Comprehensive Psychoneuroendocrinology 15 (2023) 100189

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

journal homepage: www.sciencedirect.com/journal/comprehensive-psychoneuroendocrinology

Close encounters with oxytocin

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ARTICLE INFO

Keywords:
Oxytocin
Vasopressin
Lactation
Maternal behavior
Stress

ABSTRACT

The purpose of this narrative review is to use a personal perspective to describe unanticipated and pivotal findings that drew the author into the study oxytocin. Oxytocin was originally described as a "female reproductive hormone." However, supporting reproduction is only one of a myriad of functions now attributed to oxytocin. Oxytocin promotes survival and resilience in both sexes and across the lifespan, especially in the context of stress or trauma and helps to explain the health benefits of relationships. Oxytocin works in the context of individual histories and in conjunction with other molecules, as well as the autonomic nervous system and immune factors. The chemical properties of oxytocin make it biologically active, but difficult to measure. As a deeper understanding of the biology of oxytocin is emerging, we may use knowledge of the properties of oxytocin to uncover adaptive strategies that protect and heal in the face of stress and adversity in both males and females.

"I find it intriguing to contemplate how one starts out on a trail of exploration in the laboratory, not knowing where one is eventually going – starting out, to be sure, with some immediate objective in mind but also have a vague sense of something beyond the immediate object toward which one is striving … As one looks back on a trail of research, one sees that the continuity is sometimes greater than he may have imagined at the time … Where did the sulfur trail start? I think it started at the University of Illinois …" Vincent du Vigneaud (*Trail of sulfur research: From Insulin to Oxytocin"* 1956).

1. The origin story: life in a female body

The experiences that would eventually allow me to call myself a scientist began with a fascination around the biological basis of behavior. I grew up in rural America, initially intending to be a teacher. A series of unplanned events led me to graduate school and into research [1]. In 1969, by the time I was 24, I had earned a PhD in Zoology. In 1970, after one year of postdoctoral fellowship, I married another young scientist (Stephen Porges) and together we began the perilous voyage associated with creating careers in academics.

For the next four years I experienced the ups and downs of being a trailing, sometimes unemployed, academic spouse. With support from Steve and several colleagues I eventually became a member of the University of Illinois faculty. This position included responsibilities in three separate units (Ethology, Ecology and Evolution, as well as Psychology and the School of Medicine). This complex arrangement gave me the opportunity to have my own laboratory, along with an abundance of committee assignments, departmental politics, and even physical exercise as I literally ran from building to building on the large Illinois campus.

A decade later, after I accumulating what I felt would be sufficient credentials for promotion to full professor, Steve and I had our first son. My interest in oxytocin began as I tried to manage a career and at the same time to decipher experiences associated with raising a child. Motherhood was a turning point, not just in my personal life, but also in my academic career. Like prior generations of humans, especially those living in a female body, I was bombarded by chemicals and emotions for which I had no words. Motherhood was also a master-class in the biology of attachment and stress management. I felt as if my brain and body had been hijacked by an ancient alchemy. The experiences surrounding maternity also led me to become obsessed with the molecules orchestrating my experience of motherhood, especially the one known as oxytocin [2–5].

2. Oxytocin and following the trail of sulfur

I am not sure if it was a coincidence or some bizarre destiny that brought us to the University of Illinois in 1972. But I learned later that I was living in the same small college town, where in the 1920s a young chemist, Vincent du Vigneaud had begun the research that led to the

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https://doi.org/10.1016/j.cpnec.2023.100189
Received 8 June 2023; Received in revised form 13 June 2023; Accepted 15 June 2023
Available online 29 June 2023

identification of the oxytocin molecule.

It was not the sight of oxytocin, but rather its' scent, reminiscent of rotten eggs, that helped du Vigneaud identify oxytocin [6]. Du Vigneaud was initially trying to describe the chemistry of insulin, another sulfur-containing hormone. Before du Vigneaud's work began, it was already known that extracts of pituitary glands could be used to induce birth and facilitate milk ejection. To extract a few milligrams of oxytocin, he and his students sifted through thousands of pounds of pituitary glands salvaged from stockyards. From this du Vigneaud deduced the structure of oxytocin, "the first polypeptide hormone" and later the related molecule, vasopressin. Oxytocin was a smaller, less complex molecule than insulin, but would earn for du Vigneaud the 1955 Nobel prize in Medicine. This also allowed the synthesis of oxytocin [6,7], launched a new era of biological chemistry and changed forever human birth practices [8].

3. A physical encounter with oxytocin

At 5 a.m. on July 26, 1980 I was rudely awakened by amniotic fluid gushing down my thigh. It was my due date, there was a full moon over the Illinois prairie, and daytime temperatures would hit 113° F. Steve called the hospital and they said to come in immediately. Once we crossed the threshold of Christie Clinic, I began to experience repeated pelvic examinations and other strange interventions, but very few real contractions. I found particularly unpleasant the insertion into my uterus of an "amnio-hook" (something like a large knitting needle) intended to help stimulate labor. Even more frightening, I was later told that I had only one day to deliver, since each of these procedures could allow potentially deadly hospital bacteria access to my baby.

My cervix was unaware that time for a natural birth was running out. My son was facing the wrong direction and had to be manually turned. After 20 h in the hospital, my labor was not progressing and the nurses were checking availability of a surgical suite for a C-section. At that point a plastic bag suspended from a metal frame was rolled next to my bed. For about 4 h a transparent liquid, containing saline and Pitocin (a synthetic version of oxytocin) dripped through a catheter into my arm. Exceptional pain, worse than the "amnio-hook," followed as oxytocin-facilitated contractions eventually squeezed a 14 inch cranium through my reluctant cervix. Birth could not simply be managed by "mind over matter."

In time, Pitocin, would become a staple tool in obstetrics, used to facilitate labor and reduce postpartum bleeding. Giving Pitocin to women during birth was based on the assumption that the exogenous hormone did not cross the placenta or affect the baby. However, the birth experience of mothers and babies who were "pitted out" of the uterus would seem to be radically different from those who were born in a less medicalized way.

I remember exactly when I personally encountered the hormone that I would come to recognize as oxytocin. Of course, I had experienced oxytocin's effects before in my life and academically while teaching courses on human sexuality and reproductive biology. However, it was only when I received this molecule in its synthetic form that I began to appreciate the capacity of oxytocin to influence both the body and mind. At that moment I realized that I was in the presence of a powerful force. In time, I would come to think of oxytocin as the molecule that allows us to be human [9].

4. Sex and oxytocin

In my first academic position, among my responsibilities was the supervision of a course on human sexuality. In a story to be saved for another time, the major lecture was taught not by me, but rather *in person,* by William Masters and Virginia Johnson. Their 1966 book, simply called *Human Sexual Response*, would become a landmark in the sexual revolution. Masters and Johnson were then at the peak of their fame. Their lecture was so popular that the University held it in a large auditorium and issued attendance tickets. In 1974 female researchers were rare in any field, so meeting Virginia, who co-incidentally had attended my own alma mater (Drury College), was very exciting. Virginia was not trained in science, but she brought to her work a range of life experiences and the capacity to put people at ease.

The general intent of the medical school course was to desensitize young doctors so that they would be comfortable with discussing sex with their patients. The students also viewed a graphic film from Norway showing a woman, her face discretely hidden, experiencing self-induced sexual arousal. At the point of orgasm, a tiny fountain of milk spurted out of her breasts, indicating that she was lactating. Many of the medical students viewed this movie repeatedly, in private library carrels. The students eventually wore out three copies of the film. I am not sure if these students, most of whom were male, actually became "desensitized" to sex. However, if they did not, this was not for lack of dedicated effort.

Already it was understood that oxytocin was essential for milk ejection and played a role in lactation. But the hypothesis that oxytocin might have a role in orgasm was only beginning to emerge. Although I did not know it at the time, seeing the clear association between sex and milk ejection in those films was my first academic exposure to the neural consequences of oxytocin.

5. Orgasm and oxytocin

Our first son was 6 months old when Steve and I had the opportunity to escape the winter cold of the Midwest to take a sabbatical at Stanford Medical School. I wanted to learn more about how to study hormones and human behavior, and Julian Davidson had invited us both to spend time in his laboratory. Julian was a pioneer in the field of neuroendocrinology, mostly known for work on steroid hormones.

A new project dealing with the effects of estrogen on female sexuality was being launched when we arrived in Palo Alto in January of 1981, and I was invited to work on that study. Julian had constructed a sexual psychophysiology laboratory, hidden away on the second floor of a building that predated the 1906 earthquake. Volunteers in that study inserted a small plastic recording device into their vagina. This probe was connected to a polygraph in an adjacent room. Women watched erotic videos and signaled their subjective experiences by pressing an electronic button. The button system was unnecessary. Anyone watching the polygraph could detect an orgasm by a unique electrical signal from the pelvic contractions recorded by the probe. I later learned that studies as far back as 1954 had reported similar pulsatile patterns in EEG, with physical effects throughout the entire body [10].

Prior to 1980, my own research had focused on steroid hormones in nonhuman animals. However, sexual function or dysfunction in both men and women cannot be fully explained by steroid hormones and remains poorly understood. At that time, I knew very little about human research and even less about the science of oxytocin [1]. However, the odd spindle-like patterns in those recordings grabbed my attention.

Julian's group would subsequently become one of the first to measure oxytocin's release during orgasm [11]. Oxytocin and orgasm were simultaneously associated with unique patterns of electrical activity throughout the body. In hindsight, while helping to test the effects of menstrual cyclicity on female sexual responses [12], I was once more seeing oxytocin in action.

6. Lactation: another close encounter with oxytocin

The University of Illinois, where I was working when my children were born, was a highly ranked and very competitive academic environment. It was not a baby-friendly environment. No one openly criticized my decision to have children, but there was subtle pressure for mothers to not appear to request special favors. To the best of my knowledge, paid maternity leaves were not available. Nor did I ask for one. I was careful not to even mention my pregnancy in public. Most of

the women I was working with were managing their careers by avoiding altogether the "mommy track." I wanted to continue my career, but I also wanted a family. Accommodating both was a serious challenge.

Obviously our hominoid ancestors had managed to nurture and feed their offspring for millions of years, sometime drawing on the generosity of others for childcare and milk donations [13]. Given the birth experience my son had endured, I was particularly determined to provide him with human milk. I was also motivated by concern that exposure to foreign proteins, like those in cow's milk formulas, might sensitize children to allergies.

Around this time I learned of studies in rodents showing that lactational hormones, including prolactin (also a releasing factor for oxytocin), were necessary for normal reproductive function in later life [14]. There was more to milk than nutrition. Now a few decades later it is well documented that human milk contains antibodies, stem cells, microbes and various hormones including oxytocin. All of these have functions that remain only partially understood, and all are not easily added to baby formula. If I hoped to continue my career, I knew I would need to have a healthy baby. I also saw women around me suffering from a failure to lactate or "milk insufficiency." From my perspective as a biologist, lactation should have been simple. Yet the baby books and even the scientific literature from that period offered little guidance on how to accomplish this presumably "natural" task.

7. The !Kung formula for how to rear children

Fortunately, about 6 months before the birth of my first child a 3-page paper appeared in *Science* magazine that would become my "how to raise a baby" manual. In that article Mel Konner and Carol Worthman outlined the child rearing patterns of !Kung hunter-gatherers, living in southern Africa. These nomadic peoples practiced a traditional lifestyle that allowed an almost four year childbirth spacing, even without contraception or abstinence. Women of the !Kung culture were also "working mothers" traveling miles on foot each day. But they could take their infants with them when they gathered food. Especially, important from my endocrine perspective, the !Kung slept with their babies and to quote Konner and Worthman, "universally" nursed at night. Breast stimulation at night, but not during the day, could delay the postpartum return of the ovulatory surge of luteinizing hormone [15].

Following the !Kung pattern, I was able to successfully breast feed each of my sons for almost two years. I also experienced postpartum amenorrhea which lasted, not for the 3 months seen in typical Western women, but for 16 months. It was the !Kung method of child rearing and the availability of alloparents (daytime baby sitters) that allowed me to survive the dual demands of a career and motherhood. I did not trust lactation as contraception, but I did not dare to take "the pill," since it contained hormones that could interfere with lactation and also would reach the baby. Along with these concerns, I suspected that lactation was buffering me from the emotional stress of academic life and I wanted to understand how this worked.

8. Was maternal behavior an "instinct," or perhaps more about overcoming stress?

For decades the role played by the brain and fluctuating hormones in maternal behavior was a source of intense debate. The basic arguments focused on whether maternal behavior was an inborn instinct, a learned behavior, or a set of hormone-facilitated responses, stimulated by the endocrinology of birth and lactation [1].

Around 1980, two high profile studies of maternal behavior in rats, conducted by Cort Pedersen, supported the hypothesis that maternal behavior could be facilitated by oxytocin. However, these initial findings could not be replicated, even in Pedersen's own lab. As I recall, he had been forced by his university to switch to study germ-free animals. Apparently in germ-free rats, oxytocin was no longer effective in facilitating maternal responses. In fact, a later study by Susan Fahrbach and Donald Pfaff revealed that the effects of oxytocin could only be measured when female rats were tested in novel environments [16]. These findings suggested that the beneficial effects of oxytocin were most easily detected when females were experiencing some kind of stress or adversity.

I was increasingly convinced that oxytocin's capacity to facilitate maternal responses was due in part to its' many interactions with hormones of the hypothalamic-pituitary-adrenal (HPA) axis. For example, corticosterone increased the expression of oxytocin receptors in brain regions that managed stress [17]. But in general, oxytocin reduces activity in the HPA axis. Watching this drama play out reinforced my personal experiences of feeling emotionally buffered when I was lactating, and supported my growing conviction that oxytocin played a major role in stress and coping that might extend beyond maternity.

9. Sex, love and oxytocin: Lessons from prairie voles

Insights regarding oxytocin, gleaned from motherhood and studies of human behavior, became of value to me professionally as I tried to understand the neurobiology of attachment, a subject that was central to my early academic interests [1,2,4]. My own research on prairie voles and social monogamy began around 1980 as well [18]. Remarkably the biology of prairie voles as a species shared unique features with the maternal biology associated with lactation, possibly because in both cases there is dependence on peptides and relatively little reliance on steroid hormones [1,19–21].

In early vole research conducted with my postdoctoral fellow, Jessie Williams, we found that social bond formation was facilitated by sexual interactions [22]. However, pair bonding could still occur even in gonadectomized animals with low levels of sex steroids. We were subsequently able to show that oxytocin was essential for the formation of the social bonds that were at the heart of social monogamy, and that it affected both sexes [23,24].

Our vole research was picked up by the Media in the 1990s and oxytocin continues to the present – for better or worse - to be described as "the love hormone." However, the early identification of oxytocin as a molecule necessary for love was not helpful to my basic research program. As I have described elsewhere, associations with the metaphor of "love" created difficulties that would slow our progress in funding studies of the neurobiology of oxytocin [25]. I do believe that oxytocin is a critical component of what we humans experience as love. But there was so much more that oxytocin and lactation had to teach us [26] (Table 1).

10. The maternal brain is plastic

My early thoughts about oxytocin and lactation were very focused on

Table 1
EXAMPLES OF FUNCTIONS AND BENEFITS (AMONG MANY) OF OXYTOCIN AND/OR LACTATION FOR THE PARENT AND OFFSPRING (Due to space considerations references cited are primarily reviews.).

Economical, efficient and optimal nutrition, automatically adjusting over time [27]
Supports later capacity for sociality and relationships in parent and offspring [28]
Supports parental attachment and investment [28]
Stress-buffering and promoting recovery after injury [29]
Lactational amenorrhea can be contraceptive, allowing birth spacing [27]
Lactation protects against cancers, auto-immune disorders and obesity in later life [27]
Lactation and oxytocin promote neural plasticity [30]
Oxytocin is epigenetically tuned and context dependent [31]
Oxytocin is anti-inflammatory/anti-oxidant [32]
Oxytocin is anxiolytic/analgesic [26]
Oxytocin and lactation may increase longevity [33,34]
Human milk contains regulatory hormones, growth factors, antibodies and stem cells [27]
Human milk transfers maternal immunity to offspring [27]

the nervous system. Stunning evidence appeared in the 1980s indicating that lactation was associated with morphological and electrical changes in the hypothalamus. By the early 20th century it was well known that the mammary gland was a target for oxytocin. I began to dig into the literature to understand the role of the brain in milk ejection and maternal behavior. Electrical recordings in lactating rats revealed patterns similar to the spindles seen in orgasmic women. In lactating rats these rhythmic patterns were recorded from hypothalamic neurons. Furthermore, research on lactation revealed that only the magnocellular neurons containing oxytocin (but not vasopressin) showed this pulsatile signature [35].

At this time, theories in mainstream neurobiology, built on work in male rats, were just beginning to appreciate the capacity of the mammalian brain for neuroplasticity. Birth and especially long-term lactation can create anatomical and biochemical changes that appear to be specific to the maternal brain [36]. Two independent groups of scientists, led by Dionysia Theodosis [37] and Glenn Hatton [38], had discovered that hypothalamic neurons releasing oxytocin were surrounded by and dynamically regulated by glia. Based on sensory inputs glia could physically retract allowing synchronous electrical communication between oxytocin neurons. The patterning of pulses we saw during orgasm and lactation were likely based on this novel adaptation. In addition, these studies of glia were early indications of what we now recognize as interwoven relationships between oxytocin and the immune system [32,39].

11. Birth, lactation and the effects of oxytocin are epigenetic and influence development

I literally got up from a birthing bed in 1980 and began a quest to try to understand the developmental effects of oxytocin [9,40,41]. I was motivated by a need to know what had happened to my child. However, most contemporary births are complicated. In general the effects of exogenous oxytocin are dose-dependent and these interact with other drugs, such as the opioids used in epidural anesthetics [42,43]. C-sections, currently occurring in about one in three births in the United States, are yet another endocrine intervention that has epigenetic consequences [44,45].

Given the complex nature of modern birth interventions, many of which can affect the oxytocin system [46,47], there remains urgent need for a deeper understanding of the developmental functions of oxytocin as well as the possible benefits of human milk [48,49]. As only one example, a recent study has revealed that oxytocin rescued infants from withdrawal symptoms in a rat model of neonatal opioid abstinence [50]. Whether oxytocin or other molecules in human milk could improve outcomes in infants exposed to various drugs or other forms of perinatal stress deserves deeper study [51]. Ongoing studies in prairie voles by Jessica Connelly, Karen Bales, Allison Perkeybile, Joshua Danoff, Will Kenkel, and their colleagues, have since revealed that neonatal exposure to oxytocin, as well as early nurture can epigenetically tune the oxytocin receptor [52]. Furthermore, these effects differ in males and females.

12. Oxytocin as "Nature's medicine"

Oxytocin can affect virtually every cell and organelle in the body, including mitochondria [25] and the microbiome [53]. Particularly exciting are recent studies using elegant molecular methods to map the dynamic functions of oxytocin and the oxytocin receptor. These studies are suggesting that the oxytocin molecule has very precise targets throughout the brain and body, allowing the discovery of new functions for oxytocin [54–56].

In my enthusiasm for oxytocin it became important to recognize that this molecule was part of an evolved system that includes not only oxytocin but also vasopressin [3,26]. Oxytocin binds both to its own receptor, but also vasopressin receptors, with effects that can seem paradoxical [57–59]. Oxytocin and vasopressin and their receptors operate as an adaptive system helping to coordinate reproduction, healing and survival, in the context of threat versus perceived safety [1,4,26,60]. Oxytocin is primarily anti-inflammatory, while vasopressin may support inflammation [32]. The oxytocin-vasopressin system also plays a modulatory role in other major neural systems, including those regulating sociality, immunity, metabolism, pain, stress, trauma, fear, trust, addiction and likely other functions yet to be discovered [61].

13. Chasing the elusive oxytocin molecule

I wanted to know what regulates the abundance of oxytocin? However, without the capacity to quantify oxytocin, vasopressin and their receptors we could not properly study this system.

When I first began to measure oxytocin in my lab, it was in studies in voles and it was the 1990s. We were living in Bethesda Maryland and I had an appointment at the intramural NIH. An NIH scientist, Konstantine Kalogeras, who was skilled in measuring peptides, kindly did radioimmunoassay (RIA) determinations of oxytocin in prairie vole blood for me. Oxytocin levels were about four times higher in voles than in rats. However, voles are only slightly bigger than mice and to have enough blood to do a single RIA would require the sacrifice of five voles. This was not a practical solution to the questions about individual behaviors that we were trying to answer. Another NIH endocrinologist, Larry Tamarkin, who also ran a small biotech company, tried to develop an oxytocin enzyme-immunoassay (EIA) for us. During this same period a commercial EIA appeared on the market from a company called Assay Designs. Larry's lab tested this EIA and he assured me that the assay was valid and could be run with dilution and without extraction, allowing us to begin to study individual voles [62].

However, Assay Designs was later sold to Enzo Life Science, a larger company. Without warning Enzo changed the oxytocin antibody in their assay system. This is when I realized that antibody-based assays could vary dramatically in their affinity for oxytocin. Antibody variation made quantitative comparisons across assay methods impossible. Enzo also began to recommend a pre-assay extraction procedure, which requires a large quantity of blood. What exactly happens to oxytocin during "extraction" is still not clear. Despite this chaotic situation, and even without an extraction, we and many others have detected functional associations between oxytocin and behavioral measures in hundreds of studies [63–65]. In one recent study we assayed oxytocin in individuals diagnosed with severe and chronic PTSD compared to healthy people exposed to acute stressors (Horn, Carter et al., in preparation). Oxytocin levels were about half and vasopressin levels were two-fold higher in PTSD patients than those in healthy controls. Run in our lab by the same person (Hans Nazarloo), two assays from two different companies (with different antibodies) gave identical patterns of oxytocin in PTSD versus controls. But when we compared across assays the values reported by the assays differed by an order of magnitude.

Two other laboratories have recently compared relationships between oxytocin and behavior in extracted versus unextracted samples. The relationships between oxytocin and behavior were **stronger in assays using unextracted samples** [66,67]. Whether sample extraction prior to assay removes **biologically relevant** molecules that can influence the functions or availability of oxytocin remains to be determined.

It appears that the sulfur bonds that give oxytocin its unique chemistry and odor also make this molecule biologically active [68], but also hard to study [5,69]. Using various methods, including gene expression [70], antibody-based assays and mass spectrometry, it appears that oxytocin may be one of the most abundant molecules in the body. One proteomic study measuring total oxytocin (free and bound) in human plasma described "startlingly high," levels of oxytocin ranging from high pg/mL to ng/mL [71]. (After extraction, assays in human blood typically report values in the low pg/mL.)

Even while potentially abundant, oxytocin also is essentially invisible. Based on its' novel biochemistry, oxytocin can shifts its shape, bind

to other molecules and hide in plain sight [5,69,71]. Even when different assays are conducted under comparable conditions, quantitative values often vary dramatically [72,73]. Our solution for research in humans has been to run studies under blinded conditions, with extreme technical care (provided consistently by Dr. Nazarloo) and to make snapshot comparisons only within a given study. However, these measures are just proxies for oxytocin, and they do not describe function. The controversy surround oxytocin measurements is likely to continue until better methods capable of assaying oxytocin and its receptors, in small samples and also in real time, are available [74,75].

14. What else are we learning?

There is now no doubt that the systems responsible for oxytocin are delicately tuned in both parents and children. Traumas around birth or across the lifespan, possibly mediated by disruptions in the oxytocin system, may leave humans vulnerable to somatic and psychological disorders such as postpartum depression [76,77] or addictions in later life [78]. The effects of oxytocin can help to epigenetically recalibrate and return these systems to normal [20]. However, how this happens is only now becoming understood [26,31,79].

Reproduction is dangerous and costly. With or without breastfeeding, motherhood is metabolically and economically expensive, especially challenging for mothers without a social support network [13]. Economic analyses of childrearing often fail to factor in opportunities lost and other career costs. As one recent article states, "there is no such thing as a free lunch" [80]. However, the benefits to parents may include emotional growth, reductions in the impact of stress [20,26], a lower disease burden and even increased longevity [34]. These may be overlooked or underestimated. Parenthood is only one of many pathways into the oxytocin system [26] and these alternatives need to be studied.

Oxytocin is intimately connected to the autonomic nervous system, endogenous opioids and other hormones and neurotransmitters [26]. Of these one of the most mysterious is the relationship of the oxytocin-vasopressin system with steroids. For example, chronic exposure to steroid molecules, including estrogens and glucocorticoids, elicits withdrawal symptoms when they are stopped [81,82]. Is it possible that oxytocin could protect against withdrawal-like symptoms associated with drug addiction, postpartum depression and perimenstrual and menopausal dysphoria [83–85]? Understanding these relationships might allow patients to avoid or treat symptoms associated with declines in steroids [86]. Chronic exposure to steroids can be toxic, but also can functionally increase oxytocin. Some of oxytocin's magic may lie in its capacity to adaptively modulate the actions of steroids in both sexes [87]. Perhaps steroids generate their own functional antidotes in the form of oxytocin. Although, beyond the scope of this review, interactions of oxytocin with steroids and opioids are of tremendous importance and deserve much deeper study [88].

Based on the ancient history of oxytocin we are learning that there are many co-factors in the oxytocin-vasopressin pathways. Among these are basic elements (like oxygen) [32], minerals (including magnesium) [89,90] and other factors such as hydrogen sulfide [91]. Salt, found in high levels in Western diets, may play a disruptive role in regulating both oxytocin and vasopressin. Exercise, breathwork, meditation and spiritual experiences may influence the oxytocin system. Each of these is a piece of a larger puzzle.

Embedded within female reproductive biology and oxytocin lie unrecognized secrets to health and longevity. Women tend to live 5–7 years longer than men [34], even though they suffer more pain, anxiety, depression [92] and auto-immune disorders. Understanding how oxytocin fits into this story has implications for all aspects of survival, health and wellbeing, across the lifespan [26,34].

I began my close encounters with oxytocin over forty years ago. We might even say I was emotionally abducted by oxytocin. While attempting to maintain my career and avoid being sucked into the "leaky pipeline" associated with women in academics [93], I began to "biohack" motherhood and then oxytocin. Based on biology and anthropology, I uncovered a few strategies for being a more efficient and resilient mother. Overtime I initiated research studies hoping to understand what had happened to me and to share what I learned with the scientific community [20,94]. While trying to discover the biology of "what every baby knows," [95] I was also undergoing my "on the job training" in the school of maternal hard knocks. The !Kung mothers "Pleistocene manual" was useful, and had a major influence on both my academic and personal journey. But this guidance was not always well matched to the modern world. Motherhood is not simple in a complex contemporary world and not all mothers can take their babies to work or even breast feed. We have to find new ways to listen to and support our bodies and those of future generations. At the same time we will need to apply the sophisticated tools of science to allow a deeper appreciation of the ancient biology that is essential for reproducing and sustaining healthy human lives.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This paper is dedicated to Stephen, Eric and Seth Porges who were the guiding forces that permitted the ideas described here to emerge. I am also extremely grateful to John M. Davis who became my supervisor when I worked for the Illinois Department of Mental Health in 1973 and who 50 years later continues to be my research collaborator. John assigned me the task of studying the biology of maternal behavior, and has on more than one occasion rescued my research program. Another special thanks must be given to Sarah Hrdy, whose insights into "mother nature" have inspired my research. I am of course grateful to the federal agencies (NSF, NIH and DOD) and private foundations (the Templeton Foundation and Fetzer Institute) that have helped fund my laboratory during the more than half a century that I have had the privilege to do research. Hundreds of amazing scientists, too many to list, have earned my admiration for conducting the studies that inform this review.

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