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upregulations in the group of genes involved in neurotransmission. In particular, genes encoding the transporters and receptor components of glutaminergic transmission were significantly upregulated in exercised muscles, as exemplified by *Gria 1*, *Gria 2* and *Grin2c* encoding glutamate receptor 1, 2 and 2C respectively, *Grin1* and *Grin2b* encoding N-methyl-D-aspartate receptors (NMDARs), *Nptx1* responsible for glutaminergic receptor clustering, and *Slc1a2* and *Slc17a7* regulating synaptic uptake of glutamate. These changes were accompanied by an increase in post-synaptic NMDARs and acetylcholine receptors (AChRs), as well as their innervation at neuromuscular junctions (NMJs). These results suggest that neural responses predominate aged skeletal muscle following exercise, and indicate a possibility that glutaminergic transmission at NMJs may be responsible for synaptic protection and neural remodeling accompanying the exercise-induced functional enhancement in aged skeletal muscle.

GENES CONTRIBUTING TO RESILIENCE AND SENSITIVITY TO LISINAPRIL AT OLD AGE: CLINICAL TRANSLATION OF GWA IN DROSOPHILA

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Despite impressive results in restoring physical performance in rodent models, treatment with Renin-Angiotensin System (RAS) inhibitors such as Lisinopril have highly mixed results in humans, likely, in part, due to genetic variation in human populations. To date, the genetic determinants of responses to drugs such as RAS inhibitors remain unknown. Given the complexity of the relationship between physical traits and genetic background, genomic studies which predict genotype- and age-specific responses to drug treatments in humans or vertebrate animals are difficult. Here, using 126 genetically distinct lines of *Drosophila*, we tested the effects of Lisinopril on climbing speed and endurance at young and old age (N=14,310). Our data show that functional response and sensitivity to Lisinopril ranges from significant protection against physical decline (8–100% faster, $P < 0.0001$) to increased weakness ($P < 0.0001$) depending on both genotype and age ($P < 0.0001$). Genome-wide analyses revealed little to no overlap in candidate polymorphisms influencing sensitivity between ages nor between treatments within each age. Furthermore, network analyses led to identification of evolutionarily conserved genes in the WNT signaling pathway as being significantly associated with variations in sensitivity to Lisinopril. Genetic knockdown of *Axin*, *frizzled*, *nemo*, and *wingless*, genes with human orthologs *AXIN1*, *FZD1*, *NLK*, and *WNT1*, respectively, abolished the effects of Lisinopril treatment. Our results implicate these genes as contributors to the genotype- and age-specific effects of Lisinopril treatment and as potential therapeutic targets for improvement of resiliency. Our approach should be widely applicable for identifying genomic variants that predict age-dependent responses to pharmaceutical treatments.

IMMATURE PEAR EXTRACT CONSTITUENTS EXERT MULTIFACETED ANTI-AGING EFFECTS

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Cellular senescence causes a gradual loss of physiological functions and induces chronic diseases, which negatively affect the quality of human life. Intervention in the cellular senescence process may reduce the incidence of these diseases while delaying the progression of age-related diseases, thereby prolonging human lifespan. In our previous study, we found that extending the chronological lifespan of budding yeast cells, a suitable cellular model for research on mammalian cells, could be achieved by adding immature pear extract (iPE). Moreover, at the 2020 GSA meeting, using a colony-counting method, we reported that both hydrophilic (WiPE) and hydrophobic (OiPE) iPE components exhibited a chronological lifespan prolongation on yeast cells. In this study, the expression of sirtuin-related genes, which regulate cellular senescence, was verified by quantitative real-time reverse-transcription polymerase chain reaction. Interestingly, sirtuin-related gene expression was significantly increased in the WiPE-treated cells only, and OiPE could extend the chronological lifespan of yeast cells through the mechanisms not involved in sirtuin-related gene expression. In general, hydrophobic and hydrophilic components exhibit different degradation and metabolism in cells. Since each component has a different strategy of absorption and excretion in the body, we hypothesize that iPE with multiple active components will have multifaceted effects on anti-aging. Our research on elucidating the mechanism of lifespan extension by OiPE and its application to mammalian cells is ongoing.

KYNURENINE METABOLISM LIFESPAN EXTENSION MEDIATED BY OXIDATIVE STRESS RESPONSE AND HYPOXIC RESPONSE IN C. ELEGANS

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Aging is characterized by a progressive decline in the normal physiological functions of an organism, ultimately leading to mortality. Metabolic changes throughout the aging process disrupt the balance and homeostasis of the cell. The kynurenine metabolic pathway is the sole de novo biosynthetic pathway for producing NAD⁺ from ingested tryptophan. Altered kynurenine pathway activity is associated with both aging and a variety of age-associated diseases, and kynurenine-based interventions can extend lifespan in *Caenorhabditis elegans*. Our laboratory recently demonstrated knockdown of the kynurenine pathway enzymes kynureninase (KYNU) or 3-hydroxyanthranilic acid dioxygenase (HAAO) increases lifespan by 20–30% in *C. elegans*. However, the mechanism of how these interventions may modulate response against different stressors during the aging process has yet to be explored. Fluorescent reporter

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