SYMPATHETIC INVOLVEMENT IN INE STRESS

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. their concentration (presence 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 limbic system)
2. Inputs from the periphery (via the hypothalamus)
3. Sensory efferent nerves

C. Inputs signals to the brain from the periphery can be circulating cytokines such as IL-1β, or, stimulation of sensory nerve fibers by cytokines.

D. Brain activated SNS 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.

E. 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.

   b. The SNS directs migration of immune cells to sites of inflammation.
F. 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. 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: 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.

III. Neurotransmitters of the SNS

A. Apart from norepinephrine, sympathetic neurotransmitters include neuropeptide Y, methionine-enkephalin, luceine-enkephalin, beta-endorphin, and ATP.

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

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

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

1. Cortisol enters the tissues without restraint. Loss 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.

IV. SNS neurotransmitters modulate immune responses.

A. Migration of immune cells

1. Norepinephrine (as well as cortisol) mobilizes many types of immune cells.
a. Directed migration of monocytes is partly mediated via beta-adrenergic signaling.
b. Adenosine can attract neutrophils.
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).

2. As 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. These and other mediators lead to vasodilation. Norepinephrine counteracts the vasodilation via alpha-1 adrenergic receptors.

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

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

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

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

B. SNS neurotransmitters modulate apoptosis.

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. 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.

6. With respect to immune-mediated diseases, the dominance of a specific B or T lymphocyte immune reaction is often not detectable.

a. A mixture of different types of immune reactions with innate and adaptive (B, Th1, Th2, T regulatory) aspects is present in humans and 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 the time-point of the immune response.

1. In the early, pre-symptomatic phase of an immune-mediated disease, T cells, B cells, and antigen-presenting cells 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 first phase of an inflammation, during which directed migration is maximally important, is supported by the SNS, while later phases of tissue destruction by cells of the innate system are inhibited by the SNS. --- The dual role of the SNS depends on the immune mechanisms involved.

V. SNS damage in inflammation (---Damage done to, as opposed to by the SNS)

   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. 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.

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

G. 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.

H. A second 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 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. Inhibition of norepinephrine release supports the chronicity of inflammation due to loss of sympathetic inhibition of innate and Th1-mediated immune responses.
M. (Neurogenic secretory diarrhea is not found in ulcerative colitis, thus supporting the increase in sympathetic nerve fibers in this disease.)

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

VI. NS 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. On the other hand, 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.

VII. 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 typically 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.

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.

F. The parallel inadequate secretion of cortisol together with loss of beta adrenergic receptor mediated effects leads to inadequate anti-inflammatory capacity.

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.

VIII. SNS associations with FMS

A. FMS involves a number of factors, including abnormalities in the neuroendocrine 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 low 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 presynaptic 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. It is hypothesized that dorsal horn glia are active by the release of nitric oxide, prostaglandins, fractalkine, substance P, ATP, and excitatory amino acids from pain transmission neurons and primary afferents. The glia, in turn, release pro-inflammatory cytokines, nitric oxide, prostaglandins, ROS, ATP, and excitatory amino acids (--- note the positive feedback loop). 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 involved aberrations in the descending pain inhibition pathways. Efferent 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 in 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 apply in the morning.

I. Abnormal autonomic nerve function including decreased microcirculatory vasoconstriction and orthostatic hypotension are characteristic of FMS.

1. There are decreased vasoconstriction response to col 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, that that decreased HRV was associated with sleep disturbance and fatigue, and that it was much more common in women than in men.

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.

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?)

J. FMS patients tend to have insomnia, early morning awakening, 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 are 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.

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 in women with FMS, there is a decrease in presynaptic dopamine metabolism in several CNS regions where dopamine normally contributes to pain inhibition.
- Adrenergic activity, and particularly plasma norepinephrine, is directly related to the concentration of salivary alpha-amylase. 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.

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

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

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.

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.).

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

Significant differences are found between individuals undergoing a psychosocial stress test and 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.

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.
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.

- 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, and cortisol subsequently causes cells to migrate to lymphoid tissue. Moderate exercise increases leukocyte numbers mainly in response to increasing plasma norepinephrine concentrations. But with more intense exercise, epinephrine concentrations assume major importance. As exercise continues, finally plasma cortisol levels also rise, inducing an influx of neutrophils from bone marrow and an efflux of other leukocyte subsets.

- Horrobin has suggested that evolutionary brain changes occurring 2 million years ago coincided with the appearance of both psychoses and creativity, and that creativity and psychoses-proneness have made us truly human. He hypothesizes that those brain changes are related to changes in dietary fat intake, with an increased dietary intake of highly unsaturated fatty acids (HUFA). --- Alterations in FA metabolism are demonstrated in both psychotic individuals and extremely creative individuals. Those fatty acid metabolic pathways are also intimately related to catecholamine neurotransmitter function, particularly norepinephrine activity.

- Variations in endogenous NE levels with exercise and sleep can help assess noradrenergic effects on creative thought. Increases in alpha-amylase are found after rigorous exercise and correlates with elevations in plasma NE. Anaerobic exercise in particular will elevate NE and salivary amylase. Exercise has also been shown to enhance creative thought, and anaerobic exercise is more effective than aerobic exercise. Looking at sleep/wake cycles, NE activation is low just before falling asleep, a time when subjects are more likely to have a moment of insight. Such holistic problem solving as opposed to a stepwise process are more likely to be resolved while the NE system is less activated, and general cortical arousal is low.

During REM sleep, any neurons in the locus coeruleus (LC) (the site of NE synthesis in the brain) become silent, as REM sleep cannot occur in the presence of NE arousal and activity. Instead, acetyl cholinergic neurons in the PONS become active during REM sleep. Waking subjects after periods of sustained REM sleep in order to assess creativity or behavior assures that the NE system has been constrained. Results of testing patients under such conditions show that decreased NE functioning contributes to enhancing creativity that requires divergent rather than convergent
thinking. (Convergent tasks, however in contrast, are extremely resistant to sleep loss, while divergent creative thinking ability suffers as a result of sustained sleep loss.)

- As stress increases, so does NE activity, and performance on cognitive tasks declines. Giving propranolol improves the performance on cognitive tasks.

- Since the NE system arising from projections in the LC is associated with mediating changes in arousal and vigilance as a consequence of novelty in the environment, a substantial link to creative cognition from NE systems may be through neural mechanisms of arousal. EEG evidence shows that creative thinkers are less aroused than non-creative thinkers when determining creative solutions to problems. EEG alpha activity from the thalamus increases in creative subjects compared to subjects exhibiting low to medium levels of creative ability. Interestingly, EEG alpha wave activity is associated with decreased arousal, as it is an inverse measure of the general cortical arousal response. It has also been shown that EEG alpha relative activity is directly correlated with changes in CSF levels of NE. As NE increase, alpha relative activity decreases.

Subjects who exhibit fewer creative traits do focus their attention more narrowly, supporting the idea that creative people have a broader focus of attention and greater attentive capacity related to specific mechanisms of cortical activation. In addition to levels of arousal being decreased in divergent thinking, EEG complexity increases during the same type of thinking. This indicates that although general cortical arousal is lower, more neuronal elements are activated. (--- Noncreative people think narrowly but deeply, while creative people think more broadly.) Direct manipulation of the noradrenergic system produces changes in brain EEG waves. NE tends to vary directly with arousal levels, but inversely with EEG alpha and beta activity.

- From its production site in the LC of the caudal region of the PONS, NE neurons innervate each of the brain cortices, plus the hypothalamus, the cerebellum, and the spinal cord. This widely distributed network of fibers has been traditionally studied behaviorally in terms of attention, arousal, and mood. As regards creative thinking, moderate levels of effective states such as positive feelings achieved after exercise do enhance creative thinking skills, and moderate (compared to extremely high or low) levels of vigilance and attention either improves creative production or is associated with better performance in creative vs. noncreative thinking.

The noradrenergic system has been extensively studied for its effects on emotion, behavior, cognition, and physiological states. The systems most general role is in addressing vigilance and arousal and regulation attention resources, especially needs arising to novel environmental stimuli.
But LC neurons respond differently to general motivational and exploratory states compared to more specific demands that require goal attainment and specific attention.