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THERAPY WITH ELECTRICAL STIMULATION - A PHARMACOKINETIC APPROACH

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ABSTRACT

A hypothesis on the mechanism of electrotherapy is proposed. The model assumes that electrical stimulation excites nerve endings which release substances with antagonistic activities. Pathological syndromes are the result of an imbalance in release of excitatory and inhibitory substances. Electrical stimulation difusely stimulates both types of endings but its effect is more enhanced in endings which have not been adequately activated by natural nerve excitation. Thus electrical stimulation improves the balance and contributes to restoration of normal activity.

INTRODUCTION

For more than one hundred years various modalities of electrical currents have been applied to the human body in order to alleviate different pathological conditions (1). Unfortunately a scientifically proven rationale for the numerous "electrotherapies" was usually missing and the field has been "often associated with medical quackery and mysterious gadgets with wild, unsubstantiated claims" (2). In spite of some scepticism of the medical profession towards electrotherapy several applications such as cardiac pacing and functional electrical stimulation became well accepted since the basic mechanisms - triggering of action potentials and subsequent muscle contraction - are today rather well understood.

Pain relief with electrical stimulation was boosted after Melzack and Wall proposed their gate theory (3) and TENS (transcutaneous electrical nerve stimulation) devices are at present perhaps the most popular electrotherapeutic devices. While it seems today that the gate theory "was too simple and was incomplete" (4) and several studies have failed to provide adequate empirical support (5) it is obvious that a new therapy is accepted only if at least a hypothesis attempts to explain the underlying mechanism. The next rather widespread application of electrotherapy came by chance: Cook stimulated the dorsal column of the spinal cord in a multiple sclerosis patient for intractable pain and observed as a remarkable side effect improved motor control (6). Since then the technique of spinal cord stimulation (SCS) has been applied to thousands of patients with pain and various disorders of bladder, bowel and motor system (7).

Most theories regarding the mechanisms of electrical therapy assume neurophysiological or morphological changes. The gate theory supposed presynaptic inhibition, Phillips suggested disruptive action of stimulation (8), Dimitrijević (9) assumed

that SCS induced ascending impulses which affected several supraspinal structures and Illis found increased synaptic vesicles after stimulation (17) (18).

There is however at least one phenomenon which can not be readily explained only in neurophysiological or morphological terms - it is the duration of effects after stimulation has been switched off. Already early experiments on posttetanic potentiation showed that increased reflex responses may persist for minutes after a short burst of electrical stimulation (10). Therapeutic effects which may outlast the stimulation period for several hours or even days have been observed in pain relief stimulation (5), functional electrical stimulation (16) and spinal cord stimulation (7). Phillips (8) considered the persistence of beneficial effects for hours as an outstanding problem and speculated on changes in synaptic morphology and accumulation of chemical transmitters (12). That biochemical phenoma might be responsible for therapeutic effects of electrical stimulation might be deduced from reports of chemical changes due to electrical stimulation. Levin et al. (13) showed that spinal cord stimulation causes release of plasma norepinephrine, epinephrine and dopamine as well as norepinephrine in the cerebrospinal fluid. Tielen et al. (14) observed after a tetanic stimulation was applied to the fascia dentata of the rat that electrophysiological changes were also accompanied by biochemical ones. After stimulation an increase in EPSP became well established after 5 min and persisted for many hours. Accompanying this potentiation there was a change in the incorporation of phosphate into a membrane protein. Also changes in the phosphorylation of proteins in the mitochondrial fraction have been reported after a tetanus. These changes in phosphorylation may be related to conformational membrane changes which may in turn be related to a long lasting increase in synaptic efficiency.

Perhaps the most extensive studies of chemical changes due to electrical stimulation have been performed in pain research. In human patients analgesic relief of chronic clinical pain has (after an initial latent period of 10-15 min) been seen to outlast the period of stimulation by over 24 hours. The determinants of the asynchronous time course of stimulation produced analgesia remain one of the major unresolved questions surrounding the phenomenon, and perhaps hold the key to its mechanism of action (5).

Current theories on pain mechanisms rely upon the discovery of endogenous opioid peptides, the endorphins and enkephalins,and localisation of opiate receptors in the central nervous system. There is a powerful pain-inhibiting system originating in the periaqueductal gray substance surrounding the cerebral aqueduct in the midbrain.

The most important findings is however the fact that neurons in this region can be activated by morphine or by electrical stimulation. These neurons activate other neurons in the brainstem that project to the spinal cord and release serotonin, which activates an interneuron, releasing enkephalin at the presynaptic site of the primary afferent. The same mechanism of pain suppression is probably active also in electroacupuncture (15). It seems therefore that in pain suppression electrical stimulation activates chemical changes in the brain with an ultimate release of pain relieving enkephalin.

In view of these data we are proposing that some therapeutic effects of electrical stimulation might be biochemical by nature and that the laws of pharmacokinetics should be applied when studying long term effects of electrical stimulation.

NERVE ENDING WITHOUT AND WITH RESYNTHESIS OF TRANSMITTER

Assume a nerve ending (e.g. synaptic knob) contains at $t = 0$ an amount Q_o of transmitter substance. After an action potential or stimulation impulse arrives, the substance is released into the synaptic cleft. The release is governed by the equation

$$\frac{d\,Q_i}{dt} = -\frac{Q_i}{T_1} \tag{1}$$

where Q_i represents the amount of substance within the knob.

An analog electronic circuit is depicted in Fig. 1 where $\dot{Q}_i$ is equivalent to i, $T_1 = RC$ and switch S closes at $t = 0$.

The time course for Q_e outside the knob is then

$$Q_e = Q_o\,(1-e^{-\frac{t}{T_1}}) \tag{2}$$

and the rate of release of Q_e into the synaptic cleft is:

$$\dot{Q}_e = \frac{Q_o}{T_1}\,e^{-\frac{t}{T_1}} \tag{3}$$

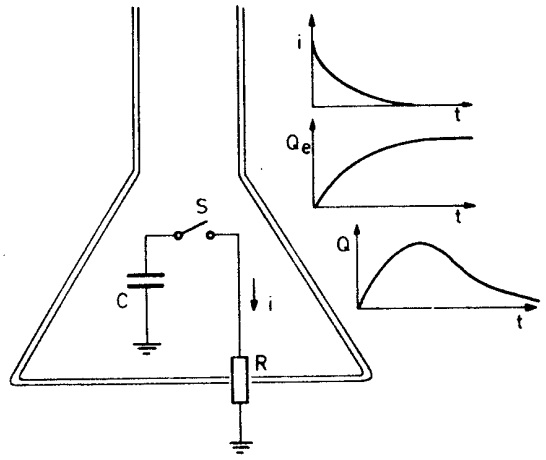

Fig.1. Release of transmitter without replenishment

If the released Q_e would be responsible for the effect of electrical stimulation, this effect would be according to equation (2) permanent. It is known however, that the effects subside after a certain amount of time which means that Q_e disappears due to diffusion or other chemical processes. Therefore the rate of change of Q outside the nerve ending is proportional to the input flow of release but diminishes through at least first order process governed by a time constant T_2.

$$\frac{dQ}{dt} = \frac{Qo}{T_1} e^{-\frac{t}{T_1}} - \frac{Q}{T_2} \qquad (4)$$

Solving for Q yields

$$Q = \frac{Q_o}{T_1} \frac{1}{\frac{1}{T_2} - \frac{1}{T_1}} \left[e^{-\frac{t}{T_1}} - e^{-\frac{t}{T_2}} \right] \qquad (5)$$

which is a typical curve found in posttetanic potentiation and also as an approximation of therapeutic effects if the duration of stimulation is short compared to T_1 and T_2.

After a short train of action potentials (switch S closed) the synaptic knob in Fig.1 would be depleted and later action potentials or stimulation trains could not release any further Q_e. A normal healthy synapse must therefore provide for resynthesis of transmitter substance which is modelled in Fig.2 with an energy source U and resistance R_1. A normal nerve ending

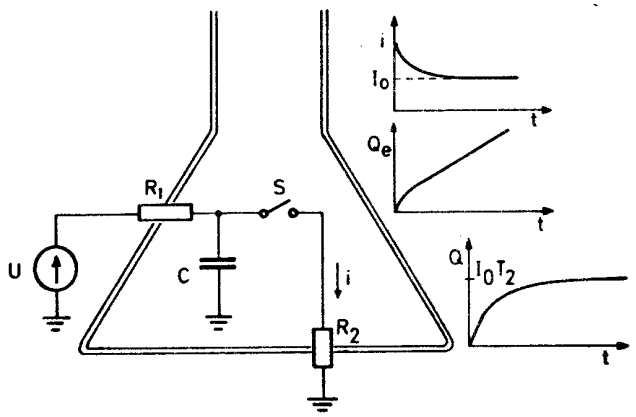

Fig.2. Release of transmitter with replenishment (resynthesis)

exhibits regular activity which may be modelled with repeated closing and opening of the switch or even simpler - a permanent closure of S. In the stationary state the release current I_o is constant and eq.4 becomes

$$\frac{dQ}{dt} = I_o - \frac{Q}{T_2} \tag{6}$$

which gives for $t \to \infty$, $Q = I_o T_2$.

Thus, a permanent effect is achieved by a normally active nerve ending.

SPECIFIC EFFECTS THROUGH NONSPECIFIC STIMULATION - THE BALANCE HYPOTHESIS

Investigations of therapeutic effects of electrical stimulation report beneficial or neutral effects but very seldom of impaired conditions due to stimulation. The site of stimulation as well as specific techniques do not seem to be of primary importance (16). Since proper functioning of a normal physiological system depends on a delicate balance between excitation and inhibition at all levels of the nervous system, it is puzzling that electrical stimulation mostly improves the balance in an "unbalanced" system and rarely impairs this balance. It looks as though the stimulating signals would "know" where to be active: if the system is normal they exert little influence; if the system has too much excitation they act inhibitory and if there is too little excitation they increase it. Thus quite specific and selective effects are obtained through generalized, nonspecific stimulation. A model attempting to explain these phenomena is presented in Fig.3. Suppose nerve endings A and B release antagonistic substances into a synaptic cleft, or a body fluid (e.g. blood, cerebrospinal fluid). The endings could be excitatory or inhibitory axonal endings of the somatic nervous system or adrenergic or cholinergic endings of the autonomous nervous system. Suppose further, that a pathological situation arises due to a lack of balance between antagonistic activities in a physiological system. Thus let nerve ending B have an abnormally low activity whereas nerve ending A is normally active. This situation is symbolized with switch S_2 open and S_1 closed. If B acts inhibitory, there would be an abnormally low flow of inhibitory substance i_{22} and since excitatory flow i_{12} is normal an imbalance would occur with an overall excitatory effect. Conversely, if A would fire with abnormally low activity and B would be normal the overall effect would be inhibition.

If electrical stimulation acts on such an unbalanced system it might activate the subnormally active ending but exert little influence on the normally active one which releases its substance close to it saturation rate. In the case of Fig.3 stimulation would activate to a larger degree the "unused" ending B than the active ending A. The result would be an increase in i_{22} with a resulting improvement in balance. The same mechanism holds of course true if A would be less active than B. Stimulation would then increase the activity of A more than the activity of B and a shift towards a more balanced state would be achieved again.

The improved balance between i_{12} and i_{22} results in chemical changes which are manifested as therapeutic effects.

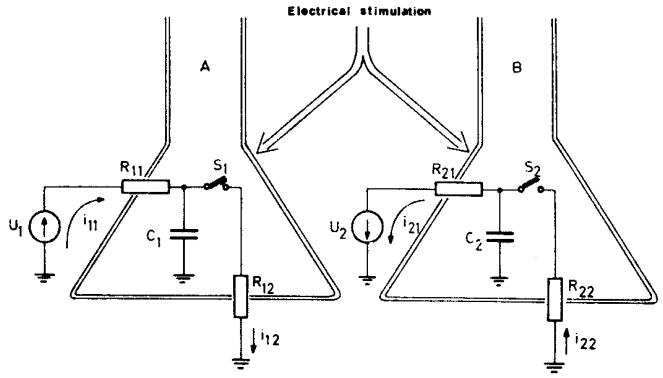

Fig.3. Model of transmitter flow in nonactive (B) and normally active (A) nerve endings. The physiological properties of both endings are antagonistic.

ELECTROTHERAPY OF SPASTICITY AND PARESIS - A TEST OF THE BALANCE HYPOTHESIS

There are probably many mechanisms which produce the clinical syndrome of spasticity but one of the most evident seems to be an over excitability of the α-motoneurone. Suppose B in Fig.3 represents the inhibitory synapses and A the excitatory ones. Their transmitter currents influence the postsynaptic membrane potential of the motoneurone by means of a chemical process with a first order kinetics simulated by the time constant RC (Fig.4). In a normal system ΔU_m is about zero and the membrane has a resting potential of U_m. Spasticity appears due to a lack of inhibition which is interpreted in our model as reduction of i_{22}. A positive ΔU_m results and produces a partial depolarisation of the membrane which makes it hyperexcitable. Therapeutic electrical stimulation increases i_{22}, thus reducing ΔU_m and bringing the membrane closer to normal. In an analogous way the improved volitional control of a paretic extremity after electrotherapy could be explained. The mechanism by which i_{12} and i_{22} affect the membrane potential is not known. One of the possibilities might be an influence of the transmitter currents on the number of receptors or on the activity of the ionic pumps in the membrane.

The proposed model can explain in principle the fact that therapeutic effects are obtained by stimulating different sites such as the spastic muscle, its antagonist (16), the dermatomes (20), the spinal cord (7) or cerebellum (21). However, to

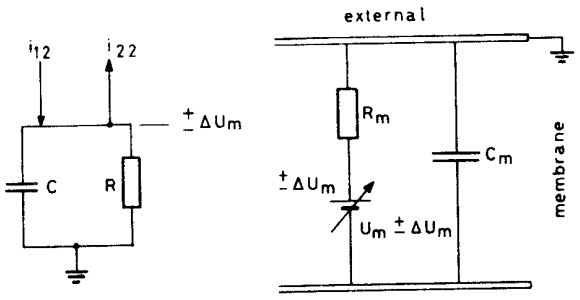

Fig.4. Changes in membrane potential due to electrical stimulation

interpret the time course of the effects the model is still inadequate. Several findings from our group as well as other authors have shown that in some patients the maximum effect is obtained not immediately after stimulation but later. Thus Walker (19) for example observed a maximum in relaxation one hour after stimulation. Several possibilities exist to modify the model in order to account for this phenomenon.

1. A simple delay may be introduced to simulate transport lag or processing time in a chemical reaction.
2. The kinetics of changing i_{12} and i_{22} into ΔU_m might be of higher order.
3. During stimulation two antagonistic processes with different time constants are started. If the process which supresses the therapeutic effect has a smaller time constant it dies out faster after stimulation and the therapeutic effect becomes maximal only after the stimulation is ended.

An example of delayed effects of therapeutic stimulation is shown in Fig. 5. On a tetraplegic patient (C5-C6) with quadriceps spasticity the relaxation index (22)* was measured 5 min before stimulation and just before stimulation started. Thereafter for 20 min the m.quadriceps was stimulated with pulses of 100 Hz frequency and 0,1 ms pulse width. The duration of the

* Relaxation index ranges from
0 - strong spasticity to
1 - no spasticity

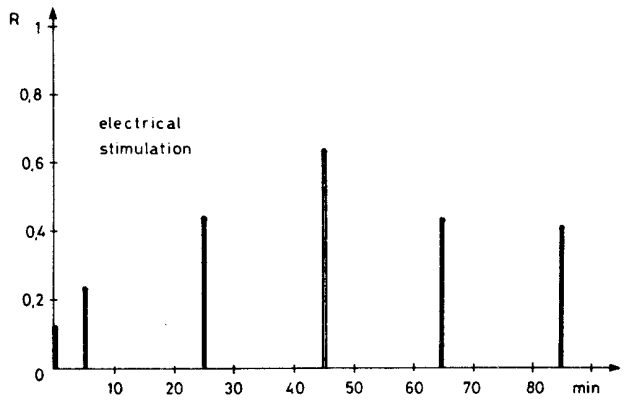

Fig.5. Relaxation index of quadriplegic patient before and after electrical stimulation

pulse train was 4 seconds and the pause 4 seconds. After stimulation the relaxation index was measured immediately and then still 3 times in 20 minutes intervals. From Fig.5 it is evident that maximum relaxation was obtained about 20 min after the stimulation therapy. Thereafter the relaxation index started to decrease. Similar data have been also published for the improvement of voluntary control in hemiparetic patients after a 20 min session of electrical stimulation (23).

No direct experimental evidence was presented which would be applicable to support our hypothesis for electrotherapy in spasticity. However, Jurna for example speculated that muscle tone is regulated by two antagonistic substances acetylcholyn for excitation and dopamin for inhibition. They are integrated in the neostriatum and affect the excitability of the α-motoneurone (24).

It is expected that further work along the directions discussed in this paper will improve our understanding of electrotherapy and enhance its status as a viable alternative to pharmacotherapy.

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