**Mechanism of SOD1 Regulation in ALS**

Superoxide Dismutase-1 (SOD1) is a homodimeric radical-scavenging enzyme that plays a central role in the protection of neurons and other tissues against oxidative stress. SOD1 mediates its tissue-protective effect by converting potentially toxic superoxides to molecular oxygen and hydrogen peroxide. Importantly, defects in SOD1 activity are known to underlie the neurodegeneration that causes amyotrophic lateral sclerosis (ALS). Published work has shown that defective SOD1 activity in a subset of ALS patients (comprising 22% of ALS patients overall) can be traced to increased acetylation of SOD1 at Lysine 120. Our recent data suggest that this acetylation blocks the dimerization of SOD1, which is necessary for its radical-scavenging activity.

While it is known that acetylation of SOD1 is upregulated in ALS and that acetylation inhibits its activity, what is not clear is how SOD1 acetylation is regulated. Specifically, the deacetylase enzyme that governs SOD1 acetylation is unknown. Furthermore, the environmental stimuli (e.g., metabolic stress) that modulate SOD1 acetylation are poorly understood. Lack of such knowledge is an important problem, because, without it, acquiring the ability to pharmacologically target SOD1 in ALS patients is highly unlikely.

Our long-term goal is to develop strategies to manipulate SOD1 for therapeutic purposes in neurodegenerative disease. The objective of this proposal, which is the next step in the pursuit of our long-term goal, is to determine how acetylation of SOD1 is regulated. Our central hypothesis is that increased acetylation of SOD1 at Lysine 120 in ALS is induced by glucose deprivation, which leads to the loss of activity of an unidentified deacetylase. This hypothesis has been formulated on the basis of our preliminary data acquired by analyzing tissue homogenates from ALS and healthy patient samples. The rationale for the proposed research is that, once it is known how acetylation of Lysine 120 is regulated, SOD1 activity can likely be modulated pharmacologically. This would result in new and innovative approaches for the prevention and treatment of ALS.

We plan to test our central hypothesis and thereby accomplish the objective of this proposal by pursuing the following two specific aims:

1. **Identify the deacetylase that governs SOD1 acetylation.**
   Based on preliminary data referred to above, our working hypothesis is that a metabolically regulated deacetylase, which is inactivated in ALS tissue, deacetylates SOD1 at Lysine 120.

2. **Determine whether SOD1 acetylation is induced by glucose starvation.**
   We postulate, based on our preliminary data, that SOD1 acetylation is triggered by glucose deprivation stress, which is commonly observed in ALS-affected brain tissue.

The work proposed in aims 1 and 2 is expected to characterize the cellular and environmental factors that govern SOD1 acetylation and thereby account for the loss of SOD1 activity in ALS patients. These results are expected to have a positive impact because the identified components are very likely to be new targets for therapeutic interventions in ALS. In addition, the completion of these aims will significantly advance the fields of acetylation biology and neurodegenerative disease.
Template

Title:

Introductory sentence(s) (1-2 sentences):

Current knowledge (4 sentences):

Define the gap in current knowledge or unmet need (2 sentences):

Long-term goal (2 sentences):

Proposals overall objective (2 sentences):

Central hypothesis (2 sentences):

Rationale for hypothesis and proposed research (3 sentences):

We plan to test our central hypothesis and, thereby, accomplish the objective by pursuing two specific aims:

1. (2 sentence):

2. (2 sentence):

The expected outcomes, (significance and impact), of the specific aims are (limit of 4 sentences).