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Hypoxia Defined as a Common Culprit/Initiation Factor in Mitochondrial-Mediated Proinflammatory Processes

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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In mammals and invertebrates, the activities of neuro- and immuno-competent cells, e.g., glia, which are present in nervous tissues, are deemed of critical importance to normative neuronal function. The responsiveness of invertebrate and vertebrate immuno-competent glia to a common set of signal molecules, such as nitric oxide and endogenous morphine, is functionally linked to physiologically driven innate immunological and neuronal activities. Importantly, the presence of a common, evolutionarily conserved, set of signal molecules in comparative animal groups strongly suggests an expansive intermediate metabolic profile dependent on high output mitochondrial ATP production and utilization. Normative bidirectional neural-immune communication across invertebrate and vertebrate species requires common anatomical and biochemical substrates and pathways involved in energy production and mitochondrial integrity. Within this closed-loop system, abnormal perturbation of the respective tissue functions will have profound ramifications in functionally altering associated nervous and vascular systems and it is highly likely that the initial trigger to the induction of a physiologically debilitating pro-inflammatory state is a micro-environmental hypoxic event. This is surmised by the need for an unwavering constant oxygen supply. In this case, temporal perturbations of normative oxygen tension may be tolerated for short, but not extended, periods and ischemic/hypoxic perturbations in oxygen delivery represent significant physiological challenges to overall cellular and multiple organ system viability. Hence, hypoxic triggering of multiple pro-inflammatory events, if not corrected, will promote pathophysiological amplification leading to a deleterious cascade of bio-senescent cellular and molecular signaling pathways, which converge to markedly impair mitochondrial energy utilization and ATP production.

MeSH Keywords: Cell Hypoxia • Microglia • Mitochondria • Morphine • Nitric Oxide • Nitrites

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Background

In mammals and invertebrates, the activities of immuno-competent glial cells, which are present in nervous tissues, are deemed of critical importance to normative neuronal and immune function in the brain [1]. In earlier reports, invertebrate immuno-competent glial cells have been demonstrated to possess similar properties as previously described for mammalian microglia and central nervous system (CNS) directed activated macrophages [1–4]. These morphological and functional similarities suggest that their presence in invertebrate ganglia demonstrates an evolutionary driven functional convergence of function of immuno-competent glial cells. In this regard, our group and others have demonstrated many similarities between invertebrate immunocytes/microglia and mammalian monocyte/macrophage lineages, including utilization of a shared set of chemical messengers [5–18].

The responsiveness of invertebrate and vertebrate immuno-competent glia to a common set of signal molecules, such as NO and endogenous morphine, is functionally linked to physiologically driven innate cellular activities [2,3,12,19]. Accordingly, immuno-competent glia represent a cell-type intimately linked to optimal mitochondrial metabolic rate, as is the case for neurons in their physiological responses to diverse stimuli [2,20]. This phenomenon is visualized by stationary microglia becoming amoeboid, macrophage-like and mobile following traumatic stimuli, which can alter metabolic rate [2–4,21]. Given these commonalities in evolutionarily divergent animals, it would not be surprising to find the same similarities in regulating mitochondrial energy processes in the order that these events occur. Because mammalian microglia and astrocytes are involved in a wide variety of immunological activities as well as the growth and maintenance of neurons, a strong functional coupling to mitochondrial energy processes is required [22]. A recent report demonstrates that within a cell, e.g., neurons, mitochondria can be found in all processes and under low oxygen and ATP supply can withdraw, allowing that portion of the cell to deteriorate [23]. This clearly demonstrates a micro intracellular environmental response to a low energy supply, suggesting if allowed to continue will destroy the respective cells and later multiple cells [9,24–32]. In sum, the presence of a common set of signal molecules in comparative animal groups, their innate immunological stimulating activity functionally linked to the induction of significant morphological cellular changes, strongly suggests an expansive intermediate metabolic profile dependent on high output mitochondrial ATP production and utilization.

In mammals, interestingly, immuno-competent microglia may play a possible role in the onset of certain neurological diseases and/or the etiology of particular psychiatric states [28] e.g., HIV dementia, psychoses, schizophrenia, etc. [33–35]. In sum, a commonality exists in cell-types and chemical messengers involved in intra- and inter-cellular communication within CNS structures with accelerated mitochondrial energy processes required to achieve this complex level of integration.

Common Signal Molecules and Their Interactions

The above evolutionary conserved processes are only possible if other systems are conserved as well. An extensive biomedical literature demonstrates both conservation and enhancement of function of common sets of chemical messenger compounds engendered by evolutionary pressure. Retention of primordial signaling molecules, such as the free radical gas NO, appears to have started before the evolutionary divergence of plant and animal phyla. Thus, the elucidation of basic mechanistic information regarding diverse mechanistic roles of common sets of chemical messenger molecules has tremendous predictive value within biomedical model systems. Briefly, it is contended that a likely mechanistic driving force underlying the phenomenon of chemical messenger retention during evolution resides in stereo-selective recognition of enantiomeric compounds within multiple stereo-selective enzyme and receptor signaling pathways [36]. Thus, the basic preservation of essential chemical information required for recognition and activation by distinct classes of enzyme and receptors within discrete signaling pathways provides the molecular basis for retention of shared sets of chemical compounds in diverse plant and animal phyla. Hence stereo-selective conformational matching in a multiple enzyme or multiple receptor mediated pathway presents a systemic driving force to retain basic chemical identities across animal and plant phyla [9,36–40] and in remarkably different cell types. Another common chemical feature of retained signal molecules is the widely expressed precursor to product relationship that allows temporal release of biologically active chemical compounds and peptide sequences from biologically inactive prohormone-like molecules, notably via the action of endo-proteolytic cleavage enzymes [10,41–47].

Chronically activated classes of immune cells may be involved in the etiology of a wide variety of neuropsychiatric conditions related to infection such as Lyme neuroborreliosis and chronic fatigue syndrome and autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, and multiple sclerosis. Importantly, a chronic state of prolonged peripheral or central pro-inflammation may represent a common causal factor in the persistence of diverse psychiatric disorders [48], thereby implicating aberrant bidirectional communication between neurons and immune cells as potentially novel therapeutic targets [49–51]. Retroactively, an evolutionary blue print for elucidation of neural-immune bidirectional communication

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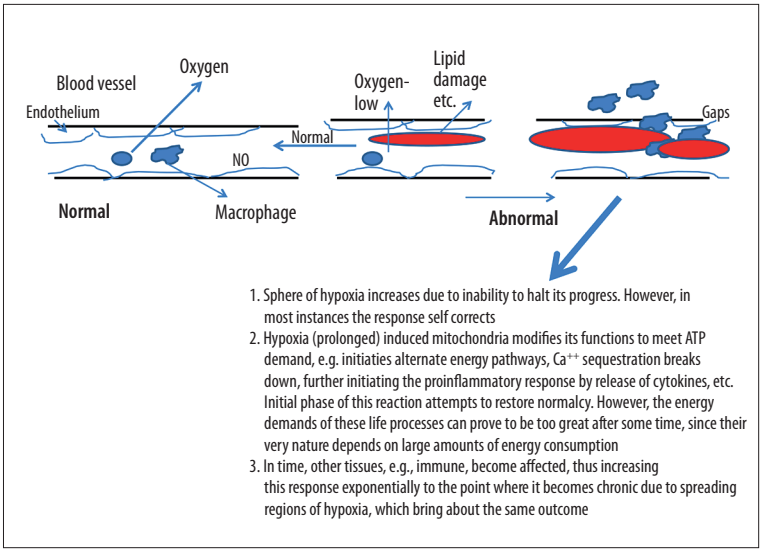

Figure 1. Initial hypoxic event.

mechanisms of higher animals may be gleaned from examination of neural and immune processes of invertebrates.

Unifying principles responsible for normative bidirectional neural-immune communication across invertebrate and vertebrate species reside in common anatomical and biochemical substrates and pathways involved in energy production and mitochondrial integrity. Within this closed-loop system, it is predicted that abnormal perturbation of immunological function, for example, will have profound ramifications in functionally altering associated nervous and vascular systems [52–56]. An initial priming event may appear to be pro-inflammatory in nature [48]. We contend, however, that the initial trigger to the induction of a physiologically debilitating pro-inflammatory state is a micro-environmental hypoxic event. This can come about by trauma, intrinsic (free radicals) and/or extrinsic factors, low oxygen levels, compromised oxygen delivery etc. It is also evident that requisite mitochondrial ATP production for optimal health and long-term survival is critically dependent on oxygen availability for these dynamic purposes. Hence, temporal perturbations of normative oxygen tension may be tolerated for short but not extended periods.

Significance of Hypoxia-Driven Dysfunctional Mitochondria

Trauma, infection and vascular compromise, even short-term acute stimulatory phenomena, can elicit innate immune responses that are existentially protective in nature and required for long term survival of an organism [2,20,57–61]. If an initial immunological response cannot be effectively terminated, a pathophysiological chronic pro-inflammatory state may ensue, with dire functional consequences for systemic overall health [48]. Maintenance of healthy nervous tissue function requires approximately 20% of total oxygen intake that is complemented by the high oxygen requirement of active vascular and immune cells. In many chronic disorders involving extended pro-inflammatory processes, it is apparent that there are micro- and macro-environmental states of hypoxic stimuli [60,62–64], which in turn trigger additional compromised metabolic processes within multiple organ systems (Figure 1). It therefore comes as no surprise that ischemic/hypoxic perturbations in the oxygen delivery represent significant physiological challenges to overall cellular and multiple organ system viability [49, 65]. Hypoxic triggering of multiple pro-inflammatory events, if not corrected, will promote pathophysiological amplification leading to a deleterious cascade of bio-senescent cellular and molecular signaling pathways which converge to markedly impair mitochondrial energy utilization and ATP production.

Recent work has observed significant diversity in mitochondrial energy utilization and ATP production functionally linked to state dependent aerobic *vs.* anaerobic conditions [66]. This observation in itself demonstrates that sensitive mitochondrial processes exist to adapt to mitochondrial perturbations, resulting in its continued functioning under adversity. However, these processes allow the mitochondria to function at a lower level of efficiency, creating a situation if allowed to continue for a prolonged time negative outcomes can be expected, e.g., tissue damage, apoptosis etc. Interestingly, similarities have been observed in the biochemical and architectonic properties of anaerobically functioning mitochondria from crown gal tissues of the invertebrate bivalve *M. edulis* and anaerobically active mitochondria from human tumors [65]. According to the classic Warburg effect, diverse classes of tumorigenic cancer cells have been observed to maintain glycolytic metabolic processes for cellular ATP production under aerobic conditions, which normally activate mitochondrial TCA and oxidative phosphorylation

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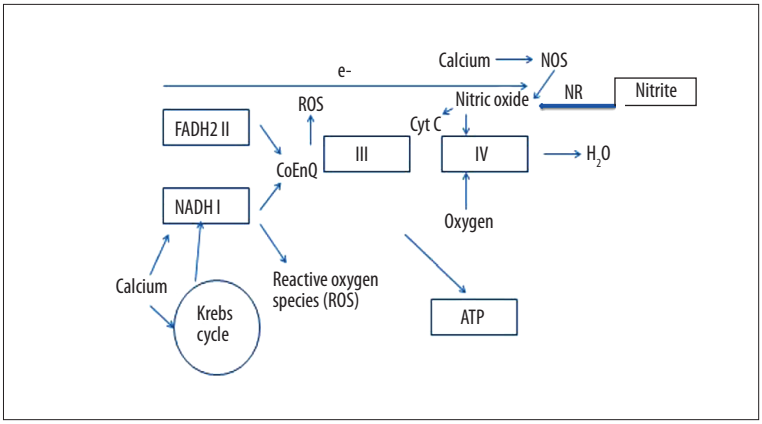

Figure 2. This illustration represents the electron transport system as it generates ATP and utilizes oxygen. ATP synthesis and H+ movements regulate the mitochondrial membrane potential, which in turn modulates the rate of respiration. In the classical rendition of this pathway, we note the cytochrome oxidase (Complex IV) exerts important control of this process because nitric oxide enhances the Km for oxygen [79,90,91]. In the hypoxia scenario, calcium sequestration in mitochondria will be compromised allowing it to, at first stimulate the Krebs Cycle as well as nitric oxide synthase (NOS) to produce NO, allowing for more efficient oxygen utilization. Simultaneously, these same end products may enhance ROS from the Coenzyme Q complex, which in turn will inhibit the electron transport system [92]. In this inhibitory phenomenon, we surmise peroxynitrite is involved as a ROS member, suggesting it originates as a "sink" for the constitutive NOS released NO. Nitrite presence (upper right) in cells is then metabolized to form NO, under hypoxic situations, acting as a reservoir to continue to allow for the oxidation of NADPH. Thus, nitric oxide, an old evolutionary messenger, is present in the mitochondria as a critical regulatory messenger.

events. Pathophysiological alterations of mitochondrial energy metabolism and ATP production under hypoxic, anoxic and even during normoxic conditions [67–69] have been proposed to promote tumorigenic and metastatic processes and with resultant disruption of the normal metabolic flux of TCA cycle intermediates and electron transport complexes.

Normative mitochondrial function in non-proliferating cells affects relatively high cytosolic ATP/ADP ratios resulting in functional inhibition of aerobic glycolysis [70]. Conversely, the classic Warburg effect describes the bioenergetics of tumor cells as highly dependent on enhanced glycolysis under aerobic and anaerobic conditions with compensatory suppression of normative aerobic mitochondrial metabolic processes [67–69,71]. By hypothetical functional criteria, aerobic mitochondrial respiration in rapidly proliferating cancer cells will lead to the production of deleterious free radicals and pro-oxidant molecules that can damage DNA, proteins, and essential lipids with resultant induction of pro-apoptotic gene products. In basic terms, aerobically induced free radical damage is proposed to recruit convergent cellular mechanisms designed to significantly diminish the existential viability of cancer cells. Along these lines, it has been proposed that a tumor cell may be viewed as a phenotypic reversion to the last common eukaryotic ancestor of the host cell, i.e., a facultative anaerobic microbe with unlimited replication potential [72]. Interestingly, anaerobic mitochondria in gill cilia of *M. edulis* have evolved to utilize the phenotype of a facultative anaerobe, demonstrating that this primitive type of respiration has been evolutionarily conserved [73,74]. Accordingly, anaerobically functioning mitochondria may represent a re-emergence or evolutionary retrofit of primordial metabolic processes, some of which are fully active under hypoxic conditions.

Conclusions

Mitochondria, enslaved bacteria, are capable of very dynamic behaviors that allow them to survive as well as the host cell but not to the same degree of performance. This phenomena occurs because of substrate and chemical messenger similarities. For example, it has been proposed that under hypoxic conditions reduction of inorganic nitrite to NO is sufficient to activate mitochondrial electron transport chain complexes, thereby allowing for a limited amount of ATP to be formed [75–83] (Figure 2). This novel mechanism occurs via NOS-independent production of NO via the action of mitochondrial nitrite reductases [81–87]. Inorganic nitrite, previously thought to represent an inert cellular metabolite of NO, is currently proposed as a critically important cellular reservoir available for immediate enzymatic conversion to NO in response to hypoxic conditions whereby it may reciprocally regulate mitochondrial respiratory processes. This phenomenon also gains meaning from an evolutionary perspective given the high rate of nitrogen within the earth's biosphere and suggests this mechanism occurred before animals and plants split into diverse phyla. Given the pivotal nature of NO signaling in mitochondrial regulation, it has also been proposed that reversible nitrite reductase activity may be central to oxygen-sensing and overall modulation of mitochondrial respiration

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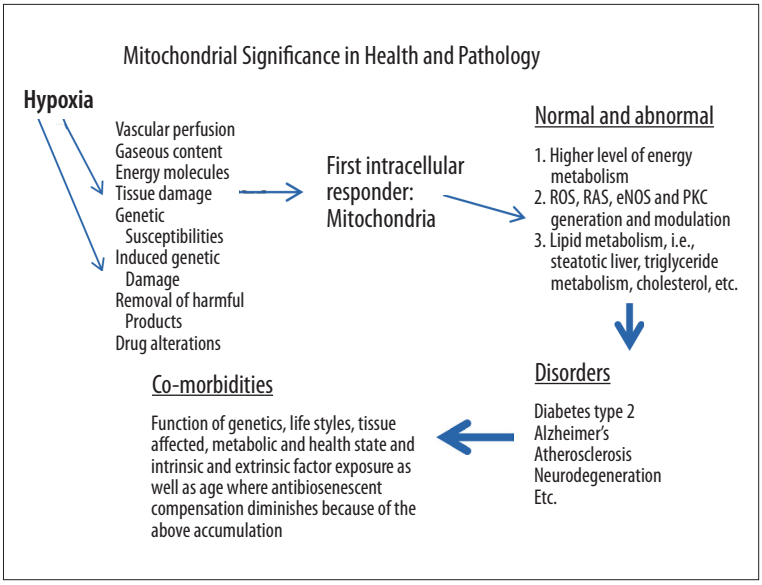

Figure 3. Mitochondrial significance in health and pathology.

[88]. This novel mechanism, in part, occurs via NO inhibiting cytochrome c oxidase and affecting other mitochondrial entities on the inner membrane [81,89].

The overall physiological significance of reversible nitrite reductase activity is highlighted by its presence in all mitochondria and by its shared identity with key enzymes within electron transport chain complexes. Again, it illustrates the dynamic nature of the mitochondria in utilizing an "older" regulatory/supply mechanism to maintain its function and host dependency. Given the early contribution of hypoxia to the exacerbation of various metabolic disorders associated with diseases, e.g., Alzheimer's, Diabetes Type 2 etc., this modulating influence of nitrite, oxygen and NO has gone undetected because later events appear larger in influence, masking this prime event (Figure 3). Taken together, it would appear this common hypoxic trigger is a fundamental event in initiating different types of disorders and its sensitivity and speed of occurrence is such, that it can and has gone undetected [89]. The ability of nitrite to provide an energy process, yielding lower levels of ATP, probably is one of the reasons associated disorders can exist and go undetected for a long period of time. In this regard, novel mitochondrial targeted pharmaceuticals in all probability will constitute future research and development.

Conflict of interest

No conflict of interest.

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