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Endocannabinoids and the Endocrine System in Health and Disease

Cecilia J. Hillard, PhD

Medical College of Wisconsin; Milwaukee, WI 53226 USA

Abstract

Some of the earliest reports of the effects of cannabis consumption on humans were related to endocrine system changes. In this review, the effects of cannabinoids and the role of the CB1 cannabinoid receptor in the regulation of the following endocrine systems are discussed: the hypothalamic-pituitary-gonadal axis; prolactin and oxytocin; thyroid hormone and growth hormone; and the hypothalamic-pituitary-adrenal axis. Preclinical and human study results are presented.

Keywords

gonadotropin; gonadotropin releasing hormone; testosterone; prolactin; oxytocin; growth hormone; thyroid hormone; HPA axis; corticosterone

1. Introduction

Endocannabinoid signaling (ECS) plays a wide variety of modulatory roles throughout the central nervous system (CNS). The endocannabinoid system consists of two G protein coupled receptors, CB1 receptor (CB_1R) and CB2 receptor (CB_2R); the vanilloid subtype of transient potential receptor and members of the peroxisome proliferator activated receptor family. Two endocannabinoid (eCB) ligands have been identified: *N*-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG). Both are synthesized from phospholipid precursors in an “on demand” manner and are metabolized by hydrolysis. AEA is hydrolyzed by fatty acid amide hydrolase (FAAH), while 2-AG is hydrolyzed by monoacylglycerol lipase (MGL) and by alpha-beta hydrolase 6 (Marrs et al., 2010). Both AEA and 2-AG are also substrates for cyclooxygenase 2, which converts them to ethanolamide and glycerol substituted prostaglandins, respectively (Hermanson et al., 2014).

Within the CNS, ECS mediates activity-dependent, retrograde signaling in many brain regions, including the hippocampus, prefrontal cortex, amygdala and cerebellum (Freund et al., 2003). In most cases, 2-AG is mobilized in postsynaptic neurons by receptors that activate phospholipase C (PLC), including the metabotropic glutamate family of receptors. The diacylglycerol (DAG) that is produced is further metabolized by DAG lipase to monoacylglycerol, including 2-AG. 2-AG acts on presynaptic CB_1Rs to inhibit

Address correspondence to: Cecilia J. Hillard, PhD, Professor of Pharmacology, Director of Neuroscience Research Center, Medical College of Wisconsin, 8701 Watertown Plank Road, Milwaukee, WI 53226 USA, Phone: 414-955-8493, chillard@mcw.edu.

neurotransmitter release, through inhibition of the opening of voltage operated calcium channels.

The CB_1R is also present outside the CNS, including adipose tissue, liver and the adrenal gland. The CB_1R in adipose and liver promotes the storage of fat and reduces fat utilization (Silvestri et al., 2011). There is little known about the sources of the eCBs that innervate the non-CNS CB_1R. However, the eCBs are present in the circulation and recent data indicate that the circulating concentrations of 2-AG are nearly 4 times higher at noon than at 4 am in healthy humans (Hanlon et al., 2014), leading to the hypothesis that circulating eCBs activate these receptors and thereby coordinate adipose and liver function with caloric intake.

Formulations of the cannabis plant have been used by humans for thousands of years for the treatment of a variety of conditions, including pain and spasticity (Kumar et al., 2001). Δ^9-Tetrahydrocannabinol (THC) is a direct agonist of the CB receptors and is responsible for these medicinal effects as well as the feeling of euphoria or “high” that is sought by those using cannabis recreationally. There are many other chemicals in the plant that also have beneficial effects, but whose mechanisms are not as well understood (Devinsky et al., 2014).

CB_1Rs are present in the hypothalamus at relatively low density compared to other brain regions (Herkenham et al., 1991); however, it is argued that this population of cannabinoid receptors is highly active, given the broad range of endocrine effects of the cannabinoids (Fernandez-Ruiz et al., 1997). Within the hypothalamus, the CB_1R protein is heterogeneously distributed (Wittmann et al., 2007). CB_1Rs are present on both symmetrical and nonsymmetrical synapses and most immunoreactivity is in preterminal and terminal portions of axons. There is sparse CB_1R distribution within the suprachiasmatic and lateral mammillary nuclei, but other regions of the hypothalamus express significant amounts of CB_1R.

Hypothalamic CB_1R density differs between male and female rodents (Rodriguez de Fonseca et al., 1994) and this likely reflects important sex-related endocrine differences as well as differences in cannabinoid effects between male and female animals and humans (Craft et al., 2012). CB_1R mRNA has been identified in the external zone of the median eminence (Wittmann et al., 2007, Herkenham et al., 1991) and CB_1Rs are expressed at low levels in the intermediate and anterior lobes of the pituitary gland (Pagotto et al., 2001).

2. Cannabinoid interactions with the hypothalamic-pituitary-gonadal (HPG) axis

The first step in the regulation of the HPG axis involves the peptide hormone, gonadotropin releasing hormone (GnRH), which is produced by neurons in the preoptic area of the hypothalamus. GnRH secretion is pulsatile and it affects the release of two pituitary hormones through receptors in the anterior pituitary: low frequency GnRH pulses induce the release of follicle stimulating hormone (FSH) while high frequency pulses induce luteinizing hormone (LH) release. In males, the frequency of GnRH release is constant; while in females, frequency increases significantly at the time of ovulation, resulting in a surge of

LH. FSH and LH regulate follicular growth, ovulation and maintenance of the corpus luteum in females and spermatogenesis in males.

CB_1R activation inhibits the release of GnRH through effects in the hypothalamus in male rats. Studies in isolated hypothalamic tissue demonstrated THC-induced suppression of simulated but not basal GnRH release (Rettori et al., 1990) and inhibition of pulsatile GnRH release by other CB_1R agonists (Gammon et al., 2005). Mediobasal GnRH was increased by intracerebroventricular (i.c.v.) THC treatment, data consistent with a reduction in GnRH release in the pituitary (Wenger et al., 1987). However, another study demonstrated reduced concentrations of GnRH in the preoptic area and mediobasal hypothalamus following *in vivo* THC treatment (Kumar and Chen, 1983). It is possible that the discrepancy between these two studies is the result of different stimulus durations.

Cells adjacent to GnRH-secreting cells express CB_1R mRNA (Gammon et al., 2005) and a subset of neurons forming symmetrical synapses with GnRH neurons express CB_1R protein (Farkas et al., 2010). CB_1R activation inhibits gamma aminobutyric acid (GABA) release onto GnRH neurons (Glanowska and Moenter, 2011, Farkas et al., 2010), data in agreement with the predominant effect of CB_1Rs being suppression of neurotransmitter release (Freund et al., 2003). Reduced release of GABA is associated with increased excitatory drive, so these data seem to contradict the findings described above that CB_1R agonists inhibit GnRH release. However, GABA can depolarize GnRH neurons under some circumstances (Herbison and Moenter, 2011), and thus, inhibition of GABA release could paradoxically decrease GnRH neuronal activation. Alternative mechanisms have been suggested; for example AEA-induced inhibition of GnRH release evoked by NMDA in mediobasal hypothalamic fragments was blocked by both a CB_1R antagonist and bicuculline, suggesting an increase in GABA release (Fernandez-Solari et al., 2004). Other data suggest that THC acutely suppresses norepinephrine stimulation of GnRH release (Steger et al., 1990, Murphy et al., 1990). Chronic treatment of male mice with bhang (a cannabis preparation) results in reduced expression of receptors for GnRH in the pituitary (Banerjee et al., 2011). Thus, while the effect of activation is consistently depression of GnRH release, currently available evidence suggests that multiple mechanisms are involved.

Given the differences in patterns of release of GnRH between male and female, it is not surprising that sex steroid status profoundly affects CB_1R regulation of GnRH release (Scorticati et al., 2004). In particular, AEA had no effect on GnRH release in ovariectomized (OVX) rats and increased GnRH release in hypothalamic tissues from OVX rats in which estrogen is replaced (Scorticati et al., 2004). In agreement with findings obtained in experiments with other systems (Craft et al., 2012), it seems that estradiol is an important contributor to differences in response to CB_1R activation. An earlier study also found opposite effects of *in vivo* THC treatment on hypothalamic GnRH in male and OVX female rats (Kumar and Chen, 1983).

In accord with the evidence that CB_1R activation suppresses GnRH release, many studies also find that THC decreases circulating LH concentrations in male rats (Marks, 1973, Murphy et al., 1990); intact female mice (Dalterio et al., 1983a); OVX female rats (Tyrey, 1978); and OVX female monkeys (Smith et al., 1979). The effect of THC in monkeys was

reversed by the administration of GnRH (Asch et al., 1981), which is consistent with THC-induced suppression of hypothalamic GnRH release. AEA treatment reduced circulating concentrations of LH in wild type but not CB_1R −/− mice (Wenger et al., 2001), data supporting the CB_1R as the site of action for THC- and other cannabinoid-induced suppression of LH release. Administration of THC by i.c.v. administration also decreases LH but not FSH release, support for a CNS site of action (Wenger et al., 1987).

It is well known that stress dysregulates the HPG axis, resulting in negative consequences on reproduction. Stress elevates hypothalamic endocannabinoid concentrations (Patel et al., 2004), likely through glucocorticoid receptor activation (Evanson et al., 2010), leading to the hypothesis that ECS mediates stress-induced inhibition of the HPG axis. In support of this hypothesis, recent data demonstrate that immobilization stress-induced decrease in LH release in male rats is reversed by CB_1R antagonist treatment (Karamikheirabad et al., 2013).

There is considerable evidence that systemically administered THC and other cannabinoid agonists suppress testosterone production and circulating concentrations in animal models (Dalterio et al., 1977, Jakubovic et al., 1979) and chronic exposure induces regression of testes (Dixit et al., 1977, Kumar and Chen, 1983). These data are consistent with an ability of THC to suppress LH release, secondary to reduced GnRH. However, CB_1R −/− mice exhibit decreased circulating testosterone (Battista et al., 2008), which is at odds with the inverse effect of CB_1R activation and HPG activation outlined above. However, there is evidence that CB_1Rs are also expressed in the testes and play a role in the postnatal differentiation and maturation of Leydig cells (Cacciola et al., 2008). Thus the reduction of testosterone in CB_1R−/− mice could be the result of abnormal Leydig cell development. Components of the ECS are also present in Sertoli cells (Maccarrone et al., 2003) and THC inhibits FSH-induced signaling in Sertoli cell cultures (Heindel and Keith, 1989). Thus, ECS can alter the responsivity to testosterone in addition to its production.

Cannabinoid-mediated dysregulation of HPG activity has been found to have consequences on female reproduction as well. THC treatment blocks ovulation and the LH surge in rats (Nir et al., 1973) and high doses of cannabis extract decrease progesterone concentrations during the luteal phase of mice (Kostellow et al., 1980). THC treatment of monkeys in the follicular phase decreases both ovulation, and LH, FSH and estrogen concentrations in the circulation (Asch et al., 1981). On the other hand, THC has been show to facilitate sexual receptivity in female rats, possibly as a result of direct effects on the progesterone receptor (Mani et al., 2001).

In spite of consistent findings of changes in HPG function by ECS in both male and female preclinical models, data from humans using cannabis are far less consistent (see Gorzalka et al., 2009 for an excellent review). A recent meta-analysis of the effects of cannabis use on male fertility concluded that THC can have negative effects on male fertility (Fronczak et al., 2012), but epidemiological studies do not support this conclusion in the population at large (Hall and Solowij, 1998). It is possible that tolerance or sensitization develops to the effects of THC on reproduction in humans (Gorzalka and Dang, 2012). A study in Korean males in which cannabis effects on the ratio of urinary testosterone/epitestosterone was

examined, an 8-fold suppression was detected in 30 year old cannabis users (total number studied was 18), but not in other age groups (Moon et al., 2014). More to the point, 3.7% of couples presenting to an infertility clinic in Italy were positive for cannabis, which exceeds the incidence of cannabis use in the overall population (Pichini et al., 2012). These studies suggest that cannabis use can contribute to infertility in some couples.

3. Interaction of cannabinoids with hormones of lactation

3.1. Prolactin

Prolactin, a peptide hormone secreted from lactotrophs of the anterior pituitary, is essential for lactation and its release is promoted by suckling. Prolactin release is also evoked by copulation, ovulation and eating, and it plays roles in a diverse number of physiological processes in addition to milk production, including sexual satisfaction, immune regulation and hematopoiesis (Majumdar and Mangal, 2013). Prolactin release is tonically inhibited by dopamine, released from tuberoinfundibular neurons and acting through D2 dopamine receptors (Majumdar and Mangal, 2013).

Preclinical studies consistently demonstrate that CB_1R agonists reduce prolactin concentrations in the circulation through an effect upstream of the pituitary. Both intravenous (Hughes et al., 1981) and i.c.v. (Rettori et al., 1988) administration of THC produce long-lasting inhibition of prolactin release in male rats. This effect is shared by AEA and inhibited by the CB_1R antagonist, rimonabant (Fernandez-Ruiz et al., 1997). THC has no effect when the pituitary is removed from hypothalamic influence (Hughes et al., 1981) and does not affect prolactin release when incubated directly with dispersed pituitary cells (Hughes et al., 1981, Rettori et al., 1988), suggesting an effect in the hypothalamus or CNS. Data from nonhuman primates are in accord with the rat findings; in particular, THC suppresses prolactin basally but does not inhibit prolactin release induced by thyrotropin releasing hormone (TRH) (Asch et al., 1979). There is evidence that cannabinoids can also regulate prolactin secretion through effects in the pituitary. For example, 2-AG was found to potentiate forskolin- and adenosine-induced prolactin secretion from cultured pituitary cells from Syrian hamsters in a CB_1R-dependent manner (Yasuo et al., 2014). CB_1R antagonist treatment does not affect prolactin concentrations in rats (Black et al., 2011), evidence that the CB_1Rs involved in regulating prolactin release are not tonically active.

Cannabinoids have been shown to increase the release of dopamine in several brain regions, including the hypothalamus (Rodriguez De Fonseca et al., 1992, Hao et al., 2000, Murillo-Rodriguez et al., 2007, Murillo-Rodriguez et al., 2011). Given that dopamine exerts inhibitory control over prolactin release, cannabinoids could potentiate dopamine-mediated inhibition of prolactin through this mechanism. In support of this hypothesis, AEA inhibition of prolactin release in male rats is accompanied by an increase in dopamine turnover in the anterior pituitary (Scorticati et al., 2003) and the inhibitory effect of THC is occluded by dopamine antagonist treatment (Kramer and Ben-David, 1978).

The effects of cannabinoid agonists on prolactin in female rats is more complicated. Administration of THC to female rats in the morning of estrus results in decreased prolactin and increased dopamine turnover in the hypothalamus, a pattern that parallels the changes

seen in males (Bonnin et al., 1993). However, administration of THC in the afternoon of estrus, or in proestrus and diestrus, was without effect on prolactin, and had variable effects on dopamine turnover. Similarly, while an i.c.v. injection of AEA decreased circulating prolactin in males, the same dose had no effect on prolactin in OVX female rats and very significantly increased prolactin in OVX-estrogen replaced rats (Scorticati et al., 2003). While AEA increased pituitary dopamine turnover in male rats, AEA treatment decreased this measure in both OVX and OVX-estrogen replaced females in a CB_1R-dependent manner. CB_1R blockade significantly reduced prolactin in the OVX-estrogen replaced but not OVX rats, suggesting an increase in tonic CB_1R activity in the OVX-estrogen replaced setting. These data are consistent with other evidence that estrogen increases the synthesis of eCBs in females (Huang and Woolley, 2012). Interestingly, THC was found to reverse the stimulatory effect of estrogen on prolactin release in female rats *in vitro* (Murphy et al., 1991a) and *in vivo* (Murphy et al., 1991b). Since THC has low efficacy at the CB_1R (Kearn et al., 1999), it is possible that it acts as an antagonist in this situation in which eCB tone is high. Several mechanisms have been suggested by which CB_1R activation alters prolactin release in females, including direct effects on CB_1Rs of dopaminergic terminals resulting in inhibition of dopamine release (Scorticati et al., 2003) or alterations in the sensitivity of lactotrophs to stimulation (Murphy et al., 1991a).

Cannabinoid effects on prolactin in humans parallel those seen in rodents. In a study carried out in young men, THC was found to produce a slight decrease in prolactin concentrations (Liem-Moolenaar et al., 2010). Two other studies in which THC was administered by inhalation to cannabis-experienced young men also found small but significant reductions in circulating prolactin concentrations measured 90 min after treatment (Klumpers et al., 2012, Kleinloog et al., 2012). Another study, which compared the effects of intravenous THC administration to experienced cannabis users and healthy controls, found no acute effect of THC on prolactin in either group (Ranganathan et al., 2009). On the other hand, these investigators found that baseline prolactin concentrations were very significantly lower in the cannabis users than controls, which could reflect dysregulation of prolactin release or be persistent effects arising from a significant body burden of THC.

Two studies have examined the role of dopamine signaling in the mechanism of action of THC. In one, haloperidol pretreatment abrogated the reduction in prolactin by THC (Liem-Moolenaar et al., 2010), while in the other, THC continued to reduce prolactin in olanzapine-pretreated individuals (Kleinloog et al., 2012). These limited data and the very large increase in prolactin that results from dopamine receptor inhibition make these studies difficult to interpret.

3.2 Oxytocin

The hypothalamic-neurohypophyseal axis consists of magnocellular neurons within the supraoptic (SON) and periventricular nuclei (PVN) of the hypothalamus. These neurons synthesize the neuropeptides oxytocin (OXT) and vasopressin (VP) and send axonal projections to the posterior pituitary. Activation of magnocellular neurons results in the release of OXT and VP from axon terminals in the posterior pituitary. OXT and VP regulate reproduction and body fluid homeostasis through effects in peripheral organs. The release of

OXT and VP occurs in response to a wide variety of stimuli, including suckling, mating behavior, stress, fever and infection (McDonald et al., 2008).

In addition to acting as a hormone, OXT is also released within multiple limbic and cortical brain regions (McGregor et al., 2008). OXT receptors are present in non-hypothalamic brain areas (Neumann et al., 1993) and centrally released OXT contributes to maternal behaviors, and increases sexual and social interactions (McGregor et al., 2008).

A series of important and interesting papers have characterized a role for ECS in the regulation of activity in the magnocellular neurons of both the SON and PVN. CB_1R activation by endogenously produced eCBs reduces glutamate release onto magnocellular neurons of the PVN and SON (Hirasawa et al., 2004, Di et al., 2005a, Di et al., 2003, Di et al., 2005b, McDonald et al., 2008). A variety of mechanisms can evoke eCB release from magnocellular neurons, including glucocorticoids, acting via a membrane receptor (Di et al., 2003, Di et al., 2005a, Di et al., 2005b), OXT itself (Hirasawa et al., 2004, McDonald et al., 2008), and alpha-melanocyte stimulating hormone (Sabatier and Leng, 2006). OXT also recruits ECS in layer V of the infralimbic region of the prefrontal cortex to decrease glutamate release (Ninan, 2011). A recent *in vitro* study suggests that AEA can also decrease the release of OXT through a mechanism requiring increased nitric oxide synthase activity, and CB_2Rs and vanilloid receptors but not CB_1Rs (Luce et al., 2014).

CB_1Rs are also present on GABA terminals in the hypothalamus (Wittmann et al., 2007) and several studies support a role for ECS in the suppression of tonic GABA release onto magnocellular neurons (Oliet et al., 2007, Di et al., 2009, Wang and Armstrong, 2012). Low concentrations of OXT in the dendritic regions of the magnocellular neurons recruit ECS to produce a tonic inhibition of GABA release (Oliet et al., 2007). This process is hypothesized to provide a mechanism by which OXT itself can regulate inputs in an autocrine fashion that is coordinated and easily reversed when needed. The eCB that subserves this process is not known, although i.c.v. administration of the FAAH inhibitor, URB597 increases, while AM251 inhibits OXT release evoked by lipopolysaccharide (De Laurentiis et al., 2010). These data are consistent with an ability of AEA to inhibit GABAergic influence over the magnocellular SON neurons and thus potentiate OXT release.

Data from Tasker and colleagues suggest that 2-AG mediated inhibition of GABA release is normally opposed by efficient buffering by astrocytes of 2-AG released from magnocellular neurons (Di et al., 2013). When astroglia are retracted, as during dehydration, or metabolically inactivated, 2-AG-mediated inhibition of GABA release is revealed. These data are very interesting and suggest that the primary role for 2-AG is to regulate glutamate inputs into magnocellular neurons, but that under certain circumstances, an effect on GABA release can also occur. These data also suggest different roles for 2-AG versus AEA in the regulation of magnocellular neuronal activation.

In vivo studies of the effects of cannabinoids on circulating OXT, lactation and maternal behaviors suggest an inhibitory effect of the CB_1R over OXT release, and are therefore in accord with evidence that CB_1R activation inhibits glutamatergic drive onto magnocellular neurons. Early studies demonstrated that THC and a variety of cannabis extracts interfere

with nest building behavior in mice (Moschovakis et al., 1978) and rats (Sieber et al., 1980). In a more recent study, a synthetic CB_1R agonist was demonstrated to produce a very significant reduction in circulating OXT concentrations and to reduce maternal behaviors (Vilela and Giusti-Paiva, 2014). Dexamethasone-induced disruption of suckling-induced secretion of OXT and maternal behavior is also blocked by CB_1R antagonism (Vilela et al., 2013). These data, together with the evidence that glucocorticoids mobilize ECS in the hypothalamus to inhibit glutamate release in the SON (Di et al., 2005a), are consistent with ECS-mediated suppression of OXT neurons.

Paradoxically, both dams treated with a CB_1R antagonist (Schechter et al., 2012) and CB_1R −/− dams (Schechter et al., 2013) also exhibit poor maternal care, as measured by time to retrieve pups. However, circulating OXT concentrations are not different between wild type and CB_1R−/− dams, suggesting that release of OXT is not affected by loss of CB_1R signaling. CB_1R−/− dams had significantly lower amounts of OXT receptor mRNA and protein in hippocampus than wild type dams and did not exhibit a postpartum-mediated increase as occurred in the wild type dams. These data indicate that the CB_1R is needed for proper increases in CNS sensitivity to OXT following delivery, through regulation of increased OXT receptor expression.

Receptors for OXT are expressed in many brain regions involved in reward and drug seeking, including the nucleus accumbens and ventral tegmental area (VTA) (Vaccari et al., 1998). OXT in these brain regions is thought to be involved in the production by cannabinoids of enhanced feelings of sociability (McGregor et al., 2008). The OXT system exhibits significant neuroplasticity and it has been hypothesized that chronic exposure to rewarding drugs, including THC, can down-regulate OXT-mediated signaling, and that loss of OXT signaling contributes to withdrawal (McGregor et al., 2008). Indeed, the administration of a moderate dose of THC for 7 days resulted in a significant reduction in expression of mRNA and protein for OXT in nucleus accumbens and VTA of rats without any effect in the hypothalamus (Butovsky et al., 2006). Similarly, chronic THC exposure results in lasting dysregulation of social interactions in rodents (O′Shea et al., 2004, O'Shea et al., 2006, Quinn et al., 2008). OXT itself is not a useful therapeutic, since it does not cross the blood brain barrier. However, lithium was shown to alleviate all of the symptoms of precipitated withdrawal induced by CB1R antagonism in CB1R agonist-tolerant rats, and this effect was accompanied by a large increase in circulating OXT concentrations (Cui et al., 2001).

A small study demonstrated that lithium treatment reduced withdrawal signs and promoted abstinence in chronic cannabis users (Bowen et al., 2005). However, a larger clinical trial recently published did not find any overall effects of lithium on withdrawal, although some of the individual withdrawal symptoms, including loss of appetite, stomach aches and nightmares were reduced (Johnston et al., 2014). While this study concluded that there was no clear advantage of lithium over placebo, the timing of lithium administration was such that its concentrations may not have been in a therapeutic range during the period of greatest withdrawal and further studies are warranted.

4. Interaction of cannabinoids with hormonal regulation of growth, development and metabolism

4.1 Thyroid Hormones

The thyroid hormones, 3,5,3′-triiodothyronine and L-thyroxin, regulate development and metabolism in many mammalian tissues. Receptors for the thyroid hormones function as transcription factors, regulating gene transcription through thyroid hormone response elements in promoter regions of multiple genes (Flamant et al., 2007). Thyroid hormone release is the end-product of a regulatory cascade that includes hypothalamic TRH and pituitary thyroid stimulating hormone (TSH), defining a hypothalamic-pituitary-thyroid (HPT) axis.

Treatment of adult rats with THC reduces thyroid hormone concentrations in the circulation (Nazar et al., 1977, Rosenkrantz and Esber, 1980, Hillard et al., 1984). Several possible mechanisms for the effect have been suggested. Data showing that THC does not inhibit TRH-induced increases in circulating thyroid hormone (Hillard et al., 1984) together with evidence that CB_1Rs are expressed on neurons innervating TRH-expressing neurons (Di et al., 2003, Deli et al., 2009) suggest that THC and other CB_1R agonists can inhibit TRH release through effects in the hypothalamus. It is interesting in this regard that glucocorticoid-induced mobilization of ECS has been shown to inhibit glutamate release onto TRH-positive neurons in the hypothalamus (Di et al., 2003), suggesting that eCBs link stress and suppression of the HPT axis. Cannabinoids have also been shown to suppress the HPT axis at the pituitary (Veiga et al., 2008) and thyroid gland (Porcella et al., 2002). However, inhibition at the first step in a cascade such as the HPT axis will have the greatest impact *in vivo*.

TSH and thyroid hormone concentrations were all within normal limits and did not correlate with concentrations of THC or its major metabolites in a study of chronic cannabis users (Bonnet, 2013). These findings suggest that chronic exposure of adults to THC does not produce a long-lasting impact on HPT axis function in otherwise healthy adults. However, perinatal hypothyroidism can result in severe and irreversible cognitive deficits in later life (Bernal, 2007), suggesting that cannabis use during pregnancy could have adverse effects on fetal development through dysregulation of the HPT axis. In support of this notion, treatment of a trophoblast cell line with THC results in inhibition of proliferation and a nearly 3-fold reduction in the expression of thyroid receptor β1 (TRβ1) (Khare et al., 2006). This effect on TRβ1 expression is similar to what occurs in fetal growth restriction (FGR) (Ohara et al., 2004). Since cannabis use has been associated with FGR (Zuckerman et al., 1989), it is possible that THC exposure during pregnancy could interfere with growth as a result of decreased expression of TRβ1 and, thus, a decrease in thyroid hormone effect.

One recent study indicates that thyroid hormone status also modulates ECS. Hypothyroid rats exhibit an increase in the inhibitory effect of CB_1R agonism on the formation of spatial memories (Gine et al., 2013). This defect was normalized by administration of thyroid hormone. There was no difference in hippocampal CB_1R expression between control and hypothyroid rats, suggesting that the effect of the thyroid hormone is to enhance CB_1R

signaling. Hypothyroid rats have also been shown to have a 50% reduction in the cerebral expression of G protein receptor kinase 2 (GRK2) (Penela et al., 2000, Penela et al., 2001), an enzyme that participates in the desensitization of a variety of G protein-coupled receptors, including the CB_1R (Kouznetsova et al., 2002). Thus, it is possible that loss of thyroid hormones results in dampening of a negative regulatory process that affects the CB_1R.

4.2 Growth Hormone

Growth hormone (GH) is a polypeptide released from somatotrophs of the anterior pituitary that stimulates growth and regulates energy homeostasis. GH secretion is negatively and positively regulated by the hypothalamic peptides somatostatin and growth hormone releasing hormone (GHRH), respectively. Somatostatin and GHRH release are regulated by biogenic amines, metabolic status, sex hormones and sleep. GH is released in a pulsatile manner, with the largest GH peak occurring about an hour after the onset of sleep (Takahashi et al., 1968). Surges in GH release occur during waking as well, with a frequency of approximately 3–5 hours (Natelson et al., 1975).

Acute and chronic THC treatment of adult and adolescent rodents decreases basal circulating GH concentrations (Kokka and Garcia, 1974, Dalterio et al., 1983b, Dalterio et al., 1981) and suppresses episodic release of GH in adult male rats (Falkenstein and Holley, 1992). A synthetic CB_1R agonist also produces a dose-dependent suppression of GH in male rats (Martin-Calderon et al., 1998). Data that THC administration into the third ventricle also suppresses GH (Rettori et al., 1988); and THC increases somatostatin release from hypothalamic explants (Rettori et al., 1990), support the hypothesis that THC inhibits GH via increased somatostatin. CB_1Rs are also expressed by GH secreting cells in the human pituitary, and CB_1R agonist treatment inhibits GH secretion from acromegaly-associated pituitary adenomas in culture (Pagotto et al., 2001), although another study found no effect of THC on GH release from isolated pituitary cells (Rettori et al., 1988). The ability of ghrelin to increase GH release is not affected by CB_1R antagonist treatment (Kola et al., 2013).

5. Cannabinoids and the hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis contributes to the circadian regulation of physiological function and is an essential component of the stress response. HPA axis activation begins with the neuropeptide, corticotrophin releasing hormone (CRH), which is synthesized by PVN neurons that respond to and integrate inputs from the amygdala, prefrontal cortex (PFC) and hippocampus (Herman et al., 2003). CRH induces the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary which stimulates glucocorticoid synthesis and release from the adrenal cortex.

Output of the HPA axis, the glucocorticoids cortisol and corticosterone (CORT), have wide-ranging effects on the body, influencing metabolism, immune function and behavior. The HPA axis is activated by both physical and psychological stress and glucocorticoids, acting via the glucocorticoid receptor (GR) are responsible for many of the homeostatic changes that follow stress, including increased food consumption and suppression of the immune system. However, the HPA axis also has “housekeeping” duties at basal concentrations that

are mediated by mineralocorticoid receptor (MR) activation, as these receptors have higher affinity for the corticosteroids than GRs. Circulating glucocorticoid concentrations are circadian and the highest concentrations of corticosterone are reached shortly after the beginning of the active period of the day.

As is the case for the other endocrine systems discussed, the ECS plays an important role in the regulation of the HPA axis at the level of the hypothalamus. Activation of CB_1Rs in the PVN inhibits the release of glutamate onto CRH neurons, data consistent with CB_1R-mediated inhibition of the HPA axis (Di et al., 2003, Di et al., 2005b). ECS at this synapse is rapidly activated by CORT, leading to the hypothesis that ECS regulates CORT-mediated feedback inhibition (Evanson et al., 2010). In addition to effects in the PVN, CORT-mediated increases in 2-AG also contribute to feedback regulation of the HPA axis in the medial PFC (Hill et al., 2011) and hippocampus (Wang et al., 2012). As a result of actions in all of these brain regions, deficient or absent ECS results in prolonged activation of the HPA axis by restraint stress (Hill et al., 2011).

ECS in the basolateral amygdala (BLA) also regulates the HPA axis: in particular, it constrains the initiation of HPA axis activation by stress. Intra-BLA injections of a CB_1R agonist and antagonist decrease and increase, respectively, CORT responses to stress in male rats (Hill et al., 2009, Ganon-Elazar and Akirav, 2009). Since stress exposure produces a rapid decrease in BLA AEA concentrations (Hill et al., 2009), it has been suggested that AEA concentrations in BLA are high at rest and function to inhibit spurious activation of the HPA axis (Patel et al., 2004, Hill et al., 2009). In order for a robust HPA axis activation to occur, the concentration of AEA in the BLA must decrease. This is accomplished via activation of FAAH in the amygdala (Hill et al., 2009), likely through CRH acting through the CRH-R1 receptor (Gray et al., 2013). In further support of this mechanism, low concentrations of direct CB_1R agonists and inhibition of FAAH inhibit activation of the HPA axis by restraint stress (Patel et al., 2004), while systemic administration of rimonabant increases circulating CORT concentrations in response to injection (Wade et al., 2006) and restraint stresses (Patel et al., 2004).

There is evidence that ECS negatively regulates basal and circadian HPA axis activation states as well. For example, i.c.v. administration of high doses of rimonabant increases circulating CORT and ACTH concentrations in rat, suggesting a tonic inhibition of HPA axis activation by the CB_1R (Manzanares et al., 1999). Female $CB_1R^{-/-}$ mice exhibit significantly elevated concentrations of both CORT and ACTH at the onset of the active period (i.e. dark phase) compared to wild type mice (Cota et al., 2007). CB_1R antagonist treatment increased both ACTH and CORT concentrations in non-stressed rats; however, it had a far greater effect on CORT concentrations when administered during the diurnal trough than during the diurnal peak (Atkinson et al., 2010). These data suggest that endogenous tone at the CB_1R is higher in the early light period than in the early dark period. In accord with this notion, we have recently demonstrated that hypothalamic contents of AEA are highest at the times of 07:00 and 11:00 and are low between 15:00 and 03:00 (Liedhegner et al., 2014).

In vivo studies showed that low doses of CB_1R agonists other than THC reduced basal and stress-induced HPA axis responses in rodents (Patel et al., 2004, Saber-Tehrani et al., 2010), data that are consistent with the regulatory mechanisms discussed above. However, high doses of synthetic agonists (Patel et al., 2004), and THC treatment, increase circulating concentrations of CORT (Steiner and Wotjak, 2008). A pharmacological study in rats suggests that the cannabinoid-induced increase in HPA axis activity is secondary to activation of monoaminergic hindbrain nuclei as both noradrenergic and serotonergic blockade reduced the stimulatory effects (McLaughlin et al., 2009). It is interesting that this circuit seems to be preferentially activated by THC, while higher efficacy cannabinoids and AEA inhibit HPA axis through direct actions on limbic and hypothalamic circuitry as described above.

There is some evidence that CB_1R activation regulates the HPA axis via effects in the pituitary and adrenal gland as well as in the brain. Pituitary cells isolated from $CB_1R^{-/-}$ mice exhibited greater secretion of ACTH in response to both CRH and forskolin stimulation (Cota et al., 2007), suggesting an inhibitory role for the CB_1R in the pituitary. CB_1R mRNA is expressed in the adrenal gland of rodents (Buckley et al., 1998) and humans (Ziegler et al., 2010) and AEA-mediated activation of the CB_1R has been found to decrease basal and stimulated adrenocortical steroidogenesis (Ziegler et al., 2010). Additionally, CB_1R activation decreases epinephrine release from adrenal medullary cells (Niederhoffer et al., 2001). Therefore, ECS could decrease glucocorticoid synthesis within adrenocortical cells directly or via reduced sympathetic drive. This conclusion is supported by a study in which systemic administration of a CB_1R antagonist elevated circulating CORT concentrations without an effect on ACTH or pituitary c fos expression, suggesting a direct effect of the antagonist on the adrenal gland (Newsom et al., 2012).

Human studies reproducibly demonstrate that acute consumption of cannabis (Cone et al., 1986) or THC (D'Souza et al., 2004, D'Souza et al., 2008, Klumpers et al., 2012, Ranganathan et al., 2009, Kleinloog et al., 2012) increases the secretion of cortisol in individuals who were either naive to cannabis or infrequent users. The stimulatory effect of THC administration on cortisol levels was blunted in chronic cannabis users, suggesting that tolerance develops (D'Souza et al., 2008, Ranganathan et al., 2009). On the other hand, some (King et al., 2011, Somaini et al., 2012), but not all (Block et al., 1991), studies have reported that chronic cannabis users exhibit elevated basal cortisol levels, and other studies demonstrate that stress-induced activation of the HPA axis is blunted in chronic adult and adolescent cannabis users (Somaini et al., 2012, van Leeuwen et al., 2011). In adolescents with an early onset of use, chronic cannabis use is associated with altered diurnal cortisol rhythms such that cortisol concentrations are higher than normal at night and blunted in the morning (Huizink and Mulder, 2006). Taken together, the human data suggest that chronic cannabis use has the potential to dysregulate basal, circadian and stress-regulated HPA axis activity in a complex manner.

6. Summary

The hypothalamus is an important center for the regulation of metabolism, reproduction, and responses to stress. Although the density of the CB_1R in the hypothalamus is lower than

other brain regions, it is clear from a vast number of studies that ECS plays a highly significant role in hypothalamic function through regulation of neurotransmitter release from glutamatergic, GABAergic and possibly other nerve terminals. The ECS is designed to act in a localized manner, and it is clear that it can regulate the activation state of several hypothalamic neuronal subtypes in an independent manner. However, stress produces an increase in eCBs in the hypothalamus, and it is possible, although not validated completely, that CB_1Rs mediate the effects of stress on multiple endocrine systems.

A consistent theme throughout all available studies is that THC has relatively inconsistent effects in humans, in spite of consistent effects seen in preclinical studies. It is possible that individual differences in the underlying ECS result in inconsistent effects of THC. While it is tempting to conclude that THC does not have significant endocrine effects in humans, it is possible that THC could have significant effects in some individuals that increase the risk of health problems, including infertility, hypothyroidism, or problems in stress responding.

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Abbreviations:

2-AG	2-arachidonoylglycerol
ACTH	adrenocorticotropic hormone
AEA	*N*-arachidonoylethanolamine
BLA	basolateral amygdala
CB_1R	type 1 cannabinoid receptor
CB_2R	type 2 cannabinoid receptor
CNS	central nervous system
CRH	corticotrophin releasing hormone
DAG	diacylglycerol
eCB	endocannabinoid
ECS	endocannabinoid signaling
FAAH	fatty acid amide hydrolase
FGR	fetal growth restriction
FSH	follicle stimulating hormone
GABA	gamma amino butyric acid

GH	growth hormone
GHRH	growth hormone releasing hormone
GnRH	gonadotropin releasing hormone
GR	glucocorticoid receptor
HPA	hypothalamic pituitary adrenal
HPG	hypothalamic pituitary gonadal
HPT	hypothalamic pituitary thyroid
i.c.v.	intracerebroventricular
LH	luteinizing hormone
MGL	monoacylglycerol lipase
MR	mineralocorticoid receptor
OVX	ovariectomized
OXT	oxytocin
PLC	phospholipase C
PVN	periventricular nucleus
SON	supraoptic nucleus
THC	Δ^9-tetrahydrocannabinol
TRß1	ß1 subtype of the thyroid hormone receptor
TRH	thyrotropin releasing hormone
TSH	thyroid stimulating hormone
VTA	ventral tegmental area

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