A microbiome-dependent neuronal pathway regulates the motivation for exercise in mice

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Funded by Grants for Faculty Mentoring Undergraduate Research

Abstract

Exercise exerts a wide range of beneficial effects for healthy physiology, and the sedentary lifestyle of modern human societies is associated with several major diseases. However, the mechanisms regulating an individual's motivation to engage in physical activity remain incompletely understood. An important factor stimulating the engagement in both competitive and recreational exercise is the motivating pleasure derived from prolonged physical activity, colloquially referred to as the "runner's high", which is triggered by exercise-induced release of neurotransmitters. Here, we report on the discovery of a connection between the intestinal microbiome, endocannabinoid metabolites, afferent sensory neurons, and the ventral striatum that enhances exercise performance by augmenting physical activity-induced dopamine signaling. Microbiome-dependent production of fatty acid amides in the gut stimulates the activity of Trpv1-expressing neurons and thereby elevates dopamine levels in the nucleus accumbens during physical activity. Consequently, microbiome depletion, ablation of sensory neurons, endocannabinoid receptor inhibition, or dopamine blockade abrogate exercise performance. These findings indicate that the rewarding properties of exercise are influenced by gut-derived interoceptive circuits and provide a microbiome-dependent explanation for inter-individual variability in exercise performance. Our study also suggests that interoceptomimetic molecules that stimulate the transmission of gut-derived signals to the brain may enhance the motivation for exercise.

Introduction

Apart from muscle function, a major contributor to exercise performance is the motivational state[1-2]. A brain region critically involved in motivated behavior as well as the initiation of physical activity is the striatum[3-4]. To explore the impact of the microbiome on the striatal response to exercise, we performed single-nucleus RNA-sequencing of the striatum of antibiotics-treated mice and controls before and after treadmill exercise.

Given that striatal medium spiny neurons are controlled by dopamine, which is a critical regulator of the drive for physical activity[5-6], we next measured striatal dopamine levels in microbiome-depleted mice. Expectedly, striatal dopamine levels were increased after exercise.

Remarkably, striatal expression of *Maoa* was suppressed in exercising mice, which did not occur in the absence of the gut microbiome (**Fig. 1d**). We thus hypothesized that sustained MAO levels are responsible for the blunted dopamine response to exercise in microbiome-depleted mice, and that blockade of MAO would normalize dopamine signaling.

Given that Trpv1 is broadly expressed by sensory neurons, we sought to determine whether spinal and vagal afferents were the primary mediator of the microbiome impact on exercise. To this end, we examined dorsal root ganglia (DRGs) and nodose ganglia (NGs) from exercising mice. We noted that treadmill running induced neuronal activity, as indicated by cFos, in Trpv1^{+} neurons

Results

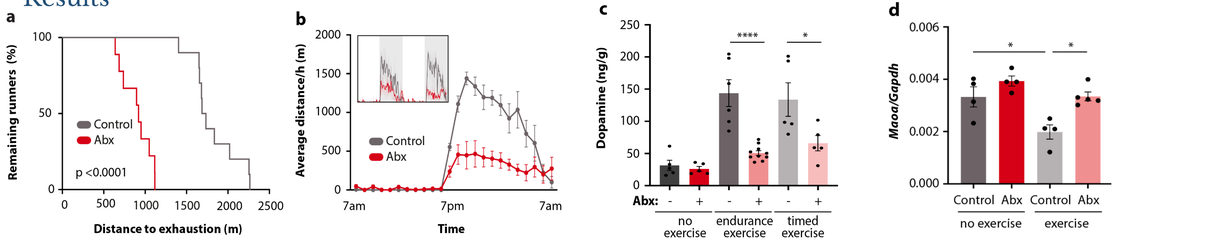

Fig.1 a) Kaplan-Meier plot of distance on treadmill of broad-spectrum antibiotics (Abx)-treated mice and controls. b) Averaged hourly distance of voluntary wheel activity of Abx mice and controls. Inset shows representative recording traces. c) Dopamine levels in the brains of Abx-treated mice and controls, at steady-state, after exhaustion from endurance exercise, and after 60 minutes of timed exercise. d) Expression of Maoa in the striatum before and after exercise in control and Abx-treated mice

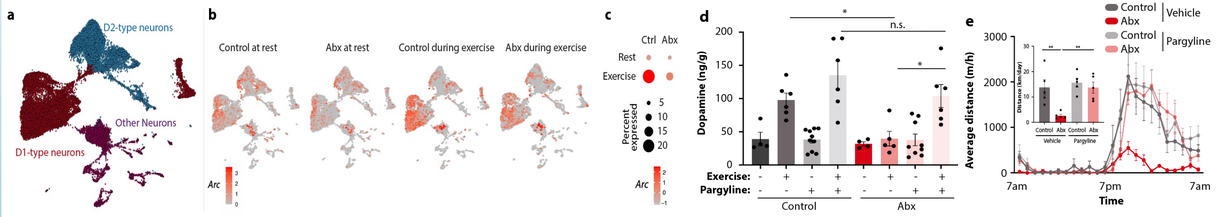

Fig. 2 a) UMAP plot of neurons from single-nucleus RNA-seq of the striata of control and Abx-treated mice before and during exercise. b) UMAP plots and quantification (c) of Arc expression in striatal neurons from control and Abx-treated mice before and during exercise. d) Dopamine levels in the brain of Abx-treated and control mice, both steady state and post-exercise, injected i.p. with vehicle or the MAO inhibitor pargyline. e) Quantification of voluntary wheel activity of Abx-treated mice injected with the MAO inhibitor pargyline

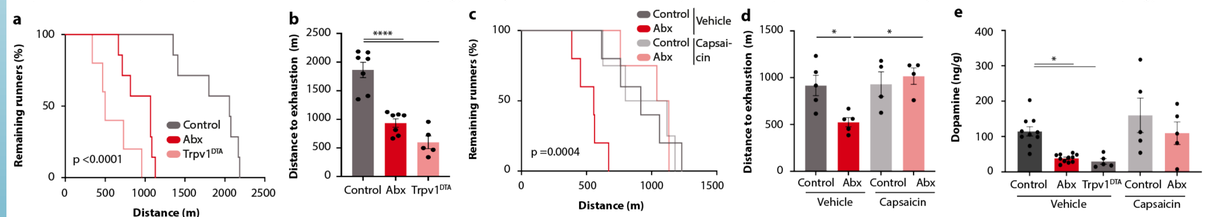

Fig. 3 a) Kaplan-Meier plot and b) quantification of distance on treadmill of controls, Abx-treated mice and Trpv1DTA mice. c) Kaplan-Meier plot and d) quantification of treadmill distance of Abx-treated mice and controls, with or without capsaicin treatment. e) Dopamine levels in the brain of control mice, Abx-treated mice, and Trpv1DTA mice, with or without capsaicin treatment.

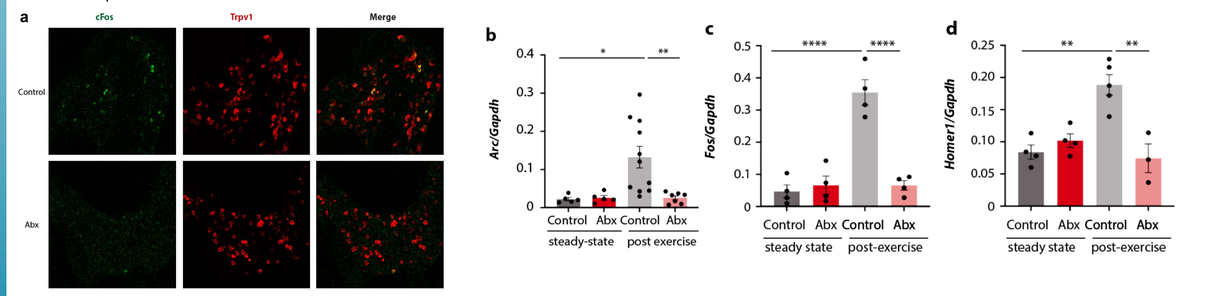

Fig. 4 a) Representative RNAScope images of dorsal root and nodose ganglia before and after exercise, with and without Abx treatment. b) Expression of Arc in the dorsal root ganglia of sedentary and post-exercise mice, with or without Abx treatment. c) Expression of Fos (d) and Homer1 in the dorsal root ganglia of sedentary and post-exercise mice, with or without Abx treatment.

Error bars indicate means ± SEM. One-way ANOVA with multiple comparison test; * p <0.05, ** p <0.01, *** p <0.001, **** p <0.0001.

Conclusion

First, we investigated that the neurochemical effects mediating the "runner's high" – the phenomenon of pleasure, reward, anxiolysis and analgesia associated with prolonged physical activity – can be influenced microbiome in the gastrointestinal tract.

Second, these results show neuronal link between the gut and the striatum, by demonstrating that their activity is enhanced by exercise. This impact of exercise depends on intestinal metabolites produced largely by microbiota, and that exercise-induced activity of spinal sensory neurons is critically involved in the regulation of striatal dopamine signaling through the downstream regulation of MAO.

Finally, our study provides a mechanistic basis for understanding inter-individual variability in exercise motivation and performance. Specifically, we demonstrate that mesolimbic dopamine-dependent reward and motivation circuits can be modulated via an interoceptive pathway that originates in the gastrointestinal tract.

Our findings suggest that interoceptomimetics that stimulate the motivation for exercise might present a powerful opportunity to counteract the detrimental health impact of a sedentary lifestyle.

Acknowledgements

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