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Corresponding letter

Reply to "Is physical performance (in mice) increased by *Veillonella atypica* or decreased by *Lactobacillus bulgaricus*?"

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Dear editor,

In a recent longitudinal metagenomic study of the gut microbiome in elite athletes,[1] we conducted multiple, repeated sampling from runners in the 2015 Boston Marathon as well as sedentary controls approximately 1 week prior to and 1 week after marathon day. We also analyzed an independent cohort of endurance athletes, including Olympic-caliber rowers, marathoners, and ultramarathoners, all in a longitudinal fashion, obtaining stool samples before and after intense exercise sessions. Across the athlete cohorts, we identified a significant increase in the relative abundance (i.e., relative DNA copy number) of genes belonging to the methylmalonyl-coenzyme A (CoA) pathway after exercise, suggestive of a "bloom" in the metabolic capacity of the gut microbiome for metabolism of muscle-derived L-lactate into the short-chain fatty acids (SCFAs) acetate and propionate. This metabolic phenomenon was correlated with increased relative abundance of the bacterial genus *Veillonella* species, which is relatively unusual among human gut microbes in its ability to metabolize L-lactate into propionate. We also observed that *Veillonella* was increased in abundance in athletes pre-exercise relative to sedentary controls. Notably, a previous study identified a higher abundance of the family *Veillonellaceae* in the gut microbiome of cyclists relative to both low body mass index and high body mass index control individuals, though approximately 11 other bacterial families were similarly correlated.[2] Following the gavage of an athlete-derived isolate of *Veillonella atypica* (*V. atypica*) in a 2-week, 3-day per week crossover study, we observed that mice exhibited increased treadmill runtime-to-exhaustion in a randomized crossover study relative to yogurt-derived *Lactobacillus bulgaricus* (*L. bulgaricus*). Further, we observed that systemic lactate penetrates into the intestinal lumen and that intrarectal delivery of propionate relative to pH-matched SCFAs phosphate buffered saline similarly resulted in increased treadmill endurance ability, suggesting that the effect observed with *V. atypica* gavage could be accounted for by a lactate and *Veillonella*-dependent increase in propionate. Interestingly, around the time our work was published, multiple independent groups reported that the microbiota-dependent increase of serum SCFAs results in increased treadmill runtime-to-exhaustion.[3,4] Taken together, this study introduces multiple lines of evidence supportive of the hypothesis that the mammalian gut microbiome may provide its host an extra boost in endurance running ability via the metabolism of muscle-derived lactate into propionate. Further, because *Veillonellaceae* has been observed to be increased in athletes relative to sedentary controls in multiple independent human studies, this raises the possibility these microbes have an adaptive advantage in the guts of athletes by capitalizing on a unique metabolic niche: L-lactate metabolism. It may be possible that this results in a positive feedback loop, reinforcing exercise in, perhaps, some small capacity. In other words, because repeated exercise behavior is expected to result in increased gut L-lactate concentrations and the expansion of a metabolic niche for L-lactate metabolizers, these L-lactate metabolizers are, in turn, expected to promote the production of the exercise-enhancing molecule propionate, thus potentially further increasing exercise behavior.

In an associated Commentary in this issue of the *Journal of Sport and Health Science*, Fernández-Sanjurjo et al.[5] report a new study of progressive treadmill endurance training in C57BL/6N male mice consisting of 4 weeks of 5-day per week running. Importantly, they report a significant increase in α-diversity (Shannon Index) of mice following this training program. This is an important result because it has previously been shown that low exercise capacity and frailty in elderly people is associated with a low-diversity microbiome[6] and that mice treated with an antibiotic cocktail (resulting in low α-diversity) exhibited decreased exercise capacity.[3,4] Therefore, this new result is consistent with and extends the previous literature, demonstrating that an intensive training program is sufficient to drive increased gut microbiome diversity.

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The authors further observe that there is no significant change in the abundance of the family *Veillonellaceae* in these mice, nor do we expect there would be, as this family is quite heterogeneous and the genus *Veillonella* is a human symbiont that is generally not present in laboratory mice. The species *V. atypica* is particularly unusual among *Veillonella* in its carriage of the full complement of genes encoding the methylmalonyl-CoA pathway.[1] The authors do not explicitly state so, but neither this species nor any other *Veillonella* species is likely to be present in any of the mice in the study. Although there is much focus on potential trends observed in the genus *Lactobacillus* in the Commentary,[5] the authors do not find a significant difference in this microbe or any other particular microbe, so it is not prudent to speculate on biological insights therein.

The authors raise the point that an alternative interpretation of the crossover animal treadmill experiment in our study is that perhaps *V. atypica* did not provide an improvement to runtime as much as the negative control, *L. bulgaricus*, negatively impacted runtime. So, although our data clearly demonstrate that *V. atypica* outperforms *L. bulgaricus*, the question becomes what other controls can *V. atypica* outperform? A genetic mutant, of course, would be ideal, but *V. atypica* exhibits very poor growth in the absence of lactate, so the comparison to a lactate-metabolism-deficient mutant would not work well, and it is not obvious what other mutants may be viable alternatives. Fernández-Sanjurjo et al.[5] suggest, in their Commentary, that a vehicle control could work, which presumably would be bacterial growth media. But this vehicle control would contain nutrients that may directly impact running performance, and it would also not control for the 1 billion live bacterial cells present in the positive control, so again, such a control would not provide interpretable results.

Turning back to the bigger picture, *L. bulgaricus* was chosen as a control precisely because it is a lactate producer rather than utilizer, which allowed us to test head-to-head the outcome on running ability of gut microbial lactate anabolism *vs.* catabolism dynamics in mice. Understanding these underlying molecular mechanisms, which are generalizable, is of much greater value than the specific impacts of any particular microbial species. The novelty of our study was the concept that a major biochemical end-product of exercise, lactate, accumulates in the gut lumen and serves as a substrate for microbial metabolism into SCFAs propionate, and that colonic propionate alone can increase running duration.

Competing interests

The author has no competing interests, meanwhile, he is a cofounder of FitBiomics Inc., and holds equity in the company. The FitBiomics had no involvement in the study design and writing of the manuscript or the decision to submit it for publication.

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