Muscle Fiber Type Switch as a Potential Therapeutic Target for ALS.
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Endurance athlete's muscles are characterized by a higher percentage of slow-type fibers innervated by motoneurons thought to be resistant in ALS. Some of the physiological adaptations to endurance exercise are: increased mitochondria size and number, increased vasculature, and higher proportion of slow type fibers. From what we understand about ALS, these adaptations should be beneficial to promoting motoneuron health and function. One would then expect that endurance athletes are less susceptible to ALS; however, this is not the case. One possible explanation for this dichotomy could be that exercise induced-injury could be an explanation for the lack of exercise benefit, where the effects of this injury negate muscle adaptations that promote motoneuron health. *A possible therapeutic approach for ALS could be to induce the positive effects of exercise, (increase mitochondria number and size, switch fiber type towards a more resistant phenotype, prevent atrophy, and increase vasculature) but without any of the possible negative effects (exercise induced-injury).*

AICAR is a chemical that was given to mice that did no exercise. These mice could then run 44% farther on a treadmill than those that did not receive the drug (1). The same study showed that AICAR treated mice had more muscles with characteristics slow-type fibers than the untreated mice. While there is much controversy regarding the use of AICAR to substitute for exercise and its use in athletes, this chemical could provide the endurance exercise benefits to ALS patients while allowing them to avoid the exercise induced-injury. Furthermore, AICAR has been tested in humans for a variety of conditions.

AICAR activates AMPK. AMPK is a fuel-sensing serine/threonine kinase in cells that is activated under conditions of energetic demands, such as exercise, to restore energy balance (2). Chronic administration of AICAR activates AMPK increasing the expression of genes implicated in oxidative metabolism, mitochondrial biogenesis and in muscles a switch to slow-type fibers.

Aim 1: *Confirm AICAR induces AMPK activation in muscle and spinal cord, ad determine optimal effective dose.*
In these experiments we have determined the effective dose of AICAR to increase activation of AMPK and increase mitochondria. This determination of effective dose of AICAR provides "proof of concept," and lays the foundation for the next series of experiments described below.

Aim 2: *Will administration of AICAR to the mouse model of ALS prevent early muscle denervation?*
We have determined that denervation of the TA muscle begins between days 14 and 30 [Figure 1]. By days 60-75, a high percentage of the FF/type IIb fibers in the TA are denervated. For this study we will determine if AICAR can prevent, or delay this early denervation. Animals will administered AICAR or saline daily beginning at 30 days post-natal (P30) and will continue until day 60. At the end of treatment the extent of muscle denervation, muscle fiber type composition, and number of motor neurons in the lumbar spinal cord will be determined.

We believe that these critical preliminary data provide the foundation for future experiments that will determine if administration of AICAR can delay symptom onset and extend survival in the $SOD1^{G93A}$ mouse model of ALS. These experiments are critical pre-clinical studies that are necessary before patient trials.

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