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EDITORIAL

Exercise as metabolic medicine: Movement counters diet-induced behavioral despair via gut-brain signaling

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Nowadays, ultra-processed foods that are high in energy are cheaper, more delicious, and more easily available than ever before in human history, as more screens become available and sedentary time increases. At the same time, depression and anxiety are prevalent, enduring, and costly. It is a biological overlap that is manifesting at a macro level, not just a coincidence of modern-day life. If you want to see how these forces interact, check out this preclinical study, which examines the effects of cafeteria food on exercise, behavioral change, hormones, neurogenesis, and changes in gut-derived metabolites.

In their study, "Exercise mitigates the effects of a cafeteria diet on antidepressant-like behaviour associated with plasma and microbial metabolites in adult male rats," published in this issue of *Brain Medicine*, Nota *et al.* provide a detailed, multidimensional view of how lifestyle factors interact (1). Adult male Sprague-Dawley rats at approximately 9 weeks of age were fed either standard chow or a rotating "cafeteria" menu high in saturated fat and sugar. Half of each group had access to a running wheel. Rats were tested for antidepressant-like and anxiety behaviour (forced swim test, elevated plus maze, novelty-suppressed feeding), cognition (spontaneous location recognition, novel object recognition, Morris water maze), adult hippocampal neurogenesis (2), circulating metabolic hormones: insulin, leptin, GLP-1, PYY, FGF-21, ghrelin, C-peptide, glucagon, and an untargeted caecal metabolome panel.

The title is easy to understand and must be stressed: exercise counteracts the cafeteria diet's increase in immobility in the forced swim test. Running pushed behavior in an antidepressant-like direction (reduced immobility in the forced swim test) with junk-style food aboard. This is not a trivial observation. The brain remains responsive to behavioral interventions that we can provide to almost anyone at almost any time, even under adverse dietary conditions.

There is more. Exercise eased anxiety in a conflict-sensitive test. This test was latency to eat in a novelty-suppressed feeding paradigm. The exercised rats also had better spatial learning in the Morris water maze.

On the endocrine front, voluntary running reduced the increases in insulin and leptin caused by cafeteria diets, while increasing GLP-1 and PYY (though with some diet-specific nuances). The cafeteria diet significantly altered the caecal metabolome in the gut, whereas exercise reinstated the abundance of three metabolites that the diet had lowered: anserine, indole-3-carboxylate, and deoxyinosine.

Finally, a different neurogenesis story can provoke great interest: exercise increased doublecortin (DCX)-positive immature neurons in chow-fed rats, but a cafeteria diet blunted that pro-neurogenic effect. It appears that diet quality can influence the functioning of brain neurons during exercise.

When you piece everything together, it depicts what clinicians know

Exercise induces antidepressant-like behavioral effects, even when food is working against us. Exercise supports the metabolic milieu and the gut's metabolome. One route we focus on regarding brain plasticity is adult hippocampal neurogenesis, which appears to be less resilient if your diet is highly processed (3). How can we implement lifestyle prescriptions that are compatible with each other's biology?

The clear signals and the necessary caveats

The cognitive results warrant a measured interpretation, as the effects were modest and mixed in their statistical significance. While exercise improved spatial learning during Morris water maze training (with a significant time-exercise interaction), the probe trial outcomes were less compelling, with only search latency showing clear changes. Pattern separation and recognition memory tasks revealed primarily trends rather than robust effects. This is not a weakness of the study; instead, it provides valuable data showing that an adult-onset cafeteria diet and voluntary exercise do not significantly impact cognitive performance over seven weeks.

The cognitive resilience of adult rats to these interventions contrasts with the more pronounced effects typically seen when similar manipulations begin during adolescence or extend over longer periods (3).

The findings on neurogenesis are the most interesting and significant. We have become very comfortable with a story in which exercise reliably increases adult hippocampal neurogenesis, which in turn leads to improved pattern separation and stress resilience. Here, that is true on standard chow. However, with the cafeteria diet, the DCX increase is blunted. This does not question the exercise-neurogenesis-mood link but refines it in a manner with clinical implications (4). In other words, the condition of the diet may lessen the cellular response we hope exercise will prompt. If you want to use exercise to "rejuvenate" hippocampal plasticity, the surrounding metabolic context matters.

In terms of hormones, the outcomes match up well with clinical experience. A cafeteria diet caused increases in insulin and leptin; exercise attenuated both. This is precisely what we often see in the case of humans who may have diet-induced insulin resistance in response to adiposity. When they increase mobility signals from the periphery, they often normalize before weight changes do. Exercise can increase GLP-1, but this effect is blunted when a cafeteria diet is used. This may be linked to the finding of enhanced neurogenesis, as GLP-1 receptors are known to increase AHN (5). In the cafeteria-diet cohort, exercise increased PYY levels, which possibly contributed to the observed effect. No single hormone explains any behavior, but together they outline a shift in hormonal context, with moderation in amplitude by nutrition, for better central signaling.

The metabolomics data are where this paper opens a door. The cafeteria diet altered the metabolite landscape of the caecum, as amino acid metabolism, tRNA biosynthesis, and the tryptophan pathway were prominent. Exercise did not reverse everything. In fact, exercise appears to only buffer a few key molecules important for the brain, which include the following. Anserine is a histidine-containing dipeptide that has both antioxidant and neuroprotective properties (6). Indole-3-carboxylate is an indole derivative that sits in the broader tryptophan–indole–AhR

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Figure 1. The metabolic tug-of-war: Exercise versus ultra-processed diet. Voluntary exercise exerts an antidepressant-like behavioral effect and attenuates metabolic dysregulation in rats fed a cafeteria diet. However, diet quality still significantly influences the neuroplasticity response, highlighting the complex interplay between movement and nutrition in brain health. Image Credits: Left panel from Grok XAI; Right panel satyrenko via Depositphotos.

signalling pathway (7). Deoxyinosine is a purine nucleoside with documented links to stress physiology (8). Importantly, the authors do not overclaim. None of these metabolites could predict the behaviour across conditions. Cytosine and other caecal compounds were the stronger correlates of immobility and 5-hydroxyindole-3-acetic acid, 1-phenylethyl acetate, and 4-vinylguaiacol. 2-aminopimelic/aminoadipic acid was negatively correlated with the MSLR cognitive measure. That is precisely what we should expect from a real biological system: many small pushes and pulls, a set of mechanistically tempting candidates, and a web where diet and exercise change the baseline on which those metabolites act.

Just because two things look alike does not mean they are. However, they connect behavioral readouts to measurable molecules in the gut that are modifiable by the two most scalable interventions we have: diet and exercise. That is the start of an actionable biomarker story.

Where does this relate to the clinic?

Clinicians do not treat rats, but we do treat analogous biological processes. Several practical messages emerge.

Exercise has an antidepressant-like effect in the "wrong" dietary context, which is good news for those who have trouble changing their diet. We can say that moving your body helps your brain, even if your diet is not perfect (9). This is particularly applicable in the context of depression, whereby exercise has demonstrated antidepressant effects comparable to first-line treatments such as medications and therapy (10), even with the potential to reduce suicide attempts (11, 12), yet remains significantly underprescribed (12). Although those with depression typically have a poor diet (13), this should not be seen as a barrier to the prescription of antidepressant effects of exercise (14).

Diet quality matters for brain plasticity. When we prescribe exercise, one of our hopes is that it will lead to hippocampal neurogenesis. A heavily processed, high-fat/high-sugar/high microplastic diet may blunt the cellular response (15). This does not mean deferring exercise until the diet is fixed, but rather to frame exercise and diet as partners, not substitutes. Similar to exercise, diet has demonstrated significant associations with depression (16). Particularly, people who consume more ultra-processed foods had a 22% higher risk of incident depression, and those who adhere to a nutrient-dense diet were 30% less likely to have features of depression (17). Beyond this, randomized controlled trials involving people with depression have demonstrated moderate-to-large improvements for those receiving a Mediterranean diet (18). Although most studies have analyzed the Mediterranean diet in relation to depression, there is no single superior diet; any dietary pattern that emphasizes nutrient-dense foods, tailored to individual patient preferences, may be beneficial (19).

Metabolic health is closely tied to mental health (20). Normalization of insulin and leptin levels is associated with improved behavior. On the contrary, insulin resistance is associated with a doubled risk of depression (21). When we help our cells resist insulin, it seems to fix our moods and cognition. It is a reminder to continue screening for metabolic dysfunction in psychiatric care and to take it seriously when we find it.

The gut is not a spectator. Changes in the caecal metabolome (tryptophan derivatives, amino acid catabolites, and dipeptides) are similar to those observed in humans. This similarity provides evidence that gut microbiome-derived metabolites are related to depression and cognitive performance (22, 23). Although we are still sifting through the true mechanism from noise, the broad signal is consistent: the microbiota–gut–brain axis is a lever that plays a crucial role in developing new treatment strategies.

What to build next

The artifacts generated by a good preclinical study should create better questions than it started with. Here are a few that this paper puts squarely on the table.

Do female and older animals behave the same way? Neurogenesis, metabolism, and microbiota composition are influenced by sex and age. Like other studies, this research focuses on males who have reached adulthood. We should now reproduce these efforts with women and test middle-aged and elderly cohorts.

What is the time course and dose response? A reasonable window is seven to eight weeks, but the benefits of diet and exercise accumulate over months, years, or even a lifetime. More prolonged exposure may amplify cognitive effects and neurogenesis. It will also refine metabolite signatures.

Can we restore the neurogenesis response through dietary adjustments? Does targeted dietary improvement (high-fibre intake, availability of tryptophan, low sucrose) restore the pro-neurogenic effect of exercise if a cafeteria diet blunts it? GLP-1 receptor agonists and PYY analogues are now widely used in the clinic; do they induce a normal neurogenesis response on faulty diets?

Which metabolic changes are causal to the interaction between exercise and diet? The paper offers testable candidates such as anserine or indole-3-carboxylate. Efficiently altering aminoadipic acid pathways or 5-hydroxyindoleacetic acid (5-HIAA) in the caecum may also offer insights into causality by providing some behavioural and neurogenic consequences.

How do we translate to humans? The hormones correlate, but the behavioral assays do not. Insulin, leptin, GLP-1, and PYY can be measured before and after supervised exercise in individuals consuming high-sugar/high-fat diets. New non-intrusive ways to measure brain networks through high-resolution fMRI of the dentate gyrus/CA3 combined with cognitive testing may go along with stool metabolomics.

A note on nuance

One approach might be to rephrase a complicated finding into a snappy phrase, such as 'exercise fixes junk food.' The evidence suggests a more subtle and more hopeful one. Exercise induced an antidepressant-like behavioural effect despite junk food. Yes, the quality of a person's diet does impact their brain's deeper plasticity response. There are both unidirectional and bidirectional communication patterns between the gut and the brain.

That nuanced view mirrors people's lived experience. Patients often start moving before they can change their diet. When they feel better, diet becomes more approachable. Increased sleep and less despair lead to a person making a better breakfast. By accepting that the effect size unambiguously depends on the biology, we can design achievable treatment sequences: start with what is doable (walking, stationary cycling, light resistance), stack modest dietary improvements, and let the physiology turn in your favour. We can measure insulin and leptin, not as shaming yardsticks but as early indications that the body is responding.

Why this matters for brain medicine

Psychiatrists and neurologists have long recognized that the brain does not function in isolation. What this paper adds is specificity. The authors show changes in insulin, leptin, GLP-1, and PYY in response to diet and linked them to the antidepressant-like effects of exercise. They showed that a cafeteria diet can suppress hippocampal neurogenesis (new neuron formation), which is elevated after exercise. Finally, they demonstrated that gut metabolites, both endogenous and diet-driven, correlate with behavioral variations. That is work worth chasing. The framework of translational lifestyle psychiatry consists of mechanistic, measurable, and, hence, improvable prescriptions, rather than fuzzy advisories to "eat better and move more."

There is, finally, an ethical dimension. When provided without tools, follow-up, or respect for circumstance, lifestyle change can sound moralizing (24). A paper like this helps us do better. It helps us tell a struggling patient: "Your walks are currently helping you for at least three biological reasons. Your insulin and leptin levels are declining, while your gut generates various compounds, and your brain's mood circuits stabilize. We can make that effect bigger by changing some food, and we will track the biology with you." That is not blame. That is a partnership grounded in physiology.

The take-home

Exercise had an antidepressant-like behavioural effect in adult male rats fed a cafeteria diet. It also produced modest anxiety-reducing effects and cognitive effects.

Exercise has a positive effect on metabolic hormones. GLP-1 and PYY levels increased, whereas insulin and leptin levels decreased. The cafeteria diet blunted some of those gains.

Increased exercise enhanced adult hippocampal neurogenesis; however, this effect was only observed when rats were fed a healthy diet and not a cafeteria diet, suggesting that diet quality can gate plasticity.

The profiles of the caecal metabolome shifted significantly with the diet and selectively with exercise. A handful of metabolites were rescued by running. They include anserine, indole-3-carboxylate and deoxyinosine. Similarly, many other metabolites correlated with behaviour under both conditions.

This is preclinical work, and it should be read as such. However, it conveys a simple yet durable message: the brain remains trainable under metabolic duress; it is possible to be plastic; the gut keeps score; and diet quality moderates the yield of exercise. At the clinic, that means a humane order: help people move first, support metabolic health early on, nudge diet quality up a notch, and monitor their biology when possible. The rest is steady work and time.

Julio Licinio[1], Ma-Li Wong[2], and Nicholas Fabiano[3]
[1]Editor-in-Chief, Genomic Press, New York, New York 10036, USA; [2]Genomic Press, New York, New York 10036, USA; [3]Department of Psychiatry, University of Ottawa, Ottawa, Ontario K1H 8M5, Canada
✉ *e-mail: julio.licinio@genomicpress.com*

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