doi:10.2478/enr-2026-0011

Endocannabinoid signalling in the regulation of hypothalamic-pituitary neuroendocrine circuits: A review

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The endocannabinoid system (ECS), comprising cannabinoid receptors, endogenous lipid ligands, and enzymes that regulate their synthesis and degradation, has emerged as an important modulator of neuroendocrine regulation. This review summarises current evidence on the role of endocannabinoid signalling in hypothalamic-pituitary neuroendocrine circuits, with particular focus on the hypothalamic-pituitary-adrenocortical, gonadal, thyroid, and somatotropic axes, as well as prolactin and posterior pituitary hormones regulation. Available data indicate that endocannabinoid signalling predominantly influences neuroendocrine function by modulating synaptic transmission within hypothalamic circuits. Acting mainly as retrograde messengers at presynaptic CB1 receptors, endocannabinoids regulate excitatory and inhibitory inputs to neurosecretory neurons and thus shape endocrine output in a context-dependent manner. Among the systems discussed, the hypothalamic-pituitary-adrenocortical axis is the best characterised, with relatively well-defined links between glucocorticoid feedback and rapid endocannabinoid-mediated suppression of synaptic input to corticotropin-releasing hormone neurons. In other neuroendocrine systems, evidence supports a predominantly modulatory, often inhibitory, role for endocannabinoid signalling, although the underlying cellular processes remain less well-defined and are largely based on preclinical studies. Interactions with glucocorticoids, gonadal steroids and neuropeptidergic pathways further underscore the integrative nature of ECS signalling. Overall, the ECS should be viewed not as a primary endocrine driver, but as a dynamic regulatory network that fine-tunes the translation of neural activity into hormonal responses.

Keywords: endocannabinoid system, hypothalamus, CB1 receptor, neuroendocrine regulation, glucocorticoids

The endocannabinoid system (ECS) is a lipid signalling system comprising cannabinoid receptors, their endogenous ligands, and the enzymatic machinery responsible for their biosynthesis and degradation. Research into the ECS originated from efforts to understand the biological and psychotropic effects of compounds derived from *Cannabis sativa*, particularly Δ9-tetrahydrocannabinol (THC). The isolation and structural elucidation of THC in 1964 represented a key milestone in cannabinoid research (Gaoni and Mechoulam 1964). This discovery enabled the subsequent identification of specific, high-affinity cannabinoid binding sites in the brain, which led to the cloning of cannabinoid receptor type 1 (CB1) in 1990 and cannabinoid receptor type 2 (CB2) in 1993 (Matsuda et al. 1990; Munro et al. 1993). The identification of these receptors prompted the search for their endogenous ligands. Anandamide (AEA) was the first endogenous cannabinoid to be identified and characterised in 1992. This was followed by the identification

The authors would like to dedicate this research article to the Endocrine Regulations 60th anniversary.

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of the 2-arachidonoylglycerol (2-AG) in 1995. The term "endocannabinoids" was subsequently introduced for these arachidonic acid-derived ligands (Di Marzo and Fontana 1995). Together with the enzymes responsible for their synthesis and degradation, these ligands constitute the core components of the endocannabinoid signalling system.

Over the past three decades of research, the ECS has been recognised as a widely distributed network present across various tissues and organ systems. Within the central nervous system (CNS), it is present in numerous brain regions, including the cerebral cortex, hippocampus, amygdala, basal ganglia, cerebellum and hypothalamus. In the hypothalamus, cannabinoid receptors, endocannabinoids and their metabolic enzymes are expressed in nuclei involved in neuroendocrine regulation (Hillard 2015; Tretiakov et al. 2025). Beyond the brain, ECS components are also expressed in peripheral tissues, where they participate in the regulation of immune function, energy balance and reproductive processes. Consistent with this broad distribution, the ECS is implicated in the integrative control of key homeostatic and neuroendocrine processes, including stress responsiveness, metabolic regulation and reproductive function, many of which are coordinated through hypothalamic-pituitary pathways (Pagotto et al. 2006).

This review aims to summarise evidence on endocannabinoid signalling in the regulation of hypothalamic-pituitary neuroendocrine circuits, including the hypothalamic-pituitary-adrenocortical, gonadal, thyroid, and somatotropic axes. In addition, the review addresses the role of endocannabinoid signalling in the regulation of prolactin and posterior pituitary hormones, oxytocin and vasopressin.

Components of the endocannabinoid system

Cannabinoid receptors. Endocannabinoid effects are primarily mediated by CB1 and CB2 receptors, both of which are membrane $G\alpha_{i/o}$ protein-coupled receptors (Matsuda et al. 1990; Munro et al. 1993). Upon activation, these receptors primarily inhibit adenylyl cyclase, thereby reducing cAMP production and downstream signalling by protein kinase A. They also modulate ion channel activity and engage mitogen-activated protein kinase (MAPK) cascades, linking endocannabinoid signalling to both rapid changes in cellular excitability and longer-term effects on gene expression and metabolism (Howlett et al. 2002). CB1 receptors are highly expressed in the CNS and are predominantly localised at presynaptic terminals of glutamatergic and γ-aminobutyric acid (GABA)-ergic neurons, where their activation suppresses neurotransmitter release (Tasker et al. 2015). Beyond their localisation in the plasma membrane, CB1 receptors were detected in intracellular compartments, including mitochondria, where their activation has been associated with modulation of mitochondrial respiration and cellular energy metabolism (Hebert-Chatelain et al. 2016). CB2 receptors, although less abundant in neurons, are expressed in microglia and peripheral immune cells, where they influence neuroimmune and metabolic processes (Atwood and Mackie 2010). Their contribution to neuroendocrine regulation remains not exactly defined.

In addition to classical cannabinoid receptors, endocannabinoids interact with several non-cannabinoid targets. AEA activates transient receptor potential vanilloid type 1 (TRPV1) channels, which are well known for their role in nociception and thermosensation. Their activation leads to calcium influx and increased neuronal excitability, in contrast to the inhibitory effects mediated by CB1 receptors (Zygmunt et al. 1999). Endocannabinoids may also act at orphan G protein-coupled receptors such as GPR55 (Ryberg et al. 2007), although their physiological roles remain incompletely characterised. Endocannabinoid signalling involves nuclear receptors, particularly peroxisome proliferator-activated receptors (PPARs), through which lipid mediators can directly influence gene transcription (O'Sullivan 2016). These interactions indicate that endocannabinoid signalling extends beyond classical CB1/CB2 receptor pathways and includes ion channels, G protein-coupled receptors, and nuclear receptor-mediated mechanisms.

Endocannabinoids. Endocannabinoid signalling is mediated by endogenous lipid ligands, primarily AEA and 2-AG. These molecules belong to distinct lipid families, N-acylethanolamines and 2-acylglycerols, and differ in their biosynthetic pathways, receptor affinity, and temporal dynamics of signalling (Di Marzo et al. 2004; Tasker et al. 2015). Endocannabinoids are synthesised on demand from membrane phospholipid precursors in response to activity-dependent increases in intracellular calcium and the activation of Gq/11-coupled receptors, which initiate enzymatic pathways that lead to their synthesis (Kano 2014). Unlike classical neurotransmitters, they are not stored in synaptic vesicles, but are synthesised as needed, enabling rapid and spatially restricted signalling. Recent evidence suggests that endocannabinoids may also be transiently stored in intracellular compartments, although the functional relevance of this remains unclear.

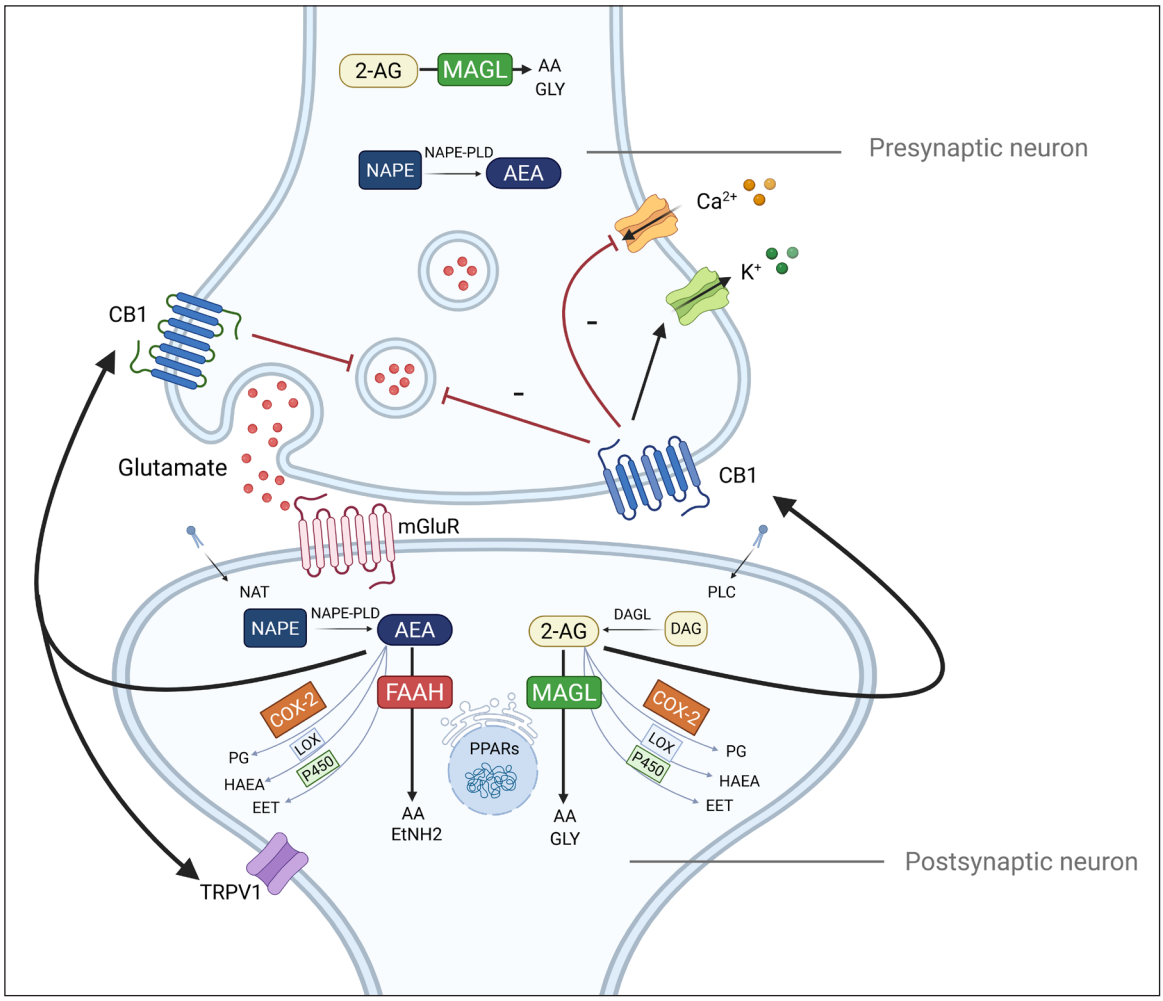

Figure 1. Components of the endocannabinoid system and schematic pathways of endocannabinoid signalling. Schematic illustration of endocannabinoid signalling between postsynaptic and presynaptic neurons. Endocannabinoids are synthesised on demand from membrane phospholipid precursors, primarily in the postsynaptic neuron. Anandamide (AEA) is generated from N-acyl phosphatidylethanolamine (NAPE) via N-acyltransferase (NAT) and NAPE-specific phospholipase D (NAPE-PLD), whereas 2-arachidonoylglycerol (2-AG) is produced from diacylglycerol (DAG), formed by phospholipase C (PLC), via diacylglycerol lipase (DAGL). Following postsynaptic activation, endocannabinoids act as retrograde messengers and diffuse across the synaptic cleft to activate presynaptic cannabinoid receptor type 1 (CB1). CB1 receptor activation suppresses neurotransmitter release by inhibiting presynaptic calcium influx and promoting potassium conductance, thereby reducing vesicular glutamate release. Endocannabinoid signalling may also interact with postsynaptic metabotropic glutamate receptors (mGluR) and non-cannabinoid targets such as transient receptor potential vanilloid type 1 (TRPV1), while intracellular signalling can involve peroxisome proliferator-activated receptors (PPARs). Signal termination occurs mainly through enzymatic degradation: AEA is hydrolysed by fatty acid amide hydrolase (FAAH) to arachidonic acid (AA) and ethanolamine ($EtNH_2$), whereas 2-AG is degraded predominantly by monoacylglycerol lipase (MAGL) to AA and glycerol (GLY). Both AEA and 2-AG may also undergo oxidative metabolism via cyclooxygenase-2 (COX-2), lipoxygenases (LOX), and cytochrome P450 enzymes (P450), generating bioactive oxidized lipid derivatives.

Once released, endocannabinoids act locally, most commonly as retrograde messengers (Figure 1). They are produced in postsynaptic neurons and diffuse across the synaptic cleft to activate presynaptic CB1 receptors, thereby suppressing neurotransmitter release and modulating synaptic input to target neurons (Wilson and Nicoll 2001).

Enzymatic regulation of endocannabinoid signalling. Endocannabinoid signalling is tightly regulated by enzymatic pathways that control both the synthesis and degradation of endocannabinoids (Figure 1). AEA is primarily synthesised from N-arachidonoyl phosphatidylethanolamine via N-acyl phosphatidylethanolamine (NAPE)-specific

phospholipase D, although multiple alternative pathways have been described, indicating redundancy in its biosynthesis (Simon and Cravatt 2006; Hillard 2015). In contrast, 2-AG is generated predominantly through the hydrolysis of diacylglycerol by diacylglycerol lipase (Hillard 2015).

The termination of endocannabinoid signalling is mediated by enzymatic degradation. AEA is hydrolysed mainly by the enzyme fatty acid amide hydrolase (FAAH), whereas 2-AG is primarily degraded by monoacylglycerol lipase (MAGL) (Cravatt et al. 1996). These enzymatic processes represent a key control point in endocannabinoid tone and are targets for pharmacological modulation to enhance endocannabinoid signalling. In addition to hydrolytic degradation, endocannabinoids can be metabolised through oxidative pathways. The enzyme cyclooxygenase-2 (COX-2) converts AEA and 2-AG into prostaglandin ethanolamides and prostaglandin glycerol esters, respectively, thereby linking endocannabinoid signalling to eicosanoid pathways. Similarly, lipoxygenases and cytochrome P450 enzymes can generate bioactive oxidised derivatives of endocannabinoids with distinct biological activities (Kozak et al. 2002; Di Marzo et al. 2004). Local enzymatic activity influences the balance between cannabinoid receptor-dependent and alternative lipid-mediated signalling, which is relevant for neuroendocrine regulation. The spatial distribution of these enzymes across cell types and subcellular compartments further contributes to the regulation of endocannabinoid tone (Miralpeix et al. 2021).

Endocannabinoid regulation of neuroendocrine function

The hypothalamus represents a key integrative centre for neuroendocrine regulation, where neuronal populations control pituitary hormone secretion and coordinate homeostatic responses. Endocannabinoid signalling modulates neuroendocrine function primarily by influencing synaptic transmission within hypothalamic circuits (Tretiakov et al. 2025).

Cannabinoid receptors are expressed in several hypothalamic nuclei involved in neuroendocrine regulation, including the paraventricular nucleus (PVN), arcuate nucleus, lateral hypothalamus and preoptic area (Wittmann et al. 2007; Suarez et al. 2010). At the cellular level, CB1 receptors are predominantly localised at presynaptic terminals, where their activation suppresses neurotransmitter release and modulates both excitatory and inhibitory synaptic inputs to neurosecretory neurons.

Endocannabinoids primarily act as retrograde messengers in these circuits. They are synthesised in postsynaptic neurons and act on presynaptic CB1 receptors to regulate synaptic drive to hypothalamic neurons controlling endocrine outputs. Within specific hypothalamic circuits, endocannabinoid signalling interacts with neuroendocrine systems that regulate the stress response, reproduction, metabolism, growth, and fluid homeostasis. Endocannabinoid signalling in the hypothalamus is therefore best understood as a synaptic modulatory system that dynamically regulates neuronal activity within neuroendocrine circuits, rather than as a primary driver of hormone secretion.

Hypothalamic-pituitary-adrenocortical (HPA) axis. The HPA axis is the most extensively studied neuroendocrine axis in relation to endocannabinoid signalling. It represents the principal neuroendocrine system of the stress response, integrating neural and hormonal signals to coordinate adaptive physiological and behavioural responses. HPA axis activity is initiated at the level of corticotropin-releasing hormone (CRH) neurons in the PVN of the hypothalamus, which integrate inputs from the limbic regions such as the amygdala, hippocampus, and prefrontal cortex. Endocannabinoid signalling influences these neurons primarily by regulating synaptic transmission. CB1 receptors are localized on presynaptic terminals of both GABAergic and glutamatergic neurons within these circuits, and their activation suppresses neurotransmitter release, altering the balance of inhibitory and excitatory input reaching CRH neurons (Katona et al. 1999; Marsicano and Lutz 1999; Di et al. 2003). By regulating synaptic input, endocannabinoid signalling can influence CRH release from the hypothalamus, thereby altering adrenocorticotropic hormone (ACTH) secretion from the anterior pituitary and glucocorticoid output from the adrenal cortex.

In addition to hypothalamic mechanisms, components of the endocannabinoid system have been identified at other levels of the HPA axis. CB1 receptor expression has been reported in the pituitary and adrenal glands, and endocannabinoids have been detected in these tissues, suggesting that endocannabinoid signalling may influence HPA axis function at both central and peripheral levels (Pagotto et al. 2006; Ziegler et al. 2010; Micale and Drago 2018). However, the best characterised mechanisms remain those operating within hypothalamic and limbic circuits (Tasker et al. 2015).

A key mechanism linking endocannabinoid signalling to HPA axis regulation is

glucocorticoid-mediated feedback. Glucocorticoids can rapidly mobilise endocannabinoids, particularly 2-AG, in the PVN and in limbic regions. This endocannabinoid acts on presynaptic CB1 receptors to suppress excitatory synaptic input to CRH neurons, thereby contributing to rapid feedback inhibition of HPA axis activity (Di et al. 2003; Evanson et al. 2010).

Endocannabinoid signalling contributes to the regulation of HPA axis activity under both basal and stress conditions (Micale and Drago 2018). Under resting conditions, tonic CB1 receptor activity exerts an inhibitory influence on the HPA axis (Tasker et al. 2015). When CB1 receptor signalling is blocked or genetically disrupted, this inhibitory tone is lost, and basal HPA activity increases. Conversely, enhancement of endocannabinoid signalling, for example by inhibiting FAAH, is associated with reduced endocrine responses to stress (Hillard 2015).

The two principal endocannabinoids, AEA and 2-AG, appear to participate in different phases of the stress response (Hill and Tasker 2012). Acute stress is commonly associated with a rapid decline in AEA levels, often linked to increased FAAH activity, especially in the amygdala (Hill et al. 2009; Morena et al. 2016). This reduction is thought to remove a tonic inhibitory influence on stress-responsive circuits, allowing stronger activation of the HPA axis during the early phase of the response. In contrast, 2-AG often rises with a delayed time course in the hypothalamus, hippocampus, and prefrontal cortex, and glucocorticoids contribute to this increase (Rademacher et al. 2008; Evanson et al. 2010). The later increase in 2-AG is consistent with a role in limiting ongoing HPA activation and supporting recovery after stress by strengthening CB1 receptor-mediated suppression of synaptic input to CRH neurons. In this framework, reduced AEA favours stress initiation, whereas elevated 2-AG supports feedback restraint and recovery. Repeated or chronic stress also alters endocannabinoid tone, although the pattern depends on the stress paradigm. Chronic stress is often associated with reduced AEA levels and increased FAAH activity, while changes in 2-AG signalling are less consistent across studies (Hill et al. 2009; Morena et al. 2016).

Pharmacological studies further support this view. Blockade or genetic deletion of CB1 receptors increases circulating ACTH and glucocorticoid concentrations, supporting the existence of an endogenous cannabinoid tone that constrains basal HPA axis activity (Patel et al. 2004; Cota et al. 2007). Enhancement of endocannabinoid signalling, particularly through FAAH inhibition, attenuates stress-induced activation of the HPA axis in animal models, whereas CB1 receptor blockade amplifies endocrine responses to stress (Patel et al. 2004; Hill et al. 2009). In line with these observations, our recent experimental data show that FAAH inhibition reduces plasma ACTH and corticosterone concentrations following cognitive challenge (Nagyova et al. 2025).

Most of these findings come from animal studies. In humans, the available evidence is less consistent. Acute stress has been associated with changes in circulating endocannabinoid levels, particularly AEA, but the direction and magnitude of these responses vary across studies (Dlugos et al. 2012; Morena et al. 2016; Childs et al. 2017). A meta-analysis by Gowatch et al. (2024) have found no consistent overall change in AEA or 2-AG after acute psychosocial stress and highlighted substantial heterogeneity across experimental conditions. Experimental administration of THC has been associated with increased cortisol concentrations, although the endocrine effects of cannabinoids depend on dose, pattern of exposure and individual characteristics (Ranganathan et al. 2009).

Taken together, current evidence indicates that endocannabinoid signalling shapes HPA axis activity mainly through synaptic regulation of CRH neurons, rapid glucocorticoid feedback, and dynamic changes in endocannabinoid tone during stress. Within this framework, AEA appears to be more closely linked to basal restraint and early stress reactivity, whereas 2-AG contributes more strongly to feedback inhibition and recovery. ECS signalling may also act at pituitary and adrenal levels, but these components remain less clearly defined than the central pathways.

Hypothalamic-pituitary-thyroid (HPT) axis. The HPT axis regulates basal metabolic rate and energy homeostasis by tightly controlling the secretion of thyroid hormones, primarily triiodothyronine (T3) and thyroxine (T4). Its activity is driven by thyrotropin-releasing hormone (TRH) neurons in the PVN of the hypothalamus, which integrate neural, hormonal, and metabolic signals to regulate pituitary thyroid-stimulating hormone (TSH) release and downstream production of T3 and T4. Compared with the HPA axis, the role of endocannabinoid signalling in HPT regulation has been studied less extensively and remains incompletely defined. Even so, available experimental evidence suggests that cannabinoids exert a predominantly inhibitory influence on HPT axis activity (Hillard 2015).

The first indication that cannabinoids influence thyroid function came from early pharmacological studies showing that acute administration of THC reduced circulating TSH and serum T4

and T3 in rodents (Nazar et al. 1977; Hillard et al. 1984). Importantly, pretreatment with THC does not impair the TSH response to exogenous TRH, indicating that pituitary responsiveness to the hypothalamic stimulation remains preserved under these conditions (Hillard et al. 1984). These findings point to a predominantly central site of action, although they do not identify the precise level at which cannabinoids act.

Although direct functional evidence for endocannabinoid regulation of TRH neurons remains limited, several findings support the hypothalamic involvement. Immunohistochemical studies have shown that hypophysiotropic TRH neurons in the PVN receive synaptic inputs from CB1 receptor-positive axon terminals, indicating that these neurons are anatomically positioned to be modulated by endocannabinoid signalling (Deli et al. 2009). In parallel, electrophysiological studies in hypothalamic neuroendocrine circuits demonstrate that endocannabinoids suppress excitatory synaptic transmission to PVN neurosecretory neurons through CB1 receptor-dependent mechanisms (Di et al. 2003). These findings were primarily obtained from studies of CRH neurons rather than TRH neurons. Even so, they provide a plausible mechanistic framework in which endocannabinoid signalling could reduce excitatory input to TRH neurons, thereby decreasing TRH release. At present, however, this remains an inference rather than a directly demonstrated mechanism.

A stronger mechanistic basis has been established at the pituitary level. In rats, the endocannabinoid AEA decreases circulating TSH after systemic administration and also suppresses TSH release from isolated anterior pituitary explants. Both effects were blocked by the CB1 receptor antagonist AM251, indicating that AEA acts through CB1 receptor-dependent mechanisms to inhibit TSH secretion (da Veiga et al. 2008). In the same study, AM251 alone increased circulating TSH, supporting the view that endogenous cannabinoid signalling exerts a tonic inhibitory influence on thyrotrophic activity. Whether cannabinoids also act directly at the level of the thyroid gland remains less clear. Although cannabinoid receptors have been detected in thyroid tissue, their functional role in regulating thyroid hormone synthesis and release has not been clearly established (Hillard 2015).

Human data are sparse and do not provide consistent support for a major role of cannabinoids in thyroid regulation. Clinical observations in chronic cannabis users have generally shown minimal or no sustained alterations in circulating thyroid hormone concentrations (Bonnet 2013). However, these studies are limited by heterogeneity in exposure patterns, duration of use and study design, and more subtle or context-dependent effects cannot be excluded.

Overall, current evidence suggests that endocannabinoid signalling exerts a predominantly inhibitory influence on HPT axis activity. This effect appears to involve at least two levels of regulation: reduced hypothalamic drive to TRH neurons, supported primarily by indirect anatomical and electrophysiological evidence, and direct inhibition of pituitary TSH secretion, demonstrated experimentally. Possible peripheral effects at the thyroid gland have also been proposed but remain insufficiently characterised.

Hypothalamic-pituitary-gonadal (HPG) axis. The endocannabinoid signalling has been shown to modulate the HPG axis at multiple levels. However, the underlying mechanisms are less well characterised than those described for the HPA axis. Most of the available evidence derives from experimental studies in animal models, whereas data from human studies remain limited and heterogeneous. Components of the endocannabinoid system are expressed in the hypothalamus, pituitary gland, and gonads, supporting both central and peripheral sites of action (Gorzalka and Dang 2012; Kalak et al. 2025).

At the hypothalamic level, endocannabinoid signalling influences reproductive neuroendocrine function by acting on neuronal circuits that generate the pulsatile release of gonadotropin-releasing hormone (GnRH). GnRH neurons, located predominantly in the preoptic area, form part of a network responsible for rhythmic hormone secretion rather than acting as simple output units. The frequency and amplitude of GnRH pulses critically determine the relative secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), making temporal patterning a key regulatory feature of the HPG axis (Tasker et al. 2015). Endocannabinoid signalling modulates this process by altering synaptic inputs that shape GnRH neuronal excitability and firing pattern (Wilson and Nicoll 2001; Kano 2014).

A central mechanism involves regulating GABAergic transmission. In contrast to many other neuronal populations, GABA can depolarise GnRH neurons under certain physiological conditions. CB1 receptor activation reduces GABA release onto GnRH neurons, thereby decreasing their excitatory drive and leading to suppression of GnRH secretion (Farkas et al. 2010). Endocannabinoid signalling also modulates glutamatergic inputs and interacts with additional neuromodulatory systems, indicating that its effects are distributed across multiple components

of the GnRH regulatory network rather than confined to a single pathway (Tasker et al. 2015). Through these mechanisms, endocannabinoids influence not only the magnitude of GnRH output, but also the frequency and amplitude of its release, thereby modulating downstream gonadotropin secretion.

Consistent with the hypothalamic mechanisms, activation of cannabinoid receptors is generally associated with reduced pituitary gonadotropin secretion. Animal studies demonstrate that administration of THC or related cannabinoid agonists decreases circulating LH levels, an effect that can be reversed by exogenous GnRH, supporting predominantly the hypothalamic site of action (Murphy et al. 1990). CB1 receptor expression has also been reported in the anterior pituitary, suggesting that direct pituitary effects may contribute, although these mechanisms remain less well-defined (Pagotto et al. 2006).

At the gonadal level, components of the ECS are expressed in both male and female reproductive tissues, including Leydig cells, Sertoli cells, and ovarian structures (Hillard 2015). In the testes, endocannabinoid signalling modulates testosterone production both indirectly, via reduced LH stimulation, and directly through local effects on steroidogenic pathways (Gorzalka and Dang 2012). Endocannabinoids also influence spermatogenesis and sperm function, indicating regulatory roles that extend beyond central neuroendocrine control (Kalak et al. 2025). In females, cannabinoid exposure has been associated with disruption of ovulatory cycles and attenuation of LH surges, consistent with an overall suppressive effect on reproductive endocrine function (Hillard 2015).

An important feature of the ECS–HPG axis interaction is its bidirectional crosstalk. Endocannabinoid signalling modulates GnRH and gonadotropin release, while gonadal steroid hormones regulate multiple components of the endocannabinoid system, including CB1 receptor expression, endocannabinoid levels, and enzymatic activity (Gorzalka and Dang 2012; Forner-Piquer et al. 2024). Oestrogens, in particular, influence endocannabinoid tone and CB1 receptor signalling within hypothalamic circuits in a region- and context-dependent manner, contributing to sex-dependent and cycle-dependent variability in neuroendocrine output (Forner-Piquer et al. 2024). In addition to direct effects on GnRH neurons, endocannabinoid signalling may influence upstream regulators of the HPG axis. Modulation of neuronal populations that control GnRH activity, such as kisspeptin-expressing neurons, has been proposed as an indirect mechanism linking endocannabinoid signalling to reproductive function; however, the underlying pathways and their physiological relevance remain incompletely defined (Marino et al. 2023).

In contrast to experimental findings in animal models, evidence from human studies is limited and often inconsistent. Cannabis exposure has been associated with alterations in circulating gonadotropins, sex steroid levels, and fertility parameters; however, results vary across studies and are influenced by differences in exposure patterns, dose, and study design (Gundersen et al. 2015; Payne et al. 2019). These discrepancies highlight the need for further translational research to clarify the role of endocannabinoid signalling in human reproductive endocrinology.

Taken together, current evidence indicates that endocannabinoid signalling modulates HPG axis activity through coordinated actions at hypothalamic, pituitary, and gonadal levels. Rather than acting as a primary driver, the ECS functions as a modulatory network that shapes neuroendocrine output in a context-dependent manner. The predominance of inhibitory effects observed in experimental models, together with bidirectional interactions with sex steroid signalling, underscores the complexity of ECS–HPG regulation and the need for further mechanistic investigation.

Somatotropic axis. The somatotropic axis regulates growth and metabolic homeostasis through pulsatile secretion of growth hormone (GH) from pituitary somatotrophs. GH secretion is regulated by the hypothalamic growth hormone-releasing hormone (GHRH), which stimulates GH release, and by somatostatin, which inhibits GH release. The balance between these opposing influences determines both the amplitude and timing of GH secretion and enables the integration of metabolic, circadian, and neuroendocrine inputs.

Available experimental evidence indicates that cannabinoid signalling is associated with suppression of GH secretion. Systemic administration of THC or cannabinol reduced circulating GH levels and attenuated pulsatile GH release in mice or rats (Dalterio et al. 1981; Falkenstein and Holley 1992). The balance between these opposing influences determines both the amplitude and timing of GH secretion and enables the integration of metabolic, circadian, and neuroendocrine inputs. Rettori et al. (1988) have found that intracerebroventricular administration of THC suppresses GH secretion in male rats. They also observed that THC increased somatostatin release from hypothalamic explants,

supporting the hypothesis that THC inhibits GH via increased somatostatin (Rettori et al. 1990).

In addition to hypothalamic mechanisms, cannabinoid signalling can influence pituitary function. CB1 receptors are expressed in GH-secreting cells, and activation of these receptors has been shown to inhibit GH release in cultured human pituitary adenoma cells (Pagotto et al. 2006). However, findings at this level are not entirely consistent, as other studies report no significant effect of cannabinoids on GH secretion from isolated pituitary cells (Rettori et al. 1988), suggesting that direct pituitary effects may depend on cellular context or experimental conditions.

The relationship between cannabinoid signalling and the ghrelin system introduces an additional regulatory dimension. Ghrelin is a potent stimulator of GH secretion acting via the growth hormone secretagogue receptor (GHSR). Neuroanatomical and molecular data indicate an overlapping distribution of CB1 and GHSR receptors in brain regions involved in energy balance and neuroendocrine regulation. Functional studies show that ghrelin-induced GH secretion is not abolished by CB1 receptor blockade (Kola et al. 2008), suggesting that ghrelin and cannabinoid signalling regulate GH secretion through at least partly independent mechanisms.

Human studies examining the effects of cannabinoids on GH secretion are limited. Acute administration of cannabis or THC has been associated with reductions in circulating GH levels (Benowitz et al. 1976; Mendelson and Mello 1984), although findings are variable and influenced by experimental conditions, including dose and prior exposure.

Thus, current evidence indicates that cannabinoid signalling modulates the somatotropic axis through mechanisms that include hypothalamic regulation, particularly involving somatostatin signalling, and, to a lesser extent, direct effects at the pituitary level. Interactions with ghrelin-related pathways further suggest a role in integrating metabolic and neuroendocrine control of GH secretion. However, the physiological relevance of these mechanisms remains incompletely defined.

Prolactin. Prolactin secretion differs from the regulation of most anterior pituitary hormones in that it is primarily controlled by tonic inhibition rather than stimulation by a hypothalamic releasing hormone. This inhibition is mediated by tuberoinfundibular dopaminergic neurons, which release dopamine into the hypophyseal portal circulation and suppress lactotroph activity via dopamine D2 receptors. It has been suggested that endocannabinoid signalling modulates prolactin secretion primarily through its effects on hypothalamic dopaminergic neurons rather than by directly regulating pituitary lactotrophs (Hillard 2015).

Studies in rodents have shown that administration of THC, either systemically or intracerebroventricularly, reduces circulating prolactin levels (Hughes et al. 1981; Rettori et al. 1988). In contrast, *in vitro* experiments using dispersed anterior pituitary cells demonstrate that THC does not alter prolactin secretion or its response to releasing stimuli, indicating that its inhibitory effects are not exerted directly at the level of lactotrophs but require intact hypothalamic input (Rettori et al. 1988). Comparable findings have been reported in non-human primates, where THC reduces basal prolactin concentrations without affecting prolactin responses to exogenous stimulation (Mendelson and Mello 1984).

The most consistent mechanistic explanation for these effects involves modulation of hypothalamic dopaminergic activity. In rodent models, cannabinoid administration increases dopamine release and turnover in hypothalamic regions, thereby strengthening inhibitory control over prolactin secretion (Hillard 2015). This interpretation is supported by pharmacological studies showing that dopamine receptor antagonists attenuate or abolish cannabinoid-induced suppression of prolactin (Scorticati et al. 2003). Similar effects have been observed following administration of the endocannabinoid AEA, indicating that endogenous cannabinoid signalling can engage this pathway (Scorticati et al. 2003).

The hormonal milieu strongly influences the effects of cannabinoids on prolactin secretion. In male rodents and in ovariectomized females, cannabinoid administration is generally associated with reduced prolactin secretion (Murphy et al. 1990). In contrast, in oestrogen-primed ovariectomized rats, cannabinoids can increase prolactin levels (Murphy et al. 1990; Scorticati et al. 2003). These opposing effects have been linked to differential modulation of dopaminergic activity, with evidence for reduced dopamine turnover under high-oestrogen conditions (Scorticati et al. 2003). These findings indicate that gonadal steroids substantially modify ECS–dopamine interactions.

Findings from human studies are less consistent. Acute administration of THC has been associated with modest reductions in circulating prolactin in some controlled studies (Liem-Moolenaar et al. 2010; Kleinloog et al. 2012), whereas others report no significant changes (Ranganathan et al. 2009). Variability across studies likely reflects differences in dose, route of administration, prior exposure,

and physiological state. In addition, a synthesis of available data indicates substantial heterogeneity in prolactin responses to cannabinoids in humans (Gowatch et al. 2024).

Data on prolactin regulation during pregnancy and lactation remain limited. Experimental studies in rodents indicate that cannabinoids can suppress prolactin secretion during these physiological states and interfere with prolactin responses to stimuli such as suckling (Vilela and Giusti-Paiva 2014). However, corresponding human data are scarce, and the relevance of these findings for maternal endocrine regulation remains unclear (Hillard 2015).

Overall, current evidence indicates that endocannabinoid signalling modulates prolactin secretion primarily by affecting hypothalamic dopaminergic neurons. The direction and magnitude of this effect depend on physiological context, particularly gonadal steroid status, and reflect modulation of inhibitory control rather than direct regulation of pituitary secretion.

Oxytocin and vasopressin. Secretion of posterior pituitary hormones differs fundamentally from the organisation of classical hypothalamic-pituitary axes. Oxytocin and arginine vasopressin are synthesised in magnocellular neurons of the paraventricular and supraoptic nuclei of the hypothalamus and released directly into the circulation from axon terminals in the posterior pituitary. In this system, endocrine output is closely linked to the electrical activity of magnocellular neurons rather than to an intermediate pituitary trophic signal. This organisation positions endocannabinoid signalling to influence hormone release, mainly by altering synaptic input to oxytocinergic and vasopressinergic neurons and, in some settings, by acting at the level of the posterior pituitary itself (Di et al. 2003; Luce et al. 2014; Tasker et al. 2015).

Evidence from the hypothalamic slice studies indicates that endocannabinoids regulate magnocellular neurosecretory cells in both the PVN and supraoptic nucleus (SON) through retrograde suppression of synaptic excitation. Glucocorticoids rapidly induce endocannabinoid synthesis in magnocellular neuroendocrine neurons, and the released endocannabinoid acts on presynaptic CB1 receptors to reduce excitatory glutamatergic input (Di et al. 2003; Evanson et al. 2010; Harris et al. 2019). Recent work further showed that this rapid glucocorticoid-induced response depends on sequential kinase activation, phospholipase C signalling and intracellular calcium mobilisation, and that 2-AG is likely the principal endocannabinoid involved at glutamatergic synapses (Harris et al. 2019). Importantly, oxytocin and vasopressin magnocellular neurons appear to respond to glucocorticoids in a qualitatively similar manner (Harris et al. 2019). These findings support a model, in which endocannabinoid signalling provides a rapid route through which stress-related glucocorticoid signals restrain ongoing neurosecretory activity in posterior pituitary systems.

Oxytocin itself may also recruit endocannabinoid signalling locally within magnocellular circuits. In SON magnocellular neurons, activation of postsynaptic oxytocin receptors, which are coupled to protein kinase C and calcium signalling, induces retrograde endocannabinoid release (Hirasawa et al. 2004). This observation suggests that oxytocin does not act only as a final hormonal output but can also participate in local feedback regulation of synaptic input to magnocellular neurons. A broader oxytocin–endocannabinoid interplay has also been described outside hypothalamic neuroendocrine circuits, particularly in reward-related pathways, where oxytocin-dependent modulation of synaptic transmission involves recruitment of endocannabinoid signalling (Bakos et al. 2018; Borie et al. 2022). Although these extra-hypothalamic findings do not directly address posterior pituitary hormone secretion, they support the broader concept that oxytocin can engage endocannabinoid mechanisms in a circuit-dependent manner.

More direct evidence for endocrine regulation comes from studies examining oxytocin and vasopressin secretion themselves. AEA decreased both oxytocin and vasopressin release from the neurohypophysis *in vitro*, and this inhibitory effect was reported to involve nitric oxide signalling (Luce et al. 2014). *In vivo* studies also support an inhibitory influence of cannabinoid receptor activation on posterior pituitary output. Acute administration of the cannabinoid agonist WIN55,212-2 reduced the activity of hypothalamic oxytocin neurons, lowered circulating oxytocin concentrations and was accompanied by diminished maternal care in female rats (Vilela and Giusti-Paiva 2014). Taken together, these observations indicate that cannabinoids can suppress posterior pituitary hormone release both by reducing magnocellular neuronal excitability and by acting directly at the neurohypophysis.

These findings are consistent with the physiological roles of oxytocin and vasopressin in lactation, maternal behaviour, stress adaptation, and fluid and electrolyte homeostasis. In the hypothalamus, endocannabinoid signalling has been implicated in processes such as the milk ejection reflex, hydromineral regulation and rapid glucocorticoid feedback (Harris et al. 2019). Overall, current evidence indicates

that endocannabinoid signalling modulates oxytocinergic and vasopressinergic function in a manner distinct from the regulation of anterior pituitary axes. Rather than acting mainly through hierarchical hypothalamic-pituitary signalling, endocannabinoids act at the level of magnocellular neurosecretory neurons and the neurohypophysis, where they regulate synaptic excitation, neuronal activity and hormone release. The best-supported pattern is an inhibitory influence on oxytocin and vasopressin output, particularly under conditions engaging glucocorticoid feedback or local oxytocin-dependent retrograde signalling. Even so, the available evidence remains dominated by rodent *ex vivo* and *in vivo* studies, and more work is needed to distinguish oxytocin-specific from vasopressin-specific pathways and to determine how these findings translate to human neuroendocrine regulation.

Perspective and future directions

The evidence reviewed here indicates that endocannabinoid signalling influences neuroendocrine function mainly by regulating hypothalamic and related limbic circuits rather than by directly controlling peripheral endocrine glands. Among the neuroendocrine systems discussed, the HPA axis remains the best characterised, with relatively clear links between glucocorticoid feedback and rapid endocannabinoid-dependent suppression of synaptic input to hypothalamic neurosecretory neurons. In other systems, including the HPG, HPT, and somatotropic axes, available evidence supports a modulatory role for endocannabinoid signalling. However, the underlying cellular processes remain less clearly defined and are often inferred from indirect anatomical, pharmacological, or electrophysiological findings. A similar principle appears to apply to oxytocinergic and vasopressinergic systems, in which endocannabinoids regulate magnocellular neuronal activity and hormone release at the level of synaptic integration and neurohypophyseal output. Overall, the endocannabinoid system should not be viewed as a primary endocrine driver, but rather as a context-sensitive signalling network that shapes how neural inputs are translated into hormonal responses.

Several important questions remain unresolved. First, the relative contributions of central and peripheral endocannabinoid signalling are still unclear in most neuroendocrine systems. Second, interactions between endocannabinoids and other regulatory signals, particularly glucocorticoids, gonadal steroids and metabolically relevant neuropeptides, require more precise definition, since they appear to determine both the direction and magnitude of endocrine effects. Third, although many experimental studies demonstrate robust effects on synaptic transmission and neuronal excitability, direct links between these cellular events and changes in circulating hormone levels remain limited, especially outside the HPA axis. In addition, the specific contributions of AEA and 2-AG, as well as the roles of CB1-dependent versus non-canonical signalling pathways, remain incompletely resolved in several neuroendocrine contexts.

Future studies should aim to integrate circuit-level analyses with endocrine measurements in order to connect synaptic and cellular observations with physiologically meaningful hormonal outcomes. Particular attention should be given to sex differences, reproductive state, stress exposure, metabolic status and developmental stage, as these variables are likely to shape endocannabinoid regulation in a system-specific manner. More rigorous longitudinal and translational human studies will also be needed to determine to what extent endocannabinoid signalling contributes to physiological neuroendocrine regulation under basal conditions, and in which settings it becomes especially important as an adaptive or maladaptive modulatory system.

Acknowledgments

This work was supported by the Scholarship for Excellent Researchers R2–R4, funded by the European Union – NextGenerationEU through the Recovery and Resilience Plan for Slovakia, project No. 09I03-03-V04-00442/2024/VA.

Conflict of interest: *The authors declare no conflict of interest.*

References

Atwood BK, Mackie K. CB2: a cannabinoid receptor with an identity crisis. Br J Pharmacol 160, 467–479, 2010.

Benowitz NL, Jones RT, Lerner CB. Depression of growth hormone and cortisol response to insulin-induced hypoglycemia after prolonged oral delta-9-tetrahydrocannabinol administration in man. J Clin Endocrinol Metab 42, 938–941, 1976.

Bakos J, Srancikova A, Havranek T, Bacova Z. Molecular mechanisms of oxytocin signaling at the synaptic connection. Neural Plast 2018, 4864107, 2018.

Bonnet U. Chronic cannabis abuse, delta-9-tetrahydrocannabinol and thyroid function. Pharmacopsychiatry 46, 35–36, 2013.

Borie AM, Young LJ, Liu RC. Sex-specific and social experience-dependent oxytocin-endocannabinoid interactions in the nucleus accumbens: implications for social behaviour. Philos Trans R Soc Lond B Biol Sci 377, 20210057, 2022.

Childs E, Lutz JA, de Wit H. Dose-related effects of delta-9-THC on emotional responses to acute psychosocial stress. Drug Alcohol Depend 177, 136–144, 2017.

Cota D, Steiner MA, Marsicano G, Cervino C, Herman JP, Grübler Y, Stalla J, Pasquali R, Lutz B, Stalla GK, Pagotto U. Requirement of cannabinoid receptor type 1 for the basal modulation of hypothalamic-pituitary-adrenal axis function. Endocrinology 148, 1574–1581, 2007.

Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterisation of an enzyme that degrades neuromodulatory fatty-acid amides. Nature 384, 83–87, 1996.

da Veiga MA, Fonseca Bloise F, Costa-E-Sousa RH, Souza LL, Almeida NA, Oliveira KJ, Pazos-Moura CC. Acute effects of endocannabinoid anandamide and CB1 receptor antagonist AM251 in the regulation of thyrotropin secretion. J Endocrinol 199, 235–242, 2008.

Dalterio SL, Michael SD, Macmillan BT, Bartke A. Differential effects of cannabinoid exposure and stress on plasma prolactin, growth hormone and corticosterone levels in male mice. Life Sci 28, 761–766, 1981.

Deli L, Wittmann G, Kallo I, Lechan RM, Watanabe M, Liposits Z, Fekete C. Type 1 cannabinoid receptor-containing axons innervate hypophysiotropic thyrotropin-releasing hormone-synthesizing neurons. Endocrinology 150, 98–103, 2009.

Di S, Malcher-Lopes R, Halmos KC, Tasker JG. Nongenomic glucocorticoid inhibition via endocannabinoid release in the hypothalamus: a fast feedback mechanism. J Neurosci 23, 4850–4857, 2003.

Di Marzo V, Fontana A. Anandamide, an endogenous cannabinomimetic eicosanoid: "Killing two birds with one stone." Prostaglandins Leukot Essent Fatty Acids 53, 1–11, 1995.

Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nat Rev Drug Discov 3, 771–784, 2004.

Dlugos A, Childs E, Stuhr KL, Hillard CJ, de Wit H. Acute stress increases circulating anandamide and other N-acylethanolamines in healthy humans. Neuropsychopharmacology 37, 2416–2427, 2012.

Evanson NK, Tasker JG, Hill MN, Hillard CJ, Herman JP. Fast feedback inhibition of the HPA axis by glucocorticoids is mediated by endocannabinoid signaling. Endocrinology 151, 4811–4819, 2010.

Falkenstein BA, Holley DC. Effect of acute intravenous administration of delta-9-tetrahydrocannabinol on the episodic secretion of immunoassayable growth hormone in the rat. Life Sci 50, 1109–1116, 1992.

Farkas I, Kallo I, Deli L, Vida B, Hrabovszky E, Fekete C, Moenter SM, Watanabe M, Liposits Z. Retrograde endocannabinoid signaling reduces GABAergic synaptic transmission to gonadotropin-releasing hormone neurons. Endocrinology 151, 5818–5829, 2010.

Forner-Piquer I, Giommi C, Sella F, Lombo M, Montik N, Dalla Valle L, Carnevali O. Endocannabinoid system and metabolism: the influences of sex. Int J Mol Sci 25, 11909, 2024.

Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc 86, 1646–1647, 1964.

Gorzalka BB, Dang SS. Minireview: Endocannabinoids and gonadal hormones: bidirectional interactions in physiology and behavior. Endocrinology 153, 1016–1024, 2012.

Gowatch LC, Evanski JM, Ely SL, Zundel CG, Bhogal A, Carpenter C, Shampine MM, O'Mara E, Mazurka R, Barcelona J, Mayo LM, Marusak HA. Endocannabinoids and stress-related neuropsychiatric disorders: a systematic review and meta-analysis of basal concentrations and response to acute psychosocial stress. Cannabis Cannabinoid Res 9, 1217–1234, 2024.

Gundersen TD, Jorgensen N, Andersson AM, Bang AK, Nordkap L, Skakkebak NE, Priskorn L, Juul A, Jensen TK. Association between use of marijuana and male reproductive hormones and semen quality. Am J Epidemiol 182, 473–481, 2015.

Harris C, Weiss GL, Di S, Tasker JG. Cell signaling dependence of rapid glucocorticoid-induced endocannabinoid synthesis in hypothalamic neuroendocrine cells. Neurobiol Stress 10, 100158, 2019.

Hebert-Chatelain E, Desprez T, Serrat R, Bellocchio L, Soria-Gomez E, Busquets-Garcia A, Pagano Zottola AC, Delamarre A, Cannich A, Vincent P, Varilh M, Robin LM, Terral G, Garcia-Fernandez MD, Colavita M, Mazier W, Drago F, Puente N, Reguero L, Elezgarai I, Dupuy JW, Cota D, Lopez-Rodriguez ML, Barreda-Gomez G, Massa F, Grandes P, Benard G, Marsicano G. A cannabinoid link between mitochondria and memory. Nature 539, 555–559, 2016.

Hill MN, McLaughlin RJ, Morrish AC, Viau V, Floresco SB, Hillard CJ, Gorzalka BB. Suppression of amygdalar endocannabinoid signaling by stress contributes to activation of the HPA axis. Neuropsychopharmacology 34, 2733–2745, 2009.

Hill MN, Tasker JG. Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic-pituitary-adrenal axis. Neuroscience 204, 5–16, 2012.

Hillard CJ, Farber NE, Hagen TC, Bloom AS. The effects of delta 9-tetrahydrocannabinol on serum thyrotropin levels in the rat. Pharmacol Biochem Behav 20, 547–550, 1984.

Hillard CJ. Endocannabinoids and the endocrine system in health and disease. Handb Exp Pharmacol 231, 317–339, 2015.

Hirasawa M, Schwab Y, Natah S, Hillard CJ, Mackie K, Sharkey KA, Pittman QJ. Dendritically released transmitters cooperate via autocrine and retrograde actions to inhibit afferent excitation in rat brain. J Physiol 559, 611–624, 2004.

Howlett AC, Barth F, Bonner TI, Cabral G, Casellas P, Devane WA, Felder CC, Herkenham M, Mackie, K, Martin BR, Mechoulam R, Pertwee RG. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacol Rev 54, 161–202, 2002.

Hughes CL Jr, Everett JW, Tyrey L. Delta 9-tetrahydrocannabinol suppression of prolactin secretion in the rat: lack of direct pituitary effect. Endocrinology 109, 876–880, 1981.

Kano M. Control of synaptic function by endocannabinoid-mediated retrograde signaling. Proc Jpn Acad Ser B 90, 235–250, 2014.

Kalak P, Kupczyk P, Szumny A, Gebarowski T, Jasiak M, Niedzwiedz A, Nizanski W, Dziecioł M. Molecular mechanisms of the endocannabinoid system with a focus on reproductive physiology and fertility. Int J Mol Sci 26, 7095, 2025.

Katona I, Sperlagh B, Sík A, Kafalvi A, Vizi ES, Mackie K, Freund TF. Presynaptically located CB1 cannabinoid receptors regulate GABA release from axon terminals of specific hippocampal interneurons. J Neurosci 19, 4544–4558, 1999.

Kleinloog D, Liem-Moolenaar M, Jacobs G, Klaassen E, De Kam M, Hijman R, Van Gerven J. Does olanzapine inhibit the psychomimetic effects of THC? J Psychopharmacol 26, 1307–1316, 2012.

Kola B, Farkas I, Christ-Crain M, Wittmann G, Lolli F, Amin F, Harvey-White J, Liposits Z, Kunos G, Grossman AB, Fekete C, Korbonits M. The orexigenic effect of ghrelin is mediated through central activation of the endogenous cannabinoid system. PLoS One 3, e1797, 2008.

Kozak KR, Crews BC, Morrow JD, Wang LH, Ma YH, Weinander R, Jakobsson PJ, Marnett LJ. Metabolism of endocannabinoids into prostaglandin derivatives. J Biol Chem 277, 44877–44885, 2002.

Liem-Moolenaar M, Te Beek ET, De Kam ML, Franson KL, Kahn RS, Hijman R, Touw D, Van Gerven JM. CNS effects of haloperidol on THC. J Psychopharmacol 24, 1697–1708, 2010.

Luce V, Solari JF, Rettori V, De Laurentiis A. The inhibitory effect of anandamide on oxytocin and vasopressin secretion from neurohypophysis is mediated by nitric oxide. Regul Pept 188, 31–39, 2014.

Marino M, D'Auria R, Mele E, Pastorino GMG, Di Pietro P, D'Angelo S, Della Rocca N, Operto FF, Vecchione C, Fasano S, Pierantoni R, Viggiano A, Meccariello R, Santoro A. The interplay between kisspeptin and endocannabinoid systems modulates male hypothalamic and gonadic control of reproduction *in vivo*. Front Endocrinol 14, 1269334, 2023.

Marsicano G, Lutz B. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur J Neurosci 11, 4213–4225, 1999.

Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor. Nature 346, 561–564, 1990.

Mendelson JH, Mello NK. Effects of marijuana on neuroendocrine hormones. NIDA Res Monogr 44, 97–114, 1984.

Micale V, Drago F. Endocannabinoid system, stress and HPA axis. Eur J Pharmacol 834, 230–239, 2018.

Miralpeix C, Reguera AC, Fosch A, Zagmutt S, Casals N, Cota D, Rodriguez-Rodriguez R. Hypothalamic endocannabinoids in obesity. Cell Mol Life Sci 78, 7469–7490, 2021.

Morena M, Patel S, Bains JS, Hill MN. Interactions between stress and the endocannabinoid system. Neuropsychopharmacology 41, 80–102, 2016.

Munro S, Thomas KL, Abu-Shaar M. Peripheral receptor for cannabinoids. Nature 365, 61–65, 1993.
Murphy LL, Steger RW, Smith MS, Bartke A. Effects of cannabinoids on LH and prolactin. Neuroendocrinology 52, 316–321, 1990.
Nagyova A, Jezova D, Hlavacova N. Inhibition of fatty acid amide hydrolase (FAAH) by URB597 counteracts cognitive deficit and alters neuroendocrine stress responses in male and female rats. bioRxiv 2025.12.20.695675, 2025.
Nazar B, Kairys DJ, Fowler R, Harclerode J. Effects of THC on thyroxine. J Pharm Pharmacol 29, 778–779, 1977.
O'Sullivan SE. PPAR activation by cannabinoids. Br J Pharmacol 173, 1899–1910, 2016.
Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. Endocannabinoid system in endocrine regulation. Endocr Rev 27, 73–100, 2006.
Patel S, Roelke CT, Rademacher DJ, Cullinan WE, Hillard CJ. Endocannabinoid modulation of HPA axis. Endocrinology 145, 5431–5438, 2004.
Payne KS, Mazur DJ, Hotaling JM, Pastuszak AW. Cannabis and male fertility. J Urol 202, 674–681, 2019.
Rademacher DJ, Meier SE, Shi L, Ho WS, Jarrahian A, Hillard CJ. Effects of acute and repeated restraint stress on endocannabinoid content in the amygdala, ventral striatum, and medial prefrontal cortex in mice. Neuropharmacology 54, 108–116, 2008.
Ranganathan M, Braley G, Pittman B, Cooper T, Perry E, Krystal J, D'souza DC. Effects of cannabinoids on cortisol and prolactin. Psychopharmacology 203, 737–744, 2009.
Rettori V, Wenger T, Snyder G, Dalterio S, McCann SM. THC inhibits prolactin and GH release. Neuroendocrinology 47, 498–503, 1988.
Rettori V, Aguila MC, Gimeno MF, Franchi AM, McCann SM. In vitro effect of delta 9-tetrahydrocannabinol to stimulate somatostatin release and block that of luteinizing hormone-releasing hormone by suppression of the release of prostaglandin E2. Proc Natl Acad Sci USA 87, 10063–10066, 1990.
Ryberg E, Larsson N, Sjogren S, Hjorth S, Hermansson NO, Leonova J, Elebring T, Nilsson K, Drmota T, Greasley PJ. GPR55 as cannabinoid receptor. Br J Pharmacol 152, 1092–1101, 2007.
Scorticati C, Mohn C, De Laurentiis A, Vissio P, Fernandez Solari J, Seilicovich A, McCann SM, Rettori V. Anandamide effect on prolactin. Proc Natl Acad Sci USA 100, 2134–2139, 2003.
Simon GM, Cravatt BF. Endocannabinoid biosynthesis pathway. J Biol Chem 281, 26465–26472, 2006.
Suarez J, Romero-Zerbo SY, Rivera P, Bermudez-Silva FJ, Perez J, De Fonseca FR, Fernandez-Llebrez P. Endocannabinoid system in rat brain. J Comp Neurol 518, 3065–3085, 2010.
Tasker JG, Chen C, Fisher MO, Fu X, Rainville JR, Weiss GL. Endocannabinoid regulation of neuroendocrine systems. Int Rev Neurobiol 125, 163–201, 2015.
Tretiakov EO, Hevesi Z, Boroczky C, Alpar A, Harkany T, Keimpema E. Molecular fingerprint of endocannabinoid signaling. Cells 14, 788, 2025.
Vilela FC, Giusti-Paiva A. Cannabinoid receptor agonist disrupts responses during lactation. Behav Brain Res 263, 190–197, 2014.
Wilson RI, Nicoll RA. Endogenous cannabinoids mediate retrograde signalling. Nature 410, 588–592, 2001.
Wittmann G, Deli L, Kallo I, Hrabovszky E, Watanabe M, Liposits Z, Fekete C. Distribution of CB1 receptor axons. J Comp Neurol 503, 270–279, 2007.
Ziegler CG, Mohn C, Lamounier-Zepter V, Rettori V, Bornstein SR, Krug AW, Ehrhart-Bornstein M. Expression and function of endocannabinoid receptors in the human adrenal cortex. Horm Metab Res 42, 88–92, 2010.
Zygmunt PM, Petersson J, Andersson DA, Chuang H, Sorgard M, Di Marzo V, Julius D, Hogestatt ED. Vanilloid receptors mediate vasodilation. Nature 400, 452–457, 1999.