Hormone issues underlying Fibromyalgia

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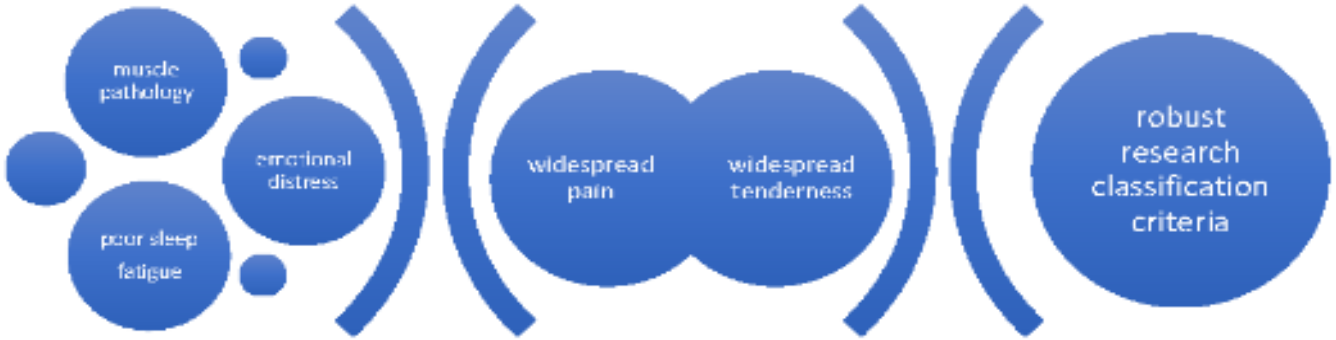
Fibromyalgia: Introduction

Fibromyalgia is a commonly encountered syndromic disorder charecterized by chronic widespread musculoskeletal pain, stiffness, disturbed sleep, easy fatigability along with multiple painful, tender points which are symmetrically distributed.

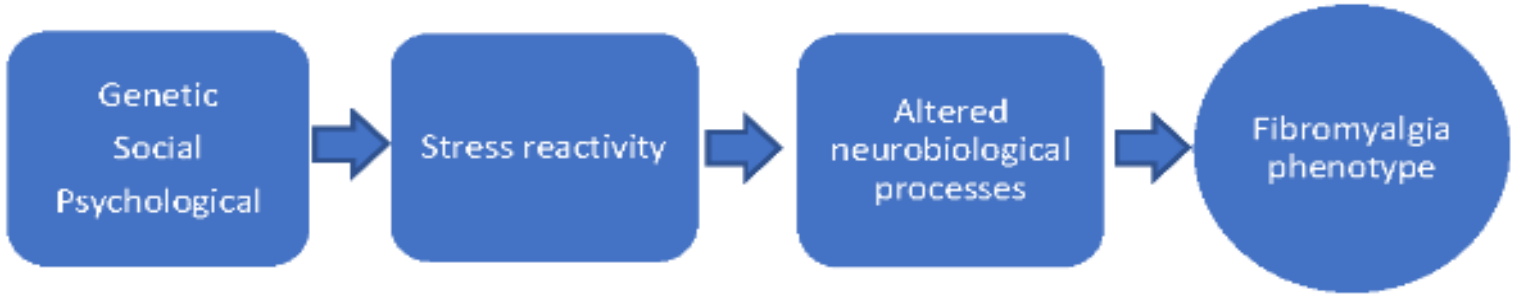
- The prevalence of FM varies widely from 0.66–10.5% of the general population according to the diagnostic criteria applied and it remains highly underdiagnosed and undertreated.
- Affects predominantly women in a ratio of 9:1 compared to men (age range mid 30s-mid 70s)
- Approximately 3.7 million people affected in the world
- New ACR diagnostic criterion have supplanted the previous diagnosis of counting tender points with widespread pain index (WPI) and symptom severity score (SS).

1990 ACR criteria better classified fibromyalgia



elements of "fibrositis" | 1990 ACR criteria | fibromyalgia better defined

Subsequently there has been enhancement of understanding of contributors to altered neurobiological processes underlying the fibromyalgia phenotype



2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria

Criteria:

A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:

Widespread pain index (WPI) ≥7 and symptom severity (SS) scale score ≥5 or
Widespread pain index (WPI) 4-6 and symptom severity (SS) scale score ≥9.

Generalized pain: **Pain must be present in at least 4 of 5 regions.**

Jaw, chest, and abdominal pain are not included in generalized pain definition.

Symptoms have been generally for at least 3 months.

A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important comorbidities.

SS scale score
The SS scale score is **the sum of the severity of the 3 symptoms** (fatigue, waking unrefreshed, cognitive symptoms) **plus the sum of the number of 3 symptoms** (headaches, pain or cramps in lower abdomen, depression). The final score is between 0 and 12

2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria

WPI

Note the number of areas in which the patient has had pain over the last week. In how many areas has the patient had pain?
(Score will be between 0 and 19)

Region 1: Left Upper Region -Jaw, left * -Shoulder girdle, left -Upper arm, left -Lower arm, left	Region 2: Right Upper Region -Jaw, right * -Shoulder girdle, right -Upper arm, right -Lower arm, right	Region 5: Axial Region -Neck -Upper back -Lower back -Chest * -Abdomen *
	Region 3: Left Lower Region -Hip (buttock, trochanter), left -Upper leg, left -Lower leg, left	Region 4: Right Lower Region -Hip (buttock, trochanter), right -Upper leg, right -Lower leg, right

Fibromyalgia

ACR Criteria: Symptom Scale Score

The Symptom Scale Score is the sum of the severity of the three symptoms (fatigue, waking unrefreshed, cognitive symptoms) plus the extent of somatic symptoms in general. The final score is between 0 – 12

0 = no problem
1 = slight or mild problems, generally mild or intermittent
2 = moderate, considerable problems, often present and/or at a moderate level
3 = severe, pervasive, continuous, life-disturbing problems

1. Fatigue (0 – 3)
2. Waking unrefreshed (0 – 3)
3. Cognitive symptoms (0 – 3)
4. General somatic symptoms (0 – 3)

Fibromyalgia: common complaints

- The main presenting complains of patients with fibromyalgia include chronic widespread pain (also called multisite pain), fatigue and poor sleep. Excessive sensitivity to normally painful stimuli, such as pressure or heat (hyperalgesia) and painful sensation to normally non-painful stimuli, such as touch (allodynia) are significant features of fibromyalgia
- Additional pain symptoms: abdominal pain, chest wall pain, symptoms suggestive of irritable bowel syndrome, pelvic pain and bladder symptoms of frequency and urgency suggestive of interstitial cystitis.
- Sleep issues: non-refreshing sleep, frequent awakening during the night and difficulty falling back to sleep. Sleep apnea and nocturnal myoclonus can also be present along with a sensation of light-headedness, dizziness, and faintness.
- Cognitive difficulties such as short-term memory loss, groping for words and poor vocabulary, are common among patients with fibromyalgia. Mood Issues: depression, anxiety and heightened somatic concern
- Other often co-existing conditions include multiple chemical sensitivity, “allergic” symptoms, ocular dryness, palpitations, dyspnea, vulvodynia, dysmenorrhea, premenstrual syndrome, sexual dysfunction, weight fluctuations, night sweats, dysphagia, restless leg syndrome, temporomandibular joint pain, chronic fatigue syndrome (systemic exertion intolerance disease), Raynaud`s phenomenon, autonomic dysfunction and dysgeusia

New Perspectives On FM/CFS

Coexisting Disorders

- Irritable Bowel Disease
- TMJ
- Tension/Migraine Headaches
- Interstitial Cystitis
- Vulvodynia
- Psychiatric disorders (anxiety/depressions/PTSD)
- Sleep disorders with chronic fatigue (within this arena CFS sits)
- Inflammatory Rheumatologic Diseases (RA, Psoriatic Arthritis, Sjogren's Syndrome, SLE)

Understanding Fibromyalgia

Fibromyalgia is considered as a phenomenon of central disinhibition leading to aberrant neurochemical processing of sensory signals, lowering threshold for pain, amplification of normal sensory signals resulting in chronic pain that is generated by environmental, biological and genetic factors

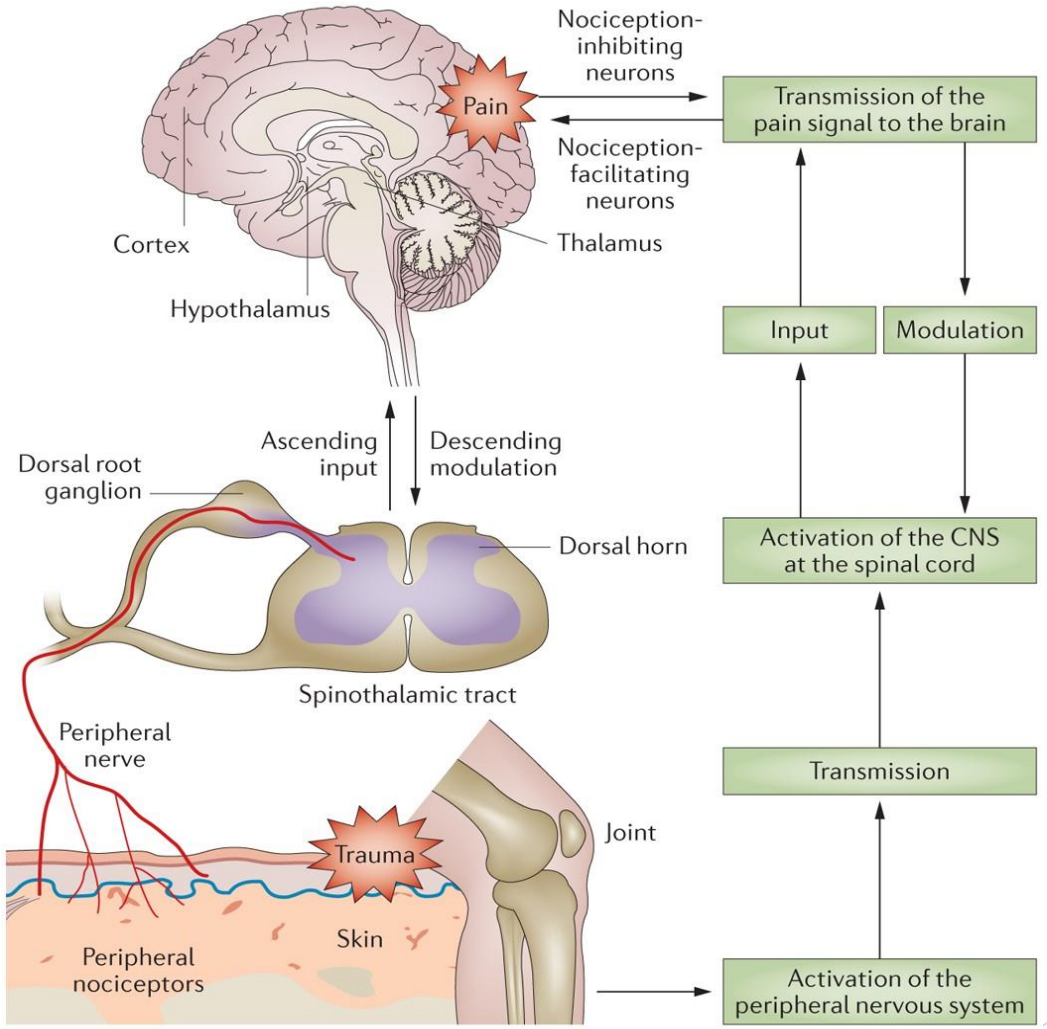
Central causes

- **Central sensitization to pain**
- **blunting of inhibitory pain pathways**
- **autonomic nervous system dysregulation**
- **sleep disruption**
- **chronic systemic inflammation**
- **alteration in neurotransmitter levels**
- **disruption in neuroendocrine signaling**

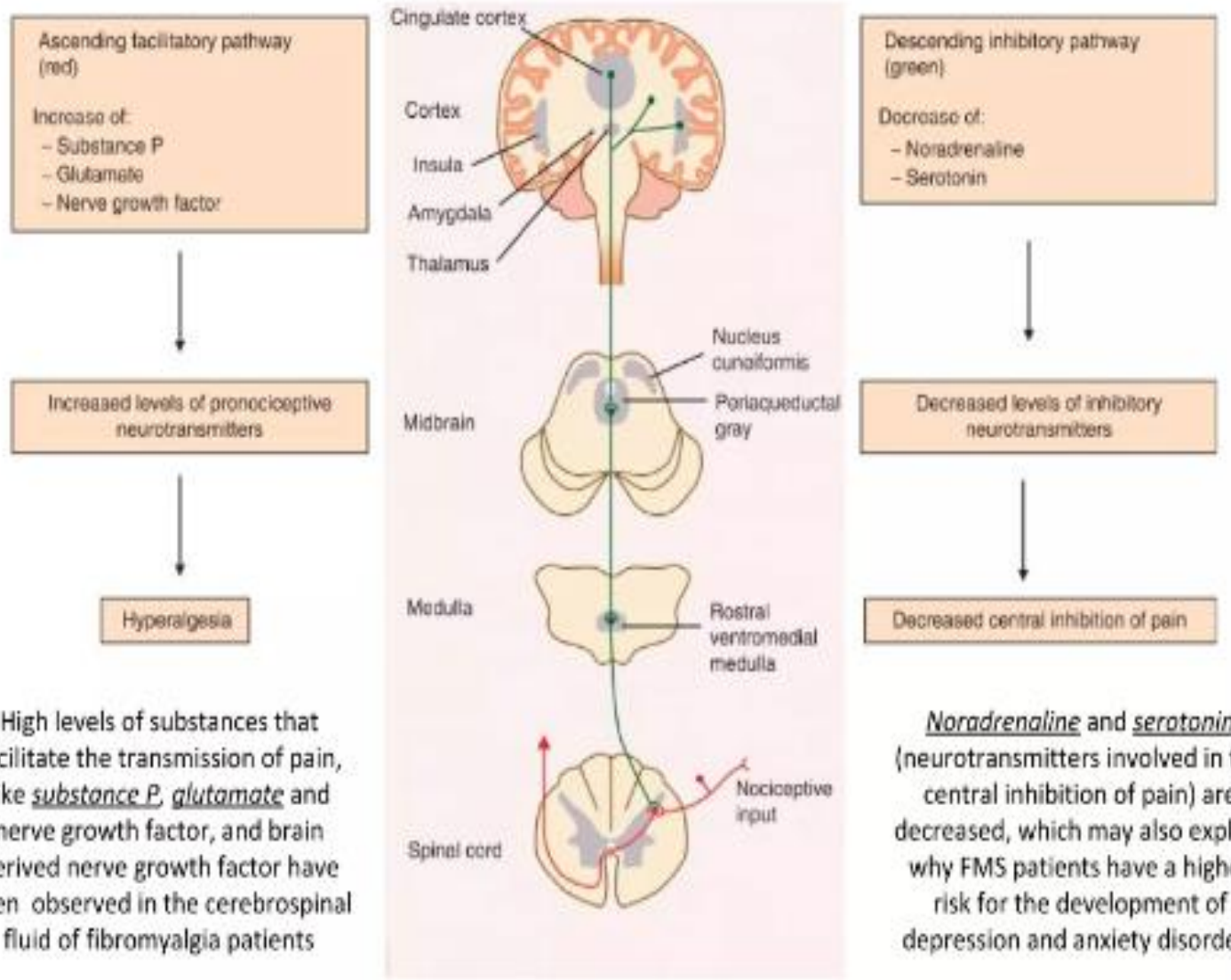
Mechanism of central sensitization to pain

- The main mechanism of central sensitization (CS) to pain involves **hyper-excitement of the second-order neurons in the dorsal horns of the spinal cord**, by various synaptic and neurotransmitter and neuromodulator activities.
- The **second-order neurons have ascending projections** to the thalamus, hypothalamus, the limbic system and the somatosensory cortex. These supraspinal structures are involved in the sensory, evaluative and affective dimensions of pain (e.g. unpleasantness, emotional reaction).
- Several descending pathways from the cortico-reticular system, locus ceruleus, hypothalamus, brain stem, and local spinal cord interneurons terminate to the dorsal horn cells. A **decrease in the top-down inhibitory activity (dysregulation of serotonin (5-HT), norepinephrine, epinephrine, dopamine, endogenous opioids, γ-amino-butyric acid (GABA), enkephalines, adenosine**) and **increase in the bottom-up excitatory activity of pain pathways** is noted
- The **dysregulation of the nociceptive system**, either at the level of the dorsal horns of the spinal cord, or at the level of the ascending and descending pathways, can lead to its hyper-excitability.
- Several factors may amplify and sustain central sensitization through interactive and synergistic actions. **Central sensitization can become self-sustained**, even when the event that triggered it no longer exists, **due to long-term CNS plasticity.**

Mechanism of central sensitization to pain



Nature Reviews | Disease Primers



High levels of substances that facilitate the transmission of pain, like *substance P*, *glutamate* and nerve growth factor, and brain derived nerve growth factor have been observed in the cerebrospinal fluid of fibromyalgia patients

Noradrenaline and *serotonin* (neurotransmitters involved in the central inhibition of pain) are decreased, which may also explain why FMS patients have a higher risk for the development of depression and anxiety disorders

Littlejohn G. Neurogenic neuroinflammation in fibromyalgia and complex regional pain syndrome. Nat Rev Rheumatol. 2015 Nov;11(11):639-48.

Autonomic disturbances in Fibromyagia

- Sympathetic hyperactivity, often associated with sympathetic hypo-activity (chronic hyperstimulation of β-adrenergic receptors leads to receptor desensitization and downregulation in response to stressors), or parasympathetic underactivity has been described in fibromyalgia.

- **Nocturnal heart rate variability** indices have been shown to be significantly different in fibromyalgia women compared to healthy individuals, indicating a sympathetic predominance.

- **Orthostatic hypotension and increased pain** have been noted in response to tilt table test have been described in some studies along with **increased resting supine heart rate and decreased heart rate variability.**

- IL-6 administration causes exaggerated norepinephrine responses and increases in heart rate, as well as delayed ACTH release, suggesting an incapacitated stress-regulating system.

The Role of Melatonin: a biomarker of circadian dyregulation and implication in FM

- Melatonin is centrally secreted by the pineal gland and exhibits a secretory rhythm with well-defined onset and offset phases with circulating concentrations high at night and lower during the day. **There is a disruption of melatonin circadian rhythm secretion in FM.**
- **A higher load of melatonin secretion during daytime hours** makes those with FM are more susceptible to pain, inadequate sleep quality, and present larger NTPs and higher rates of depressive symptoms.
- **Chronic stress disrupts the physiological rhythm of melatonin secretion** via hyperactivation of the sympathetic system and as part of the prolonged and sustained glucocorticoid stress-related secretion.
- In turn, **impairments of the rhythmic secretion of melatonin impacts information transmitted to brain areas that regulate the limbic-HPA and sympathetic-adrenergic-noradrenergic systems** because high levels of melatonin receptors exist in the hippocampus.

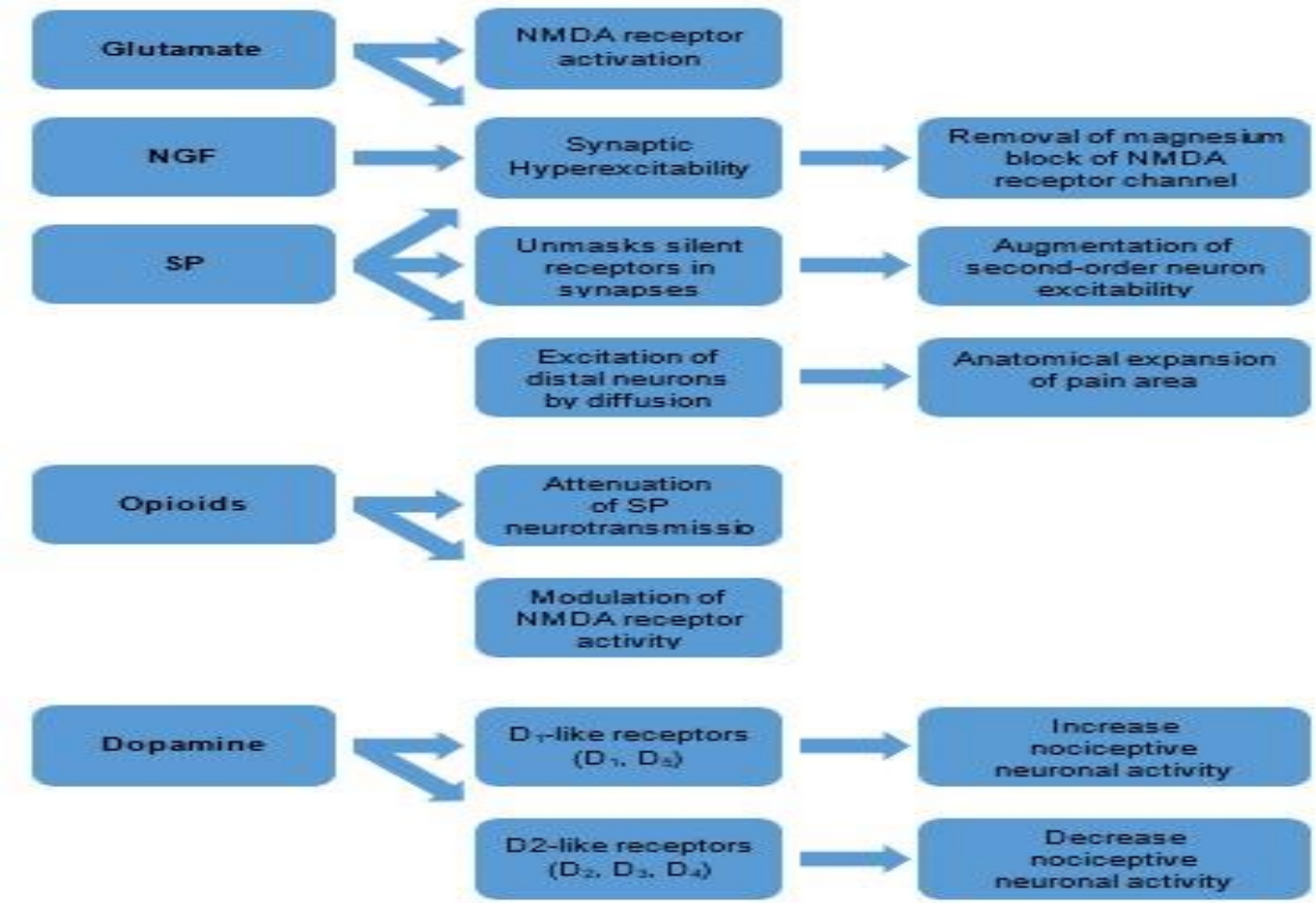
Melatonin as a biomarker of the impact of circadian disruption on neurophysiological, behavioral, and metabolic processes.

- Melatonin is a **primary circadian pacemaker quantifiable by measuring 6-sulfatoxymelatonin (MT6s),** which is its major metabolite excreted in urine.
- **24 hour Urine MT6s is a stable, reproducible and accurate measurement with reliability to measure circadian phase position over other circadian markers** (ie, core body temperature and cortisol) because the melatonin concentration remains relatively uninfluenced by external factors such as stress, physical activity, and excessive carbohydrate intake. In contrast, these factors can mask the cortisol and core body temperature.
- One study looked at the hypothesis of whether a **higher secretion during daytime hours (06:00–18:00 hours) might be a factor that underpins the physiopathology of FM.** In this study, although the 24 hr secretion of urine Mt6s was not quantitatively every different from the control subjects, the **disruption in the circadian rhythm of secretion was correlated with the severity of mood and other physiological disturbances in FM patients.**
- Persistent high level of urinary aMT6s during the daytime maybe an expression of the sympathetic system hyperactivation (primary compensatory mechanism) or consequent to chronic pain and depression.
- If urinary aMT6s were an indirect measure of sympathetic activity, it is possible to suppose that in FM, **relentless sympathetic hyperactivity exists throughout 24 hours and desynchronizes the melatonin secretion to environmental timing cues**, associated with clinical symptoms commonly observed in FM, such as worse sleep quality.

Neurotransmitter disturbances in Fibromyalgia

- **The levels of Substance P (SP) in the cerebrospinal fluid (CSF) in patients with fibromyalgia are significantly increased** compared to normal individuals, whereas CSF levels of serotonin metabolites are decreased, as are metabolites of dopamine and norepinephrine.
- **An abnormal dopamine response to pain has been substantiated** from PET scans using competitive binding studies using the D_2/D_3 receptor antagonist [^{11}C] raclopride.
- Disturbances of the opioidergic system occur in fibromyalgia patients, as there is an **up-regulation of opioid receptors in the periphery, with a reduction of the brain opioid receptors**. This implies an increased baseline endogenous opioidergic activity. Opioids can activate glial cells, via a non-stereoselective activation of toll-like receptor 4 (TLR4). Glial cells in turn can mediate pain by releasing neuroexcitatory, pro-inflammatory products.

The role of the major neurotransmitters of the nociceptive system that participate in signal conduction at the level of the spinal cord.



SP: Substance P, NGF: nerve growth factor, NMDA: N-methyl-D-aspartate, D: dopamine

Activation of the *N*-methyl-D-aspartate (NMDA) receptor (i.e. glutamate) results in increased sensitivity of spinal cord and brain pathways that process sensory information, particularly those which relate to pain

When pain turns from acute to chronic, it involves opening the NMDA pain receptor

•Patients with fibromyalgia have been shown to have an increased expression of NMDA receptors in their skin (Kim *et al.* 2006)

•Thus people with fibromyalgia appear to already have overly active NMDA pain receptors, making them more susceptible to the stimulation

•A 4-week exclusion of monosodium glutamate (MSG), aspartame, and other excitotoxins resulted in over 30% improvement in fibromyalgia symptoms in 84% of those who completed the diet (Holton *et al.* 2012)

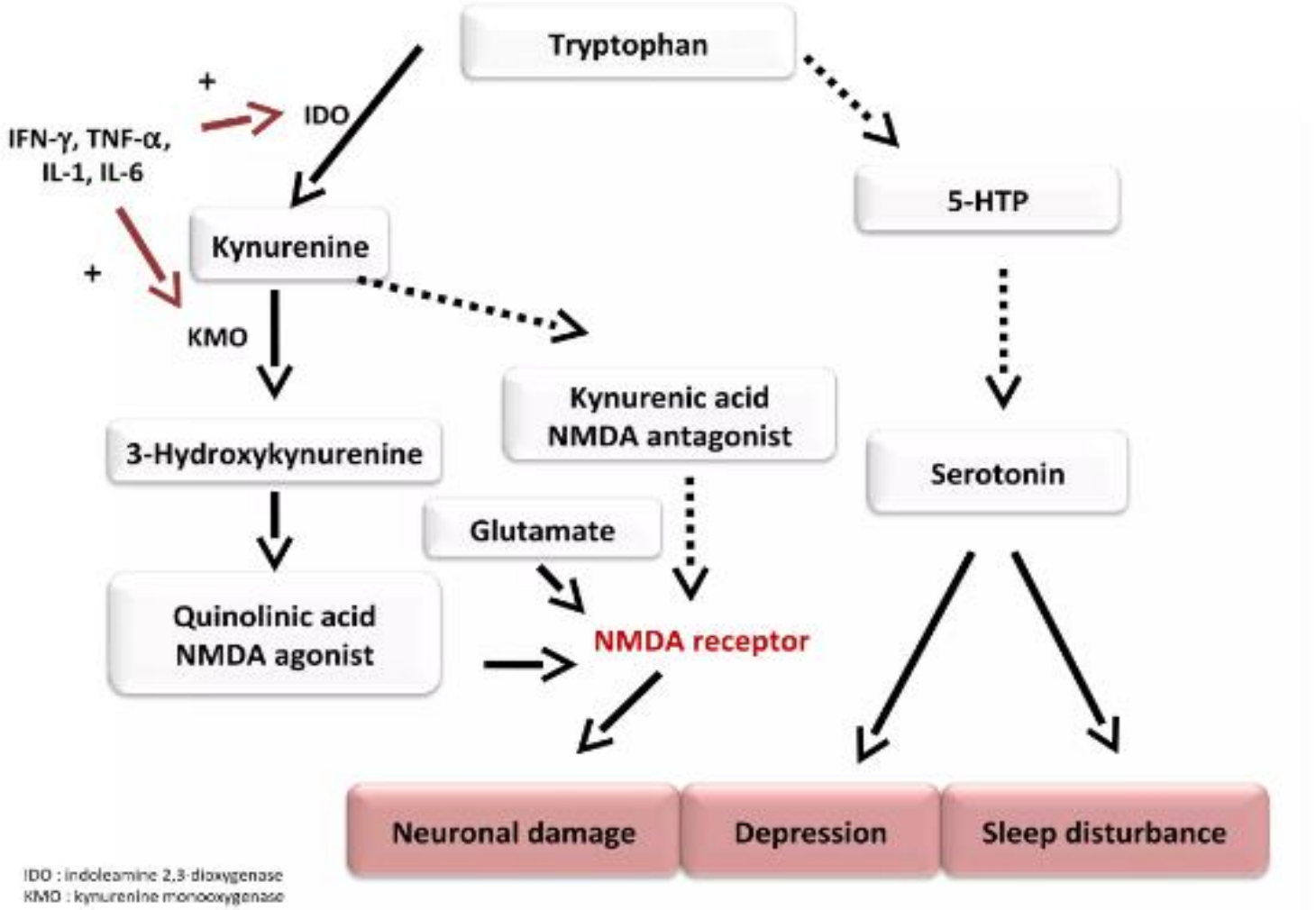
Kim SH, Jang TJ, Moon IS. Increased expression of N-methyl-D-aspartate receptor subunit 2D in the skin of patients with fibromyalgia. Rheumatol. 2006 Apr;33(4):785-8.

Holton K.F., Taren D.L., Thomson C.A., Bennett R.M., Jones K.D. The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms. Clin. Exp. Rheumatol. 2012;30:10–17.

Neurotransmitter disturbances in Fibromyalgia (contd)

- In a study where fibromyalgia patients were evaluated for cortical excitability and intracortical modulation using transcranial magnetic stimulation of the motor cortex, it was shown that there were **deficits in intracortical modulation of GABAergic and glutamatergic mechanisms.**
- Diminished inhibitory neurotransmission resulting from **lower concentrations of GABA** within the right anterior insula of patients with fibromyalgia was documented using proton magnetic resonance spectroscopy.
- Evidence for **enhanced glutaminergic neurotransmission in fibromyalgia** patients is derived from studies that used magnetic resonance spectroscopy. It was shown that **fibromyalgia patients have significantly higher levels of glutamine within the posterior insula and in the right amygdala**.
- The levels of **brain-derived neurotrophic factor**, which is involved in neuronal survival and synaptic plasticity of the central and peripheral nervous system, **have been found to be increased** both in the brain and in the plasma of fibromyalgia patients.

Disruption in Tryptophan and serotonin axis as a result of inflammatory cytokines



Hippocampal atrophy = fibro fog?

Abnormal glutamate excitatory neurotransmission and glucocorticoid dysfunction can lead to neuronal atrophy, through excitotoxicity, and disrupt neurogenesis in the hippocampus – with magnetic resonance imaging (MRI) scans having shown significant hippocampal atrophy in the brains of FMS patients compared to healthy controls

Hippocampal atrophy may play a role in memory and cognitive complaints among fibromyalgia patients

•Hippocampal atrophy resulting from FMS may, in turn, worsen or exacerbate FMS symptomatology

•FMS patients often report a subjective worsening of cognitive function characterised by short-term memory problems ('fibro fog')

•Hippocampal atrophy and dysfunction may "feed forward", resulting in more severe pain, discomfort, and anxiety in FMS patients, due to its central role in limbic circuits and pain modulation networks

McCrae CS, O'Shea AM, Boissoneault J, Vatthauer KE, Robinson ME, Staud R, Perlstein WM, Craggs JG. Fibromyalgia patients have reduced hippocampal volume compared with healthy controls. J Pain Res. 2015 Jan 30;8:47-52.

Cytokine disturbances in Fibromyalgia

- **The role of cytokines and inflammation is unclear in whether cytokine changes are the cause of pain in these patients, or just its consequence.**
- Serum levels of **interleukin 1 receptor antibody (IL-1B), IL-6 and IL-8 are higher** in fibromyalgia patients, compared to controls
- Lower levels of IL-4 and IL-10 (anti-inflammatory) have been reported in fibromyalgia patients
- **Inflammatory cytokines like IL-1β, IL-6 and TNFα cause activation of the hypothalamic-pituitary-adrenal (HPA) axis** alone, or in synergy with each other.
- There is evidence to suggest that **IL-6, which is the main endocrine cytokine**, plays the most significant role in the immune stimulation of the axis, especially in chronic inflammatory stress.
- **IL-6 can stimulate the hypothalamic secretion of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), leading to the increase of serum adrenocorticotropic hormone (ACTH) and cortisol levels.**

Fibromyalgia and cytokines

Studies of cytokine levels in patients with fibromyalgia suggest that levels of the proinflammatory cytokines IL-1, IL-6 and IL-8 are elevated, whereas TNFα levels are normal, and levels of the antiinflammatory cytokines IL-4 and IL-10 are unchanged or reduced

IL-1β	Hyperalgesia, fatigue, fever, sleep, myalgias, substance P anti-nociception (increases GABA and decreases NMDA); noradrenaline and adrenaline stimulate its release
TNFα	Stress; regulates substance P expression, rapid eye movement sleep, allodynia; increases excitatory amino acids; noradrenaline and adrenaline stimulate its release
IL-1Ra	Stress; inhibits IL-8 expression
IFNγ	Stress, anxiety; lowers substance P; myalgias
IL-2	Myalgia, cognitive dysfunction
IL-4	Decreases the production of Th1 cells, macrophages, IFN-γ
IL-6	Stress, fatigue, hyperalgesia, depression; noradrenaline, adrenaline and substance P stimulate its release; activates sympathetic nervous system
IL-8	Substance P stimulates production, mediates sympathetic pain
IL-10	Blocks pain

Wallace DJ, Linker-Israeli M, Hallegua D, Silverman S, Silver D, Weisman MH. Cytokines play an aetiopathogenetic role in fibromyalgia: a hypothesis and pilot study. Rheumatology (Oxford). 2001 Jul;40(7):743-9.

Fibromyalgia and cytokines

FMS is common in patients with autoimmune disorders, such as systemic lupus erythematosus, Sjogren's Syndrome, and rheumatoid arthritis and while the chemokine/cytokine patterns found in FMS patients may not be unique to FMS, it is worth considering that:

- substance P induces IL-8 expression and the release of IL-6

- because IL-8 promotes sympathetic pain and IL-6 induces hyperalgesia, fatigue and depression, it is hypothesised that they may play a role in modulating FMS symptoms

- increased levels of inflammatory cytokines can induce glutathione depletion, which, in turn, may activate redox-sensitive transcription factors, such as NF-κB

- elevated levels of cytokines activate microglia and astrocytes in the brain leading to further production of elevated cytokines and ROS/RNS causing mitochondrial and metabolic dysfunction contributing to fatigue

- the subsequent ATP deficit together with inflammation and ROS/NOS are responsible for the landmark symptoms of ME/CFS/FMS, including post-exertional malaise

Morris G, Berk M, Walder K, Maes M. Central pathways causing fatigue in neuro-inflammatory and autoimmune illnesses. BMC Med. 2015 Feb 6;13:28.

Morris G, Maes M. A neuro-immune model of Myalgic Encephalomyelitis/Chronic fatigue syndrome. Metab Brain Dis. 2013 Dec;28(4):523-40.

Genetic associations seen in Fibromyagia

- ***Serotonin transporter (5-HTT) gene***

- An increased frequency of the S/S genotype of the 5-HTT gene has been found in fibromyalgia patients compared to controls. However this putative association may be limited to patients with concomitant affective disorders, since it was not confirmed in fibromyalgia patients without depression or anxiety .

- ***D_4 receptor gene***

- Polymorphisms affecting the number of repeats in the third cytoplasmic loop of the dopamine D_4 receptor gene have been shown to be significantly decreased in frequency in fibromyalgia patients.

- ***Catechol-O-methyl transferase (COMT) gene***

- The homozygous low activity (met/met) and the heterozygous low activity (val/met) COMT genotypes occur more often in fibromyalgia patients than in controls. The met/met genotype has been associated with greater fibromyalgia illness severity across the domains of pain, fatigue, sleep disturbance, and psychological distress.

- ***Opioid receptor μ 1 gene (OPRM1)***

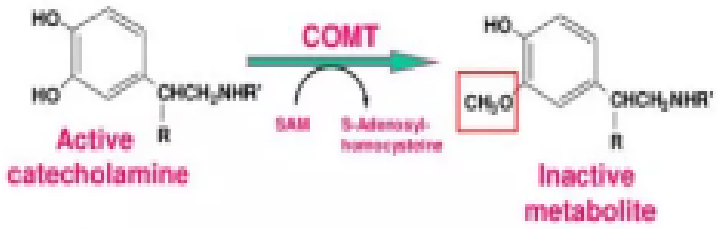
- The 118G allele frequency has been described to be significantly lower in patients with fibromyalgia than in the control group.

- ***Other genes:*** Adrenergic receptor genes, trace amine-associated receptor 1 (TAAR1) gene, regulator of G-protein signaling 4 (RGS4) gene, cannabinoid receptor 1 (CNR1) gene, and glutamate receptor, ionotrophic, AMPA 4 (GRIA4) gene, have been associated with fibromyalgia

Catechol-O-methyltransferase (COMT) catalyzes the transfer of a methyl group from S-adenosylmethionine (SAMe) to catecholamines, including the neurotransmitters dopamine, adrenaline and noradrenaline

Clinical symptoms in fibromyalgia are associated to *COMT* gene Val158Met polymorphism

The COMT gene codes for the COMT enzyme, which breaks down dopamine in the brain's prefrontal cortex. The wild-type allele is a (G) coding for a valine amino acid; the (A) substitution polymorphism changes the amino acid to a methionine



rs4680(A) methionine = lower COMT enzymatic activity, therefore higher dopamine levels; lower pain threshold, enhanced vulnerability to stress

rs4680(G) valine = higher COMT enzymatic activity, therefore lower dopamine levels; higher pain threshold, better stress resiliency

FMS women with the homozygous met/met genotype evidenced more pain on days when pain attention was elevated relative to those with the homozygous val/val genotype

Inanir A, Karakus N, Ates O, Sozer S, Bozkurt N, Inanir S, Yigit S Clinical symptoms in fibromyalgia are associated to catechol-O-methyltransferase (COMT) geneVal158Met polymorphism. Xenobiotica. 2014 Oct;44(10):952-6.

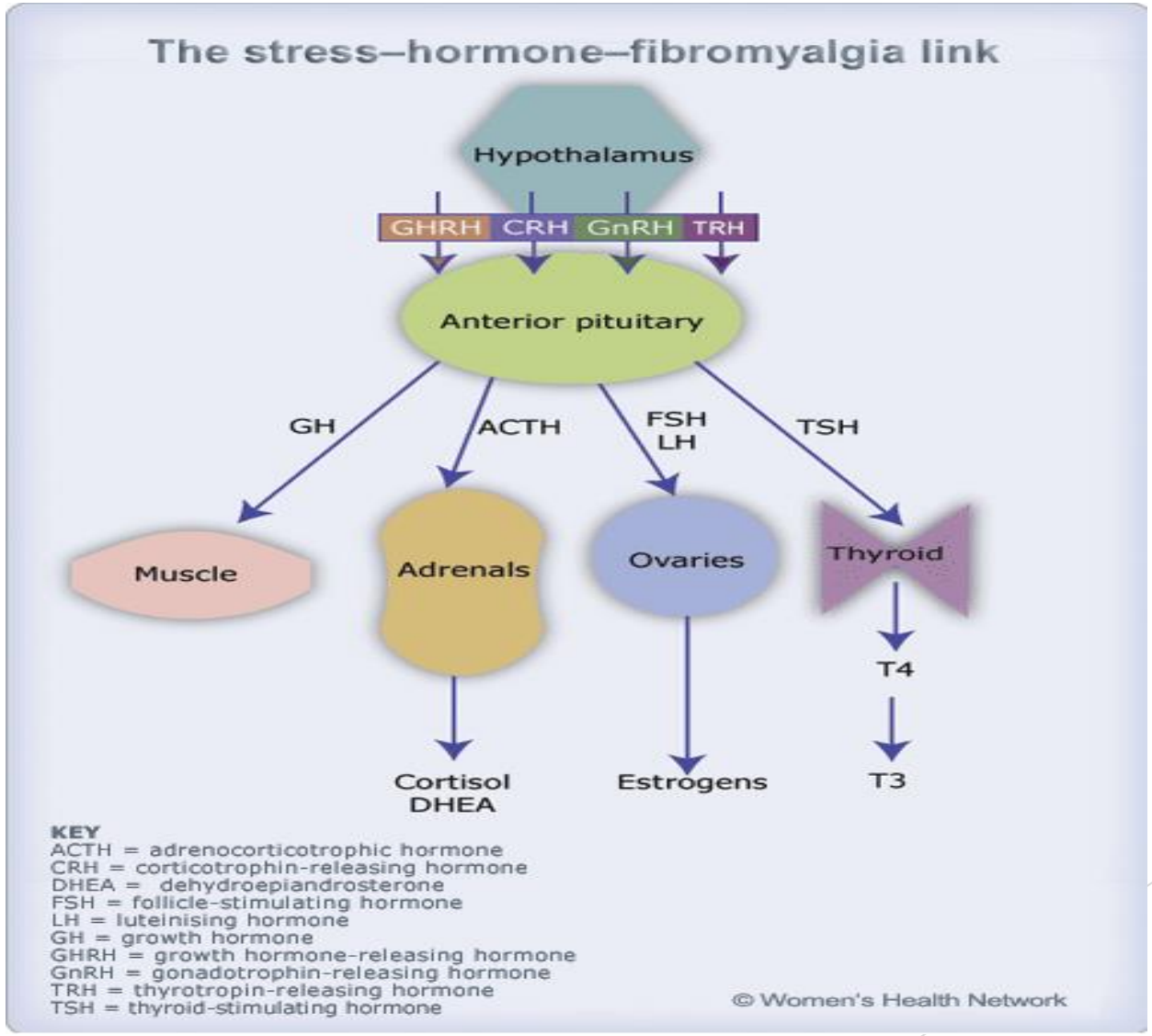
Finan PH, Zautra AJ, Davis MC, Lumley-Chalfant K, Covault J, Tennen H. COMT moderates the relation of daily maladaptive coping and pain in fibromyalgia. Pain. 2011 Feb;152(2):300-7.

Endocrine disruption in Fibromyalgia

Multiple Hormonal pathways are implicated in the pathogenesis of Fibromyalgia

- Hypothalamic signaling issues (including disruption of melatonin synthesis and release)
- Disordered pituitary production (secondary to Hypothalamic dysfunction) of Growth hormone (GH), thyroid stimulating hormone (TSH), Adrenocorticotrophic hormone (ACTH), Gonadotropins (FSH, LH)
- Thyroid autoimmunity
- Dysregulation of tryptophan metabolism and serotonin secretion
- Dysregulation of glucose metabolism and insulin resistance at the level of liver and skeletal muscle contribute to generalized inflammation.

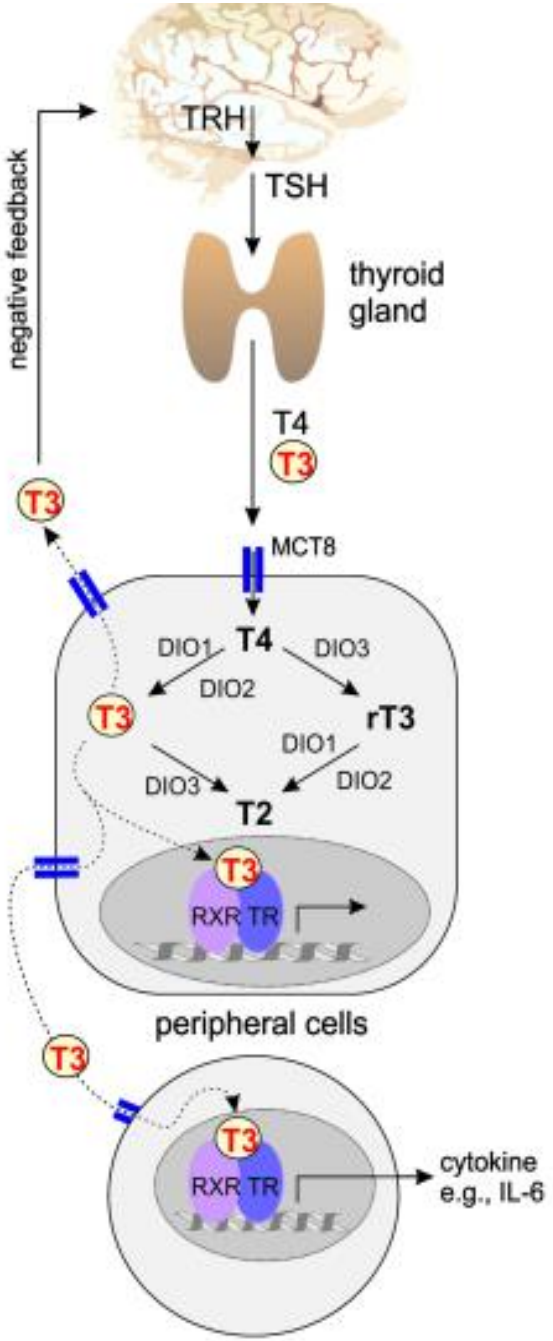
Endocrine disruption in Fibromyalgia



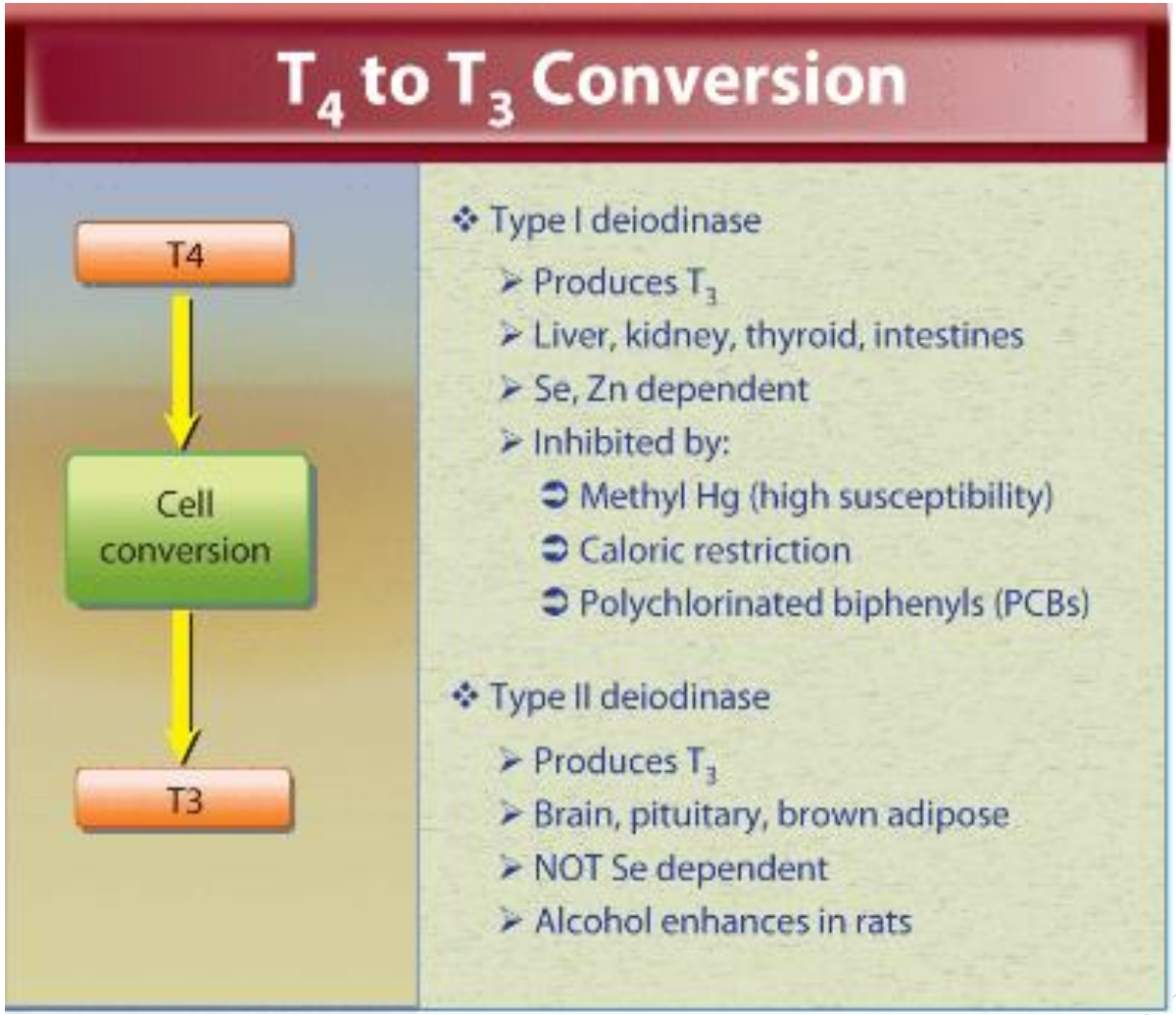
The central role of thyroid dysfunction in FM

- FM patients as a group have a slightly higher incidence of abnormal thyroid function tests showing primary clinical or subclinical hypothyroidism. More rarely, central hypothyroidism like pattern (similar to sick-euthyroid syndrome) has also been seen.

- A collective line of evidence indicates that most patients with FM also have abnormal thyroid production and utilization. Studies indicate that inadequate thyroid hormone regulation or peripheral resistance to thyroid hormone, may both be underlying mechanisms causing cellular thyroid deficiency.



Schematic drawing of the Hypothalamic Pituitary Thyroid axis. Hypothalamic TRH stimulates Thyrotropin (TSH) release from the pituitary gland stimulates the thyroid to produce T3 and T4. In serum, these hormones are bound to transport proteins. Thyroid hormones enter cells via thyroid hormone receptors and transporter (MCT8 transporter required in the brain). Intracellularly, the biologically inactive T4 is converted to the biologically active T3 and to the degradation product reverse T3 (rT3). T3 and rT3 can be further converted to T2, which has no classical thyroid hormone activities. Conversion happens with deiodinases 1–3 (DIO). T3 exerts its action via the retinoic acid receptor (RXR) and the thyroid hormone receptor alpha and beta (TRα, TRß).
Abbreviations: T3, triiodothyronine; T4, thyroxine; TRH, thyrotropin releasing hormone.


T_4 to T_3 Conversion
T4
Cell conversion
T3
Type I deiodinase
Produces T_3
Liver, kidney, thyroid, intestines
Se, Zn dependent
Inhibited by:
Methyl Hg (high susceptibility)
Caloric restriction
Polychlorinated biphenyls (PCBs)
Type II deiodinase
Produces T_3
Brain, pituitary, brown adipose
NOT Se dependent
Alcohol enhances in rats

Potential interaction between thyroid and cortisol dysfunction in FM

- In a study looking at serum thyroxine uptake in cultured hepatocyte cells from patients with non thyroidal illness, it was noted that **significant physiologic stress inhibits the uptake and transport of T4 into the cell** (Sarne D.H. et al, J Clin Endocrinol Metab 1985;61:1046-52).
- Investigators examined the relationship between stimulating thyroid hormone (TSH) levels and cortisol in a study of young, healthy adults without known thyroid disease or other underlying health conditions. **Hypothyroid patients were noted to have elevated cortisol levels** suggesting that hypercortisolemia in primary hypothyroidism is probably because of **decreased metabolic clearance of cortisol** and a speculative decrease in negative feedback effect of cortisol on the HP axis (Walter K.N. et al, n. Thyroid Res 2012;5:13).
- Chronic emotional or physiologic stress associated with FM can cause significant increases or decreases in cortisol, reductions of T4 transport into cells, and **reductions in peripheral conversion of T4 to T3.**

The role of thyroid autoimmunity as a predisposing factor for fibromyalgia

- Autoimmune thyroid disease is characterised by the **existence of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb**, less specific and seen in only 80% cases).It is a matter of controversy whether they play a direct role in the pathogenesis or occur merely as a by-product of T-cell-mediated destruction of thyroid cells,
- The **frequency of thyroid autoimmunity is known to be higher in FM** (335-41%) but unfortunately, most studies in the literature are based on relatively small sample sizes that are insufficient to determine the association between thyroid autoimmunity and FM individually.
- A recent small metanalysis of 5 case-control studies published in 2020 (J.W. Park et al, Clin Exp Rheumatol 2022; 40: 1210-1220) showed **thyroid autoantibody positivity was more prevalent in FM patients** than in healthy controls. (TPO Ab: OR 3.41; 95% CI 1.97–5.90, TgAb: OR 2.23; 95% CI 1.23–4.01). No heterogeneity was detected among the studies (I2 =0%). **Among thyroid autoantibodies, the presence of TPO Ab imposed a higher risk for FM compared to Tg Ab.**
- Association between presence of thyroid autoantibodies and severity of FM symptoms is conflicting and inconsistent (although postmenopausal status appears to worsen severity of some FM symptoms in patients with positive anti TG antibody).

The role of thyroid autoimmunity as a predisposing factor for fibromyalgia (contd)

- FM is commonly found in autoimmune disease patients (Hashimoto's Disease, Celiac disease, Type 1 diabetes and multiple Rheumatoid conditions).
- Autoimmune thyroid disease is characterised by the existence of thyroid peroxidase antibody (TPOAb) and thyroglobulin antibody (TgAb, less specific and seen in only 80% cases).It is a matter of controversy whether they play a direct role in the pathogenesis or occur merely as a by-product of T-cell-mediated destruction of thyroid cells,
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- Association between presence of thyroid autoantibodies and severity of FM symptoms is conflicting and inconsistent (although postmenopausal status appears to worsen severity of some FM symptoms in patients with positive anti TG antibody).

HPA axis dysfunction in Fibromyalgia

- Research on the HPA axis in FM has shown variations in cortisol levels, increased sensitivity to glucocorticoid feedback, and increased cortisol release in response to a stressor.
- Cortisol which is a marker of stress follows a circadian rhythm with elevated levels in the early morning and decreased levels later in the day with nadir at night. The altered functioning of HPA axis is reported to be an important factor in the perturbation of circadian symptoms of FM.
- Studies have shown the **blunting of normal diurnal cortisol rhythm**, with elevated evening serum cortisol levels in FM patients.
- Most studies have revealed **low 24-h urinary free cortisol excretion** despite higher average serum cortisol, exaggerated adrenocorticotropic hormone (ACTH) release in response to corticotropin-releasing challenge (CRH stimulation test). FM patients also have an **inability to suppress plasma cortisol levels in dexamethasone suppression tests and an attenuated cortisol awakening response**.
- Assessment of baseline serum cortisol or 24 hr UFC are of limited value as they fail to assess the function of the HPA axis during stress and lack sensitivity in detecting central HPA axis dysfunction.
- **Low dose (1 µg ACTH) stimulation may be slightly more sensitive than conventional (250 µg ACTH) testing**, but it still suffers from very poor sensitivity and misses approximately 50% of individuals with established central hypoadrenalism determined by IST, d-fenfluramine, CRH stimulation or metyrapone testing.

Problems with lab estimations of HPA dysfunction

- There are a large number of seemingly contradictory studies that measure basal cortisol levels or utilize standard dynamic ACTH stimulation tests to evaluate HPA axis function in CFS and FM, which has led to confusion and controversy as to the incidence of HPA axis dysfunction in these conditions.
- One likely contributing cause of the confusion and controversy is that it has been shown that the plasma cortisol immunoassays used by the majority of laboratories, institutions and studies suffer from considerable inaccuracy and variance and can significantly overestimate serum cortisol levels when compared to gold standard assays such as gas-chromatograph/mass spectrometry (GC/ MS) and high performance liquid chromatography (HPLC).
- This has led to controversy, a high degree of misdiagnosis and the misclassification of patients as having normal HPA function despite significant dysfunction or severely underestimating the severity of the dysfunction.
- **Baseline cortisol levels and ACTH dynamic testing have very low sensitivities in detecting central HPA axis dysfunction and fail to diagnose the majority of patients.**
- Further confounding results is the fact that CFS and FM patients are a very heterogeneous group in terms of illness severity, illness duration and associated psychiatric comorbidities, which likely influence HPA dysfunction.

Studies assessing hypothalamic–pituitary–adrenal axis activity

Measurement	Result in fibromyalgia compared with healthy controls
Basal activity measured over 24 h	
Every 10–20 min blood draw	Cortisol-similar [12,13]
Urine collected over 24 h	Free cortisol-similar [14,15], low [16–18]
Response to the following stressors	
Hypoglycemia induced by hyperinsulinemic clamp technique	Corticotropin-reduced and cortisol-similar [14]
Hypoglycemia induced by	Cortisol-reduced [19]
insulin bolus	Corticotropin-increased and cortisol-similar [20]
Exercise	Cortisol-reduced [21,22,31]
Response to the following hypothalamic or adrenal agonists	
CRH	Corticotropin response-generally increased [16,18,20,23]
IL-6	Corticotropin response-delayed [24]
Corticotropin	Cortisol-similar [14,18] and reduced [19]

Hypothalamic-Pituitary-Adrenal and ANS Functioning in Fibromyalgia Adler GA et al, Rheum Dis Clin N Am 31 (2005)

Step wise approach to evaluate patients for secondary adrenal insufficiency

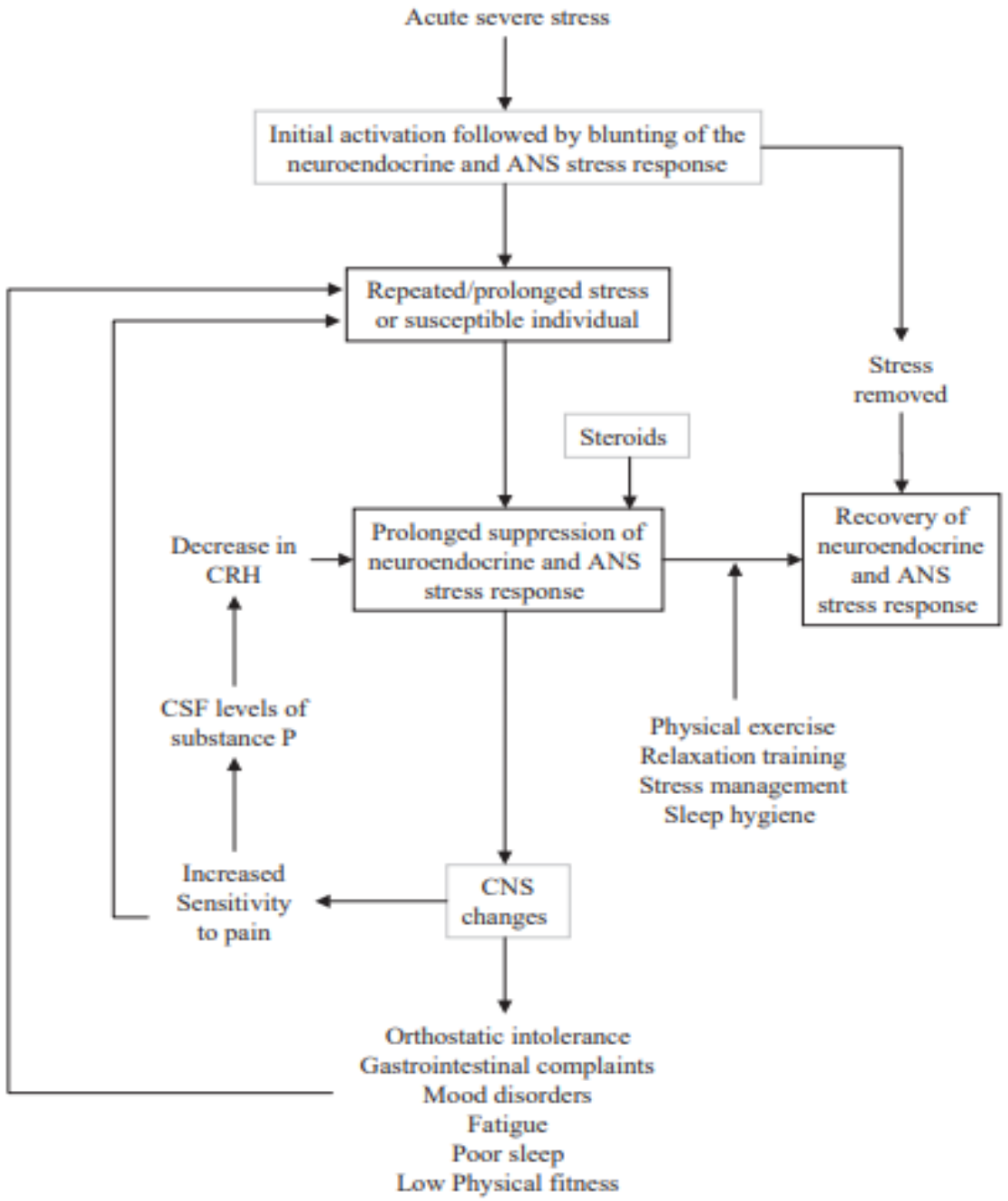
Baseline serum 8 am cortisol checked: When the screening cortisol is low or low-normal (< 10 mcg/dL raises suspicion for SAI. A cortisol value of < 5 mcg/dL is consistent with SAI and additional testing is often unnecessary. For baseline cortisol levels above 5 mcg/ dL, additional testing can help determine if a patient has SAI.

A cosyntropin stimulation test is helpful if the test is abnormal, but a normal cortisol response does not rule out SAI. (highly specific but low sensitivity).

Alternative testing such as an ITT or potentially a metyrapone stimulation test may be needed. Both SAI and GH deficiency can be assessed simultaneously with an ITT, but the test is cumbersome and contraindicated in patients with cardiac disease or epilepsy.

A metyrapone stimulation test is a good option for patients with FM when there is concern for SAI as it assesses hypothalamic-pituitary function but has fewer contraindications to administration compared to ITT.

The test is performed by administering a weight-based dose of metyrapone at 11:00 pm followed by a blood draw at 8:00 am the next day to test cortisol and 11-deoxycortisol levels.



A model of the possible interactions between stress, stress responsiveness and symptoms of fibromyalgia. CSF, cerebrospinal fluid; CNS, central nervous system; CRH, corticotropin-releasing hormone.

Growth Hormone axis in Fibromyalgia

- GH is an important component of the neuroendocrine response to stress.
- Impaired GH responses to arginine, clonidine, and L-dopa have been reported in some subjects with FM (however, studies not controlled for factors that alter GH secretion, such as medications, obesity, age, estrogen status, and aerobic fitness). When controlled for weight, GH response to exercise with hypoglycemia was impaired but response was normal at resting state.
- In some patients (particularly those with severe FM), an impairment of GH secretion due to an altered neurosecretory regulation of the somatotropic axis may be present .In addition, an impaired action of GH at different peripheral tissues indicating some degree of GH resistance has also been postulated
- IGF-I has been used as a screening tool when investigating the GH axis in FM though IGF-I may vary in relation to different physiological and pathological situations.
- A report by Yuen et al. reported a 17% prevalence of GH deficiency GHRH-arginine) in a low IGF-I FM population. ITT has been considered the gold-standard dynamic testing for GH secretion, but Arginine Glucagon test is clinically utilized more often as a substitute (arginine inhibits somatostatinergic tone which has been proposed to be hyperactive in FM).
- High GH levels in some FM patients suggest GH insensitivity, possibly reflecting an adaptive neuroendocrine response to chronic stress. An initial hyperactive anterior pituitary may lead in the long term to an exhaustion of the somatotrope cell response to provocative tests, as seen in other chronically stressed models

Hormonal Evaluation for Fibromyalgia

- Compete blood count
- Comprehensive metabolic panel
- Thyroid lab tests (TSH, FT4, FT3, rT3, TPO, anti TG)
- Nutrient analysis (zinc, copper, selenium, vit D 25, vit B12, Folate, magnesium)
- 4 point salivary cortisol testing with 8 am cortisol and ACTH
- Serum melatonin, IGF-1
- FSH, LH, Gonadal sex steroid panel, DHEAS
- A1C, F insulin, Insulin resistance index, CGM devicd download
- Inflammatory and autoimmune markers (hsCRP, celiac disease, ANA)
- Iron panel, ferritin, serum Iron
- recommend performing GH secretion dynamic tests as a part of the biological workup in low IGF-I FM patients
- Perform Cotrosyn stim test and if normal, consider metyrapone testing for SAI in those with high suspicion (low 24 hr UFC, borderline low am cortisol)

Hormone management issues : Thyroid

- Thyroid hormone replacement is controversial and routine replacement is not recommended unless T4/T3 imbalance exists in a young or middle aged patient.
- Older patients tend to have lower FT3 levels which is considered protective (lowered basal metabolic rate with reduction in energy expenditure).
- However, anecdotal reports note an improvement in subjective well being, fatigue, pain, mood, exercise tolerance in the elderly with judicious addition of small doses of T3.
- TSH can be low at baseline signifying central hypothyroidism in the setting of severe stress, multiple illness in a compromised patient. In such a setting, TSH cannot be used to monitor treatment and focus must be placed on FT4 and particularly on FT3 levels.
- Attention to Functional parameters that affect thyroid function (Iron, copper, Zinc, Mb, selenium, iodine, Gut issues, methylation issues, addition of Tyrosine, acupuncture, Vagal balancing, Breath techniques).
- If using glandular thyroid preparations, avoid addition of T3 and T4 and monitor labs.

Hormone management issues: Adrenal

- ADRENALS
- The use of glucocorticoids is not recommended as a standard of care unless secondary adrenal insufficiency is proven. Controversy abounds as to how much and for long to treat FM patients.
- Tietelbaum et al report treating cohort of patients (38) meeting ACR criterion for diagnosis with a stepwise integrated algorithm with doses of Hydrocortisone ranging from 5-15 mg daily (considered replacement doses). Tietelbaum et al used an algorithm that is not considered the standard for Cotrosyn stim test (Cortisol was administered if there was a baseline cortisol level = 12; the ACTH stimulated cortisol increase was < 7 at 30 minutes, < 11 at 60 minutes or the 60 minute cortisol was < 28). Overall, patients had significant improvements vs. placebo in the Fibromyalgia Impact Questionnaire ($p < 0.0005$), the tender point index ($p < 0.0001$) and overall response ($p < 0.0001$). No patients were found to have any adrenal suppression with post-treatment ACTH simulation tests.
- Holtorf et al also using a stepwise integrated algorithm introduced low dose cortisol after the second visit if symptoms were consistent with adrenal dysfunction based on 24 symptoms and/or having low blood pressure and/or having a baseline cortisol level in the low or low-normal range. If patients met the protocol criteria, they were given a therapeutic trial of 5-15 mg of timed-released cortisol per day. Patients were also given fludrocortisone if they had signs of neurally mediated hypotension. 94% patients reported 75% improvement after the 4the visit.

Hormone management issues: Adrenal

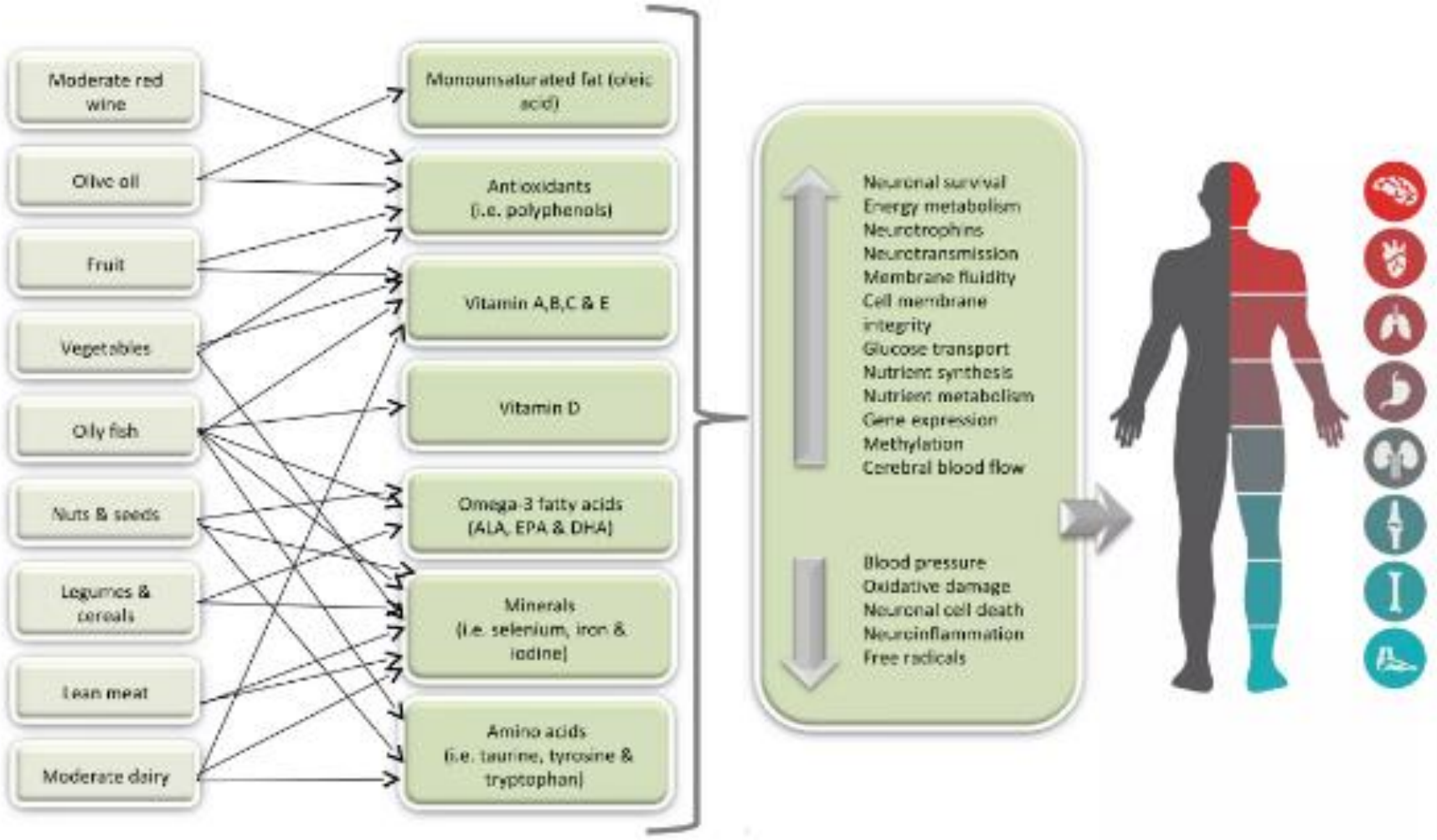
- I advocate a cautious trial of very low dose Hydrocortisone in patients with FM ONLY if 8 am cortisol is low or low normal, patients have symptoms of adrenal insufficiency and +/- positive cotrosyn stimulation test.
- I advocate a 6 month trial of 5-15 mg Hydrocortisone in divided doses.
- The lowest dose of Hydrocortisone that can maintain hemodynamic stability is to be preferred.
- ACTH stim test must be performed 6-8 weeks after completion of taper to avoid adrenal crisis following treatment.
- Some patients may need treatment for life and will need precautionary advice to avert adrenal crisis in times of stress or emergency.
- On rare occasions, patient may need addition of Fludrocortione as well.
- Glandular adrenal extracts may be tried with mild symptoms again on a trial basis and not long term.

Hormone management issues: Growth Hormone, Melatonin

- Growth Hormone administration is not considered standard practice of care unless IGF-1 is low and patient fails conventional GH stimulation (Arginine Glucagon or IIH) to establish the diagnosis of Adult Growth Hormone Deficiency.
- A.Nadal et all (BMC Musculoskeletal Disorders 2007, 8:119) conducted a prospective, randomized, open-label clinical trial in 25 women aged 18-50 with baseline IGF-1 <250 who met ACR criterion for diagnosis and followed them for 1 year on . Patients were randomized to receive either 0.0125 mg/kg/d of r-hGH subcutaneously added to standard intensive therapy or standard intensive therapy alone during one year. Additionally, an insulin tolerance test (ITT) and a cranial magnetic resonance imaging (MRI) were performed at baseline visit at investigator's discretion when IGF-1 levels were < 150. Patients reported a statistically significant reduction in pain, tender points, fatigue and improvement in FIQ and VAS questionnaire scores compared to controls. Only 10 people reported minor side effects and no patients were lost.
- I advocate baseline IGF-1 and GH stimulation testing in FM patients who present with severe symptoms. IGF-1 alone cannot be used to determine candidacy for treatment.
- I advocate checking 24 hr urine MT6 and considering a trial with 3 mg Melatonin qhs.
- A connection between low gonadotropins or sex steroids and FM has not been conclusively proven. I would address this problem independently of a diagnosis of FM.

Nutritional Advice

Focus on clean eating / maintain a healthy weight



Parletta N, Milte CM, Meyer BJ. Nutritional modulation of cognitive function and mental health. J Nutr Biochem. 2013 May;24(5):725-43.

GUT HEALTH MEASURES

Consequence: disrupted gut function leads to excess inflammation in the gut lining and changes in the normal gut flora (dysbiosis/candida)

Solution: Increase nutrients known to support gut heath, mucus production, support tight junctions and secretory immunoglobulin type A (SIgA) levels

- ✓L-glutamine (L-alanyl-L-glutamine) fuels gut cells (preferred fuel source) and boosts immunity
- ✓Pau d'arco is a great antifungal
- ✓Coconut oil/MCTs
- ✓Protein powder (provides essential amino acids) - protein requirements increase during times of increased stress/illness/inflammation
- ✓N-acetyl glucosamine is anti-inflammatory and helps protect the lining of the stomach and intestines
- ✓Increase natural stomach acid production by drinking water with a slice of lemon, a squeeze of lemon juice or a teaspoon of apple cider vinegar / betaine HCl supplements/high dose ascorbic acid
- ✓Garlic (Allicin MAX) for *Helicobacter pylori*
- ✓Mushrooms rich in beta glucans such as reishi, shiitake and maitake
- ✓Bone broth / gelatine / collagen
- ✓Vitamins D3 and A -SigA
- ✓Aloe vera/liquorice/quercetin
- ✓Digestive enzymes

Adrenal support

- ✓ Avoid sugar/ artificial sweeteners
- ✓ Avoid caffeine
- ✓ Focus on a 'clean diet'
- ✓ High-protein, low carbohydrate breakfast
- ✓ Eat every 3-4 hours to maintain optimal blood sugar levels
- ✓ Rest!

- ✓ B-Complex
- ✓ Vitamin C
- ✓ Magnesium
- ✓ Liquorice root
- ✓ Ashwagandha
- ✓ Siberian ginseng
- ✓ Rhodiola rosea
- ✓ DHEA

Increase glutathione levels

Up-regulate glutathione-related enzymes including glutathione reductase (GR) and glutathioneS-transferase (GST) - anthocyanins are members of the flavonoid group of phytochemicals, a group predominant in teas, honey, wine, fruits, vegetables, nuts, olive oil & cocoa

Cruciferous vegetables such as broccoli, kale and cabbage contain antioxidants that increase the production of detoxifying enzymes in the body

Sulphur-rich foods such as onions and garlic, cauliflower, eggs, Brussels sprouts & broccoli

Cysteine-rich foods: soya beans, egg white, oats & tofu, providing the body with the balance of nutrients that make (glutathione = L-cysteine + L-glutamic acid + glycine)

Supporting antioxidant defences

Alpha lipoic acid is an endogenous antioxidant and essential cofactor for many enzyme complexes that interrupt cellular oxidative processes

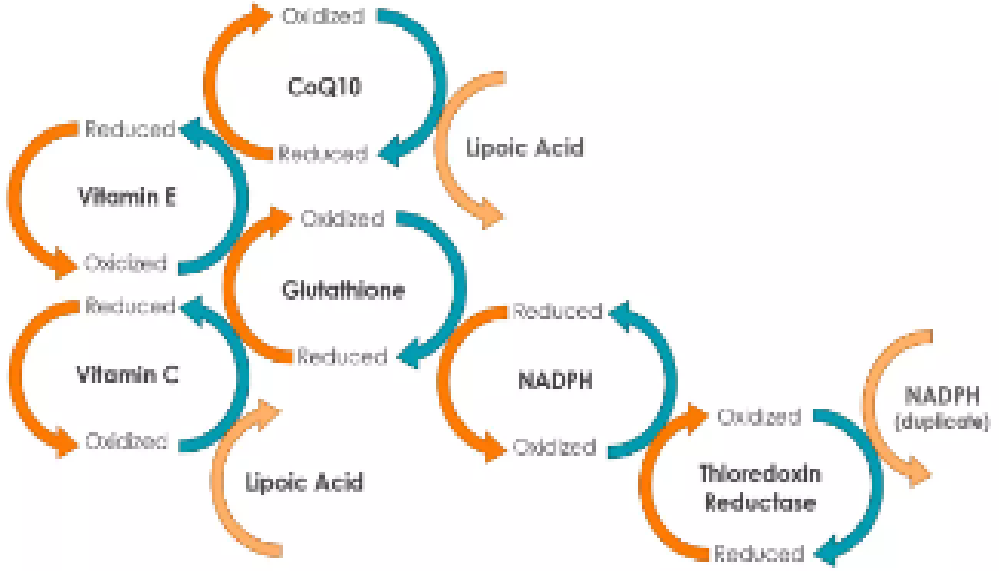
- ✓ Increases acetylcholine production by activation of choline acetyl-transferase
- ✓ Increases glucose uptake
- ✓ Acts as a metal chelator
- ✓ Down-regulates the expression of redox-sensitive pro-inflammatory proteins including TNF-α and inducible nitric oxide synthase
- ✓ Scavenges lipid peroxidation products such as 4-hydroxynonenal (HNE) and acrolein

Vitamin E

✓ Antioxidant protection

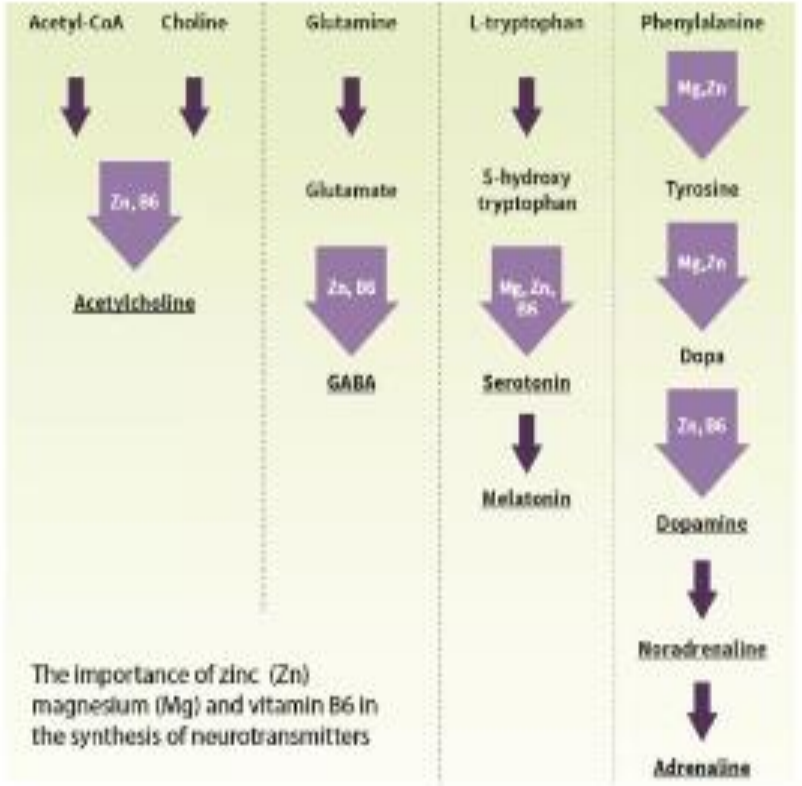
Vitamin C

- ✓ Further supports detoxification, provides antioxidant protection against free radicals
- ✓ Reduces tiredness and fatigue
- ✓ Necessary for the proper functioning of the CNS and psychological functioning



Magnesium, B6 and zinc modulate glutamatergic neurotransmission and key role in regulating the NMDA receptor, the main glutamate receptor implicated in excitotoxicity

- Magnesium blocks the NMDA receptor and must be removed in order for excitation to occur
- Zinc is co-released with glutamate into the synaptic cleft, and is thought to negatively modulate the excitatory response
- A deficiency in vitamin B6 can lead to higher levels of glutamate and reduced levels of GABA inhibition, thereby facilitating excitotoxicity
- Thus, low magnesium, zinc and or vitamin B6 levels could support excitotoxicity



The importance of zinc (Zn) magnesium (Mg) and vitamin B6 in the synthesis of neurotransmitters

Holton K. The role of diet in the treatment of fibromyalgia. Pain Manag. 2016 May;6(4):317-20.

Holton KF, Taren DL, Thomson CA, Bonnett RM, Jones KD. The effect of dietary glutamate on fibromyalgia and irritable bowel symptoms. Clin Exp Rheumatol. 2012 Nov-Dec;30(6 Suppl 74):10-7.

Thank You!

Hormone issues are complex and daunting. I hope this brief presentation has helped to shed some light on the matter.

To those who struggle with Fibromyalgia, my regards on your courage to persist in finding answers.