Leveraging exercise mimetics as potential therapeutics

Robert Wessells, Associate Professor at Wayne State University, explores whether identifying potential exercise mimetics can deliver the benefits of exercise to patients with reduced mobility

Exercise is an indispensable part of our daily life to maintain a healthy body and brain across ages. Regular exercise has been shown to reduce the incidence of many age-related diseases and preserve healthy function during normal aging, improving quality of life and independence.

However, chronic exercise remains inaccessible to portions of the population due to injury, illness, advanced age, or job-enforced sedentary periods. Therefore, identifying potential exercise mediators or mimetics that can deliver the benefits of exercise to sedentary people would be potentially transformative in reducing disease burden worldwide.

Powerful exercise mimetics

At Wayne State University in Detroit, Michigan, U.S., Dr. Robert (RJ) Wessells and his Lab team have used the many genetic tools available for use in fruit flies to identify several single molecules that act as powerful exercise mimetics in the brain and muscle of sedentary flies. (1)

The fruit fly Drosophila melanogaster is an excellent model organism for studying mechanisms of exercise due to its short lifespan, large sample sizes, and low maintenance cost. Moreover, about 60% of Drosophila's genes have known human homologs, making genetic discoveries highly likely to be relevant to humans.

The Wessells Group first established an automated exercise device called the Power Tower to understand how flies respond to exercise. It utilizes flies' inherent response for negative geotaxis, an instinctive behavior to climb upwards after being dropped to the bottom of their vials. After a three-week program of ramped daily training, the endurance and speed of the exercised group are dramatically higher than unexercised controls.

A specific subset of neurons in the brain

Using this system, the Wessells Group identified a specific subset of neurons in the brain that were necessary and sufficient to coordinate a systemic response to exercise training. These neurons are responsible for the synthesis and synaptic release of the invertebrate functional equivalent of norepinephrine, known as octopamine.

In humans, norepinephrine is a well-known player in acute bouts of exercise, where it acts to increase heart rate and blood pressure to ensure sufficient delivery of oxygen to exercising muscle. Hence, the involvement of octopamine in fly exercise was not completely surprising. However, the idea that this conserved acute response could also be acting to coordinate the long-term systemic response to chronic exercise training was unexpected and exciting.

To confirm the central role of octopamine, they next expressed an inducible depolarizing construct, specifically in octopaminergic neurons, making it possible to turn octopamine production on and off at will. Using this, they performed an experiment in which octopaminergic neurons were activated with the exact time and duration of the flies' normal training program but without any actual exercise. Amazingly, this pulsatile release of octopamine in sedentary flies caused the exact same increases in speed, endurance, and cardiac performance as that delivered by actual exercise.

Conceptually, this means that, at least in flies, the coordinated response to chronic endurance exercise training is completely mediated by a subset of neurons in the brain and does not absolutely require actual movement to occur, provided the brain can be induced to initiate its normal response to exercise.

What molecules are responding to octopamine in muscle to mediate the benefits of training?

The next question was, what molecules are responding to octopamine in muscle to mediate the benefits of training? The Wessells Group has identified several proteins that are induced by circulating octopamine and can mimic the effects of exercise training when overexpressed in muscle. (2) Each has conserved orthologs or analogs in humans, suggesting that these molecules may serve as promising therapeutics for humans who cannot exercise because of injury or illness.

Work has begun to use these exercise-induced molecules as therapeutic avenues for treating various diseases. Already, the Wessells Group has collaborated with the Todi Lab at Wayne State University to show that genetically inducing expression of some of these proteins can dramatically restore mobility and slow disease progression in a fly model of Spinal Cerebellar Ataxia 2 (SCA2), a neurodegenerative disease for which there is presently no cure.

Mechanisms by which exercise can preserve memory during aging

Recently, the Lab has focused on exploring mechanisms by which exercise can preserve memory during aging. Both studies in rodent models and cohort studies in humans have strongly suggested that frequent exercisers retain "younger" levels of memory as they age compared to age-matched sedentary individuals. If this is also true in flies, then the Lab could utilize all the genetic tools available in the fly system to identify critical

molecular mechanisms required for exercise to preserve memory and follow by testing whether stimulating these molecular pathways could preserve memory even in sedentary flies.

Memory can be assessed in flies by training them to associate certain odors with reward or shock. Then, one can quantitate how well they remember by putting them in a T-shaped maze and asking if they continue to avoid the odor that had been paired with the aversive stimulus. Others have used this system to establish some of the key molecules required for memory formation and retention.

Interestingly, one of the major pathways previously identified (Protein Kinase A – cyclic AMP Pathway) is well-known to be stimulated by octopamine. Since we have shown that octopamine is stimulated by regular exercise, we hypothesize that exercise protects memory by stimulating octopamine to activate Protein Kinase A and its downstream effectors.

Initial tests in the Wessells Group so far support this hypothesis, with wild-type flies doing better in memory tests if they have been exercising throughout life. Stimulation with octopamine seems to partially mimic the effect of exercise, although this effect is much stronger in male flies than female for reasons that are not yet clear.

Can flies be used to model Alzheimer's?

Our next steps are to examine if the effects of exercise and octopamine can be used to protect against memory loss in Alzheimer's Disease model flies. Flies can used to model Alzheimer's by taking human proteins that accumulate in the neurons of Alzheimer's patients and expressing them in fly neurons. Such flies show progressive memory loss and neurodegeneration and can be used as a living model to test therapeutic avenues.

The Wessells Lab has begun testing the exercise response molecules they have identified in Alzheimer's model flies and hopes to establish mechanistic targets that can be used to establish novel therapeutic avenues for patients.

References

1. Wessells, Robert J. "The Mechanisms and Benefits of Exercise." Open Access Government, 2023, https://doi.org/10.56367/oag-040-10954.
2. Wessells, Robert J. "How Brain Research Is Making the Benefits of Regular Exercise Accessible to All." Open Access Government, 2023, https://doi.org/10.56367/oag-039-10925.

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Senescence: Examining genetic responses, exercise benefits and age-related decline

Robert Wessells' lab at Wayne State University has been focusing on the field of functional senescence, particularly age-related decline in mobility and exercise capacity The capacity of the elderly population to retain mobility is a substantial quality of life issue and an important way of avoiding health complications from inactivity and/or falls. Therefore, understanding the […]