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Brain trust

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ABSTRACT

This narrative describes a personal journey that led to the discovery of a profound connection between microbial symbionts and oxytocin. Pivotal oxytocin discoveries began to emerge in 2011 while this researcher's multidisciplinary team explored gut microbial priming of the immune system and perinatal health. Inspired by oxytocin's role in early life events of milk release, neural connections, and social bonding, the team hypothesized a symbiotic relationship between microbes and oxytocin. Scientific experiments demonstrated that specific milk-borne microbes boosted oxytocin levels through a vagus nerve-mediated gut-brain pathway, affecting immune functions and wound healing capacity in the host animal. The exploration then expanded to microbial impacts on reproductive fitness, body weight, and even mental health. Overarching hypotheses envisioned a nurturing symbiosis promoting survival and societal advancement. Ultimately, this oxytocin-mediated partnership between microbes and mammals is portrayed as a harmonious legacy of neurological stability, empathy, and universal wisdom, transcending generations. The author's personal journey underscores the beauty and inspiration found in her scientific exploration.

1. Introduction

I was asked to describe what inspired the discovery of a relationship between microbial symbionts and oxytocin. My goal here is to share enough of myself to inspire future scientists to think boldly and trust their instincts. This is my personal story.

1.1. Childhood adventures revealed clues to better understand the interconnectedness of life

First of all, a bit of introduction to a little girl who was unusually curious and thoughtful. I would describe myself as a kind and gentle kid, as I spent hours every day protecting bugs and other small animals from my insensitive friends or family. I imagined that trees and grasses had feelings, too, and I felt compelled to take care of them. To me, every living thing deserved to be treated with respect and gratitude. Even tiny things in our world were interesting to me, and each revealed clues to better understand our world. My father, an analytical chemist, worked at Bell Labs in a 'think tank'. He was a patient parent who had lots of fanciful ideas and hobbies that he generously shared with his children. I loved his inquisitive perspective. My mom was loving, kind and sensitive, with a career as a medical technologist, but she was more serious and practical than my father. I was thrilled when our family moved from suburbia to a farm to live-off-the-land. Everyday existence felt like a magical adventure to me, wandering endlessly through farm fields and wooded streams. In those years, my public-school education gave me friends with diverse backgrounds, and most classmates went on to become farmers or workers in local factories after graduation. In high school, I was a good athlete who was physically and mentally strong from farm work and had nicknames like "Susie swimmer record breaker" that in retrospect helped me blend in with my classmates. Childhood farm living gave me humility and respect for nature, a resourceful perspective, and a solid work ethic.

1.2. Childhood awe and wonder about the interconnectedness of life led to unique scientific insights

My earliest childhood memories involved wondering about simple things like how people experience colors. Upon learning the label of 'green', as a toddler, I reasoned broadly about life concluding that these color names are simply labels to help people communicate, and that each of us may experience small things such as colors or big things such as life in very different ways. Likewise, a vivid memory from my tween years happened while I was sitting in the grass on a hilltop field with my pet dog and horse. I had a sensation of floating through time and space, seeing different civilizations over thousands of years. From this, I suddenly felt I understood why human societies need organized religions. Entirely through visual imagery, and through my child mind's eye, I

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somehow 'knew' these things had neurophysiological underpinnings. Since then, this concept of life on a vast temporal continuum, available to sample visions at will, has been a recurring event in my oxytocin-enhanced life.

In the years that followed, I've had what many describe as near-death experiences and have seen the so-called Akashic Record. I've spent years of my life thinking about how to make a difference in the world without destroying what we care about most. Sometimes I suffer from analysis paralysis. A quirky and less serious thing about me is my unusually good memory. This was helpful for passing tests during formal schooling, when being outdoors exploring and enjoying nature seemed more interesting to me than studying for exams. Sometimes, I can recall useless details about the day of the week when a particular thing happened, details about the weather or people's clothing - or even pop-culture - involving something that happened decades ago. I mostly use this to entertain friends or re-live beautiful things that have happened in my life.

Nowadays, I would describe my unifying life philosophy as one of reverence for our earth and cosmos, most similar to that of Native American beliefs in the interconnectedness of all living things. This perspective is essentially the same as my musings from childhood described above. My husband and I have during many years of marriage accumulated acres of naturally forested property we've dedicated to a wildlife refuge and land preservation in perpetuity. We've adopted many retired track greyhounds that live in our home. Fundamentally, I believe you-are-what-you-eat, and I teach yoga and other fitness classes with hopes of inspiring others to take good care of themselves and our world.

1.3. A diversity of professional experiences helped develop and test novel hypotheses

In terms of my professional journey, after high school I went to college and veterinary school. These choices were driven by motivations of intellectual curiosity and my hope to do something practical for the well-being of animals. I'm so grateful for my undergraduate mentors from the field of evolutionary biology that further stimulated my insatiable curiosity about the continuum of life. This background continued to influence my research studies at MIT and guides me to this day. My veterinary medical training and later postdoctoral experiences in Comparative Medicine at MIT provided a great foundation to explore scientific and biomedical questions. I did postdoctoral training at Harvard School of Public Health, too. Taken together this was an unlikely career trajectory. I've had the good fortune to have federal and private grant funding and work with a spectacular and synergistic team of scientists at MIT and around the world.

1.4. Coworkers stimulated delightful and multidimensional thinking about science

About the initial discovery linking microbes and oxytocin, the year was 2011. We had an amazing team of people including most notably researchers Tatiana Levkovich, Bernard Varian, Theofilos Poutahidis, Sean Kearney, and Eric Alm. At the time, my R01-funded research lab at MIT had been focusing on perinatal health and early-life microbial priming of the immune system. We'd been working on gut microbiota and the immune system in whole body health for a decade [1], but elsewhere widespread interests in the microbiome were just emerging [2–7]. Our team's chemistry, and diverse veterinary/comparative medicine and microbiology backgrounds stimulated thinking about scientific questions in ways that were both delightful and multidimensional. As a veterinarian, I understood hormone oxytocin in birthing and lactation and was intrigued by its roles in sociability [8]. At home my life was supportive with a loving and tolerant husband, along with six retired track greyhounds.

1.5. Childhood quest to understand interconnectedness of life inspires discovery

Behind the scenes in 2011, I was busily searching for unifying threads to better understand the continuum of life. As a snapshot from May 2011, I had written these flow-of-consciousness musings to a friend, *"The more I think about this … the more I realize this microbe-vertebrate symbiosis is a thing of beauty. Newborns will rapidly be colonized with lots of microbial stuff. It would make sense that events favoring immediate colonization with a probiotic is advantageous during vulnerable infancy. All subsequent microbial exposures for newborns are then chaperoned by probiotics. This concept seems like it would apply to all species. Even those laying eggs. Does nesting mother's skin favor probiotic overgrowth? Is this how milk production evolved from sweat glands? Tapping into some universal concepts that maternal skin secretions favor probiotics in nest and offspring? And simultaneously favor advancement of internal fertilization?"* To put it more simply, I wondered if it's advantageous to protect the host with beneficial microbes when you have delicately balanced internal fertilization or fragile altricial infants.

I went on to write, *"How else could mammals survive the profound immune tolerance needed for placental pregnancy? Following that line of reasoning, the modified sweat glands can coat their eggs (monotremes?) … and - one step further – mammals feed their offspring milk (prototherians and eutherians). In this context, probiotics may usher neonates through the microbially-vulnerable period",* in other words as they transition to life beyond the womb. We envisioned that probiotic microbes protect naive body surfaces and help stimulate healthy immunity in newborns. It is amazing that mammalian breast tissue provides food to support both the infant and their symbiotic microbial passengers. Breast tissue is believed to have evolved from modified skin sweat glands. My reasoning then took this one step further: that oxytocin influenced the secretion of modified sweat glands throughout mammalian evolution, culminating in mammary glands and breast milk, most of these being concepts already supported in the literature [9].

1.6. Early life-centric thinking links oxytocin and microbiota

Clearly in a brainstorming mode, a week later, in June 2011, casually pondering perinatal skin and mucosa that favors probiotics, I wrote, "*is this due to oxytocin? My reasoning goes like this: Oxytocin is a social bonding hormone. Maybe babies have lots of this, too? That would make sense since they need to bond strongly with their mom. That would be very cool with interesting mammalian evolutionary societal implications. This gets better and better! Oxytocin is also involved in milk production and release - an obvious link with mammalian physiology. I definitely need to research that further."*

Continuing on, still in early June 2011, I had written, "*So the more I think about it, the more I like the concept that probiotics and oxytocin collaborate in mammalian evolution. Of course, I've no idea of whether it's supported by data. We need to plan experiments in mice - they won't take long to do.*" Ah, my unwavering optimism shines through. Going on in the same message, I wrote: "*I'm in my home office now – the greyhound 'brain trust' is here with me. Sometimes* (referencing our pet dogs) *Ned, Betty, Zappy and Lady join in, but Julio and Breeze do the intellectual heavy lifting.*" Even today I credit this discovery to the 'brain trust' and the canine muses that helped inspire my bursts of insight and creativity. With an added twist, the expression 'brain trust' also refers to having confidence or trust in one's own reasonings and insights.

1.7. Experiments to test our far-reaching hypotheses about probiotics and oxytocin

In 2011 and 2012, we went on to do those proposed experiments described above to test these putative microbial underpinnings of microbial symbiosis by feeding mice with *Lactobacillus reuteri* previously extracted from human breast milk [10]. We chose *.L. reuteri* as a model

organism representing the concept of an early-life microbial chaperone and symbiont rather than to specifically characterize that specific organism. The concept of a probiotic early-life chaperone is that certain beneficial microorganisms can play a crucial role in shaping the development and health of an individual, particularly during the early stages of life. They can help in the development of a healthy gut microbiota by promoting the growth of beneficial bacteria and inhibiting the overgrowth of potentially harmful ones. At the same time, gut microbiota stimulate beneficial immune system development. Although this isolate of *L. reuteri* came from human milk, a necessary feature to test our overarching hypotheses, it had other features of being tractable in mouse models and growing easily in a benchtop incubator under aerobic or microaerobic conditions. This organism was hardy in drinking water for easy dosing in our animal models. Building upon earlier work of microbiology colleagues Jim Versalovic [6] and John Cryan [7] and oxytocin research pioneers such as Sue Carter [8,11–13] we set out to test our hypotheses. We were thrilled but not entirely surprised to discover a microbe-triggered boost in circulating oxytocin levels by a vagus-nerve-mediated pathway - research that was finally published in 2013 [14]. Other labs later independently repeated these findings, substantiating our earlier discoveries [15,16].

Our initial paper linked microbial symbionts and oxytocin with host immune functions, specifically revealing an oxytocin-dependent aspect to immune system competency during tissue injury repairs in animal models [14]. Remarkably, the diverse components of the immune system were normally represented in detailed time-course experiments, displaying a complete repertoire of inflammation needed for counteracting the external environment, with each type of inflammatory cells on-the-scene faster in probiotic-treated mice. This resulted in a wound healing process that had epithelial closure occurring twice-as-fast as experimental control counterparts [14,17]. In this paradigm, we proposed that host animal wound repair capacity served as a proxy for whole body healthful longevity. In 2014 we began human subject trials testing probiotics and oxytocin in wound healing in women. This and our subsequent work with mouse models showed that sterile microbial lysates were sufficient for significant improvements in wound closure, raising the possibility of safer formulations that didn't require live bacteria in vulnerable patients [18].

1.8. Developing a unifying Grand hypothesis linking microbes and oxytocin

In 2012, we developed an overarching hypothesis that probiotic microbes and oxytocin were the foundation for a nurturing symbiosis for mutual survival and societal advancement. Feeding *L. reuteri* gave the mice thicker skin and mucosae, a fortifying body armor, and, in females, more acidic vaginal mucus [19]. Interestingly, a similar change in pH of mucus is correlated with increased fertility in humans [19–21]. These were the separate building blocks of the unifying master hypothesis, and despite their scientific gravity these lab projects in 2011–2013 had whacky but informative names, "Glow of Good Health", "You are what you eat, sort of', and "Healing by Gut Feeling'. All of this was great fun, with serious underlying scientific and biomedical implications.

In our other studies starting in 2011, we discovered links between microbiota and host immune system functions with slenderizing effects even in animals consuming a junk food-style diet. This emerged after a prospective epidemiological study showed dietary 'fast food' contributed to obesity whereas eating yogurt prevented age-associated weight gain [22]. Seeking clues, we tested mouse models and found that eating yogurt or purified probiotic microbes entirely prevented age-associated obesity irrespective of their baseline diet. In those studies probiotics altered host immune cells without changing the existing GI microbial composition, suggesting an immune-mediated mechanism. Our data show probiotic microbes yielded significantly leaner animals regardless of their 'fast food' dietary indiscretions [23]. Later we showed that consuming *L. reuteri* led to slimmer physique in mouse models by an oxytocin-dependent mechanism [24] inversely correlated with the stress hormone corticosterone [18]. This made good sense; microbial symbionts promoted host fitness and protected from dietary indiscretions, providing a survival edge to host animals and their microbial passengers. Separate work in human subjects shows potent effects of oxytocin regulating food intake and related satiety behaviors [25].

1.9. The thrills and perils of being ahead of the curve

During this exhilarating time our setbacks didn't bother us much. However, it sometimes took years and many tries to publish our scientific manuscripts. We had branched out into studying human disorders; however, our first grant proposals in 2013 testing therapeutic roles for microbial-triggered oxytocin and GABA in Autism Spectrum Disorder [ASD], were rejected. Looking back, I would say our shared vision, the thrills of discovery, and inspiring team dynamic, led us ahead of the curve and the joys had far outweighed any day-to-day setbacks in our progress. Our collective curiosities were never really satisfied, and our various defeats more deeply unified our efforts, and so we ventured onward.

2. Our studies showed mom's diet can lead to multigenerational effects

We envisioned that this flourishing microbial mammary niche stimulated milk release from mammae and at the same time boosted mom's interest in nursing her young. We saw these as foundations for mammalian success. Unsurprisingly, we discovered that mouse moms drinking the human milk microbe took better care of their offspring, especially when compared with mouse moms eating a junk-food diet, a project we affectionately called "My Bacteria Made Me Do It" [26]. The 2012 mouse cage cards from these studies were labeled with this identifying acronym "MBMMDI", and we still laugh together about this.

Our 2013 studies in animal models using fast-food diets and yogurt or probiotics in pregnant animals showed later multigenerational effects involving reproductive fitness, body weight management, mental health, and even risks for developing cancer; all effects that were found to be caused by gut bacteria in microbiome transplantation experiments [27,28]. Progeny of fast-food eating moms suffered from a progeria [accelerated aging] syndrome linked with premature thymus gland involution [27] implicating the interlocking effects of diet, microbiota, host endocrinology, and the immune system. We later proposed that microbiota and oxytocin served as part of a quorum-sensing mechanism wherein offspring were epigenetically programmed *in utero* for future success.

2.1. A partnership for evolutionary symbiosis

In this arena of far-reaching ideas, we reasoned this partnership was a vivid example of evolutionary symbiosis, wherein the mammalian host and their microbial passengers both derive benefits [29]. To pick a few other favorites, our lab had shown in mouse models that host thyroid hormone levels were also stabilized by our model microbial symbiont *L. reuteri* [30]. Along these lines of contemplation in 2011, I wrote "*maybe microbial organisms drove evolution of endothermic mammals? Sustained core temperatures improve host reproductive fitness and internal incubation options, with microbes symbiotically driving the metabolic furnace…*". Returning to the roots of these 2011 musings, I postulated that thermophilic microbes in decaying swamps may stabilize body temperature of their hosts for a mutual survival advantage. This microbial symbiosis and resulting endothermy may have ushered the evolution from external egg laying to internal placental pregnancy.

Another separate series of unifying experiments showed microbial upregulation in transcription factor Forkhead Box N1 (FoxN1) [31]. Importantly, this transcription factor helps build the thymus gland that produces specialized immune cells which in turn modulate host

immunity that would facilitate placental pregnancy in mammals. FoxN1-deficiency in mice [referred to as nude mice] leads to embryological defects including defective thymic T lymphocyte programming and absent hair growth. It's a delightful twist that the FoxN1 gene is also involved in the growth of body hair, which when coupled with thyroid hormone supports the stable body temperature needed for an extended internal pregnancy. FoxN1 is also implicated in development of mammary glands, as nude mouse females lacking FoxN1 have underdeveloped mammary glands and are unable to effectively nurse their young. Thus, our lab investigated FoxN1 as a candidate unifying factor that supports sustained placental pregnancy, including immune tolerance, body hair for thermoregulation, and mammary glands for nursing infants. There were layers and layers of these unifying hypotheses involving microbiota stimulating the pineal gland and downstream hypothalamic-pituitary-adrenal axis featuring oxytocin and the immune system for host management of external challenges. This loops us back to May 2011, when I had written to a friend, "*The more I think about this … the more I realize this microbe-vertebrate symbiosis is a thing of beauty.*"

2.2. A symbiotic survival manual locked in our brains

Yes, it's profoundly important that oxytocin has foundational roles in stimulating reproductive behaviors, inducing childbirth, releasing breast milk, bonding babies with their moms, and joining societies to share in infant rearing. We hypothesized that a synergy between microbes and oxytocin might be driving other aspects of mammalian evolution and became interested in oxytocin's roles in promoting neural connections and creativity that have been integral in social organizations and even spirituality of our humanity. This concept is scientifically supported by work of pioneering researcher Sue Carter and others proposing these same aspects of human consciousness and the capacity for what humans experience as 'spirituality' and 'love' are unlikely to have emerged without oxytocin [11–13].

We envisioned a symbiotic survival manual locked deeply within our brains providing clues to universal harmony or maybe our mutual destruction. While oxytocin is often associated with pro-social behaviors, bonding, trust and altruism in humans, there is also evidence to suggest that it can have xenophobic or exclusionary effects in certain situations [32]. Following this line of reasoning, emotional fear processing is headquartered in a part of the brain referred to as the amygdala, next to the hippocampus. Both the hippocampus and amygdala are littered with oxytocin receptors that stimulate recall of bundled memories; perhaps even ancestral memories are passed via microRNAs [33]. Knowing that oxytocin may be boosted during meditation or prayer provides a guiding voice or a sort-of Akashic Record library, conveying a sense of purpose and meaning to life, as well as feelings of comfort and salvation. People who meditate often describe profound insights and inspiring bursts of creativity. I had imagined these hugging molecules helped to sustain mammalian evolution under the most challenging circumstances. In collaboration with Liz Lawson and other fantastic biomedical research collaborators, we eventually progressed to human subject trials to further test these same concepts.

2.3. In closing

When asked to share my story of inspiration I would reply with the narrative outlined above. It is, indeed, an elegant symbiosis in microbial partnerships with mammals that allowed for mutual survival and passed a legacy of neurological stability and sociability to their offspring. Taken together, this oxytocin-mediated neuronal engagement forms the basis of our instincts, gut feelings, intuition, and creativity, all stored in our brains until times of need. It helped to have the 'brain trust' to explore ideas outside what's well known and understood. At its best, this oxytocin-biased nurturing holobiont bestows empathy, altruism, and universal wisdoms transcending generations. Whatever we choose to call this magical chemistry anchored in oxytocin, it is truly beautiful and deeply inspiring.

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Susan E. Erdman: Conceptualization, Funding Acquisition, Visualization, Writing—original draft, review & editing.

Declaration of competing interest

No conflict.

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