
Endocrine Effects of Marijuana

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In the 35 years since the active compound of marijuana, Δ^9 -tetrahydrocannabinol, was isolated, the psychological and physiological impact of marijuana use has been actively investigated. Animal models have demonstrated that cannabinoid administration acutely alters multiple hormonal systems, including the suppression of the gonadal steroids, growth hormone, prolactin, and thyroid hormone and

the activation of the hypothalamic-pituitary-adrenal axis. These effects are mediated by binding to the endogenous cannabinoid receptor in or near the hypothalamus. Despite these findings in animals, the effects in humans have been inconsistent, and discrepancies are likely due in part to the development of tolerance. The long-term consequences of marijuana use in humans on endocrine systems remain unclear.

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In the late 1960s, the dramatic increase in the casual use of marijuana raised questions about its potential adverse effects on health. In 1972, Harmon and Aliapoulos¹ provided the first report of marijuana's clinical impact on the endocrine system with the initial description of marijuana-associated gynecomastia. Further investigation has demonstrated that marijuana and its active component, Δ^9 -tetrahydrocannabinol (THC), have widespread effects on multiple hormonal systems, including gonadal, adrenal, prolactin, growth hormone, and thyroid hormone regulation in experimental models. In addition, the effects on the neuroendocrine mechanism of feeding are being delineated. Many of these acute effects, however, are transient as tolerance likely develops, and the long-term impact of marijuana smoking on the endocrine systems in humans remains unclear. This review will outline the effects of cannabinoids on the various hormonal systems both in animals and in man and evaluate the evidence of possible clinical consequences on the endocrine system with marijuana use.

HYPOTHALAMIC-PITUITARY-GONADAL AXIS

In both males and females, the secretion of sex hormones is directly controlled by the pituitary and indirectly influenced by the hypothalamus. From cells in the medial basal hypothalamus, gonadotropin-

releasing hormone (GnRH) is secreted in a pulsatile fashion under the influence of a variety of other factors, including endogenous opiates, catecholamines, prolactin, corticotropin-releasing hormone (CRH), and neuropeptide Y. GnRH stimulates the production of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) in the anterior pituitary gonadotrophs. In both males and females, FSH and LH act on the gonads, leading to the secretion of testosterone in males and estradiol and progesterone in females. These hormones feed back to the hypothalamus and anterior pituitary to modulate GnRH and gonadotropin release.

Marijuana, Δ^9 -THC, and other cannabinoids acutely alter hypothalamic-pituitary-gonadal (HPG) integrity and affect reproductive function by acting at the hypothalamus either directly through GnRH or indirectly through other modulators (Figure 1). These effects are likely mediated by central cannabinoid (CB1) receptors in the hypothalamus.² CB1 receptors have also been found in the testes³ and the ovaries⁴ of experimental animals, suggesting a possible direct effect of cannabinoids on the gonads. In addition, marijuana condensate and Δ^9 -THC inhibit binding of dihydrotestosterone (DHT) to the androgen receptor,⁵ and noncannabinoid components of marijuana extract have been shown to bind to the estrogen receptor.⁶ The extent to which these non-CB1-mediated pathways contribute to marijuana's effects on the HPG axis has not been clarified.

HPG AXIS EFFECTS IN MALES

LH stimulates the Leydig cells in the testes to produce testosterone, while FSH primarily acts on the Sertoli

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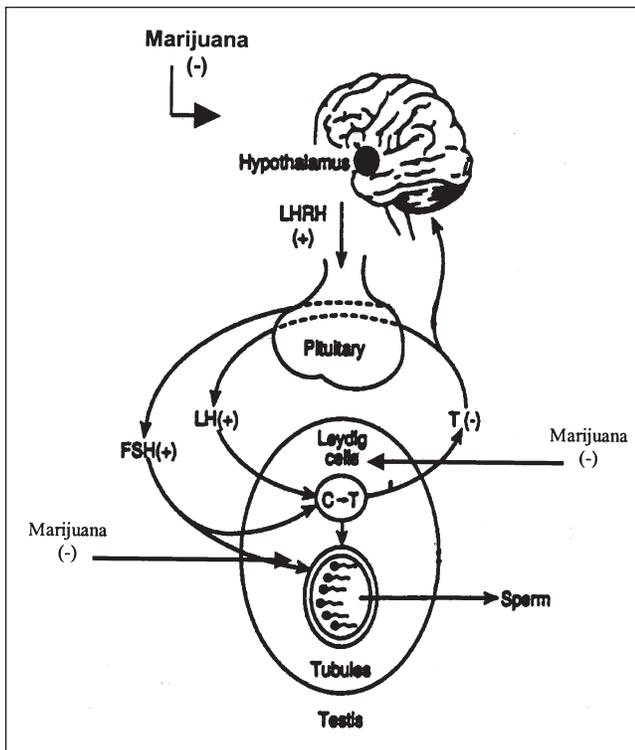


Figure 1. Effects of marijuana and Δ^9 -THC on male hypothalamic-pituitary-gonadal (HPG) function. Animal models demonstrate inhibition of the HPG axis by indirect suppression of LHRH (GHRH) secretion. In addition, direct effects on Leydig and Sertoli cells have been observed. Inconsistent results in human studies may be due to the development of tolerance. LH, luteinizing hormone; LHRH, luteinizing hormone-releasing hormone; GHRH, growth hormone-releasing hormone; FSH, follicle-stimulating hormone; C, cholesterol; T, testosterone. Adapted from Griffin JE, Wilson JD: Disorders of the testes, in: Isselbacher KJ, et al (eds.), Harrison's Principles of Internal Medicine, 13th ed. New York: McGraw-Hill, 1994.

cells to regulate spermatogenesis. In the adult human male, testosterone has a variety of actions throughout the body, including the maintenance of secondary sex characteristics, the facilitation of Sertoli cell function, and the promotion of sexual function. Hypogonadism results in decreased quality of life marked by fatigue, decreased libido, diminished sense of well-being, impaired fertility, and changes in body composition, including reduced bone mineral density and lean body mass. In experimental animals, acute administration of cannabinoids has been shown to both decrease testosterone levels and disrupt normal spermatogenesis. Findings in humans have not been consistent.

EFFECTS ON REPRODUCTIVE HORMONES IN MALES

Studies in male rodents have shown significant decreases in both testosterone and gonadotropins⁷ with acute administration of Δ^9 -THC due to inhibition of the GnRH pulse generator⁸ in the hypothalamus. Similar effects have been demonstrated in primates. In the rhesus monkey, THC reduced testosterone levels by 65%, which lasted 1 hour.⁹ Chronic effects of cannabinoid administration are less clear. Although dose-dependent decreases in LH have been observed with chronic administration of Δ^9 -THC,¹⁰ the effect of chronic exposure is less dramatic than that of acute administration⁷ and may be related to the development of tolerance.¹¹

Human studies investigating the effects of cannabinoids on reproductive hormones have been conflicting. Lower testosterone levels have been reported in chronic marijuana users compared to nonusers,¹² and acute decreases in both LH and testosterone have been observed after marijuana smoking,¹³ but multiple subsequent studies have not confirmed these findings.¹⁴⁻¹⁷ In one study, heavy chronic users were found to have similar testosterone levels compared to casual users at baseline and did not experience any significant alterations in testosterone after a 21-day period of intense marijuana smoking in a controlled research setting.¹⁴ A subsequent study of similar design by the same investigators showed no significant changes in integrated LH levels over the study period.¹⁶ These inconsistent observations may be due to differences in study design but also may reflect the development of tolerance, as suggested by the animal studies. Down-regulation and desensitization of CB1 receptors in the hypothalamus may underlie the weakening of effect observed with chronic cannabinoid administration.^{18,19}

EFFECTS ON TESTICULAR FUNCTION

Marijuana and Δ^9 -THC can have direct effects on the testes. Reductions in testicular size have been observed in rodents²⁰ and dogs²¹ with administration of cannabis extract. Degeneration of the seminiferous tubules may provide an explanation for this observation²¹ and is dose dependent, with lower doses showing no appreciable effect.²² Abnormal sperm morphology has been characterized in rodents exposed to marijuana smoke²³ or Δ^9 -THC²⁴ for a 5-day period. In vitro studies have demonstrated that cannabinoids directly inhibit

Leydig cell function.²⁵ The observed effects of cannabinoids on the testes notwithstanding, the impact on fertility is not clear. While Δ^9 -THC administration to mice 4 weeks prior to and during mating had no effect on fertility,²⁶ impregnation rates for mates of THC-treated mice were significantly lower than untreated controls.²⁷ This observation may be due in part to reduction in copulatory behavior.²⁸

In humans, effects on sperm production and morphology have also been observed. Dose-related oligospermia has been observed in chronic users.¹² Similarly, a 58% decrease in sperm concentration was reported in chronic users after intensive marijuana smoking without a significant change in LH or testosterone.²⁹ Reversible reductions in sperm concentration were seen 5 to 6 weeks after the initiation of intensive smoking, suggesting an effect on sperm production.³⁰ In addition, abnormal sperm morphology has been noted in chronic smokers.³¹ Although these findings imply a significant effect on gonadal function in humans, the true impact of marijuana on fertility is not known. However, discontinuation of casual marijuana use is recommended for infertile men.³²

GYNECOMASTIA

Gynecomastia is defined as the accumulation of breast tissue in men and results from increases in the circulating estrogen/androgen ratio.³³ Marijuana has been associated with the development of gynecomastia in an early case series,¹ but a case control study showed no association.³⁴ Given the effects of marijuana on the HPG axis in males and the possibility that noncannabinoid components of marijuana smoke have affinity to the estrogen receptor,⁶ an association with gynecomastia is plausible but has not been convincingly demonstrated.

HPG AXIS EFFECTS IN FEMALES

The secretion of estrogen from the ovary and the regulation of the ovulatory cycle are tightly controlled by the secretion of gonadotropins from the anterior pituitary. With waning levels of estrogen and progesterone at the end of menses, FSH levels increase, stimulating the growth and development of an ovarian follicle and thus the production of estrogen. Estrogen reduces FSH and LH secretion by negative feedback, but when estrogen levels peak, a LH surge is provoked by positive feedback, causing ovulation. LH then stimulates the production of estrogen and progesterone by the corpus luteum. Marijuana and Δ^9 -THC have been shown to disrupt the normal ovulatory cycle and hormonal secretion in both animals and humans. However, similar

to the findings in males, tolerance may develop over time, and the consequences of chronic use have not been firmly established.

As seen in male rodents, studies in female rodents have shown that the acute administration of cannabinoids markedly decreases LH levels^{35,36} by suppressing LH pulsatile secretion. Direct and indirect effects on GnRH secretion have been implicated.² The inhibition of gonadotropin secretion underlies the disruption of the ovulatory cycle. Administration of cannabinoids to rats blocked the LH surge normally leading to ovulation³⁷ and abolished the ovulatory cycle in rats^{38,39} and rabbits.⁴⁰

Studies in monkeys have demonstrated similar acute effects of cannabinoids on female reproductive function. Δ^9 -THC decreased LH levels by 50% to 80% in monkeys⁴¹ and has been shown to suppress the LH surge, resulting in anovulation.⁴² After 3 to 4 months of chronic administration, however, normal menstrual cycles spontaneously returned in treated monkeys, which is thought to be related to the development of tolerance.⁴³ Evidence for tolerance with long-term administration also comes from a study of rhesus monkeys given oral THC that showed no difficulties with conception.⁴⁴

The impact of marijuana and THC on humans has been less clear than in female animals. Some studies report a suppressive effect on LH secretion,⁴⁵ while others show a stimulatory effect.⁴⁶ These inconsistencies may be due to the timing of cannabinoid administration in relation to the ovulatory cycle. Mendelson et al⁴⁵ showed a 30% decrease in LH in women compared to controls 1 hour after administration of a marijuana cigarette (1 g 1.8% THC) when in the luteal phase but reported no effect in the follicular phase. In another study, a marijuana cigarette given in periovulatory stages increased LH levels,⁴⁶ while no acute change in LH was seen in menopausal women.⁴⁷

Studies of the effects of marijuana on ovulation have also been inconsistent. While female chronic smokers have been shown to have normal menses after intensive smoking,⁴⁸ some reports demonstrate increased anovulatory cycles and decreased length of the luteal phase.⁴⁹ Women who smoke marijuana may have a slightly increased risk of infertility due to an ovulatory abnormality, which was shown in a case control study of female recreation drug users with primary infertility.⁵⁰

EFFECTS ON PROLACTIN

Prolactin is synthesized in the anterior pituitary and is important in the stimulation of milk production and maintenance of lactation in mammals. Its release is un-

der tonic inhibition by dopamine secretion from tuberoinfundibular neurons in the hypothalamus. Cannabinoids, including components of marijuana, modulate the activity of dopaminergic neurons,⁵¹ thereby altering prolactin secretion. Animal studies have demonstrated an acute reduction of prolactin levels after THC administration in both rodents⁵² and primates.⁵³ Smith et al⁵³ showed that prolactin was reduced by a maximum of 84% in ovariectomized female monkeys and 74% in males at 30 to 90 minutes by a single injection of THC.⁵³ Not all findings in animals have been consistent, however, and may be dependent on the stage of the ovulatory cycle⁵⁴ or the timing of prolactin measurement in relation to cannabinoid administration.⁵⁵ Initial increases in prolactin after acute administration followed by significant decrements below baseline have been reported and may be due to a direct effect on the anterior pituitary.⁵⁶

Findings in humans reflect the inconsistencies seen in animal studies. Some studies have shown an acute prolactin decrease with administration,⁴⁹ while others have found no changes.⁵⁷ Similar to the observations in animals, changes in prolactin may be dependent on the menstrual cycle stage as an acute decrease in prolactin in females was reported after smoking a marijuana cigarette in the luteal phase but not in the follicular phase.⁵⁸ It is unknown whether changes in prolactin are seen with chronic marijuana use. Block et al¹⁷ found no differences in prolactin levels in both men and women in the largest cross-sectional study of chronic marijuana users.

EFFECTS ON THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS

Glucocorticoids (GC) are secreted by the adrenal gland in a diurnal pattern and play an essential role in carbohydrate, protein, and lipid metabolism; immunologic action; and renal and cardiac function. Physiological and psychological stresses provoke increased release of glucocorticoid, which is essential for the survival of the organism. The secretion of glucocorticoids is regulated by adrenocorticotrophic hormone (ACTH) released by the anterior pituitary. Corticotropin-releasing hormone (CRH) synthesized in the hypothalamus regulates ACTH secretion and is affected by multiple hypothalamic neurotransmitters, including serotonin, dopamine, and catecholamines. Cannabinoids alter HPA axis function by modulating CRH release either directly through CB1-mediated effects on CRH neurons in the paraventricular nucleus⁵⁹ or indirectly through other hypothalamic pathways.²

In multiple animal studies, acute administration of cannabinoids increased both ACTH and GC in a dose-related fashion,⁶⁰⁻⁶² an effect that is likely mediated by an increase in CRH.⁶³ Rodents administered potent CB1 agonist HU-210 had marked activation of the HPA axis, but at the highest doses, ACTH decreased while GC increased, suggestive of rapid negative feedback by GC.⁶⁴ However, tolerance to these effects develops quickly with chronic administration.⁶²

Human studies have shown variable effects of marijuana and component cannabinoids on the HPA axis. Similar to the effects in animals, increased cortisol levels have been reported after acute administration of marijuana.⁶⁵ However, in contrast to these findings, no change in the diurnal rhythm of cortisol secretion was observed during THC ingestion in chronic smokers.⁵⁷ Marijuana may also impair cortisol response to a stressful stimulus. Benowitz et al⁶⁶ reported an impaired response to insulin-induced hypoglycemia after 4 days of oral THC ingestion.⁶⁶ It is possible that prolonged activation of the HPA axis led to a reduction in adrenocortical reserve. It should be noted, however, that despite these statistically significant differences, clinical significance is unlikely in that all subjects had a cortisol response in the normal range (mean cortisol at maximum stimulation = 31.7 ± 3.2 mcg/dl).

EFFECTS ON GROWTH HORMONE

Growth hormone (GH) is secreted by the anterior pituitary, stimulated by the hypothalamic release of growth hormone-releasing hormone (GHRH), and inhibited by somatostatin. Serotonin from the limbic system, dopamine in the arcuate nucleus, and catecholamines in the ventromedial nucleus influence GH secretion by increasing GHRH release. In the adult, GH has widespread effects on many aspects of metabolism. Adult onset growth hormone deficiency is characterized by changes in body composition (increased fat mass and decreased muscle mass), impaired sense of well-being, reduced bone mineral density, and reduced cardiac performance.

Cannabinoids have been shown to inhibit GH secretion due to stimulation of somatostatin release.⁶⁷ Acute decreases in GH have been observed with THC⁶⁸ or HU-210 (a synthetic CB1 agonist) administration in rats.⁶⁴ There are few studies investigating the effect of marijuana and other cannabinoids on GH secretion in humans. Benowitz et al⁶⁶ showed that 4 days of oral THC blunted the normal GH response to insulin-induced hypoglycemia, the "gold standard" test of GH axis in-

tegrity. Long-term effects on GH dynamics in chronic marijuana users are unknown.

THYROID HORMONE AXIS

Thyroid hormones have widespread effects on cellular metabolism. Their synthesis and secretion are regulated by thyroid-stimulating hormone (TSH) from the anterior pituitary, which in turn is controlled by thyrotropin-releasing hormone (TRH). Cannabinoid effect on thyroid function was first noted in 1965, when marijuana extract was shown to reduce iodine accumulation in the rat thyroid.⁶⁹ Acute administration of THC in rodents^{70,71} reduces levels of thyroxine and TSH by as much as 90% for up to 6 hours. In addition, marijuana extract has been shown to decrease the release of radioactive iodine from the thyroid.⁷² These effects are reversed by administration of exogenous TSH, suggesting a hypothalamic site of action.^{71,72} With chronic administration of THC, however, the thyroid depressant effect of cannabinoids is lost, which may indicate the development of tolerance.⁷¹ There are no data regarding the effect of cannabinoids on thyroid function in humans.

EFFECTS ON THE NEUROENDOCRINE REGULATION OF FEEDING

The neuroendocrine mechanisms underlying appetite and feeding behavior are being clarified. Hunger and satiety signals from the GI tract, adipose tissue, and various endocrine systems regulate a vast array of hypothalamic hormones that modulate feeding behavior. Leptin, a polypeptide hormone secreted by adipose tissue, is thought to be a major satiety factor and central regulator on hypothalamic feeding centers. Leptin may cause appetite suppression by down-regulating endogenous cannabinoids, such as anandamide and 2-arachidonyl glycerol and other appetite-stimulating peptides.⁷³ Exogenous cannabinoids (i.e., marijuana and THC) also stimulate appetite,⁷⁴ likely through the activation of CB1 receptors in hypothalamic feeding centers. This effect provides the rationale for the use of oral THC in AIDS wasting.

SUMMARY AND CONCLUSIONS

Marijuana and its active component THC affect multiple endocrine systems. A suppressive effect is seen on the reproductive hormones, prolactin, growth hormone, and the thyroid axis, while the HPA axis is activated. These effects are mediated through CB1 receptor

activation in the hypothalamus, which directly or indirectly modulates anterior pituitary function. Many of the responses observed, however, are lost with chronic administration, which is likely due to the development of tolerance. Studies in humans have had inconsistent results that may reflect differences in study design, the hormonal milieu (e.g., stage in menstrual cycle), or the development of tolerance. Long-term effects on the various endocrine systems have not been clearly demonstrated, and clinical consequences, if present, are likely to be subtle.

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