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Focused Review

Anti-inflammatory Effects of Electronic Signal Treatment

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Inflammation often plays a key role in the perpetuation of pain. Chronic inflammatory conditions (e.g. osteoarthritis, immune system dysfunction, micro-circulatory disease, painful neuritis, and even heart disease) have increased as baby boomers age. Medicine's current anti-inflammatory choices are NSAIDs and steroids; the value in promoting cure and side effect risks of these medications are unclear and controversial, especially considering individual patient variations.

Electricity has continuously been a powerful tool in medicine for thousands of years. All medical professionals are, to some degree, aware of electrotherapy; those who directly use electricity for treatment know of its anti-inflammatory effects. Electronic signal treatment (EST), as an extension of presently available technology, may reasonably have even more anti-inflammatory effects.

EST is a digitally produced alternating current sinusoidal electronic signal with associated harmonics to produce theoretically reasonable and/or scientifically documented physiological effects when applied to the human body. These signals are produced by advanced electronics not possible even 10 to 15 years ago.

The potential long-lasting anti-inflammatory effects of some electrical currents are based on basic physical and biochemical facts listed in the text below, namely that of stimulating and signaling effective and long-lasting anti-inflammatory effects in nerve and muscle cells. The safety of electrotherapeutic treatments in general and EST in particular has been established through extensive clinical use.

The principles of physics have been largely de-emphasized in modern medicine in favor of chemistry. These electrical treatments, a familiar application of physics, thus represent powerful and appropriate elements of physicians' pain care armamentaria in the clinic and possibly for prescription for use at home to improve overall patient care and maintenance of quality of life via low-risk and potentially curative treatments.

Key words: Electroanalgesia, electronic signal treatment (EST), inflammation, anti-inflammatory effects, immune system, neurogenic inflammation, chronic pain, steroids, NSAIDs, oscillo/torsional effect, cAMP, membrane repair and stabilization, pain care/management

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Multiple challenges face the clinician in the effective treatment of inflammation with the current pharmacotherapy (e.g. steroids, NSAIDs, COX-2s). Despite their well-documented short-term efficacy in a wide variety of settings, anti-inflammatory drugs directly interfere with healing (1-7). Even with the short-term benefit, dangers exist with long-term utilization of both classes of drugs. Popular literature refers to over 15,000 deaths annually among patients following the doctor's prescriptions for NSAIDs. In fact, a recent colorful account of the psuedoaddiction of Howard Hughes by Forest Tenant, MD (8) reveals that Hughes died of NSAID induced renal failure.

Inflammation and pain may both play a role in the perpetuation of the other. Sensitization of the pain system can be pro-inflammatory. It is important to understand this relationship in diagnosing, treating, and managing inflammatory pain syndromes (9). When acute inflammation is the starting point and the source, if we can cut the inflammation short, then we can stop chronic pain .

Inflammation has been proposed as the origin of pain (10). Omoigui (10) and others argue that many of our chronic pain syndromes — arthritis, low back pain, fibromyalgia, interstitial cystitis, neuropathic pain, migraine headaches, CRPS — should be reclassified as variations of inflammation-induced pain. Thus the regulation and inhibition of inflammatory mediators which stimulate afferent and efferent neural traffic may be central to the management of these seemingly unrelated syndromes.

There is debate regarding efficacy of epidural and intraarticular steroids for pain management. Many studies and reviews support the short- and long-term use (11,12). However, other studies show mixed results, without long-term efficacy (13). Controlled trials on intraarticular steroids in osteoarthritis, for example, involving over 300 patients, show a short-term benefit that lasts only 1–3 weeks (13).

Steroids may lead to other complications such as steroid-induced osteoporosis, vascular necrosis, and fractures (14). Furthermore, immune disorders secondary to environmental insults contribute to growing inflammation problems. The impact of these physiological challenges is further affected by the inability of physiological repair mechanisms to keep up.

Definition of Inflammation

Inflammation is a complex process that occurs as a response to trauma, heat, chemicals, bacteria, or other phenomena, and is mediated by a variety of electrically-charged signal molecules produced locally by mast cells, nerve endings, platelets, and white blood cells (15).

The physiological act of the insulted tissue to repair itself and return to normal happens when naturally occurring bio-chemicals (i.e. arachidonic acid, etc.) are liberated to trigger a response to protect the local tissue and surrounding areas from a specific threat or pathogen (16).

This complete bio-process is essential to the chaotic self-organizing mechanisms of the human biosystem, which allow for normalization of the affected area (17). Exogenous intervention with chemical steroids or NSAIDs may actually restrict this normal biosystem process and possibly produce immediate or long-term undesired side effects to the specific tissue involved, as well as regional or systemic undesired effects (1,18,19).

Inflammation is characterized by

1) vasodilatation of the local blood vessels with consequent excess local blood flow,
2) increased permeability of the capillaries with leakage of large quantities of fluid into the interstitial spaces,
3) clotting of the fluid in the interstitial spaces because of excessive amounts of fibrinogen and other proteins leaking from the capillaries,
4) migration of large numbers of granulocytes and monocytes into the tissue, and
5) swelling of the tissue cells.

The inflammatory response produces pain, erythema, heat, and edema, all caused by changes in local blood vessels (15). Classes of biochemical mediators of pain include cytokines, neuropeptides, growth factors, and neurotransmittors (10); examples include phospholipase A-2, interleukin 1 (IL-1), IL-6, leukotrienes, prostaglandin E2, nitric oxide (NO), tumor necrosis factor alpha (TNF-α), hydrogen ion (H+), NF-κB, substance P, cGRP, bradykinin, vasoactive intestinal peptide (VIP), nerve growth factor (NGF), and others.

Steroid Mechanisms of Action in Blocking the Inflammatory Process

The actions of steroids are generally associated with several principle effects: 1) blocking phospholipase A-2 (PLA-2), a key step in the inflammatory process; 2) membrane stabilizing and consequent analgesic effects, resulting from inhibition of neurotransmission

in c fibers (20); 3) immunosuppression; and 4) anti-edema effects. Other additional mechanisms probably remain undiscovered or not elucidated (21).

Blocking of PLA-2 seems to be the most important effect of steroids. The inflammatory cascade starts when arachidonic acid is released from the disrupted cell membrane. The 2 principle pathways of arachidonic acid metabolism are the 5-lipooxygenase pathway, which produces leukotrienes, and the cyclooxygenase pathway, which produces prostaglandin H2 (PGH2). PGH2 serves as the substrate for 2 enzymatic pathways: one leading to the production of several other prostaglandins, and the second leading to thromboxane. The action of PLA-2 converts arachidonic acid to cyclooxygenase, which, as stated, is blocked by steroids.

The local anesthetic, or membrane stabilizing, effect is considered weak. Steroids are a mainstay for the pharmacologic immunosuppression in organ transplant and auto-immune disease patients, and the anti-edema properties derive from their blocking the anti-inflammatory effects of PLA-2 and other pro-inflammatory agents.

The side effects of steroids have been well described for many years. The practice of the treatment of auto-immune disorders with high dose steroid therapy has carried with it some serious well documented systemic side effects. These are outlined in Table 1 (22).

Serious side effects can also occur even after a single injection of a depot steroid (Table 2). Although these occurrences are relatively uncommon, multiple anecdotal reports suggest that these single dose misadventures do occur more often than expected.

Table 2. *Possible effects of one-shot steroid injection (22).*

1.	Lowered resistance to infections
2.	Decreased or altered vision
3.	Frequent urination & increased thirst (including Cushing's syndrome)
4.	Mental status changes
5.	Skin rash and/or hives
6.	Local tissue (fat and collagen) necrosis (after single injection, not common, but within the experience of most interventional pain physicians)

Table 1. *Side effects of steroids (22)*

1.	Facial flushing (common, but passes quickly)
2.	Hyperglycemia (common and can be noted for two weeks after procedure); latent diabetes mellitus often becomes manifest
3.	Increased blood pressure (usually high doses; after single injection, not common, but within the experience of most interventional physicians)
4.	Hypertension, fluid and sodium retention, edema, worsening of cardiac insufficiency; increases likelihood of MI (unlikely after single injection, cumulative, but not common)
5.	Local tissue (fat and collagen) necrosis (after single injection, not common, but within the experience of most interventional physicians)
6.	Cushing's syndrome (very common after multiple injections)
7.	GI disturbances (common, but all degrees of severity and not necessarily cumulative dose related); ulceration of esophagus, stomach, duodenum possible
8.	Increased appetite leading to significant weight gain (causation a problem, but probably common after multiple injections, even if oral forms not used)
9.	Immunosuppressant action, particularly if given together with other immunosuppressants such as cyclosporine; fever as a warning symptom often suppressed
10.	Osteoporosis with pathological fractures after long-term treatment
11.	Possible psychological changes, e.g. depression, personality changes
12.	Increased cholesterol (usually high doses; after single injection, not common, but within the experience of most interventional physicians)
13.	Avascular necrosis of the hip (would seem to be rare, except from hip joint injections)
14.	Steroid myopathy, catabolism (usually after long-term oral use)
15.	Dermatologic — wide variety of effects, including, allergic dermatitis, dry scaly skin, ecchymosis and petechiae, erythema, impaired wound-healing, others
16.	Epidural lipomatosis (difficult to know; if it occurs, usually subclinical)

NSAID Mechanisms of Action in Blocking the Inflammatry Process

NSAIDs block inflammation by interfering with the action of COX-1 and COX-2 enzymes. These enzymes facilitate the conversion of arachidonic acid to prostaglandins and thromboxane.

Side effects of NSAIDs include interference with platelets, gastric irritation and bleeding, and renal effects. Since NSAIDs are taken regularly by approximately 33 million Americans, this is a huge epidemiologic challenge. COX-2 inhibitors avoid many of the side effects, but 2 — rofecoxib and valdecoxib — have been pulled off the market because of a higher risk of cardiac dysfunction and death and (in the case of valdecoxib) Stevens-Johnson syndrome. As stated previously in the introduction, various reports estimate that more than 15,000 deaths occur each year as the result of NSAID toxicity. This toxicity is especially noticed in the elderly where NSAID toxicity is more prevalent.

History of Electricity's Use in Medicine

Electricity has been used for centuries in both diagnostic and therapeutic applications. The 2 earliest recorded uses were in 2750 BC wherein the electrical properties of the Nile catfish were discussed and Hippocrates use of electric fish for medical treatment in 420 BC. In the 1700s European physicians used controlled electrical currents for numerous medical problems including pain and circulatory dysfunction. Ben Franklin documented pain relief using electric currents for a variety of ailments including frozen shoulder. A citation in the early 1900s expounds the benefits of electric current for "…the relief of the superimposed infiltration and chronic inflammation" for an enlarged prostate (23). The same reference goes on to state that "The employment of electricity is amply justified in [cases of pathologically incurable diseases] for the improvement of metabolism, the promotion of comfort and the prolongation of life, but no cure can be expected" (23).

Introduction to Concept of Electric Signal Energy as a Therapeutic Modality

More recently, the most significant development occurred when Becker and Seldon electrically induced limb regeneration in frogs and rats. In 1982 they reasoned that electromagnetic fields exist that control all aspects of life processes. His studies of extra-neuronal analog electrical morphogenetic fields have eliminated any rational arguments against the importance of bioelectricity for all basic life processes (24). Becker and Seldon asserts in their landmark book that modern scientific knowledge of life's electrical dimension has yielded fundamental insights into pain, inflammation, healing, growth, consciousness, and the nature of life itself (24). The authors now apply these concepts further by showing the influence of EST on inflammation.

An electric field forms around any electrical charge. This means that any other charged object will be attracted (if the polarities are opposite) or repelled (if they are the same) for a certain distance around the first object (24). Electric currents have numerous direct and indirect effects on tissue; these effects will be discussed in more detail in the section "Discussion of the Anti-Inflammatory Effects of EST." Medical/scientific investigations are ongoing and these discoveries could presage a revolution in biology and medicine. According to Becker and Seldon, in the not-to-distant future, physicians may have the ability to control and stimulate bio-system healing at will with the use of exogenous energy fields (24).

The Present Role of Electricity in Medicine

It is well known and well accepted that electricity plays an important role in contemporary medicine (25). In diagnostic applications there are a number of valuable devices such as electrocardiography (ECG), electro-encephalography (EEG), electromyography (EMG), nerve conduction velocity (NCV), electrooculography, electroretinography, electronystography, electrocochleography, evoked potentials, skin galvanic/impedance tests, current perception threshold (CPT) testing, and sensory nerve conduction testing (Neuralscan).

Therapeutic applications with electrical modalities include a number of medical devices: transcutaneous electric nerve stimulator (TENS), percutaneous electric nerve stimulator (PENS), powered muscle stimulators, interferential current devices (IFC), spinal cord stimulator (SCS), electroconvulsive therapy (ECT), high-voltage galvanic stimulators (HGVS), transcranial electric stimulation, microcurrent stimulators, bone growth stimulators, deep brain probe stimulators, and others.

Defining Electronic Signal Therapy and Its Effects

Sensory and motor neural activity is associated with the action potential, and most chemical interventions become electrical events. We therefore introduce the concept of treating inflammation with specific parameter electronic signal treatment (EST), defined as a digitally produced sinusoidal electronic signal with associated harmonics to produce desired physiological effects. The signals are produced by advanced electronics not available even 10 to 15 years ago.

EST appears to modulate or accelerate the anti-inflammatory process to reduce perpetuation that leads to chronic conditions, especially chronic pain. Concomitant cellular mechanisms support the anti-inflammatory effects of EST; numerous citations exist from the molecular biology, physics, and biochemical literature supporting these ideas. These actions include the oscillo/torsional effect, pH normalization, balancing metabolic concentration differences, cAMP formation and activation (leading to the normalization of cell function), cell membrane repair and stabilization, salutary effects on metabolism, sustained depolarization of the nerve cell membrane (producing nerve block), immune system support, and the obvious macro benefits of increases in blood flow and edema reduction.

The newer systems are EST energy devices which use frequency modulation (FM) alone or amplitude modulation (AM) combined with FM as the basis for signaling the bio-system to initiate complex biochemical responses and actions, e.g., hormone imitative effects, second-messenger formation (cAMP), inhibition of contraction of smooth muscle, vasodilatation, membrane stabilization, and others.

The early systems, or transcutaneous electrical nerve stimulators (TENS), use AM only with frequencies at or between approximately 1–200 Hz. These AM frequencies tend to stimulate and cause neurons to fire. Depending on the rate of nerve impulse firing, a number of physiological mechanisms of action can occur. A simple way of thinking about the differences between EST and TENS is that EST frequency ranges tend to signal, while well known TENS ranges tend to stimulate.

To hypothesize and project how TENS and next-generation EST devices will affect or manipulate the naturally occurring electrical properties of the human bio-system is a daunting and currently impossible task. Although a complete description is beyond the scope of this paper and our current knowledge base, every journey begins with a single step. A purpose of this paper is to provide this first step and a foundation to pique the interest of basic scientists and clinicians alike.

Overview of How Electric Signals May Be More Physiologically Effective Than Exogenous Chemicals

The intent of chemical interventions for the treatment of the inflammatory process is to block the process at one or more of the initial steps in the cascade. The authors postulate that EST facilitates the naturally occurring inflammatory process without interfering with the normal inflammatory cascade progression until inflammation is resolved, an idea which at first glance may seem counterintuitive. This facilitation in turn accelerates the anti-inflammatory process to reduce the probability that it becomes drawn out and leads to chronic inflammation. The specific mechanisms of action of the applied electronic signal energy can be effectively used to reduce or modify the undesired symptoms normally present during this inflammatory0 cascade process. This is illustrated in the box below.

Inflammation → Faciliation → Diffusion → Repair → Normalization

Ten mechanisms are outlined below, which highlight how EST appears to facilitate and accelerate this naturally occurring cascade and eliminate lingering inflammation and its effects on the introduction and proliferation of chronic pain.

The following therapeutically beneficial primary and secondary effects of EST would apply specifically in the anti-inflammatory actions of EST: dilution of toxic substances that cause pain and inflammation; pH normalization; increased tissue metabolism; and improved exchange between intracapillary and interstitial fluid, which in turn results in an improvement of tissue absorption (26). Table 3 lists the primary and secondary effects of electronic signal energy as it applies to its anti-inflammatory activity (27).

Understanding that the human biosystem is primarily electric in nature (24), it is worth mentioning other known physiological effects of electricity (electronic signaling) that will be discussed in future works. These effects or mechanisms of action include: signal

Table 3. *Effects of electronic signal energy as it applies to anti-inflammatory activity (27).*

Primary effects (arising directly from the signal energy)	
i.	cellular oscillo/torsional (ionic movement) effect
ii.	neuron blockade
iii.	imitation of hormone/ligand activity to create an electrical conformation change in the cell membrane G-protein
iv.	sympathetic stimulation (function-imitation)
v.	sympathetic stimulation (function-exhaustion)
Secondary effects (resulting from the primary effect)	
vi.	metabolite movement, dilution & redistribution
vii.	sustained depolarization
viii.	cAMP formation/activation
ix.	cell membrane repair & stabilization
x.	facilitation of metabolism
xi.	vasoconstriction
xii.	vasodilatation
xiii.	immune system support

competition effect via the A-β system (Melzak/Wall's Gate Control Theory), sustained depolarization (Wedensky Inhibition), neuropeptide release (adrenergic response), increase in dopamine concentration (pain inhibitory transmitter), decrease in NE and 5-HT, acceleration of the re-innervation process, activation of muscle pump, repeated cell membrane depolarization and repolarization activity, muscle training/strengthening, vasomotive imitation, muscle relaxation/spasmolysis (decreasing referred pain and directly decreasing local muscular pain), and accommodation (preventing nerve from "trying to get around" an antidromic block).

Safety

The safety of EST has been established throughout extensive use over the past 15 years. Nausea, vomiting, dizziness, etc. are commonly associated with chemical therapies, but are rare with EST. It appears that any EST undesired side effects are minimal and easily avoided.

One notable parameter of importance involving treatment with EST for inflammation processes is dosage, or intensity. Increasing the EST dose too much above the sensory threshold may exacerbate the inflammatory process by directly constricting the small vessels necessary for moving (diluting) inflammatory mediators. When using the alternating, sequentially generated modulated and unmodulated middle frequencies associated with EST, the electronic signal current sensation felt by the patient decreases as the frequency increases (higher current perception threshold). The clinician asks the patient about his/her sensation of the current as the current is gradually adjusted to the desired therapeutic level. The patient's sensory response often assists in determining the optimum dose, unless a lower dose is otherwise dictated by treatment protocols, which is desired for inflammatory indications.

As long as normal sensory responses are maintained with the administration of EST medium frequencies, there is insufficient electrical signal energy delivered to cause tissue damage.

Excess and damaging currents, which could otherwise cause harmful tissue heating, are completely avoided in the conscious patient. There are multiple heat effects on tissue that occur when using much higher frequencies, such as those delivered during Radio Frequency Thermocoagulation (RFTC – 512,000 Hz) treatment: e.g. nerve cell damage occurs over 45° C. and collagen destruction over 67° C. These heat effects are simply not possible when the electrical energy is delivered transcutaneously by current FDA cleared EST generation devices.

The heart is always a concern with electrical devices. The electrophysiological implications of these frequency ranges are shown in Fig. 1 (28). Depending on the frequency and the electrode position (transthoracic or neck-abdomen) of applied alternating current, dangerous ventricular fibrillations were induced roughly exponentially with increasing frequency. At frequencies above 4,000 Hz, the risk of interference with cardiac conduction pathways is almost non-existent because the electrical output capabilities of EST devices are much lower than those necessary to trigger ventricular fibrillation. Even if the electrodes are placed across the heart, which is not typically recommended, the electronic signal energy power density field is not high enough to trigger ventricular fibrillation.

Discussion of the Anti-Inflammatory Effects of EST

The authors have listed below some of the identified mechanisms of action that appear to provide anti-inflammatory effects via EST application. One theoret-

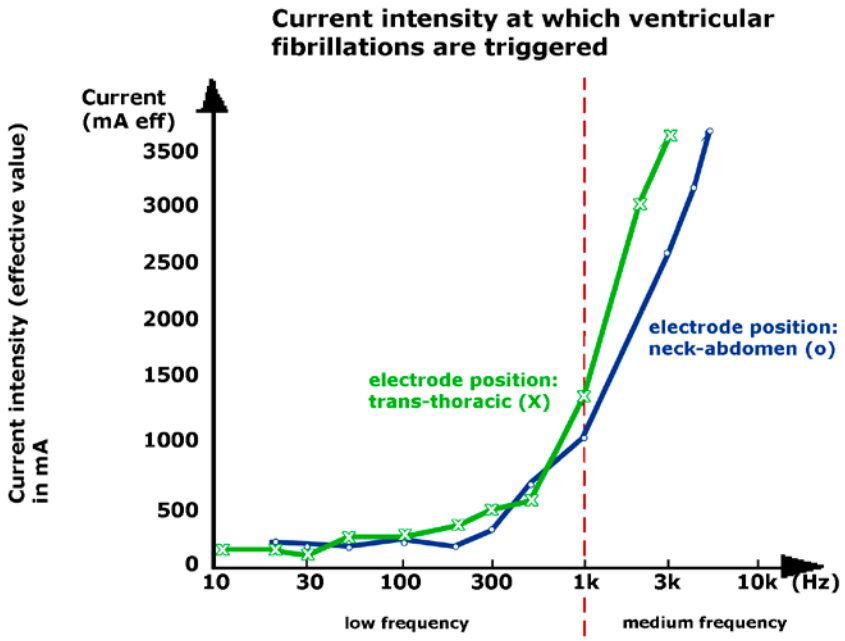

Fig. 1. *Current intensity and ventricular fibrillation threshold as function of frequency (1).*
The red line indicates the demarcation between low frequency and middle frequency. For both electrode positions, note the exponential increase of ventricular fibrillation threshold at middle frequencies (28).

ical mechanism of action (facilitation) listed below is currently postulated by the authors based upon biological responses which may occur in tissues.

- Facilitation
- Oscillo/torsional response
- Enhancement of filtration/diffusion process
- pH normalization
- cAMP formation
- Cell membrane repair
- Influence on metabolism
- Sustained depolarization
- Immune system support
- Increase in blood flow

Facilitation: Acceleration of Normal Inflammatory Process

The inflammation/migration response is initiated by a variety of electrically charged and active signal molecules produced locally by cells or by complement activation. These mediators act on capillary endothelial cells lining the blood vessels, causing them to dilate and become permeable to fluid and proteins (29).

In this paper, we postulate that normally occurring inflammatory processes appear to be facilitated by exogenous administration of alternating polarity electric fields via EST. Specific-parameter EST appears to support the naturally occurring inflammatory process with the following benefits. As the inflammatory metabolic cascade and bio-response is initiated, the oscillo/torsional effect (a direct effect on the cell described in the next section) of the applied electronic signal energy (with imposed rapidly alternating electric polarity-reversals) is delivered to the targeted anatomical inflamed area. The high concentration of electrically charged signal molecules that temporarily exist within the inflamed anatomical treatment field are aggressively moved to and fro in response to the EST energy and concomitant alternating polarity reversals (30,31). Figure 2 illustrates this effect. This enhances the movement, dilution, and redistribution of these charged molecules that are directly linked to pain and inflammation mediators (H ions, etc).

It is hypothesized that, unlike anti-inflammatory drugs, which block the inflammatory mediators or their precursors, electric alternating polarity EST appears to facilitate and support the physiological in-

flammatory process and minimize the time necessary for tissue to repair through a variety of mechanisms which are outlined in the sections which immediately follow.

These mechanisms (e.g. second messenger [cAMP]formation) minimize the normally occurring inflammatory side effects of pain and swelling (32) by initiating repair processes, by balancing chemical concentration differences, and by aggressive filtration and diffusion processes (15).

Oscillo/torsional Response (Vibration, Oscillation, Twisting and Turning Effects)

The oscillo/torsional effect is obtained by an electro-vibratory effect upon the cell itself due to the rapid alternation of electrical polarity charges in response to the higher alternating current signal frequencies used with specific parameter EST energy. The signal's electrical polarity continually reverses from a positive (anodal) charge to a negative (cathodal) at a rate equaling 2 times the delivered EST frequency, i.e. 20,000 PPS = 40,000 polarity reversals per second. The influence of electrically alternating fields can be expected to enhance the general movement of all charged molecules with additional rotary movement of the charged particles (Fig. 3). This alternating polarity energy increases the probability that specific chemical groups of substrates and enzymes (with normally opposed charges) will meet more readily in the required physiological orientation (33). This effect may be of great importance in enhancing the enzymatic breakdown of pain and inflammatory mediators.

Enhancement of Filtration/Diffusion Processes

EST electrical fields influence enzyme/substrate activity involved in the metabolic process by increasing the kinetic energy of the molecules, an effect which lowers the differences to the required activation energy and transition state (30,32). This increases the probability of important contact and correct orientation connection between enzymes and substrates, which is necessary for the breakdown of pain produc-

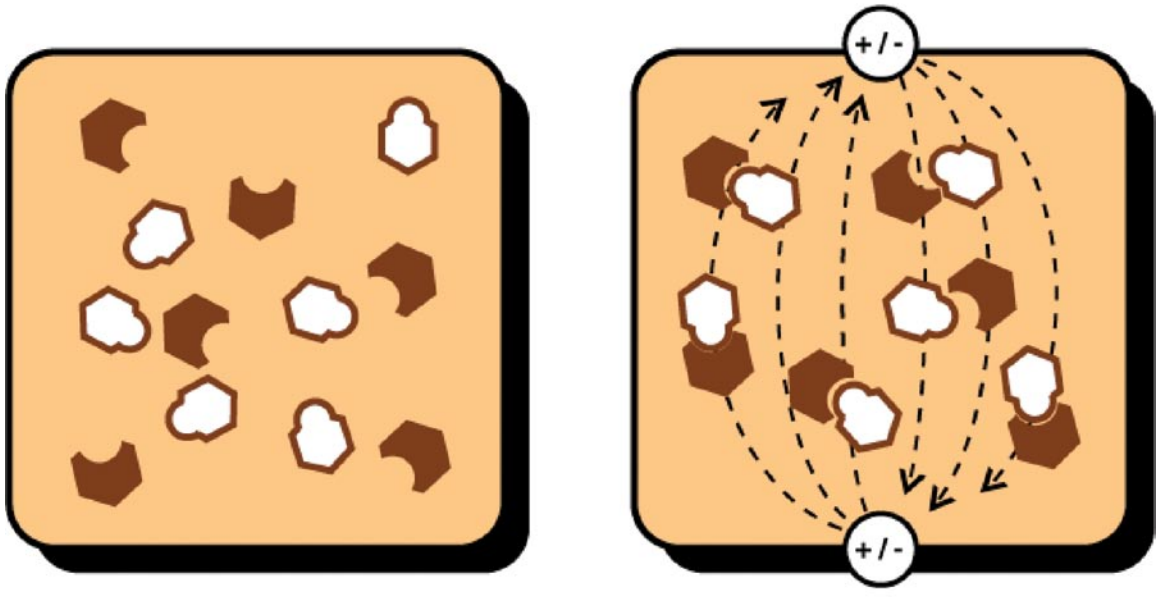

Fig. 2. *Metabolic redistribution and enhancement of filtration/diffusion process by increasing the accidental collisions of enzymes and substrates of enzymes and substrates under the influence of electronic signal treatment. The additional kinetic energy from EST is manifested as 1) enhancement of translational movement, 2) enhancement of rotational movement, and 3) increased activation energy.*

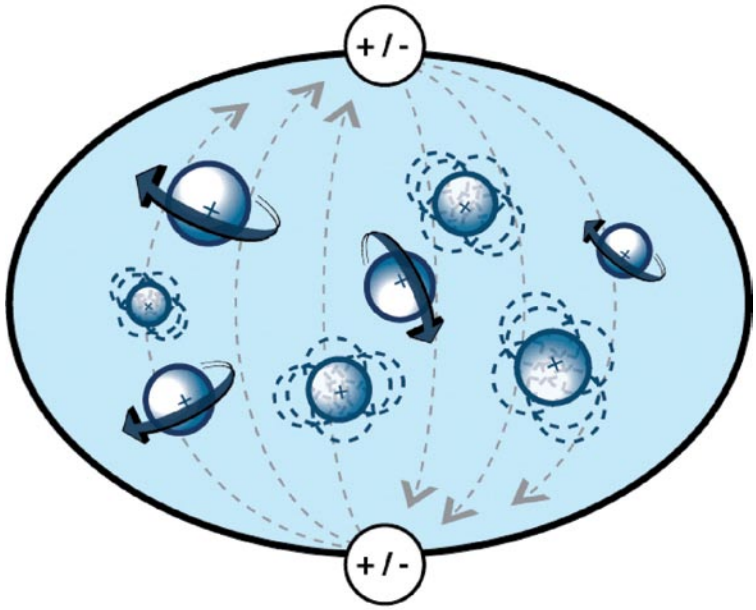

Fig. 3. *Influence of an alternating electric field on the orientation and energy of molecules in the cell. This alternating polarity energy increases the probability that specific chemical groups of substrates and enzymes (with normally opposed charges) will chemically react.*

ing mediators (33).

The oscillo/torsional response in the cell enhances the naturally occurring filtration and diffusion processes, described in standard physiology texts (34). This effect appears to bring about a balance of metabolic concentration differences where pathologically altered metabolic concentration of substrates and intermediate or final products of metabolism are present in the area of inflammation. This is most likely achieved via the additional kinetic energy supply to the affected region causing an acceleration of the natural filtration/diffusion processes (tissue clearance).

The diffusion/dilution effect and the increase in distribution of the electrically charged substances mediated by EST results in:

a) dilution of toxic, pain, and/or inflammation producing substances,
b) increase of filtration and diffusion processes (tissue clearance),
c) increase in local blood flow,
d) improvement of exchange processes of intracellular and extracellular fluids,
e) enhanced water electro-osmosis within the tissue, and
f) improvement of the resorption processes that are important for treating inflammatory conditions and edematous conditions.

Thus EST balances metabolic concentration differences, improves trophism and assists in minimizing undesired tissue inflammation, and normalizes the pH in the local and surrounding tissues.

pH Normalization (Ion Effect) and Balancing Metabolic Concentration Differences

The following description is based on common electrochemical principles and the logical extension of that knowledge. The electronic signal energy that is applied will create an electric field with rapidly alternating polarity reversals within that field as described earlier. This electromagnetic field has a direct effect upon the charged molecules positioned within the targeted anatomical field activating a redistribution effect (diffusion) of the charged metabolites that are

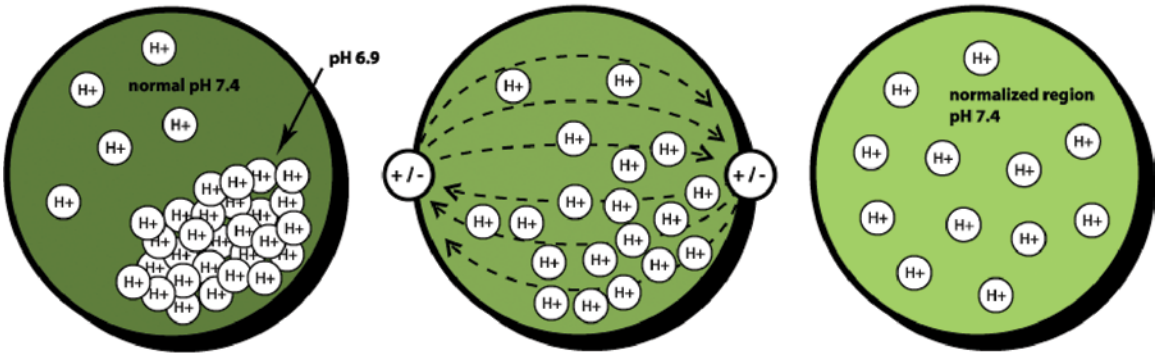

Fig. 4. *Influence of an alternating electric field on an area of higher hydrogen ion concentration. Note the movement of hydrogen ions into a normal area of lesser concentration; the extra hydrogen ions absorbed into surrounding tissues do not significanlty perturb their normal pH of 7.4.*

present in higher concentrations and enhancing the natural filtration process (dilution). The higher concentration of metabolites is electrically moved and head toward other adjacent anatomical areas of less concentration (basic physics law). Hydrogen ions, which are linked to pain and inflammatory mediators (35), are most affected since they are the smallest and most mobile electrically charged ions. This fact has a direct effect by normalizing pH levels in the tissues of the treated anatomical field (balancing metabolic concentration differences). The body functions most normally at pH 7.4, and healing (e.g. anti-inflammatory activity) is optimized.

H+ ions are linked directly to pain and inflammation mediators. Figure 4 reveals how middle frequency electric fields via EST decrease H+ ions in the inflammatory (concentrated) region. The movement of the H+ ions from the inflamed region (pH of 6.9 is used in this example) normalizes the pH in that region, contributing to the healing. The surrounding tissue can easily absorb the extra H+ ions without a significant overall drop in pH of the surrounding tissue.

Experimental evidence of activation of the filtration/diffusion process can be readily shown in vitro (36). Figure 5 demonstrates the effects of the oscillo/torsional action and response generated by EST. This effect gives time to the biosystem to overcome the effects of adverse and increased metabolite concentrations.

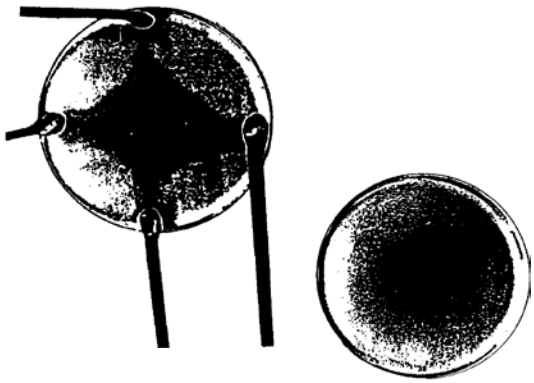

Fig. 5. *In vitro view of hydrogen ion (H+) concentratiOn (pH) and subsequent movement under the elecrical influence of the medium frequecy EST fields. Note the attraction toward each of the electrode poles (36).*

cAMP Formation/Activation – Normalization of Cell Function

EST energy produces a hormone-like effect by triggering an electrical conformation change to the

cell membrane G protein. This influences adenylate cyclase activity, resulting in the formation of the second messenger cAMP, which may direct cell specific activities, including cellular repair processes. cAMP- induced repair processes are necessary to stabilize the cell membrane and inhibit continued leakage of acids which may contribute to pain and inflammation mediators (29). EST and its effect of a direct electrical conformation change in the cell membrane G protein which ultimately normalizes (increases) cAMP levels may play the most critical role towards normalization of cell function (37).

Multiple references exist to support that cAMP will increase from sustained depolarization of the cell membrane (pharmacological or specific-parameter electrical energy causing sustained cell depolarization) (38). Schwartz (39) states that there are "numerous citations that demonstrate… second messenger formation within the cell at various ion voltage gates when exposed to frequency specific electrical currents." This direct effect of EST serves to increase available cAMP for cell normalization (40,41).

Signaling cAMP leads to the opening of voltage gated channels in efferent c-fibers of pain neurons and the sympathetic nervous system. Vessels will then vasodilate, increasing local circulation, allow incoming nutrients and the washing out of waste products. This cascade will eliminate the primary chemical causes of local pain. In addition, signaling cAMP also leads to decreased afferent c-fiber firing, which in turn decreases ephatic cross firing of afferent A-delta fibers.

Cell Membrane Repair/Stabilization

Research has shown that electrical field stimulation (EST energy) has a direct effect upon ACTH stimulation, which controls the secretion of cortisol (23). This is the body's own "measured steroid response." Cortisol has 2 basic anti-inflammatory effects: 1) it can block the early stages of the inflammation process or 2) if inflammation has already begun, it causes rapid resolution of the inflammation and increased rapidity of healing. It is believed that cortisol effects assist in the liberation and mobilization of amino acids that can be used to repair the damaged tissues. Endogenous cortisol is much more effective and safe than exogenous cortisol or equivalent because it is "just enough" (15).

The mechanism by which ACTH activates cortisol from adrenocortical cells is a function of cAMP. The principal effect of ACTH on the adrenocortical cells is to activate adenyl cyclase in the cell membrane. This induces the formation of cAMP in approximately 3 minutes. The cAMP in turn activates the intracellular enzymes that cause the formation of the adrenocortical hormones (32). EST, as shown above, also facilitates the naturally occurring processes necessary for control and mitigation of inflammatory conditions without the usual undesired side effects that accompany the introduction of chemical steroid compounds.

Since second messenger formation (cAMP) directs cell specific activity to membrane repair and stabilization, arachidonic acid release from membrane breakdown is obviously diminished and thus the prostaglandin (inflammation and pain mediator) cascade is attenuated or terminated.

EST frequencies greater than 2,000 Hz have been shown to stimulate utilization of cAMP through sustained depolarization, and cAMP is linked to cell membrane repair (42). Membrane stabilization and repair decreases the supply of arachidonic acid which, in turn, decreases the inflammatory substrate.

Influence on Metabolism

Metabolism means simply the sum total of all the chemical reactions in all of the cells of the body and it can be influenced by EST signal energy in several different ways. The first mechanism is by using lower frequency (0.1 to 200 Hz) electronic signals with specific parameters to stimulate repetitive action impulses (depolarization and repolarization activity) in excitable cells. Repetitive depolarization activity requires a subsequent repolarization response, and this directly challenges the existing metabolic level to increase to meet the demands placed upon the cell.

The second mechanism is by triggering cAMP formation, which activates and initializes metabolism: EST signal energy releases noradrenalin from sympathetic nerve endings resulting in a reaction with receptors on the cell membrane. This triggers cAMP formation from ATP and cAMP activates metabolic processes in the cell.

The third mechanism is by the oscillo/torsional (O/T) effect created by EST signal energy and alternating electric polarity reversals in the target anatomical field: The O/T effect can be expected to achieve facilitation of metabolism through the increase in activation energy. The O/T effect and its electrical effect on the electrically charged enzymes and substrates within the anatomical treatment field also increases the probability that these enzymes and substrates (with specific lock and key components) meet in favorable orientation more often (33).

Sustained Depolarization (Plateau Effect)

Cell membrane sustained depolarization (also termed Wedensky inhibition) occurs with middle frequencies above approximately 2,000 Hz. This leads to nerve cell stabilization as the nerve cell is "locked open." This opening of voltage gated channels induces cellular ion influx/efflux activity. The movement of ions occurs until equilibrium is met, and metabolic activity is now at optimal levels (43).

This effect occurs when higher EST frequencies are applied at a stimulation rate faster than the excitable cell membrane is able to follow (multiple stimulations occur within the absolute refractory period of the membrane). With enough dosage and for as long as the electronic signal is actively delivered, the membrane will not immediately repolarize, but instead the potential remains on a plateau near the peak of the spike (44). These EST middle frequencies have a direct effect upon voltage dependent gates and the alteration in the membrane physiology is objectively measurable (45). cAMP is utilized and decreased in absolute amounts as it relays the message to open the voltage-gated channels and activates other metabolic activities in the intracellular organelles (46). These EST-induced effects can be described as direct normalization of the cell function, which directly reverses sensitized pain and inflammation feedback circuits and possibly promotes overall healing (25).

As shown in Table 4, the relatively low resistance of nerve and muscle cells favors electrical conduction.

Table 4. *Nomenclature and definitions.*

1. **Voltage:** The tension that results from a difference in the supply of positive and negative charges between two points.
2. **Current:** The movement of charged particles (ions and electrons).
3. **Resistance:** The force that inhibits the flow of charged particles typically measured in Ohms.
   a. Nerves 1000 Ω
   b. Blood Vessels 1600 Ω
   c. Muscle 5000 Ω
   d. Bone 160,000 Ω
4. **Impedance:** The property of resistance to alternating current flow, which includes self inductance, capacitance, and ohmic resistance.
5. **Ohm:** The Standard International (SI) unit of electrical resistance. Ohm's law: V = IR.
6. **Conductance:** The ease with which an alternating electrical current flows through a substance and is the reciprocal of resistance. C = 1/R.
7. **Cell:** In this paper, cell most often refers to the nerve cell, or neuron; however, it may also refer to the muscle cell, which is commonly affected by inflammation. Electricity has its greatest affinity for these 2 types of cells and blood vessels, given their resistance (impedance) values outlined above. These two types of cells also happen to be electrically excitable.
8. **Low Frequencies:** 0.1 – 1,000 Hz
9. **Middle Frequencies:** 1,000 – 100,000 Hz
10. **Metabolic "challenge":** Repeated cell membrane depolarization activity requires subsequent membrane repolarization activity. This requires additional energy production, increasing the metabolism to meet the new demand.
11. **Higher levels of ATP:** Increased requirements for ATP (adenosine triphosphate; the main energy storing molecule) energy levels challenge the metabolism to increase ATP production to meet the demand.
12. **EST:** Electronic signal treatment, a term coined by the authors to characterize the basic mechanism of action.
13. **cAMP:** Cyclic adenosine monophosphate; a second messenger inside most cells.
14. **cGMP:** Cyclic guanidine monophosphate; a second messenger inside most cells.
15. **Specific parameter:** This term is used to identify the requirement for applying a specific electronic signal frequency, a "range" of frequencies or combinations of frequencies to achieve the desired physiological response.
16. **Ephatic conduction**: This is the excitation of a cell membrane due to its coming into contact with another cell membrane which is excited.

EST works on the excitatory membrane of the muscle cell just as it does on nerve tissue. Higher dose and higher frequency EST signals cause sustained depolarization and the contracture of the smooth muscles of the blood and lymph vessels. This causes a temporary vasoconstriction and an increase in the centripetal transport of the blood and lymph away from the inflammatory, swollen tissue region. Continued application of EST-induced sustained depolarization may result in a block of the release of noradrenalin and therefore vasodilatation (inhibition of smooth muscle contraction). The increase in circulation also favors an earlier resolution of inflammation.

Immune System Support

EST appears to improve and support the immune system (unlike chemical steroids) by improving gap-junction intercellular communication via EST oscillo/torsional effects.

Gap junctions are protein-lined channels that directly link the cytosol of one cell with another adjacent cell providing a passageway for movement of very small molecules and ions between the cells (Fig. 6) (47). This allows metabolic coupling or metabolic cooperation between cells. Another important compound transferred from cell to cell through gap junctions is cAMP. The fact that cAMP can transfer from cell to cell through gap junctions means that hormonal stimulation of just one or a few cells can initiate a metabolic reaction in many of them (48). Cell to cell gap junctions are formed quickly when 2 healthy cells come into contact, linking them metabolically as well as electrically.

Gap junctions are also influenced by many other changes in their surroundings, i.e. by changes in the electric membrane potential or the phosphorylation of substances inside the cells produced by hormonal attachment on receptor molecules, which transfer information via signal molecules. This transfer and the common use of small molecules is the basis for intercellular metabolic cooperation and fulfill the precondition for intercellular chemical and electric cooperation.

EST energy influences the electrically charged ion movements through gap junctions by increasing the transport through the cell to cell canals and by facili-

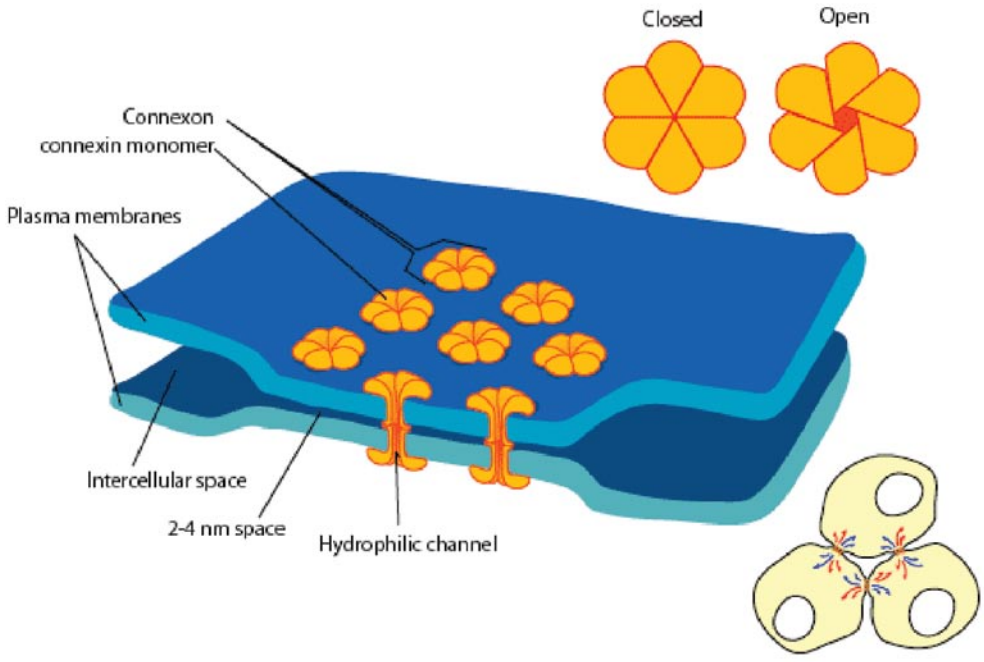

Fig. 6. *Model of the Gap Junction. Note the hydrophilic channels which facilitate intercellular communication. Alternating electric fields serve to influence electrically charged ion movements and transport through the channels and facilitate intercellular electric and chemical communication and metabolic cooperation.*

tating intercellular electric and chemical communication and metabolic cooperation. EST energy fields contribute to a functional improvement in tissues which are dysfunctional, e.g., in the healing phase of injured tissue, in degenerative tissue changes, in metabolic conditions, in edema, and in regions of decreased blood supply (49).

In contrast to nature's "measured ACTH and steroid response" described in the section "Cell Membrane Repair/Stabilization," exogenously administered (chemical) steroids may dramatically suppress immune system activity. Therefore, the "appropriate immune response" to the chemical therapy of inflammation is sacrificed.

Increase in Blood Flow/Edema Reduction (Macro Effect)

The physiological effects (metabolic challenge) of electronic signal energy on motor nerves and muscle stimulation are accomplished by lower frequencies. This effect results in subsequent increased metabolism autoregulatory vascular mechanisms that produce a decrease in peripheral resistance of the vasculature in the stimulated treatment field. These autoregulatory vascular mechanisms are controlled by the end products of metabolism — CO_2, lactate (pH decrease), and adenosine release. ATP consumption is initiated by depolarization of excitable cells and because these cells attempt to immediately repolarize their membrane potential, there is an increased demand for ATP as the source of energy. Higher EST frequency and dosage has a blocking effect (25,27,37) on sympathetic vasoconstrictory nerve fibers resulting in vasodilatation within the vasculature innervated by these sympathetic fibers. In this way, blocking afferent c-fibers increases local circulation.

Multiple mechanisms of action apply in the treatment of edematous conditions with EST. When lower frequency parameters are employed at dosage levels above the nerve's firing threshold, the activated nerve stimulation would enhance the centripetal transport of venous blood and lymph via sympathetic stimulation. Higher EST dosage above the muscle contraction threshold would activate the muscle pump response, enhancing also the centripetal flow of blood and lymph. Alternating frequency parameters of applied EST energy are effectively used to assist in the movement of inflammatory mediators and end-products away from the area of inflammation. This effect will also directly lead to the reduction of inflammation. These physiological effects can be produced in EST-capable devices by programming the use of alternating AM and FM middle frequencies in certain specific-parameter sequences. Edema reduction by EST is so important and complex that a full explanation of current understanding is deferred to a future paper.

Two Applications: Neurogenic and Neural Inflammation

The inflammatory response is categorized into 3 types: 1) traumatic — neutrophils and macrophages; 2) immunogenic — lymphocytes and other immune cells; and 3) neurogenic — sprouting nerve cells, degranulating mast cells, altered vascular endothelial cells (1).

Multiple mechanisms for minimizing the effects of the standard inflammatory response by EST have been identified and described. The application of these principles to neurogenic inflammation is now described. Neurogenic inflammation is defined as a process stimulated by chronic severe pain in which the "central nervous system will undergo changes and start generating signals that will maintain and drive the peripheral inflammatory response" (49). This process is a functional as well as an anatomic change. Several pathological processes occur at once: sprouting nerve cells, degranulation of mast cells, and altered vascular endothelial cells. A critical component of this process is the anti-dromic transmission of signals from the dorsal horn cells, which have been stimulated chemically by mast cell release of 5-HT, histamine, and substance P, and electrically by the release of cGRP and substance P to blood vessels resulting in the release of NO, bradykinin, and vasoactive intestinal peptide (VIP) operating directly on nerve endings.

This process is one of the most likely mechanisms for the propagation of chronic pain and is one way of differentiating chronic pain from the acute pain process. An excellent, well-written and easily understood explanation of this important concept can be found in Brookoff's review article (50).

Application of electronic signal treatment can interfere with this pathological process by multiple mechanisms. Cell membrane repair and stabilizing effects of EST are postulated to specifically stabilize mast cells, inhibit their degranulation, and block the release of the algOric pro-inflammatory mediators. This effect, in turn, will serve to block generation of the antidromic transmission originating in the dorsal horn. The sustained depolarization effect directly blocks an-

tidromic propagation from the dorsal horn to the periphery. In addition, the depolarizing effects of EST will block all nerve cell transmission, pro-dromic and antidromic. The membrane stabilizing effects of vascular endothelium will also serve to reduce vascular leakage of inflammatory mediators, hydrogen ions, and fluid, and thus block the generation of edema. Also, blocking afferent c-fibers will increase local circulation and further decrease neurogenic inflammation.

Neural inflammation directly results from neural injury. This type of inflammation is directly associated with neuropathic pain, since there are changes in the anatomic structure of the infrastructure. Neural inflammation is very elegantly described in the same article by Brookoff (50) as the result of the interplay of the 3 types of glial cells, all recruited by macrophages, in response to neural injury: 1) microglia; 2) astrocytes; and 3) oligodendrocytes. The microglia are the mediators of the proinflammatory response; their upregulation can lead to the chronic inflammatory state. The astrocytes surround synapses and can send and modify neural signals; and the oligodendrocytes form myelin. According to Brookoff, there is experimental evidence "…implicating neural inflammation as a driver of pain, hyperalgesia, and allodynia" (50).

Just as with neurogenic inflammation, EST can diminish the effects of neural inflammation by minimizing the inflammatory response at multiple points in this cascade. Mitigating the initial inflammatory response by all mechanisms described above would have the overall effect of decreasing the activity of microglia cells to "nip the process in the bud." The EST-induced electrical conformation changes in the cell membrane G-protein as well as other membrane stabilization properties of EST described above, could serve to decrease microglial activity. Likewise, because of the ability of EST to block nerve conduction by causing a sustained depolarized state of the nerve cells, synapses are quiet, non-transmitting, and less likely to be influenced by inflammatory driven astrocyte activities. cAMP formation/activation further will serve to begin the healing process in the nerve cells themselves and minimize the effects of the insult.

The EST effect on both neurogenic and neural inflammation is enhanced by its action on the overall immune function. Important effects include activation of cells of the immune system, sustained depolarization, cAMP formation, facilitation of intracellular communication, an increase in the generation of the natural killer cells (NK) (51), and enhancement of the efficacy of the activity of the cells of the immune system. This enhanced immune response can serve to manage the development of the neural inflammation response as it does in non-neural inflammation.

Financial Ramifications

Health care costs are increasing at an alarming rate (52). Third party payers are becoming increasingly alarmed at the costs of pharmacological treatment and drugs are becoming more expensive per se. Additional costs are iatrogenic — incurred because of complications resulting from the side effects of drugs. Because of the safety profile of EST, there are virtually no expenses associated with side effects.

We also postulate that the safety profile of EST will promote less professional liability exposure. The verification of this statement will only come with the increasing widespread use of EST as an alternative to steroids and NSAIDs.

Summary

We postulate that pharmaceuticals have a tendency to overwhelm biosystems, a very unnatural progression as evidenced by the side effect profiles. EST works through biosystems and their controls. We have presented multiple mechanisms, most documented and one postulated, which demonstrate initial facilitation and then quick resolution of the inflammatory process to prevent it from leading to chronic inflammation and chronic pain. While complex, all concepts above fit together when taken into the context of signaling cAMP; however, the basic signaling mechanism could easily be the oscillo/torsional ionic action on cyclic AMP. Through this and the other mechanisms discussed, cellular derangements are returned to normal in optimum physiological time.

A paradigm shift in our approach, thinking "out of the box," should begin soon, for several reasons. Many patients in chronic pain are simply being under treated for a variety of reasons. Narcotic medications are being diverted in increasing numbers. Most importantly, a recent study on adverse drug events based on the FDA voluntary reporting system has found that the death rate has increased out of proportion to the increase in the number of prescriptions written, and the greatest culprits are pain medications and immune modulating drugs (3). The authors emphasized that these findings "show that the existing system is not adequately protecting patients and underscores the importance of recent reports urging far-reaching

legislative, policy, and institutional changes" (3). One of the purposes in writing this paper is to get the pain management physician to start to think about modifications in his or her therapeutic approach, which might begin by emphasizing the physics approach as well as the pharmacological approach.

The following paragraphs from Potter and Funk (23), written in 1917, still apply and quite nicely summarize the subject: "Success in electrotherapeutics depends on an adequate knowledge of physiology and pathology as related to the human body; on a mastery of the laws that govern electricity [physics]; on the possession of efficient apparatus, the achievement of good technic by practice and the good judgment to apply all these acquirements to the best advantage… Electrotherapeutics is not a system to be used to the exclusion of other therapeutic measures, but is a worthy additional unit to any physician's armamentarium …".

Conclusion

While we believe that additional studies involving the treatment of inflammatory processes with EST are important, there appears to be enough evidence to encourage the primary or adjuvant use of EST for inflammatory conditions and for the potential replacement of chemical steroids. Finally, we believe that EST and the evidence presented have placed us on a threshold of discovery; it is time to apply this knowledge in the clinical setting. The alternative role of EST (the electric signaling of the cells) will depend on the outcomes of well conducted clinical trials which utilize this reasonable and safe approach.

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