Identifying potential exercise mediators

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Dr Robert Wessells and his team at Wayne State University are researching exercise mediators and mimetics in fruit flies (Drosophila melanogaster) to explore how to provide the benefits of exercise to individuals who are unable to access it. Here, he shares what he has discovered during his research

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.

At Wayne State University in Detroit, Michigan, US, Dr Robert (RJ) Wessells and his lab team have used the many genetic tools available 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 have known human homologs, making genetic discoveries highly likely to be relevant to humans.

Power Tower

To understand how flies respond to exercise, the Wessells group first established an automated exercise device known as the Power Tower. It 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 are dramatically higher than 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. It does not 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.

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. Likewise, the expression of some of the same molecules can restore mobility to fly models of the mitochondrial disease Barth Syndrome, a disease that severely restricts the energy metabolism of its patients and currently has no cure.

In parallel with their studies in disease models, they are also actively engaged in discovering ways to use exercise-induced models to prevent accumulated pathologies resulting from long sedentary periods in otherwise healthy individuals. One such target population is shift workers, whose work activities lead to disrupted circadian rhythms, which are the naturally occurring rhythms regulated by a central clock in the brain, along with peripheral clocks in other tissues, that govern the daily ebb and flow of appetite, sleep drive, digestion, and general metabolism. Disruption of these rhythms can gradually lead to dysregulation of metabolic activity and increase the incidence of cardiovascular disease and other medical issues. In addition, humans and animal models with disrupted circadian rhythms experience reduced exercise capacity and seem to benefit less from exercise training than controls.

Recent work in the Wessells lab demonstrates that exercise can preserve memory in flies during normal aging. They are following up on these experiments using fly models of Alzheimer's disease to see if exercise can preserve memory during disease states. If so, this will open up a new avenue to test the exercise-induced molecules identified in the Wessells lab for their ability to preserve memory in flies expressing human disease genes. They hope this work can lead to future therapies to help patients with dementia or Alzheimer's Disease.

However, it is not possible to manipulate gene expression precisely in humans, as we can in experimental models such as fruit flies. Therefore, the Wessells group is working to identify a safe way of 'tricking' the brain into coordinating an exercise response in sedentary humans. One promising avenue for executing this is sensory stimulation by virtual reality (VR).

VR integrates auditory and visual simulations to deliver an immersive experience to its users while allowing users to retain a sense of identification and control over the virtual environment. Using a customized virtual environment created by collaborators at the company 4Experience, the Wessells group has begun pilot experiments to examine whether 'virtual' exercise could cause the release of norepinephrine that, if applied safely in a pulsatile fashion, might mimic some of the benefits of exercise. They and others have demonstrated that 'virtual' exercise can increase heart rate and alter heart rate variability in a way consistent with activation of norepinephrine. It remains to be seen whether chronic application of VR stimulation could have the same benefits in humans, and this will be an active area of investigation in the next few years. If so, they imagine a future in which patients confined to bed rest or people with jobs that prevent them from regular exercise could use 'virtual' exercise to maintain metabolic health and avoid the complications induced by enforced sedentary behavior, a potentially transformative, low-cost change to healthcare.

Contributor Details

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