

Vicious Circle of Metaboreflex Dysregulation in Amyotrophic Lateral Sclerosis

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Amyotrophic Lateral Sclerosis (ALS) is a fatal disease of unknown origin without effective treatment identified so far. The metaboreflex is activated by skeletal muscles during physical exercise to meet the raised demand for oxygen in energy production. With increased activity of the mitochondrial respiratory chain, uncoupling proteins counteract the risk presented by the generated harmful reactive oxygen species but at the expense of energy generation. The enhanced metaboreflex with raised sympathetic nervous system activity, and the enhanced uncoupling may explain motoneuron degeneration and muscle wasting, which are the main symptoms in ALS. Here it is proposed that dysregulation of the metaboreflex, maintained by mitochondrial respiratory chain uncoupling, initiate a vicious circle that account for the pathogenesis of ALS. Thus, this publication comments on a potential insight that may inform the search for effective therapy.

Introduction

For Amyotrophic Lateral Sclerosis (ALS), a fatal disease of unknown origin, no effective treatment is known. The primary focus of latest research is on cellular stress response pathways evoked by several mechanisms including e.g. mutations in superoxide dismutase (SOD), however, this results only explain the cause of less than 10% of sporadic ALS cases. Currently, ALS is researched mostly using rodents as model systems. Locomotion control in rodents is without extrapyramidal regulation that have been found in apes or humans, potentially leading to false ALS treatment approaches in

human patients. This discrepancy between model and human beings might provide a reasonable explanation why tested medication showed positive results in animal studies, but failed in clinical trials.

Recent observations imply direct involvement of skeletal muscles and certain mitochondrial function in the origin of ALS. Specifically, modulation of mitochondrial respiratory chain capabilities for energy generation by uncoupling proteins (UCPs) might be critical for pathogenesis of ALS symptoms. It has been suggested that enhanced UCP activity as a cause for the origin of ALS rather than a consequence (1-3).

Physical exercise may promote ALS development, especially people playing sports appear to be more affected by this disease than others (4, 5). This finding correlates with several metabolic reactions to sporting activity, specifically mechanisms such as the muscle metaboreflex and the arterial baroreflex which were activated during exercise to ensure proper supply of oxygen to working muscles and to avoid oxygen overload at once (6). Also, uncoupling proteins (UCPs) are upregulated as a response to physical exercise to decrease cellular damage inflicted by oxygen derivates originating from mitochondria during elevated energy production (7, 8). It seems possible to link effects of metaboreflex dysregulation and UCP signaling in ALS patients.

In this publication, skeletal muscle metaboreflex as well as UCP signaling in ALS patients are described. As conclusion, enhanced metaboreflex activity without reasonable arterial baroreflex reaction and maintained enhanced UCP

activity might exist in ALS.

The aim of this manuscript is to provide new ideas to understand of ALS that may lead to prospective studies and finally may provide new treatment approaches of this fatal disease.

Main Text

To discover a source for ALS onset and consequently provide effective therapies, numerous candidates had been already suggested to be a cause for ALS, e.g. enhanced thyroid function or exposure to certain toxic substances especially heavy metals (9, 10). But none of these candidates could be identified as unambiguous cause for most sporadic ALS cases. Thus, the origin of ALS is still elusive.

It is noteworthy, that physical exercise correlates with ALS incidence in numerous studies suggesting a primary involvement of systems that are activated directly by physical exercise (5). In working muscles and during physical activity an increased demand of energy exists. To cover this demand, oxygen is utilized to generate energy in form of Adenosine Triphosphate (ATP) by the mitochondrial respiratory chain in muscle cells. To prevent formation of harmful reactive oxygen species (ROS) during increased ATP generation, the respiratory chain activity is tightly regulated by uncoupling proteins (UCPs). Uncontrolled or elevated activity of UCPs are described in model systems to both diminish ROS formation but at the same time exceedingly reduce ATP production (11). In addition, certain other metabolites produced by working skeletal muscles or a lowered pH activate the metaboreflex. It should be

mentioned, that mechanisms involved in metaboreflex activation have not yet been fully described so far.

The metaboreflex coordinates supply of an increased oxygen demand in working muscle cells by communication to the sympathetic nervous system (SNS) and affecting *inter alia* blood flow (12). As a kind of antagonist to metaboreflex effects, the arterial baroreflex is also activated by physical exercise (13). Thus, effects of arterial baroreflex are in short term partially contradictory to metaboreflex actions avoiding harmful oxygen overload in muscle cells.

Not been noticed so far, certain independent studies published in the past decades deliver evidence of enhanced metaboreflex and probably reduced arterial baroreflex activity in ALS that can be connected to an increased and obviously uncontrolled UCP activity. A study on ALS patients published in 1991 describes a significant lower incidence for hypertension in patients affected by ALS compared to controls (14). The authors of this study suggested, that hypertension may be some kind of protective factor against ALS. I suppose another plausible explanation that hypertension incidence is triggered by the underlying cause of ALS, resulting in a reduced hypertension risk to simply be an indicator for a reduced response of arterial baroreflex and/or enhanced metaboreflex. As a consequence of this assumption, the metaboreflex and the arterial baroreflex should show significant changes in ALS patients, as both reflexes have been demonstrated to mutually regulate each other and also contribute to regulation of hypertension (15-17).

Assuming enhanced muscle metaboreflex and reduced arterial baroreflex contribution to initiation of ALS development, should allow prediction of risk factors as well as protective factors to further support this hypothesis. Consequently, impairment of metaboreflex control must be a protective factor.

In this context, metaboreflex control is reduced in obesity and is

enhanced during weight loss (18, 19). Interestingly, most ALS patients have a reduced fat content and are slim if compared to control groups, and weight loss in ALS is associated with worse prognosis (20). At the first glance, this correlations might clearly be a coincidence but further evidence suggests a causal relationship between metaboreflex dysregulation and ALS incidence. Activation of the metaboreflex by oral administration of the widely used pain and inflammation medication aspirin is possible (21). As a consequence, application of aspirin may therefore be a risk factor for ALS development. Strikingly it has been demonstrated that application of aspirin to ALS patients enhances disease progression, thus confirming aspirin as a risk factor (22).

The question arises if there are further studies supporting the idea that mechanisms mediated by enhanced metaboreflex or reduced arterial baroreflex are implicated in the control of ALS development. In this regard, caffeine is a substance that is capable to block the metaboreflex by interference with adenosine receptor signaling (23, 24). In mutant mice that serve as a ALS model, caffeine seems to have a negative influence on disease progression, which is not in line with the here presented hypothesis (25). However, in mice the opposite effect of aspirin on ALS disease progression has been observed, assuming that significant differences between humans and mice must exist (26).

Indeed an explanation might be, that extrapyramidal control during physical exercise is different from rodents to humans, thus in another study, caffeine is suggested to have a preventive role in ALS (27). In regard of the hypothesis that enhanced metaboreflex and diminished arterial baroreflex activity might contribute to ALS onset, the question arises if ALS main symptoms can be connected to other diseases. ALS show mutual disease progressions and also the initial symptoms are variable, but one of the first effects of ALS is muscle wasting, predominantly found in

upper extremities. This symptom can be observed in congestive heart failure.

Indeed, the arterial baroreflex is reduced in patients with congestive heart failure and those patients can also present with muscle wasting possibly due to metabolic abnormalities in skeletal muscles (28, 29). One conceivable explanation for muscle wasting might be that the reduced arterial baroreflex is not capable to interfere with the metaboreflex, which is more sensitive and consequently more active under circumstances it normally would not. It has been shown in congestive heart failure, that the SNS is increased at rest probably due to attenuated metaboreflex (30).

In healthy humans, the metaboreflex directly activates the SNS, which is required during exercise and also during normal conditions to *inter alia* maintain blood flow and oxygen delivery to working muscles. As already stated above, oxygen delivery mediated by metaboreflex effects is utilized in working muscle cells for ATP generation via the mitochondrial respiratory chain. This is crucial to cover the raised demand for energy in working muscles. In ALS, the metaboreflex is already activated by UCPs, which mimics physical activity. However, no acute demand for the supplied oxygen is present in muscles. Thus, the respiratory chain is uncoupled to avoid harmful ROS production which consequently reduce energy generation.

A drop of energy and oxygen levels in muscles have been shown to activate the metaboreflex, thus in a combined view a vicious circle can be drawn (31). A model of the here proposed vicious circle is depicted in figure one. Of note and as stated above, incidence for hypertension is significantly reduced in ALS patients which might serve as an indicator for both a disturbed baroreflex and metaboreflex regulation. Also in numerous studies, signs of enhanced SNS function in ALS have been reported, which might be consequences of altered metaboreflex sensitivity (32-34). Not surprisingly in

this regard, hyperactivation of the SNS is capable to induce muscle wasting, one of the main symptoms in ALS (35).

Although communication of muscle cells to the central nervous system and vice versa is not completely understood, integration of signals in the medulla oblongata, which also regulates blood pressure and where the pyramidal tracts originate, seems to be crucial (36). More detailed studies are required to test, whether alternative energy sources, e.g. creatine phosphate, could play an important role to counteract the ATP deficit resulting from enhanced uncoupling.

Summary

This paper suggests that the fatal neurodegenerative disease ALS develops due to maintained metaboreflex dysregulation based on enhanced uncoupling of the mitochondrial respiratory chain. Candidates, that are supposed in the past to initiate ALS, i.e. heavy metals like mercury or certain herbicides, have already been identified as uncoupling agents (37, 38). As a result of maintained uncoupling of the respiratory chain, ATP levels decrease. It remains to be shown whether interference with the proposed vicious

circle by blocking UCP activity e.g. by application of Genipin might indeed lead to recovery of the symptoms in ALS (39). However, validation of the vicious circle existence in future studies should be feasible, thus providing novel and effective treatment opportunities.

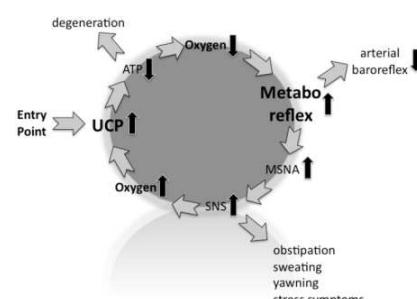


Figure 1. Vicious circle of metaboreflex dysregulation maintained by enhanced uncoupling of the respiratory chain

The entry point to vicious circle in ALS is an induced uncoupling of the mitochondrial respiratory chain, evoked by induction of UCP activity. A direct consequence of enhanced respiratory chain uncoupling is a diminished generation of energy in form of ATP as well as a drop in oxygen levels, which activate the metaboreflex. If respiratory chain uncoupling is maintained, sensitivity of systemic acting metaboreflex raises and consequently, muscle sympathetic nerve activity (MSNA) and the

sympathetic nervous system (SNS) are activated. As a result, transport of oxygen to muscle cells is increased. To avoid cellular damage inflicted by supplied oxygen, UCP is furthermore active.

Signs of enhanced MSNA/SNS activation are detectable in ALS patients, as well as a significantly reduced incidence for hypertension, supporting systemic vicious circle existence of metaboreflex dysregulation in ALS. Persistent reduction in ATP generation as a consequence of raised UCP activity leads to death of motoneurons, which are highly sensitive to energy depletion.

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