Roepke et al., 2008), and decreases the gene expression and secretion of NPY from N-38, mHypoE-42 and mHypoA-2/12 cell lines (Dhillon and Belsham, 2011; Titolo et al., 2008). Estradiol replacement in ovariectomized females reduces energy intake *per se*, and rapidly and markedly attenuates the increase in energy intake caused by WIN 55,212-2, and also reduces the magnitude and duration of the agonistinduced hypothermia (Kellert et al., 2009). Again, this can be drilled down to the level of the hypothalamic feeding circuitry, where estradiol rapidly diminishes the endocannabinoid-mediated, retrograde inhibition of glutamatergic input onto POMC neurons as assessed through depolarization-induced suppression of excitation (DSE), as well as the enhancement of the I_A in these cells (Borgquist et al., 2015a; Kellert et al., 2009).

This estrogenic disruption in endocannabinoid signaling is due to activation of estrogen receptor (ER)α and the putative G_q-coupled membrane ER (G_q-mER) (Washburn et al., 2013). Activation of these receptors by estradiol elicits a signal transduction cascade involving phosphatidylinositol-3-kinase (PI3K), protein kinase C (PKC), protein kinase A (PKA) and neuronal nitric oxide synthase (nNOS) to unravel the coupling of the presynaptic CB1 receptors to their effector systems (Borgquist et al., 2015a; Mela et al., 2015; Washburn et al., 2013) (Figure 1). PI3K is a signaling molecule that is activated upon both ERα and ERβ stimulation (Gingerich and Krukoff, 2008; Smith et al., 2013), as well as by other anorexigenic hormones such as leptin and insulin (Hill et al., 2008; Mela et al., 2015; Qiu et al., 2014), within various elements of the hypothalamic feeding circuitry. PI3K signaling in murine POMC neurons plays an important role in the ERα-mediated regulation of appetite and insulin sensitivity (Zhu et al., 2015). It, along with PKC and PKA, are also involved in the G_q-mER-mediated uncoupling of other metabotropic, $G_{i/o}$-linked receptors like the μ-opioid and $GABA_B$ receptors from their GIRK channels in POMC neurons (Kelly et al., 2002; Malyala et al., 2008; Qiu et al., 2006). Similarly, nNOS is a signaling molecule that is located downstream of PI3K (Gingerich and Krukoff, 2008; Haynes et al., 2003), decreased by fasting, and activated by leptin to help carry out, at least in part, the effects of the adipostat on energy homeostasis (Leshan et al., 2012; Otukonyong et al., 2000). Collectively, these findings are largely consistent with the fact that estradiol downregulates CB1 receptors in the rat hypothalamus (Riebe et al., 2010).

Conversely, testosterone replacement in orchidectomized males increases energy intake *per se*, an effect that is blocked by the CB1 receptor antagonist AM251 (Borgquist et al., 2015b). This effect can be attributed to a testosterone-induced increase in inhibitory GABAergic input onto POMC neurons, as well as a potentiation of endocannabinoid-mediated retrograde inhibition of glutamatergic input via DSE (Borgquist et al., 2015b). Testosterone increases the phosphorylation of AMP-activated kinase (AMPK) in the ARC (Borgquist et al., 2015b). Moreover, the testosterone-induced potentiation of DSE is blocked by the AMPK inhibitor compound C, and mimicked by AMPK activator metformin during recordings in slices from vehicle-treated males (Borgquist et al., 2015b), which indicates that AMPK is a signaling molecule integral to the androgenic regulation of endocannabinoid-mediated retrograde inhibition and thus energy homeostasis (Figure 2). AMPK is a cellular energy sensor, whose activity is increased by phosphorylation of the threonine residue at the 172nd position of the catalytic α subunit via liver kinase β1 or Ca^{2+}/calmodulin-activated protein kinase kinase β (Hardie et al., 2012). This occurs in response to elevated AMP:ATP and ADP:ATP ratios brought on by metabolic stresses and a negative energy balance (Hardie et al., 2012). This triggers biochemical and behavioral processes that ultimately lead to increased production of ATP. In addition, the activity of AMPK within the hypothalamus is stimulated by orexigenic hormones like ghrelin (Andersson et al., 2004; Kola et al., 2008) and inhibited by anorexigenic hormones like leptin (Andersson et al., 2004; Minokoshi et al., 2004). Thus, testosterone, by virtue of activating AMPK in the ARC within the hypothalamic feeding circuitry, compels the organism to increase its consumption of energetic substrates.

As mentioned above, there are species differences concerning the sexually disparate cannabinoid regulation of pain processing. The same is likely to hold true for the cannabinoid regulation of energy balance. Estradiol negatively modulates metabotropic, $G_{i/o}$-coupled receptor function in guinea pigs, rats and mice (Mela et al., 2015; Qiu et al., 2006). However, there is striking variability in how (or if) cannabinoids influence POMC neuronal excitability to affect changes in energy intake in mice. For example, in enhanced green fluorescent protein-POMC mice, exogenously administered cannabinoid receptor agonists presynaptically inhibit glutamatergic input onto POMC neurons, but no retrograde inhibition of this input by endocannabinoids was observed (Hentges et al., 2005). In A^y mice that overexpress AgRP, changes in energy intake caused by CB1 receptor activation or blockade do not appear to involve POMC neurons, but rather mesolimbic dopamine neurons emanating in the ventral tegmental area (Sinnayah et al., 2008). On the other hand, in POMC-cre mice, CB1 receptor activation directly excites POMC neurons, and stimulates the expression of proteases that increase the production of β-endorphin during posttranslational processing (Koch et al., 2015). Thus, not only are there species differences in the cannabinoid regulation of energy balance, but there are also clear strain differences among the different lines of transgenic mice. Given these disparities, it is therefore not surprising that no one has attempted to investigate sex differences in the cannabinoid regulation of energy homeostasis in mice.

The litany of anecdotal and experimental evidence that cannabinoid receptor agonists augment energy intake has effectively translated into the use of *cannabis* and oral formulations of THC like marinol or dronabinol as therapeutic adjuncts in the treatment of cancer- and HIV/AIDS-related cachexia. In all of the available literature extolling the efficacy of these compounds to ameliorate the lack of appetite and body wasting, whether it comes in the form of case reports, epidemiological studies or randomized, double blind, placebo controlled investigations, the overwhelming majority of the study participants were male (Beal et al., 1995; Haney et al., 2005; Nelson et al., 1994; Sacks et al., 1990; Woolridge et al., 2005). However, in the one study in which the gender ratio was more evenly distributed, neither *cannabis* extract nor THC produced significant increases in appetite or quality of life relative to placebo-treated controls (Strasser et al., 2006). These observations provide some credence to the idea that sex differences in the cannabinoid regulation of appetite extend to humans. In addition, the discrepant activational effects of gonadal steroids on the cannabinoid regulation of energy balance that we have found in our guinea pig animal model indicate that androgens could be used in conjunction with either *cannabis* or oral THC to combat cachexia.

The synthetic androgen nandrolone has proven effective in increasing lean body mass, fat-free mass, and other body composition measures such as body cell mass and intracellular water in HIV-infected men experiencing low to moderate weight loss (Storer et al., 2005). It has also been shown to produce a modest yet statistically insignificant increase in energy intake and appetite score (Batterham and Garsia, 2001). This suggests that the effectiveness of nandrolone in improving cachexic symptoms is due primarily to its anabolic and metabolic actions (Bardin, 1996; Bhasin et al., 1997), and is consistent with our findings that testosterone *per se* increases O_2 consumption, CO_2 and metabolic heat production, as well

as core body temperature (Borgquist et al., 2015b). On the other hand, dronabinol significantly increases appetite in patients with HIV/AIDS-related cachexia, but is comparatively less effective in increasing body weight (Batterham and Garsia, 2001; Beal et al., 1995). However, to date there are no published accounts describing how nandrolone and dronabinol directly compare with one another, or how combined therapy might maximize gains in appetite and weight gain. Bear in mind that during the female ovarian cycle, energy intake is at its lowest during the periovulatory phase, when estradiol is the preeminent constituent of the gonadal steroid hormonal milieu, and at its highest during the progesterone-dominated luteal phase (Johnson et al., 1994). Therefore, it should not be surprising that the synthetic progesterone derivative, megestrol acetate, can effectively counter the cachexia associated with HIV/AIDS. Indeed, it is comparatively more efficacious than nandrolone in increasing appetite, energy intake, weight gain and adiposity (Batterham and Garsia, 2001). In addition, it increases appetite and weight gain to a significantly higher degree than does dronabinol (Jatoi et al., 2002). Interestingly, a study investigating the effects of combined megestrol acetate and nandrolone decanoate reported significant elevations in weight gain and fat-free mass but not adiposity (Cuerda et al., 2005).

The negative modulatory effects of estradiol on the cannabinoid regulation of energy homeostasis that we demonstrated in the female guinea pig would suggest that cannabinoid sensitivity fluctuates over the course of the reproductive cycle. Accordingly, one might predict that cannabinoid responsiveness would be at its lowest during the estradiol-dominated follicular and periovulatory phases of the reproductive cycle. Likewise, it follows that under hypoestrogenic states brought on by primary amenorrhea (e.g., anorexia nervosa) or secondary amenorrhea (e.g., menopause), CB1 receptor-mediated signaling would proceed to the fullest extent possible. Indeed, dronabinol significantly increased weight gain in women with anorexia nervosa of at least five years duration (Andries et al., 2014), which is consistent with findings that THC diminished activity-based anorexia in female rats as assessed by THC-induced increases in energy intake, decreases in running wheel activity, reductions in weight loss, decreases in thermogenesis in brown adipose tissue and decrements in lipolysis in white adipose tissue (Verty et al., 2011). While the hypoestrogenemia that is associated with anorexia certainly appears to confer responsiveness to the appetite-stimulating properties of cannabinoid receptor agonists, different allelic forms of the CB1 receptor (CNR1) gene are reported to be preferentially transmitted in the binging/purging and restricting types of anorexia nervosa (Siegfried et al., 2004). In addition, a point mutation in the gene encoding for GPR55 that substitutes a valine for a glycine residue at the 195th position diminishes agonist-stimulated phosphorylation of extracellular signal-regulated kinase, and is more abundant in Japanese women diagnosed with anorexia nervosa (Ishiguro et al., 2011).

On the other hand, the RIO-North American clinical trial that examined the anti-obesity effects of Rimonabant comprised ~80% women, over half of whom were 45 years or older (Pi-Sunyer et al., 2006). Rimonibant effectively reduced body weight, waist circumference, circulating triglycerides and fasting insulin levels, and elevated HDL cholesterol levels (Pi-Sunyer et al., 2006). Were it not for the increased incidence of a few adverse side effects (i.e., nausea, anxiety, depressed mood) experienced by a small percentage of the study

participants, it is hard to imagine this drug not being approved by the Food and Drug Administration or remaining on the market in Europe. Given that ≥40% were either peri- or post-menopausal women, the subsiding of the estradiol-induced attenuation of CB1 receptor-mediated signaling could constitute a major reason behind the enhanced endocannabinoid tone that is blocked by Rimonabant. However, adult female rats in which obesity was induced by the antipsychotic olanzapine exhibited reduced CB1 receptor binding in the ARC (Weston-Green et al., 2012).

A major source of ARC CB1 receptors comes from SF-1-containing VMN neurons. The selective knockout of the CB1 receptor in these neurons leads to a lean phenotype associated with increased sympathetic tone, lipolysis and leptin sensitivity in normal chow-fed mice, but an obese phenotype concomitant with leptin resistance in animals fed a high-fat diet (Cardinal et al., 2014). Thus, these SF-1-containing, CB1 receptor-bearing VMN neurons, the preponderance of which also express the vesicular glutamate transporter (Cardinal et al., 2014), may serve as a molecular switch that confers metabolic flexibility in the face of an ever-changing diet. The axon terminals of these cells synapse with POMC neurons in the ARC (Lindberg et al., 2013). As such, they likely represent a critical target for endocannabinoid-mediated retrograde inhibition of excitatory input impinging on POMC neurons.

It has long been known that energy balance is inexorably linked to reproductive status (Sinchak and Wagner, 2012). It should therefore not be surprising that there are sex differences in the manner in which cannabinoids affect reproductive behavior. For example, women are more likely to report an increase in sexual desire following the consumption of low to moderate amounts of *cannabis*, whereas men are more apt to experience decrements in sexual performance due to the suppression of the reproductive axis and erectile dysfunction (Gorzalka et al., 2010). This parallels findings from animal studies, in which THC facilitates sexual receptivity in ovariectomized, estradiol-primed and progesterone-treated female rats (Mani et al., 2001), whereas it decreases copulatory behavior, increases mount latency, and blocks the associated catecholaminergic discharge in the mediobasal hypothalamus of male rats (Murphy et al., 1994).

6. Summary and Concluding Remarks

From the research carried out over the past several decades, it is clear that sex differences in cannabinoid-regulated biology are pervasive and far-reaching. While this review focused on the most recent advances into our understanding of sex differences in the metabolic fate, abuse liability, as well as the antinociceptive and appetite-stimulating properties of cannabinoids, it should not be misconstrued that this list is by any means comprehensive. Indeed, there are sex differences reported for the endocannabinoid-mediated neonatal development of the amygdala (Krebs-Kraft et al., 2010), the THC-induced impairment of spatial learning during adolescence and adulthood (Cha et al., 2007), as well as a number of behavioral and endocrine disturbances that develop as a result of chronic or subchronic exposure to cannabinoid receptor agonists during adolescence (Viveros et al., 2011b).

Although the disparities spotlighted in this review have been more thoroughly investigated, there is still much more work that needs to be done in order to complete our understanding. For example, we still do not know whether gonadal steroids exert activational effects on the metabolic disposition of cannabinoids, how the sequelae varies over the course of the estrous cycle, or whether this phenomenon is found in humans and non-human primates. High doses of progesterone and testosterone stimulate the conversion of 7β-OH-Δ^8-THC to 7-oxo-Δ^8-THC in microsomes from male monkey liver (Funahashi et al., 2005), but it is not known if there are underlying sex differences with regard to cannabinoid metabolism in the primate. Sex differences in cannabinoid abuse have been documented in both humans and animal models, although information pertaining to the activational effects of gonadal steroids, and to the potential fluctuations that may be observed over the reproductive cycle, is non-existent. We have a more complete picture regarding how gonadal steroids modulate cannabinoid-induced antinociception, but further investigation into the gonadal steroid receptor-mediated transduction mechanisms that modulate cannabinoid receptor signaling within the spinal and supraspinal pain-processing sites is warranted, as is a determination of which animal model best reflects the human condition. We have also gleaned some considerable mechanistic insights into how gonadal steroids influence the cannabinoid regulation of the hypothalamic feeding circuitry and how this impacts cannabinoid-induced changes in energy balance. However, we have yet to see how effectively this translates to the human condition, and how (or if) we can parlay this information into appropriately tailored theraupeutic strategies in men and women to help combat HIV/AIDS- and cancer-related cachexia as well as obesity.

What is more, most of the discussion concerning the activational effects of gonadal steroids centers around estradiol and testosterone; comparatively little work has been done on potential modulatory effects of progesterone on sexually discrepant, cannabinoid-regulated biology. Furthermore, CB2 receptors are expressed in CNS structures such as the brainstem and hypothalamus (Gong et al., 2006; Van Sickle et al., 2005), and evidence suggests that these receptors contribute to sexually differentiated, cannabinoid-induced antinociception (Craft et al., 2012). Moreover, loss-of-function mutations at the GPR55 receptor confer vulnerability to the development of anorexia nervosa (Ishiguro et al., 2011). It would therefore be worthwhile to explore the role of the CB2 and GPR55 receptors in the regulation of energy balance, whether this regulation is sexually differentiated, and if so, whether this regulation is subject to activational effects of gonadal steroids. The culmination of research findings spanning over two decades has made it abundantly clear that sexually distinct cannabinoid-regulated biology is the norm, rather than the exception. At the same time, they provide an indelible reminder that there is much more to be accomplished in elucidating the molecular underpinnings of these inherent differences between males and females, and how these can be leveraged to better serve humanity.

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Highlights

- Sex differences are fundamental to cannabinoid-regulated biology
- Males are more sensitive to the appetite-stimulating properties of cannabinoids
- Sex steroid hormones have divergent roles in determining cannabinoid sensitivity

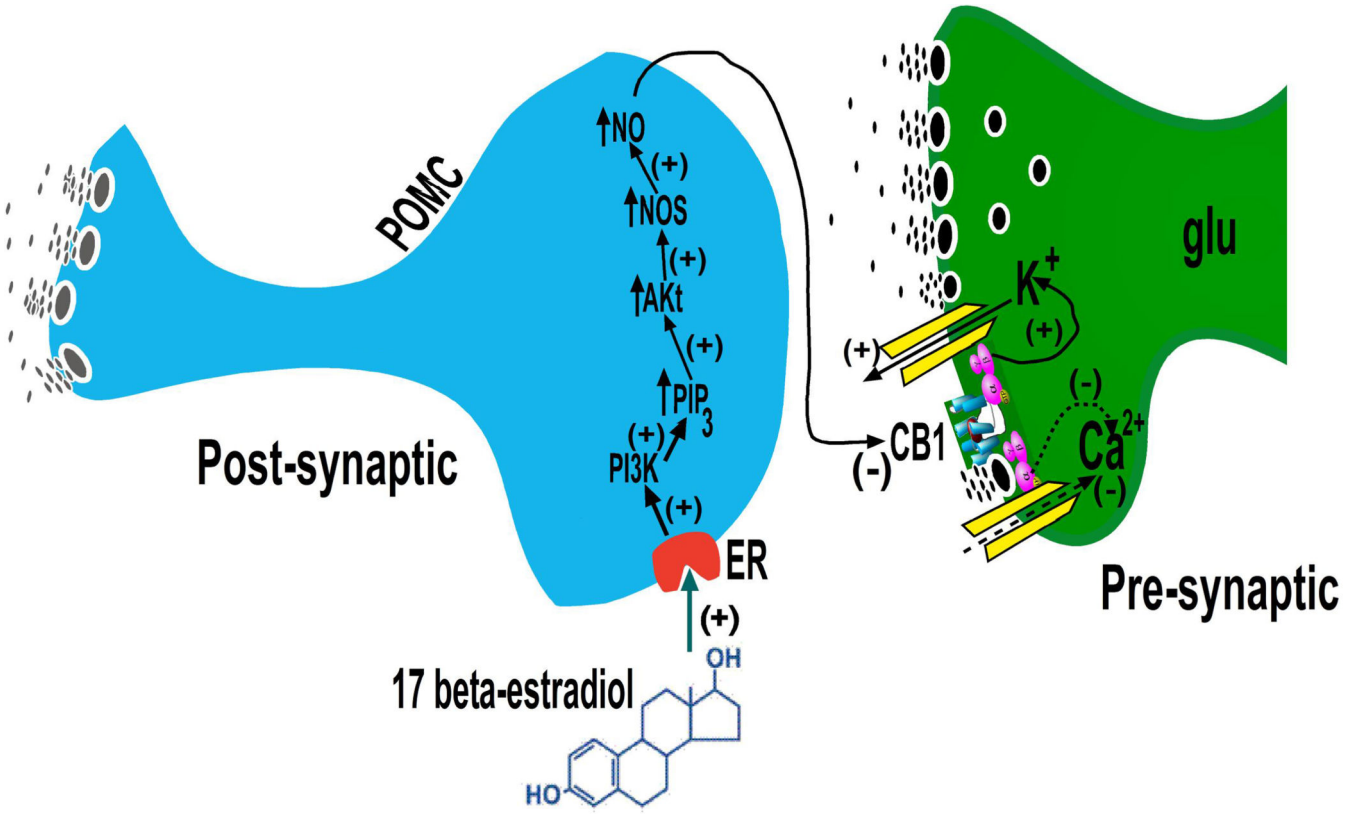

Figure 1.

Schematic illustration of how estradiol impairs CB1 receptor-mediated signaling at glutamatergic inputs onto POMC neurons. Estrogens rapidly uncouple cannabinoid CB1 receptors from their effector systems in the glutamatergic nerve terminal by activating nNOS. This is achieved through an increase in PI3K, which enhances phosphatidylinositol triphosphate (PIP_3), in turn up-regulating Akt leading to augmented nNOS. The increased enzyme activity may reduce endocannabinoid tone either by inhibiting synthesis, enhancing breakdown, or promoting reuptake and removal from the synaptic cleft. Alternatively, the nitric oxide produced may act retrogradely to uncouple the CB1 receptor from its effector system(s) in the glutamatergic nerve terminal. Modified from (Mela et al., 2015).

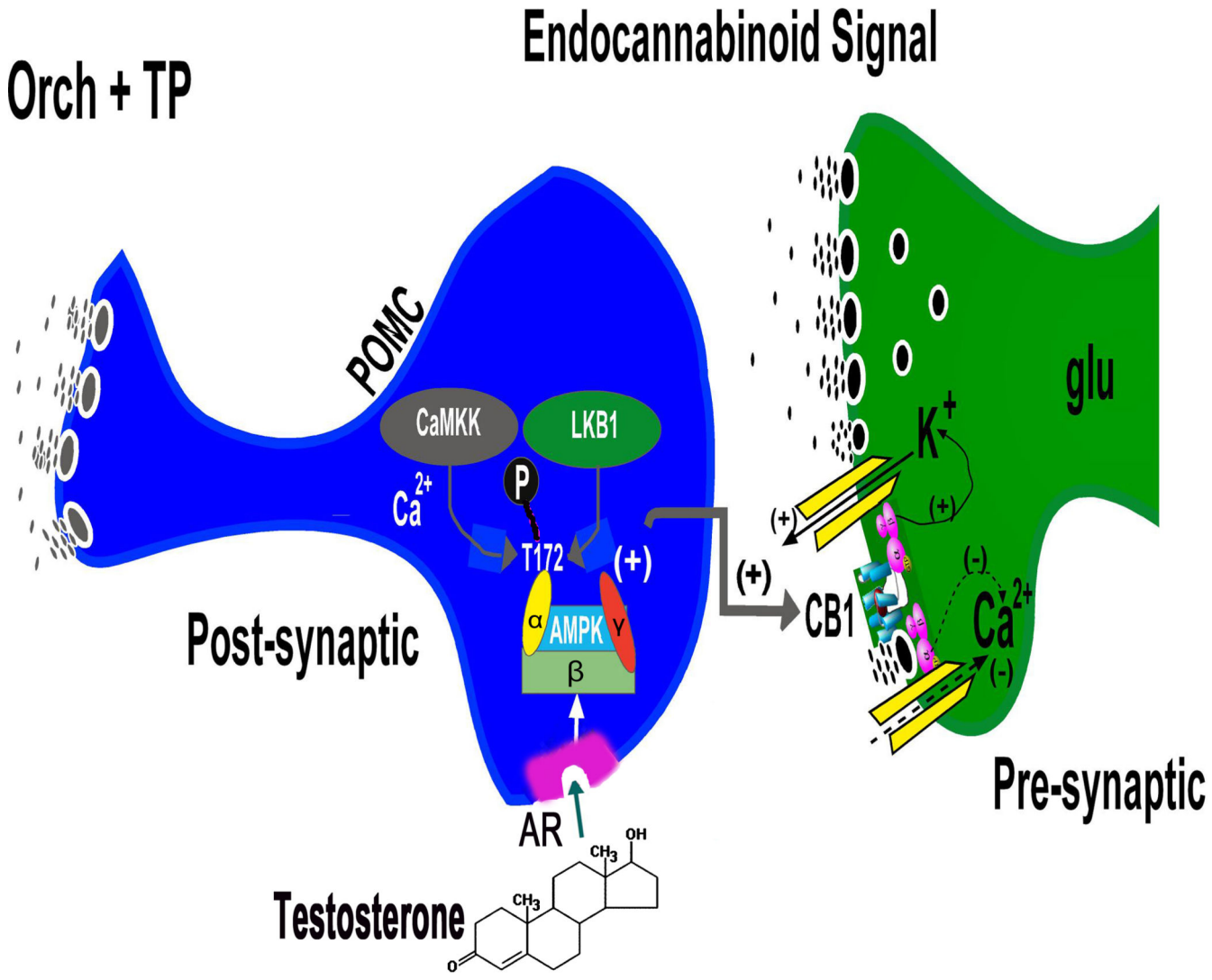

Figure 2.

A schematic illustrating the testosterone-induced enhancement of CB1 receptor-mediated signaling at glutamatergic inputs impinging upon POMC neurons. Testosterone produces hyperphagia and heightens cannabinoid tone at the CB1 receptors in the glutamatergic nerve terminals by activating cellular energy sensor, AMPK. The activation of this heterotrimeric AMPK complex is due to upstream kinases like Ca^{2+}/calmodulin-dependent protein kinase kinase (CaMKK) and liver kinase B1 (LKB1) via phosphorylation of threonine residue 172 of the α subunit that occurs in response to increases in intracellular calcium and the AMP/ATP ratio. This, in turn, leads to increased endocannabinoid tone either by enhancing synthesis, inhibiting breakdown, or attenuating reuptake and removal from the synaptic cleft. The endocannabinoids could then act retrogradely at the CB1 receptor to augment the cannabinoid-induced presynaptic inhibition of glutamate release. Modified from (Borgquist et al., 2015b).

Table 1

A list of the cannabinoid agonists, antagonists and metabolites described in this review.

Compound	Abbreviation/Nickname	Function/Purpose
2-arachidonoyl glycerol	2-AG	Endogenous CB1/2 receptor agonist
Δ^9-tetrahydrocannabinol	THC	Cannabinoid CB1/2 receptor agonist
7-hydroxy-THC	7-OH-THC	THC metabolite
7-oxo-THC	N/A	THC metabolite
8α, 11-dihydroxy-THC	8α, 11-diOH-THC	THC metabolite
9α, 10α-epoxyhexahydrocannabinol	N/A	THC metabolite
11-hydroxy-THC	11-OH-THC	Primary THC metabolite
Cannabidiol	CBD	Cannabinoid receptor ligand
4-hydroxy-CBD	4-OH-CBD	CBD metabolite
6-hydroxy-CBD	6-OH-CBD	CBD metabolite
7-hydroxy-CBD	7-OH-CBD	CBD metabolite
Cannabielsoin	N/A	CBD metabolite
CP 55,940	N/A	CB1/2 receptor agonist
L-α-lysophosphatidylinositol	N/A	GPR55 agonist
Marinol (dronabinol)	N/A	Oral THC formulation
N-arachidonoylethanolamine	Anandamide	Endogenous CB1 receptor agonist
Rimonabant	N/A	CB1 receptor antagonist
THC-11-oic acid	N/A	THC metabolite