



A General Theory on Pain as an Integrated Thermodynamic Mechanism

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Abstract. The phenomenological concepts to describe pain as a primarily unidirectional warning mechanism for the existence of specific noxae appear to be insufficient. Here we present a theory and a model according to which pain can be represented as an integrated mechanism of local cell energy homeostasis. It postulates the occurrence of a pain sensation in case of a relative deficit of the intracellular metabolic power balance in tissues. In that connection, power deficits are primarily seen in a relative dysfunction of the mitochondrial respiratory chain phosphorylation. Through a resulting reduced activity of ATP-dependent ion pumps and ion channels, there occurs an extracellular ion shifting in the interstitial space. This changes, according to the Hodgkin-Huxley model, the conditions of the membrane potential of regionally competent terminal afferent nerve fibers. The neuronal excitability pattern modulated therefrom is demodulated as pain signal in the CNS. This signal may lead there, as a closed-loop mechanism, to a negative feedback activation **in order** to counterbalance the deficit of the peripheral power balance. **SUMMARY:** The origin of a pain is represented as a disturbed energy cycle efficiency of an impaired cell. Operatively the phenomenon results from a mechanism that couples the current status of the intracellular energetic power balance to neuronal excitation. In this mechanism the pain phenomenon per se represents an implied signal only that indicates various parameters of a power balance deficit. The implicit functional relation of pain to the energy deficit can be summarised as $P = f(-\Delta Q_0)$. Projections and clinical implications are discussed.

INTRODUCTION

It is a basic problem to describe pain as a homogenous phenomenon. On the one hand, this is due to the diversity of noxae and sensory receptors and, on the other hand, to the diversity of biochemical mediators and mechanisms that occur in the cell after noxae. Since also the therapeutic measures are oriented by these different targets, they are fragmented, too. For example in the field of non-steroidal anti-inflammatory drugs (NSAIDs), that is the case for the inhibition of cyclooxygenases [1]. Accordingly, pain is subject to a number of different interpretations that refer to the description of specific targets and processes, without however the phenomenon of pain itself being explained through them. It is the target of this representation to examine in a theoretical-exemplary manner whether the diversities of the pain process involve a general mechanism by which that phenomenon can be comprehensively explained. Cell-energetic considerations served as a starting point because some adverse reactions of NSAIDs can be associated with their inhibitory effect on the mitochondrial oxidative phosphorylation (OXPHOS) and thus with the cellular efficiency of Adenosine-5'-Triphosphate (ATP) production and utilisation [2], and possibly also with a relation on neuronal impulse generation [3]. There also exist studies on pain models suggesting that inhibitors of the mitochondrial electron transport chain complexes influenced pain-related behaviour however had no effect on a prostaglandin E induced hyperalgesia [4].

DEDUCTION OF THE MODEL

Scope and Method

It was the principal overall aim to describe a general mechanism and its functional causality on the pain origin and its initial transformation. A model that based on the analysis of neuronal consequences due to an inhibition of the mitochondrial oxidative phosphorylation (OXPHOS) 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 (FNS). The following exemplary deductions are limited only to a "second" pain and/or a chronic pain as a peripheral metabolic cell process and to a "single fiber model". They exclude a detailed consideration of the subsequent neuronal processes.

Common basic processes as a premise

All cell impairing external or internal stimuli influence the energetic status of a cell, either physically or chemically. They i.a. cause functional or disintegrative effects on membranes and intracellular components with shifts in intracellular electrolytes, which has also a power-reducing effect on the energy formation. All physical or chemical factors represent thermodynamically only a different state of aggregation of an energetic entity [E]. Thus their negative effects on cells can be summarized as a specific absolute value of a noxic energy [E_N]. The reparation processes following the [E_N] damages are accompanied by an increase in cellular power need. Finally, all cell-impairing 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 summarily follow the model according to Hodgkin & Huxley [5]. It is of central significance to the process that a neuron is surrounded by an interstitial space. Consequently a signal induction on the neuronal transduction area must first be conveyed via this sub-compartment of extracellular fluid. Since all cell noxae express themselves through changes of E_m it is justified to gather therefrom that the intracellular processes upstream of the neuron form the causal matrix for the formation of pain signals.

Definitions on the power deficit of the cell and Q_o

Metabolically intact cells operate energetically as an open system of input/output processes. In terms of total power, these correlate to a large extent with the ATP energy available from the OXP as *main* energy source. In a formally qualitative manner, there can be formulated a total power balance of the cell, Q, that shall correspond to the extent of energetic coverage of the acute power need. Therefrom, Q can be represented as a difference of acutely available total power of the cell, p_A, and the acutely required total power requirement, p_N, therefore $Q = \Delta (p_A - p_N)$. In this connection p_A shall be the available cell concentration of ATP as the inner energy mainly present in that form and p_N shall be the sum of all cell powers utilizing that form of energy. Therefore, depending from the current input/output situation of the energy, the difference p_A-p_N can result in a positive or negative *absolute* value. As a physiological reference point to that, there shall be considered the special case Q_o in which $\Delta (p_A - p_N) = 0$, i.e. a power balance in which the energy available in that cell completely covers a current energy need of this cell. This equilibrium may be reached, depending from the current requirements, on a high or low energy level. Thus Q_o represents a ratio of a balanced energy cycle efficiency only, not an absolute value.

Noxic energy and power deficit of the cell

In contrast to the metabolically intact cell, the impaired cell shows, depending from [E_N], a disturbed energy balance. The impaired status represents an absolute value of power deficit between available energy and energy need, thus a negative difference $|\Delta Q_o|$. Energy deficits are i.a. caused by a disturbed influx and/or utilisation of oxygen, substrates and co-factors. Furthermore, the induced intracellular distribution disorders of the electrolytes as well as the dysfunction of mitochondrial membranes accelerate the breakdown of the ATP synthesis. This also requires increased power from anaerobic glycolysis. The pH change resulting therefrom decreases in addition the ATP yield of OXP. The OXP reduction moreover leads, as a consequence of the decrease in oxidation water, to a reduced hydrolysis capacity. This impairs also the general chemical reaction conditions for a Q_o. Moreover, the damaged cells have also an increased power demand for reparative processes, which further increases the absolute power deficit $|\Delta Q_o|$.

Transformation of a cellular power deficit into an electrophysiological signal

In order to reach an intercellular communication, the impaired cell as signal generator and the afferent neuron as signal transducer need a joint place as well as also a substrate as "compilation" of their respective different processes into a signal that can be processed on both sides: The joint place is the interstitial space (IS) and the substrate is the ionic composition in the IS. The ATP implicitly reduced in the absolute value of the actual power deficit $|\Delta Q_o|$ of an impaired cell reduces the performance of its ATP-dependent ion pumps and ion channels, specifically of Na⁺/K⁺-ATPase, Ca²⁺-ATPases and of the ATP-dependent K⁺-channel (KATP). That power reduction leads on its part, in the interstitial fluid (ISF) of the IS between impaired cell and transduction area of the neuron to a shift in the relations of membrane-effective ion concentrations. Therefore, there occurs, in comparison to a physiological ion product IP_o the formation of a deviating relative ion product ΔIP_o in the ISF. This i.a. regards the extracellular ion composition of Na⁺, K⁺, Ca²⁺. According to the Hodgkin-Huxley model, such ion shift

leads to a change of E_m , and thereby to a changed neuronal excitability ΔE_m and conductivity. Consequently the IS acts, functionally, like a synapse, because its ΔIP_o effects a neuronal excitability product ΔE_m .

In addition the localisation of the power balance deficit has to be considered. The deficit may exist in the peripheral cell, in the neuron, or in both the cell and the neuron as the source of the defect ion pump function. This localisation influences the process of the generation of ΔIP_o , thus of ΔE_m : An impaired cell generates a process of an anterograde induction of ΔIP_o in the ISF. Hereafter this ΔIP_o is processed by an intact neuron. In contrast, if the deficit exists in the neuron, then a physiological IP_o in the ISF is insufficiently processed. In this case the neuron acts as both biochemical signal generator and signal transducer, therefore also as its own source of ΔE_m . This process may be considered as a “retrograde induction” of ΔIP_o . **Thus an impaired neuron can create a self-excitation resulting in a (neuropathic) pain signal.** If **both cell and neuron are impaired, then** a cross-over interaction of both processes results.

Finally, an additional possibility that modifies ΔIP_o , can be a direct effect on the ion composition in the ISF. This can be the result of a systemic interference factor, e.g. a hormonal action, and/or due to a Gibbs-Donnan equilibrium.

All processes of the ΔE_m generation appear to be controlled by local feedback mechanisms: Principally ΔIP_o results from dynamic deviations in the intracellular status of Q_o , which on its part control the operative status of the ion flux of inward and outward ion channels (i.e. closed or open). However, also the resulting extracellular ISF product, the ΔIP_o composition, influences on its part the status of Q_o by influencing the ion flux activity of ion channels. In sum this is technically comparable with a bidirectional feed-back with flip-flops of ion channels, controlled by both ΔQ_o and ΔIP_o . (Figure 1).

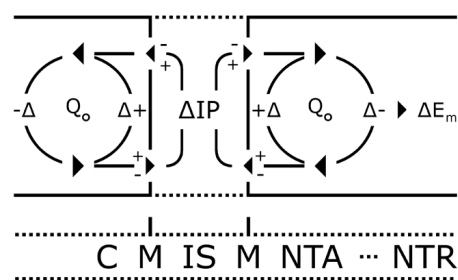


Figure 1. Scheme of the interactions of possible ion shifts and coupling with neuronal excitability due to intracellular dynamic ($\pm\Delta$) changes in the status of Q_o . Switch-over of a power balance deficit into a relative ion product ΔIP_o in the interstitial space and subsequent change into a neuronal excitability product ΔE_m . A deficit can be localised in the cell (left side), in the neuron (right side), or in both. Depending from the location of the deficit an anterograde or retrograde induction of ΔIP_o , or a cross-over interaction is induced (s. text). ΔIP_o is a result of the relation of inward and outward flux activities of ion channels (\pm -open/closed) controlled by the status of Q_o . Vice versa the flux activities due to ΔIP_o also influence the status of ΔQ_o . This signal transformation process outlines a bidirectional feed-back with integrated flip-flops. (Abbreviations: Q_o : relative energetic equilibrium of power balance; C: Cell; M: Membrane IS: Interstitial space; NTA: Neuron, transduction area; NTR: Neuron, transformation area).

Synopsis

The initial pain mechanism represents the peripheral generation of a biochemical signal and its conversion into a neuronal signal. Single steps of this intercellular communication are: (a) induction of an OXP inhibition with an intracellular power balance deficit $-\Delta Q_o$, (b) conversion of $-\Delta Q_o$ into a relative ion product ΔIP_o in the IS, (c) induction of a changed neuronal excitability product ΔE_m . The via ΔE_m afferently transmitted signal pattern is demodulated in the CNS. This demodulated signal can be assumed to be the subjective pain sensation (P) as such. Thus, P is an implied result of a sequence of differential-proportional functions that create an increase in central neuronal excitability. The last step to P is the induction of the neuronal excitability product ΔE_m . The sequence includes four functional relations: (I) $-\Delta Q_o = f(E_N) \rightarrow$ (II) $\Delta IP_o = f(-\Delta Q_o) \rightarrow$ (III) $\Delta E_m = f(\Delta IP_o) \rightarrow$ (IV) $P = f(\Delta E_m)$. **Therefore** in sum P can also be represented as a signal occurring as a subjective perception entity that represents a coupling of the absolute value of the deficit in the acute intracellular power balance and

neuronal excitability. P therefore corresponds with a negative difference to Q_o and can be formalized as implicit functional relation $P = f(-\Delta Q_o)$.

Subsequent steps represent the signal distribution in cortical regions, as warning indicator and for damage localisation. However due to the **activation and/or efferent release of hormones and/or neurotransmitters** this stage may also be considered as a negative feedback mechanism **in order** to counterbalance a deficit of the peripheral power balance. The process is synoptically shown in Fig.2 and refers to an elementary model of a “single fiber input”.

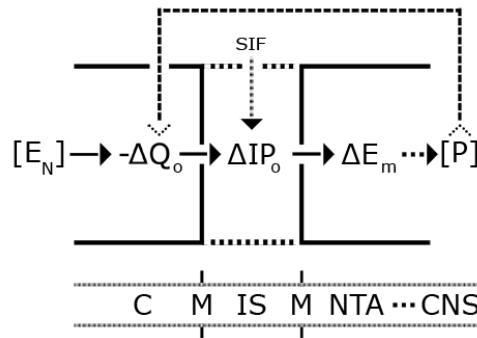


Figure 2. Schematic synopsis of pain as a mechanism coupling a noxally induced intracellular deficit of power balance and neuronal excitability: Sequence of the involved reaction products: $[E_N]$ induced change in the cellular power balance Q_o into $-\Delta Q_o \rightarrow$ switch-over into a relative ion product ΔIP_o in the interstitial space $\rightarrow \Delta IP_o$ induced change of the neuronal membrane E_m potential into the modulated excitability product $\Delta E_m \parallel > \text{CNS}$ demodulation of the excitability product ΔE_m into a subjective entity of pain sensation $[P]$ and a subsequent induction of a negative feedback ($--->$) in order to counterbalance the power balance deficit $-\Delta Q_o$ (“pain cycle”). (Abbreviations: $[E_N]$: Noxic energy entity; Q_o : Energetic equilibrium of power balance; $[P]$: Subjective pain entity, demodulated pain signal; C: Peripheral Cell; M: Membrane; IS: Interstitial space; NTA: Neuron, transduction area; CNS: Central nervous system, demodulation area; SIF: Systemic interference factor in the ISF; direct change of ΔIP_o).

DISCUSSION

This theory postulates in a *biologically conceptual* way the function of pain as an integrated mechanism of cell energy homeostasis, which is activated in case of a deficit of the energetic cell power balance. *Operatively* it postulates a coupling of the intracellular power deficit and neuronal activity. This mechanism results in a neuronal excitability product ΔE_m which is perceived in the CNS as a phenomenon of pain. Contextually pain is considered as an implied signal only, that indicates and distributes information on a deficit in the physiological power balance. Consequently a pain, or changes in the perception of a pain, should be expected for all acute cell impairments or metabolic diseases, e.g. a diabetes, that generate deficits in the energetic cell power balance. Vice versa there should not occur pain in a status of a metabolic-energetic equilibrium Q_o , hence $P=0$ if $-\Delta Q_o \neq 0$. In this mechanistic context it may also be speculated, if an occurrence of an “energetic surplus” $|\Delta Q_o|$ in the cellular power balance could induce an opposite phenomenon of a “negative pain”, thus a “positive perception” such as e.g. a mood upswing or euphoria. A potential model to study this aspect could be the evaluation of the activity of the Na/K-ATPase in the manic phase of a bipolar depression.

A central precondition in this theory is a mechanism of intercellular communication that an impaired cell can convert its biochemical power deficit into a signal, that is readable for the neuronal transduction area. The model postulates for this purpose the ISF as a technical mediator. This appears to be obvious as cell and nerve are separated and surrounded by this fluid microenvironment. In addition the ISF represents within the extracellular fluid compartments a subcompartment that offers good conditions for rapid ion diffusion and changes of e.g. K^+ and Na^+ . Therefore a key element in this signal pathway is the relative ion product ΔIP_o in the ISF. The production of ΔIP_o is a result of the reduced performance of the ATP-dependent ion pumps, which effects the shifts in the relations of membrane-effective ion concentrations. ΔIP_o on its part induces the excitability product ΔE_m . Consequently, in this context, also the IS may be, functionally, regarded as an unspecific synapse (a “root synapse”) because its ΔIP_o induces the neuronal excitability product ΔE_m . An altered excitability in cortical neurons has already

been demonstrated for small extracellular changes of Ca^{2+} , Mg^{2+} [6], and Na^+ [7]. Also changes in the neuronal excitability have been reported as being correlated with an inhibition of Na^+/K^+ -ATPases via ATP-dependent ion pumps [8], also that a lowering of intracellular ATP could change action potential duration [9]. Moreover also a Gibbs-Donnan effect in the ISF may principally aggravate the reduced function of Na^+ pumps of impaired cells.

The described mechanism is basically an unspecific membrane process. Therefore the principal electrophysiological consequences should be the same for all species of afferent terminal neuronal fibers thus should influence free nerve endings, such as e.g. C- and A δ - fibers, as well as the nerve endings that are part of specialised sensory organs and/or of polymodal receptors. For a calculation of a resulting ΔE_m , considering the relation of several monovalent ions there may be used, in extension of the Nernst relation, the Goldman-Hodgkin-Katz equation. However, the ion shift resulting from this process may on its part also modify the reactions of specific ion channels on specific mediators. Further factors may also modify the mechanism via *direct* influence on the ionic composition in the ISF. Respective factors can be i.a. a systemic hormonal disturbance, electrolyte infusions, the interference of an electric current injury, kidney disorders, or a Gibbs-Donnan effect, e.g. in inflammation/edema.

The mechanism suggests a direct role of the ISF microenvironment in the induction of pain signals. Thus, in painful tissues of e.g. a myalgia, fibromyalgia, soft tissue rheumatism etc. a shift of the ISF ion composition should be detected. However that needs analytic methods which clearly differentiate between intracellular fluid and ISF. In addition also a reduction of the intracellular concentration of ATP and ATPase activities should be found. Only relative values of more than one parameter appear to be of sufficient evidentiary value.

Within this energetic context, a pain can also be regarded as transient, if the elimination of the cause of its metabolic power balance deficit, e.g. of a regional hypoxia or a pathological ion shift, can be reached. Therefore a principal *causal* approach may be an external substitution with substances that are suitable to provide a sustained improvement of the OXP efficiency, e.g. essential cofactors in the respiratory chain.

In context with this model also a *symptomatic* reduction of pain may be effected via reduction of the *absolute* level of Q_o . This analgesic approach appears to be a paradoxon, however can be deduced as a relativistic process: Q_o represents a *relative* cell condition of a balanced energy cycle efficiency, i.e. $\Delta (p_A - p_N) = 0$, not an absolute value. However regarding its *absolute* levels these may imply low or high input/output relations which on their part depend from the acute energetic requirements of the cell. These requirements are higher if more energy is needed for e.g. reparation processes. It is evident that in order to maintain the equilibrium both Q_o factors, p_A and p_N , must change proportionally. On the other hand the occurrence of an *absolute* difference $|\Delta Q_o|$, is the formal lead parameter for a pain induction. It is evident, that also an absolute difference $|\Delta Q_o|$ becomes numerically smaller if the absolute level of the metabolic energy equilibrium is reduced. In the context of the model a reduced difference $|\Delta Q_o|$ effects a reduction of ΔIP_o which on its part reduces the excitability product ΔE_m .

However the energy reduction in an impaired cell also implicates some biological consequences, in particular anti-proliferative effects. As far as pain is concerned that may be positive if it effects a reduction of the synthesis of enzymes that are involved in the production of pain inducing mediators, e.g. of cyclooxygenases. On the other hand the energy gap generally effects prolonged regeneration processes, i.a. delayed wound healing, and a reduced elimination of degradation products, which on their part may induce systemic degenerative actions. This are typical adverse effects of e.g. NSAIDS [2]. In sum and from an energetic view, the price of such approach in a pain relief appears to be a prolongation of regeneration processes.

It appears also to be obvious that such peripheral homeostatic mechanism interacts in the CNS with other mechanisms that systemically regulate energetic deficits. Such a closed loop mechanism of a "pain cycle" would suggest that pain is not only an unidirectional passive phenomenon and indicator signal but also an actuator that triggers repairing functions.

Conclusions.

(1) Pain can be represented as an integrated system of local cell energy that couples neuronal activity to the actual status of the cellular power balance. (2) As cause of a pain a power deficit is represented, which is primarily due to a relative dysfunction of the mitochondrial oxidative phosphorylation. Operatively the subsequent ion pump defects induce a change in the interstitial ion composition that results in neuronal hyperexcitability. (3) Contextually pain is represented as an implied signal. Its implicit relation to a power balance deficit is formally described as $P = f(-\Delta Q_0)$. (4) Markers of painful tissues may be relative deviations in the ISF ion composition. (5) As a whole pain may represent closed-loop that both indicates a local peripheral energy balance deficit and triggers repair actions.

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