The Biochemical Origin of Pain: The origin of all Pain is Inflammation and the Inflammatory Response. PART 2 of 3 –Inflammatory Profile of Pain Syndromes

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The biochemical origin of pain: The origin of all pain is inflammation and the inflammatory response. Part 2 of 3 — Inflammatory profile of pain syndromes

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Summary Every pain syndrome has an inflammatory profile consisting of the inflammatory mediators that are present in the pain syndrome. The inflammatory profile may have variations from one person to another and may have variations in the same person at different times. The key to treatment of Pain Syndromes is an understanding of their inflammatory profile. Pain syndromes may be treated medically or surgically. The goal should be inhibition or suppression of production of the inflammatory mediators and inhibition, suppression or modulation of neuronal afferent and efferent (motor) transmission. A successful outcome is one that results in less inflammation and thus less pain. We hereby briefly describe the inflammatory profile for several pain syndromes including arthritis, back pain, neck pain, fibromyalgia, interstitial cystitis, migraine, neuropathic pain, complex regional pain syndrome/reflex sympathetic dystrophy (CRPS/RSD), bursitis, shoulder pain and vulvodynia. These profiles are derived from basic science and clinical research performed in the past by numerous investigators and serve as a Foundation to be built upon by other researchers and will be updated in the future by new technologies such as magnetic resonance spectroscopy. Our unifying theory or law of pain states: the origin of all pain is inflammation and the inflammatory response. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response. Activation of pain receptors, transmission and modulation of pain signals, neuro plasticity and central sensitization are all one continuum of inflammation and the inflammatory response. Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arise from inflammation and the inflammatory response. We are proposing a re-classification and treatment of pain syndromes based upon their inflammatory profile. Published by Elsevier Ltd.

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Description of the prior theories

Prior theories

The prior theories do not contain any unifying Law of Pain. Each disease entity e.g., fibromyalgia, complex regional pain syndrome/reflex sympathetic dystrophy (RSD/CRPS), carpal tunnel syndrome, rheumatoid arthritis and ankylosing spondylitis is considered distinct from the other entities and is classified in terms of symptomatology, structural pathology, genetic markers, presence of autoantibodies etc. The prior theories assign a different mechanism to nociceptive and neuropathic pain, a different mechanism to acute and chronic pain, and a different mechanism to peripheral and central pain. The prior theories result in a treatment of pain syndromes that focuses mainly on structural pathology. Where present, treatment of inflammation in these disease entities has hitherto addressed one biochemical mediator of inflammation at a time (mostly focused on prostaglandin), instead of addressing the inflammatory soup of biochemical mediators that are present in all pain syndromes.

Based upon our unifying Law of Pain, we now provide a brief description of the complex inflammatory profile of several common pain syndromes.

Inflammatory pain syndromes

Arthritis

Arthritis means inflammation of the joints. People of all ages including children and young adults can develop arthritis. The symptoms are intermittent pain, swelling, redness and stiffness in the joints. There are many different types of arthritis, some of which are rheumatoid arthritis, osteoarthritis, infectious arthritis and spondylitis. In rheumatoid arthritis, and other autoimmune diseases like systemic lupus erythematosus (SLE), the joints are destroyed by the immune system. Osteoarthritis pain is due to inflammation which may be present in bone tissue, cartilage, joints, disk, ligaments, soft tissue and muscle. In normal, adult articular cartilage, the extracellular matrix (ECM), is constantly being degraded and repaired. These two processes of degradation and repair are normally kept in balance by the activity of the chondrocytes. The chondrocytes are stimulated by and secrete a number of enzymes that help regulate the balance of synthesis and degradation of the ECM. Interleukin-1 (IL-1), a cytokine produced by chondrocytes and other cells in the joint, plays an important role in cartilage degradation by stimulating the synthesis of degradative enzymes that inhibit the production of proteoglycans. Other cytokines that appear to act synergistically with IL-1 to promote matrix breakdown are tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6). All of these cytokines are routinely found in inflamed joints. Enzymes secreted by the chondrocytes are released into the ECM and degrade the matrix structure. Among the enzymes that have been identified as playing a major role in proteoglycan and collagen degradation are the matrix metalloproteinases (MMPs), such as collagenase, stromelysin, and gelatinase. Other proteinases include cysteine, proteinases, cathepsin, and serine proteases, such as tissue plasminogen activator. Under normal circumstances, the activation of these degradative enzymes is held in check by inhibitors, such as tissue inhibitor of metalloproteinase (TIMP) and plasminogen activator inhibitor-7 (PAI-7). These inhibitors work by forming complexes that inactivate the degradative enzymes. Chondrocytes are responsible for maintaining the balance between the degradative enzymes and their inhibitors. In osteoarthritis, there is an imbalance between the levels of these degradative enzymes such as MMPs, and their inhibitors, such as TIMP. As part of the cartilage degradation and synthesis process, polypeptides, such as insulin-like growth factor-1 (IGF-1) and transforming growth factor beta (TGF-beta), stimulate chondrocytes in the matrix to synthesize proteoglycans. IGF-1 and TGF-beta regulate matrix metabolism in normal cartilage and may play a role in matrix repair in patients with osteoarthritis. Osteoarthritis affects not only the articular cartilage, but also the underlying bone and adjacent joint structures. As the cartilage becomes eroded, fragments may break loose and float within the joint capsule. These loose pieces of cartilage can damage the synovial lining of the joint and interfere with proper joint function. Progressive damage to the cartilage results in narrowing of the space between the two bones (joint space). Areas of bone become denuded of cartilage, causing the loss of the shock-absorbing mechanism and allowing for the contact of bone on bone [1]. The underlying subchondral bone may form a new articulating surface in the joint and become smooth and polished, like marble. In subchondral bone, osteoblasts begin to form new bone tissue, probably in response to chemical messengers produced by the chondrocytes. This leads to bone remodeling. Around the edges of the joint, bony and cartilaginous overgrowths or ''spurs'', called osteophytes may develop in non weight-bearing areas of the joint. Osteoarthritis

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has previously been considered a non-inflammatory form of arthritis. It is our theory that the underlying origin, like all other pain syndromes is inflammation and the inflammatory response. The changes that occur within the joint are due to inflammation and the inflammatory response. Inflammation is aggravated by the introduction of bone and cartilage breakdown products into the synovial fluid. These products are phagocytized by cells in the synovium, resulting in chronic, low-grade inflammation. Consequently, the synovial membrane becomes thickened. Inflammation of the synovial membrane may be absent in the earlier stages of Osteoarthritis; however, as the disease progresses, some degree of synovitis usually exists.

Once mild synovial inflammation is established, the synovium becomes a source of cartilage-degrading enzymes (e.g., MMPs) and cytokines, including IL-1, IL-6, and TNF-alpha. These substances diffuse through the synovial fluid and cause further degradation of articular cartilage. IL-1 and TNF-alpha stimulate the chondrocytes to produce more degrading enzymes, and the process continues in a vicious cycle. IL-1, IL-6, and TNF-alpha are believed to be the main cytokines linked to the disease process. Nitric oxide (NO) is found at higher levels in osteoarthritic cartilage than in normal cartilage. A form of NO can be expressed after the activation of chondrocytes by cytokines. Once formed, NO may contribute to IL-1-induced degradation of cartilage, mainly by decreasing the synthesis of the ECM. Studies have shown that IL-1 derived from the osteoarthritic cartilage stimulates the production of prostaglandin E_2 (PGE_2). Once formed, PGE_2 increases the synthesis of stromelysin, a cartilage-degrading protein (MMP). PGE_2 also has important pro-inflammatory properties and contributes to vasodilation and pain in patients with osteoarthritis.

In rheumatoid arthritis, and other autoimmune diseases like systemic lupus erythematosus (SLE), the joints are destroyed by the immune system. TNF-alpha and Interleukin 1-beta play an important role in rheumatoid arthritis by mediating cytokines that cause inflammation and joint destruction. TNF-alpha, Interleukin 1-beta and Substance P are elevated in the joint fluids in patients with rheumatoid arthritis [2]. These inflammatory mediators are also elevated in the joint fluid in patients with osteoarthritis albeit to a far less extent. Along with mechanical factors, growth factors and cytokines such as TGF beta 1, IL-1 alpha, IL-1 beta and TNF-alpha may be involved in the formation and growth of osteophytes, since these molecules can induce growth and differentiation of mesenchymal cells. The incidence and size of osteophytes may be decreased by inhibition of direct or indirect effects of these cytokines and growth factors on osteoid deposition in treated animals [3,4]. Inhibition of IL-1 receptor also decreases the production of metalloproteinase enzymes collagenase-1 and stomelysin-1 in the synovial membrane and cartilage. These enzymes are involved in connective tissue breakdown [5].

Back and neck pain

Back and neck pain most commonly result from injury to the muscle, disk, nerve, ligament or facet joints with subsequent inflammation and spasm. Degeneration of the disks or joints produces the same symptoms and occurs subsequent to aging, previous injury or excessive mechanical stresses that this region is subjected to because of its proximity to the sacrum in the lower back.

Herniation of disk tissue (nucleus pulposus) produces a profound inflammatory reaction with release of inflammatory chemical mediators especially tumor necrosis factor alpha. Subsequent to release of TNF-alpha, there is an increase in the formation of inflammatory mediator prostaglandin and Nitric Oxide. It is now known that tumor necrosis factor alpha is synthesized by herniated or degenerate disk tissue (nucleus pulposus), and contributes to the nerve injury and behavioral manifestations of experimental sciatica associated with herniated lumbar discs [6]. This has been confirmed by numerous animal studies and research wherein application of disk tissue (nucleus pulposus) to a nerve results in nerve fiber injury, with reduction of nerve-conduction velocity, intracapillary thrombus formation, and the intraneural edema formation [7,8]. One study demonstrated that disk tissue (nucleus pulposus) increases inducible nitric oxide synthetase activity in spinal nerve roots and that nitric oxide synthetase inhibition reduces nucleus pulposus-induced swelling and prevents reduction of nerve-conduction velocity [9]. Tumor necrosis factor alpha and other inflammatory mediators induce phospholipase A2 activation. High levels of phospholipase A2 previously have been demonstrated in a small number of patients undergoing lumbar disc surgery. Phospholipase A2 is the enzyme responsible for the liberation of arachidonic acid from cell membranes at the site of inflammation and is considered to be the limiting agent in the production of inflammatory mediator prostaglandins and leukotrienes [10]. Culture media from the herniated lumbar discs show increased levels of matrix metalloproteinase activity, nitric

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oxide, prostaglandin E2, and interleukin-6 compared with the control discs [11,12]. Subsequent to the release of inflammatory mediators, activation of motor nerves that travel from the spinal cord to the muscles results in excessive muscle tension, spasm and pain. Back or neck pain with or without herniated disk is due to inflammation and the inflammatory response. Most cases can be treated medically in accordance with the principles that we have outlined and do not require surgery. Surgery is indicated when there is compression of the nerve roots producing continuous release of inflammatory mediators, significant muscle weakness and or urinary or bowel incontinence.

Fibromyalgia

Fibromyalgia is a chronic, painful musculoskeletal disorder characterized by widespread pain, pressure hyperalgesia, morning stiffness, sleep disturbances including restless leg syndrome, mood disturbances, and fatigue. Other syndromes commonly associated with fibromyalgia include irritable bowel syndrome, interstitial cystitis, migraine headaches, temporomandibular joint dysfunction, dysequilibrium including nerve mediated hypotension, sicca syndrome, and growth hormone deficiency. Fibromyalgia has been proposed to be due to neurogenic inflammation induced by an inflammatory response to allergens, infectious agents, irritants, chemical exposures or emotional stress [13]. Several studies have shown that there are increased levels of the inflammatory transmitter Substance P (SP) and calcitonin gene-related peptide (CGRP) in the spinal fluid of patients with fibromyalgia syndrome (FMS) [14–16]. The levels of platelet serotonin are also abnormal [17]. Furthermore, in patients with fibromyalgia, the level of pain intensity is related to the spinal fluid level of arginine, which is a precursor to the inflammatory mediator nitric oxide (NO) [18]. Another study found increases over time in blood levels of cytokines Interleukin-6, Interleukin-8 and Interleukin-1R antibody (IL-1Ra) whose release is stimulated by substance P. The study authors concluded that because Interleukin-8 promotes sympathetic pain and Interleukin-6 induces hypersensitivity to pain, fatigue and depression, both cytokines play a role in producing Fibromyalgia symptoms [19].

Interstitial cystitis

Interstitial cystitis is a severe debilitating bladder disease characterized by unrelenting pelvic pain and urinary frequency. This sterile painful bladder disorder is associated with a defective glycosaminoglycan bladder mucosal layer and an increased number of activated mast cells. Mast cells are ubiquitous cells derived from the bone marrow and are responsible for allergic reactions as they release numerous vasodilatory, nociceptive and pro-inflammatory mediators in response to immunoglobulin E (IgE) and specific antigen. Mast cell secretion is also triggered by a number of peptides, such as bradykinin and substance P, and may also be involved in the development of inflammatory responses [20]. SP-containing nerve fibres are increased in the submucosa of the urinary bladder of interstitial cystitis (IC) patients and are frequently seen in juxtaposition to Mast cells [21,22]. There is enhanced sympathetic innervation of the bladder in the submucosa and detrusor muscle. In interstitial cystitis the number of neurons positive for inflammatory mediator vasoactive intestinal polypeptide and neuropeptide Y is higher compared with control subjects [23]. Substance P (SP) and bradykinin (BK) influence the excitatory motor innervation of the urinary bladder. These peptides potentiate the responses to the purinergic component of the neurogenic stimulation (that part of the contractile response that remains after treatment with atropine) and potentiate the responses to exogenously applied adenosine triphosphate (ATP) [24]. Significant elevations in Interleukin-2, Interleukin-6, and Interleukin-8 have also been found in the urine of subjects with active interstitial cystitis compared with subjects with interstitial cystitis in remission and control subjects [25].

Migraine

Migraine headache is caused by activation of trigeminal sensory fibers by known and unknown migraine triggers. There is subsequent release of inflammatory mediators from the trigeminal nerve. This leads to distention of the large meningeal blood vessels in the skull and brain and the development of a central sensitization within the trigeminal nucleus caudalis (TNC). Genetic abnormalities may be responsible for altering the response threshold to migraine specific trigger factors in the brain of a migraineur compared to a normal individual [26].

The painful neurogenic vasodilation of meningeal blood vessels is a key component of the inflammatory process during migraine headache. The cerebral circulation is supplied with two vasodilator systems: the parasympathetic system stor-

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ing vasoactive intestinal peptide, peptide histidine isoleucine, acetylcholine and in a subpopulation of nerves neuropeptide Y, and the sensory system, mainly originating in the trigeminal ganglion, storing inflammatory mediator substance P, neurokinin A and calcitonin gene-related peptide (CGRP) [27]. A clear association between migraine and the release of inflammatory mediator calcitonin gene-related peptide (CGRP) and substance P (SP) has been demonstrated. Jugular plasma levels of the potent vasodilator, calcitonin gene-related peptide (CGRP) have been shown to be elevated in migraine headache. CGRP-mediated neurogenic dural vasodilation is blocked by anti-migraine drug dihydroergotamine, triptans, and opioids [28]. In cluster headache and in chronic paroxysmal hemicrania, there is additional release of inflammatory mediator vasoactive intestinal peptide (VIP) in association with facial symptoms (nasal congestion, runny nose) [29]. Immunocytochemical studies have revealed that cerebral blood vessels are invested with nerve fibers containing inflammatory mediator neuropeptide Y (NPY), vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP). In addition, there are studies reporting the occurrence of putative neurotransmitters such as cholecystokinin, dynorphin B, galanin, gastrin releasing peptide, vasopressin, neurotensin, and somatostatin. The nerves occur as a longitudinally oriented network around large cerebral arteries. There is often a richer supply of nerve fibers around arteries than veins. The origin of these nerve fibers has been studied by retrograde tracing and denervation experiments. These techniques, in combination with immunocytochemistry, have revealed a rather extensive innervation pattern. Several ganglia, such as the superior cervical ganglion, the sphenopalatine ganglion, the otic ganglion, and small local ganglia at the base of the skull, contribute to the innervation. Sensory fibers seem to derive from the trigeminal ganglion, the jugular-nodose ganglionic complex, and from dorsal root ganglia at the cervical spine level C2. The noradrenergic and most of the NPY fibers derive from the superior cervical ganglion. A minor population of the NPY-containing fibers contains vasoactive intestinal peptide (VIP), instead of NA and emanates from the sphenopalatine ganglion. The cholinergic and the vasoactive intestinal peptide (VIP)-containing fibers derive from the sphenopalatine ganglion, the otic ganglion, and from small local ganglia at the base of the skull. Most of the substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP)-containing fibers derive from the trigeminal ganglion. Minor contributions may emanate from the jugular-nodose ganglionic complex and from the spinal dorsal root ganglia. Neuropeptide Y (NPY) is a potent vasoconstrictor in vitro and in situ. Vasoactive intestinal peptide (VIP), peptide histidine isoleucine (PHI), substance P (SP), neurokinin A (NKA), and calcitonin gene-related peptide (CGRP) act via different mechanisms to induce cerebrovascular dilatation [30]. Meningeal blood vessels are involved in the generation of migraine pain and other headaches. Classical experiments have shown that blood vessels of the cranial dura mater are the most pain-sensitive intracranial structures. Dural blood vessels are supplied by trigeminal nerve fibers, and dilate in response to activation of the trigeminal nerves and release of neuropeptide cytokines such as substance P (SP) and calcitonin gene-related peptide (CGRP) [31]. CGRP can be released experimentally from dural nerve fibers, and there is evidence that this occurs also during migraine attacks. Stimulation of dural nerve fibers causes vasodilatation and an increase in dural arterial flow, which depends on the release of CGRP but not SP. SP, on the other hand, is known to mediate plasma leakage (extravasation) from small veins in the dura mater. The dural arterial flow depends also on the formation of cell wall nitric oxide. The introduction of serotonin (5-HT_1) receptor agonists such as sumatriptan changed the treatment strategies for migraine. Sumatriptan and other triptans may inhibit the release of inflammatory mediators from the trigeminal nerve. Sumatriptan has been shown to block the release of vasoactive cytokines from trigeminal nerves that surround the blood vessels in the dura mater during migraine. Sumatriptan blocks nerve fiber induced plasma extravasation but has only minor effects on nerve fiber mediated vasodilatation and dural arterial flow. Foods like cheese, beer, and wine can also induce migraine in some people because they contain the mediator histamine and/or mediator-like compounds that cause blood vessels to expand. Women tend to react to histamine-containing foods more frequently than men do, on account of a deficiency in an enzyme (diamine oxidase) that breaks histamine down. Taking supplemental B6 has been shown to be helpful in migraine, as it can increase diamine oxidase activity.

Nerve (neuropathic) pain syndromes

Nociceptive pain is mediated by receptors on A-delta and C nerve fibers, which are located in skin, bone, connective tissue, muscle and viscera. These

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receptors serve a biologically useful role at localizing noxious chemical, thermal and mechanical stimuli. Nociceptive pain can be somatic or visceral in nature. Somatic pain tends to be well-localized, constant pain that is described as sharp, aching, throbbing, or gnawing. Visceral pain, on the other hand, tends to be vague in distribution, spasmodic in nature and is usually described as deep, aching, squeezing and colicky in nature. Examples of nociceptive pain include: post-operative pain, pain associated with trauma, and the chronic pain of arthritis.

Neuropathic pain in contrast to nociceptive pain, is described as ''burning'', ''electric'', ''tingling'', and ''shooting'' in nature. It can be continuous or paroxysmal in presentation. Whereas nociceptive pain is caused by the stimulation of peripheral A-delta and C-polymodal pain receptors, by peripheral release of inflammatory mediators, (e.g., histamine bradykinin, substance P, etc.) neuropathic pain is produced by release of inflammatory mediators including neuropeptides and neurotransmitters secondary to injury or damage to peripheral nerves or the central nervous system The hallmarks of neuropathic pain are chronic allodynia and hyperalgesia. Allodynia is defined as pain resulting from a stimulus that ordinarily does not elicit a painful response (e.g., light touch). Hyperalgesia is defined as an increased sensitivity to normally painful stimuli.

Examples of neuropathic pain include carpal tunnel syndrome, trigeminal neuralgia, post herpetic neuralgia, phantom limb pain, complex regional pain syndromes and the various peripheral neuropathies. In one study, monocytes/macrophages (ED-1), natural killer cells, T lymphocytes, and the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6), were significantly produced in nerve-injured rats. Interestingly, ED-1-, TNF-alpha- and InterLeukin-6-positive cells increased more markedly in allodynic rats than in non-allodynic ones. The authors determined that the considerable increase in monocytes/macrophages induced by a nerve injury results in a very high release of Interleukin-6 and TNF-alpha. This may relate to the generation of touch allodynia/hyperalgesia, since there was a clear correlation between the number of ED-1 and Interleukin-6-positive cells and the degree of allodynia. The magnitude of the inflammatory response was not related to the extent of damage to the nerve fibers because rats with complete transection of the nerves displayed much lower production of inflammatory cytokines than rats with partial transection of the nerve [32]. This is a finding commonly observed in patients where a minor injury results in severe pain that is out of proportion to the injury. In another study, animals exhibiting heat hyperalgesia as a sign of neuropathic pain seven days after loose ligation of the sciatic nerve exhibited a significant increase in the concentration of brain derived neurotrophic factor (BDNF) in their lumbar spinal dorsal horn [33]. Administration of nerve growth factor to rodents has resulted in the rapid onset of hyperalgesia. In clinical trials with nerve growth factor for the treatment of Alzheimer disease and peripheral neuropathy, induction of pain has been the major adverse event [34]. In one study, the use of trkA-IgG, an inhibitor of Nerve Growth Factor (NGF) reduced neuroma formation and neuropathic pain in rats with peripheral nerve injury [35] In another study, the systemic administration of anti-nerve growth factor (NGF) antibodies significantly reduced the severity of autotomy (self mutilating behavior induced by nerve damage) and prevented the spread of collateral sprouting from the saphenous nerve into the sciatic innervation territory [36].

Reflex sympathetic dystrophy/complex regional pain syndrome (RSD/CRPS)

Reflex Sympathetic Dystrophy (RSD) syndrome also called Complex Regional Pain Syndrome (CRPS) has been recognized clinically for many years. It is most often initiated by trauma to a nerve, neural plexus, or soft tissue. Diagnostic criteria are the presence of regional pain and other sensory changes following a painful injury. The pain is associated with changes in skin color, skin temperature, abnormal sweating, tissue swelling. With time, tissue atrophy may occur as well as involuntary movements, muscle spasms, or pseudoparalysis [37]. The inflammatory mediators that are generated (especially IL-6) accelerate the rate at which bone is broken down. The bone loss is further aggravated by decreased use of the affected body part due to pain. Complex regional pain syndrome, type I (reflex sympathetic dystrophy; CRPS-I/RSD) can spread from the initial site of presentation. In one study of 27 CRPS-I/RSD patients who experienced a significant spread of pain, three patterns of spread were identified. 'Contiguous spread (CS)' was noted in all 27 cases and was characterized by a gradual and significant enlargement of the area affected initially. 'Independent spread (IS)' was noted in 19 patients (70%) and was characterized by the appearance of CRPS-I in a location that was distant and non-contiguous with the initial site (e.g., CRPS-I/RSD

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appearing first in a foot, then in a hand). 'Mirror-image spread (MS)' was noted in four patients (15%) and was characterized by the appearance of symptoms on the opposite side in an area that closely matched in size and location the site of initial presentation. Only five patients (19%) suffered from CS alone; 70% also had IS, 11% also had MS, and one patient had all three kinds of spread [38]. In 1942 Paul Sudeck suggested that the signs and symptoms of RSD/CRPS including sympathetic hyperactivity might be provoked by an exaggerated inflammatory response to injury or operation of an extremity. His ideas found no followers, as most doctors incorrectly believe that RSD/CRPS is solely initiated by a hyperactive sympathetic system. Recent research and studies including various clinical and experimental investigations prove that Sudeck started on the right path [39]. We now have a better understanding of the complexity of the inflammatory response, and we believe that inflammation and the inflammatory response do not just provoke the signs and symptoms of sympathetic hyperactivity. It is our theory that the entire pain experience in RSD/CRPS and other pain syndromes is due to inflammation and the inflammatory response.

Soft tissue or nerve injury causes release of the inflammatory mediators and excitation of sensory nerve fibers. Reverse (antidromic) firing of these sensory nerves causes release of the inflammatory neuropeptides at the peripheral endings of these fibers. These neuropeptides may induce vasodilation, increase vascular permeability, attract other immune cells such as T helper cells and excite surrounding sensory nerve fibers — a phenomenon referred to as neurogenic inflammation. At the level of the central nervous system, the increased input from peripheral pain receptors alters the central processing mechanisms. Sympathetic dysfunction in RSD/CRPS has been suggested to consist of an increased rate of outgoing (efferent) sympathetic nerve impulses towards the involved extremity induced by increased firing of the sensory nerves. Activity in sympathetic fibers is associated with excessive sweating, temperature instability of the extremities and can induce further activity in sensitized pain receptors and, therefore, enhance pain and allodynia (sympathetically maintained pain). This pathologic interaction acts via noradrenaline released from sympathetic terminals and newly expressed receptors on the afferent neuron membrane [40]. Perpetuation of the sympathetic response has been proposed be related to central dysregulation of nociceptive impulses. This dysregulation may be mediated by wide dynamic range neurons in the spinal cord [41]. Populations of C fibers contain peptides such as substance P (sP) and calcitonin gene-related peptide (CGRP), as well as amino acids such as glutamate. Small afferent activation will evoke the Ca2+-dependent spinal release of these inflammatory neuropeptides. Substance P and glutamate evoke excitation of second-order neurons through an effect mediated by the tachykinin neurokinin 1 (NK-1) and the glutamatergic α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)/N-methyl-D-aspartate (NMDA) receptors, respectively. In situ hybridization shows labeling for NK-1 and NMDA receptor units in the dorsal gray matter, particularly in the substantia gelatinosa where small afferents are known to terminate [42]. Prolonged ischemia from the sympathetic vasoconstriction produces more pain, establishing a reflex arc that promotes further sympathetic discharge and vasospasm. This is compounded by the local response to trauma, with liberation of substantial amounts of proinflammatory mediators, such as histamine, serotonin, and bradykinin. The result is a swollen, painful, stiff, nonfunctioning extremity. Local tissue inflammation can also result in pain hypersensitivity in neighboring uninjured tissue (secondary hyperalgesia) by spread and diffusion of the excess inflammatory mediators that have been produced as well as by an increase in nerve excitability in the spinal cord (central sensitization). This can result in a syndrome comprising diffuse muscle pain and spasm, joint pain, fever, lethargy and anorexia. The results of several experimental studies suggest that sympathetic dysfunction may also consist of super sensitivity to catecholamines induced by nerve injury (autonomic denervation) [43]. Part of this occurs due to injured sensory nerves and immune cells developing receptors for the chemical transmitter norepinephrine and epinephrine (catecholamines), which are normally released by sympathetic nerves and also circulate in the blood. Stimulation of these receptors by locally released or circulating catecholamines produces sympathetic effects such as sweating, excessive hair growth and narrowing of blood vessels [44]. In addition and under certain conditions, catecholamines may boost regional immune responses, through increased release of Interleukin-1, tumor necrosis factor-alpha, and Interleukin-8 production. In several studies, patients with RSD/CRPS showed a markedly increased level of the inflammatory peptide bradykinin as well as calcitonin gene-related peptide [45]. The levels of bradykinin were four times as high as the controls. A few showed increased levels of the other inflammatory chemical mediators [46].

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Sports injuries/bursitis/tendonitis/rotator cuff tears

Inflammation of the bursa is known as bursitis. A bursa is a small sac containing fluid that lies between bone and other moving structures such as muscles, skin or tendons. The bursa allows smooth gliding between these structures. A bursa allows a tendon or muscle to move smoothly over a bone by acting as an anti-friction device and shielding the structures from rubbing against bones. Bursae are found in the knee, elbow, shoulder and wrist. If the tendons become thickened and bumpy from excessive use, the bursa is subjected to increased friction and may become inflamed. Tendonitis is inflammation or irritation of a tendon. Tendons are the thick fibrous cords that attach muscles to bone. They function to transmit the power generated by a muscle contraction to move a bone. Since both tendons and bursae are located near joints, inflammation in these soft tissues will often be perceived by patients as joint pain and mistaken for arthritis. Symptoms of bursitis and tendonitis are similar: pain and stiffness aggravated by movement. Pain may be prominent at night. Almost any tendon or bursa in the body can be affected, but those located around a joint are affected most often. The most common cause of tendonitis and bursitis is injury or overuse during work or play, particularly if the patient is poorly conditioned, has bad posture, or uses the affected limb in an awkward position. Occasionally an infection within the bursa or tendon sheath will be responsible for the inflammation. Tendonitis or bursitis may be associated with diseases such as rheumatoid arthritis, gout, psoriatic arthritis, thyroid disease and diabetes. In one study of 39 patients with rotator cuff diseases, the levels of the cytokine Interleukin-1 beta was significantly correlated with the degree of pain. The combined results of immunohistochemistry indicate that both synovial lining and sublining cells produce IL-1beta, while synovial lining cells predominantly produce the anti-inflammatory intracellular InterLeukin-1 receptor antagonist (icIL-1ra) and sublining cells secrete InterLeukin-1 receptor antagonist (sIL-1ra) [47]. In one study, the levels of interleukin-1 beta were significantly higher in the shoulder joints in patients with anterior instability and chronic inflammation of the joint [48]. In another study, immunohistological staining demonstrated the expression of Interleukin-1 beta (Interleukin-1 beta), Tumor necrosis factor alpha (TNF-alpha), transforming growth factor beta (TGF-beta), and basic fibroblast growth factor (bFGF) in subacromial bursa derived from the patients suffering from rotator cuff tear [49].

Stress

During times of stress or inflammation Substance P, IL-1 and IL-6 levels are increased. IL-6, in turn, can induce release of corticotrophin-releasing factor [50,51], which results in elevated systemic levels of corticosteroids.

Vulvar vestibulitis syndrome (VVS)/vulvodynia

Vulvar vestibulitis syndrome is a major subtype of vulvodynia. It is a constellation of symptoms and findings involving and limited to the vulvar vestibule that consists of (1) severe pain on vestibular touch to attempted vaginal entry, (2) tenderness to pressure localized within the vulvar vestibule, and (3) physical findings confined to vulvar erythema of various degrees. The syndrome has been seen in association with subclinical human papillomavirus, chronic recurrent candidiasis, chronic recurrent bacterial vaginosis, chronic alteration of vaginal pH, and the use of chemical and destructive therapeutic agents [52]. In a study of VVS cases and asymptomatic controls, median tissue levels of inflammatory cytokines: IL-1 b and TNF-a, from selected regions of the vulva, vestibule, and vagina were 2.3-fold and 1.8-fold elevated, respectively, in women with VVS compared to pain-free women. Analysis revealed a significant 2.2-fold higher median level of TNF alpha at the vulvar site compared to the vestibule. The study authors concluded that inflammatory cytokine elevation may contribute to the pathophysiology of mucocutaneous hyperalgesia [53].

Conclusion

In accordance with our Law of Pain, the origin of all pain is inflammation and the inflammatory response. The biochemical mediators of inflammation include cytokines, neuropeptides, growth factors and neurotransmitters. Irrespective of the type of pain whether it is acute or chronic pain, peripheral or central pain, nociceptive or neuropathic pain, the underlying origin is inflammation and the inflammatory response. Activation of pain receptors, transmission and modulation of pain signals, neuro plasticity and central sensitization are all one continuum of inflammation and the inflam-

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matory response. Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arise from inflammation and the inflammatory response. We are proposing a re-classification and treatment of pain syndromes based upon their inflammatory profile. Treatment of pain syndromes should be based on these principles:

1. Determination of the inflammatory profile of the pain syndrome.
2. Inhibition or suppression of production of the appropriate inflammatory mediators e.g., with inflammatory mediator blockers or surgical intervention where appropriate.
3. Inhibition or suppression of neuronal afferent and efferent (motor) transmission e.g., with anti-seizure drugs or local anesthetic blocks.
4. Modulation of neuronal transmission e.g., with opioid medication.

At the L.A. Pain Clinic, we have successfully treated a variety of pain syndromes by utilizing these principles. This unifying theory of the biochemical origin of pain is compatible with, inclusive of, and unifies existing theories and knowledge of the mechanism of pain including the gate control theory, and theories of pre-emptive analgesia, windup and central sensitization. Our current knowledge is rudimentary and but a beachhead in the vast frontier of inflammation and the inflammatory response. We have medications for only a few of these mediators. More research is needed to understand and develop new drugs and interventions to treat inflammation and the inflammatory response and thus to conquer pain.

Conflicts of interest

There is no conflict of interest.

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