How brain research is making the benefits of regular exercise accessible to all

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Robert Wessells from Wayne State University looks to the brain to understand how the benefits of regular exercise can be delivered to those who are unable to move as easily

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, including type-2 diabetes, several types of cancer, heart disease, Alzheimer's and other neurodegenerative diseases.

Regular exercise also preserves 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 which 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, USA, Dr Robert J. (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 benefits of regular exercise modelled by a fruit fly

The fruit fly Drosophila melanogaster is an excellent model organism to study mechanisms of exercise due to its short lifespan, large sample sizes, and low cost of maintenance.

Moreover, about 60% of Drosophila's genes have known 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 that utilizes flies' inherent response to negative geotaxis, an instinctive behaviour to climb upwards after being dropped to the bottom of their vials.

The Power Tower raises a platform full of fly vials up and drops them every 15 seconds. Each drop induces flies to climb up the sides of the vials.

Concurrently, unexercised control flies are placed on the Power Tower, but their climbing is restricted by pushing the foam plug down near the bottom of the vials. After a three-week program of ramped daily training, the endurance and speed of the exercised group is dramatically higher than unexercised controls.

Coordinating a systemic response to regular exercise training

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 regular 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, so 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 regular exercise training was unexpected and exciting.

Controlling octopamine production at will

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 regular 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?

So far, the Wessells group has identified two 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 that are unable to exercise because of injury or illness.

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These molecules may be promising therapeutics for those unable to exercise:

Sestrin

Sestrins are small stress-activated proteins found from invertebrates to humans. Muscle-specific overexpression of sestrin can boost exercise benefits in unexercised flies, including increased speed, endurance, metabolism, autophagy, and mitochondrial respiration. In collaboration with the Lee lab at University of Michigan, requirements for Sestrins during exercise have also been demonstrated in mice. In collaboration with the Todi lab at Wayne State University, they have also shown that Sestrin can preserve mobility in a fly model of the neurodegenerative disease SCA2.

Spargel

Spargel is the fly homolog of the well-known mammalian exercise response gene PGC-1α. Muscle-specific overexpression of spargel can mimic the effects of exercise training on speed, endurance and cardiac performance, and they have recently shown that spargel is sufficient to restore exercise tolerance in a fly model of the mitochondrial disease Barth syndrome.

Having established that the benefits of exercise can be mediated by communication between brain and muscle, the Wessells group is working to identify a safe way of 'tricking' the brain into an exercise response in humans. One promising avenue for executing this is with sensory stimulation by virtual reality (VR).

The power of sensory stimulation by virtual reality

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 so far demonstrated that "virtual" exercise can increase heart rate and alter heart rate variability in a way consistent with the 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 could use “virtual” exercise to maintain metabolic health and avoid the complications induced by enforced sedentary behavior, a potentially transformative, low-cost change to health care.

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