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Review article

The underlying sex differences in neuroendocrine adaptations relevant to Myalgic Encephalomyelitis Chronic Fatigue Syndrome

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ABSTRACT

Introduction: Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME/CFS) is a complex multisystem disease characterised by severe and disabling new-onset symptoms of post-exertional malaise (PEM), fatigue, brain fog, and sleep dysfunction that lasts for at least six months. Accumulating evidence suggests that sex and endocrine events have a significant influence on symptom onset and moderation of ME/CFS, with female sex being one of the most consistent and credible predictive risk factors associated with diagnosis. Such sex differences suggest sex chromosomes and sex steroids may play a part in the development of the condition or moderation of symptoms, although this has yet to be explored in detail.

Methods/Aims: This narrative review outlines sex differences in ME/CFS in terms of vulnerability factors and clinical phenotype and explores the known sex differences in neuroendocrine systems affected in ME/CFS and how this may relate to disease risk, onset, pathophysiology, and potential treatment avenues.

Conclusions: There is clear evidence of a sex dimorphism with regards to prevalence (3:1 female preponderance), clinical phenotypes, and aetiological triggers prior to symptom onset of ME/CFS. Endocrinological events, particularly those throughout the female lifespan, are associated with ME/CFS and include reproductive menstrual cycle fluctuations, pregnancy, post-partum and perimenopause. Further, there is evidence for gonadal sex, adrenal stress and renal neuroendocrine systems as implicated in ME/CFS, including changes in estrogen, progesterone compounds, aldosterone, and cortisol levels, of which there are established sex differences. The broad effects of steroid hormones on the physiological systems may also speak to the diversity of ME/CFS symptomatology observed in patients. Further attention must be paid to sex, age, and steroid biology in ME/CFS.

1. Introduction

1.1. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex multisystem disease characterised by severe and disabling new-onset symptoms of post-exertional malaise (PEM), fatigue, brain fog, and sleep dysfunction that lasts for at least six months. A broad spectrum of accompanying symptoms are also commonly experienced, including problems with blood pressure regulation, muscle pain, tender cervical or axillary lymph nodes, and neurocognitive disability, resulting in diverse symptom presentations, illness trajectories, and prognosis (Carruthers et al., 2011). Despite the diversity of accompanying symptoms that may present, diagnostic criteria have become more stringent over the decades, ensuring a more homogenous population. The Canadian Consensus Criteria (CCC) (2003) (Carruthers et al., 2003) and the International Consensus Criteria (ICC) (2011) (Carruthers et al., 2011) are now often adopted for research purposes, both of which require PEM as a core symptom and at least one other new onset symptom from neurological, autonomic, or immune domains. Despite high prevalence rate estimates of 0.89–1.14% (Lim et al., 2020), comparable to the prevalence of multiple sclerosis, which has similar phenomenological and neuroimmune characteristics (Morris and Maes, 2013), ME/CFS remains largely under-researched, poorly resourced, and profoundly stigmatised.

The most common aetiological events reported by patients are a history of infection, stressful incident, and exposure to environmental toxins, but many aetiological triggers or 'insults' to the body are

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believed to be able to initiate and propagate the disease state (Chu et al., 2019). The most widely accepted hypothesis of disease manifestation proposes that such environmental triggers interact with an underlying susceptibility, driving dysfunction in vulnerable cardiovascular, renal, metabolic, gastro-intestinal, neurological, and immune systems. The diversity of physiological systems affected is thought to be responsible for the variable symptom expression patterns observed in different ME/CFS patients. Research has yet to find a pathogen or central dysfunction consistent in all ME/CFS patients or even a significant proportion of ME/CFS patients that could explain the disease or the variable symptom patterns. There also may be no single underlying cause for this illness and ME/CFS may serve as an umbrella term for multiple different diseases associated with overlapping symptoms (Maclachlan et al., 2017).

Even though diagnostic biomarkers have yet to be established for ME/CFS there is a large and accumulating body of evidence demonstrating a wide range of biological abnormalities in ME/CFS patients, most notably in the neuroendocrine, autonomic, neurological, metabolic, and immunological domains. There is also evidence for genetic heritability (Albright et al., 2011; Schlauch et al., 2016). The male / female ratio is approximately 1:3 (Lim et al., 2020), with estimates varying across studies with one study suggesting a ratio of 1:9 (Faro et al., 2014). The prevalence rate of ME/CFS has been challenging to estimate due to a lack of specific diagnostic tests, multiple case definitions, different methodologies, and confusion about diagnostic coding (Lim et al., 2020). Regardless, the female sex is one of the most consistent and credible predictive risk factors of a ME/CFS diagnosis (Lacerda et al., 2019). Assuming equal exposure levels of environmental insults or triggers, including infectious agents and physical stressors, and environmental toxins for all sexes, it can be proposed that genotype coupled with the host response ultimately drive the ME/CFS phenotype (Norris et al., 2017). The host response includes sex and age-specific endocrine hormone mediation, which may explain the sex and age discrepancies, although this has yet to be explored in detail.

This narrative review aims to outline sex differences in ME/CFS, in terms of vulnerability factors and clinical phenotype, and explore the known sex differences in neuroendocrine systems affected in ME/CFS and how this may relate to disease risk, onset, pathophysiology, and potential treatment avenues.

1.2. Sex differences in ME/CFS clinical presentation, onset, and aetiological triggers.

Both biological sex (defined as sex assigned at birth throughout this review, although the necessity of considering gender attributes in all diseases is noted) and age discrepancies are observed regarding ME/CFS onset and diagnosis. A study (Bakken et al., 2014) of 5,809 ME/CFS patients using Norwegian population-based registry data explored the distribution of ME/CFS incidence by sex and age. Incidence rates peaked for both males and females between the ages of 10–19-year-old, suggesting that gonadal sex and stress endocrine systems may be involved in ME/CFS. Adolescence represents a significant developmental period with considerable pubertal endocrine changes and represents a period of substantial psychosocial development. In line with this, an epidemiological study found that females had an increased risk of ME/CFS during late adolescence, while children under 12 were equal between males and females (Bakken et al., 2014). In the Norwegian based study, an additional second age peak between 30 and 39 years old was observed for females only. For females, the ages between 30 and 39 also often represent periods of rapid hormonal changes, including pregnancy and post-partum periods. Again, the increased incidence in this age group may indicate sex hormone endocrine changes or susceptibility of stressors reflecting the increased responsibilities at both work and home. Further, both adolescence and the 30–39 age bracket represent times of immune event susceptibility as direct exposures to infectious agents peak in adolescents, and subsequent reactivation of latent infections can be triggered by pregnancy or acute or chronic stressors (Faro et al., 2016).

Few studies have comprehensively investigated differences in clinical phenotypes or aetiological triggers between sex (Rubinow, 2018), mainly due to the lack of statistical power, although many studies have noted incidental findings. Differences in muscle symptoms, immunological symptoms and cardiac activity have been noted in the literature with differing rates of reported aetiological triggers between the sexes. Males report a younger onset, and fewer associated comorbidities such as fibromyalgia, osteoporosis, anxiety/ depression, and thyroid disease. 11% of women reported pregnancy or childbirth as their aetiological trigger (Wawrzkiewicz-Jałowiecka et al., 2021).

Endocrinological events, particularly those throughout the female lifespan, feature throughout the ME/CFS literature despite few studies directly investigating the link. Reproductive menstrual cycle fluctuations, pregnancy, post-partum and perimenopause involve rapid changes in gonadal sex hormones which directly and indirectly moderate metabolic and immune physiology, including changes in lipid metabolism, glucose homeostasis, energy metabolism (Bhatia et al., 2014; Gold, 2011), and the number of circulating immune cells and their responses (Panay and Studd, 1998). A prospective qualitative study of 150 ME/CFS females showed a significant percentage (42%) reported pregnancy negatively impacted their ME/CFS symptoms (Allen, 2008) which contrasts with a separate small study in ME/CFS showing 81% of women claimed to have been ‘very well’ during pregnancy, though in this latter study a high incidence of postnatal depression was reported (45% of women) (Harlow et al., 1998). Moreover, US-based ME/CFS specialists published their clinical impression that pregnancy attenuated ME/CFS symptoms to the point of remission (Boneva et al., 2015). The various responses recorded for pregnancy impact on ME/CFS may be due to failing to define symptom severity according to pregnancy stage (eg. first, second, third trimester). Each stage of pregnancy has very different hormonal and physiological environments which could be responsible for driving the change in symptoms (Chu et al., 2019).

Menopause and menstrual cycle fluctuations have also been reported to negatively impact ME/CFS symptomatology, in addition to females citing hormone-based contraception and hormone replacement therapy having a deleterious effect on their ME/CFS symptoms (Allen, 2008). It should be noted that the type of hormonal contraceptive or menopause hormone replacement therapy (oral contraceptive pills, transdermal patches, implants) were not defined, nor were the different synthetic and naturally derived estrogen and progestin formulations available. Considering menopausal and premenstrual cycle symptoms of increased fatigue, hot flushes, insomnia, and cognitive difficulties are similar to symptoms experienced in ME/CFS, it is surprising that the potential link has yet to be well explored. Five published studies have shown an association between an ME/CFS diagnosis and endocrinological and gynaecological conditions including polycystic ovarian syndrome, ovarian cysts, hyperlactatemia, pelvic pain, menstrual cycle abnormalities including amenorrhea, and early/ surgical menopause. One study reported that *a third* of their ME/CFS female patients reported endometriosis as a comorbidity, a full body condition in which cells like those in the endometrium grow outside of the uterus (Boneva et al., 2011; Boneva et al., 2019; Wolfe et al., 2018; Bakken et al., 2014; Mansfield et al., 2016).

Interestingly, sex differences and associated endocrine events mirror several other conditions that also implicate the central nervous system and also observe a female preponderance, including fibromyalgia (Hoy et al., 2012), chronic pain (Trojano et al., 2012; Petersen et al., 2020) and autoimmune disorders including multiple sclerosis (Ramagopalan et al., 2009). Epidemiological studies show that female/ male sex bias ratios are 3:2 for fibromyalgia (Hoy et al., 2012) and 2:1 for chronic widespread pain disorders (Trojano et al., 2012), both of which share high comorbidity rates with a ME/CFS diagnosis (Wawrzkiewicz-Jałowiecka et al., 2021; Voskuhl and Momtazee, 2017) Multiple sclerosis (MS), the most common autoimmune disease involving the nervous system, shares remarkable levels of similarity to ME/CFS in multiple

dimensions, including disease progression, the relapsing-remitting nature of the illness', the use of 'pacing' as an energy conservation strategy and symptomatology that includes disabling fatigue, severe exercise intolerance, orthostatic intolerance cardiac dysrhythmias, and postural hypotension (for review see [5]). The female/ male ratio in MS has been estimated to be 2.7:1 (Ramagopalan et al., 2009). As observed for ME/CFS diagnoses, following the onset of puberty, disparity changes rapidly and pubertal girls are at greater risk of developing MS than pre-pubertal girls (Ngo et al., 2014). Moreover, another major clinical observation is that pregnancy is a 'naturally occurring disease modifier' of MS associated with a 70% reduction in relapse rates in the third trimester (Jonsjö et al., 2020). Overall, women with MS who have been pregnant have a better long-term outcome than those who have not been pregnant, and this effect seems cumulative since multiparous women seem to have a better outcome than women with fewer, or who have no pregnancies (Wallis et al., 2016).

Despite sex differences in prevalence rates, comorbidities, and the clinical observation that symptom presentation changes during times of vulnerable endocrine fluctuation, few studies have directly investigated hormone-related events and medications in ME/CFS and the biological mechanisms driving these phenomena. Physiological differences between males and females have critical implications for differential susceptibility and response to various diseases, treatment efficacy and the differences in the way medications are metabolised.

Key physiological systems currently being investigated in ME/CFS have also noted sex differences including the immune system (Shan et al., 2016), gut microbiota (Thapaliya et al.), and metabolic processes. A major driver of such sex differences is thought to be system modulation via sex hormones, particulary estrogens and testosterones. Although outside the scope of this manuscript, detailed reviews on these broad topics will contribute remarkably to the ME/CFS literature. The following section will summarise the evidence of steroid hormone contribution to ME/CFS susceptibility or disease mediation, and where possible, their contribution to the modulation of biological systems, and how they may give rise to sexual dimorphism.

1.3. Steroids and Sex differences in systems affected in ME/CFS

Dysfunction of the nervous system has been postulated as one the possible causes of ME/CFS (Carruthers et al., 2011), with the World Health Organisation (WHO) classifying it as a neurological disorder. Autonomic dysfunction, including orthostatic intolerance, evidence of macro and microstructural brain changes and neuroinflammation of the brain (Nakatomi et al., 2018; Cvejic et al., 2016; Miller, 2017), in addition to neurocognitive and neuropsychological dysfunction (Kovats, 2015) all indicate involvement of the brain and nervous systems. The hypothalamus-pituitary complex, located in the diencephalon of the brain, has both neural and endocrine functions, producing and secreting many hormones. It continually adjusts according to internal and external environments using feedback mechanisms and represents a key facilitator of homeostatic function. Once the hypothalamus-pituitary signalling cascade is triggered, pituitary hormones stimulate steroidogenesis in target glands and organs.

Steroidogenesis predominately occurs in adrenal and gonadal glands (e.g., cortisol and mineralocorticoids are synthesised in the adrenal glands, estrogens in ovaries and testosterone in testis). It is also well-documented to occur in extra-glandular tissues, including the brain, adipocytes, leukocytes, skin, gut, lung, bone, heart, and thymus (Liao et al., 2015). Newly produced steroid hormones are then released into the blood circulation where they act both on peripheral target tissues and the central nervous system (CNS), consequently affecting diverse bodily functions, including blood pressure and heart rate, metabolic and immune function, body temperature maintenance, cognitive processes, the sleep-wake cycle, and emotional states (e.g. fear, pain), in addition to reproduction. Circulating steroids predominately work in a negative feedback manner, allowing systems to respond appropriately in the biological context and then self-stabilise. As such, the hypothalamus-pituitary endocrine system is one of the most important regulators of physiology across the lifespan and contributes to the vast sex differences observed. These above systems are all implicated in ME/CFS, and as such, the wholly integrated picture of a person's steroid metabolome should be explored in ME/CFS. Fig. 1 briefly summarises the broad effects of steroid hormones on the physiological systems and ME/CFS symptomatology.

Steroid hormone synthesis involves a series of enzymatic steps in the mitochondria and endoplasmic reticulum of steroidogenic tissues that convert the precursor molecule, cholesterol (a cholestane, 27 carbons), to pregnenolone (21 carbons). Pregnenolone is then catalysed into other steroids by a series of oxidative enzymes, with the resultant functional steroids determined by the gland or tissue. Steroids are broadly classified into five groups: glucocorticoids, mineralocorticoids and progestins (21 carbons) predominately synthesised in the adrenal gland, and androgens (19 carbons) and estrogens (18 carbons), predominately synthesised in the testis and ovaries, respectively. Their structures are remarkably similar with minor variations in the number of carbons and functional groups. Fig. 2 demonstrates the simplified network of steroidogenesis.

Despite their relatively simple chemical structure, steroids occur in a wide variety of biologically active forms. This variability is not only due to the extensive range of compounds secreted by endocrine glands and organs but also because circulating steroids are extensively metabolised peripherally, notably in the liver and in their target tissues, where conversion to an active form is often required before they can elicit their biological responses. Steroid metabolism is therefore important for both the production of these hormones and the regulation of their cellular and physiological actions.

1.4. ME/CFS and gonadal hormones

The 'sex hormone' endocrine hypothalamic-pituitary–gonadal (HPG) axis is a hormone-regulating mechanism containing three different component structures that operate in a coordinated fashion. Gonadotropin-releasing hormone (GnRH) is released from the hypothalamus, GnRH then stimulates the pituitary gland to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH), stimulating the gonads to produce estrogens, progesterone, and testosterone. The increase in LH and FSH during puberty induces the maturation of the gonads, leading to marked increases in estradiol and testosterone in females and males, respectively. Although concentration levels are vastly different in males, females, and intersex, it is important to note that estrogen and testosterone are synthesised and circulate in all individuals. Sex steroids, particularly in females, fluctuate significantly during the menstrual cycle and across the reproductive lifespan, particularly during puberty, pregnancy and perimenopause. Testosterone also fluctuates in a diurnal nature and also declines in male ageing, albeit with a slower decline. Sex steroids produced by the ovaries and, to a smaller extent, the adrenal glands and *de novo* in the brain, circulate throughout the body where they have effects on most organ systems, including the brain, cardiovascular (heart and vasculature), immune, reproductive (ovaries and uterus), bladder, skin, and bone. As the endocrine system broadly regulates the metabolism and development of most body cells and systems, major endocrine events, including puberty, pregnancy, and menopause-related hormone changes, can be proposed as moderating mechanisms underpinning the vulnerability of age groups and female ME/CFS pathophysiology. Although a simple relationship between absolute gonadal hormone levels and ME/CFS has not been found and is unlikely to be found due to the complexity of the integrated homeostatic steroid network that exists and the commonly cross-sectional methodology adopted, novel preclinical and clinical studies are revealing new insights of the multimodal mechanisms of these steroid hormones. Of the sex steroids, estrogens are the most studied sex steroid in relation to physiological system

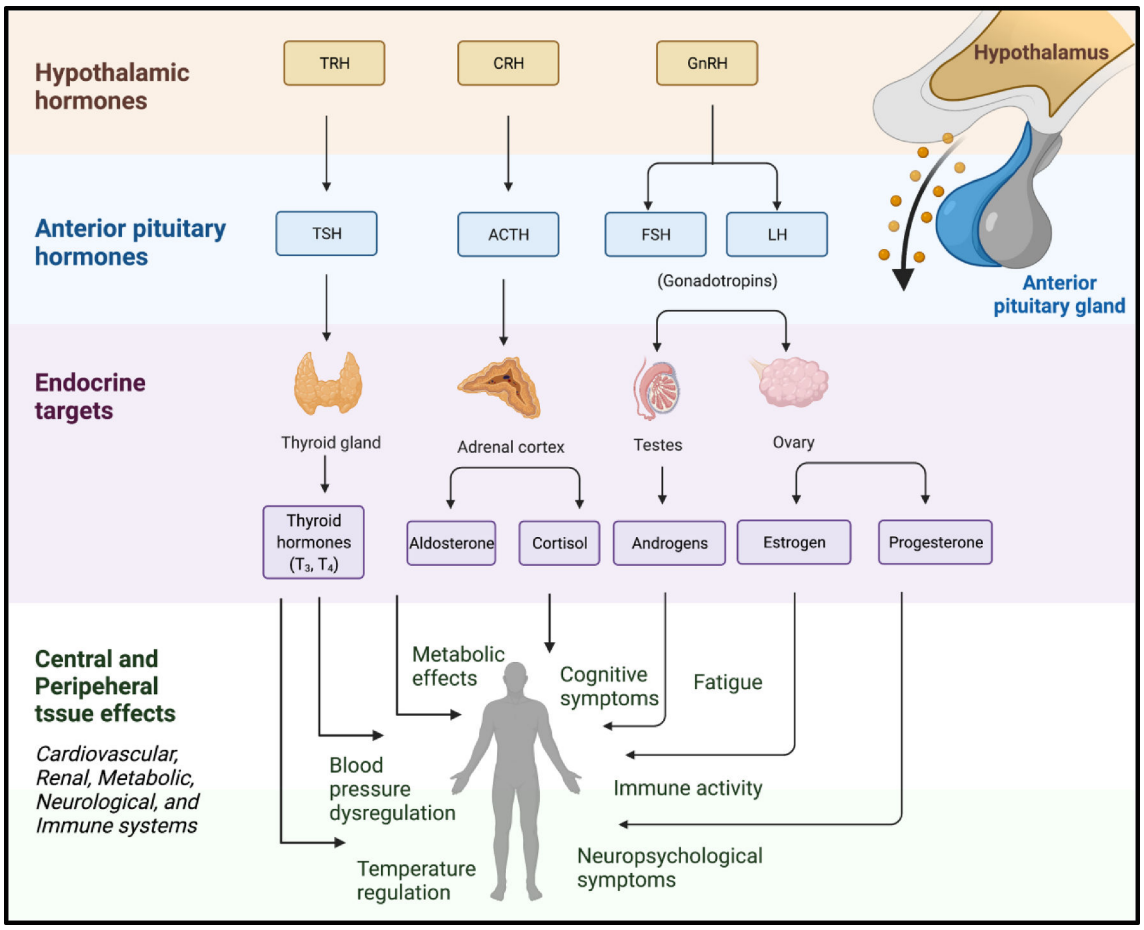

Fig. 1. Summary of the broad effects of steroid hormones on the physiological systems and Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome symptomatology. Thyroid releasing hormone (TRH), Adrenocorticotropic Hormone (ACTH); Follicular stimulating hormone (FSH); Luteinising Hormone (LH); Triiodothyronine (T3), Thyroxine (T4).

regulation and ME/CFS.

Three major endogenous estrogens that have estrogenic hormonal activity; estrone (E1), the major estrogen produced post-menopause; 17β-estradiol (E2), the predominant estrogen produced during human female reproductive years with the highest relative potency; and estriol (E3), the major estrogen produced during pregnancy. These estrogens exert their broad effect by binding to the estrogen receptors (ERs), of which there are three main types, the two nuclear receptor isoforms, Erα and ERβ and the G protein-coupled receptor, G protein-receptor 30 (GPR30). The activity of estrogen is more pronounced in those tissues where its receptors are abundant, such as the ovary, breast, brain, kidney, bone, and bone marrow. Although outside the scope of this review, ERα and ERβ have also been shown to be expressed in immune cells, where they regulate cells and pathways in both innate and adaptive immune systems (for review (Saito and Cui, 2018). ERβ is imported into the mitochondria where estrogen has been shown to enhance mitochondrial function (for review (Cevik et al., 2004) and necessary for neural transmission and modulation (for review (Murphy et al., 2004) – all which likely play critical roles in ME/CFS onset and disease progression.

Although few studies have thoroughly explored the molecular underpinnings of the HPG axis in ME/CFS, studies available do suggest a role in the pathophysiology of ME/CFS. In a small ME/CFS female population (n = 22), a higher incidence of severe premenstrual syndrome, a clinical diagnosed disabling form of premenstrual syndrome (PMS), was demonstrated (79%) with estradiol levels below clinically normal thresholds of 75 pmol/l, in 25% of the study population. FSH levels were shown to be within the normal clinical levels. Four of the females also had a low bone density at the spine and hip, suggestive of a chronic estrogen deficiency state (Harlow et al., 1998). In contrast, an earlier study found no significant differences in mean concentrations of estradiol, progesterone, FSH, and LH between ME/CFS and controls, nor when they divided up the groups into luteal and follicular phases (Jacobsen and Horwitz, 2012).

A separate study (De Nicola et al., 2018) assaying blood plasma from 20 female ME/CFS and 13 female controls obtained during the follicular phase demonstrated that progesterone and metabolites of progesterone were significantly higher in ME/CFS patients, including the allopregnanolone metabolites. The precursor, pregnenolone, was not significantly higher. Progesterone binds in the cytosol and acts via its nuclear receptor, which induces changes in gene expression through direct binding to promoter elements or through protein–protein interactions with other transcription factors (Gaignard et al., 2018). Like estrogens, progesterone plays a mediating role in the immune system (for review (Liang and Rasmusson, 2018) and can influence mitochondrial function and neuroprotection (for review (Schüle et al., 2014). Allopregnanolone is a neurosteroid metabolite of progesterone which is an allosteric modulator at gamma-amino-butyric acid $(GABA)_A$ receptors, and when sulfated, antagonises N-methyl-D-aspartate (NMDA) receptors. In this way, allopregnanolone is involved in a plethora of neurophysiological homeostatic functions, including anti-nociceptive, anticonvulsant, anti-inflammatory, sleep-promoting, memory stabilizing, anxiolytic, and neuroprotective effects (for review (Gräns et al., 2007). The elevated levels of allopregnanolone is in contrast to the consistent findings of reduced levels observed in major depressive disorder and other psychiatric disorders, including post-partum depression (Perez et al., 2019),

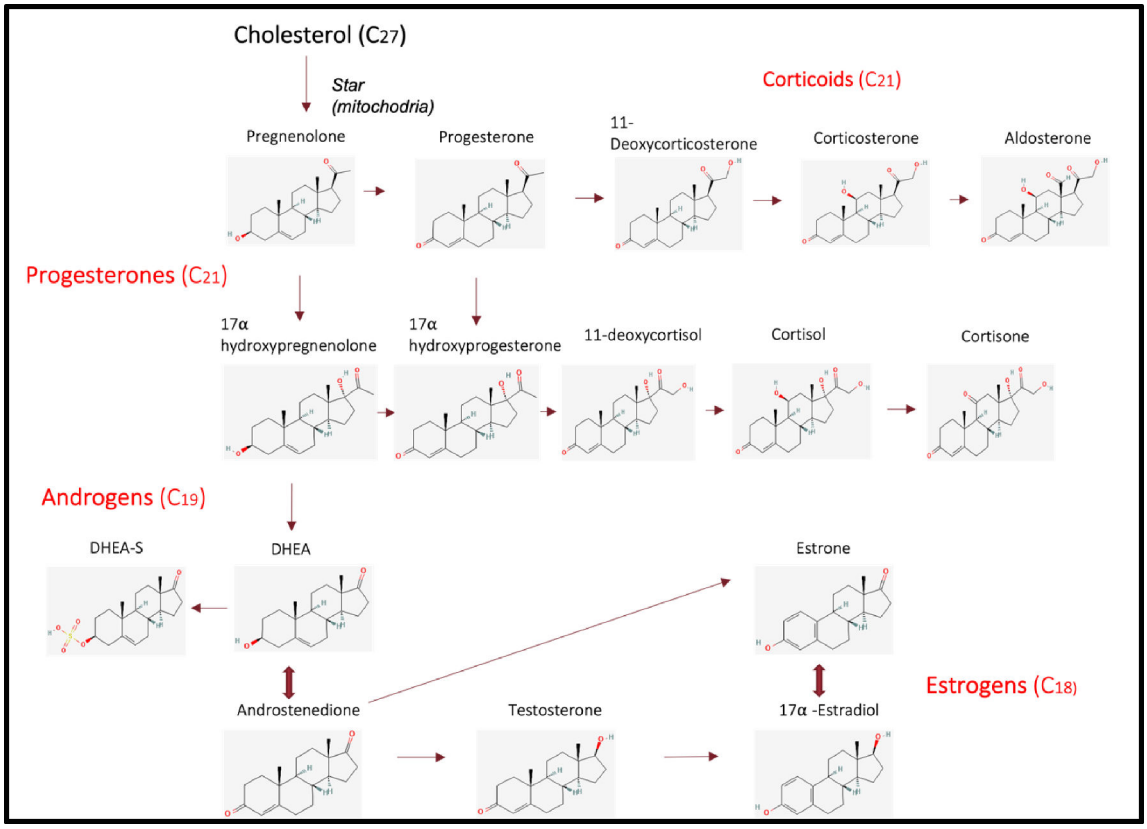

Fig. 2. Biosynthesis and metabolism pathways of steroidogenesis. Structures obtained from PubChem. Dehydroepiandrosterone (DHEA), Dehydroepiandrosterone sulphate (DHEA-S).

providing further support that ME/CFS is distinct from a neuropsychiatric disorder. At the receptor level, messenger RNA (mRNA) levels of ERβ investigated in peripheral blood mononuclear cells (PBMC) from 30 patients with ME/CFS and 36 healthy controls by quantitative real-time polymerase chain reaction, showed the ME/CFS group had significantly lower mRNA expression levels of ERβ compared with the healthy control group. No differences were observed for levels of ERα mRNA between patients and controls (Germain et al., 2020). Although important and novel in their conduct, all studies outlined consist of assays at one time point which can fail to elucidate fluctuation dysfunction over cycles and did not objectively confirm ovulation in their subjects when comparisons were made.

A genome-wide single-nucleotide polymorphism (SNP) analysis (Voskuhl et al., 2016) was conducted in 383 ME/CFS participants and compared to frequencies from a reference database. Functional analysis of SNPs identified three main clusters of pathways relevant to the immune system, metabolism, and the nuclear receptors meta pathway, which encompass hormone-related pathways including estrogen, androgen, and corticoid biosynthesis. Of the fifty most frequent deleterious SNPs found in the patient cohort compared to the reference database, ten were found to have a frequency of 70% or more in the ME/CFS group. Of this group, SNP CYP2D6 and LHB were reported. CYP2D6 is relevant to androgen and estrogen biosynthesis. LHB encodes for the β-subunit of the heterdimeric luteinizing hormone, which is a central hormone in the HPG axis, essential for stimulating the testes and ovaries to synthesise sex steroids, as defined above (Voskuhl et al., 2016).

These SNP results are largely consistent with a recent extensive mass spectrometry metabolomics analysis carried out on the plasma of 52 female subjects (26 diagnosed with ME/CFS) (MacKenzie-Graham et al., 2018). Over 1700 blood compounds spanning 20 'super-pathways' were examined. Using a statistical enrichment approach, in addition to significant differences in acyl choline metabolism and sphingolipids, three steroid classes including androgenic, progestin and corticosteroids were reduced in the ME/CFS patient cohort (MacKenzie-Graham et al., 2018).

Although no studies have investigated the clinical efficacy of sex steroids on symptom improvement in ME/CFS, a recently completed phase 2 clinical trial in women with relapsing–remitting multiple sclerosis (MS) demonstrated that estriol treatment, the pregnancy estrogen, led to improvement in the patient group defined by the preservation of localised brain grey matter (Pozzilli et al., 1999). Higher levels of estriol in the blood were also correlated with greater improvement on the paced auditory serial addition test (PASAT), a measurement of cognitive processing speed and flexibility (Pozzilli et al., 1999). This study was expanded to also demonstrate that the grey matter sparing during estriol treatment was associated with improvement in cognitive testing (Bansil et al., 1999). The results of these studies may be of value to the ME/CFS research community, as in addition to clinical similarities between the two diagnoses, there are also striking similarities at the biological level, including immune-inflammatory, metabolic pathway dysfunction and neurological imaging results (for review see (Morris and Maes, 2013). Further, serial brain magnetic resonance imaging (MRI) during follicular and luteal phases of the menstrual cycles in eight women with relapsing-remitting MS showed a significant correlation between Progesterone/β-estradiol ratios with both the numbers and volumes of lesions (Oakley and Cidlowski, 2013), and another MRI study demonstrated that MS patients with high estrogen to progesterone ratio had a significantly greater number of active MRI lesions than those with a low ratio, suggestive of estradiol and progesterone influencing disease activity (Reul et al., 2015). These studies are yet to be carried out in ME/CFS.

1.5. ME/CFS and adrenocorticoid hormones

Activation of the hypothalamus–pituitaryadrenal (HPA) endocrine axis in response to a stressor or osmotic pressure detection allows the

mobilisation of resources critical for survival. Initiated at the level of the hypothalamus via corticotrophin-releasing hormone (CRF), a signalling cascade then ensues with adrenocorticotropin hormone (ACTH) released from the anterior pituitary, followed by adrenocorticoids being synthesised from cholesterol in the adrenal cortex and released directly into the bloodstream. The adrenocorticoid steroids include corticosteroids, responsible for the endocrine stress response and increasing glucose and glycogen concentrations in the body while moderating the inflammatory response, and aldosterone, essential for the regulation of sodium homeostasis and blood volume and pressure.

The 'stress' corticosteroids (predominantly cortisol in humans) are lipophilic and consequently can readily cross the blood–brain barrier, exerting broad action at both the central nervous system level and systemic peripheral levels, where it induces or represses the transcription of a plethora of target genes (Kern et al., 2013). In this way, glucocorticoids orchestrate a vast repertoire of adjustments to adapt to external or internal changes to the environment throughout the entire body, ensuring body-wide optimal regulation of several interlinked regulatory systems, including endocrine, nervous, energy expenditure, immune, and digestive systems (Godfrey et al., 2014). As such, chronic over or under activation, as seen in disease states or chronic stress or trauma, with a chronic loss of homeostasis of the axis results in broad dysfunction common to a number of pathologies, including multiple sclerosis (Tak et al., 2011) and chronic pain sensitivity. (Powell et al., 2013) As stated above, women are at twice the risk of men for developing these disorders, likely due to sex differences in the function and regulation of the HPA axis (see below).

There is evidence for anomalous HPA endocrine stress response outputs in ME/CFS, consistent with the recognised relationship between physical trauma and psychological stressors and the onset of ME/CFS. In the context of ME/CFS, quantitative *meta*-analyses largely support hypocortisolism in ME/CFS, particularly in terms of dynamic responses to waking and variations across the day reflecting circadian activity (Nater et al., 2008; Nijhof et al., 2014). Attenuated cortisol awakening response (CAR), representing the normal physiological surge in cortisol levels upon awakening, has been shown in both ME/CFS adults (Roerink et al., 2018) and ME/CFS adolescence (Herman et al., 2016). In a recent study of female CFS patients (without comorbid depression) compared to matched controls, lower CAR levels were shown in blood and in hair cortisol concentrations, representing chronic cortisol levels. Additionally, a negative correlation was shown between pain and both CAR and hair concentrations in the ME/CFS patients but not in controls (den Boon and Sarabdjitsingh, 2017). The above-mentioned metabolomics analysis in plasma also demonstrated corticosteroids were reduced in the ME/CFS patient cohort (MacKenzie-Graham et al., 2018).

Glucocorticoids mediate their own stimulatory activity and termination via two receptors; the high-affinity type I mineralocorticoid receptor (MR) and lower affinity type II glucocorticoid receptors (GR) (Vangeel et al., 2018). The high affinity of MR to glucocorticoids is thought to be responsible for regulating tonic activity and dictates the basal circadian and ultradian rhythms observed across the day (Castro-Marrero et al., 2017). GR are found widely distributed throughout the brain, with high density found in most neurons and glia. Enhanced negative feedback response to glucocorticoids has been shown in ME/CFS. Hypomethylation of the glucocorticoid receptor gene NR3C11F region has been demonstrated, in line with HPA axis dysregulation and enhanced glucocorticoid receptor sensitivity in ME/CFS (Rincón-Cortés et al., 2019).

Cortisol levels are relevant to the core symptom of fatigue, being a key regulator of energy metabolism. High prevalence of fatigue are characterized by low cortisol levels, in conditions including Addison's disease and short-term fatigue, which both can be improved with steroid treatment. The use of cortisol steroids, including hydrocortisone and fludrocortisone, to treat ME/CFS symptoms has been attempted with noticeable improvements for some patients (Kitay, 1961). However, due to the broad, diverse range of adrenal manipulation that steroids have, the negative side effects of such steroids are considered to outweigh their benefit.

Substantial sex differences in HPA-axis dynamics and cortisol levels during regular diurnal maintenance and in response to stress are well described in the literature, which may contribute to differential vulnerability to ME/CFS between the sexes (Oyola and Handa, 2017). Much of what is known about sex differences in the HPA axis comes from studies done in rodents; in vitro models have shown that female rodents exhibit greater basal corticosterone production by the adrenal glands (Toufexis et al., 2014) and have a more robust HPA axis response to both physical and psychological stressors, thought to be a result of circulating estradiol levels (Handa et al., 2009). Clinical investigations have also provided support for the sexual dimorphism of the HPA axis stress response (Herman et al.), although they are less pronounced than seen in rodents. The HPA axis stress response in females is characterised by a larger, more sustained secretion of ACTH and cortisol, suggesting enhanced activity and reduced negative feedback (Viau, 2002). In addition, there is evidence indicating that both GRs and MRs are less sensitive to cortisol modulation in females than males, suggesting reduced feedback by autoregulation of these receptors (Roelfsema et al., 2016). Although the exact mechanism of action remains to be elucidated, estradiol has been shown to enhance HPA activity, while testosterone appears to have an inhibitory effect by acting upon the hypothalamus (De Bellis et al., 2021). In contrast, there is also evidence to indicate that estradiol, but not testosterone, heightens the cortisol-mediated negative feedback on pulsatile ACTH secretion in both aged men and women (Patel et al., 2017). Due to the nature of females more likely being diagnosed with ME/CFS, majority of the studies assessing HPA axis functioning in ME/CFS were either solely female or consisted of majority of females. No specific analysis of sex differences in HPA dynamics have been conducted in ME/CFS, and the majority of studies exclude males, presumably for recruitment feasibility due to increased female prevalence and to increase the power of experiments.

Recently, a study of 30 ME/CFS patients compared to 25 age-matched controls were evaluated for hypothalamic and pituitary autoimmunity (Nelson et al., 2019). The authors investigated antibodies against the hypothalamus (anti-hypothalamus (AHA)) and the pituitary (anti-pituitary (APA)) in people with ME/CFS. They also looked at functional impairment by looking at basal anterior pituitary hormones, including ACTH, FSH, LH, and thyrotropin, and their respective target organ hormones, including cortisol, testosterone, estradiol, free thyroxine (T4), free 3,5,3′-triiodothyronine (t3). AHA was detected in 10 (33%) and APA in 17 (56%) out of the 30 patients but in none of the 25 age-matched controls. Mirroring the studies outlined above, levels of ACTH/basal cortisol and cortisol peak levels were significantly lower in ME/CFS. Further, ME/CFS patients were divided into patients with high titres of AHA or APA ($n = 13$); middle/low titres ($n = 7$) and antibody-negative patients ($n = 10$). All those with anterior pituitary deficiencies were included in the group with severe ME/CFS, while those with normal hormonal function were included in the group with a moderate/mild form of ME/CFS, suggesting severe ME/CFS is related to impaired pituitary function caused by a strong autoimmune involvement of the hypothalamic/pituitary region. The authors suggested that in patients with ME/CFS, the onset of anterior pituitary deficiency could be the result of an autoimmune attack to selective pituitary hormone-secreting cells or by AHA to hypothalamic-releasing hormone-secreting cells potentially favoured by mediators of inflammation triggered by viral infections. Of note, all participants in this study were female. (Nelson et al., 2019).

1.6. Adrenocorticoid aldosterone steroids

The adrenal glands are also responsible for the secretion of aldosterone, activated in response to CRH from the hypothalamus and ACTH from the anterior pituitary. Elevated or relatively high plasma (blood) potassium (hyperkalemia) and low blood volume are two factors that

activate the release of CRH. The *Renin-Angiotensin-Aldosterone System* (RAAS) is a multi-hormonal system that coordinates this physiological process for the proper regulation of blood volume and pressure, composed of renin, angiotensin II, and aldosterone. In brief, these act in concert to elevate arterial pressure in response to decreased renal blood pressure, decreased salt delivery to the distal convoluted tubule, and beta-adrenergic agonism. Through these mechanisms, the body can regulate blood pressure. Aldosterone is a steroid hormone that works by stimulating the increased level of sodium reabsorption, increasing total body sodium leading to an increase in osmolarity and subsequent increase in blood and ECF volume. As a steroid, it enacts change by binding to the nuclear receptor, MR, and altering gene transcription, affecting cardiac and renal function. Excess activation of the 'activator' system leads to renal and cardiovascular disorders, such as hypertension and chronic kidney disease, and is a major risk factor for stroke, myocardial infarction, congestive heart failure, atherosclerosis, and renal failure. For review (Capdevila et al., 2021).

Cardiac dysfunction, as defined by low cardiac output or volume, has been observed in ME/CFS patients, suggesting a hypovolemic condition.

A previous *meta*-analysis provides evidence of altered cardiac autonomic regulation in ME/CFS, including heart rate variability (HRV) and cardiac output (Miwa, 2017), although the authors note they could not analyse the results based on sex due to insufficient numbers of males included in the studies. However, a recent analysis aimed to directly compare males and females when investigating HRV in ME/CFS. This study included 77 ME/CFS patients (32 men and 45 women) and 44 age-matched healthy controls (19 men and 25 women). Similar to females, male ME/CFS participants observed increased scores compared with control men in all symptoms and scores of fatigue and autonomic dysfunction. However, no differences in any HRV parameter were observed between male ME/CFS patients and controls in contrast to the findings in females, demonstrating key sex differences in HRV in ME/CFS (Aoyagi et al., 2008).

In a 2017 study (Miwa, 2017), echocardiographic examination revealed that the mean values for the left ventricular end-diastolic diameters, stroke volume index, and cardiac index, as well as the mean blood pressure, were all significantly smaller in the ME/CFS group than in a control group. Mean plasma renin activity, plasma aldosterone, and antidiuretic hormone were all significantly lower in the ME/CFS group (Miwa, 2017). These plasma differences are in line with the cardiovascular complaints shared by many ME/CFS patients, including chest pain, palpitation, temperature regulation difficulties, dizziness, and fainting. Moreover, many ME/CFS patients experience orthostatic intolerance, characterised by the inability to remain upright, which appear to be related to reduced cerebral blood flow with or without impaired cerebral circulatory autoregulation, and the compensatory activation of the sympathetic nervous system.

In 50% of patients (5/10) who were orally administered Desmopressin for five successive days, a synthetic version of arginine vasopressin which can stimulate the *RASS* system (Toering et al., 2018), symptoms of orthostatic intolerance during a 10 min active standing test was ameliorated in association with a significant increase in urinary osmotic pressure and decrease in heart rate. Furthermore, the performance status scores for the activities of daily living were improved (Shahid et al., 2021).

Orthostatic intolerance also exhibits a female preponderance, and although the study did match for sex, analysis of sex differences was not conducted. As stated by the authors, this was a consequence of a lack of power due to significantly more females recruited in the study (Miwa, 2017). Interestingly, a comparison of aldosterone and volume status in healthy young adult men and women, under strictly standardized conditions on both high- and low-sodium diets, demonstrated sex differences in the regulation of aldosterone, characterized by a higher aldosterone and a lower adrenal response to exogenous angiotensin II infusion in men, which were associated with a higher extracellular volume and blood pressure in men (Ortiga-Carvalho et al., 2016). These sex-related differences are suggestive of a protective mechanism of higher aldosterone levels in males, although it is likely that this may change across the lifespan.

1.7. ME/CFS and thyroid hormones

Like the majority of endocrine steroids, thyroid hormones affect virtually every organ system in the body, including the heart, CNS, autonomic nervous system, bone, and metabolism. In general, when the thyroid hormone binds to its nuclear receptor, it activates the genes for increasing metabolic rate and thermogenesis, increasing oxygen and energy consumption (DeGroot et al., 2015). Hypothyroidism, caused by an underactive thyroid gland, typically manifests as bradycardia, cold intolerance, fatigue, and weight gain. In contrast, hyperthyroidism caused by increased thyroid gland function manifests as weight loss, heat intolerance, diarrhea, fine tremor, and muscle weakness.

The thyroid gland, anterior pituitary gland, and hypothalamus comprise a self-regulatory circuit called the hypothalamic-pituitary-thyroid axis (HPT axis). Hypothalamic thyrotropin-releasing hormone (TRH) stimulates the synthesis and secretion of pituitary thyrotropin (thyroid-stimulating hormone (TSH)), which acts at the thyroid to stimulate all steps of thyroid biosynthesis and secretion, including thyroxine (T4) and triiodothyronine (T3) (Parra-Montes de Oca et al., 2021). Thyroid hormones are lipophilic and circulate inactive bound to transport proteins, with only a fraction of T3 and T4 unbound and active (free T3, T4). Once the target site is reached, T3 and T4 can dissociate from their binding protein to enter cells either by diffusion or carrier-mediated transport. Increased free T4 and T3 inhibit the release of TRH and TSH through a negative feedback loop. In a basel state, the HPT axis regulates energy expenditure, with energy status regulating the activity of the HPT axis. Other signalling compounds, including stress induced glucocorticoids, and dopamine also inhibit TSH production. Cold, stress, and exercise increase TRH release (DeGroot et al., 2015). After its release from the thyroid gland, T4 is converted to T3, which is the active thyroid hormone, or to Reverse T3 (rT3). (rT3) is a stereoisomer of T3 that has antagonistic properties and is biologically inactive. It is produced in the body, particularly during periods of stress. The rate and ratio of T4 conversion to either T3 or rT3 depend on the body's metabolic needs.

Symptoms of hypothyroidism include fatigue, temperature sensitivity, muscle weakness, blood pressure changes, and anxiety, which resemble common features of ME/CFS. No marked changes in thyrotropin (TSH) have been consistently demonstrated in ME/CFS patients, with the majority of patients within the clinically healthy range. However, in a recent case–control study [85] comprehensively investigating the HPT axis, 98 ME/CFS and 99 controls, age and sex-matched, demonstrated ME/CFS exhibited lower FT3, T4, T3, and T3/T4 ratios, lower protein binding of thyroid hormones, and lower 24-hour urinary iodine excretion, together with higher % rT3. Sixteen (16%) ME/ CFS patients exhibited biochemical characteristics of "low T3 syndrome" as compared to seven (7%) controls. Low T3 can be seen in a condition called non-thyroidal illness. It can occur during starvation and critical illness and is generally resolved when health is restored. To a lesser degree, it has been hypothesised to occur during any chronic illness (He et al., 2021).

Although no sex differences at any level of the HPT axis have been explicitly studied in ME/CFS compared to controls, sex dimorphisms of HPT activity have been reported on in healthy adults. Again, despite females presenting with higher incidences of HPT dysfunction than men, research on HPT axis physiology has been performed preferentially in males (d'Herbomez et al., 2005). At basal levels, serum FT4 and FT3 concentrations in males are greater than in females (Roelfsema et al., 2014). TSH varies across lifespan and healthspan, with one of the reasons thought to be due to varying estrogen levels throughout the lifespan which upregulates thyroxine binding globulin, a major plasma transporter of thyroid hormones (Uygur et al., 2018). Prior to menopause, no

differences are seen observed in serum TSH levels of health adult humans (Morris et al., 2019), however after menopause it is higher in females (Fuite et al., 2008). Appropriate analysis of sex differences in ME/CFS thyroid hormones and HPT axis physiology are desperately needed.

1.8. ME/CFS and homeostasis

Although many of the steroids and their metabolites explored in this review have largely been studied in isolation, the implicated systems are integrated, overlapping, and interdependent. In light of this fact, some networked approaches have begun to be employed with regards to ME/CFS. A computational model (Martinkovich et al., 2014) examining the regulatory relationships between HPA and HPG endocrine and immune signalling pathways in ME/CFS was derived based on signalling parameters extracted from published literature using automated natural language processing. The model comprised 28 entities and 214 regulatory edges (the relationship between two pairs of parameters). Peripheral blood samples of 43 patients with ME/CFS and in 45 healthy control subjects were also assayed for 17 targeted immune markers before, during, and after a graded exercise challenge, establishing response trajectories. Statistically significant variations in 8 of the 17 measured immune markers supported model predictions, with these 8 markers exactly matching their expression at rest in both patients with ME/CFS and in healthy control subjects. These estimates were used to define constraints for the model (Martinkovich et al., 2014). Predictions by the model of endocrine and immune markers pointed to possible context-specific overexpression in ME/CFS patients, at rest, of CRH, estrogen, FSH, and LH, gonadotropin-releasing hormone 1, and interleukin (IL)–23, and chemokine (C-X-C motif) ligand8. The model also predicted underexpression of adrenocorticotropic hormone, cortisol, interferon-γ, IL-10, IL-17, and IL-1α. As suggested by the authors, the model supported a disrupted co-regulatory network between the endocrine and immune circuitries in ME/CFS. Although HPG estradiol and progesterone were measured in the same patients and control subjects, they were not used to constrain parameter identification for the model. Based on qualitative interpretations of the literature and not from the data, a constraint requirement imposed on the model was for elevated estrogen levels and low cortisol levels applied to the ME/CFS group at rest. It is unclear how the authors confidently concluded estrogen levels would be elevated, as although our appraisal of the literature suggests dysfunction of the HPG axis, the direction of increased or decreased levels are not consistently reported (Martinkovich et al., 2014). However, this important hypothesis-generating model does support that the system network is dysregulated in ME/CFS, and suggests a validation study in patients and controls is important.

In another exploratory analysis (Gaignard et al., 2017), network mapping between 30 neuroendocrine measures and 7 immune cell gene sets were compared globally in terms of weighted graph edit distance (a measure of similarity (or dissimilarity between two graphs) in a 37 non-fatigued control population and a 39 ME/CFS population. Although the overall abundance of connections was conserved in both patient and control networks, in terms of % change in connectivity in control to ME/CFS, nodes associated with pituitary, thyroid and ovarian function generally increased their direct connectivity to the larger network in ME/CFS, whereas adrenal cortex function was uniformly less integrated. Estradiol nodes also increased connectivity in ME/CFS. Estradiol, monocyte, and neutrophil immune functional nodes were also more connected in ME/CFS, whilst NK cell and down-regulated B cell nodes dissociated from the larger network. Comparing baseline measures between groups, only two of the thirty neuroendocrine functional indicators were significantly different, with circulating aldosterone significantly higher and lower levels of unbound thyroxin (free T4) in ME/CFS. Similarly, of the 7 gene sets describing immune activation, only the CD19 + B cell up-regulated set was differentially expressed. This highlights the importance of considering networked mediators and suggests a subtle re-modelled network where homeostasis is maintained albeit with significantly altered function (Gaignard et al., 2017). ME/CFS may be characterised as an alternative homeostatic set-point driven from the failure of an initial physiological system or a spontaneous restructuring of this homeostatic network. Such changes may be indicative of ME/CFS aetiology, or the body's response to chronic illness where systems become overwhelmed and unable to normalise homeostatic physiological functioning, continuing a pattern of chronic, pathophysiological imbalance of systems.

2. Discussion

The collective evidence of sex differential mechanisms in ME/ CFS supports further exploration into gender and sex biology, both at the clinical and biological levels. ME/CFS primarily affects women, representing approximately 75% of all case diagnoses (Lim et al., 2020). Such sex differences suggest sex chromosomes and sex steroids may play a part in the development of the condition or moderation of symptoms. Puberty and the years after puberty are well-known vulnerable periods for the onset of several diseases, including autoimmune disorders (e.g. MS), fibromyalgia and pain disorders. Considering ME/CFS onset often occurs during adolescence and in reproductive years when reproductive hormones are changing dramatically, exceptionally few studies have comprehensively evaluated the impact of sex hormones (e.g. estrogen, progesterone, testosterone) and reproductive events on ME/CFS. Further, the impact of oral hormonal contraceptives and hormonal replacement therapies (HRT) on ME/CFS symptoms is yet to be formally evaluated. As there is wide variation in the type and dose of estrogens and progesterones used in commonly prescribed hormonal contraceptives and HRT, an in-depth investigation is required. Studying these potential underlying mechanisms can increase understanding of the pathophysiology and may inform novel treatment avenues. Many repurposed endocrine drugs have been applied to disease states with beneficial effects, including estrogens, progesterone, and selective estrogen receptor modulators, which have selectivity for tissues, including brain tissue (Nilsen and Brinton, 2003). Repurposing drugs in the field of ME/CFS is one way we can fast track effective treatments in a population so desperate for help.

The complexity of symptoms, in addition to the multiple organs and systems affected, makes it difficult to ascertain if ME/CFS has one underlying pathophysiological mechanism driving the diversity of symptoms or many causative contributors driving biological subgroups within the diagnosis umbrella. Multiple pathways can lead to diverse but similar grouped clinical patterns, including: (1) dysfunction of a core biological function (e.g. mitochondrial energy metabolism); (2) "top-down" dysfunction of central brain activity whereby messaging from the brain disrupts vulnerable downstream physiological systems; and (3) "bottom-up" dysfunction whereby a loss of homeostasis in the periphery driven by vulnerable systems results in an overburdened 'allostatic load'. Correspondingly, steroids have a bi-directional dependence with mitochondrial function, with the mitochondria being the first site of the first step of steroidogenesis (Wensveen et al., 2019), and with steroids influencing numerous functions of mitochondria, including energy production, oxidative stress regulation, and apoptosis (Stanculescu et al., 2021; Hatziagelaki et al., 2018). The brain is both the target of steroid action, with broad roles of brain functioning, and is the site of their *de novo* synthesis. And cross-talk and co-regulation exist between the endocrine, immune, and metabolic systems in healthy subjects (Olesti et al., 2021), critical to maintaining homeostasis, and which likely is disturbed in ME/CFS [103, 104]. The ubiquitous influence of steroid biology on many functions implicated in ME/CFS and their value in numerous theoretical frameworks relevant to ME/CFS biology further support the need for comprehensive investigations of steroids in ME/CFS.

Neuroendocrine, immunological, and metabolic metabolites tend to be highly variable and context-specific, leading to inconsistent

biomarker characteristics. Within-subject, repeated-measure study designs can overcome significant variability observed in case-controlled experiments, although these experiments are lacking in the field. The reproductive phase and menstrual cycle phase, in addition to sex, must not only be adequately controlled for but also adequately statistically compared to understand their effect on ME/CFS. In addition to sex differences in metabolism, immune, and endocrine, and intracellular signalling, males and females may achieve homeostasis by different means. Steroids are part of complicated, networked pathways of precursors, active steroids and their metabolites. Accordingly, there is a growing interest in steroidomics, an analytical technique which aims to analyse the complete representation of total steroid content [105]. Importantly, attention must be paid to sex, age, and steroid biology as ignoring these factors will prevent appropriate design implementation to understand, ameliorate, or correct symptoms of ME/CFS. Even if the identified sex differences are subtle and easily ignored, in the aggregate, they can profoundly alter phenotype, especially under stressful conditions including adolescence, pregnancy, and exercise, which in ME/CFS are key times of vulnerability. As previously stated, many studies in the field of ME/CFS exclude male participants entirely, presumably for recruitment feasibility due to increased female prevalence and to increase the power of experiments. Considering the heterogeneity of this population and the move toward 'personalised/ precision' medicine approaches by studying differences in genes, physiological systems, and environment, ignoring potential differences of half of the population seems like a lost opportunity. Critically, due to this lack of research, males with ME/CFS may present with neuro-endocrine abnormalities but which may be overlooked and untreated for years.

This review highlights the necessity of all ME/CFS research reporting outcomes by sex. Important questions that remain to be answered include: (1) is ME/CFS onset clearly associated with endocrine events; (2) are symptoms of ME/CFS moderated by steroid levels, and if so, are disturbed individual steroids or steroid network relationships responsible; (3) do different types of hormonal medications, e.g. oral contraceptives, thyroid medications, or transdermal estrogens or progesterone, as well as gender-affirming hormone therapies, exacerbate or mitigate symptoms of ME/CFS; (4) and should ME/CFS diagnosis be a consideration when practitioners prescribe oral contraceptive and hormone replacement medication. Investigating these topics will allow clinical questions relevant to ME/CFS patients during different stages of their lives to be answered and shed light on the pathophysiology of the disease with the aim to develop novel pharmacological innovations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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