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5

Fibromyalgia syndrome: a pain modulation disorder related to altered limbic function?

JAY A. GOLDSTEIN

As a physician who specializes in the diagnosis and treatment of chronic fatigue syndrome (CFS) and fibromyalgia syndrome (FMS), I see a large number of patients who also have such problems as irritable bowel syndrome, panic disorder, amnestic disorder, allergic rhinitis, blurred vision, muscle fasciculations, myasthenia, interstitial cystitis, sleep disorders, headache, bruxism, irritable bladder, alopecia, thermoregulatory dysfunction, lymphadenalgia, dyspnoea, chemical sensitivity, endometriosis, late luteal phase dysphoric disorder, heart palpitations, photophobia, vertigo, Raynaud phenomenon and dysmenorrhoea. Some patients have immune activation related to 'overlap syndromes' with such disorders as systemic lupus erythematosus and multiple sclerosis. Over half report feeling well until they had 'the worst flu of my life', after which they never felt the same, so that investigation of persistent viral infection or 'hit and run' viral episodes that result in long-term functional impairment of affected and bystander cells is relevant.

It is quite common for me to consult with individuals who have many of the above disorders. Initially, most of them seemed unrelated. Looking for a mechanism to produce such a wide range of illnesses led me to the study of neuroimmunoendocrine networks, especially the limbic system and its projections. This myriad of signs and symptoms may be explained by limbic dysfunction.

The literature discussing the structure and function of the limbic system and its cortical projections (Figure 1), an example of a neural network which uses a parallel distributed computational strategy, is complex and may be unfamiliar to many readers of this volume. These topics have been well discussed by M.-Marsel Mesulam (1985, 1990), and these works form a good foundation for the understanding of limbic physiology and its derangements.

One can view the limbic neural network functioning as a computer, processing intero- and exteroceptive stimuli (input), primarily via a bewildering array of chemically transduced messages, integrating them with experiences and attitudes (processing), and selecting responses (output) that should ideally maximize the survival capabilities of the individual (Figure 2).

Baillière's Clinical Rheumatology—
Vol. 8, No. 4, November 1994
ISBN 0-7020-1867-8

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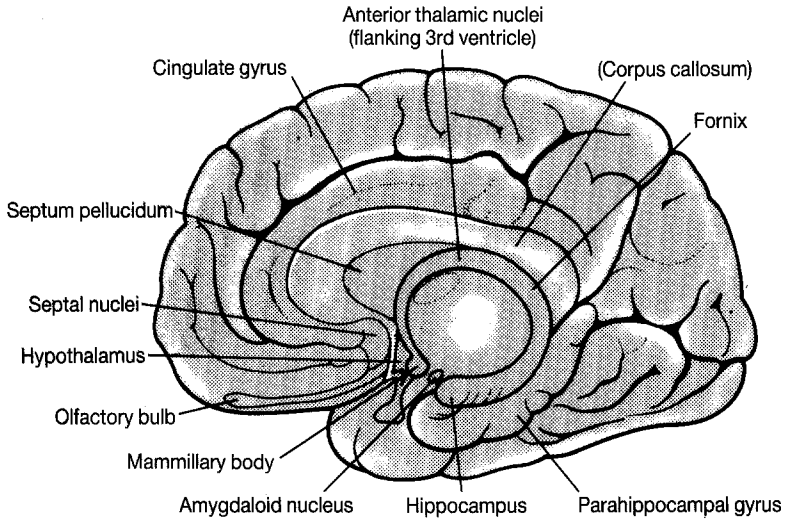

Figure 1. The limbic system. Medial view of the brain, showing some of the structures that constitute the limbic system – the emotional-visceral brain. The brain stem is not illustrated. From *Human Anatomy and Physiology*, Second Edition, by Elaine N. Marieb. Copyright [©] 1992 by The Benjamin/Cummings Publishing Company. Reprinted by permission.

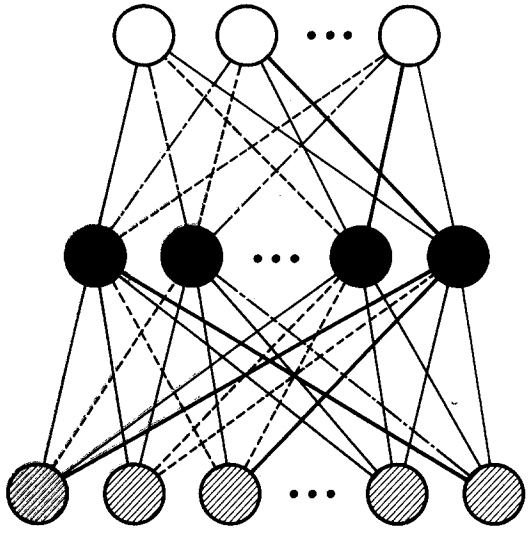

Figure 2. Common neural network. Figure adapted from page 106, Hinton G. How neural networks learn from experience. *Scientific American*, September 1992, **267(3)**. Copyright © 1992 by Scientific American Inc. All rights reserved.

The limbic system is the highest order functional regulator (integrative processing) in the body, and has effects on fatigue, pain, sleep, weight, appetite, libido, respiration, temperature, blood pressure, memory, attention, concept formation, mood, vigilance, the immune and endocrine systems, and the modulation of the peripheral nervous system (to name a few). If there is limbic dysregulation, any or all of these functions could be deranged. Since there is a neurobiological mechanism for limbic functional disorders, I shall use the term 'neurosomatic' to describe them.

Such a complex regulatory system could have many specific areas of vulnerability. Dysfunction could have a primary central aetiology, or could occur in response to peripheral stressors of various sorts. Since the limbic system is involved in selecting adaptive responses to stress, and stress could be defined as any event which could alter actual or perceived homeostasis, the range of stimuli which could cause limbic dysregulation is large.

Not only could processing of sensory input be aberrant in CFS/FMS, resulting in dysfunctional responses, but the 'weight' given to various sensations seems to be increased, perhaps accounting for the phonophobia, photophobia and odorant sensitivity about which many patients complain (Figure 3). The weight given to sensory input is called 'sensory gating', and has been studied by examining the startle reflex, which is inhibited when the startling stimulus is preceded by a weak prepulse. This phenomenon is termed prepulse inhibition (PPI), and has been studied in animals and schizophrenics. The technique has also been used to see whether men differ from women in the degree of inhibition by prepulses (Bickford et al, 1993; Swerdlow et al, 1993a,b). Animal studies implicate the hippocampus and

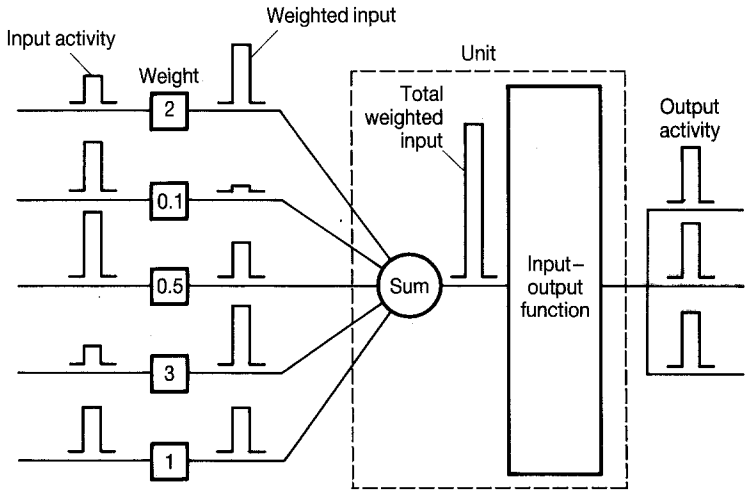

Figure 3. Representation of a neurone processing activities or signals. Each input activity is multiplied by a number called the weight. The 'unit' adds together the weighted inputs. It then computes the output activity using an input-output function. Figure adapted from page 106, Hinton G. How neural networks learn from experience. *Scientific American*, September 1992, **267(3)**. © 1992 by Scientific American Inc. All rights reserved.

reticular formation in PPI, and women inhibit less well than men. The research on schizophrenics does not yield any consistent results. We are studying CFS patients using this technique, and found in a pilot study that most patients have abnormal waveforms (unpublished results). If these results hold up, they may represent a diagnostic test for CFS/FMS. The treatments discussed in this chapter may markedly improve PPI deficits. We have not been able to perform double-blind, placebo-controlled experiments because of lack of funding, but it is possible that some of the observed pharmacological effects of thse medications reproduce alterations in neurochemical and neurophysiological parameters caused by placebo administration (Peck and Coleman, 1991).

It is likely that FMS and the commonly comorbid anxiety, fatigue, migraine headaches and irritable bowel syndrome (IBS) (Goldenberg, 1993) have a common neurobiological mechanism, which is almost certainly supraspinal. Pain, a major symptom of FMS as well as of IBS, CFS and migraine headaches, has numerous descending inhibitory pathways from the brainstem (e.g. raphe nuclei, locus ceruleus, periaqueductal grey, reticular formation) as well as from higher centres such as the hypothalamus, thalamus, limbic system and cortical structures. The regulation of pain by higher centres is poorly understood (Tasker and Dostrovsky, 1989; Coderre et al, 1993). The muscle fatigue of CFS appears to be central (Kent-Braun et al, 1993). Just as pain and fatigue are dysregulated, so are many other neural network functions. There is an increasing tendency to view FMS and CFS as variable presentations of the same pathophysiological process (Waylonis and Heck, 1992; Goldstein, 1993), which appears to be neurobiological. About one third of CFS patients do not meet the tender point criteria for FMS.

Numerous neurochemical abnormalities have been described in CFS/FMS. A basic finding is a low level of central corticotrophin-releasing hormone (CRH) (Demitrack et al, 1991). This polypeptide has other central nervous system (CNS) functions besides regulating proopiomelanocortin and adrenocorticotrophic hormone (ACTH) secretion, and is involved in the regulation of the sympathetic nervous system as well as the prefrontal cortex (Fisher, 1989; Takamatsu et al, 1991). Interleukin-1 beta (IL-1 beta), a pluripotential cytokine, regulates CRH secretion through interleukin-6 (IL-6) and prostaglandins E_2 and F_2 alpha (Rothwell, 1991). Cerebrospinal fluid (CSF) IL-1 beta levels were normal in a study of CFS patients (Lloyd et al, 1991), as well as in an FMS cohort (I.J. Russell, personal communication), suggesting antagonism of IL-1 beta effect. CRH is also stimulated by other agents (see below). Postulating decreased IL-1 effect leaves the increased CSF substance P levels (Vœrøy et al, 1988) poorly explained, since IL-1 is known to stimulate substance P secretion (Martin et al, 1993). Substance P, however, inhibits the release of CRH (Larsen et al, 1993). It also unmasks connections in the dorsal horn and may be involved in the formation of new receptive fields (Hoheisel et al, 1993).

Using the model of decreased central IL-1 beta effect resulting in decreased secretion of CRH, the peripheral immune activation found in CFS can be accounted for (Saperstein et al, 1992), since CRH is immu-

nosuppressive by virtue of its stimulation of cortisol secretion as well as its sympathetic activity in the spleen and regional lymphatic organs. IL-1 beta may, however, stimulate secretion of biogenic amines directly without prostaglandin involvement or elevation of CRH levels (Shintani et al, 1993).

We have used exercise ergometry as a stressor in patients with CFS/FMS to compare IL-1-regulated functions pre- and post-exercise, as has been done by others (Griep et al, 1993). We failed to find the expected increases in cortisol, IL-1, IL-6, catecholamines, growth hormone, beta-endorphin, somatostatin and core body temperature after exercise (Goldstein, 1993). These results were markedly different than those found in normal and anxious groups of exercising adolescents (Gerra et al, 1993). Hyperventilation was more common among the CFS patients who had greater than 11 out of 18 fibromyalgia tender points, as was a marked irregularity in tidal volume at maximal exercise, a finding not previously reported. The regulation of automatic respiration is a function of the limbic system (Munschauer et al, 1991), and this sort of abnormality is more evidence of limbic dysfunction in CFS/FMS.

We (Goldstein et al, 1994) and others (Ichise et al, 1992; Mountz et al, 1993) have found brain single photon emission computerized tomography (SPECT) with technetium hexamethyl propyleneamine oxime (HMPAO), a measure of regional cerebral blood flow (rCBF), to be abnormal in CFS. Patients with CFS/FMS in our study had the same regional hypoperfusion (anterior temporal, dorsolateral prefrontal, right hemisphere worse than left) as CFS patients without FMS, and the FMS patients had more severe hypoperfusion. CFS/FMS patients had significantly different patterns of perfusion to a matched comparison group with depression. We consistently find rCBF measured using xenon-133 (^{133}Xe) to decrease after exercise in this population, the opposite of what occurs in normals (Mena, 1993).

Research increasingly points to a genetic propensity to develop CFS/FMS. We have found HLA-DR4 to be significantly increased in patients compared with normals ($P = 0.02$) (Goldstein, 1993), and others have (Klimas, 1993) or have not (Middleton et al, 1991) confirmed these findings. All clinicians seeing a large number of such patients note an increased familial incidence, with panic disorder (Hudson et al, 1992) being the familial comorbid disorder with the highest occurrence. Panic disorder is generally believed to have a predominantly limbic mechanism (Caplan et al, 1992). However, a hereditary predisposition to develop a certain illness may range from strong to weak. Those with a strong tendency to be afflicted with CFS/FMS may have been sick since childhood. Others may require one or more triggering stimuli such as child abuse, viral infections, surgery, pronounced physical or mental overexertion, childbirth or emotional stress.

It is fairly well accepted that victims of child abuse are more likely to develop somatic symptoms as adults (Fry, 1993). Since the limbic system is the primary mediator of the stress response, it is reasonable to assume that functional changes, which may be long lasting, could occur in the neurones in this network (Teicher et al, 1993). The hypercortisolaemia of prolonged stress may damage neurons in the cornu ammonis, area 1 (CA1) region of the hippocampus and alter the regulation of hippocampal corticosteroid

receptors, an effect which may be ameliorated by the CNS calcium channel blocker nimodipine (Levy et al, 1993). Changes may not only occur in transmitters and receptors, but also in the second messenger cascade, transcription factors, peptides, proteins and growth factors (Post, 1992).

Viral infections affect patients differently, perhaps depending on how viral sequences are processed and presented. Some individuals may present an epitope that others do not. Viruses may produce a latent infection that does not cause an immune response (Joly et al, 1991), may alter secretion of only one neurotransmitter (Oldstone, 1989), or may cause 'hit and run' infections in which long-lasting alterations of cellular function can occur after the virus has disappeared (Demitrack and Greden, 1991). A virally induced neurotransmitter deficit may be corrected with appropriate medication (Mehta et al, 1993). Latent herpesvirus infections are well known to exist in nerve ganglia and to appear at times of stress (Bonneau et al, 1993). The trigeminal nerve, which can modulate limbic activity through projections to the pontine reticular formation and hypothalamus (Burstein et al, 1993), is commonly involved in the production of herpes labialis, for example. Herpes simplex is the most common virus to infect the limbic system, usually in the anterior temporal cortex. Viruses may enter the limbic system via retrograde neuronal transport (Lavi et al, 1988). Thus a viral infection could alter neuronal function in a genetically vulnerable person, who may already have some premorbid limbic-related disorders such as bruxism, IBS and allergic rhinitis, in such a way that the function of the neural network could be further dysregulated, and sensory gating and processing abnormalities would become manifest as deranged responses produced symptoms. The aspects of viral infection relevant to CFS/FMS are given in Table 1. Thus far, there is no single viral candidate for precipitating CFS, and perhaps multiple agents could be implicated.

Human immunodeficiency virus (HIV) glycoprotein 120 (gp120) blocks the CD4 receptor, which is also the vasoactive intestinal peptide (VIP) receptor. VIP stimulates the production of nerve growth factors (Buzy et al, 1992), as well as nitric oxide (Yamamoto et al, 1993) and IL-1 alpha and beta

Table 1. Aspects of viral infection relevant to CFS/FMS.

1. *Infection is not lytic and does not cause structural alteration.*
2. *More than one virus may be involved.* Two viruses may interact with each other and enhance virulence, a process known as transactivation, well known with human herpesvirus-6 and human immunodeficiency virus. Viral gene products and host gene products may interact as well.
3. *Viral gene products and/or cellular products may affect bystander cells.* These products may be cytokines, glycoproteins such as gp120 in HIV infection, or other transmitter substances. They may also cause systemic effects or immune activation if acting at a distance. A viral infection may also cause *decreased* secretion of a cellular product.
4. *Superantigens may be produced.* These are viral gene products that bind to the variable segment of the T-cell receptor and the major histocompatibility complex molecule, to cause fairly non-specific immune activation. Bacterial exotoxins may also act as superantigens. Toxic shock syndrome and postinfectious arthritic disorders have been suggested as being caused by superantigens (Sissons, 1993).
5. *A persistent CNS viral infection which does not provoke an immune response, a limbic encephalopathy, is also possible.*

(Brenneman et al, 1992). gp120 can also block neuronal L-type calcium channels, a process which can be prevented by nimodipine, a centrally acting dihydropyridine calcium-channel blocker (Stefano et al, 1993). VIP and IL-1 are important for neuronal survival (Brenneman et al, 1992). It has been suggested that antagonism of VIP and IL-1 by gp120 is responsible for the HIV cognitive/motor complex, which is often the first manifestation of the acquired immunodeficiency syndrome (AIDS). Peptide T, a synthetic VIP analogue, may be useful in blocking the central effects of gp120. The use of nimodipine in HIV encephalopathy is being investigated. Cognitive dysfunction could similarly occur in patients with CFS/FMS if a persistent or hit-and-run viral infection were implicated in the pathogenesis, or could even occur *de novo*.

There is a genetic difference in HLA haplotypes which may determine which antigenic determinant of the Epstein–Barr virus causes immune activation (de Campos-Lima et al, 1993). With variable epitopes, there would be variable immune responses, perhaps accounting for such conundrums as why only 5% of the population develops acute infectious mononucleosis. Similar considerations could apply to the development of CFS/FMS.

What can the presumed pathophysiology of CFS/FMS as a limbic neural network disorder suggest about using pharmacological probes to explore therapeutic approaches?

LIMBIC REGULATION BY TRIGEMINAL NERVE MODULATION

The trigeminal nerve may be viewed as a major integrator of somatic and visceral input. Spinal, cervical and some cranial nerves synapse with the spinal and mesencephalic trigeminal nerve tracts. The trigeminal nerve may produce expansion of the receptive field zones of wide dynamic range and nociceptive-specific neurones under certain conditions, so that a greater number of neurones will be activated by stimulation of a receptive zone, causing innocuous stimuli to be perceived as painful (Dubner, 1992; Fromm et al, 1993). Most of this work has been done in the spinal cord dorsal horn, but could also apply to the rostral and caudal trigeminal nerve nuclei, especially the trigeminal subnucleus caudalis, which is considered to be the homologue of the spinal dorsal horn. This research has focused mainly on peripheral noxious stimuli, but has been applied to central processes such as deafferentation pain and phantom limb syndrome (Melzack, 1992).

There are numerous ways to modulate trigeminal nerve activity. The one I use the most is adrenergic eyedrops such as naphazoline hydrochloride 0.1% (Vasocon, Naphcon, etc.). One drop is placed in each eye and the patient is assessed 2–3 s later. In about one third of the patients there will be significant relief of pain and tender point sensitivity, as well as decreased fatigue and more mental clarity. CFS/FMS patients with prominent anxiety symptoms respond the best to this treatment, but any patient may.

I have tried to understand the mechanism of this action by performing pre- and post-treatment ^{133}Xe brain SPECT. There is a significant diminution of

rCBF after a drop in the first eye, which becomes profound after the second eye is instilled. The response is not ipsilateral, as would occur from stimulation of the trigeminal neurovascular system, which causes vasodilation in only one hemisphere. I have proposed that there is a multisynaptic pathway from the mesencephalic trigeminal tract to the pontine reticular formation, and/or to the hypothalamus and thalamic reticular nuclei, and subsequently to the cortex and the limbic system, perhaps the hippocampus (Goldstein, 1993). Sensory inputs produced by touch and pain are transmitted to the thalamus by separate pathways, but travel to the cortex in a single projection. When pain occurs, touch neurotransmission from the thalamus is inhibited by GABAergic interneurones in the thalamic reticular nuclei. Impairment of thalamic gamma-aminobutyric acid (GABA) secretion could result in touch sensation being perceived by the cortex as being noxious, and could be one mechanism of central pain (Barinaga, 1992). Benzodiazepines such as alprazolam enhance the effect of GABA and could act in the thalamus to reduce the central pain of FMS.

The naphazoline-induced cerebral vasoconstriction may be due to the release of a neuroactive substance which also affects arterial tone. A transmitter secreted by the endothelium as well as by other cell types would be a likely candidate. The list of endogenous cerebral vasoconstrictors is shorter than that of vasodilators. It includes noradrenaline, neuropeptide Y, endothelin, thromboxane, IL-1 receptor antagonist protein, angiotensin II, vasopressin and serotonin (depending on which serotonin receptor is involved) (Matsui et al, 1991; Peticlerc et al, 1992; Uddman et al, 1993). Non-adrenergic ophthalmic agents usually have no effect, except for proxymetacaine (proparacaine *USP*), which sometimes transiently reduces pain in FMS and has been touted as a treatment for trigeminal neuralgia (Zavonik and Fichte, 1991). Proxymetacaine may work by decreasing excessive firing of low-threshold mechanoceptive neurones in the spinal trigeminal nucleus oralis (Fromm, 1991).

It is somewhat unusual in published reports of brain functional imaging to see a worsening of hypoperfusion correlated with symptomatic improvement, since cerebral metabolism and blood flow should be directly related. Regional rates of perfusion are regulated tightly to the corresponding level of substrate demand for metabolic activity. However, imipramine produces cerebral hypoperfusion (Lottenberg, 1993), and endothelin increases cerebral metabolism with an uncoupling of blood flow, since it is a powerful cerebral vasoconstrictor (Gross et al, 1992). The hypermetabolic activation is mediated by L-type calcium channels and is inhibited by nimodipine.

POSSIBLE LIMBIC REGULATION BY ENDOTHELIN

Endothelin, a 21 amino acid peptide, was discovered in 1988. There are three endothelins (ET-1, ET-2 and ET-3) and two endothelin receptor types (ET_A and ET_B). Endothelin receptors are found in neuronal, neuroendocrine and endocrine cells as well as in endothelial cells. Endothelins promote the release of vasopressin, substance P, luteinizing hormone,

follicle-stimulating hormone, prolactin and growth hormone. Rapid development of sensitization to prolonged or repetitive stimulation with endothelin is usual, probably by endocytosis of the endothelin-receptor complex (Stojilkovic and Catt, 1992). Tolerance to naphazoline ophthalmic solution is common, as it is to other agents which may stimulate endothelin secretion (see below). Perhaps pertinent to CFS/FMS, endothelin stimulates CRH neurones (Hirai et al, 1991). Complicating the issue somewhat, ET-1, acting at the ET_B receptor, is vasodilatory, generating prostacyclin, nitric oxide, and an endothelium-dependent hyperpolarizing factor distinct from nitric oxide (Haynes et al, 1993).

ET-1, acting at the ET_A receptor, stimulates neuronal release of dopamine (Kurosawa et al, 1991), a neurotransmitter important in regulating mood and activity. The effect of dopamine on rCBF is somewhat similar to its action in the peripheral circulation. Low doses cause vasodilation and high doses produce vasoconstriction (Koyama et al, 1990; Grasby et al, 1993). The dopamine-releasing properties of ET-1 have thus far been studied only in relation to its production of ischaemia, and can be attenuated by calcium channel blockers (Ooboshi et al, 1993) and hydralazine (Fuxe et al, 1992), both of which are sometimes effective treatments for CFS/FMS. ET-1 given by intracerebroventricular injection to mice produces long-lasting, dose-dependent antinociception, which is not antagonized by naloxone (Nikolov et al, 1992). Because of the high density of endothelin receptors in the hypothalamus and the limbic system, CSF endothelin levels were measured in patients with depression and in normal controls (Hoffman et al, 1989). Endothelin levels in the depressed group were about half of that of the control population. Endothelins are thought to be 'paracrine factors normally involved in long-term cellular regulation, but which may be important in several pathologies, many of them stress-related' (Huggins et al, 1993). Numerous endothelin agonists have been synthesized (Huggins et al, 1993) and an agent with appropriate receptor specificity may be a useful treatment for neurosomatic disorders.

LIMBIC REGULATION BY NITRIC OXIDE

Nitric oxide (NO) is the primary vasodilator in the brain. It 'might serve as a diffusible signal within neuronal tissue that is necessary for the release of catecholamines and possibly other neurotransmitters evoked from axonal terminals. This proposed function for NO would be in addition to the three roles for the substance in vertebrate nervous systems—that is, regulation of local blood flow, regulation of synaptic efficacy, and segregation of axonal arbors of the basis of neuronal activity' (Hanbauer et al, 1992). NO synthase, a fairly ubiquitous enzyme, is heavily concentrated in the hippocampus (Valtschanoff et al, 1993) as well as in the rostral ventrolateral medulla, another site for sensory gating (Iadecola et al, 1993).

In the hippocampus, NO and another gaseous neurotransmitter, carbon monoxide, serve as retrograde messengers that produce activity-dependent

presynaptic enhancement during long-term potentiation (Zhuo et al, 1993). Other putative retrograde messengers, more difficult to supply exogenously, include arachidonic acid and platelet-activating factor (Zorumski and Izumi, 1993). Long-term potentiation, which can last hours or days, refers to prolonged changes in a target neurone resulting from intense but brief trains of stimuli delivered to a presynaptic neurone. When I saw the profound regional cerebral hypoperfusion in CFS/FMS brain SPECTS, one of my first inclinations was to reverse it with NO. The best available marketed source of NO is glyceryl trinitrate, which exerts its vasodilatory actions by conversion into NO. Giving CFS/FMS patients very low (0.04 mg) doses of sublingual glyceryl trinitrate sometimes results in an amelioration of symptoms, especially pain, in about 2 min. It is also effective in central pain such as deafferentation syndrome and reflex sympathetic dystrophy. Patients with failed back syndrome often respond to it. Tolerance to this effect of glyceryl trinitrate often develops, but vasodilation still occurs.

One would expect considerable cerebral vasodilation on brain SPECT after glyceryl trinitrate, but this is not always the case. Sometimes there is actually vasoconstriction. NO is sometimes released by endothelin to decrease vasoconstriction, but NO does not stimulate endothelin release (Webb, 1991). This result again suggests that symptomatic improvement in CFS/FMS is not dependent on reversing hypoperfusion, and that post-treatment blood flow changes are epiphenomena. Perhaps contributing to this effect, human endothelial cells can synthesize and release inhibitors of NO production (Fickling, 1994).

Some of the agents I use are vasodilators, and it appears that their effect on rCBF in CFS/FMS patients is a summation of their intrinsic vasodilator capability and whatever vasoconstrictors are concomitantly released. Naphazoline, however, an adrenergic agonist in the eye, always results in cerebral vasoconstriction in patients who have a beneficial effect, although this result is the end-product of a multisynaptic pathway. Patients who do not respond to naphazoline have little or no reduction in their rCBF.

NO influences transmitter secretion from so many types of neurones that it is difficult to pin down a role for it in CFS/FMS.

Possible roles for nitric oxide in CFS/FMS

Effects on glutamate secretion

NO enters firing presynaptic neurones by retrograde diffusion, where it stimulates guanylyl cyclase which produces cyclic guanosine monophosphate (GMP) (Kandel and Hawkins, 1992) and the latter compound then induces glutamate secretion. NO diffuses only into neurones that are already secreting neurotransmitter, potentiating the signals in that particular microneural network, a process called long-term potentiation (LTP). LTP has been most studied in the hippocampus in relation to the making of new memories, the function most impaired in the neuropsychological testing of CFS/FMS patients. Increasing 'synaptic strength' in other types of neural assemblies may be an important aspect of CFS/FMS treatment. CFS/FMS

may also be viewed as a synaptic *convergence* deficiency syndrome, convergence being defined as a process by which each neurone has stronger connections with fewer target cells (Greenough and Bailey, 1988). The role of NO in LTP could be an example of convergence.

Serotonergic agents are often useful in CFS/FMS, and application of serotonin in LTP paradigms mimics the behavioural and electrophysiological effects of LTP and produces a long-term enhancement of synaptic efficacy (Patterson, 1992).

Effects on short-term memory

Short-term memory ('encoding') is so poor in CFS that we consider this deficit to be diagnostic (Sandman et al, 1993). LTP also occurs in the frontal cortex (Bear and Kirkwood, 1993), and impaired secretion of NO could detract from the precision of interneuronal communication in the region. Twelve FMS patients with few other symptoms besides pain were tested to see whether an encoding problem was present. All patients had evidence of this deficit, although none were aware of it (J.A. Goldstein and C.A. Sandman, unpublished results). Encoding deficits often respond rapidly and dramatically to the treatments discussed in this chapter.

Anxiolytic effects

NO is anxiolytic. Chlordiazepoxide had no effect when administered to mice pretreated with an NO synthase inhibitor, but chlordiazepoxide action returns when the mice are given L-arginine, a NO precursor (Quock and Nguyen, 1992).

Effects on dopamine and serotonin

NO releases dopamine (Hanbauer et al, 1992), which could relieve fatigue and produce behavioural stimulation, as well as enhance cognition and attention. NO also increases the release of serotonin (Lorrain and Hull, 1993).

Effects on VIP

NO stimulates the secretion of VIP, and NO secretion is also stimulated by VIP (Grider and Jin, 1993). NO may be colocalized with VIP, and is found in the trigeminal ganglion.

Effects on neuropeptide Y

Neuropeptide Y, a cerebral vasoconstrictor, is the neuropeptide with the highest concentration in the brain, and is released primarily in the limbic and cortical regions (Heilig and Widerlov, 1990). It is anxiolytic, colocalized in noradrenergic neurones, and is known to stimulate appetite and cause weight gain (independently of its effect on appetite) (Heinrichs et al, 1993).

It has an inverse relationship with CRH, however, and thus is not likely to be stimulated by drugs effective in CFS/FMS. In certain circumstances neuropeptide Y releases NO (Kobari et al, 1993) or is colocalized with it (Nozaki et al, 1993).

Effects on the action of opiates

Partly by its indirect dopaminergic effect, NO increases morphine withdrawal symptoms in adult male rats (Adams et al, 1993). Morphine treatment stimulates NO synthesis (Ferreira et al, 1991). NO increases morphine-related behavioural changes in mice (Calignano et al, 1993), perhaps related to the effect of opioids of increasing dopamine release in the corpus striatum. Antinociception induced by intracerebroventricular NO may potentiate only beta-endorphin, but not mu, gamma or kappa agonists. It is thus thought to be involved in descending pain inhibition (Xu and Tseng, 1993). Some of my fibromyalgia patients have reported that glyceryl trinitrate significantly potentiates the effect and duration of their opioid analgesics.

Relationship with IL-1 beta

Neuronal NO synthase is activated by a calcium-dependent mechanism, but can also be stimulated by IL-1 beta. It is not known for certain whether this latter mechanism is constitutive in the brain, but decreased regional levels of NO could be related to decreased IL-1 beta production or inhibition of its action by other cytokines or neuropeptides (Goldstein, 1993). Such a mechanism could also produce lower levels of CNS serotonin, dopamine, certain prostaglandins, IL-6 and CRH. IL-1 beta messenger RNA (mRNA) and IL-1 receptor antagonist protein mRNA are densely localized in the dorsal raphe nuclei that synthesize serotonin (E. De Souza, personal communication).

The antinociceptive effect of NO in the brain is the opposite of what has been found in the spinal cord, where *N*-methyl-D-aspartate (NMDA) receptor activation is implicated in nociceptive processing (Meller and Gebhart, 1993). Many effects of NMDA receptor activation appear to be mediated by NO, since glutamate is a primary ligand for the NMDA receptor. Thermal hyperalgesia in animals is potentiated by NO causing an increase in cyclic GMP and thus an increase in glutamate, and NMDA receptor antagonists and NO synthase inhibitors are being developed as novel analgesics (Woolf and Thompson, 1991). It thus appears that peripheral thermal pain processing is modulated by NO in an opposite manner to central pain, and certainly glyceryl trinitrate has had no effect on peripheral noxious stimulation in my patients. A corollary to this hypothesis is that NO-modulated sensory gating in CFS/FMS occurs rostral to the dorsal horn. NMDA receptor antagonists given by the intracerebroventricular route have been shown to attenuate the antinociceptive effect of NMDA receptor antagonists, given intrathecally, which would have primarily a spinal site of action (Nasstrom et al, 1993).

This explanation is similar to that proposed by M. B. Yunus, i.e. that the pain of fibromyalgia is a result of central sensory dysregulation (Yunus, 1992). Yunus conceives of a 'heterogeneous neurohormonal dysfunction' as the primary problem and describes peripheral and supraspinal structures interacting at the level of the dorsal horn to cause sensory gating abnormalities. My view is that the dorsal horn is one of many sensory 'gates' that might be dysfunctional, and that most of them are rostral to the spinal cord. This expansion of Yunus' basic concept would better explain the wide variety of symptoms and specific findings on functional imaging of the brain and neuropsychological testing.

Patients with myalgic encephalomyelitis, the British Commonwealth term for CFS, have been found to have red blood cells with an altered shape, so that they are non-discocytic or 'cup forms' (Simpson, 1989). Such red cells are less deformable than normal. At the proper concentration, however, NO can preserve or enhance red cell deformability (Korbut and Gryglewski, 1992).

Although NO is found mainly in parasympathetic neurones and can be potently stimulated by acetylcholine, it is also found in sympathetic postganglionic neurones and cell bodies, and is responsible for vasodilation when alpha-1 antagonists are used (Lewis et al, 1993). NO is also colocalized with substance P and calcitonin gene-related peptide, vasodilator substances produced in the trigeminal vascular system (Edvinsson et al, 1987).

I have noted for several years that CFS/FMS patients are more likely to have or develop endometriosis than the average individual (Goldstein, 1990). CFS monocytes do not behave like monocytes from controls (Prieto et al, 1992). This defect can be reversed in vitro with naloxone. One cause for endometriosis is the failure of monocytes/macrophages to ingest endometrium that is normally refluxed through the fallopian tubes during menstruation. CFS patients may be more likely to have this defect, especially since the cytotoxicity of macrophages in the peritoneum is related to macrophage ability to produce NO (Sotomayor et al, 1993).

Female patients with CFS/FMS usually have premenstrual exacerbations of their symptoms. Most of the symptoms of late luteal phase dysphoric disorder are similar to CFS, and it is likely that this disorder has a limbic aetiology similar to CFS/FMS.

NEURAL PLASTICITY

'Neural systems adapt to the changing demands of their environment by modulating both the intrinsic membrane properties of neurones and the strength of the synaptic connections between them' (Kennedy and Marder, 1992). In recent years it has been found that the adult brain has much more plasticity in its neuronal circuits than previously thought. Ongoing morphological changes occur in dendrites to modify the synaptic communication between neurones and glia. Synapse density of adult mammalian hippocampal neurones has been found to fluctuate depending on the circulating levels of oestradiol. In the adult primate oestradiol valerate treatment

resulted in a 39% decrease in the number of axosomatic synapses in the infundibular hypothalamic nucleus (Naftolin et al, 1993), a possible example of synaptic convergence. Such variations in synapse density could account for the cognitive dysfunction associated with late luteal phase dysphoric disorder and a decrease in the efficiency of synaptic gating and sensory input processing. The mechanism of this effect of oestradiol is uncertain at present.

EFFECTS OF NIMODIPINE IN CFS/FMS: POSSIBLE MECHANISMS

Calcium-channel blockers act at various sites at the L-type calcium channel to inhibit calcium influx during neuronal depolarization. Under certain circumstances, they may also inhibit calcium efflux. This property has been demonstrated for the calcium-channel blocker nimodipine (Azmitia et al, 1993). L-type calcium channels are widely distributed in the brain and the central action of calcium-channel blockers is well known in the prophylaxis of migraine.

One class of L-type calcium-channel blockers is the dihydropyridines. These include isradipine, nifedipine, nicardipine, felodipine, nitrendipine, nisoldipine, amlodipine and nimodipine. Each of these drugs is slightly different from the others. Nimodipine is used primarily for its effects in counteracting cerebral vasospasm from subarachnoid haemorrhage, since it has fewer systemic hypotensive effects than other dihydropyridines and is more lipophilic, enabling it to cross the blood-brain barrier more easily. Nicardipine is a better cerebral vasodilator (Alborch et al, 1992), but it lowers blood pressure too much to be prescribed in the acutely ill patient with a ruptured aneurysm. It may be, however, that the neuroprotective effects of nimodipine in subarachnoid haemorrhage are not related to vasodilation, but to some other mechanism (Tettenborn and Fierus, 1993).

I have found nimodipine to be uniquely effective among the drugs of its class in managing CFS/FMS. It is also the most useful in treatment-resistant panic disorder (Gibbs, 1992), a related limbic dysfunction. Neuronal plasticity is related to calcium-dependent pre- and postsynaptic processes such as occur with LTP in the hippocampus (Ginspen, 1993). Nimodipine strongly enhances the firing rate of single aged hippocampus neurones recorded in vivo, while two other calcium-channel blockers, nifedipine and flunarizine, do not (Disterhoft et al, 1993). A 30 mg nimodipine capsule usually works in about 45 min, often producing relaxation, increased energy, a decrease in tender point sensitivity, improved exercise tolerance and enhanced mental clarity. Calcium-channel blockers of other sorts have previously been reported to be useful in panic disorder (Goldstein, 1985; Klein and Uhde, 1988) and in potentiation of opioid analgesics (Pereira et al, 1993). Nimodipine is also being investigated in treating HIV cognitive/motor complex. Calcium-channel blockers potentiate the action of lignocaine (lidocaine *USP*) (Taniguchi et al, 1993) and are analgesic as monotherapy when given epidurally (Dey et al, 1993) or topically in the eye (Chen et al,

1993). Some of my patients with developmental learning disorders have had remarkable improvement with nimodipine. The drug also has antidepressant effects, both in patients and in animal models (de Jonge et al, 1993).

Besides binding to the CD4/VIP receptor, gp120 irreversibly binds to L-type neuronal calcium channels and inhibits cellular chemotaxis. This binding can be antagonized by nimodipine (Stefano et al, 1993). gp120 also has a sequence homology to CRH which is related to induction of ACTH from lymphocytes by HIV (Stefano et al, 1993). It is possible that there could be endogenous analogues to gp120 sequences, or that such peptides could be neurotoxic gene products produced by other viruses which could trigger CFS/FMS. Obviously, a CRH agonist is not one of these products.

About two-thirds of the time, nimodipine causes further vasoconstriction on post-treatment CFS/FMS ^{133}Xe brain SPECT, sometimes to a profound degree. This paradoxical response is another demonstration that therapeutic benefit in CFS/FMS derives from release of a substance that has intrinsic vasoconstrictive properties. Nimodipine has been shown to release dopamine, serotonin and acetylcholine (Azmitia et al, 1993; Fanelli et al, 1993; Rezvani et al, 1993). Of these transmitters, only serotonin can be vasoconstrictive in the human brain at physiological concentrations. Tolerance does not develop to the vasodilatory properties of nimodipine, but it sometimes does to its effect in CFS/FMS. Nimodipine does not cause release of any substance known to increase secretion of endothelin. Such compounds include angiotensin II, thrombin, bradykinin, adenosine triphosphate (ATP), ACTH, platelet-activating factor, cytokines, vasopressin, and various growth factors including transforming growth factor beta (TGF beta) (Stojilkovic and Catt, 1992) and insulin-like growth factor (IGF) (Matsumoto et al, 1990). None of these are known to be deficient in CFS/FMS except IGF. I have prescribed vasopressin in the form of desamino-D-arginine vasopressin (DDAVP) for numerous patients over the years with minimal results and have also combined it with fenfluramine as a secretagogue in an attempt to increase CRH secretion, with no effect. Vasopressin levels are actually elevated in CFS (G. Chrousos, personal communication). TGF beta, if anything, is elevated in CFS (Goldstein, 1990; Chao et al, 1991), and angiotensin-converting enzyme (ACE) inhibitors such as captopril, an effective antidepressant (Zubenko and Nixon, 1984), have some limited utility in ameliorating CFS/FMS symptoms, probably because captopril is an endopeptidase inhibitor which can increase concentrations of certain peptides, including the enkephalins. ACE inhibitors also increase bradykinin secretion, which increases endothelin levels as well as stimulating release of NO from endothelial cells. Captopril, the only ACE inhibitor to have a sulphydryl group, is also the only marketed agent of its class with antidepressant properties.

HYDRALAZINE

Reasoning that hydralazine, thought to dilate arteries by stimulating cyclic GMP (Nathanson, 1992), works via a NO-type mechanism, I began to use it

in therapeutic trials in CFS/FMS. Responders reported amelioration of one or more target symptoms within an hour after a dose of 10 to 25 mg. Hydralazine has also been reported to potentiate the effects of nitrovasodilators in vascular smooth muscle prior to cyclate activation. It was hypothesized that hydralazine inhibited pyridoxal-dependent reactions inactivating sulphydryl groups that are thought to be involved in the action of glyceryl trinitrate (Unger et al, 1993). Indeed, methionine and cysteine, sulphur-containing amino acids, have been advocated for reversing nitrate tolerance, but have not been helpful in my CFS/FMS population. Some patients benefiting from hydralazine have also had worsening arterial vasoconstriction on post-treatment brain SPECT.

PYRIDOSTIGMINE

Muscle weakness in CFS may sometimes be treated with pyridostigmine bromide in a manner similar to its use in myasthenia gravis. Surprisingly, pyridostigmine, a cholinesterase inhibitor which does not cross the blood-brain barrier, may alleviate mental 'fogginess', increase energy and reduce pain. This drug has been reported to increase secretion of growth hormone (Arvat et al, 1993) by potentiating growth hormone-releasing hormone via a central cholinergic mechanism. Somatomedin C/IGF-1, a growth hormone related peptide, has been found to be low in patients with FMS (Bennett et al, 1992). As noted previously, IGF may increase the central secretion of endothelin. Pyridostigmine may also induce the adrenal glands to secrete more corticosteroids and catecholamines. It could further act by altering peripheral autonomic input to the CNS.

MEXILETINE

Mexiletine was introduced as a type IIb antiarrhythmic, with a major site of action in the brain. It is related to lignocaine and tocainide, and has few serious adverse reactions in low doses. More recently, mexiletine has been used successfully for neuropathic pain, particularly dysaesthesias. Its mode of action is unknown, but it may act by increasing central CRH secretion (Calgero et al, 1990). Lignocaine and procaine act as local anaesthetics at sodium channels, but their action in the hypothalamus to stimulate CRH is independent of their effect on sodium conductance. Mexiletine also blocks the release of substance P from mouse spinal nociceptive terminals (Kameli et al, 1992).

CONCLUDING REMARKS

A possible mechanism of action for the medications discussed in this chapter could be stimulation of endothelin release with subsequent enhancement of CRH secretion. CRH might also be stimulated directly. Since CRH enhances peripheral sympathetic neurotransmission when given centrally, it may cause cerebral arterial vasoconstriction directly or do so by causing

release of noradrenaline. The stimulation by IL-1 of CRH is blocked by NO in one experimental model (Rivier, 1993), however, and such a result could not support a facilitatory role of NO in CRH secretion, at least by an IL-1-dependent process. Local anaesthetics have also been shown to inhibit uptake of choline, noradrenaline and GABA in several human- or rat-derived clonal cell lines (Lukas and Bencherif, 1993).

It would be possible to continue this pharmacological litany, citing H_2 receptor antagonists, serotonin receptor subtype agonists and antagonists, cyclic antidepressants, serotonin reuptake inhibitors, monoamine oxidase inhibitors, bupropion, neuroactive steroids and a host of other centrally acting agents (Goldstein, 1993). Double-blind, placebo-controlled testing of these drugs has not been performed because of lack of funding, but the clinician may wish to try them, as I do, sequentially in individual patients (see Appendix).

The basic point that I wish to convey, however, is that most, if not all, disorders of regulatory physiology have important limbic components. Thus far they seem to involve sensory gating and processing of sensory input, and are probably multifactorial in aetiology. The regions of the limbic neural network most affected, and the way in which the function of the neuronal machinery is deranged, markedly influence patient symptomatology. The rapid response to the medications described here and the concomitant profound post-treatment alteration in brain SPECT suggests, at least on a neurophysiological basis, that many neurosomatic disorders may be improved by ameliorating state-dependent deranged neural network function.

APPENDIX

A typical CFS/FSM new patient treatment protocol

Agents, tried sequentially	Onset of action	Duration of action
1. Naphazoline hydrochloride 0.1% one drop in each eye	2–3 s	3–6 h
2. Glyceryl trinitrate 0.04 mg sublingually	2–3 min	3–6 h
3. Nimodipine 30 mg by mouth	20–40 min	4–8 h
4. Mexiletine 150 mg by mouth	30–45 min	6–8 h
5. Pyridostigmine 30–60 mg by mouth	30 min	4–6 h
6. Hydralazine 10–25 mg by mouth	30–60 min	6–12 h
7. Ranitidine 150 mg b.i.d.	1 h–1 week	12–24 h
8. Doxepin hydrochloride elixir 2–20 mg hs	1 h	Variable
9. Sertraline 25–50 mg every morning or paroxetine 10–20 mg QAM	1 h–6 weeks	1–2 days

I halt sequential trials when the patient is virtually asymptomatic, using other medications if tolerance should develop. These drugs are all relatively free of adverse reactions and do not appreciably interact with one another. Two selective serotonin reuptake inhibitors (SSRIs) should not be given conjointly. I prefer sertraline (Zoloft) because it does not inhibit hepatic cytochrome P_{450}, and thus does not increase serum levels of other agents metabolized by the liver. Paroxetine, however, is less likely to cause agitation and gastrointestinal side-effects. SSRIs do not have as effective an analgesic effect as the other agents.

Disclaimer

Medicine is an ever-changing science. As new research and clinical experience broaden our knowledge, changes in treatment and drug therapy are required. While many suggestions for drug usage are made here, this article is intended for educational purposes only, and the author, editor and publisher do not accept liability in the event of negative consequences incurred as a result of information presented in this article. We do not claim that this information is necessarily accurate by the rigid, scientific standard applied for medical proof, and therefore make no warranty, express or implied, with respect to the material herein contained. Therefore the patient is urged to consult his or her own physician prior to following a course of treatment. The physician is urged to check the product information sheet included in the package of each drug he or she plans to administer to be certain the protocol followed is not in conflict with the manufacturer's insert. When a discrepancy arises between these inserts and information in this article, the physician is encouraged to use his or her best professional judgement.

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