Electrotonic Homeostasis: A New Perspective in Metabolic Modulation

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Abstract

There is sufficient evidence in the literature to support the postulate of the existence of a more comprehensive electrochemical cellular homeostasis. This homeostasis, which is termed electrotonic homeostasis, represents an all-pervading internal electrochemical milieu within a volume conductor (the living organism). Every living cell within the organism contributes to this milieu in varying amounts and every cell in turn is affected by this milieu. The characteristics of this electrochemical milieu are modulated by the many secreted intercellular messengers. At source is the volition of higher cortical centres which plays a pivotal role in maintaining adequate threshold activity of this milieu. The mode of influence of this milieu at the cell interface is via the process of electroconformational coupling (ECC) – the modulation of enzyme activity by AC resonance.

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Introduction

The chemical reaction rate of reactions catalysed by enzyme activity depends on several identifiable variables: [1]

1. The concentration of the substrate
2. The availability of co-enzymes (co-factors)
3. The concentration of the product
4. Conditions within the micro-environment - ph, ionic concentrations, temperature and presence / absence of inhibitors

In the typical energy-producing biological system it has been accepted that as long as the above-listed variables and conditions have been met, the living process would be maintained. Conversely any interference with the variables and conditions would impair energy production culminating in the extreme situation with the cessation of biological activity. Death follows if the interference results in irreversible changes to enzymatic activity.

In effect, this biological process should be expected to function perpetually as long as substrate remains abundant, the build-up of product is prevented and micro-environmental conditions are optimally maintained. The issue that needs to be further elucidated is the identification of factors that drive this biological activity.

The discussion which follows is based on an analysis of the function of a specific, associated sub-group of enzymes involved in ATP production and utilization, namely:

1. ATP synthase (mitochondrial-based)
2. Na-K dependant ATPase (Intra-membranous sodium-potassium pump)
3. Free radical-neutralising superoxide dismutase (SOD)

In a coupled reaction, ADP is converted into energy-rich ATP from a catalysed oxidative reaction by ATP synthase. Any free radicals resulting from the oxidative process are neutralised by enzymes such as superoxide dismutase. One of the major energy (ATP) utilising processes is that of the intra-membranous sodium-potassium pump (Na-K dependant ATPase). It is estimated to use up to forty percent of the total cellular energy production. The active process of transporting three sodium ions into the extracellular environment for two potassium ions transported into the intracellular environment maintains the electrical gradient between the compartments. The role of this enzymatic reaction becomes critical following the generation of an action potential. In an action potential, a self-perpetuating electrochemical process propagates along a cell membrane resulting in potassium extrusion into the extracellular compartment while sodium flows down its chemical gradient into the intracellular space. The Na-K dependant ATPase restores the respective ion concentrations and thereby, the electric gradient.

Electroconformational Coupling

Following the extensive studies of Tsong we now recognise the effects of electroconformational coupling (ECC) upon the activity of the enzymes referred to above.[2,3] ECC refers specifically to the observation of the effects of an alternating current (AC) upon enzyme activity. AC activity has been shown to resonate with and influence enzyme configuration changes through critical resonance ranges. In effect the potential energy of the AC electric field provides the energy for the enzymatic conformational change to a higher energy configuration. In this way, the specific enzyme catalysed reaction is driven by the ECC dynamic. It has been shown that the extrinsic ECC provides the energy for ATP formation from ADP which in turn provides the energy for Na-K dependant ATPase activity. In later studies it was also shown that the ECC derived energy directly drives the Na-K pump, thus uncoupling it from ATPase dependence.

The AC emf which is proposed as the ECC drive, reflects the electrochemical activity within the internal milieu of the organism (volume conductor). This electrochemical milieu represents the resultant activity of several contributing sources:

1. Action potentials of cellular activity (mainly myogenic and neurogenic)
2. Active intra-membranous ionic pump activity
3. Ionic fluid in circulation
4. Ionic movement down electrical and chemical gradients
5. External environmental electro-magnetic emission

The activity of the first four contributing sources is further modulated by neurotransmitters, hormones and a host of other intercellular chemical mediators. Much of this modulating activity originates in the frontal and pre-frontal cortices of the brain. This cortex however receives formidable input from association areas as well as from sensory and co-ordinating regions. From the frontal and pre-frontal cortex, tracts connect to the deep nuclei and thence to thalamus, hypothalamus and

brainstem structures. It is from these areas that modulation occurs of the whole organism via the neuro-endocrine outflow. This outflow includes the bi-directional movement of neurotransmitters, cytokines, leukotrines and other identified secretions of the immune system.[4]

It may be discernable at this point that much of the electrochemical activity represents higher cortical volition. The greatest amount of activity would be generated by active movement which necessarily invokes neurogenic, myogenic (including cardiomyogenic) and metabolic activity. Conversely, a paucity of movement results in a quietening of electrochemical activity.

The ECC-Cell Metabolic Interface

Returning to cellular metabolism it is possible to recognize three states of activity reflecting the interaction of cell-based enzymatic function with ECC (electrochemical milieu):

- **Idling** – intrinsic cell-based ATPase activity with threshold ECC stimulation
- **Driven** – above threshold ECC stimulation
- **Suppressed** – below threshold ECC

In the idling situation, energy metabolism is driven for the most part by intracellular enzymes subject to the influences of substrate, product, co-enzymes and micro-cellular environmental conditions. Some ECC stimulation occurs which drives a small proportion of activity.

The driven condition represents a highly ECC geared process where a significant amount of activity is disconnected from pure enzyme limitations. The rate limitation of this process is dependant primarily upon substrate availability and enzyme recovery. Secondary limitations are once again those listed previously, namely: product build-up, co-enzymes and micro-cellular environmental conditions. This situation would occur in volitional activity such as movement.

In the suppressed situation ECC activity is markedly deficient. The metabolic process is essentially cell-based. Recognizing the biological probability that ECC stimulation of enzyme activity is integral to optimal metabolic function, it is proposed that deficient ECC activity may well result in sub-optimal efficiency of enzymatic function. This applies not only to ATP generation and utilization but also to SOD and related enzyme activity. The consequence of this deficiency may well be the inability of the cell to neutralize free radical formation with a resultant increase in free radical concentrations. This would result in damage to cellular organelles, most notably, nuclear DNA integrity.

Current research indicates that increased concentrations of free radicals are noted to occur with increasing age and in over-exposure to UV radiation.[1] The increased free radical concentration has been shown to interfere with DNA replication, result in anomalous splicing of the strands and in some cases, proceed to eventual neoplasia.

Local Voltage Gradients and Pathological Processes

Voltage changes associated with cellular activity was first investigated by Burr.[5] In his earlier studies he showed that voltage gradients preceded the re-growth of amputated salamander limbs. Regeneration could be manipulated or interrupted by manipulating or reversing local voltage gradients. He postulated that if a normal voltage gradient gave rise to normal cellular activity, an abnormal gradient should give rise to pathological cellular activity. To test this hypothesis he investigated 1000 random gynaecological patients with a variety of pathologies. Voltage gradients were measured between the cervix and the ventral abdominal wall. In 102 cases where there was a significant shift in the voltage gradient, surgical confirmation of malignancy was found subsequently in 95 cases (uterine and ovarian carcinoma). Although this did not directly substantiate the hypothesis, it was nevertheless a significant finding in regard to the co-existence of abnormal local voltage gradients and neoplasia.

Following on from the work of Burr, Becker later showed that voltage changes preceded the inflammatory response in relation to injury.[6] Quantitative changes in voltage were also associated with cellular differentiation. Further studies indicated that voltage gradients at the site of injury were mediated by neural innervation. If the neural innervation was interrupted, healing was either delayed or did not occur. It appeared therefore that neural innervation (a product of central nervous system outflow) generated local tissue voltage gradients which had a determining influence on the inflammatory response and subsequent cellular differentiation.

These studies have revealed the profound effects of varying voltage gradients on cellular activity. It is proposed that the suppression of neural innervation results in a quietening of the local extra-cellular milieu with the subsequent development of pathological processes.

Clinical Correlates

Following surgery and other physical injury, a well defined metabolic state follows for varying periods thereafter.[7] This metabolic state is termed the post-traumatic metabolic response. One of the features of this state is the development of raised serum potassium levels with decreased sodium levels. This configuration could feasibly result from diminished Na-K ATPase activity. It is postulated that the immobility associated with acute injury gives rise to a quietening of the electro-chemical milieu with subsequent diminished ECC activity. Consequent upon this is the extracellular accumulation of potassium with the concomitant in-flow of sodium into the cell down its chemical and electrical gradients. Ultimately this gives rise to increased levels of extra-cellular potassium levels and decreased sodium levels. Once recovery is underway, mobility increases (as does volition) and the metabolic state reverses back to normal.

In the rapidly expanding field of psychoneuroimmunology (PNI) also referred to as neuroimmunomodulation, specifically defined stress situations have been shown to result in varying degrees of immunosuppression.[8] Studies have also revealed impaired immune function consequent upon the development of states of depression.[9] Other studies have shown a correlation between stressed psychological

states and delayed wound healing.[10] The factor which appears to be common to the psychological states resulting in immuno-suppression is that characterised by a hopeless-helpless mind state. This describes an individual in an extremely negative psycho-social situation, further compounded by the subjective perception that the situation is intractable or unchangeable

The hopeless-helpless mind state has also been shown to result in chronic inflammatory changes.[4] Cells involved in an inflammatory pathology have increased concentrations of free radicals. This may explain the increased incidence of neoplasia in tissues subjected to chronic inflammation for prolonged periods. Neurochemical changes associated with the hopeless-helpless mind state also stimulate the macrophages of the immune system to secrete pro-inflammatory cytokines Il-1, Il-6 and TNF-alpha. Raised levels of pro-inflammatory cytokines have been shown to decrease the activity of Na-K ATPase activity thus compounding the diminished electrotonic influence upon the enzyme.[11] Recent research has also indicated that Il-6 suppresses intra-nuclear enzymes associated with the correction of DNA splicing anomalies.[12] The pro-inflammatory cytokines circulate back into the brain. Chronically raised pro-inflammatory concentrations in the brain have been shown to damage the hippocampus and pre-frontal cortical areas. In this way, volition and motivation may be further compromised.

It is proposed that these aforementioned observations may be seen to reflect deficient volitional states with subsequent diminished ECC-cell activity. The observation of the increased incidence of neoplasia in hopeless-helpless mind states probably reflects the interaction of three processes:

1. Immunosuppression due to the impairment of immune cell function.
2. The increase in intra-cellular free radical concentrations resulting in damage to intra-nuclear DNA.
3. Suppression of intra-nuclear enzymes involved with DNA splicing correction

Conclusion

It is proposed that the maintenance of optimal metabolic processes requires sustained activity of the all-pervading electrochemical milieu. The driving force of this activity is cerebral-based volition. Thus it is postulated that fundamental to a healthy metabolic existence is the need for sustained volition, the absence of which impacts negatively upon threshold levels of required metabolic activity necessary for life.

The most stimulatory volition is that which leads to increased movement. However volition in mental function alone with or without secondary autonomic activity would also lead to an enhancement of the electrochemical milieu and subsequent ECC activity.

The process of volition-driven electrotonic homeostasis may be seen to be one of the explanations for the observed beneficial effects of exercise on cardiac wellness.[13] Similarly clinical programs encouraging early mobilization and exercise following injury or surgery result in accelerated healing and recovery.

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