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Review article

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.

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, 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

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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. 11-OH-THC is also 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 to 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

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