Identifying potential exercise mimetics that deliver the benefits of exercise

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Robert Wessells, Associate Professor at Wayne State University, discusses his research on identifying potential exercise mediators or mimetics to deliver the benefits of exercise to less mobile individuals and help reduce the global disease burden

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, regular 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.

Studying the mechanisms of exercise

At Wayne State University in Detroit, Michigan, US, 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.

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 are known to be human homologs, making genetic discoveries highly likely to be relevant to humans.

To understand how flies respond to exercise, the Wessells group first established an automated exercise device known as the Power Tower. This device utilizes flies' inherent response to 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 were dramatically higher than those of unexercised controls.

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

muscles. 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 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.

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. Each has conserved orthologs or analogs in humans, suggesting that these molecules may serve as promising therapeutics to humans who are unable to exercise because of injury or illness.

Exploring exercise-induced molecules as potential treatments for various diseases

Work has begun using these exercise-induced molecules as therapeutic avenues for the treatment of 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.

Recently, the lab has turned its attention to exploring mechanisms by which exercise can protect against the harmful effects of circadian rhythm disruption. The normal daily cycles of gene expression throughout the body are highly important for the maintenance of long-term health, and these cycles can be disrupted by many aspects of modern life, such as shift work, frequent travel across time zones, or sleep disorders. People and model organisms with disrupted circadian rhythms have increased susceptibility to cardiovascular disease and mental health issues, making this an important medical issue worldwide.

Regular daily exercise itself can serve as a signal to help reset disrupted circadian rhythms. Still, unfortunately, one of the consequences of long-term circadian rhythm disruption is a decrease in exercise capacity. This decrease in exercise capacity when

rhythms are disrupted has been observed clinically in humans and model organisms. Our lab has recently shown that this reduction in exercise capacity also happens in flies with mutations that disrupt their circadian rhythm. This opens the door to the use of fly mutants with disrupted circadian rhythms as a model to study potential treatments to restore full exercise capacity.

We hypothesized that because octopamine can increase exercise capacity in sedentary flies, it could perhaps restore exercise capacity to circadian mutant flies. Indeed, this turned out to be the case. Circadian mutant flies fed with octopamine were able to exercise at wild-type speed and endurance levels, even though their circadian rhythms remained disrupted. This provides important proof of the principle that it is possible to protect exercise capacity even without fully restoring circadian rhythms.

Because the human equivalent of octopamine, norepinephrine, would be dangerous to use as a treatment due to its effects on blood pressure, we searched for other genetic factors that are activated by octopamine that could be a safer potential therapy for humans. So far, we have overexpressed three different downstream molecules that are activated by octopamine and found that each is capable of protecting exercise capacity in circadian mutants to some extent. As these experiments increased the expression of protective factors ubiquitously, we are now moving to detail which organ systems are the most important ones to receive these signals as we continue to move closer to translating these findings into human trials.

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