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Alimentary Tract

Exercise has the guts: How physical activity may positively modulate gut microbiota in chronic and immune-based diseases

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ABSTRACT

Limited animal and human research findings suggests that exercise might have a beneficial role for health gut. Cardiorespiratory fitness correlates with health-associated gut parameters such as taxonomic diversity and richness. Physical exercise may augment intestinal microbial diversity through several mechanisms including promotion of an anti-inflammatory state. Disease-associated microbial functions were linked to distinct taxa in previous studies of familial type 1 diabetes mellitus (T1D). An integrated multi-approach in the study of T1D, including physical exercise, is advocated. The present review explores how exercise might modulate gut microbiota and microbiome characteristics in chronic and immune-based diseases, given the demonstrated relationship between gut function and human health.

1. Background | the multiform protection offered by physical exercise to health

Nowadays, the appeal of practicing regular physical activity has become redundant as multiple international agencies advocate for the protective, curative, and revertive effects of exercise in a myriad of metabolic and psychological disturbances [1,2].

Increasing physical activity emerges as a mandatory forefront to abate the burden associated with longevity and expanded life expectancy of present days. In fact, exercise covers a broad spectrum of health benefits, from boosting mental wellness by enhancing mood states and neuroplasticity via augmented brain-derived neurotrophic factors (BDNF) levels [3], to help preventing excess weight gain or maintaining weight loss [1,4–6], mastering a cascade of favorable events in the metabolic equilibrium of the human body. A substantial number of both cross-sectional and longitudinal studies have indicated that regular physical exercise exerts diversified anti-inflammatory actions [7,8]. An exercise-mediated organ crosstalk orchestrates a pattern leading to the increase of anti-inflammatory cytokines, and/or the decreasing of pro-inflammatory cytokines. In contracting muscles, myokines play a major role in lowering markers of chronic inflammation and protecting against accumulation of abdominal fat [7]. Particularly, muscle-derived interleukin (IL)-6 has been recognized as a pleiotropic myokine in the modulation of immuno- and inflammatory metabolism: it inhibits tumor necrosis factor (TNF) production [9] and stimulates, at the same time, the release of the anti-inflammatory cytokines IL-1ra and IL-10 [10,11]. Furthermore, IL-6 mediates the release of cortisol from adrenal gland and it may have systemic effects on the liver and adipose tissue [12]. IL-6 increases insulin secretion by upregulating glucagon-like peptide 1 (GLP-1) [13]. It increases insulin-stimulated glucose uptake both in skeletal muscle and adipose tissue and, in fact, IL-6 stimulates, through the activation of AMPK, both lypolisis and fat oxidation, peripherally and whole-body [14,15].

Regular and adequate levels of physical activity protect against all-cause mortality: the World Health Organization (WHO) ranked physical inactivity as the fourth leading risk factor for global mortality, i.e. 6% of deaths globally [16]. It has been estimated that 21–25% of breast and colon cancers, 27% of diabetes, and approximately 30% of ischaemic heart disease burden can be attributed to physical inactivity. Exercise training has been clinically proven, cost-effective, in the treatment and cure of several of these diseases [17]. Certainly, exercise enables these extraordinarily beneficial actions by affecting energy balance and by lowering atherogenic profiles [18]. Nevertheless, alternative and novel explanations covered by exercise are gaining momentum in the current literature.

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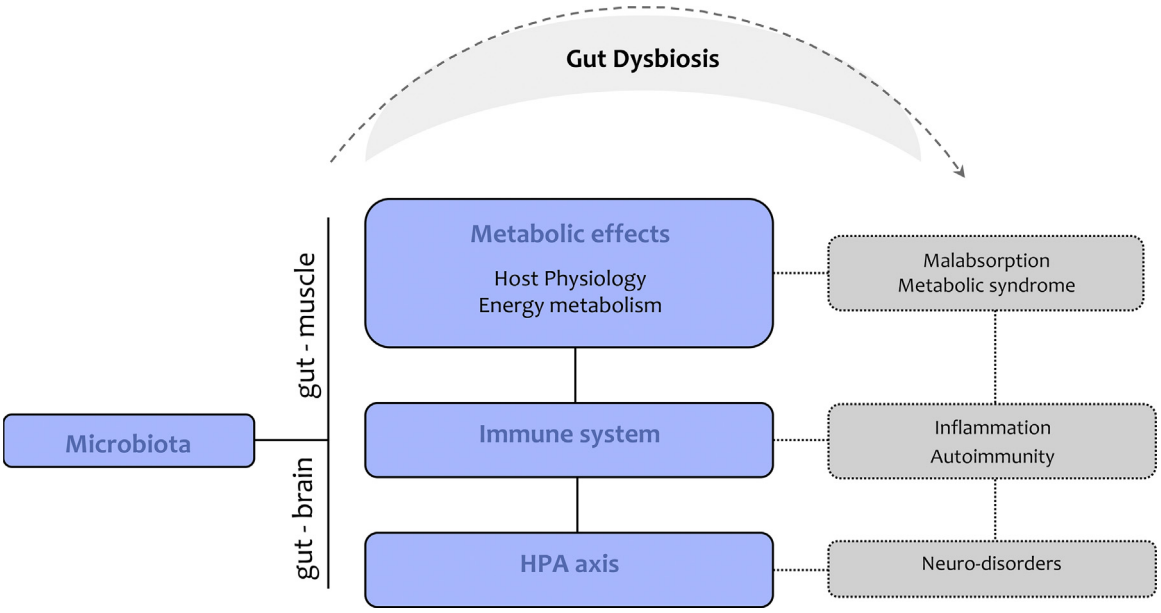

Fig. 1. Flow-chart of microbiota fuctions, interactions, and imbalances.
Gut microbiota functions are indicated in light blue, interactions by vertical lines, whereas disruptions are depicted in grey as a result of gut dysbiosis (dashed lines).

One of these hypotheses is related to a favorable modification of the human gut microbiota in health and disease.

2. Materials and methods

2.1. Literature search strategy

A systematic literature search was carried out in the Cochrane Library and MEDLINE databases for studies published in English (2000 January to 2017 September) combining the terms "gut microbiota", "gut microbiome", "exercise", "training", "physical fitness", "physical activity", "diabetes", "type 1 diabetes". We examined reference lists in original articles, reviews, trials. Study search was performed both electronically and by following up references quoted in relevant paper. Case reports, expert opinions, were excluded.

2.2. Study selection

The articles were extracted and read, and relative findings were classified by: (i) gut microbiota functions interacting with metabolism, immune system, hypothalamic-pituitary-adrenal (HPA)-axis; (ii) exercise effects on gut microbiota in different models; (iii) how exercise-interventions modulating microbiota might be therapeutically exploited to promote health.

Periods of data collections ranged from 2000 and 2017, obtaining data from human and animal models (mice, rats). A synoptic table of the relevant studies analyzed is offered (Table 1).

3. Gut microbiota: the overcalled card

The gastrointestinal tract (GIT) is inhabited by trillions of microorganisms – approximately a hundred – composing the human gut microbiota [19,20]. By including roughly 9 million genes [21], this environment represents the human gut microbiome: a gene set 150 times larger than that of the human genome [22,23]. Gut bacteria composition may be influenced by both endogenous and exogenous stimuli. The type of birth (Caesarian versus vaginalis) and lactation (formula versus breast feeding) may differentiate the gut bacterial population during infancy. During childhood, gut microbiota assumes the composition of adulthood, comprising 5 phyla and 160 species in the large intestine [24], weighing up to 2 kg [25]. In the microbial community of the human intestine, the dominant bacterial phyla are the *Firmicutes* (~60%) and *Bacteriodetes* (~20%) whereas *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia* are in relatively low abundance [26]. Although genetic, epigenetic, and environmental factors may uniquely influence the community composition, one third of the adult gut microbiota is similar within most individuals [22]. Physical activity, diet, antibiotics, gender, genetics, age, ethnicity, health and diseases might characterize distinctively the human gut bacterial population.

Gut microbiota has been increasingly advocated because of its various functions (Fig. 1). The possibility to manipulate the microbiota, on different fronts, for improving health outcomes, is being attractive. Primarily, the microbial communities contribute to the host's health through the fermentation of indigestible nutrients in the large intestine. The main products of the bacterial fermentation of carbohydrates and proteins, under anaerobic conditions of the large intestine, are short chain fatty acids (SCFAs). SCFAs such as acetate, propionate, butyrate, are secreted in the gut lumen (Fig. 2), and their signaling to the multiple gut receptors (free fatty acid receptor 2–3, FFAR2, FFAR3) are implicated in the control of anorectic hormones — like peptide YY (PYY) [27] and GLP-1 [28]. Also, SCFAs promote the release of serotonine (5-hydroxytryptamine, 5-HT) [29], an aminoacid key regulator of GIT motility and secretion (Fig. 2). Altogether, this involvement suggested a role of microbiota in the gut-brain axis, and appetite control. Furthermore, butyrate has been evoked for anticancer effects, anti-inflammatory properties and energy expenditure [30,31].

The gut microbiota harbours clusters of bacteria that are either innocuous, symbiotic, or potentially pathogens (pathobionts). This means that gut microbiota participates in a fine-tuning balance between both innocuous and harmful bacteria, by cross-talking with all immune system components [19]. The activation of the pattern recognition receptors, like the toll-like receptors (TLRs), is a consolidated mechanism by which the immune system discerns pathogens and non-harming elements [32]. Therefore the microbiota exerts a protective function to avoid GIT colonization by pathogens, via stimulation of the epithelial cell proliferation, and

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