



## A SPECIAL THEORY ON THE ORIGIN OF NEUROPATHIC PAIN

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**ABSTRACT.** The origin of neuropathic pain is subject to a number of different interpretations and controversies. Here we present a model according to which a neuropathic pain can be represented as a metabolic consequence of a relative deficit in the power balance of the neuronal cell. In that connection, power deficits are primarily seen in a relative dysfunction of the mitochondrial respiratory chain phosphorylation of the neuronal cell. Through a resulting reduced activity of ATP-dependent ion pumps and ion channels, there occurs an insufficient neuronal processing of the ionic composition in the interstitial space surrounding the neuron. This changes, according to the Hodgkin-Huxley model, the conditions of the membrane potential in the neuronal transduction area, resulting in a different excitability pattern modulated therefrom. **CONCLUSION.** The phenomenon of a neuropathic pain is represented as an implied signal in a mechanism of a disturbed energy cycle of an impaired neuronal cell which creates abnormal membrane excitability. This process is formally described as a sequence of three functional equations. Some clinical projections and pharmacological implications are discussed.

### INTRODUCTION

The origin of a neuropathic pain (NP) is subject to a number of different interpretations that refer to specific receptors and specific processes, without however the phenomenon itself being explained through them. It is the target of this representation to examine in a theoretical-exemplary manner whether the diversities in a NP process can be described within a general bioenergetic mechanism which is associated with the cellular efficiency of Adenosine-5'-Triphosphate (ATP) production and utilization of the oxidative phosphorylation (OXP). It has been described that already brief periods of cellular anoxia and aglycemia resulted in sensory neurons in a decline in Mg-ATP, which on its part may influence ion channel activities [1]. Also the actions of peripheral analgesics interfere basically in the OXP [2][3], and additive effects of analgesic combinations suggest relations to a neuronal impulse generation [4].

The following exemplary deductions are limited only to an initial membrane process of an elementary "single fiber model" and to peripheral processes, thus exclude a consideration of subsequent central neuronal processes. A descriptive model that based on the analysis of functional consequences of an intracellular defect of OXP was prepared. That was done by a modified Entity Relationship Modeling of relevant literature, supported by the application of a newly developed syntax for interactive data configuration (FNS2).

### DEDUCTION OF A MECHANISTIC MODEL

#### Basic processes as a premise

Factors that impair a neuronal cell influence its energetic status, either physically or chemically. Thermodynamically they all only represent a different state of aggregation of an energetic entity. Thus their effects can be summarized as a 'noxious energy' ( $E_N$ ).  $E_N$  i.a. causes functional or disintegrative effects on membranes or intracellular components with shifts in intracellular electrolytes. Finally, all  $E_N$  processes influence the neuronal membrane potential ( $E_m$ ) with an induction of afferent excitatory signals that are perceived as "painful". Thereby, the overall membrane flow and  $E_m$  summararily follow

in principle the model according to Hodgkin & Huxley [6]. A neuron is surrounded by the interstitial space (IS). Consequently any signal induction on a neuronal transduction area must first be conveyed via the extracellular compartment of interstitial fluid (ISF).

**Definitions on the power deficit of a neuronal cell and  $Q_o$ .**

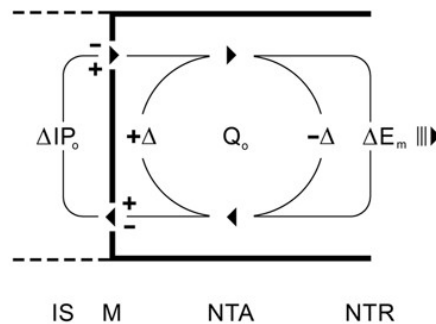
Metabolically intact neurons operate as an open system of input/output energy processes. In terms of total power, they correlate to a large extent with the ATP energy available from the OXP as main energy source. Formally there can be formulated a total power balance  $Q$  that shall correspond to the extent of energetic coverage of the acute power need. Therefore, depending from a current input/output situation,  $Q$  can result in a positive or negative absolute difference  $|\Delta Q|$ . As a physiological reference point to that, there shall be considered the special case  $Q_o$ , a ratio that reflects a status of a balanced energy cycle efficiency of the neuron. Therefore in  $Q_o$  the energy available completely covers a current energy need of this cell.

An impaired neuron shows a disturbed energy balance. This represents a power deficit between available energy and energy need, thus an absolute difference  $|\Delta Q_o|$ . That difference may be caused i.a. by a disturbed input and/or utilization of oxygen, substrates or co-factors. Moreover, an impaired neuron has an increased power demand for reparative processes, which further increases the absolute power deficit.

**Transformation of a neuronal power deficit into an electrophysiological signal.**

In the case that a biochemical power balance deficit  $|\Delta Q_o|$  exists in an impaired neuron, then the neuron acts technically in a double function, as a signal transducer and signal generator. The ATP implicitly reduced in its current power balance deficit reduces the performance of all its ATP-dependent ion pumps and channels. This insufficient pump power leads in the ISF to a shift in the relations of the surrounding extracellular membrane-effective ion concentrations. Therefore, there occurs in comparison to a physiological ion product  $IP_o$  a deviating relative ion product  $\Delta IP_o$ , in particular regarding the ionic composition of  $Na^+, K^+, Ca^{2+}$ . According to the Hodgkin-Huxley model [5], such relative ion shift leads to a change of  $E_m$ , and thereby to a changed neuronal excitability product  $\Delta E_m$ . In sum the impaired neuron therefore creates via  $\Delta IP_o$  its own  $\Delta E_m$ , thus a sensitization with abnormal excitability.

This mechanism can be described as an interactive local feedback system: The  $\Delta IP_o$  results from the deficit in the energy status of  $Q_o$ , which also controls the status of the ion flux of the inward and outward ion channels i.e. closed or open. However also the  $\Delta IP_o$  composition influences on its part the status of  $\Delta Q_o$  by influencing the extra-cellular flux activity of the ion channels. This modus of a "retrograde" self-excitation of the excitability product  $\Delta E_m$  therefore represents in sum a bi-directional feed-back with a flip-flop of various ion channels that are controlled by both  $\Delta IP_o$  and  $\Delta Q_o$  (Figure 1).



**Fig.1** "Single fiber model" on relative ion shifts due to dynamic changes in  $Q_o$  and its coupling to neuronal excitability: Switch-over of an intracellular deficit of power balance deficit  $-\Delta Q_o$  into a relative ion product  $\Delta IP_o$  in the interstitial space and a subsequent change into a neuronal excitability product  $\Delta E_m$ .  $\Delta IP_o$  is a result of the relation of the inward and outward flux activities of ion channels (+/- open/closed). These are controlled by the actual status of  $Q_o$ . The  $\Delta IP_o$  dependent ion flux activities influence on their part the status of  $\Delta Q_o$ . The

mechanism as a whole represents a bi-directional feedback with integrated flip-flops. (Abbreviations:  $Q_o$ : Relative energetic equilibrium of the neuronal power balance; IS: Interstitial space compartment; M: Cell membrane. NTA: Neuron, transduction area; NTR: Neuron, transformation area;  $III >$ : induced excitability).

### Synopsis

The process as a whole includes operatively as single steps the transformation of the intra-cellular neuronal power balance deficit  $-\Delta Q_o$  into an extra-cellular relative ion product  $\Delta IP_o$ , and a subsequent feedback induction of the neuronal excitability product  $\Delta E_m$ . The latter is hereafter afferently transmitted to the CNS. The demodulation of the  $\Delta E_m$  pattern can be assumed to be the subjective pain sensation of NP as such. The process can be formalized in a direct sequence of three functional relations:

$$\Delta IP_o = f(-\Delta Q_o) \rightarrow \Delta E_m = f(\Delta IP_o) \rightarrow NP = f(\Delta E_m)$$

Thus in sum NP can be represented as a neuronal excitability signal that results from a deficit in the current intracellular neuronal power balance.

### DISCUSSION

This model postulates neuropathic pain in a biologically conceptual way as a phenomenon that is activated in an impaired neuron at the occurrence of a deficit of its metabolic-energetic power balance. Operatively it represents the conversion of a biochemical status of the neuron into a signal of neuronal excitability. Due to the localization of the energy deficit in the neuron, as the signal processing and signal transmitting entity, an NP appears technically only a special case within a general view of a peripheral pain as an integrated thermodynamic mechanism [6].

A central precondition of the model is an interaction of the neuron with its surrounding ISF, thus a direct involvement of this extra-cellular fluid compartment where  $K^+$  and  $Na^+$  can change. A key parameter is the relative ion product  $\Delta IP_o$  which results in the ISF from the impaired function of the ATP-dependent ion pumps and channels. This energy dependent defect induces the shifts in the relations of membrane-effective ion concentrations that finally, according to the Hodgkin-Huxley model, lead to the changed excitability, thus a sensitization. Altered excitability, e.g. in cortical neurons, has already been demonstrated for small extra-cellular changes in  $Ca^{2+}$ ,  $Mg^{2+}$  [7], and  $Na^+$  [8]. In addition extra-cellular ion shifts resulting from an energy dependent process may also modify the reactions of specific ion channels which favor a hyper-excitability [9]. Changes in neuronal excitability have also been reported as being correlated with the inhibition of  $Na^+/K^+$ -ATPases via ATP-dependent ion pumps [10], also that a lowering of intracellular ATP could change action potential duration [11]. Finally also a Gibbs-Donnan Effect in the IS may aggravate the reduced function of pumps of impaired cells, for example in the case of an occurrence of an inflammation. For a calculation of the resulting  $\Delta E_m$ , there can be used, in extension of the Nernst relation, the Goldman-Hodgkin-Katz equation.

Within this bioenergetic context, NP can also be regarded as transient, if the cause of the metabolic power balance deficit of the neuron can be eliminated. In a specific clinical case, such as e.g. a diabetic neuropathy, this may be a normalization of the basic metabolic situation with an insulin therapy. However, a more principal causal approach in NP could be the external substitution of cofactors that are suitable to improve the OXP efficiency. Such kind of compounds may be designated as "OXP-Promoters". That route may be e.g. the case for some B-vitamins, e.g. Riboflavin [12] or combinations [13]. This model suggests that an effect of B-Vitamins on the OXP might be a primary cause of their anti-nociceptive activity, as well of their clinically described improvement of nerve conduction velocity [14]. Also the application of local anaesthetics, such as e.g. lidocaine, may reduce the NP via an improved neuronal utilisation of ATP [15]. In addition these compounds may also provide a neuroprotective effect due to a protection of the mitochondria to maintain the ATP content during an ischemia [16].

### CONCLUSIONS

A functional model describes neuropathic pain as an excitability signal that is based on a current deficit in the power balance of a neuronal cell: (1) The cause of the energy deficit is primarily a disturbed energy cycle with a relative dysfunction of the neuronal respiratory chain phosphorylation. (2) The

implied dysfunction of ATP-dependent pumps and channels induces a relative change in the ion composition of the ISF. (3) The changed ion composition results in a transformation of an abnormal neuronal membrane excitability pattern which is transmitted to the CNS.

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