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Microbes, Oxytocin, and Healthful longevity

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Abstract

The microbiome is shown to have important roles in human health. Recent studies in mice show intestinal microbes stimulate host neuropeptide oxytocin and immune physiology in a mind-body paradigm with diverse outputs improved systemic wound-healing capacity. Oxytocin is best known for roles in reproduction and immunity, but is more recently implicated in obesity, human bonding, and trust. Microbial reprogramming of host oxytocin may offer far-reaching benefits in physical, mental, and social health for healthful longevity.

Keywords: Beneficial microbes; Oxytocin; Healthful longevity; Immune tolerance; Wound healing; Symbiotic microbes

Introduction

The potential of the microbiome to optimize mammalian health is only now being recognized [1-4]. In a series of recent manuscripts, Poutahidis et al. has shown that model intestinal micro-organisms may stimulate host hormones and immunity to improve wound-healing capacity [5], inhibit obesity [6], and sustain reproductive functions [7]. Although a microbial pathway to stimulate oxytocin production is without precedent, alliances between gut microbes and CD4+ regulatory T lymphocytes have been shown to influence diverse inflammatory processes including body fat deposition [8]. Indeed, consuming a purified probiotic microbe lowers risk for obesity in human subjects [9]. Substantial indirect support also exists in scientific and epidemiological studies interconnecting microbes with systemic health [1-4,10-22]. Despite enormous potential to improve quality of life, exogenous administrations of pluripotent hormones such as oxytocin conveying wellness have proven difficult. Beneficial microbes may overcome this, and, as a result, have far-reaching potential benefits for human physical, mental, and social health.

Probiotic Microbes Stimulate Beneficial Immune Tolerance

It is widely recognized that alliances between gut microbes and CD4+ regulatory T (Treg) lymphocytes dramatically influence whole body health outcomes [8,11,23-26]. Immune tolerance prevents over-reactivity to self or environmental factors that otherwise elicit an unfavorable inflammatory response. Tolerance is conveyed by a subset of CD4+ lymphocytes, namely Treg cells, which serve to dampen deleterious inflammatory responses. In this way, an increased capacity for immune tolerance helps the body recover after injury, at least in part due to rapid clearance of damaging chronic inflammation in the form of neutrophils and mast cells [6,27]. It was recently found that oral purified probiotic model organism *Lactobacillus reuteri (LR)* supplementation led to complete re-epithelialization of a wound site in half the time needed for untreated controls, in an oxytocin-dependent manner, leaving afterwards only minimal scar tissue [5]. Likewise, feeding of LR induced immune tolerance and reduced mammary cancer burden in mouse models [28]. Parallels between wound healing and cancer are logical, recognizing that 'cancer is a wound that does not heal' [29]. That oxytocin upregulates interferon gamma (IFN-γ) expression with tightly controlled immunity may help explain beneficial roles protecting from cancer [5,30-32].

Substantial mechanistic insight has been gained by the observation that cell transfer of highly purified cells of immune tolerance, CD4+CD25+Foxp3+ Treg cells, were sufficient to recreate the microbe-induced wound-healing boost [5]. Transplantable Treg cells were found to be sufficient ablate age-associated weight gain [6] and cancer burden [28]. In mouse models, the potency of microbe-induced Treg relied upon presence of neuropeptide hormone oxytocin [5]. This suggests that edible microbes may be used prophylactically or therapeutically to induce dramatic hormonal and immune changes within host animals. It is tempting to extrapolate these findings in mice to encompass broader microbial ecology. However, many recent discoveries of microbe-host interactions remain to be proven in human subjects.

Microbes Up-regulate Neuropeptide Hormone Oxytocin with Improved Wound Healing Capacity

Oxytocin is a neuropeptide hormone fundamental in mammalian social bonding and reproduction. In addition to key physiological roles in childbirth and nursing, it is now widely recognized in metabolism, the immune system, plus central nervous system (CNS)-related functions, such as social memory and attachment, sexual behavior, aggression, human bonding and trust, learning ability, creativity, anxiety, feeding behavior, and pain cognition, in both male and female subjects[17-22,30,31,33]. Oxytocin was recently discovered to be integral in microbe-induced immune benefits during the wound healing process by a vagus nerve-mediated pathway [5]. An ability to heal wounds effectively ranges from recovery after minor injuries to diabetes and some types of cancer [2,3,10-12], together contributing to more healthful aging.

Recent discovery that gut microbes may stimulate oxytocin for improved wound healing and healthful longevity [5] builds on a solid foundation of science. Oxytocin was recently shown to reduce debilitating conditions and sarcopenia in aging animals, leading to more robust skeletal musculature [34]. Oxytocin has also recently

gained traction as a pivotal molecule in not only generalized immune system balance and health, but also feelings of social well-being, love, spirituality, and satisfying life experiences. Such fulfilling social bonds are known to improve human wound repair processes [35].

Finally, oxytocin also increases generosity and empathy [17-22], contributing not only to a longer life, but also to the experience of a more meaningful life.

Wound Healing, Oxytocin, and the Mind-body Connection

Human civilization has long postulated psychological wellness and a mind-body connection as the basis for healthful aging. Freedom from diseases throughout life is based upon the host ability to respond efficiently to injury, infectious agents, and social stress, with whole body homeostatic balance resulting in minimal pathology [36-39]. Discovery that beneficial bacteria improve recovery after tissue injury integrates oxytocin and immune tolerance highlights in a mind-body connection (Figure 1) [5]. This is comprised of effects whereby oxytocin reinforces immune tolerance, preventing over-reactivity to self or environmental factors that otherwise elicit an unfavorable inflammatory response. Tolerance is conveyed by a subset of CD4+ lymphocytes, namely T regulatory (Treg) cells, which serve to dampen deleterious inflammatory responses. An increased capacity for immune tolerance in the presence of oxytocin in mice helps to heal their skin wounds, at least in part due to rapid clearance of neutrophils and chronic inflammation [5, 27]. Although this overly simplifies a complicated process, it has been established that oxytocin up-regulates IFN-γ to elicit robust yet tightly regulated immunity integral in good health [5,30-32]. The sum of which is re-epithelialization in half the time needed for untreated controls, leaving afterwards only minimal scar tissue [6].

It's What Mammals are Made of: Symbiotic Microbes, Immune tolerance, and Oxytocin

It is well established that a microbe-hormone connection begins before birth. In eutherian mammals, microbes stimulate immune tolerance via sex steroid hormones, oxytocin, and Interleukin (IL)-10 to sustain a prolonged placental pregnancy [40]. Upon birth oxytocin simultaneously up-regulates IFN-γ and CD25 expression establishing self vs. non-self [30-32]. Later in life, this same oxytocin interchange sustains immune and integumentary homeostasis, biasing the immune system toward IL-10 and IFN-γ, and subsequently minimizing the deleterious systemic effects of IL-6 and IL-17 that hasten morbidity and premature death [6]. Oxytocin also regulates neurotransmitter Gamma-Aminobutyric Acid (GABA) signaling in the central nervous system [41] providing a favorable mood reward [16] for social and gluttary gratification. Emerging data connect oxytocin with obesity, fat metabolism [42,43] [6], musculoskeletal fitness [34] and the immune system [5,30,31,33], establishing its role as a global regulatory hormone.

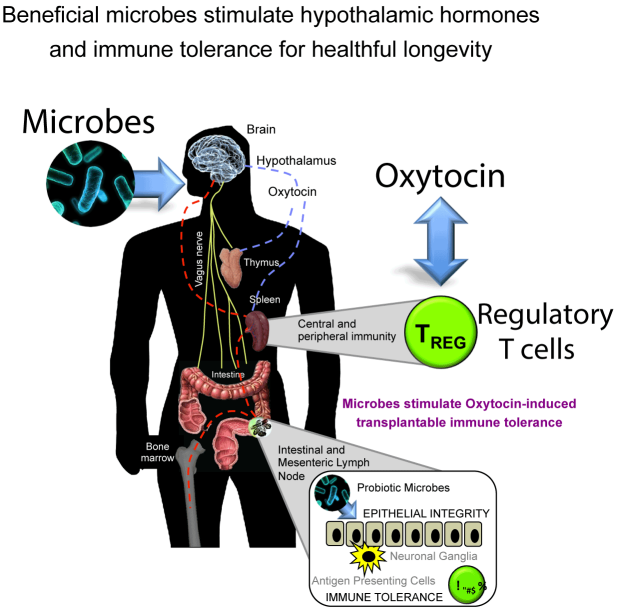

Figure 1: Gut microbes stimulate hormonal and immune signaling for healthful longevity. Healthful aging is generally associated with host ability to respond to tissue damage with efficient homeostatic balance and minimal pathology. Efficient injury repair and lifelong good health are regulated by hypothalamic hormones (e.g., oxytocin) integrated with peripheral endocrine glands (i.e., adrenal cortex, thyroid gland, and gonads) in conjunction with the systemic immune system. Beneficial gut microbes were recently found to stimulate oxytocin that up-regulates Interferon (IFN)-γ and CD25 expression for immune tolerance in a transplantable fashion. Together this prevents over-reactivity to self or environmental factors that otherwise lead to premature death.

These diverse probiotic microbe–induced phenotypes impart perinatal impact that may span generations. Oxytocin, for example, is inversely linked with post-partum depression and maternal neglect in human females [44]. While oxytocin enhances cooperation within kin groups, it promotes aggression towards competitors [45]. These inter-related roles for oxytocin may impact a natural selection process favoring complex social organizations required for mutual evolutionary success. Through actions of microbe-induced hormones such as oxytocin, gut bacteria may influence our desires and identity as human beings. Harnessing microbes for healthful longevity

In adulthood, these micro-organisms stimulate immune tolerance and the hypothalamic-pituitary axis to improve host fitness and lessen impairments of aging. Features typical of superb physical fitness and youth include mucocutaneous hyperacidity and follicular anagenesis [46]. All of this is well reasoned from an evolutionary perspective, in that symbiotic microbes co-evolved with mammals by exploiting host immunity and endocrinology for mutual gain [46,47]. During periods of fertility, immune and hormonal effects of probiotic organisms dominate environmental interfaces and facilitate host survival and reproductive success [46]. Probiotic-enhanced immune tolerance permits prolonged placental pregnancy [40], while hyperacidic mucus inhibits pathogens that otherwise impedes GI tract health, fertilization

and pregnancy. Breaking this natural symbiotic cycle with compulsive social hygiene practices leads to insufficient levels of mucosal IL-10 [24,25], contributing to immune dysregulation with elevated risk for premature death under favorable conditions, these probiotic bacteria are then passed from mother to naïve offspring during vaginal birth and nursing, imparting evolutionary success to both the symbiotic bacteria and their mammalian hosts.

In conclusion, orally administered microbes may lessen impairments of aging and impart healthful resiliency typical of much younger individuals [5,7,46], providing the psychological and physiological cornerstones of healthful longevity. Microbes have been shown in preclinical models to ablate age-associated weight gain [6] and cancer burden [28] that contributes to premature aging. Quantifiable benefits in wound healing capacity directly translate to nearly every aspect of traditional health and medicine [42,48], simultaneously unifying social support networks with improved injury repair for a healthy and meaningful life [49]. In practical terms, this microbe-endocrine-immune linkage has the potential to reduce hospitalizations, improve healing, lower risk for certain cancers, and bestow wellness and active participation in society throughout life. It's unknown with certainty whether findings in animal models will translate directly to human subjects. Nonetheless, peoples around the world have cultivated and consumed similar food-grade organisms in fermented beverages and active yogurt drinks for thousands of years, supporting a low-risk population-based approach for a long, healthy, and meaningful life.

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