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Sex differences in cannabinoid pharmacology: A reflection of differences in the endocannabinoid system?

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Abstract

Marijuana is the most widely used illicit drug in the U.S., and marijuana use by women is on the rise. Women have been found to be more susceptible to the development of cannabinoid abuse and dependence, have more severe withdrawal symptoms, and are more likely to relapse than men. The majority of research in humans suggests that women are more likely to be affected by cannabinoids than men, with reports of enhanced and decreased performance on various tasks. In rodents, females are more sensitive than males to effects of cannabinoids on tests of antinociception, motor activity, and reinforcing efficacy. Studies on effects of cannabinoid exposure during adolescence in both humans and rodents suggest that female adolescents are more likely than male adolescents to be deleteriously affected by cannabinoids. Sex differences in response to cannabinoids appear to be due to activational and perhaps organizational effects of gonadal hormones, with estradiol identified as the hormone that contributes most to the sexually dimorphic effects of cannabinoids in adults. Many, but not all sexually dimorphic effects of exogenous cannabinoids can be attributed to a sexually dimorphic endocannabinoid system in rodents, although the same has not yet been established firmly for humans. A greater understanding of the mechanisms underlying sexually dimorphic effects of cannabinoids will facilitate development of sex-specific approaches to treat marijuana dependence and to use cannabinoid-based medications therapeutically.

Keywords

adolescence; cannabinoids; endocannabinoids; estradiol; hormone; review; sex differences

Introduction

Marijuana is the most widely used illicit drug in the U.S. Although the number of men addicted to marijuana still outnumbers women, this gender gap has been steadily closing, as for most drugs of abuse, primarily because drug use in women has been increasing (Greenfield, et al., 2010). Epidemiological studies show that the patterns of drug use in women differ from those in men (Gunter, et al., 2006; Kelly, et al., 2006). For example, while women may initially take lower doses of an abused drug, they tend to become addicted faster and to relapse more frequently following a period of abstinence (Becker and

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Hu, 2008). Preliminary data suggest that the "telescoping" effect (faster trajectory from first use to dependence) initially observed in cocaine-using women may also occur for other abused drugs, including cannabis (Hernandez-Avila, et al., 2004). Additionally, recent studies report more withdrawal symptoms in women than men cannabis smokers who attempt to quit (Copersino, et al., 2010; Levin, et al., 2010). Sex differences also have been observed during other phases of the substance abuse process, including escalation and dysregulation (Carroll, et al., 2004). The purpose of the present review is to summarize the extant literature on sex differences in the CNS effects of exogenous cannabinoids and to describe how these differences may be related to underlying sexual dimorphism of the endocannabinoid system.

Sex Differences in the Effects of Exogenous Cannabinoids

Research in humans

A handful of studies has been conducted to compare the effects of cannabinoids in women vs. men. Smoked marijuana produced very similar effects on simulated driving performance in women and men (Anderson, et al., 2010), as well as on laboratory measures of impulsivity (McDonald, et al., 2003). In contrast, a dose of sublingual THC that did not affect spatial working memory performance in men significantly enhanced it in women (by decreasing between-search errors); this same dose of THC reduced errors in men but increased them in women engaged in a spatial span test (Makela, et al., 2006). Similarly, heavy marijuana-smoking women (tested while sober) were more impaired than light marijuana-smoking women on a visuospatial memory task, on which neither group of marijuana-smoking men showed impairment (Pope, et al., 1997). A single dose of oral dronabinol administered three times significantly slowed gastric emptying in women but not in men (Esfandyari, et al., 2006). Despite similar ratings of intoxication from THC and marijuana (and similar plasma THC levels), women reported more dizziness than did men (Mathew, et al., 2003). In contrast to these findings of greater cannabinoid effect in women, two studies report greater subjective THC effects (e.g., "high") in *men* (Haney, 2007; Penetar, et al., 2005), with the latter study also reporting that women took longer than men to detect marijuana's effects, experienced a shorter duration effect, and showed smaller increases in heart rate than did men. Cannabinoid effects on sexual functioning also vary between the sexes. Women report that low doses of marijuana facilitate arousal and desire whereas high doses decrease sexual motivation (Gorzalka, et al., 2010). Self-reports in men are more conflicting; however, in male rodents, cannabinoid exposure produces more consistently negative consequences on sexual functioning, including decreased motivation and erectile dysfunction (Gorzalka, et al., 2010).

Research in animals

A variety of cannabinoid effects have been compared in female vs. male animals, primarily rats. On tests of antinociception, several labs have reported that cannabinoids are more potent and occasionally more efficacious in female compared to male rats. For example, cannabinoids such as THC and CP55,940 were approximately twice as potent in female than male rats on warm water tail withdrawal and paw pressure tests (Craft, et al., 2012; Romero, et al., 2002; Tseng and Craft, 2001). Using a radiant heat tail flick test, THC was also more potent in female than male rats (Wiley, et al., 2007); although the sex difference in this study was not statistically significant, it was of the same magnitude reported by others, suggesting that the lack of significance may be due to the smaller sample sizes in this study.

Several studies also report that cannabinoid agonists are more potent in female than male adult rats in decreasing locomotor activity (Craft, et al., 2012; Tseng and Craft, 2001), as well as in producing catalepsy (Cohn, et al., 1972; Craft, et al., 2012; Wiley, et al., 2007). In

mice, 1–10 mg/kg THC significantly increased locomotor activity in females but had no effect in males (Wiley, 2003). These studies indicate that female rodents are more sensitive to the biphasic effects of cannabinoids on locomotion -- i.e., increases at lower doses and decreases at higher doses. Sex differences in cannabinoid effects on motor activity are important not only as an assessment of cannabinoid "side-effects", but also because effects like antinociception are typically measured as a lengthening of latency to respond – which may be caused by drug-induced suppression of motor activity. However, using peripheral THC administration against inflammatory pain, one study suggests that greater THC-induced antinociception is *not* secondary to greater THC-induced sedation in female compared to male rats (Craft and Kandasamy, unpublished data).

In animal models of marijuana abuse, female rodents may be more sensitive than males to the reinforcing and subjective effects of cannabinoids. For example, female rats acquired self-administration of WIN55,212-2 faster and maintained higher rates of responding than males (Fattore, et al., 2007), as well as being more sensitive to drug- and cue-induced reinstatement than males (Fattore, et al., 2010). Female mice acquired a THC discrimination in approximately 1/3 fewer sessions than did males (Wiley, et al., 2011b). Similar to some human studies of cannabinoid effects on cognition, cannabinoid-induced impairments in spatial learning were greater in female rats than males (Cha, et al., 2007). Cannabinoids are also commonly reported to enhance sexual behavior in female rodents but inhibit it in males (for a review, see Gorzalka, et al., 2010). Finally, female and male rats chronically treated with HU-210 showed similarly decreased immobility in the forced swim test (Morrish, et al., 2009), suggesting that antidepressant actions of cannabinoids are similar in females and males.

Several physiological effects of cannabinoids have been compared between the sexes. Gonadally intact female rats were more sensitive than males to cannabinoid-induced hypothermia (Borgen, et al., 1973; Wiley, et al., 2007), although the opposite sex difference was reported in gonadectomized guinea pigs (Diaz, et al., 2009). Both intact female rats and ovariectomized (OVX) female guinea pigs were less sensitive than their male counterparts to the hyperphagic effect of cannabinoid agonists (Diaz, et al., 2009; Miller, et al., 2004). Interestingly, exposure to high-fat diet profoundly decreased female rats' sensitivity to the motoric and antinociceptive effects of THC, whereas it had little or no effect in males (Wiley, et al., 2011a). Taken together, much of the research on sex differences in exogenous cannabinoid effects indicates a greater sensitivity to cannabinoids in females than in males, with opposite sex differences in a few cases (e.g., for cannabinoid-induced hyperphagia).

Importance of adolescence

In mammals, vast changes in brain functioning occurring during adolescence are associated with patterns of behavior (e.g., increased risk taking, increased interactions with peers) that may, in humans, contribute to initiation of illicit drug use, including cannabinoids (Viveros, et al., 2011; Viveros, et al., 2012). Further, early marijuana use is associated with long-term effects, including impaired reaction times in a visual attention task (Ehrenreich, et al., 1999), lower levels of academic achievement (Brook, et al., 2008), and continued reductions in brain activation in prefrontal and cerebellar regions (Chang, et al., 2006). Although the self-selection of human users limits determination of underlying mechanisms, animal research suggests that the consequences of cannabinoid exposure on the brain and behavior of adolescent rodents differ from those seen in mature individuals, and some of these differences vary by sex. For example, adolescent female rats were less sensitive than adult females to several pharmacological effects of THC (e.g., antinociception and hypothermia), while male rats did not show this age-dependent difference (Wiley, et al., 2007). In a hole board test, female rats treated with cannabinoids during adolescence showed increased motor activity compared to control females. This cannabinoid-induced motor activation was

not seen in males; however, cannabinoid-treated males showed decreased exploratory behavior compared to male controls, which was not evident in females (Biscaia, et al., 2003). Female rats chronically exposed to THC during adolescence also have been found to show depressive-like behavior, whereas the same was not true for males (Rubino, et al., 2008). Acute exposure to cannabinoids during adolescence also produced more anxiogenic responses in female than male rats (Marco, et al., 2006; Viveros, et al., 2005), and increased acquisition of cocaine self-administration in female but not male rats (Higuera-Matas, et al., 2008).

Several studies also report that adolescent rats repeatedly exposed to cannabinoids show greater memory impairment compared to rats exposed to cannabinoids as adults (O'Shea, et al., 2004; Schneider and Koch, 2003; Schneider, et al., 2008). Impairment was worse in male adolescent rats for some tasks, while other memory tasks resulted in more impairment in female adolescent rats (for reviews, see Viveros, et al., 2011; Viveros, et al., 2012). For example, adolescent male rats showed fewer THC-induced deficits in spatial learning in a Morris water maze task than did adolescent female rats (Cha, et al., 2007). In another study, chronic exposure to cannabinoids during adolescence increased the discrimination index on a spontaneous alternation task in male rats compared to control males, but this effect was not observed in females. In contrast, females exposed to cannabinoids during adolescence showed memory impairment in an object location task, an effect that was not seen in males (Mateos, et al., 2011). Stage of adolescence may also modulate sex differences in THC's effects on memory. For example, one study found that chronic exposure to THC during early adolescence decreased retention in an active avoidance paradigm only in male rats, whereas chronic exposure to THC in late adolescence produced decreases only in female rats (Harte and Dow-Edwards, 2010).

In several instances, sex differences in neuroanatomy and/or neurophysiology have been found to accompany the sex differences in behavior observed following adolescent exposure to cannabinoids. After repeated injections with THC, greater CB_1 receptor desensitization occurred in female adolescent rats compared to male adolescents, or to adult rats of either sex. This effect was not due to differences in downregulation of CB_1 receptors, which was similar across groups (Burston, et al., 2010). Adolescent exposure to cannabinoids also disrupted the homeostatic relationship between glutamate and GABA transmission in female but not male rats (Higuera-Matas, et al., 2012). Finally, McQueeny et al. (2011) reported that adolescent human female marijuana users have increased right amygdala volume compared to controls, while marijuana use in males did not affect amygdala volume. Together, these studies of adolescent exposure to cannabinoids indicate that females tend to be more deleteriously affected; however, the sparse research is far from conclusive. In addition, hormonal factors strongly influence female response to cannabinoids, as explained in the following section.

Mechanisms Underlying Sex Differences in Exogenous Cannabinoid Effects

Hormonal influences

Sex differences in exogenous cannabinoid effects appear to be strongly influenced by ovarian hormones in adult animals. For example, THC-induced antinociception depends on females' estrous stage, with females in late proestrus to estrus being the most sensitive to THC and thus the most different from males (Craft and Leitl, 2008; Wakley and Craft, 2011). Estradiol enhanced THC-induced antinociception (Craft and Leitl, 2008) and self-administration of WIN55,212-2 (Fattore, et al., 2010) in OVX female rats. Estradiol attenuated cannabinoid-induced hyperphagia and hypothermia in OVX guinea pigs (Kellert,

et al., 2009), and cannabinoid-induced disruption of acquisition and performance of an operant task in OVX rats (Daniel, et al., 2002; Winsauer, et al., 2011). Thus, there is growing evidence for activational effects of ovarian hormones – particularly estradiol – underlying sexual dimorphism of cannabinoid sensitivity. Organizational hormone effects are largely unexamined to date; however, the fact that sex differences in cannabinoid sensitivity are still observed in guinea pigs gonadectomized as adults (Diaz, et al., 2009), and that a few sex differences in cannabinoid effects have been observed in adolescent rats (Romero, et al., 2002; Wiley, et al., 2007) suggests that cannabinoid systems may develop in a sexually dimorphic manner early in life.

Sexual dimorphism of the endocannabinoid system

Sex differences in, and estradiol modulation of, the behavioral effects of cannabinoids may be due to pharmacokinetic factors in rodents (for a review, see Craft, 2005), but are also likely linked to differential brain endocannabinoid systems. The endocannabinoid system is comprised of two receptors, endogenous cannabinoids, and their synthetic and metabolic enzymes. Of the two identified cannabinoid receptors, the CB_1 receptor is the primary one found in the brain (Herkenham, et al., 1991), whereas the CB_2 receptor is localized more prominently in the immune system (Galiegue, et al., 1995), although recent research suggests that functional CB_2 receptors may also play a role in the brain (Van Sickle, et al., 2005; Xi, et al., 2011). The two best characterized endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), are metabolized primarily by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively (Cravatt and Lichtman, 2002; Dinh, et al., 2002). Sex differences in this system may appear early in development. In the rat, CB_1 receptors in the brain exhibit a progressive increase in number, but not in affinity, during the pre-weanling period [i.e., before postnatal day (PN) 21] and during early adolescence, with receptor pruning and a decline to adult levels during later adolescence (Belue, et al., 1995; McLaughlin, et al., 1994; Rodriguez de Fonseca, et al., 1993). Peak levels of CB_1 receptors are reached earlier in females (PN 30) than in males (PN 40). Further, the endocannabinoid system may be involved in neuronal migration and brain development, processes that also exhibit sexual dimorphism (Berrendero, et al., 1998; Romero, et al., 1997). For example, although the amygdala in an adult male rat is larger than that in an adult female, female rats show greater cell proliferation in this brain area as early as PN 4 compared to newborn male rats (Krebs-Kraft, et al., 2010), suggesting that changes during later postnatal development are responsible for the observed adult differences. This greater proliferation in the amygdala of female newborns was prevented by administration of WIN 55,212-2, an effect that was associated with development of male-like patterns of social play in the treated females (Krebs-Kraft, et al., 2010). Notably, WIN55,212-2 did not affect cell proliferation in males. Subsequent experiments by this group showed that the anti-proliferation effects of WIN55,212-2 in females were mediated by its action on CB_2 receptors. In addition to differences in the rate of cell proliferation, levels of endocannabinoids and their metabolic enzymes in the amygdala also differed between the sexes. Whereas the amygdala of males showed higher levels of 2-AG and anandamide, the amygdala of females contained greater concentrations of their primary metabolic enzymes, MAGL and FAAH, respectively (Krebs-Kraft, et al., 2010). Together, these results suggest that sex differences in endocannabinoid tone develop early and may set the stage for differential development of the system, with the likely consequence of later divergent responses to exogenous cannabinoids.

In adult rats, the endocannabinoid system is strongly influenced by hormonal factors, particularly circulating levels of estradiol (for review, see Lopez, 2010). Throughout most of the brain, endocannabinoid content is estrous cycle-dependent in females, with cycle-independent exceptions being sustained higher levels of 2-AG in the hypothalamus and

pituitary and lower levels in the cerebellum, in comparison to levels in adult males (Bradshaw, et al., 2006). Compared to males and OVX females, intact females also exhibit lower levels of CB_1 receptor binding in the hypothalamus and increased binding in the amygdala (Riebe, et al., 2010). Results across studies are conflicting for the hippocampus. A higher density of CB_1 receptors in the hippocampus has been reported in males compared to females (Reich, et al., 2009), but also in OVX females compared both to intact females *and* to males (Riebe, et al., 2010). As has been reported for brain endocannabinoid levels, however, CB_1 receptor numbers and mRNA transcripts in various brain areas are not static, but fluctuate across the estrous cycle in females (Gonzalez, et al., 2000; Rodriguez de Fonseca, et al., 1994), emphasizing the importance of this variable in mechanistic studies.

To date, only these relatively few published papers have focused specifically on sex differences in the endocannabinoid system. An additional smattering of studies has examined sex differences in behavioral effects of the endocannabinoids. In one of these studies, Basavarajappa et al. (2006) reported that female mice lacking the gene for producing FAAH ($FAAH^{-/-}$) consumed more ethanol and were less sensitive to its hypothermic effects than were female wildtype mice or male mice of either genotype. The authors suggested that these findings resulted from an interaction between increased brain levels of anandamide and ovarian hormones. The results of a related study were only partly consistent, in that female, but also male, $FAAH^{-/-}$ mice exhibited increased ethanol consumption compared to their wildtype counterparts (Blednov, et al., 2007). Although a role for hormonal modulation of these effects was postulated, it was not specifically investigated.

While the extent to which these findings in animals model differences in humans is unknown as yet, preliminary evidence suggests that humans also exhibit sex differences in endocannabinoid system functioning. For example, higher activity of FAAH and the anandamide transporter has been observed in the platelets of female (vs. male) migraine patients (Cupini, et al., 2006). Further, individual variability in pain sensitivity in humans has been linked to a complex interaction of many factors. Among these variables are sex and loci in genes that code for transient receptor potential vanilloid type 1 (TRPV1) receptors (Kim, et al., 2004). [In addition to its effects on CB_1 receptors, anandamide has been shown to activate TRPV1 receptors (Di Marzo, et al., 2002).] Finally, decreased serum levels of 2-AG were observed in female patients experiencing major depression, with longer duration depressive episodes associated with larger decreases in 2-AG (Hill, et al., 2008). Whether this effect would also occur in males is unknown since this study examined only female patients.

HPA axis-endocannabinoid interaction

In addition to the direct effects of the endocannabinoid system on the development of sexual dimorphism in the brain, indirect effects are also likely. A unique aspect of the endocannabinoid system is that endocannabinoids are released from neurons that are associated with release of many other neurotransmitters, including dopamine, GABA and glutamate (Howlett, et al., 2002). The predominant effect of endocannabinoids is inhibition of release of the primary neurotransmitter; however, because of the presynaptic localization of cannabinoid receptors on neurons that release both excitatory and inhibitory neurotransmitters, the end result of CB_1 receptor activation may be either inhibitory [if release of an excitatory neurotransmitter is inhibited; i.e., depolarization-induced suppression of excitation (DSE)] or excitatory [if release of an inhibitory neurotransmitter is inhibited; i.e., depolarization-induced suppression of inhibition (DSI)] (Wilson and Nicoll, 2001). It is likely that endocannabinoids play a similar modulatory role within the hypothalamic-pituitary-gonadal (HPG) or -adrenal (HPA) axes. Further, while the predominant endocannabinoid effect within these systems is tonic inhibition, hormonal and

endocannabinoid modulation of the systems is almost certainly bidirectional in nature. For example, a review of the interplay between sex steroids and the endocannabinoid system concluded that fluctuation in regional CB_1 receptor densities and endocannabinoid levels across the estrous cycle was strongly influenced by estradiol (Lopez, 2010). A primary effect of increased estradiol (e.g., near ovulation) was to disinhibit tonic endocannabinoid suppression of hormone secretion by the HPG/ HPA axes (Lopez, 2010). In females, administration of cannabinoids mimicked this endocannabinoid inhibition of hormonal secretion, an effect that was reversed by estradiol. Interaction of the endocannabinoid system with the stress response and HPA functioning has also been noted. Under normal conditions, tonic activation of the endocannabinoid system inhibits HPA axis activity in rats of both sexes (Atkinson, et al., 2010; Lopez, 2010).

An elegant series of experiments (reviewed by Farhang, et al., 2009) demonstrated that administration of the cannabinoid agonist WIN55,212-2 modulated the tonic inhibition at proopiomelanocortin (POMC) synapses of the arcuate nucleus (ARC) of the guinea pig hypothalamus in a sexually divergent and hormone-dependent manner, with males exhibiting a testosterone-dependent increase in preprocorticotropin-releasing hormone and females showing an estradiol-dependent increase in POMC (Diaz, et al., 2009; Farhang, et al., 2009). In an electrophysiological preparation, both sexes show equal cannabinoid agonist-induced reduction in glutamatergic excitation in the anorexigenic ARC neurons, but male guinea pigs are less sensitive than females to agonist-induced attenuation of a GABAergic response (Farhang, et al., 2009). The net result is that CB_1 activation in males produces a shift towards greater inhibition of the ARC neurons due to the concomitant effect of cannabinoid-induced inhibition of the excitatory effects of glutamate and resistance to cannabinoid-induced suppression of GABA (i.e., less excitation due to DSI). In contrast, more excitation is observed in females due to higher basal excitation and approximately equivalent inhibition of glutamate and GABA signaling. Behaviorally, these cellular effects are associated with greater sensitivity to agonist-induced hyperphagia (i.e., via inhibition of the anorexigenic effects of the ARC neurons) and hypothermia in male than in female gonadectomized guinea pigs (Farhang, et al., 2009). Stressful conditions can also alter functioning of the endocannabinoid system in a sexually differentiated manner. For example, under conditions of chronic mild stress, male rats showed a decrease in the density of hippocampal CB_1 receptors whereas female rats showed an increase, effects that were not dependent upon adult hormonal status as they occurred in gonadectomized and intact adults (Reich, et al., 2009).

Conclusions

Although research on sex differences in cannabinoid pharmacology is increasing, knowledge of the mechanism(s) underlying sex differences in behavioral effects of cannabinoids remains limited. While activational hormonal factors have been shown to play a strong role in modulating endocannabinoid system functioning in adults, hormone-independent sex differences in this system have also been reported. Very little is known about the organizational effects of hormones during development of the endocannabinoid system. Understanding hormonal and non-hormonal mechanisms will facilitate development of sex-specific approaches to treat marijuana dependence and to use cannabinoid-based medications therapeutically – for example, in the treatment of pain and spasticity (Aggarwal, et al., 2009). In addition, elucidating endocrinological mechanisms that modulate the endocannabinoid system could ultimately enhance treatment of a wide variety of disorders in which dysregulation of the endocannabinoid system has been implicated, including obesity (Akhas, et al., 2009; Cota, et al., 2003), substance abuse (Beardsley, et al., 2009), and various neurological disorders (Williamson and Evans, 2000). Finally, there is a long-standing paucity of research on sex differences and in females of all species in nearly all

biomedical fields, with pharmacology and neuroscience being among the weakest (Beery and Zucker, 2011). As noted in a recent editorial, "…the burden of proof is shifting from having to defend why sex-gender differences should be studied to having to defend why they should not" (Wetherington, 2007) [see also (Cahill, 2006; Mogil and Chanda, 2005)].

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Future Directions

Given the paucity of studies in this area, considerable latitude exists for future research. Some of the major unanswered questions have been highlighted below:

1. Given the ubiquity of CB receptors at multiple levels of the neuraxis, localization of sex differences in cannabinoid function is crucial. For example, agonists can produce analgesia via supraspinal, spinal and peripheral CB receptor activation (Guindon and Hohmann, 2009) -- are all levels of the neuraxis sexually dimorphic in regard to cannabinoid function?
2. Do gonadal hormones act at genomic or membrane steroid receptors, or both, to influence endocannabinoid system activity? For example, in addition to its "slow" actions at genomic estrogen receptors (ER), estradiol also influences pain and the opioid system rapidly via membrane-bound ER (Eckersell, et al., 1998; Evrard and Balthazart, 2004). Does estradiol exert both types of effects on the cannabinoid system as well?
3. Studies in humans are needed to confirm or refute sex difference findings in rodents. Furthermore, the modulatory effects of estradiol need to be studied in two ways: cannabinoid effects in cycling women tested not only during follicular and luteal phases, but also during ovulation, when the greatest changes in sensitivity have been observed in rodents.

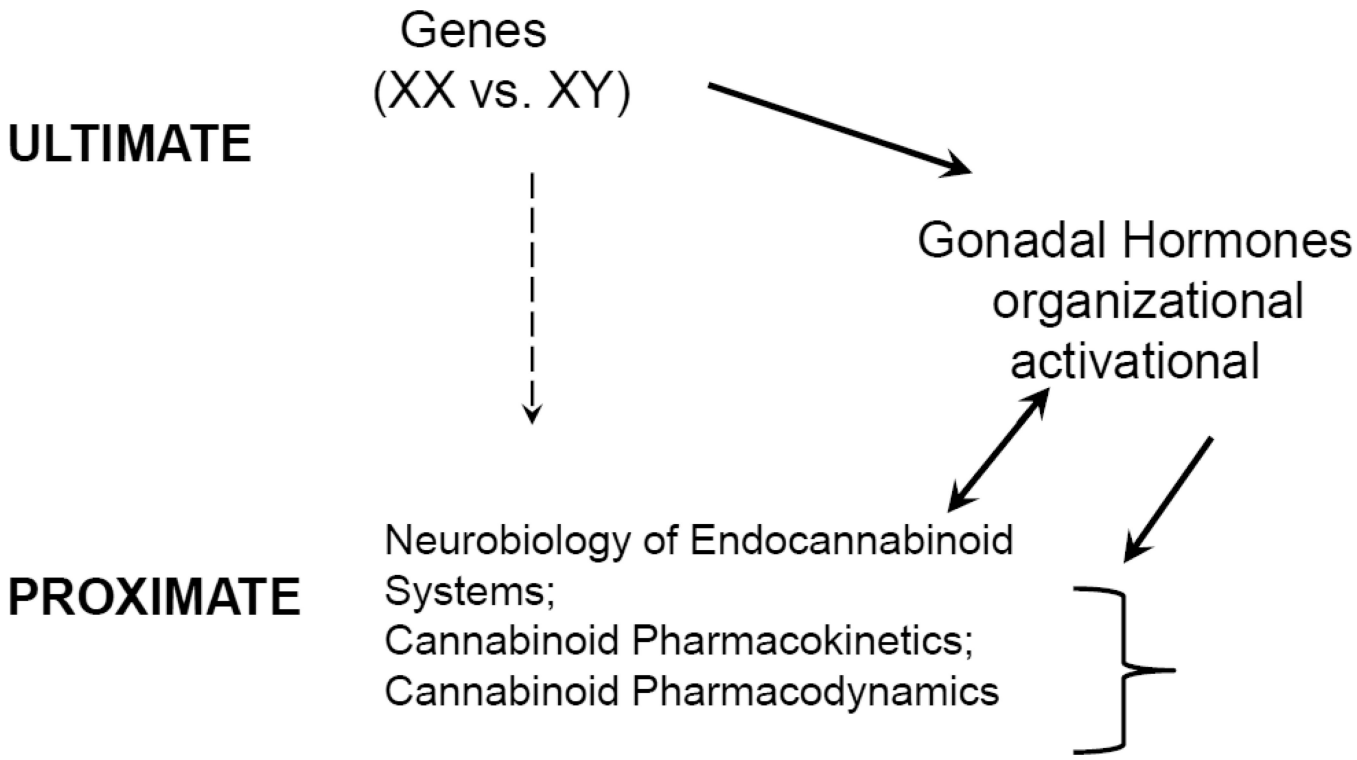

Figure 1. Sex differences in cannabinoid pharmacology: potential mechanisms