The study of metabolic alterations in Amyotrophic Lateral Sclerosis: a new therapeutic approach

Energy metabolism has been studied for almost a century but, despite our now established knowledge of the various pathways and the afferent pharmacology, its role in neurodegeneration is not fully appreciated.

In this context, about two thirds of Amyotrophic Lateral Sclerosis (ALS) patients are hypermetabolic for reasons that are not fully elucidated. Moreover, low premorbid body mass index appears to increase the risk of ALS, and survival prognosis is less favorable in the presence of weight loss and hypermetabolism.

The course of hypermetabolism in ALS is paradoxical since the progressive reduction in physical activity is accompanied by an increase in energy expenditure. In parallel with hypermetabolism, insulin resistance and glucose intolerance have been described in both ALS patients and animal models. The inability to efficiently use glucose as energy substrate increases the dependence on fats as energy fuel to counterbalance compromised ATP production as widely described in cortex, spinal cord and skeletal muscles from patients and animal models.

Muscle activity is a major determinant of the whole-body energy metabolism, so it is conceivable that skeletal muscle plays a fundamental role in the ALS hypermetabolism. Indeed, defects in muscular ATP production and alteration in metabolic substrate utilization have been reported both in patients and in animal models. Overall, it is clear that the inability to use glucose in neurons and in skeletal muscle would result in an increased dependence on the use of fat as an energy substrate in ALS. However, as endogenous energy stores are rapidly depleted, metabolic demand would be increased in a vicious cycle of bioenergetic deficit that may induce ionic dysmetabolism and sustain or exacerbate disease pathogenesis.

In this scenario, we currently have three main research lines active:

- **Line 1**, conducted in collaboration with the University of Queensland, (Brisbane, Australia), INSERM (Strasbourg, France) and the “Dipartimento di Scienze Anatomiche e dell'apparato locomotore - Sapienza Università di Roma”, is focused on the study of the early events underlying defective muscle metabolism in ALS mouse models as well as the major molecular mechanisms that cause ALS-associated hypermetabolism and defective bioenergetics homeostasis.

- **Line 2**, conducted in collaboration with the University of Queensland, (Brisbane, Australia) and INSERM (Strasbourg, France), is focused on the study of the therapeutic potential of drugs acting as metabolic modulators, already used in human clinic, aimed to stimulate glycolysis and to enhance mitochondrial metabolism in different ALS mouse models.

- **Line 3**, conducted in collaboration with “DAI di Scienze Neurologiche e Neurosensoriali, UOC di Neurologia-Neurofisiologia Clinica, Azienda Ospedaliera Universitaria Senese, (Siena, Italy)”, is focused on the validation a new metabolic biomarker in ALS patients that is altered in early stages of the disease and thus can facilitate an early diagnosis and consequently a more effective therapeutic intervention. The identification of a biomarker which itself causes hypermetabolism, which in turn is linked to a worse prognosis, might be used as prognostic biomarker and might help to shed light on the mechanisms that promote metabolic alterations observed in ALS patients.
References:


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Fondazione Italiana di ricerca per la Sclerosi Laterale Amiotrofica, AriSLA. Project title: “Modulation of hypermetabolism and hyperexcitability as a strategy to counteract degeneration in ALS” HyperALS
