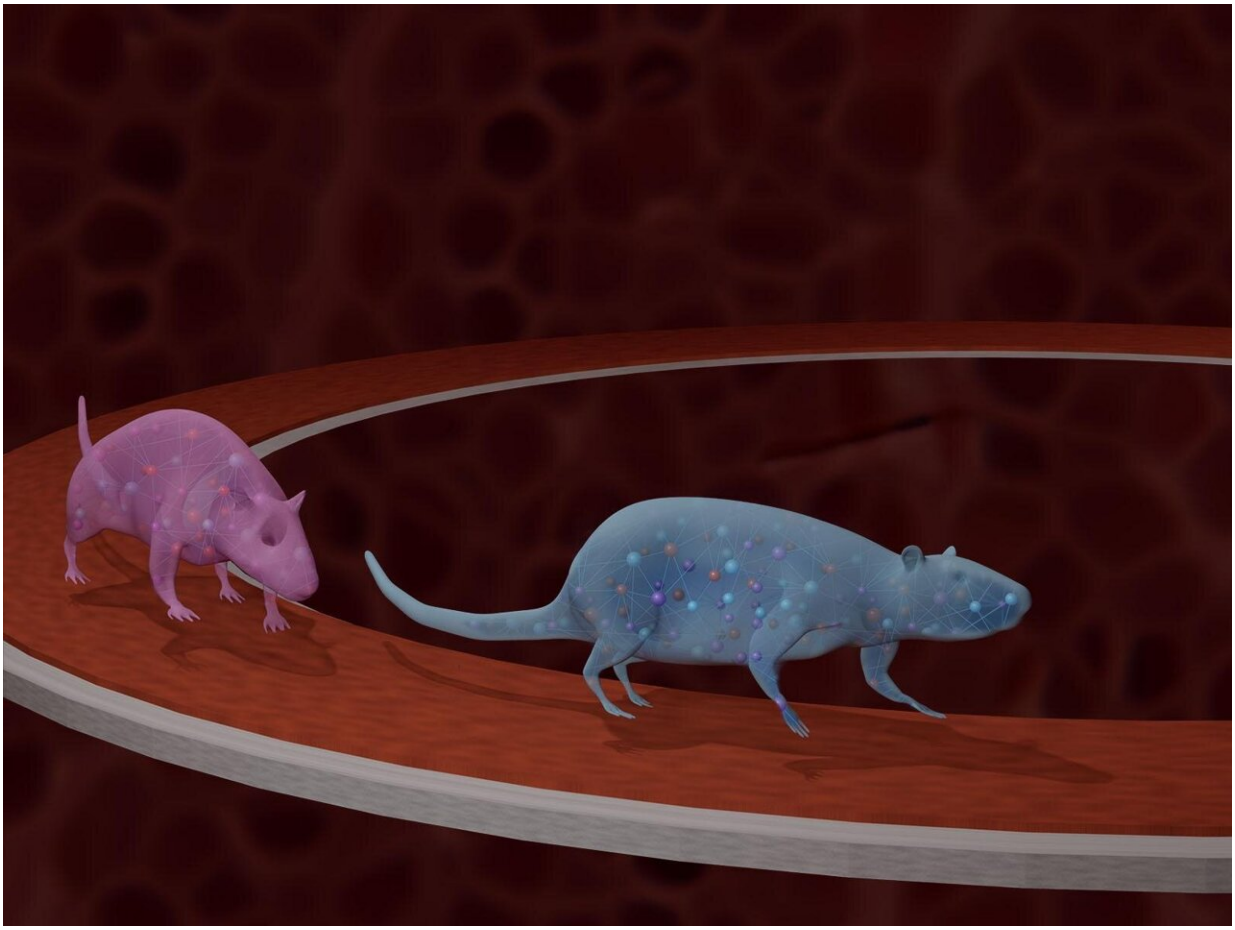
First steps toward a whole-body map of molecular responses to exercise

May 5 2024, by Coydon Ireland



Male and female rats underwent endurance training during an experiment to identify the effects of exercise at the molecular level. PNNL scientists are part of a national consortium creating the first molecular map of such effects. Credit: Nathan Johnson I Pacific Northwest National Laboratory

Research definitively confirms that muscle-moving, calorie-burning activity slows the advance of disease, improves cognitive function, boosts the immune system, and reduces rates of mortality from all causes.

Scientists are now going even deeper into the effects of exercise on humans and other mammals by investigating the impacts of exercise at the molecular level. They aim to uncover, at the smallest scales, the impacts of exercise and to better understand how the body works in states of health and disease.

Molecules are clusters of atoms. They represent the smallest unit of a chemical compound that can take part in a chemical reaction. Such chemical reactions in proteins, carbohydrates, lipids (fats), and nucleic acids—the "omics" (cellular components) that control the inner workings of every organ system.

Exercise appears to change these molecular workhorses in ways that are poorly understood. Identifying such changes, however, holds out the promise of clinical benefits for all humans, regardless of age, sex, body composition, or fitness level.

The genesis of MoTrPAC

In late 2016, to find out more about exercise-induced changes at the molecular level, the National Institutes of Health Common Fund began supporting expanded research into mapping the smallest details of how exercise helps maintain healthy tissues and organ systems. That led to establishing a national group of collaborative experts called the Molecular Transducers of Physical Activity Consortium (MoTrPAC).

From the start, Pacific Northwest National Laboratory (PNNL)—under the direction of biochemists Josh Adkins and Wei-Jun Qian—has been

among MoTrPAC's nationwide centers of expertise in animal and human exercise, biomolecular analyses, and bioinformatics.

The consortium's biomolecular analysis centers use an omics approach to analyze genes, proteins, or other biomolecules at a whole-body level. Ultimately, the goal of MoTrPAC is to create a molecular map of exercise responses in both human and animal models. From muscle to molecule, such a map would help reveal how exercise affects health.

"The ability to see broad molecular responses across organs in the body is particularly intriguing," said Qian of molecular mapping. "Such knowledge could be a strong motivating factor for exercising."

An emphasis on proteomics

PNNL's main role in MoTrPAC is to investigate exercise-induced changes in proteins and post-translational modifications (PTMs). Proteins are made of amino acid chains that fold into three-dimensional structures and that then regulate tissue and organ structure and function. PTMs are processing events that alter protein functions by chemically modifying specific amino acids within a given protein. Studying changes in all detectable proteins and their PTMs in a sample is called proteomics.

"We've been central to the study design of the consortium from the very beginning, with an emphasis on proteomics," said Adkins. He acknowledged a critical partner: Steven Carr and his proteomics group at the Broad Institute, a research center directed by Harvard University and the Massachusetts Institute of Technology.

A mapping challenge

In a 2020 perspective overview in the journal *Cell*, Adkins and PNNL biomedical scientist James Sanford joined with other co-authors to describe molecular "cross talk," a kind of chemical telegraph prompted by exercise among a variety of tissues. The study also outlined the importance of mapping such molecular exchanges.

The *Cell* paper also introduced the idea of a public MoTrPAC dataset to help find the hidden mechanisms behind the benefits of exercise. It is now thriving and growing. One of the lead analysts for the dataset is PNNL chemist Paul Piehowski.

For Adkins, Qian and others on PNNL's MoTrPAC team, proteomics research depends on instruments at the Environmental Molecular Sciences Laboratory (EMSL), a Department of Energy Office of Science user facility located on the PNNL campus. EMSL's capabilities include an array of high-end orbitrap mass spectrometers. They produce analyses that help identify and quantify proteins and other molecules from a variety of tissue types and samples.

MoTrPAC "is huge in scope," said Adkins. "PNNL's scale of operation allows us to do something of this size with very high quality and high operational reproducibility." He called the PNNL-EMSL role in MoTrPAC "a tour de force for a proteomic study. Few on this scale have been done before."

A first major paper

MoTrPAC researchers nationwide contributed to a May 2, 2024, study in the journal *Nature*. This first major paper to come out of the consortium provides the first whole-organism map of molecular responses to endurance exercise training.

The experiment's model organism was the rat. Male and female rats of

the same species ran on motorized treadmills for 1-, 2-, 4-, and 8-week periods. For controls, researchers used sedentary, untrained rats, matched for sex with their exercising counterparts.

Within 48 hours of each training interval, researchers collected samples of whole blood, plasma, and 18 solid tissues and dispersed them to omics centers like PNNL for intensive analysis.

Of the numerous samples, said Adkins, "We want to understand the integration of organ systems." Molecular responses in the body to endurance training are system-wide, say authors of the *Nature* paper—a conclusion confirmed by integrating tissue samples in a range of omics analyses.

Other results were finer tuned. Exercise enhances liver health and metabolism, for instance. It also remodels and strengthens the structure of the heart, improves pathways related to gut integrity (gut health is linked to inflammation throughout the body), enriches immune pathways, and reduces inflammation in the lungs and small intestine. Importantly, the authors relate, the sex differences observed in training responses highlight how important it is to include both sexes in exercise research.

The rat–human problem

Translating rat data into conclusions relevant to humans is challenging. However, rats are the preferred animal model because rat–human skeletal muscle and organ system signaling patterns are similar. So are exercise-induced glucose metabolism and cardiac responses. In addition, the large tissue masses of rats provide better samples than mice for multiomics analysis.

"These data will help us bring knowledge from the rat into the human

sphere," said Adkins.

To help close the rat–human data gap, the MoTrPAC consortium has an exercise-response experiment underway that records molecular responses to endurance training and resistance training across a cohort of 2,000 adult human volunteers.

Insights, with more on the way

The recent *Nature* paper provides what Adkins called "a landscape view" of multi-center national MoTrPAC research. At the same time, other studies in progress are taking narrower and more detailed views of consortium data. PNNL's Sanford is part of a research team showing how multiomics help identify key gene regulatory programs that come into play during exercise.

The Sanford team is looking at thousands of observed molecular alterations. They included how exercise regulates gene expression related to mitochondrial changes, heat shock responses, immune regulation, and other molecular processes.

Sanford has also joined PNNL biostructure and function biochemist Gina Many and PNNL data scientist Tyler Sagendorf in an analysis of the running-rats data to investigate sexual dimorphism in white adipose tissue responses.

White adipose is a storage and secretory organ system linked to the development of obesity, cardiovascular disease, type 2 diabetes, cancer, and other conditions. This fat type also has important effects on the immune system and other biological processes that maintain systemic health.

So far, the analysis seems to demonstrate that in rats there are

"profound" differences in white adipose tissue response between the sexes. While physical training benefits rats of both sexes, only male rats respond to exercise by losing white adipose tissue. In female rats, exercise prevents them from gaining fat mass.

Such narrowly focused investigations use the MoTrPAC dataset to look for insights on how exercise affects individual tissues or specific biological processes.

One MoTrPAC investigation underway, for instance, looks at how exercise affects gene transcription. That's the process of copying information from a strand of DNA onto a molecule called messenger RNA (mRNA), which relays genetic information to the areas of cells where proteins are made. Another example of research in progress deals with the impact of exercise on mitochondrial response. Mitochondria, present in mammalian cells, regulate energy production and stress response.

Every smaller study based on separate facets of MoTrPAC data, said Adkins, "is one piece of a greater vision." That vision is the consortium's: to map the body's molecular changes after exercise.

More information: Temporal dynamics of the multi-omic response to endurance exercise training, *Nature* (2024). DOI: 10.1038/s41586-023-06877-w

Provided by Pacific Northwest National Laboratory