SYMPATHETIC INVOLVEMENT IN INE STRESS

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I. The SNS has pro-inflammatory and anti-inflammatory functions.

A. Neurotransmitters such as norepinephrine, adenosine, and others can elicit different and even opposing effects, depending on:

1. neurotransmitter concentration (density of sympathetic nerve fibers and extent of neurotransmitter release),
2. receptor affinity at different receptor subtypes,
3. expression of adrenoreceptors,
4. availability of cotransmitters,
5. timing of SNS activity in relation to the inflammatory course of events.

B. Central SNS outflow is controlled by SNS control centers in the brain activated by:

1. Central nervous stimuli (cortical areas and limbic system)
2. Sensory inputs from the periphery (via the hypothalamus)
3. Sensory afferent nerves to other brain SNS centers
4. Input signals to the brain from the periphery can be via circulating cytokines such as IL-1β, or, stimulation of peripheral sensory nerve fibers by cytokines.

C. Brain activated SNS efferent pathways traverse the spinal cord and reach SNS ganglia in the aorta or the abdomen.

1. Nerve fibers are switched to postganglionic SNS noradrenergic fibers, which enter the gut through the mesenteric serosal surface.

D. As part of its fight-or-flight reaction during stressful situations the SNS plays a pro-inflammatory role in the early inflammatory response.

1. The SNS is a critical pro-inflammatory component in the neurogenic inflammation that is particularly evident during the first hours of an inflammatory response.

a. SNS neurotransmitters support plasma extravasation --- transporting WBCs to the inflammation site --- drawn by cytokines IL-1, TNF-α, and IL-8.

b. The SNS directs migration of immune cells to sites of inflammation as part of the innate immune system (immediate defense), drawing phagocytes (neutrophils, macrophages, and dendritic cells).

E. Important immune inhibitory effects of SNS neurotransmitters in the late inflammatory response are shown to inhibit pro-inflammatory cytokines such as TNF, IFN-γ, IL-2, and IL-12 via:

1. Beta-adrenoreceptors
2. A2 adenosine receptors
3. Cyclic adenosine monophosphate (cAMP)
4. Protein kinase A

II. Neurotransmitters of the SNS

A. Apart from norepinephrine, sympathetic neurotransmitters include neuropeptide Y, methionine-enkephalin, luceine-enkephalin, beta-endorphin, and adenosine (--- ATP, ADP, cAMP).

B. SNS neurotransmitters can have opposing effects, depending on the receptor involved.

1. At low concentrations, norepinephrine and adenosine bind to alpha-adrenoreceptors and A1 adenosine receptors, leading to decreased cAMP levels.
2. At high concentrations, norepinephrine and adenosine bind to beta-adrenocreceptors and A2 adenosine receptors, increasing cAMP.

C. Sympathetic adrenergic (norepinephrine) receptors of both the alpha and beta type are expressed by:

1. Keratinocytes.
2. Melanocytes
3. Receptors in natural killer cells.
4. Receptors in monocytes.
5. Receptors in T cells --- inducible by T cells.
6. Receptors in B cells.

D. Adrenergic effects include:

1. Suppress IL-12 production and increase IL-10 release in dendritic cells.
2. Inactivate NFkB.
3. Augment T-cell production.
4. Inhibit TNF-α release from monocytes.
5. Modulate keratinocyte differentiation.
6. Regulate melanogenisis.

E. The beta-adrenergic signaling pathway is further supported by cortisol in many different cell types.

1. Cortisol enters the tissues without restraint. Loss of or rapid degradation of endogenous cortisol is most probably a prerequisite for predominant alpha-adrenergic signaling since cortisol exclusively supports the beta-adrenergic pathway.

    a. The cooperative anti-inflammatory effects of corticosteroids and norepinephrine are demonstrated in inflamed synovial tissue of rheumatoid arthritis.

F. Adenosine responds to cellular damage associated with either inflammation or ischemia. Adenosine confers cytoprotection preventing tissue damage.

1. Adenosine is anti-inflammatory via regulation of innate immunity.

2. Adenosine is anti-inflammatory at the A_2A receptor.

    a. Adenosine has been used as a topical application for foot wounds in diabetics and other wound-healing deficiencies.
    b. Methotrexate's anti-inflammatory effects may be due to stimulation of Adenosine release.

G. Acetylcholine (Parasympathetic and Sympathetic cholinergic) = both nicotinic and muscarinic acetylcholine receptors.

1. Acetylcholine mediates itch in Atopic Dermatitis.
2. Acetylcholine inhibits NFkB transcription (anti-inflammatory).
3. Acetylcholine inhibits release of TNF-α and IL-1-β.

III. Adrenergic Receptors.

A. Alpha 1 receptors → Phospholipase C → Calcium moves intracellularly → smooth muscle contraction.

1. Norepinephrine has a greater effect than epinephrine.
2. Vasoconstriction in the skin.
3. Vasoconstriction in mucosa.
4. Vasoconstriction in adnominal viscera.
5. Sweat secretory.
6. Provokes histamine (H1) reactions.

B. Alpha 2 receptors → Adenyl-cyclase inhibited → inhibits calcium moving into cells → inhibits norepinephrine and epinephrine release → inhibits ATP conversion to cAMP → smooth muscle contraction.

1. Norepinephrine has less effect than does epinephrine.

2. Platelet activation === Thrombocyte aggregation.

C. Beta-1, 2 & 3 receptors → Adenyl-cyclase → ATP → cAMP → myocardial contraction + smooth muscle relaxation + glycogenolysis.

1. Beta 1 receptors → epinephrine and norepinephrine have equal effect.

    a. Increase heart rate via both the AV node and the SA node, along with increasing myocardial strength of contraction (stroke volume).

2. Beta 2 receptors, norepinephrine has less effect than does epinephrine.

    a. "Fight or flight"
    b. Smooth muscle contraction = vasodilation to muscle (but opposed by alpha 1 vasoconstriction)
    c. Bronchodilation
    d. Inhibits Mast Cell histamine release

3. Beta 3 receptors → Norepinephrine has a greater effect than epinephrine.

    a. Lipolysis in adipose, and bladder wall relaxation --- but no direct ImmunoNeuroEndocrine effects.

IV. SNS neurotransmitters modulate immune responses.

A. Migration of immune cells

1. Norepinephrine and adenosine (as well as cortisol) mobilize many types of immune cells.

    a. Adenosine can attract neutrophils.
    b. Directed migration of monocytes is partly mediated via beta-adrenergic signaling.
    c. Norepinephrine stimulates secretion of the neutrophil cytokine IL-8.
    d. Norepinephrine increases neutrophil influx to the intestinal mucosa.

e. Stress during surgery increases lymphocytes in the lymphatic tissue of the intestine.
f. Migration of immature dendritic cells to lymph nodes is mediated via alpha-1 adrenergic receptors (as seen in the skin = relevant to Dermographics and Niacin Flush).

2. Since the SNS responds very rapidly (as a nervous system), these early effects of the SNS are important at the beginning of a local inflammatory response.

3. Immune stimuli induce local production of substance P, calcitonin gene-related peptide, and NO (Nitric Oxide). These and other mediators lead to vasodilation. Norepinephrine counteracts the vasodilation via alpha-1 adrenergic receptors (--- minimizes Red Dermographics). --- However --- Adenosine is a vasodilator via cAMP.

4. Chemotactic factors, including both substance P and norepinephrine (via beta-adrenergic receptors) support leukocyte extravasation.

5. Also, exodus of relatively immature dendritic cells is supported by alpha-1 adrenergic signaling.

6. Thus, neurotransmitters of the SNS support chemotaxis, which is a very early event in the beginning of an inflammatory reaction.

7. After leukocytes are involved in an inflammatory process, they start to produce pro-inflammatory cytokines (TNF and Interleukins) and SNS nerve repellant factors, which inhibit neurotransmitter release, and lead to loss of sympathetic nerve fibers.

   a. IMPORTANT NOTE: The SNS activates the immune system at the onset of inflammation, but once the inflammatory process is activated, it actually destroys SNS nerves --- leaving the inflamed tissue in a relatively Parasympathetic state.

B. SNS neurotransmitters modulate apoptosis (beneficial cell death).

1. High concentrations of norepinephrine stimulate apoptosis in several cell types.

2. In the gut --- exercise, stress, and catecholamine infusion have been shown to induce beta-adrenergically-mediated apoptosis of intestinal lymphocytes.

3. Induction of apoptosis can be an anti-inflammatory mechanism if pro-inflammatory immune cells are targeted.

C. Sympathetic neurotransmitters modulate innate immune cells.

1. Norepinephrine at high concentration (via beta-adrenoreceptors) has been shown to inhibit immune functions such as phagocytosis, natural killer cell activity, and MHC class 2 expression, as well as secretion of TNF, IL-12, and IFN-γ from macrophages and lymphocytes.

2. Beta-adrenergic signaling inhibits many aspects of the innate immune system (natural killer cells, neutrophils, macrophages, and others).

3. --- However --- the effects of norepinephrine at low concentration mediated via alpha 2-adrenoreceptors can actually increase macrophage TNF secretion.

4. Signaling through alpha 2-adrenoreceptors is important to resist the intracellular growth of microbes.

5. Similarly, adenosine exerts opposite effects on cytokine secretion at low concentrations compared with high concentrations.

6. Adenosine responds to inflammation and ischemia as a cytoprotective preventing tissues damage. It is anti-inflammatory via regulation of innate immunity.

7. The dual role of sympathetic neurotransmitters is thus an important prerequisite for either the pro- or anti-inflammatory effects of the SNS on the innate immune system.

D. Sympathetic neurotransmitters modulate cells of the adaptive immune system.

1. Norepinephrine, via beta-adrenergic signaling, stimulates aspects of the Th2 immune responses by increasing IL-4, IL-5, IL-6, and IL-10.

2. Norepinephrine stimulates immunoglobulin production of B lymphocytes.

3. --- So --- a pro-inflammatory immune reaction with a predominance of Th2 cytokines such as in ulcerative colitis, systemic lupus, or allergic diseases is likely aggravated by the SNS.

4. In contrast, typical Th1 immune responses such as production of lymphocyte TNF, IL-2, or IFN-γ are suppressed via the beta-adrenergic receptor.

5. --- Thus --- the prevailing type of T lymphocyte reaction determines the influence of the SNS on the immune system.

    a. There are opposite effects of the SNS on immune responses in bacterial infection with gram-negative and gram-positive bacteria. TNF is bacteriostatic and is suppressed by the SNS; IL-4 is bacteriostatic, and is enhanced by the SNS.
    b. With respect to immune-mediated diseases, the dominance of a specific B or T lymphocyte immune reaction is often <u>not</u> detectable.
    c. A mixture of different types of immune reactions with innate <u>and</u> adaptive (B cells, Th1, Th2, T regulatory cells) aspects is present in humans. A dominant response largely depends on genetic makeup of the patient, the antigen, the site of the immune response, and the time-point of the immune response.

E. Direction of influence of the SNS depends on <u>the time-point of the immune response</u>.

1. In the early, pre-symptomatic phase of an immune-mediated disease, T cells, B cells, and antigen-presenting cells (APCs) will play a major role --- there are increased autoantibody titres against autoantigens (a function of the adaptive immune system) many years before the first symptoms appear.

2. After the disease becomes symptomatic, many other local cell types, particularly of the innate immune system, are involved in the destructive process. The role of the initial players of the adaptive immune system --- T cell, B cell, and APCs --- simultaneously decrease, as the other cell types become involved. --- Thus, there is a separate presymptomatic and symptomatic phase of immune-mediated disease.

3. --- Consequently --- the influence of the SNS on the immune response largely depends on the time-point of SNS activation in relation to the immune response.

    a. The <u>first phase</u> of an inflammation, during which directed migration is maximally important, is <u>supported</u> by the SNS, while <u>later phases</u> of tissue destruction by cells of the innate system are <u>inhibited</u> by the SNS. --- The dual role of the SNS depends on the immune mechanisms involved. --- So --- Complex P and other SNS supporting supplements are indicated to support <u>both</u> the immune-stimulatory and the immune-inhibitory effects of the SNS.

V. SNS damage in inflammation (---Damage done to, as opposed to by the SNS) (=== Need for Complex P and other SNS support)

A. There is loss of sympathetic nerve fibers in the inflamed area in both arthritis and diabetes.

B. There is a loss of SNS nerve fibers in Crohn's disease.

C. (Ulcerative colitis may be quite different from Crohn's in that there may be an increased density of the adrenergic network.)

D. In models of colitis, both dopamine and norepinephrine are low in the inflamed mucosa of the distal colon, but not in the non-inflamed ileum.

E. Dopamine levels in the inflamed mucosa of both Crohn's and ulcerative colitis are low, while L-DOPA is elevated. Since L-DOPA is the precursor of dopamine (and norepinephrine), these findings suggest decreased L-DOPA decarboxylase enzyme activity in inflamed tissue.

F. Gut infection with Toxoplasmosis results in colonic pseudo-obstruction due to selective sympathetic denervation.

G. Macrophages and fibroblasts in inflammatory lesions produce nerve repellent factors specific for sympathetic (but not for sensory) nerve fibers.

1. It may be that during the early process of inflammation the SNS supports directed migration, but on activation of local macrophages and fibroblasts, secreted nerve repellent factors lead to distinct loss of sympathetic nerve fibers.

H. An important factor for low catecholamine levels in inflamed tissue is inhibition of norepinephrine release from SNS nerve terminals.

1. Intestinal infection with trichinella suppresses release of norepinephrine. Even though the worm infection only lasts 17 days, norepinephrine release is inhibited for over 100 days post infection.

I. TNF inhibits release of norepinephrine in the hypothalamus.

J. IL-1β and IL-6 inhibit norepinephrine release, and the effect is mediated via the induction of nitric oxide. (Note the consistent suppression of the SNS by the Th1 inflammatory cytokine IL-1β, and by NO. Note also that the Th2 inflammatory cytokine IL6 is increased by SNS beta adrenergic activity, yet IL-6 has negative feedback on the SNS, decreasing norepinephrine.)

K. The fundamental effect of inflammation-induced inhibition of norepinephrine release is the reduction of the sympathetic brake on secretomotor neurons in the gut, thus supporting neurogenic secretory diarrhea.

1. Clostridium toxin A induces intestinal inflammation by suppressing sympathetic neurotransmission.

2. IL-1β and IL-6 excite neurons and suppress both nicotinic and noradrenergic neurotransmission in the enteric nervous system. Also, Prostaglandins such as PGE-1 and PGE-2 released on inflammation attenuate the sympathetically induced inhibition of motor neurons in the gut.

L. (Neurogenic secretory diarrhea is not found in ulcerative colitis, thus supporting the increase in sympathetic nerve fibers in this disease.)

M. With respect to SNS innervation, Crohn's disease and rheumatoid arthritis seem to be remarkably different from ulcerative colitis.

N. Inhibition of norepinephrine release supports the chronicity of inflammation due to loss of sympathetic inhibition of innate and Th1-mediated immune responses.

VI. The SNS in the gut:

A. The SNS plays a critical role in gut inflammation.

1. The role of SNS in gut inflammation has similarities to its role in rheumatoid arthritis.

2. SNS nerve fibers not only enter the enteric plexuses but also innervate the mucosa and the gut-associated lymphoid tissue (GALT).

B. There are 4 effector organs in the gut: smooth muscle, mucosa, vasculature, and immune system.

1. These effector organs receive input directly from the enteric nervous system, which includes both the mesenteric and the submucosal plexuses.

a. The enteric nervous system receives input from both the Sympathetic and Parasympathetic nervous systems.

2. The 4 effector organs also receive direct SNS activation without mesenteric or submucosal plexus involvement.

C. The SNS coordinates with the PNS to control motility, secretion, and vasoregulation.

1. Norepinephrine inhibits descending motor neurons (acetylcholine and substance P) via A2 adrenergic signals.

2. Immune stimuli from the lumen and in the mucosa stimulate sensory neurons of the vagus, which locally release substance P and send signals to higher centers.

   a. Substance P can attract leukocytes and support vasodilation.
   b. Norepinephrine leads to vasoconstriction (opposes substance P) via A1 adrenergic receptors.

3. Vascular tone is controlled via dilatory signals (substance P, calcitonin gene-related peptide, nitric oxide, and vasoactive intestinal peptide) --- and --- constriction signals (somatostatin and norepinephrine via A1 adrenergic receptors).

4. Secretory neurons are stimulated by acetylcholine and inhibited by norepinephrine via A2 adrenoceptors and by somatostatin.

5. Intrinsic afferent neurons are stimulated by serotonin --- these neurons are coupled to motor neurons and secretory neurons.

6. Local SNS nerve fibers travel along blood vessels and terminate next to epithelial cells where they modulate immune responses in the vicinity of the mucosal blood vessel via ATP.

VII. SNS tone in inflammatory bowel diseases:

A. Similar to other chronic inflammatory diseases, the tone of the SNS is increased in patients with inflammatory bowel disease.

B. In rheumatoid arthritis and SLE, this increased sympathetic tone is related to increased mortality.

C. An elevated SNS tone does not increase norepinephrine at the site of inflammation, because there is a loss of sympathetic nerve fibers. In addition, concentrations of circulating norepinephrine are only increased slightly. Thus, increased plasma concentration of norepinephrine is not sufficient to significantly increase the local concentration in inflamed tissue. The increased systemic concentration might facilitate leukocyte mobilization from non-inflamed areas, which may then migrate to sites of inflammation.

1. There is an uncoupling of the sympathetic nervous system and the HPA axis in inflammatory bowel disease.

D. In common with rheumatoid arthritis, patients with inflammatory bowel diseases show inadequately low concentration of cortisol in relation to inflammation, as measured by IL-6 and TNF. Consequently, there is low concentration of cortisol in inflamed tissue.

VIII. Summary

A. Rheumatoid arthritis and Crohn's disease are associated with Th1 lymphocyte dominance, signs of activated innate immune system in the chronic symptomatic phase (macrophage, neutrophils, and others), and overshooting responses of myofibroblasts/fibroblasts leading to scar formation.

B. --- These inflammatory reactions are normally suppressed by the SNS via beta adrenergic pathways. This suppression occurs directly at the level of T lymphocytes, macrophages, dendritic cells, NK cells, and neutrophils. The immune inhibiting effects of the SNS are lost.

C. Loss of SNS fibers in inflamed tissue as well as inflammation-induced inhibition of norepinephrine release, with a concomitant decrease in local neurotransmitter levels converts a normally beta adrenergic zone into an alpha adrenergic zone.

D. This shift from beta adrenergic to alpha adrenergic dominance is followed by a reduction in the sympathetic brake on secretomotor neurons, leading to secretory diarrhea, as well as an overall pro-inflammatory environment.

E. An increased ratio of pro-inflammatory substance P positive nerve fibers to SNS nerve fibers supports inflammation and secretory diarrhea. (=== Parasympathetic Imbalance)

F. The parallel inadequate secretion of cortisol together with loss of beta-adrenergic receptor-mediated effects leads to inadequate anti-inflammatory capacity. (=== Parasympathetic and Dysaerobic Imbalances)

G. The similarities between rheumatoid arthritis and Crohn's disease suggests that a general principle exists explaining the SNS beta adrenergic deficiency in chronic inflammation.

1. It is hypothesized that the shift from beta adrenergic to alpha-adrenergic dominance exists as a protective mechanism both for overcoming infectious diseases, and for supporting the wound healing process.

H. From reading the above facts on the SNS in the gut, SNS tone in inflammatory bowel diseases, and the Summary, you see evidence that inflammatory bowel conditions could be either associated with a Sympathetic Imbalance or Parasympathetic Imbalance. Why the apparent contradiction?

1. There is really no contradiction at all. The Sympathetic/ Parasympathetic component of gut pathology relates as much to Anaerobic/Dysaerobic Imbalances and Prostaglandin-Nitric Oxide Imbalances as it does autonomic nerve reactivity.

2. In fact, whether there is an excess Sympathetic response, a deficient Sympathetic response, an exaggerated Parasympathetic response, or a deficient Parasympathetic response, depends on the genetic tendency of the individual, and the individual's status with respect to Anaerobic/Dysaerobic and Prostaglandin-Nitric Oxide Imbalances.

3. Furthermore, some patients with inflammatory gut pathologies can be both Sympathetic and Parasympathetic reactive. These are the patients we call "Vacillator/Oscillators". They have enough capacity for both Sympathetic and Parasympathetic defensive reactivity that they can swing (sometimes violently) between one Imbalance and the other --- and again, the direction they swing relates to concomitant involvement of Anaerobic/Dysaerobic or Prostaglandin-Nitric Oxide Imbalances.

IX. Fibromyalgia Syndrome as a model for SNS immune involvement

A. Fibromyalgia Syndrome (FMS) involves a number of factors, including abnormalities in the neuro-endocrine and autonomic nervous systems, as well as genetic, psychosocial, and environmental stressors.

B. FMS tends to co-occur with other syndromes typified by recurrent pain and/or emotional stress:

1. Irritable bowel syndrome
2. TMJ disorder
3. Anxiety disorders
4. Chronic inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and SLE

C. FMS patients display enhanced sensitivity to a wide variety of stimuli, such as heat and cold, mechanical pressure, and ischemic pressure.

    1. FMS is characterized by augmentation of sensory input mediated by the CNS.

        a. This central sensitization may involve deficient levels of norepinephrine and/or serotonin --- key neurotransmitters in endogenous pain inhibitory pathways.

D. Normal (not FMS) pain is associated with excitation of pain transmission neurons by substance P and excitatory amino acids such as glutamate.

    1. Pain impulses ascend to various regions in the brain, including the thalamus, somatosensory cortices, and the limbic system, thus resulting in the perception of pain.

E. In abnormal (such as FMS) pain processing, the pain transmission neurons become over-sensitized to incoming pain signals.

    1. One mechanism underlying this sensitization is the over-activation of postsynaptic nitric oxide production, which in turn increases the pre-synaptic release of excitatory amino acids and substance P, causing the pain transmission neurons to become hyperexcitable. The enhanced nitric oxide production is fed by its precursor arginine, and the pain transmission nerve hyperexcitability is associated with excess calcium intake.

        a. The role of spinal glial cells in central sensitization is critical, as glial pro-inflammatory cytokines mediate exaggerated pain states.
        b. --- It is hypothesized that dorsal horn glia are activated by the release of nitric oxide, Prostaglandins, fractalkine, substance P, ATP, and excitatory amino acids from pain transmission neurons and primary afferents.
        c. The glia, in turn, release pro-inflammatory cytokines, nitric oxide, Prostaglandins, ROS (Reactive Oxygen Species), ATP, and excitatory amino acids (--- note the positive feedback loop).
        d. In addition to further increasing the release of substance P and glutamate and other excitatory amino acids from the afferent fibers, these substances enhance or prolong the hyperexcitability of the pain transmission neurons.

F. Approximately 50% lower stimulus intensity is needed to evoke pain in FMS --- strong evidence that the enhanced pain sensitivity is associated with CNS augmentation of relatively low levels of sensory input.

G. FMS pain probably also involves aberrations in the descending pain inhibition pathways. Afferent transmission of sensory input to the brain is inhibited by the activation of efferent fibers descending from brain stem sites through the dorsal horn, primarily through the release of norepinephrine and serotonin. In FMS, there may be deficiencies in CNS levels of these neurotransmitters.

1. FMS patients show low serum serotonin and low CSF metabolites of serotonin, norepinephrine, and dopamine.

H. FMS is a stress-related disorder involving abnormal HPA function, associated with the inability to suppress cortisol.

1. To illustrate: compared to patients with RA, FMS patients show higher overall plasma cortisol, and exhibit higher peak and trough levels of plasma cortisol. 35% of FMS patients are so high in cortisol that it cannot be suppressed with dexamethasone.

2. The relationship between salivary cortisol levels and ratings of pain, fatigue, and stress show no difference between patients and controls in terms of cortisol levels or diurnal variations. However, significant associations between cortisol levels and pain ratings are present at the time of awakening and one hour after waking. No associations between cortisol level and fatigue or stress were observed. --- So --- patients with FMS are characterized by disturbances in HPA axis function associated with elevated cortisol, however the correlation between elevated cortisol and pain only applies in the morning.

3. High cortisol, low epinephrine, and cortisol-associated morning pain correlate with Anaerobic Imbalance, Parasympathetic Imbalance and Alkaline Imbalance, as well as Prostaglandin-Nitric Oxide Imbalance.

I. Abnormal autonomic nerve function, including decreased micro-circulatory vasoconstriction and orthostatic hypotension, are characteristic of FMS. (=== Parasympathetic Imbalance)

1. There is decreased vasoconstriction response to cold pressor stimulation.

2. During 60° tilt table testing, 60% of patients with FMS showed an abnormal drop in blood pressure compared with 0% of controls. Even among those who tolerated the tilt table test, remaining in that position for 10 minutes caused a worsening of pain symptoms, while control subjects remained asymptomatic.

3. Difficulty maintaining blood pressure may directly contribute to some of the symptoms frequently associated with FMS, such as fatigue and dizziness, as well as physiologic responses to stressors.

4. One study shows that FMS patients may have significantly lower heart rate variability in the standing position, and that decreased HRV was associated with sleep disturbance and fatigue, and it was much more common in women than in men. (=== Sympathetic or Dysaerobic Imbalance)

5. In men (but not women) with FMS, there is sympathetic hyperactivity and concomitant reduced parasympathetic activity. During postural changes, male patients show an abnormal sympathovagal response. These results provide the physiological basis for the orthostatic intolerance in men with FMS. (=== Sympathetic Imbalance)

6. Heart rate is significantly higher in FMS patients compared to controls, but with a significantly lower heart rate variability. In general, the basal autonomic state of FMS patients shows increased sympathetic and decreased parasympathetic tone (--- ? increased orthostatic heart rate response, but not necessarily orthostatic blood pressure failure?) --- (--- ? increased alpha adrenergic activity, but decreased beta adrenergic activity?) (=== Sympathetic Imbalance)

J. FMS patients tend to have insomnia, early morning awakening, and non-restorative poor quality sleep. Frequent alpha-wave intrusions during delta-wave sleep have been associated with reduced production of GH and IGF-1.

   1. Since GH and IGF-1 are necessary for the repair of muscle microtrauma, sleep disturbances may impair the healing of muscle tissue damage, thus prolonging the transmission of sensory stimuli from damaged muscle.

   2. There is a correlation between poor sleep quality and pain in FMS. Improvement in sleep is reported to resolve chronic wide-spread pain independently of change in psychological factors.

K. There may be a relationship between catechol-O-methyltransferase (COMT) enzyme gene variance and pain. The involved enzyme metabolizes norepinephrine and dopamine. The COMT gene has been implicated in the pathogenesis of migraine and anxiety disorders as well as a variety of cardiovascular diseases. Abnormal COMT is also associated with TMJ disorder. COMT enzymatic activity is significantly decreased among FMS patients. In animal studies, enhanced

mechanical and thermal pain sensitivity associated with depressed COMT is completely blocked by the non-selective beta adrenergic antagonist propranolol. (=== Sympathetic Imbalance)

1. Dopamine receptor agonists and medications that selectively inhibit the reuptake of norepinephrine have been found effective in treating FMS pain --- but --- there are both negative and positive findings regarding the association between serotonin and catecholamines with FMS.

2. One study shows that in women with FMS, there is a decrease in presynaptic dopamine metabolism in several CNS regions where dopamine normally contributes to pain inhibition.

L. From reading the above facts on the SNS in FMS you see evidence that FMS could be <u>either</u> associated with a Sympathetic Imbalance or Parasympathetic Imbalance. Why the apparent contradiction?

1. There is really no contradiction at all. The Sympathetic/ Parasympathetic component of FMS relates as much to Anaerobic/Dysaerobic Imbalances and Prostaglandin-Nitric Oxide Imbalances as it does autonomic nerve reactivity.

2. In fact, whether there is an excess Sympathetic response, a deficient Sympathetic response, an exaggerated Parasympathetic response, or a deficient Parasympathetic response, depends on the genetic tendency of the individual, and the individual's status with respect to Anaerobic/Dysaerobic and Prostaglandin-Nitric Oxide Imbalances.

3. Furthermore, some patients with FMS can be <u>both</u> Sympathetic and Parasympathetic reactive. These are the patients we call "Vacillator/Oscillators". They have enough capacity for both Sympathetic and Parasympathetic defensive reactivity that they can swing (sometimes violently) between one Imbalance and the other --- and again, the direction they swing relates to concomitant involvement of Anaerobic/Dysaerobic or Prostaglandin-Nitric Oxide Imbalances

X. Salivary alpha-amylase indicates norepinephrine status. --- Adrenergic activity, and particularly plasma <u>norepinephrine</u>, is directly related to the concentration of <u>salivary alpha-amylase</u>.

A. Aerobic exercise induces a 3-fold mean increase in alpha-amylase, as both norepinephrine and epinephrine increase approximately 5-fold over control levels. Alpha-amylase and norepinephrine return to

control levels within 30-45 minutes after exercise, but epinephrine remains elevated by approximately 2-fold during the remaining first hour post exercise. Greater intensities of exercise are associated with greater increases of alpha-amylase concentrations.

B. During a written examination, alpha-amylase and norepinephrine, but not epinephrine, concentrations increase in parallel.

C. During heat exposure (in a sauna for 40 minutes), amylase, heart rate, and body temperature all increase progressively. However, during exposure to cold for 40 minutes, amylase increases rapidly, as heart rate and body temperature remain unchanged.

1. Salivary cortisol concentrations are unchanged during exposure to heat or cold.

2. Exposure to very hot conditions induces a typical stress response, with increased secretion of both catecholamines and cortisol. That response is even greater in exercise, and is greatest of all during exercise in very hot conditions. --- Under hot conditions, catecholamines induce a demargination of leukocytes (--- a large majority of WBCs is in easily mobilized reserves in bone and other tissues), and cortisol subsequently causes those cells to migrate to lymphoid tissue.

   a. Moderate exercise increases leukocyte numbers mainly in response to increasing plasma norepinephrine concentrations.

   b. But with more intense exercise, epinephrine concentrations assume major importance.

   c. As exercise continues, finally plasma cortisol levels also rise, inducing an influx of neutrophils from bone marrow and an efflux of other leukocyte subsets.

D. Other studies show that in patients with chronic pain, the salivary alpha-amylase directly parallels elevated norepinephrine, and that after epidural block to reduce pain, heart rate, systolic blood pressure, and pain (by visual analog scale) decrease proportionately.

E. Many studies indicate that salivary alpha-amylase is a clinically significant marker of the autonomic/sympathetic nervous system component of the psychology of stress.

1. When pregnant women are taken to the operating room for Caesarian, there is an increase in salivary alpha-amylase that

directly parallels an increase in systolic blood pressure (There are no significant changes in heart rate observed.).

2. Significant differences are found between individuals undergoing a psychosocial stress test, and in the same individual under resting conditions in salivary alpha-amylase, salivary cortisol, plasma catecholamines, and cardiovascular parameters such as heart rate and heart rate variability.

    a. However, general alpha-amylase responses were not associated with general responses in the catecholamine + cortisol stress response. Analyses of cardiovascular parameters indicated a positive relationship between amylase and Sympathetic tone (as expressed in the LF/HF heart rate variability) during stress. So, salivary alpha-amylase is sensitive to the Sympathetic component of psychosocial stress, but is not directly related to stress markers such as cortisol.

3. It is concluded that salivary alpha-amylase concentrations are predictive of plasma catecholamine levels, particularly norepinephrine, under a variety of stressful conditions, and may be a more direct and simple endpoint of catecholamine activity than are changes in heart rate.