

CUMULATIVE RESEARCH DATA REPORT

ELECTROCEUTICAL TREATMENT FOR

ENDOTHELIAL-RELATED DISEASE

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Abstract:

The application of specific-parameter electroceutical treatment for a variety of endothelial-related diseases such as: diabetic polyneuropathy, gangrene, dermal ulceration's, bronchial ischemia, pre-menstrual syndrome and vasospastic disorders (RSD, etc.) has produced favorable results in the resolution or the effective management of these conditions. The postulated mechanisms of action and theoretical framework underlying this procedure will be reviewed.

Keywords: specific-parameter electroceutical treatment; endothelial-related diseases.

Discussion:

Endothelial-related disease involves vascular, arteriole and neuromuscular structures and is responsible for the manifestations of many widespread diseases such as peripheral vascular dysfunction, stroke, heart disease, neuro-muscular disorders, even migraine. All blood vessels are lined by endothelial cells, which serve as barriers between blood and vascular smooth muscle. These endothelial cells also act as modulators of vascular function-regulating coagulation, lipid transfer, and vessel tone. This recognition has triggered considerable interest into vascular smooth muscle function, its control by the autonomic nervous system, including hormone/ligand receptor mechanisms and the association with concomitant pain syndromes.

The role of endothelial cells is twofold: *sensory and effector*. At least three different classes of endothelial vasoconstrictor substances have been identified:

1. Arachidonic acid metabolites - leading to prostaglandin cascade.
2. Polypeptide-like factor produced by cultured endothelial cells.
3. A newly isolated endothelium-derived vasoconstrictor peptide - *endothelin**

*Endothelin (ET) has been shown to be a potent vasoconstrictive peptide acting on the vascular system, inducing ischemia, and stenosis and provoking pain.

Action of endothelin (ET) in:

Cardiac muscle:	Coronary vasospasm, myocardial infarction, left ventricular hypertension, chronic heart failure.
Renal system:	Renal hypertension, glomerul filtration rate (diuresis) failure.
Respiratory system:	Bronchial constriction, pulmonary hypertension.
Vascular system:	Vasospasm, ischemia, stenosis, necrosis.

The biophysiological action of endothelin (ET) in response to specific-parameter endogenous electroceutical impulses lead to the concept that ET has a significant role in the endothelial modulation of vascular tone in the anatomical area of electroceutical treatment, however, resultant circulation ET is unlikely to manipulate or maintain vascular tone.

The synaptic release of numerous pharmacologically-active substance (noradrenalin, ATP, cyclic AMP, calcium) during specific-parameter bioelectric impulse treatment (producing a physiological action potential) is now well documented and widely accepted. Further, it has been demonstrated that impulse rates of around 6 to 10 pulses per second (pps) induce vasoconstriction via noradrenalin - endothelin release. Repeated exogenous electroceutical impulses above 10 pps have reactive vasodilatory effects due to the depletion of noradrenalin at the synaptic junction. ***It appears that endothelin is released in response to noradrenalin and is quiescent in the absence (depletion) of noradrenalin.***

A favorable influence was noted without any adverse side effects on nearly all patients presenting with symptoms of acute and chronic pain and of vascular dysfunction. We believe that the influence of endothelin peptide hormone accomplished by the exogenous application of specific parameter electroceutical treatment.

METHODS

Electroceutical medicine is defined as the exogenous application of specific-parameter electric pulses to induce a desired therapeutic physiological effect. Current research from the *Clinical Electromedical Research Academy (CERA)* has provided clinical data for the classification of these different types of electroceuticals.

At present, two different electroceutical classifications are known and described:

- **STIMULATORY CLASS:** Bio-physiological effects induced by repeated synchronous action potentials in excitable cells - depolarization and repolarization activity.
- **MULTI-FACILITORY CLASS:** Bio-physiological effects induced without action potentials (no repetitive depolarization and repolarization activity) - effects are achieved via multiple mechanisms of action.

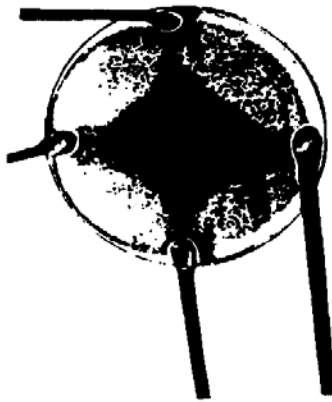
Mechanisms of Multi-facilitory (Mf) Effects:

- Cellular Oscillo Torsional Response
- Transport of Charged Ions (D.C.)
- Second Messenger Formation (cAMP)
- Sustained Reactive Depolarization (Block)
- Imitation of Hormone/Ligand Activity
- Thermal Generation

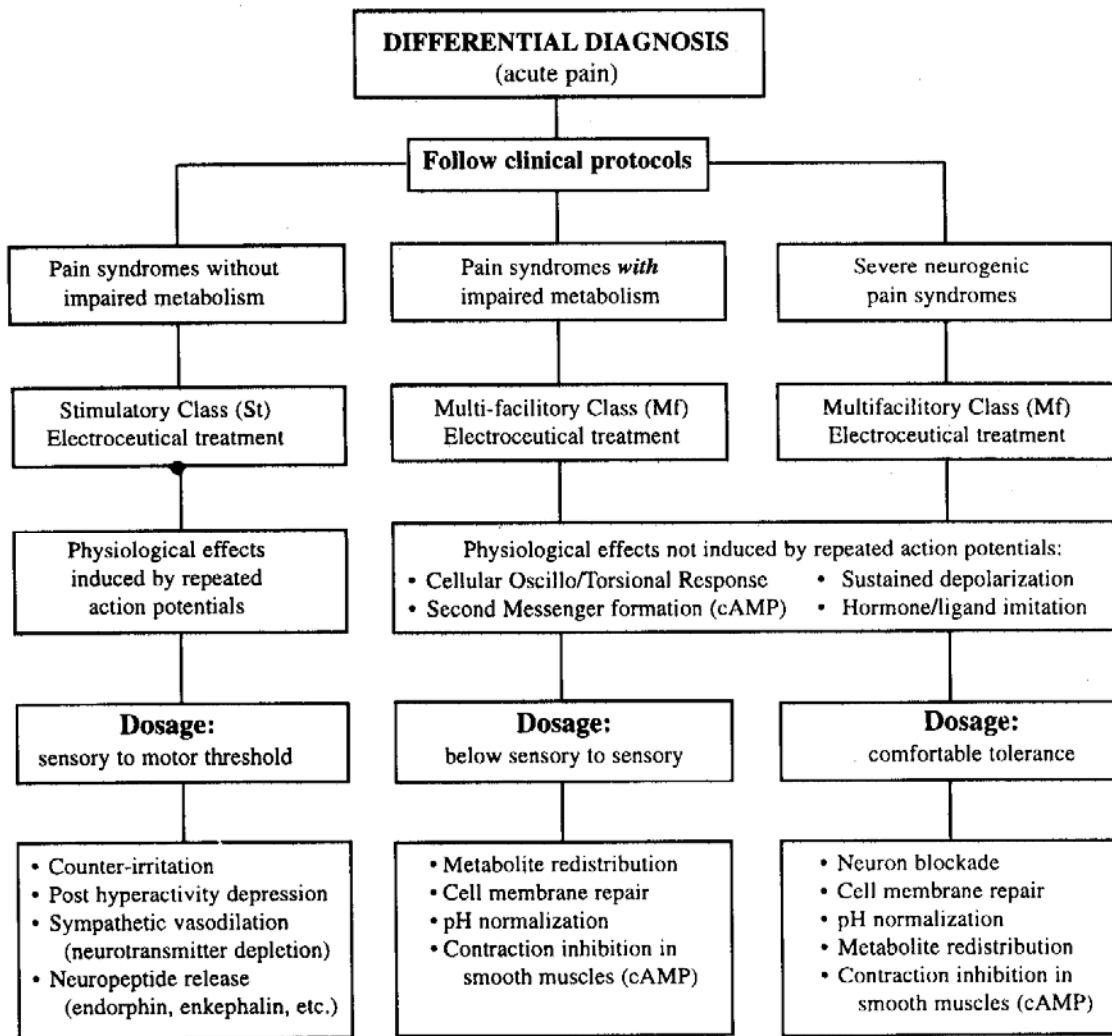
Clinical management of pain may be accomplished by using proper electroceuticals with specific bioelectric influence from the two classes listed above. Several bio-physiological mechanisms of action have been shown to be of value in the mitigation or resolution of pain.

Under the **Stimulatory Class (St):** Counter-irritation is produced by repeated excitation of afferent nerve fibers which effects neuronal signaling processes in the CNS, interferes with local pain perception and is primarily effective during the actual procedural treatment. Longer lasting analgesia is accomplished via cell receptor uptake of special pain-inhibiting neuro-peptides (beta-endorphin, enkephalin, phyllokinin, etc.) and by the depletion (via sympathetic function fatigue) of the synaptic neuro-transmitter (noradrenalin).

Under the **Multi-facilitory Class (Mf):** Application of exogenous Multi-facilitory (Mf) stimulus which falls within the absolute refractory period of the cell membrane induces sustained reactive depolarization across multiple nodes of Ranvier and inhibition of axon information (pain signal) transport. This neuron blockade effect (Wedensky Inhibition) occurs primarily during the procedure. Longer lasting analgesia is accomplished via the influence of an alternating-polarity Mf bioelectric field that generate a cellular oscillo-torsional response, balancing metabolite concentration differences = pH normalization. The relative importance of the oscillo-torsional response must not be overlooked (*see fig. 1*). This bioelectric, alternating electric field influence can be expected to supply additional kinetic energy that accelerates the diffusion process and substantially enhances the movement of all charged molecules. Therefore, the probability is considerably higher that specific enzymes and substrates with normally opposed electrical charges will meet in favorable position (lock and key mechanism) more frequently (Activation State). This appears to be clinically essential for the enzymatic breakdown of pain and inflammation mediators. Additionally, second-messenger formation directs cell-specific activity toward membrane repair - inhibiting arachidonic acid and subsequent prostaglandin (pain mediator) cascade and inhibition of smooth muscle (vessel wall contraction).



In-Vitro view of Hydrogen-Ion (pH) concentration and subsequent movement under the influence of Mf bioelectric alternating fields. Note the attraction toward each of the electric poles. This knowledge is extremely useful in the proper anatomical placement of the electrodes.



Summary and Conclusion:

Endothelin (ET) is a local peptide hormone produced by vascular endothelial cells and is the most potent vasoconstrictor yet identified. There is increasing evidence that endothelin (ET) plays a significant role in vascular tone and blood pressure and in the pathophysiology of cardiovascular, renal and respiratory disease.

It has been found that endothelin (ET) peptide hormone can be linked to multiple pathology in the circulatory system, including profound levels of pain. The desired physiological effects necessary for the resolution, mitigation, or management of these symptoms of pain and circulatory dysfunction appear to be induced or favorably influenced by administration of specific-parameter electroceutical treatment.

While the absolute mechanisms of action of electroceutical treatment on pain and different vascular disorders remain (to a large extent) unclear, it has been shown that electroceutical procedural treatment induces a normalization of cellular molecular activity. This is accomplished by the exogenous bioelectric stimulus and subsequent repeated voltage-gated ion exchange, which liberates, inhibits, or normalizes the level of second messengers such as cyclic adenosine monophosphate (cyclic AMP) - a key regulatory agent directing all cell-specific activity. Additional favorable clinical results appear to be associated with existing, well-documented synaptic activity and subsequent activation of endorphins, enkephalins and circulating catecholamines, etc.

References:

- Aiai, H., Hon, S., Aramori, I., Ohkubo, H., and Nakanishi, S. (1990). Cloning and expression of a cDNA encoding an endothelin receptor. *Nature (London)* 348, 730-732.
- Barnard, J.W., Barman, S.A., Adkins, W.K., Longnecker, G.L. and Taylor, A.E. (1991). Sustained effects of endothelin-1 on rabbit, dog and rat pulmonary circulation. *Am. J Physiol.* 261, H479-486
- Brain, S.D. (1989). The direct observation of arteriolar constriction induced by endothelin in vivo. *Eur J Pharmacol* 160, 401-403.
- Cao, L., and Banks, R.O. (1990). Cardiovascular and renal actions of endothelin: effects of calcium-channel blockers. *Am J Physiol.* 258, F254-F258.
- Chen, C., and Wagoner, P.K. (1991). Endothelin induces a nonselective cation current in vascular smooth muscle cells. *Circul. Res.* 69, 447-454.
- Emori, T., Hiratay., Ohta, K., Kanno, K., (1991). Cellular mechanism of endothelin-1 release by angiotensin and vasopressin. *Hypertension* 18, 165-170.
- Gallen, D., Cowen, T. (1982). Functional and nonfunctional nerve-smooth muscle transmission in the renal arteries of newborn and adult rabbit and guinea pig. *Blood Vessels* 19, 237-246.
- Kugelgen, I.V., and Starke, K. (1985). Noradrenalin and ATP as cotransmitters of neurogenic vasoconstriction in rabbit mesenteric artery. *J Physiol.* 367, 435-455.
- Lipplon, H.L., Hauth, Y.A., Summer, W.R., (1989). Endothelin produces pulmonary vasoconstriction and systemic vasodilation. *J Appl. Physiol.* 66, 1088-1094.
- Luscher, T.F., Van Houtte, P.M. (1990). Endothelin derived vasoactive factors. *CRC Press.*
- Masaki, T., Kimura, S. (1991). Molecular and cellular mechanisms of endothelin regulation, implications for vascular function. *Circulation* 84, 1457-1468.
- McCormack, D.C., Salonen, R.O., and Barnes, P.J. (1989). Effect of sensory neuropeptides on canine bronchial and pulmonary vessels in vitro. *Life Sci.* 45, 2405-2412.
- Ross, R. (1986). The pathogenesis of atherosclerosis - an update. *N Engl J Med.* 314, 488-500.
- Savery, F., Sorgnard, R. (1991). Clinical bioelectric treatment of diabetic neuropathy with gangrene. *Adv Ther.:* 7,5.
- Savery, F., Sorgnard, R., Schwartz, R., May, H.U., (1991). *Adv Ther* 8, 2.
- Schwartz, R., (1990). Electric sympathetic block, a review of electromedical physics. *Adv Ther* 8.1.
- Shepherd, J.T. (1963). Physiology of the circulation in human limbs in health and disease. *WB Saunders.*
- Sorgnard, R., Savery, F., Nikolova, L., Schwartz, R., Patterson, L. (1993). Alternative clinical treatment for Reflex Sympathetic Dystrophy (RSD), *CERA Sum. Rep.* (175 patients).
- Van Houtte, P.M. (1978). Heterogeneity of vascular smooth muscle. *Microcir* 2, 181-309.
- Weiner, N. (1970). Regulation of norepinephrine biosynthesis. *Ann, Rev. Pharma.* 10, 273.
- Xuan, Y., Wakins, W.D., and Whorton, A.R. (1991). Regulation of endothelin-mediated calcium mobilization in vascular smooth muscle cells. *Am J Physiol* 260, C492-C502