strains show the stress-responsive transcription factors skn-1 (ortholog of NRF2/NFE2L2; oxidative stress response) and hif-1 (ortholog of HIF1A; hypoxic stress response) to be highly upregulated when the kynurenine pathway is inhibited. We also demonstrated the increase expression of gst-4 and gcs-1 (transcriptional targets skn-1), which are involved in production of the antioxidant glutathione (GSH), as well as upregulation of cysl-2 (transcriptional target of hif-1), a regulator of cysteine biosynthesis from serine. We hypothesize that lifespan extension resulting from kynurenine pathway inhibition is mediated, at least in part, by upregulation of these transcription factors, providing elevated defense against oxidative stress and hypoxic stress.

LOSARTAN MITIGATES OXIDATIVE STRESS IN THE BRAINS OF AGED IL10-/- MICE

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Chronic inflammation has been linked to frailty and declined cognition in older adults. Activation of the renin-angiotensin system (RAS) through the angiotensin Type1 receptor (AT1R) has been suggested as a contributory factor that links both inflammation and aging. Here we examined the impact of 4 weeks of oral Losartan treatment on IL10-/- mice brains, a mouse model of chronic inflammation and frailty. Frontal cortex, cerebellar, and hippocampal tissue of aged (100 weeks old) male IL10-/- mice were studied. Western blot techniques were employed to quantify changes in brain AT1R, nitrotyrosine (NT) as an oxidative stress marker, and Tau proteins. Our data show that aged IL-10 mice have significantly higher levels of AT1R in the cortex tissue but not in cerebellar or hippocampal tissue compared to age and sex-matched WT mice (0.63 + 0.35 vs 1.5 + 0.54, WT vs IL10, respectively, $P<0.004$). When treated with LOS, brain cortical tissue of IL10 -/- mice showed significant decreases in levels of AT1R (1.5 + 0.54 vs 0.98 + 0.50, IL10 vs LOS treated IL10, respectively, $P<0.04$), NT (0.72 + 0.12 vs 0.42 + 0.10, IL10 vs LOS treated IL10, respectively, $P<0.009$), and Tau protein (1.3 + 0.31 vs 0.15 + 0.08, IL10 vs LOS treated IL10, respectively, $P<0.004$) as compared to control IL10-/- mice. Losartan treatment had no significant effect on hippocampal AT1R or NT levels. Our results highlight the impact of Losartan, a drug commonly prescribed for the treatment of high blood pressure, on the brain-specific angiotensin system and its downstream effects on brain oxidative stress and Tau pathology.

LOSS OF HYPOXIA SIGNALING LIMITS PHYSIOLOGIC AND MUSCLE ADAPTATIONS TO AEROBIC EXERCISE IN AGING

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To assess the differential effects of exercise with age, Young (Y, 10-12 weeks) and Old (O, 23-25 months) mice were subjected to regimented treadmill running or no regimented exercise. Y, trained mice experienced a significant increase in maximal distance running, maximal speed of running, and lean muscle mass in comparison to age-matched, untrained controls. O mice did not improve significantly in any of these measures following training. Transcriptome analysis of gastrocnemius from Y mice demonstrated differential regulation of 120 genes with exercise. None of these genes were similarly regulated in the O group. Genes most upregulated following exercise in Y mice were direct targets of the hypoxia signaling pathway. Immunoblotting demonstrated that aryl hydrocarbon receptor nuclear translocator (ARNT), a critical regulator of hypoxia signaling, increased 3-fold with exercise in Y mice, but this increase was absent in O mice following exercise. To assess whether this loss of ARNT in O muscle impaired the exercise response, we generated a mouse with inducible, skeletal muscle-specific knockout of ARNT (ARNT muscle (m) KO). Following regimented exercise, ARNT mKO mice did not improve maximal distance running, maximal running speed, or lean muscle mass in comparison to untrained ARNT mKO mice. Littermate, age-matched ARNT wild type mice increased significantly in all of these measures following training. Administration of ML228, an ARNT agonist, increased maximal running distance and speed in response to exercise training in O mice. These results suggest that restoration of ARNT and hypoxia signaling may restore the physiologic response to exercise in aging.

MECHANISMS OF CELL NON-AUTONOMOUS LONGEVITY REGULATION

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An organism's ability to respond to stress is crucial for long-term survival. These stress responses are coordinated by distinct but overlapping pathways, many of which also regulate longevity across taxa. Our previous work identified a cell non-autonomous signaling pathway led by the hypoxia-inducible factor and resulting in induction of flavin-containing monooxygenase-2 (fmo-2) to promote health and longevity. Our current work identifies a distinct cell non-autonomous pathway downstream of dietary restriction (DR) that also relies on fmo-2 induction to promote health and longevity. We now find that these cell non-autonomous pathways can be mimicked by small molecule interventions that increase longevity by inducing fmo-2. Based on the commonalities of these pathways, we hypothesized that fmo-2, a classically annotated xenobiotic enzyme, might play a key endogenous role in responding to metabolic stress. Our resulting data, using metabolic profiling and further epistatic analysis, both support this hypothesis and link fmo-2's mechanism to modifications in one-carbon metabolism (OCM), a key intermediate pathway consisting of the folate and methionine cycles. Using mathematical modeling and a labeled