



# Theory: Treatments for Prolonged ICU Patients May Provide New Therapeutic Avenues for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

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We here provide an overview of treatment trials for *prolonged* intensive care unit (ICU) patients and theorize about their relevance for potential treatment of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Specifically, these treatment trials generally target: (a) the correction of suppressed endocrine axes, notably through a “reactivation” of the pituitary gland’s *pulsatile* secretion of tropic hormones, or (b) the interruption of the “vicious circle” between inflammation, oxidative and nitrosative stress (O&NS), and low thyroid hormone *function*. There are significant parallels in the treatment trials for *prolonged* critical illness and ME/CFS; this is consistent with the hypothesis of an overlap in the mechanisms that prevent recovery in both conditions. Early successes in the simultaneous reactivation of *pulsatile* pituitary secretions in ICU patients—and the resulting positive metabolic effects—could indicate an avenue for treating ME/CFS. The therapeutic effects of thyroid hormones—including in mitigating O&NS and inflammation and in stimulating the adreno-cortical axis—also merit further studies. Collaborative research projects should further investigate the lessons from treatment trials for *prolonged* critical illness for solving ME/CFS.

**Keywords:** ME/CFS, treatment, suppressed endocrine axis, prolonged critical illness, oxidative and nitrosative stress, chronic critical care illness, non-thyroidal illness syndrome, post viral fatigue syndrome

## INTRODUCTION

Critical illness refers to the physiological response to virtually any *severe* injury or infection, such as sepsis, liver disease, HIV infection, SARS-CoV-2 infection, head injury, pancreatitis, burns, cardiac surgery, etc. generally resulting in intensive care unit (ICU) hospitalization (1). *Prolonged* or chronic critical illness—a term applied to patients that survive *severe* injury or infection but fail to start recovering after a few days—is characterized by the suppression of multiple endocrine axes, irrespective of the nature of the original infection or trauma (2–7). This endocrine suppression is, however, not readily observable in single or average measurements of circulating tropic and non-tropic hormone concentrations (which are a function of both hormone release

and elimination from the blood stream); instead measurements of the *frequency* and *amplitude* of pituitary secretions (i.e., of the *pulsatility*) performed on ICU patients as often as every 10 min over 24 h are required to reveal the endocrine suppression (8). Pro-inflammatory cytokines play a role in inducing and maintaining the uniform suppression of the endocrine axes during *prolonged* critical illness—predominantly at the level of the hypothalamus and pituitary (9–15). Moreover, reciprocal relationships between cytokines, oxidative and nitrosative stress (O&NS), and thyroid hormone *function* appear to perpetuate illness (c.f. “vicious circle”) (13, 16). These patterns are increasingly recognized as maladaptive and inhibiting patients’ recovery, thus requiring treatment independent of the initial infection or trauma (5, 17–19). Moreover, it has been suggested that the persistence of the endocrine disturbances could also explain “post-intensive care syndrome (PICS)” (20); i.e., “the cognitive, psychiatric and /or physical disability after treatment in ICUs,” including ICU-acquired weakness (21).

ME/CFS is a debilitating, multi-system disease of unclear etiology (22, 23). The most common peri-onset events reported by patients are infection-related episodes, stressful incidents, and exposure to environmental toxins (24). “Impaired function, post-exertional malaise (an exacerbation of some or all of an individual’s ME/CFS symptoms after physical or cognitive exertion, or orthostatic stress that leads to a reduction in functional ability), and unrefreshing sleep” are considered to be core symptoms (25, 26). The severity of the symptoms varies: “very severely affected patients experience profound weakness, almost constant pain, severe limitations to physical and mental activity, sensory hypersensitivity (light, touch, sound, smell, and certain foods), and hypersensitivity to medications” (27). The disease can be completely incapacitating: “at least one-quarter of ME/CFS patients are house- or bedbound at some point in their lives” (25). Patients with milder symptoms experience a significant reduction in previous levels of functioning (23). The disease progresses over time: similar to critical illness, an early hypermetabolic state may culminate in a hypometabolic state with low energy production (28). The progressive nature of the disease makes establishing a

set of diagnostic criteria or molecular markers particularly difficult. There are currently no effective treatments for ME/CFS (29–33).

In a previous publication (34) we argued that—without excluding possible predisposing genetic or environmental factors—the maladaptive mechanisms that prevent recovery in some ICU patients may also underlie ME/CFS. Specifically, these mechanisms are: (a) suppression of the pituitary gland’s *pulsatile* secretion of tropic hormones, and (b) a “vicious circle” between inflammation, O&NS, and low thyroid hormone *function*. Here we provide an overview of past treatment trials for *prolonged* ICU patients which specifically address these mechanisms. We relate similar experimental trials to improve outcomes in ME/CFS in order to highlight the similarities in the treatment approaches for both conditions. As part of this overview we also draw on findings from fibromyalgia because ME/CFS and fibromyalgia are often jointly considered in the literature (35, 36); fibromyalgia is similarly a syndrome that is medically unexplained, often comorbid with ME/CFS, and “shares the core symptoms of fatigue, sleep problems, and cognitive difficulties” (37). Finally, we also suggest potential lessons to be learned from treatment trials for *prolonged* critical illness for the quest to solve ME/CFS.

The lessons-learned from the field of critical care medicine for ME/CFS may also be particularly relevant for the aftermath of the COVID-19 pandemic. Coronaviruses are associated with persistent inflammation (38) and endocrine dysfunctions (39)—elements that are central to both the pathologies of *prolonged* critical illness and ME/CFS. Many COVID-19 patients continue to experience a variety of debilitating symptoms despite successfully defeating the virus—termed “post COVID-19 syndrome” or “long COVID-19”—that resembles ME/CFS (40–45). Moreover, a recent analysis has shown that ME/CFS patients and COVID-19 recovery patients “share molecular signatures”—evidence of overlaps in immune and metabolic dysregulation (46).

## COMPENSATION FOR AND CORRECTION OF SUPPRESSED ENDOCRINE AXES

Researchers have tried to correct suppressed endocrine axes in *prolonged* critically ill patients with the hope of reducing muscle wasting and mortality, and to aid recovery. The treatment trials can be grouped into two main approaches: (A) treatments with non-tropic *peripheral* hormones, and (B) the “reactivation” of the *central* endocrine glands. Whereas, the first approach compensates for suppressed endocrine axes by providing downstream hormones into circulation, the second approach attempts to correct the endocrine axes themselves through interventions at the central level. We briefly summarize various treatment trials for each of these two broad approaches below. For each approach we also relate similar experimental treatment trials for ME/CFS and fibromyalgia in order to highlight the similarities in the quests to cure the two conditions, and to derive lessons for solving ME/CFS.

**Abbreviations:** ACTH, Adrenocorticotropic hormone; AVP, Arginine vasopressin; CIM, Critical illness myopathy; CIRCI, Critical illness-related corticosteroid insufficiency; CRH, Corticotrophin-releasing hormone; GH, Growth hormone; GHIH, Growth hormone inhibiting hormone; GHRH, Growth hormone releasing hormone; GHRP-2, synthetic Growth hormone releasing peptide; GnRH, Gonadotropin-releasing hormone; GSH, Glutathione; HPA, hypothalamus-pituitary-adrenal axis; “Adreno-cortical axis”; HPG, Hypothalamic-pituitary-gonadal axis; “gonadotropic axis”; HPS, Hypothalamic-pituitary-somatotropic axis; “Somatotropic axis”; HPT, Hypothalamic-pituitary-thyroid; “Thyrotropic axis”; HSPs, Heat Shock Proteins; ICU, Intensive Care Unit; IDO, Indoleamine 2,3-dioxygenase; IGF-1, Insulin like growth hormone-1; IGFBP, Insulin like growth hormone binding proteins; JAK/STAT, Janus kinase—signal transducer and activator of transcription; LDN, Low Dose Naltrexone; LH, Luteinizing hormone; LHRH, Luteinizing hormone-releasing hormone; ME/CFS, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome; mtDNA, Mitochondrial DNA; NAC, N-acetylcysteine; NADH, Nicotinamide adenine dinucleotide; NTIS, Non-thyroidal illness syndrome; O&NS, oxidative and nitrosative stress; PICS, Post-intensive care syndrome; ROS, Reactive oxygen species; rhGH, Recombinant human GH; TRH, Thyrotropin-releasing hormone; TSH, Thyroid stimulating hormone; VIDD, Ventilator induced diaphragm dysfunction.

## Approach A: Treatments With Peripheral Hormones

The use of *peripheral* hormones—notably glucocorticoids and other adrenal hormones, growth hormone (GH), insulin-like growth hormone-1 (IGF-1), thyroid hormones, and a combination of these hormones—have been trialed to improve outcomes in *prolonged* critical illness as well as in ME/CFS and fibromyalgia with varied successes as described below.

### Treatments With Glucocorticoids and Other Adrenal Hormones

#### *In Prolonged Critical Illness*

Administration of large daily doses of hydrocortisone (200–300 mg) in patients during critical illness is quite common, particularly in sepsis or when cortisol levels are deemed low relative to the severity of the illness. The aim is to treat “critical illness-related corticosteroid insufficiency” (CIRCI) which is thought to “lead to an exaggerated proinflammatory response with increased tissue injury and organ dysfunction” (9, 47). Some researchers, however, have recently argued that such high doses of hydrocortisone may be counterproductive because they drive the inhibitory feedback loop inherent to endocrine axes, resulting in further central suppression of the axes (19). Moreover, large hydrocortisone doses heighten *catabolic* effects (i.e., the breakdown of molecules and tissues), especially if administered for too long [see review in (5, 48)].

#### *In ME/CFS*

Low production of adrenal hormones (i.e., partial hypoadrenalism) has been well-documented in ME/CFS (49–66). Several studies showed that a low dose of hydrocortisone could benefit ME/CFS patients, notably in reducing fatigue and disability scores [see reviews in (67, 68)]. Daily doses of 5–15 mg of hydrocortisone appear not to further suppress the adrenocortical axis (50, 69)—also called hypothalamic-pituitary-adrenal (HPA) axis—and may even improve the otherwise “blunted” responses of the pituitary to the signal from the hypothalamus (56). However, researchers have revealed that somewhat higher doses of hydrocortisone (25–35 mg per day) lead to a moderate decrease in endogenous adrenocorticotropic hormone (ACTH) and cortisol production in ME/CFS patients, via the negative feedback loop (50, 70). Consequently, there has been a debate since the late 1990s between researchers who argue that—despite improvement in symptoms—“adrenal suppression precludes the practical use of hydrocortisone” for ME/CFS patients (70), and those who stress that at low physiological doses hydrocortisone treatment for ME/CFS is safe and effective (67, 71–78).

The effects of supplementation with *other* adrenal hormones on ME/CFS symptoms has also been studied. Fludrocortisone (a corticosteroid) led to positive results in some trials (79–81), but not in others (82–84). In an uncontrolled pilot-study the supplementation with DHEA (an adrenal hormone with anabolic properties) led to a significant reduction in ME/CFS symptoms, including pain, fatigue, helplessness, anxiety, memory loss, and sexual problems (85). Finally, a recent study suggested pregnenolone sulfate (an endogenous neurosteroid derived from the adrenal hormone pregnenolone) may have therapeutic

potential to restore the Transient Receptor Potential Melastatin 3 (TRPM3) ion channel function in natural killer cells in ME/CFS (86).

In summary, glucocorticoids and other adrenal hormones are used in practice to compensate for lower endogenous hormone production in both *prolonged* critical illness and ME/CFS. Treatments aim to manage inflammation and improve symptoms. However, their use is questioned by researchers in both fields because they tend to reinforce central HPA axis suppression.

### Treatments With GH and IGF-1

#### *In Prolonged Critical Illness*

The hormone IGF-1 has been tested and applied in critical illness for decades, with positive results in reducing catabolism (i.e., muscle and protein loss), recovery of gut mucosal function, tissue repair, control over inflammatory cytokines, decreased protein oxidation, increased glucose oxidation, etc. [see review (87)]. However, research has shown that to avoid side effects doses must be physiological (i.e., not higher than regularly produced by the body). Some positive results have also occurred with administration of GH (or the synthetic version, rhGH) during critical illness [see reviews (87, 88)]. However, a large-scale double-blind randomized control study of rhGH infusions undertaken in 1999 resulted in increased mortality of critically ill patients (89). This led to the near cessation of the use of GH or rhGH in critical care. Other researchers argue that dosages in this study were too high, thereby overwhelming the negative feedback loops inherent to endocrine axes maintaining homeostasis (88). Finally, some promising trials have also been performed combining GH and IGF-1 in critical illness (90, 91). GH and IGF-1 have complementary roles in the balance between anabolic (i.e., the building of molecules and tissue) and catabolic activities (91).

#### *In ME/CFS*

There is also evidence for low GH secretion in ME/CFS (92, 93). A small placebo-controlled study found that treatment with GH injections in ME/CFS patients over 12 months was beneficial: a few of the patients were even able to resume work after long periods of sick leave (94). Evidence of relative GH deficiency in fibromyalgia (95–101) also spurred a series of placebo-controlled studies which demonstrated that GH injections over several months—in the form of physiological doses or doses adapted to increase IGF-1 to a specific level—reduced pain and improved quality of life scores in fibromyalgia patients (94, 102–105).

In summary, GH and IGF-1 have been trialed for both *prolonged* critical illness and ME/CFS with reports of beneficial outcomes. However, their use is not common in practice, notably because of the risks involved. Supplementation with these hormones also does not serve to relieve central endocrine axis suppression but would rather reinforce it.

### Treatments With Thyroid Hormones

#### *In Prolonged Critical Illness*

Clinicians already began in the late 1970s to suggest thyroid hormone supplementation for their critical patients in an

attempt to increase survival rates (106–108). This came out of a realization that these patients suffered from a depressed level of thyroid hormone activity independent of the health of the thyroid gland—termed “non-thyroidal illness syndrome (NTIS),” “euthyroid sick syndrome” or “low T3 syndrome” (109, 110). Supplementation of thyroid hormone during critical illness continues to be the subject of intense debate (111–115). Results with thyroid hormone supplementation have been mixed [see reviews (116–118)]. The type of supplement (synthetic T4 or T3), the timing of treatment and the dosage could explain the variable, but often poor outcomes. Specifically, given that thyroid hormone conversion from its “inactive” (T4) to “active” (T3) form by deiodinase enzymes is impaired during illness through the actions of pro-inflammatory cytokines (13, 16, 114, 119, 120), it has been suggested that T3 supplementation may be more effective than T4 supplementation (121–123). In fact, given that T4 *up-regulates* the enzyme (deiodinase D3) which converts thyroid hormones into “inactivated” forms and *down-regulates* the enzyme (D2) responsible for thyroid hormone conversion to the “active” forms (124, 125), any T4 supplementation could exasperate NTIS. Yet, because of the short half-life of T3 and its normal circadian rhythm (126), the timing and periodicity of any T3 administration is likely to be an important determinant of its effect (127, 128). Finally, recognizing the fact that thyroid hormone uptake (i.e., transport into cells and binding by cellular receptors) is downregulated in tissue-specific ways during critical illness (13, 113, 119, 120, 129), thyroid hormone supplementation doses may have to be supra-physiological to achieve results (130, 131). In conclusion, “at present, no evidence-based consensus or guideline advocates thyroid hormone treatment of NTIS in patients who are critically ill,” (117) but new calculated parameters derived from mathematical modeling of thyroid hormone *function* may in the future assist in identifying better therapeutic thyroid hormone interventions in patients (132).

### In ME/CFS

Recent studies suggest the existence of low thyroid hormone *function* in ME/CFS—i.e., low impact of thyroid hormone on target glands or tissues despite “normal” TSH and T4 lab results (133, 134). Thus, thyroid hormone *function* in ME/CFS resembles the “euthyroid sick syndrome” (NTIS) described in the field of critical medicine (34).

In small placebo-controlled studies in the 1990s, Lowe et al., showed that supraphysiologic dosages of T3 (75–150 mcg/day) were safe and significantly effective in the treatment of fibromyalgia: “significant improvement in clinical symptoms were recorded in T3 phases compared to baseline and placebo phases” (135–138). Given that patients had been euthyroid (i.e., their serum TSH and T4 values did not indicate hypothyroidism), Lowe suggested that “euthyroid fibromyalgia is a clinical phenotype of partial peripheral resistance to thyroid hormone” (135, 139) (i.e., the uptake of thyroid hormones by transporters and receptors in cells is disturbed). In a subsequent placebo-controlled study, Teitelbaum et al. showed that euthyroid ME/CFS and fibromyalgia patients treated with T4 (Synthroid) or naturally desiccated thyroid hormone (Armor Thyroid)—in addition to adrenal hormones,

vitamins, minerals, and antibiotics—also experienced significant improvements (140).

Moreover, for decades practitioners have been treating euthyroid patients suffering from ME/CFS and fibromyalgia symptoms with thyroid hormones (67, 73–78, 141–146); and several patients have written books to share their recovery stories (127, 147, 148). The treatments vary in the type of thyroid hormones used (e.g., natural desiccated thyroid, T3, or T4), the dosage (e.g., supra-physiological or physiological), the timing (e.g., circadian method, slow-release, or single dose) as well as the prescribed complementary vitamin and mineral supplements (149). Several practitioners emphasize the importance of providing adrenal hormones in tandem with thyroid hormones to enable the body to cope with an increase in metabolic rate (73–76). However, in the absence of a standard protocol, patients are discussing these treatment variations in a plethora of online discussion forums (149).

Several possible mechanisms have been proposed to explain positive outcomes of thyroid hormone supplementation in euthyroid patients (see section: Addressing low thyroid hormone *function*). In addition to their effects on mitochondrial activity, O&NS balance, immune function and neural activity, thyroid hormones stimulate ACTH secretion by the pituitary (127, 141, 150, 151). Supplementation with thyroid hormones might thus be directly relieving the central suppression of endocrine axes in *prolonged* critical illness and ME/CFS (see section: Reactivation of the adreno-cortical axis).

In this context it is necessary to mention that thyroid gland diseases (i.e., hypothyroidism, thyroiditis, and thyroid nodules) are frequently comorbid with ME/CFS (152–154). The standard medical practice in the case of underperforming thyroid glands is to prescribe levothyroxine (T4) with the aim of normalizing TSH levels. However, some researchers (in addition to the practitioners cited above) are increasingly warning that low thyroid hormone *function* in target cells (and associated symptoms) can persist despite the normalization of TSH levels with T4 treatment because of dysfunctions in the tissue-specific conversion and cellular uptake of thyroid hormones (132, 155–163)—particularly in the context of illness (as described above) or genetic polymorphism in thyroid hormone deiodinases and transporters (164–166). Consequently, these authors (and the many thyroid patient advocate groups around the world) promote treatments with T3 or T4/T3 combinations to ensure the adequate availability of the “active” thyroid hormone (T3) for target cells.

In summary, the use of thyroid hormones has been trialed for both *prolonged* critical illness and ME/CFS euthyroid patient groups. Although thyroid hormone supplementation suppresses endogenous thyroid hormone production via negative feed-back loops, their benefits may yet justify their use in the context of low thyroid hormone *function*. Positive results from early trials in ME/CFS and fibromyalgia—as well as anecdotal evidence described by ME/CFS practitioners and patients in numerous books—indicate that treatment for ME/CFS with thyroid hormone supplementation merits further investigation. The form of thyroid hormone supplementation (T3 vs. T4) is increasingly recognized as a determining factor in treatment success.

## Treatments With Peripheral Hormone Combinations In Prolonged Critical Illness

There is evidence that supplementation with a combination of peripheral hormones may lead to better survival and recovery in critical illness—compared to single hormone therapies. For example, the addition of GH and/or IGF-1 has been shown to mitigate the catabolic effects (e.g., protein wasting and osteoporosis) linked to high dose glucocorticoid treatments (167, 168). Moreover, critical care researchers have described the effects of hormones across endocrine axes (2, 169)—such as the stimulatory effect of GH on the T4 to T3 conversion (88) and the hypothalamic suppression of thyroid hormone production by high cortisol levels (11)—increasing the complexity in mitigating the effects of suppressed endocrine axes with peripheral hormones.

### In ME/CFS

Similarly, ME/CFS practitioners treating patients with peripheral hormones typically prescribe a combination of hormones, including thyroid hormones, adrenal hormones (e.g., hydrocortisone, prednisone, pregnenolone, DHEA, and fludrocortisone) and even gonadal hormones (e.g., testosterone, progesterone and estradiol) (67, 73–78). Generally, the justification provided for this approach is the complementarity in the function of various hormones. The interactions between endocrine axes—such as the inhibitory effect of glucocorticoid on GH release (101)—described in ME/CFS and related studies also contribute to the rationale for peripheral hormone combination therapies (170–173).

In summary, trials using combinations of peripheral hormones often report beneficial outcomes in *prolonged* critical illness and ME/CFS exceeding those of single hormone therapies. However, the complex interactions between hormones during such trials remain largely unexplored.

## Approach B: “Reactivation” of the Central Endocrine Glands

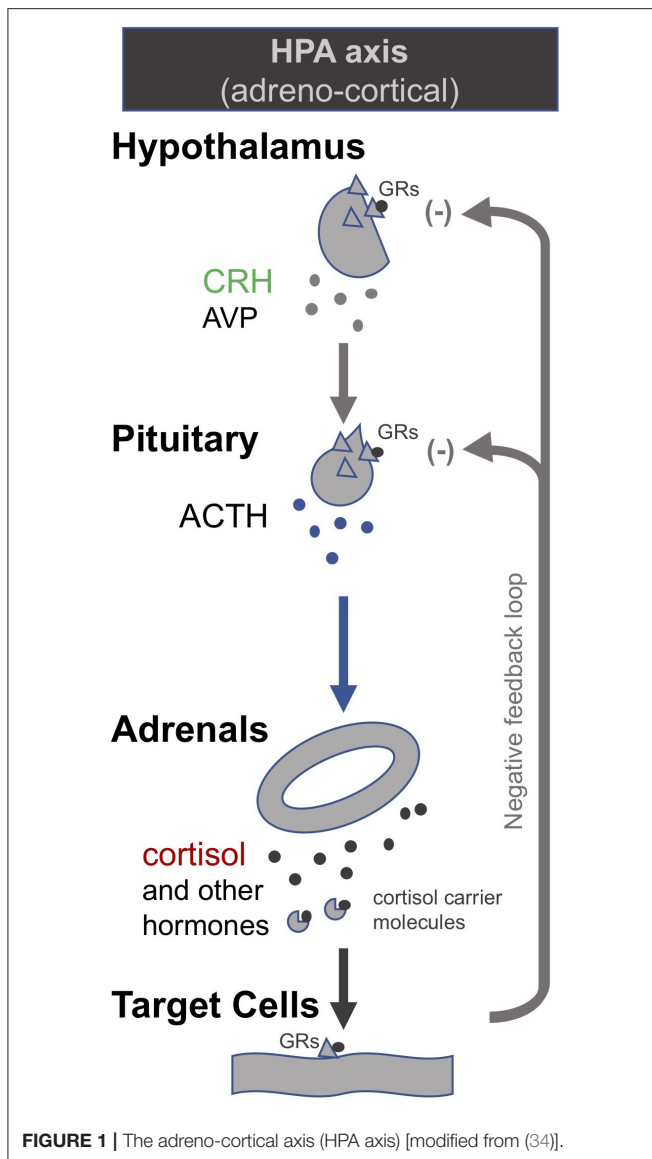
A number of critical illness researchers argue that instead of administering *peripheral* hormones, treatments to relieve suppressed endocrine axes in *prolonged* critical illness should target the central level of the endocrine axes (i.e., the pituitary and hypothalamus) (8, 19). The rationale is the following: (i) endocrine suppression during *prolonged* illness largely originates at the level of the hypothalamus (i.e., the hypothalamus is not sending the required signals to the pituitary); (ii) the pituitary and peripheral endocrine glands are in fact undamaged and could operate normally if given the signals by the hypothalamus; and (iii) by targeting the central level, treatments can avoid altering the rest of the endocrine axes—specifically, the negative feedback loops and adaptive peripheral metabolism of hormones remain intact, thus preventing the risk of toxic over-dosages. Proponents of treatments targeting the hypothalamus and/or pituitary thus argue that these may be more effective and safer than administration of the peripheral hormones. In the next paragraphs we describe trials to reactivate central endocrine glands from the field of critical medicine, and relate these to similar trials to improve outcomes in ME/CFS and fibromyalgia.

## Reactivation of the Adreno-Cortical Axis (HPA Axis) In Prolonged Critical Illness

In order to correct the suppressed HPA axes in *prolonged* critical illness, researchers have suggested stimulating the pituitary with corticotropin-releasing hormone (CRH) (174). CRH is the tropic hormone by which the hypothalamus signals to the pituitary to produce ACTH, which in turn signals to the adrenal glands to produce the various peripheral adrenal hormones (**Figure 1**). Researchers have shown that high levels of *free* cortisol during the *acute* phase of critical illness driven by peripheral mechanisms (specifically, a decrease in the abundance and affinity of the cortisol carrier molecules in circulation, and a slowing of cortisol breakdown in the liver and kidney) lead to a suppression of the release of CRH in the case of *prolonged* critically ill patients even after cortisol levels have returned to normal. Pro-inflammatory cytokines and O&NS likely play a leading role (8, 10, 18, 19, 174). Researchers liken this to the suppression of the HPA axis in patients on long-term glucocorticoid treatment. *Prolonged* critically ill patients (19, 175) and patients on long-term glucocorticoid treatment (176, 177) also both experience adrenal atrophy; it is the lack of pulsatile ACTH stimulation of the adrenal glands that results in their atrophy (178). Consequently, these critical illness researchers argue that, akin to patients that are being withdrawn from long-term glucocorticoid treatment, *prolonged* critically ill patients also require the reactivation of pituitary secretions. In the case of long-term glucocorticoid treatment, slowly weaning patients off glucocorticoids permits the pituitary to secrete ACTH which in turn promotes the regeneration of adrenals; this can take anywhere from 6 to 12 months (176, 177). In the case of *prolonged* critical illness, some researchers propose the administration of CRH may be necessary to reactivate ACTH synthesis by the pituitary (19, 174). Initial trials on *prolonged* critically ill patients show that the pituitary responds as expected to stimulation with CRH (174).

### In ME/CFS

Echoing the findings in *prolonged* critical illness, researchers have found evidence suggesting that hypoadrenalism in ME/CFS is caused by a central deficiency of CRH (50, 52, 55, 179–181). Moreover, significant adrenal atrophy has been documented in ME/CFS patients (182) and is also surmised to be present in fibromyalgia patients (98). Researchers have proposed a “bi-stability model” that serves to explain the persistence of a suppressed HPA axis in ME/CFS (183–189)—summarized in our earlier publication (34). These researchers suggest various interventions to move patients from a “low-cortisol” to a “normal-cortisol” HPA axis steady-state. In the words of one team: “a well-directed push given at the right moment may encourage the axis to reset under its own volition” (184). Some suggest artificially dropping cortisol levels even further than they already are in ME/CFS patients could be such a push (184). Models show that, given the HPA axis’ negative feedback loop, this is expected to spur an increase in ACTH secretion and, as a result, the HPA axis will naturally progress to the “normal-cortisol” HPA axis steady-state, allowing treatment to be discontinued. Similarly, others have modeled the effect of blocking the glucocorticoid receptors to reset the HPA axis



**FIGURE 1** | The adreno-cortical axis (HPA axis) [modified from (34)].

in ME/CFS patients (185). They argue that this intervention renders the “low-cortisol” steady-state unstable and thereby favors a return to the “normal-cortisol” steady-state. Finally, other researchers who have included immune system aspects in their model calculated that an initial inhibition of Th1 inflammatory cytokines (Th1Cyt), followed by a subsequent inhibition of glucocorticoid receptor function, would allow a robust return to a “normal-cortisol” steady-state in patients suffering from Gulf War Illness (186). However, given that a chronic suppressed HPA axis leads to adrenal atrophy—the result of prolonged under-stimulation of the adrenal glands by ACTH (178)—a switch to a “normal-cortisol” HPA-axis steady-state is necessarily a gradual process paced by the capacity for adrenal regeneration (190).

In this context it is necessary to mention that some researchers have administered CRH to ME/CFS patients—not in order to

assess therapeutic potential, but in order to evaluate HPA-axis dysfunction (51, 52, 56, 62, 191, 192). Several studies found that the response to CRH injection was blunted in ME/CFS patients compared to controls (i.e., ensuing cortisol or ACTH production were lower than in controls) (51, 56, 62), but this was not the case when CRH was combined with desmopressin (a synthetic analog of arginine vasopressin, AVP) which acts synergistically with CRH on the pituitary to stimulate ACTH secretion (52). Similar tests performed with fibromyalgia patients found an exaggerated ACTH response, but blunted cortisol response to CRH injection (98, 101, 170, 193). Finally, ME/CFS patients were found to have “a blunted serum DHEA response curve to i.v. ACTH injection” (54) and lower cortisol production (194). These studies generally discuss possible mechanisms for the blunted HPA axis response, including elevated levels of CRH-binding protein, enhanced sensitivity to the negative feedback of glucocorticoids (i.e., a higher abundance of glucocorticoid receptors at central level), secondary adrenal atrophy, etc. However, the therapeutic potential of CRH (or other pituitary secretagogues) to relieve the suppressed HPA axis in ME/CFS has generally not been considered.

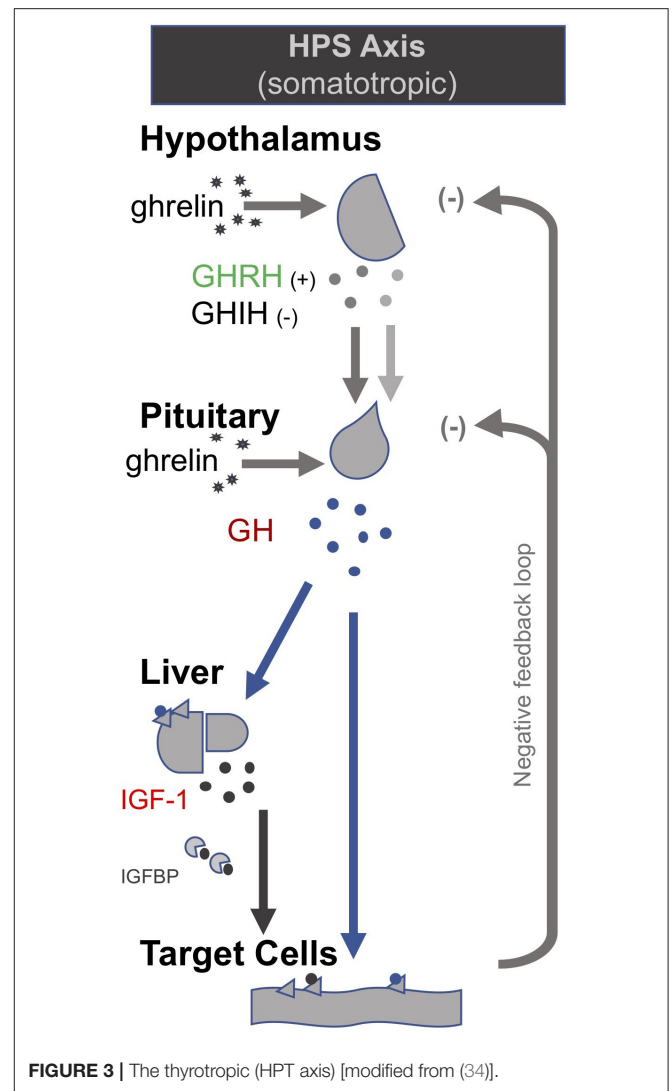
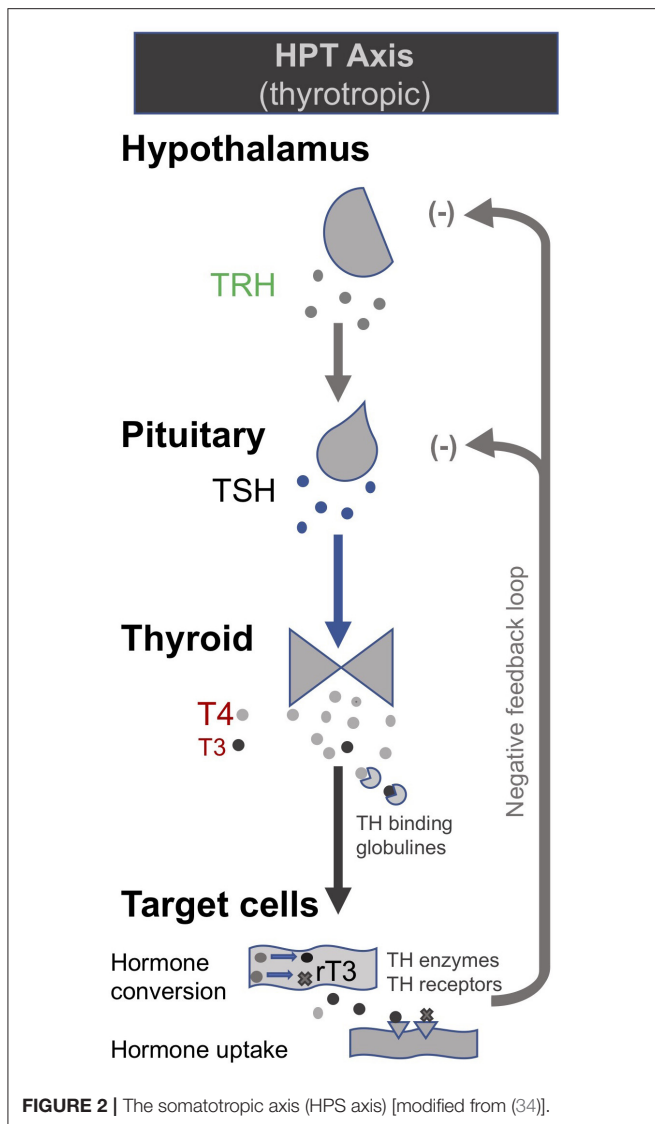
In summary, researchers in both *prolonged* critical illness and ME/CFS have sought the reactivation of the HPA axis. Researchers from the field of critical medicine suggest the use of pituitary secretagogues; ME/CFS researchers suggest that an endogenous “push” could serve to revert the HPA axis to a “normal-cortisol” steady-state. Adrenal atrophy evidenced in both conditions—a result of chronic under-stimulation of adrenals by ACTH—implies that reversing hypoadrenalism in both conditions is a gradual process.

### Reactivation of the Somatotrophic (HPS) and Thyrotrophic (HPT) Axes

#### *In Prolonged Critical Illness*

In the late 1990s van den Berghe and her team administered secretagogues that stimulate the pituitary to critically ill patients who had been in ICUs for several weeks, thereby supplementing signals produced by the hypothalamus (195, 196). Specifically, they administered thyrotropin-releasing hormones (TRH) and GH-releasing hormone (GHRH). These two secretagogues, respectively, target the hypothalamic–pituitary–thyroid (HPT) and the hypothalamic–pituitary–somatotrophic (HPS) axes. TRH stimulates the pituitary to produce thyroid stimulating hormone (TSH), which in turn signals to the thyroid gland to produce thyroid hormones (197) (Figure 2). GHRH stimulates the pituitary to produce GH which in turn stimulates the production of IGF-1 mostly by the liver (in addition to direct effects of GH on some tissues). Nearly all of the IGF-1 hormones in the plasma are bound to IGF-binding proteins (IGFBP) (198) (Figure 3). As an alternative to GHRH the researchers also trialed the use of GHRP-2, an artificial ghrelin-like peptide that also stimulates the pituitary to produce GH.

These trials showed that each of these secretagogues can reactivate the secretion by the pituitary for the relevant endocrine axis, while keeping the negative feedback loops on the pituitary intact, thus preventing overstimulation of the endocrine glands. Specifically, the administration of GHRH or GHRP-2 reactivated



the pulsatile secretion of GH by the pituitary, and the plasma concentrations of IGF-1 and IGFBP-3 increased [Interestingly, GHRP-2 had a much stronger effect than GHRH, suggesting that the inactivity of ghrelin likely plays a key role in *prolonged* critical illness (8)]. Similarly, when the team administered TRH, the pulsatile secretion of TSH by the pituitary was reactivated, and the plasma concentrations of the peripheral hormones T4 and T3 increased. However, in the latter case reverse T3 (rT3)—an *inactivated* form of thyroid hormone—also increased; this is considered problematic because rT3 contributes to low thyroid hormone *function* (see section: Addressing low thyroid hormone *function*).

Crucially, the team showed that when *prolonged* critically ill patients were treated with a combination of the secretagogues to normalize GH and TSH secretion by the pituitary (i.e., GHRH or GHRP-2 in combination with TRH), plasma rT3 concentrations did *not* increase. This is likely because GH can deactivate the D3 enzyme which converts T4 into rT3 (88), and

suggests that the normalization of the HPS axis is necessary to inhibit the production of rT3. Moreover, the administration of both secretagogues immediately inhibited *catabolism* (i.e., tissue break-down) and promoted *anabolism* (i.e., tissue building), thus halting the muscle and fat wasting of patients with *prolonged* critical illness. This has important both short- and long-term clinical consequences since the impaired neuromuscular function is considered to be the factor which most strongly correlates with the severely impaired quality of life in critical illness survivors several years after hospital discharge (199–202).

The treatments were only administered for 5 days for experimental purposes, and benefits ended a few days after the infusions were discontinued. Nonetheless, they demonstrated the possibility of reactivating suppressed endocrine axes in *prolonged* critical illness with secretagogues targeting the pituitary, as well as positive metabolic outcomes.

**In ME/CFS**

There are no comparable trials to reactivate the HPS and HPT axes in ME/CFS. One study did administer GHRH to ME/CFS

patients but only for the purpose of testing the function of the HPS axis; they found GH responses to stimulation with GHRH were no different in patients and controls, and also found no GH deficiency in ME/CFS (203). (These findings are consistent with our hypothesis that *pulsatile* pituitary GH secretions are suppressed in ME/CFS). There have, however, been attempts to reactivate pituitary GH secretions in fibromyalgia patients. Recognizing that the secretion of GH by the pituitary is controlled by both *stimulating* and *inhibiting* signals from the hypothalamus [i.e., both GH-releasing hormone (GHRH) and GH-inhibiting hormone (GHIH)], researchers treated fibromyalgia patients with pyridostigmine, a drug that inactivates the inhibiting effect of GHIH. Pyridostigmine reversed the impaired GH response to exercise in fibromyalgia patients, indicating a correction of an otherwise depressed HPS axis (97). However, it did not improve fibromyalgia symptoms (204)—this appears consistent with van den Berghe et al.'s findings described above, whereby the metabolic effects of GH only occur in combination with adequate thyroid hormone *function*. Others have administered GHRH and arginine to fibromyalgia patients—not in order to assess therapeutic potential, but in order to evaluate HPS-axis dysfunction (100).

In summary, researchers have demonstrated that the reactivation of centrally suppressed HPS and HPT axes in *prolonged* critical illness with pituitary secretagogues leads to beneficial metabolic effects. The reactivation of the HPS and HPT axes in ME/CFS for therapeutic purposes remains largely unexplored.

## Reactivation of a Combination of Endocrine Axes

### *In Prolonged Critical Illness*

Building on their earlier trials administering GHRH (or the synthetic peptide GHRP-2) and TRH in order to, respectively, stimulate the HPS and HPT axes as described above, van den Berghe et al. later also administered gonadotropin-releasing hormone (GnRH) to *prolonged* critically ill patients (205, 206). GnRH stimulates the pituitary to produce follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which in turn stimulate the gonads to produce estrogen, progesterone and testosterone (c.f. Hypothalamic–pituitary–gonadal axis: “HPG axis”; **Figure 4**). They found that the positive metabolic effect was strongest with the combination of secretagogues stimulating all 3 axes (i.e., with GHRP-2, TRH and GnRH). The authors write: “coadministration of GHRP-2, TRH and GnRH reactivated the GH, TSH and LH axes in *prolonged* critically ill men and evoked beneficial metabolic effects which were absent with GHRP-2 infusion alone and only partially present with GHRP-2 + TRH. These data underline the importance of correcting the multiple hormonal deficits in patients with *prolonged* critical illness to counteract the hypercatabolic state” (206) (**Table 1**).

### *In ME/CFS*

We are not aware of any efforts to simultaneously reactivate the pituitary secretions for a combination of endocrine axes in ME/CFS or fibromyalgia in order to improve metabolic outcomes. Researchers have injected fibromyalgia patients

simultaneously with CRH, TRH, GHRH as well as GnRH—however, this was not done in order to assess the therapeutic potential of secretagogues but to study the patients' endocrine dysfunctions (170). They found that the injection of the four releasing-hormones led to an “exaggerated” ACTH secretion compared to controls; this was not the case when CRH was administered alone [see above (101)]. They also highlighted the inhibitory effects of CRH on TSH and GH secretion. These results appear consistent with van den Berghe's findings that a combination of secretagogues most effectively improve metabolic outcomes during *prolonged* critical illness.

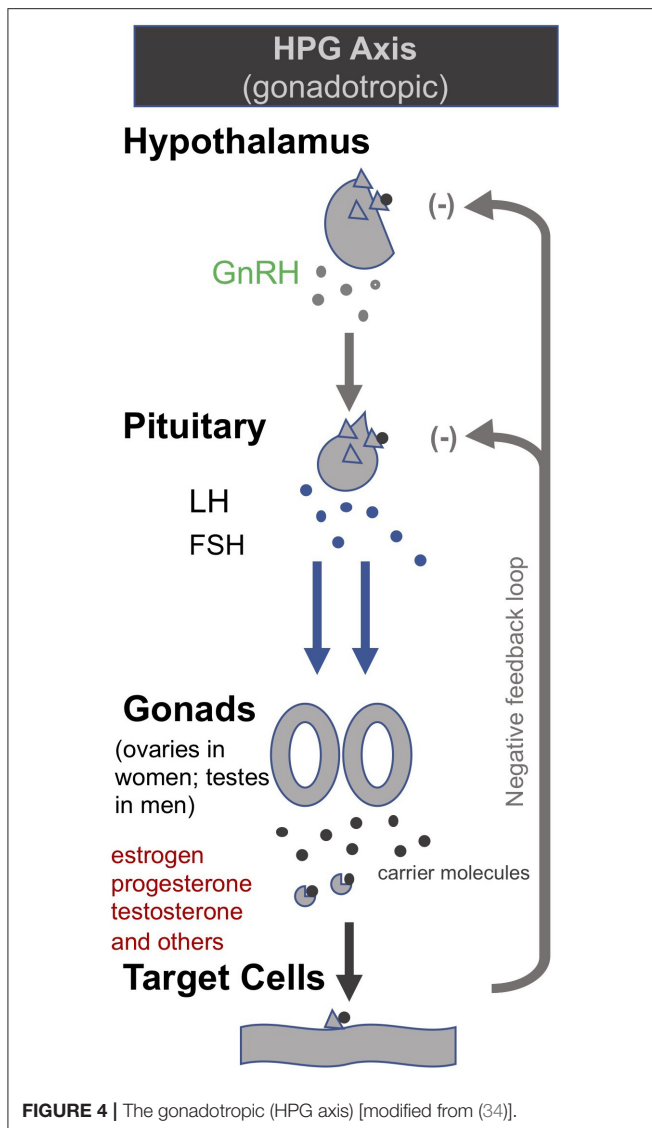
In summary, researchers have demonstrated that the concurrent reactivation of HPS, HPT and HPG axes with pituitary secretagogues in *prolonged* critical illness leads to greater beneficial metabolic effects than reactivation of just one or two of the axes. The concurrent reactivation of endocrine axes in ME/CFS for therapeutic purposes remains largely unexplored.

## Intermediate Conclusions

There are important similarities in the efforts to correct endocrine suppression in *prolonged* critical illness and ME/CFS (**Table 2**). For both conditions, researchers have trialed supplementation with peripheral hormones, including hydrocortisone, GH and IGF-1, and thyroid hormone (including T4 and T3). Evidence exists of some benefits from these treatments for patients suffering from either illness, particularly when given in combination. However, difficulties with finding optimal dosing and risks of causing harm to patients have contributed to controversies and limited their application for both *prolonged* critical illness and ME/CFS. Moreover, administration of these peripheral hormones exacerbates central suppression of the respective endocrine axes.

Researchers of *prolonged* critical illness have also trialed to reactivate endocrine axes at the central level. Unlike treatments with peripheral hormones, such an approach has the benefit that it addresses the central suppression of endocrine axes directly, and that peripheral endocrine glands are stimulated—this is particularly important for the adrenal glands which without stimulation by ACTH go into atrophy. Given that negative feedback loops and peripheral hormone metabolism remain intact, proponents argue that the approach is safer and more effective for restoring normal endocrine function. Trials on *prolonged* critical illness patients to reactivate pituitary secretions with secretagogues including CRH, GHRH (or the synthetic GHRP-2), and GnRH have had important initial successes not only in restoring *pulsatile* pituitary secretions of ACTH, GH, and LH, respectively, but also in achieving positive metabolic effects when administered in combination. Moreover, these trials also offer revelations about the interactions between the endocrine axes—including the insight that deleterious production of rT3 can be mitigated through the simultaneous reactivation of the HPT and HPS axes. These lessons-learned from the field of critical illness can complement and inform ME/CFS research. ME/CFS researchers, in turn, have proposed interventions to reactivate the HPA axis based on a “bi-stability model” with two HPA axis steady-states. However, the simultaneous reactivation of the endocrine axes in ME/CFS remains unexplored. The





potential of treatments with pituitary secretagogue to correct central endocrine axes suppression—and to enable the reversal of secondary adrenal atrophy—should be assessed for ME/CFS.

## INTERRUPTION OF THE “VICIOUS CIRCLE”

Critical illness researchers have proposed a model for how *prolonged* critical illness is perpetuated by reciprocal relationships between inflammation (notably pro-inflammatory cytokines), O&NS and reduced thyroid hormone *function* (13, 16). Simplified, this model suggests that (i) cytokines depress thyroid hormone *function*; (ii) low thyroid hormone *function* contributes to O&NS; and (iii) O&NS in turn stimulates the production of pro-inflammatory cytokines, thereby completing a “vicious circle.” Moreover, reciprocal relationships between these elements and the suppressed endocrine axes [e.g.,

pro-inflammatory cytokines suppress ACTH release (9, 10); weakened adrenals permit excessive inflammatory responses] contribute to perpetuate a hypometabolic and inflammatory state (208), and thus help to explain why some critically ill patients fail to recover. Crucially, the same elements of such a “vicious circle” have also been documented in ME/CFS (134, 209–216)—as described in our earlier publication (34).

Treatment trials to improve survival and recovery from *prolonged* critical illness have often targeted one of the elements of this “vicious circle.” In the following paragraphs we provide an overview of these various treatment trials using the “vicious circle” as a framework. We also relate analogous experimental treatments for ME/CFS and fibromyalgia in order to highlight the similarities in the quests to cure both *prolonged* critical illness and ME/CFS, and to derive lessons for solving ME/CFS.

## Addressing Low Thyroid Hormone Function

### In Prolonged Critical Illness

As described above (section: Treatments with thyroid hormones), clinicians began, as early as the 1970s, to suggest thyroid hormone supplementation for critically ill patients. The rationale was to correct what some considered a *maladaptive* hypometabolic state which was preventing recovery following *severe* infection or injury (106–108). Again, this approach remains controversial (111–115). Interestingly, there has been little research into pharmacological agents to correct the peripheral mechanisms, which to a large extent underpin the low thyroid hormone *function* during critical illness: i.e., the alterations in cellular thyroid hormone transporters, receptors, and (most crucially) deiodinases that convert thyroid hormones into their “active” and “inactivated” forms. Targeting these deiodinases could theoretically be an avenue for alleviating low thyroid hormone *function* during *prolonged* critical illness (217).

### In ME/CFS

As described above, there are accounts of positive effects of thyroid hormone supplementation to address low thyroid hormone *function* in euthyroid ME/CFS and fibromyalgia (67, 73–78, 127, 135–145, 147, 148). Proponents generally believe that thyroid hormone supplementation serves to compensate for dysfunctions in the conversion of thyroid hormones (from “inactive” to “active” forms) and/or uptake at cellular level (139, 218–223), notably associated with inflammation in ME/CFS or fibromyalgia (224, 225).

However, the mechanisms by which positive metabolic effects were achieved with thyroid supplementation in ME/CFS or fibromyalgia are not entirely clear. Rat models show that T3 and T2 thyroid hormone injections can repair mitochondrial DNA (mtDNA) damage resulting from oxidative stress (226). In cells of patients with mtDNA mutations, administration of T3 led to a *reduction* in reactive oxygen species (ROS) production (i.e., oxidative stress) and a *reduction* in cytoplasmic Ca<sup>2+</sup> (allowing for cellular signaling/regulation of enzymes and proteins). Moreover, cytochrome c oxidase activity (involved in ATP production) and ATP levels were increased. T3 also restored the mitochondrial membrane potential, complex V activity,

**TABLE 1** | Summary of the treatment trials to reactivate the pituitary in *prolonged* critical illness as described by van den Berghe et al. (195, 196, 205, 206).

Target	Secretagogues used to stimulate the pituitary	Results in <i>prolonged</i> critical illness
HPT Axis	<b>TRH</b> (which stimulates the pituitary to produce TSH, in turn stimulating the thyroid gland)	<b>Reactivation of the HPT Axis</b> Normalized TSH secretion by pituitary Normalized T4 and T3 levels <i>Increased RT3</i>
HPS Axis	<b>GHRP-2</b> (artificial ghrelin mimetic which stimulates the pituitary to produce GH)  <b>GHRH</b> (which stimulates the pituitary to produce GH)	<b>Reactivation of the HPS Axis</b> Normalized GH secretion by pituitary Normalized IGF-1 and IGFBP-3 levels  <b>Reactivation of the HPS Axis</b> Lower pituitary reactivation response than with GHRP-2
Combination HPS + HPT Axes	<b>GHRP-2 + TRH</b>	<b>Reactivation of the HPS and HPT Axes</b> Normalized GH secretion by pituitary Normalized IGF-1 and IGFBP-3 levels Normalized TSH secretion by pituitary Normalized T4 and T3 levels <b>RT3 levels do not increase!</b> <b>-&gt; Inhibit catabolism and promote anabolism</b>
Combination HPS + HPT + HPG Axes	<b>GHRP-2 + TRH + GnRH</b> (GnRH stimulates the pituitary to produce LH and FSH; trialed with men)	<b>Reactivation of the HPS, HPT and HPG Axes</b> As above and also normalized LH secretion by the pituitary <b>-&gt; Strongest beneficial metabolic effect</b>

**TABLE 2** | Summary of treatments proposed and trialed to correct for suppressed endocrine axes in critical illness, and ME/CFS and fibromyalgia.

Target	Approach A: Treatments with peripheral hormones	Approach B: “Reactivation” of the central endocrine glands
HPA Axis (adrenals)	<b>Prolonged critical illness:</b> High dose hydrocortisone (5, 48)  <b>ME/CFS or fibromyalgia:</b> Low dose hydrocortisone [see reviews (67, 68)], fludrocortisone (79–84), DHEA (85), and pregnenolone (proposed) (86).	<b>Prolonged critical illness:</b> Administration of CRH to stimulate pituitary ACTH secretion (proposed) (174)  <b>ME/CFS or fibromyalgia:</b> - Suppress cortisol levels to reactivate ACTH secretion (modeled) (184) - Blocking of central glucocorticoids receptors (GRs) (modeled) (185) - Inhibition of Th1 cytokines followed by inhibition of GRs (modeled for Gulf War Illness) (186)
HPS Axis (growth hormone)	<b>Prolonged critical illness:</b> Supplementation with GH and IGF-1 [see reviews (87, 88, 90, 91)]  <b>ME/CFS or fibromyalgia:</b> Supplementation with GH and IGF-1 (94, 102–105)	<b>Prolonged critical illness:</b> Administration of GHRH and GHRP-2 to reactivate pituitary secretion of GH (195, 196)  <b>ME/CFS or fibromyalgia:</b> Drug to inactivate GH inhibiting hormone (GHIH) (97, 204)
HPT Axis (thyroid)	<b>Prolonged critical illness:</b> Supplementation w/thyroid hormones [see reviews (116, 117)]  <b>ME/CFS or fibromyalgia:</b> Supplementation w/thyroid hormones (natural desiccated thyroid, T4, T3) (135–140) Anecdotal: (67, 73–78, 127, 141–145, 147, 148)	<b>Prolonged critical illness:</b> Administration of TRH to reactivate pituitary secretion of TSH (195)  <b>ME/CFS or fibromyalgia:</b> none?
HPG Axis (gonads)	<b>Prolonged critical illness:</b> anabolic steroid (e.g., testosterone) (207)  <b>ME/CFS or fibromyalgia:</b> as part of combined treatments (see below)	<b>Prolonged critical illness:</b> Administration of GnRH to stimulate pituitary release of LH (in men) (206)  <b>ME/CFS or fibromyalgia:</b> none?
Combination of axes	<b>Prolonged critical illness:</b> GH and IGF-1 in addition to hydrocortisone (167, 168)  <b>ME/CFS or fibromyalgia:</b> Thyroid hormone + adrenal hormones (+ gonadal hormones) (67, 73–78)	<b>Prolonged critical illness:</b> TRH + GHRP-2 + GnRH (see Table 1. above) (206)  <b>ME/CFS or fibromyalgia:</b> none?

and levels of manganese superoxide dismutase (an essential mitochondrial antioxidant enzyme). The authors conclude that “the results suggest that T3 acts to reduce cellular oxidative stress, which may help attenuate ROS-mediated damage, along with improving mitochondrial function and energy status in cells with

mtDNA defects” (227). In theory, T3 supplementation could have similar impacts on relieving O&NS and improving mitochondrial function in *prolonged* critical illness and ME/CFS.

Moreover, T3 (but not T4) administration also stimulated Na-K-ATPase activity in rat models through non-genomic

pathways (the activity of this enzyme is critical for maintaining cellular ion gradients) (228). Others have found that T3 and T4 supplementation selectively affect GABA-evoked neurotransmission in rat models thus possibly producing profound alterations in brain activity (229, 230). In addition, it has been shown that thyroid hormones also have a neuroprotective effect (231) and regulate neurotransmission (232, 233). Moreover, clinical manipulation of thyroid hormone levels also modulates immune functions (234–237). Yet others have shown that T3 treatment of human cells caused decreased viral replication (238). Finally, as mentioned above, thyroid hormones also have a stimulatory effect on the HPA axis.

In summary, there is a history of clinicians in both the fields of critical illness and ME/CFS advocating for the use of thyroid hormones supplementation in euthyroid patients. Thyroid hormones affect mitochondrial activity, O&NS balance, immune function, neuroactivity, and stimulate ACTH secretion. The mechanisms by which supplementation with thyroid hormone can promote recovery from *prolonged* critical illness and ME/CFS require further investigations. Again, the form of thyroid hormone (T4, T3, or T2) appears to be a determining factor in physiological effects of treatments. The use of pharmacological agents to correct dysfunctions in the peripheral pathways of thyroid hormones remains unexplored in both illnesses.

## Addressing Oxidative and Nitrosative Stress

### In Prolonged Critical Illness

There have been a few trials to restore oxidative balance during critical illness, often with the aim of improving thyroid hormone *function* (i.e., relieving NTIS). In one case, researchers found that treating patients of acute myocardial infarction with n-acetylcysteine (NAC)—a precursor to the antioxidant glutathione (GSH)—could virtually eliminate the decrease in serum T3 levels and prevent the increase in serum rT3 which are characteristic of NTIS (239). They propose that supplementation with NAC relieves the competition for GSH between the thyroid hormone deiodinase and antioxidant enzymes, which would otherwise negatively affect thyroid hormone conversion and enable O&NS. Likewise, controlled experiments showed that administration of sodium selenite on human cells reduces cytokine-induced oxidative stress (240), and supplementation with selenium is associated with modest normalization of thyroid hormones during critical illness (241). Thus, *in-vivo* supplementation might similarly relieve competition for selenium required in the production of both thyroid hormone deiodinase and antioxidant enzymes.

Furthermore, cytokine-activated oxidative stress induced post-translational modifications and loss of the molecular motor protein myosin are important pathophysiological mechanisms underlying the severe muscle dysfunction and muscle wasting associated with the critical illness myopathy (CIM) and the ventilator induced diaphragm dysfunction (VIDD) observed in both experimental and clinical ICU studies in response to long-term mechanical ventilation and immobilization (242–246). Administration of the chaperone co-inducer BGP-15

upregulates Heat Shock Proteins (HSPs) and mitigates the muscle dysfunction associated with CIM and VIDD (247–249). This is consistent with HSP protection of muscle cells against the damaging effects of reactive oxygen species during exercise (250). Besides upregulating HSPs, BGP-15 also acts as a membrane stabilizer, protects mitochondria, and has anti-inflammatory effects (251). The anti-inflammatory effects are of specific interest since activation of the JAK/STAT signaling pathway has been reported in respiratory and limb muscles in both experimental and clinical ICU studies (252, 253). The JAK/STAT pathway is a signaling pathway for a wide range of cytokines and growth factors and its activation is a common feature of muscle wasting induced by the cytokine IL-6 (254). Previous anti-inflammatory interventions with BGP-15, the JAK1/2/STAT3 inhibitor Ruxolitinib, and the prednisolone analog Vamrolone have all shown positive effects on limb and respiratory structure/function (252, 253, 255).

### In ME/CFS

Addressing antioxidant status is a common approach of some ME/CFS practitioners (73, 74, 211), notably with the aim of preventing mitochondrial damage (256). Pall—who described a “vicious cycle” between inflammation and oxidative stress in ME/CFS more than a decade ago (211, 257)—developed a treatment protocol based on a variety of antioxidants and anti-inflammatory agents. Moreover, placebo-controlled studies have shown that CoQ10—an important antioxidant in mitochondria—is beneficial to ME/CFS patients when provided in combination with the coenzyme NADH (258, 259). Following early positive results, a study is currently ongoing to determine the efficacy of NAC in neuroprotection against oxidative stress in ME/CFS symptoms (260). Furthermore, a placebo-controlled trial of the herbal medicine myelophil—with antioxidant and immunomodulatory properties—has had promising results in alleviating ME/CFS symptoms; the benefits may also derive from its modulatory effects on the HPA axis (68, 261).

Finally, akin to critical illness, it has been suggested (but not yet trialed) to incorporate the upregulation of HSP into future treatments for ME/CFS (262). Studies have shown that ME/CFS is also characterized by impaired HSP production (263) which—combined with O&NS and low-grade inflammation—could explain muscle dysfunction and exercise intolerance (264, 265).

In summary, there have been a few trials to mitigate O&NS in both *prolonged* critical illness and ME/CFS patients. This includes the use of various antioxidants and mitochondrial supports to rebalance oxidative stress, and the use of HSP to lessen the negative effects of O&NS. There is evidence of some beneficial results, but effects may be insufficient to interrupt detrimental and possibly self-perpetuating mechanisms.

## Addressing the Production of Pro-inflammatory Cytokines and Inflammation

### In Prolonged Critical Illness

As described above, clinical practitioners regularly seek to manage inflammation during critical illness—particularly in the

event of sepsis (see section: Treatments with glucocorticoids). Considering the relationship between pro-inflammatory cytokines and thyroid hormone *function* (9–15, 266), some researchers have tried unsuccessfully to cure NTIS (i.e., restore normal thyroid hormone *function*) by blocking IL-1 cytokine receptors (267). The unsuccessful result is perhaps not surprising, given that “cytokines are related to each other in a very complex network, and regulate positively or negatively the expression of other cytokines; it is, therefore, difficult to imagine how to interrupt this interplay and cascade of events” (268). Critical care researchers also debate using antivirals (269, 270) to treat viral reactivation observed in ICU patients (271–273).

Related to inflammation, a group of researchers has suggested inhibiting the kynurenine pathways during critical illness (274). In conditions of inflammation the indoleamine 2,3-dioxygenase (IDO) (which metabolizes tryptophan into kynurenine) is upregulated, and the kynurenine pathway preferentially produces neurotoxic metabolites (such as quinolinic acid) (274, 275). Increased kynurenine plasma levels thus precede the development and persistence of sepsis in critically ill patients (276, 277), and is associated with lower survival in ICU patients (274). Moreover, elevated kynurenic acid (also a metabolite of kynurenine) is associated with myelin damage leading to neuronal and cognitive dysfunction in critical illness (278). Based on the therapeutic literature from other diseases (275, 279–282), the critical illness researchers suggest inhibiting the IDO enzyme in order to curtail the production of neurotoxic kynurenine pathway metabolites.

### In ME/CFS

Echoing the approaches in critical care, practitioners and researchers have also long sought to manage inflammation in ME/CFS (29, 73, 211). Trials include the use of Nexavir (Kutapressin) to reduce inflammation (283) as well as the administration of Low Dose Naltrexone (LDN) (284, 285) and IL-1 receptor antagonist (anakinra) (286) to reduce pro-inflammatory cytokines. There is evidence of some positive benefits from anti-inflammatory treatments for ME/CFS patients, notably with LDN.

Researchers have also trialed treatments which could have an indirect effect on inflammation. These include the use of cyclophosphamide (287) and monoclonal antibodies (rituximab) (288) which suppress the immune system, as well as immune adsorption (IgG depletion) and plasmapheresis (filtration of blood plasma) to reduce antibodies (289). Others have conversely tried to modulate the immune system, including through the use of toll-like receptor 3 (TLR3) agonists (rintatolimod/Ampligen) (290, 291), immune-stimulants such as Imunovir (292), and intravenous gamma globulin (293). There have also been trials targeting infections directly, including with antivirals (acyclovir and valganciclovir) (294–297) for chronic viral infections in ME/CFS patients (298–300). There is evidence of some positive benefits, at least for a subset of patients, from some of these studies, but results remain largely inconclusive or

subject to controversies; readers are referred to reviews for details (29–32).

Finally, the modulation of kynurenine pathways has also been suggested as a therapeutic avenue for ME/CFS (301, 302). However, in contrast to the approach suggested by critical illness researchers, the initial emphasis of ME/CFS research is on enabling rather than inhibiting the activity of the IDO enzyme. Given that the downstream kynurenine pathways produce both beneficial and neurotoxic kynurenine metabolites (275)—and neurotoxic metabolites are preferentially produced in conditions of inflammation (274)—pharmacological agents that target specific enzymes of the kynurenine pathways may be required in order to maintain a beneficial balance of the various metabolites (303). A recent study demonstrated the safety of L-kynurenine supplementation in healthy volunteers (304); the impacts on ill patients will need to be further investigated.

In summary, many efforts in both *prolonged* critical illness and ME/CFS have focused on mitigating inflammatory processes and/or modulating the immune system in patients. There is evidence of some beneficial results from some of these studies, but effects appear insufficient to interrupt detrimental and possibly self-perpetuating mechanisms. Antivirals have also been trialed for both *prolonged* critical illness and ME/CFS (viral reactivation has been documented in both illnesses). In both fields there has also recently been discussion of modulating the kynurenine pathways to rebalance beneficial and neurotoxic metabolites.

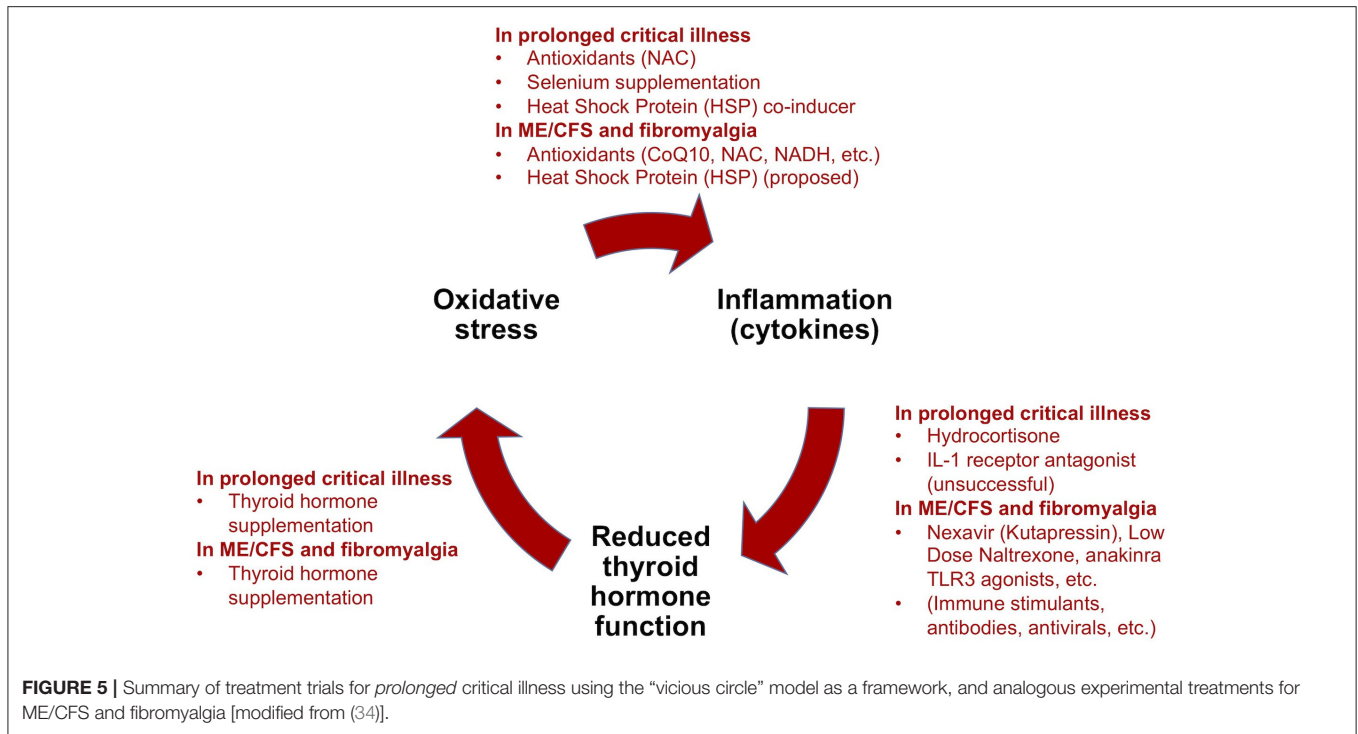
## Intermediate Conclusions

Treatment trials for *prolonged* critical illness and ME/CFS (or fibromyalgia) have both independently targeted low thyroid hormone *function*, O&NS, and pro-inflammatory cytokines and inflammation (**Figure 5**). Evidence exists for some benefits from these treatments in both conditions, but treatment trials have generally been limited in their scope, number and impact. Consequently, results have not translated into standard practices in either field. Further studies are required to fill gaps in the understanding of the physiological mechanisms behind some positive results, such as in the case of supplementation with thyroid hormones in both *prolonged* critical illness and ME/CFS.

## ADDITIONAL CONSIDERATIONS

As mentioned in the introduction, we previously advanced the hypothesis that maladaptive mechanisms that prevent recovery in *prolonged* critical illness may also underlie ME/CFS—and propose that these mechanisms could underlie the perpetuation of illness in ME/CFS regardless of the nature of the per-onset event (i.e., infection, stressful incident, exposure to environmental toxins or other) (34). Nonetheless, additional considerations must be taken into account when considering the relevance of treatment trials from critical care medicine for ME/CFS.

Firstly, the long disease duration in ME/CFS (relative to *prolonged* ICU patients) implies that dysfunctions that occur as a result of years of chronic disease must be considered as



part of treatment approaches. Secondly, research suggests that dysfunctions change over time in ME/CFS patients (28) and that there may be ME/CFS disease sub-groups (305–307); this implies that disease subtyping is necessary in order to match treatments to the patients. Thirdly, given that ME/CFS patients—similar to *prolonged* critical illness patients—have multi-system dysfunctions (e.g., endocrine, immune, nervous system, etc.), the question of sequence and/or combination of treatments must be considered. Fourthly, the side-effects of treatments described in this paper may differ between *prolonged* critical illness and ME/CFS patients (and also across ME/CFS patients) not least because of differences in severity of illness and dysfunctions. Recognizing the differences in fragility and vulnerability to side-effects of patients, an assessment of the trade-offs of treatments is necessary. Finally, it is reasonable to hypothesize that patients would have to endure long treatment courses occurring sizable costs; yet the enormous total economic costs of ME/CFS [estimated at \$36 to \$51 billion annually in the USA (308)]—not to mention the high financial and emotional toll of the disease on the millions of patients and families worldwide—makes establishing and implementing effective treatments for ME/CFS a long overdue imperative.

In summary, ME/CFS and *prolonged* critical illness are not identical illnesses. Any discussion of the relevance of treatment trials from *prolonged* critical illness for ME/CFS should take into account the specificities of ME/CFS, notably the dysfunctions arising from years of illness, the progression of the disease over time, the possible existence of sub-groups of ME/CFS patients, and potential particular vulnerabilities to side-effects.

## CONCLUSION

There are significant parallels in the treatment trials to aid recovery in *prolonged* critical illness and ME/CFS. Treatments proposed or trialed for both of these conditions have targeted (a) the correction of suppressed endocrine axes, and/or (b) inflammation, O&NS, and/or low thyroid hormone *function*. Treatment trials to date have been limited in scope and number; both *prolonged* critical illness and ME/CFS remain unsolved conditions. Incidentally, the parallels in the treatment trials would support the hypothesis that maladaptive mechanisms that prevent recovery in *prolonged* critical illness could also underlie ME/CFS.

From the brief overview and comparison of these trials provided here, we can derive some preliminary lessons to be learned. Notably, the early successes to reactivate the *pulsatile* secretions of the pituitary in *prolonged* critically ill patients with pituitary secretagogues—and the resulting positive metabolic effects—would indicate that this also could be an important avenue for ME/CFS treatments. The simultaneous reactivation of suppressed endocrine axes so far remains unexplored in ME/CFS. Conversely, the findings from ME/CFS related to the dysfunctions at the cellular and mitochondrial level can likely provide important complementary insights to the understanding of critical illness. In addition, the positive impacts from thyroid hormone supplementation described in some of the trials for both conditions merit further investigation.

Chiefly, given the similarities described above, an exhaustive analysis of the treatments already tried for either *prolonged* critical illness or for ME/CFS could help identify potential

approaches that could be immediately trialed for one or the other of these conditions. Moreover, active collaboration between critical illness and ME/CFS researchers to leverage their respective experiences could lead to improved outcomes for both conditions. More broadly—and given the similarities between *prolonged* critical illness, post-ICU syndrome, ME/CFS, fibromyalgia, and long-COVID—we suggest that collaborative efforts should be sought among the researcher community across these conditions in order to identify treatments mitigating the functional disability that they induce.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

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## AUTHOR CONTRIBUTIONS

DS wrote the first draft of the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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