Title

Sex, love and oxytocin: Two metaphors and a molecule.

Author

Carter, Cameron

Publication Date

2022-12-01

DOI

10.1016/j.neubiorev.2022.104948

Peer reviewed

HHS Public Access

Author manuscript

Neurosci Biobehav Rev. Author manuscript; available in PMC 2023 December 01.

Published in final edited form as:

Neurosci Biobehav Rev. 2022 December ; 143: 104948. doi:10.1016/j.neubiorev.2022.104948.

SEX, LOVE AND OXYTOCIN: TWO METAPHORS AND A MOLECULE

C. Sue Carter

Department of Psychology, University of Virginia, Charlottesville, VA 22904 USA

Kinsey Institute, Indiana University, Bloomington, IN 47405 USA

Abstract

Dozens of studies, most conducted in the last four decades, have implicated oxytocin, as well as vasopressin and their receptors, in processes that mediate selective sociality and the consequences of early experience. Oxytocin is critical for the capacity to experience emotional safety and healthy sexuality. Oxytocin also plays a central role in almost every aspect of physical and mental health, including the coordination of sociality and loving relationships with physiological reactions to challenges across the lifespan. Species, including prairie voles, that share with humans the capacity for selective social bonds have been a particularly rich source of insights into the behavioral importance of peptides. The purpose of this historical review is to describe the discovery of a central role for oxytocin in behavioral interactions associated with love, and in the capacity to use sociality to anticipate and cope with challenges across the lifespan – a process that here is called “sociostasis.”

Keywords

oxytocin; vasopressin; sex; love; attachment; voles; history

Metaphors and the “natural world”

> “I’ve felt for a long time that the great political questions of our time—about violent prejudice, global climate change, venal greed, fear of the Other—could be addressed in illuminating ways by considering models in the natural world. Some consider it unsophisticated to explore the nonhuman world for clues to solving human dilemmas, and wisdom’s oldest tool, metaphor, is often regarded with wariness, or even suspicion in my culture. But abandoning metaphor entirely only paves the way to the rigidity of fundamentalism.”

Address correspondence to: cscarter@indiana.edu, Phone: 1 312 545 9003.

Declaration of conflicts of interest: None

Declaration of competing interests: None

Barry Lopez (https://lithub.com/barry-lopez-love-in-a-time-of-terror/)

1. Metaphors and molecules

This narrative review is written in response to an invitation to contribute to a special issue of *Neuroscience and Biobehavioral Reviews* – an opportunity offered to past-presidents of the International Behavioral Neuroscience Society (IBNS). In this essay, using as a vantage point the early 21st century - a time when I was President of IBNS (2003–2004) - I have highlighted a few of the personal pathways, metaphors and molecules, that led me to focus my research career on "sex, love and oxytocin."

Like everyone alive today, I have lived through periods characterized by existential threats to both humanity and the planet. I was born on December 25, 1944 - nine months prior to the bombing of Hiroshima. Underground missile silos armed with nuclear bombs dotted the farmland of the rural Ozarks where I was raised. Although I grew up far from the battles of World War 2, I have vivid childhood memories of living in postwar America under the constant threat of nuclear holocaust. Other conflicts followed and I watched as males of my generation were conscripted to fight in Vietnam.

Even as a child I knew that if fear or aggression were the only features of human nature we would not be here today. Somehow the positive features of life and our capacity to experience love sustained us as a species. How was that possible? Was there a hidden biology that gave us the capacity to give and receive affection and social support, and to trust other? If so, what was the nature of this remarkable process? This was the puzzle that I wanted to solve.

I began to understand that fear and aggression are rooted in the same ancient physiology that supports love. I also began to look for mechanisms that could explain how positive experiences and nurture, especially in early life, created a sense of safety and influenced the subsequent capacity for sociality. How the body interprets and manages both love and fear seemed to me to be what matters. That journey would eventually direct me toward neurobiology and a unique neuropeptide known as oxytocin.

Early on I also realized that the tsunami of knowledge that surrounded both love and sexuality would be easier to organize if I could use as an anchor something apparently specific and I moved my focus to the endocrinology of behavior. However, there was often discordance between accepted theories about hormones and behavior and what I observed in both empirical research and my life experiences. These gaps in knowledge repeatedly brought my attention toward oxytocin. Over time the oxytocin molecule became a touchstone for other scientific and personal questions I would attempt to understand.

Prior to 1980, like almost everyone else (Leng & Leng, 2021), I had little knowledge of and very little interest in the behavioral effects of oxytocin, and I did not think of what I was doing as a study of "love." However, particularly relevant to my interests in early experience were studies in sheep of "filial imprinting" (Keverne & Kendrick, 1992). A narrow time window existed, triggered by parturition and perhaps the stress of birth,

allowing attachments to form between ewes and their lambs. That window was opened by oxytocin.

As detailed below and elsewhere (Carter, 2022), many other arrows from the scientific literature, my ongoing experiments and my personal experiences also seemed to point toward this mysterious molecule, which was capable of coordinating both physiology and behavior. The functions of the oxytocin system in turn allow social experiences to support and anticipate physiological and psychological demands, a process that I suggest fits under the broader term of "sociostasis" (Cozolino, 2021).

2. My personal pathway to peptides

I was the only one of my father's eight children to graduate from college. Our land was too rocky even for sustenance farming. My father wanted to teach me, as he had my brothers, to be a machinist or welder, although I showed no aptitude for either. I seemed to only be good at going to school.

After college I applied to graduate school at the nearby University of Arkansas, intending to get a master's degree and teach in high school. I was offered a National Science Foundation fellowship (with a $220 monthly stipend) on the condition that I would skip the masters and do a PhD in three years. However, when I began graduate school, I had no research experience and little idea of where I was headed or what would happen next.

When I started graduate school in 1966 attempts to understand behavior were arising from various disciplines. Psychology was still defining its domains, and neuroscience did not yet exist as an organized discipline. My initial training was in organismic biology and zoology. It was the ethological school of thought that I found most attractive. Ethology tended to focus on natural history, descriptive studies, and a search for unlearned behaviors or "instincts." This perspective was influenced by European ethologists including Konrad Lorenz, whose popular and also controversial books drew attention to the origins of aggression (Lorenz et al, 2021) and to apparently unlearned positive behaviors such as social imprinting (Lorenz, 1935).

3. Imprinting, instincts and other inscrutables

My first research attempts were based on the hypothesis that early experiences were at the root of individual and species identification. Originally research on these topics had been conducted in precocial birds, such as geese and ducks, which could express their preferences by following the "object of their affection" (Lorenz, 1935). With help from an experimental psychologist, Jack Marr, my first studies of social behavior used guinea pigs.

Among small mammals, guinea pigs are unusual because they have a long gestation, are fully furred and mobile at birth and their survival depends on their capacity to follow their mother. I set out to examine the role of early olfactory imprinting in the creation of social preferences. There were several issues associated with doing research in laboratory animals. No one else at Arkansas was doing this kind of work. I had no research funding and had to pay for my research with personal resources, which meant taking extra jobs in the summer.

I found a farm where guinea pigs were being raised, bought a few animals and began to create my own colony. Marr did not have an animal lab, but he helped me gain access to a Quonset storage hut near the Razorback football field. We found salvaged rabbit cages and a few abandoned refrigerators that we converted into olfactory test chambers. All animal maintenance I did myself. The guinea pigs could be reared on rabbit chow. However, guinea pigs do not synthesize vitamin C, and have to have fresh vegetables. I made daily visits to the loading docks of local grocery stores to forage for discarded lettuce. Miraculously, I obtained some results, managed to write up a few behavioral studies, typed my thesis on a manual typewriter (making three carbon copies), and by 1969, at 24 years of age, I had received a PhD.

4. Instinct: A vague metaphor or a physiological process?

Around the time I was completing my dissertation heated discussions were raging concerning the role of nature versus nurture in sculpting later behavioral responses in either parents or their offspring (Lehrman, 1953). Imprinting, as it related to species identification, was offered as an example of “one trial learning” and was believed to be an irreversible “instinct.” Ethological approaches to behavior and especially imprinting eventually earned a portion of the 1973 Nobel prize in Medicine for Lorenz, but links between either imprinting or instinct and the nervous system were obscure. See Ludwig and Welch (Ludwig & Welch, 2022) for a more complete perspective on the neurobiology of mother-infant interactions, which also reaches into the ancient history of these questions.

Much of the animal research conducted around the time I entered Science dealt with the biology of aggression (Lorenz et al., 2021). What would be later called the endocrinology of “stress” also had begun to emerge as a discipline in the 1930s (Levine, 2005). Particularly influenced by Hans Selye (Selye, 1956), the latter studies concentrated on the adrenal glands and peripheral hormones, including glucocorticoids and catecholamines. Selye’s approach focused on reactions to external events, and the role of the hypothalamic-pituitary-adrenal (HPA) axis. These studies did not address the role of positive experiences and initially were not very helpful in my personal journey.

5. In search of an engram for mother’s love

In the mid 20th century, typically using rats, it became fashionable to ablate tissues or regions of the nervous system to search for “centers” that regulated specific behaviors. These early studies were based on the idea that behaviors reliant on the cortex were learned, while behaviors dependent on subcortical regions were instinctive or unlearned. Among the species-typical behaviors that were observed even in the absence of “learning” and following the removal of substantial portions of the nervous system were maternal and female sexual behaviors.

In the 1930s Frank Beach had created large lesions in the cerebral cortex in rats in a futile search for an “engram” or specific neural substrates necessary for maternal behavior. To Beach’s frustration, maternal attention to and care of young continued after decortication (Beach, 1955). For female rats at least, having an intact cortex was not essential to being

a mother. Later studies would implicate the hypothalamus, other brain stem areas and various sensory and autonomic systems in maternal behavior (Fleming & Rosenblatt, 1974) (Numan, 2006) (Stern et al., 2010).

Finally, in the 1980s the elegant research of Barry Keverne and Keith Kendrick (Keverne & Kendrick, 1992) showed that in sheep selective maternal attachment to an offspring required either the birth experience or hormonal priming, including the release of oxytocin. Many recent studies, mostly done in rodents, have documented elaborate neural networks that coordinated the response of mothers to infants (Carcea et al., 2021). But what about the baby?

6. Learning to love: Nurture or neglect

Primate experiments begun in the 1950s by Harry Harlow had drawn public attention to the importance for offspring of experiencing early nurture or its absence. Monkeys reared without a mother, even when given access to food, warmth and a cloth mother, showed atypical social and sexual behaviors for the remainder of their lives. Harlow described these studies as evidence for “learning to love” (Harlow & Harlow, 1966).

Looking back with modern sensibilities these experiments in primates can seem cruel. However, across time, in different cultures, under conditions of adversity, and especially as a function of institutional care, human infants also have been exposed to varying degrees of nurture or abuse. Children in orphanages and intensive care units sometimes experienced rearing conditions that were not too different from those created by Harlow (Rowold, 2019) (Welch & Ludwig, 2017). Even with adequate nutrition and physical care, it is now clear that the absence of an engaged and consistent caretaker also has disastrous outcomes, including in extreme cases what was called “deprivation dwarfism” or “failure to thrive.” (Tang et al., 2021). Prior to the dramatic studies of Harlow, social development often was described in very mechanistic and behavioral terms or was assumed to be genetically preprogrammed. Studies of early experience in primates and humans, despite their theoretical importance, remain to this day a topic surrounded by economics, politics and controversy (Hrdy, 2009).

In real life most parents probably used cultural traditions or “common sense” as their guides to child rearing. However, research in rodents would soon begin to suggest that apparently subtle differences in early experiences might have lasting neural and behavioral consequences for the later capacity to give or receive positive experiences (Meaney, 2001).

Human research on the importance of early experience for the capacity for later emotional relationships became especially prominent through the influence and writings of John Bowlby (Rowold, 2019). Followers of Bowlby, and especially Mary Ainsworth created a behavioral discipline focused on the importance in young humans of secure attachments or bonds with a primary caretaker (Ainsworth, 1969). This behavioral perspective, which came to be called “attachment theory,” was focused on the infant and initially paid little attention to either neurobiology or hormones (Carter, 2017b).

7. Does mothering really matter?

Building on the theories of Sigmund Freud and beginning in the 1950s, Seymour Levine created models to study the lasting effects of early experiences in young rodents (Levine, 2005). These studies often involved separating baby rats from their mothers and looking at various outcomes. A later variant of this paradigm took advantage of individual differences, leaving babies with their mothers, but using extremes in maternal behavior to document the importance of maternal stimulation. Moshe Szyf, Michael Meaney and colleagues (Meaney, 2001) went on to demonstrate epigenetic effects of exposure to differential early mothering; these studies focused on the behavioral and neural consequences as well on the functions of the HPA axis and glucocorticoid receptors.

Taken together with many clinical observations it was becoming clear that even when other needs were met, comparative amounts of nurture or neglect had lasting consequences on both physiology and behavior. These studies launched the notion that the effects of differential parenting could be transmitted behaviorally and epigenetically from one generation to the next. However, these studies were not fully explaining why early nurture, neglect or abuse were so important to later social development.

We now understand that social behaviors, including the capacity to give and receive affection, require the functions of the whole body and coordinated actions among central and autonomic systems. Social behaviors, including mother-infant interactions, are dynamic, reciprocal and bidirectional. Furthermore, this is occurring within the contextual history of each individual (Bosmans et al., 2020). This complex perspective was very difficult to study and a role for oxytocin was not part of the original story. However, over roughly the last two decades dozens of studies had implicating oxytocin in the pathways that lead to maternal behavior, social attachment and the benefits of secure relationships (Hostinar & Gunnar, 2015) (Carter et al., 2020) (Welch & Ludwig, 2017) (Ellis et al., 2021) (Abdelwahab et al., 2021). But when I entered this field the importance of oxytocin was far from accepted and even now many questions remain unresolved.

8. At least sexual behavior would be easy to study – or so I hoped

My graduate studies of early experience left me uncertain about what to do next. Obviously behavioral studies only touched the surface of the questions that I thought were important. I remained interested in maternal behavior, early experience and social behavior, but felt I had to find less abstract research topics. I wanted to be a “neuroscientist” and I naively hoped to study mechanisms that “caused” behavior.

When I completed graduate school in 1969 I was offered a National Institutes of Health postdoctoral traineeship at Michigan State University. The advisor I selected, Lyn Clemens was studying sexual behavior and gonadal steroids. Sexual behavior was easy to operationally define and had a clear biological function. In contrast to social learning or imprinting, sexual behavior appeared to have endocrine and neural substrates related to specific endocrine organs.

At that time, it was generally accepted that female sexual receptivity, including the lordosis reflex, would only occur in the presence of ovarian hormones (Beach, 1976). The scientific goal of my first neuroendocrine project was to map brain areas in which progesterone was acting to induce lordosis in female rats. I removed the ovaries, primed the females with subcutaneous estrogen injections, and used tiny cannula to place progesterone in brainstem regions thought to be the targets for that steroid's actions. This all seemed very scientific and straight forward.

However, these studies did not go as planned. Without progesterone, and even without estrogen, the females in my study continued to show lordosis. After repeated testing, with or without gonadal hormones, female rats (at least the well-mannered, white rats we studied at Michigan State) were still remarkably sexually receptive.

9. Golden widows

Frustrated, I looked for another research animal and received permission to bring golden hamsters into the lab. Female hamsters required both estrogen and progesterone to show sexual behavior. In fact, when given estrogen followed by progesterone female hamsters went into a frozen, trance-like posture. Here at last was an animal that seemed to follow the "rules." However, after less than one hour of mating, the behavior of female hamsters changed dramatically. They began to attack their - still sexually motivated - male partner. Removal of ovaries (or even adrenal glands) had no consequence for postcopulatory aggression in hamsters (Carter, 1972) (Carter, 1973) (Carter & Porges, 1974).

Early theories regarding the hormonal basis of female sexuality had been based primarily on studies of mammals with ovarian cycles. Cyclic steroid hormones could coordinate sexual receptivity and reflexes with ovulation. Golden hamsters, originating from the deserts of Syria, did indeed require a cocktail of steroids to bring them into estrus. Female hamsters showed four-day estrous cycles and could not be persuaded to mate without steroids. They came into heat and were tolerant of mating for a very limited time, just sufficient for impregnation. Other processes, triggered by mating then took over, and female hamsters turned on their partners, showing lethal aggression. If not separated following copulation some female hamsters would kill and even cannibalize the male. Hamsters had a short gestation and large litters, but also were well known for eating their young. Females of this species were extremely asocial when not in heat, perhaps because they had evolved in a habitat where resources were too sparse to support sharing (Murphy, 1985).

Once more my research suggested that – even in hamsters - female reproductive behaviors were not fully under the "control" of sex steroids. Sexual experience had a profound effect on female hamsters as it apparently did in rats. I tried adding more steroids, but this was not the answer. The relationships between steroids and behavior were not as consistent as the rodent literature of the period suggested. Again, something was amiss. Sexual and social experiences were having consequences that seemed to override the predicted relationships between steroid hormones and behavior.

10. Hormones and sex

Around this same time period, endocrine studies of humans and other primates were encountering similar issues. Obviously, humans and many other primate species also engaged in sex for reasons that were not limited to fertility (Beach, 1976). Sexual interactions had purposes and consequences that extended beyond the transfer of sperm. Furthermore, like social behavior more generally, some aspects of sexuality including genital reflexes, continued in hypogonadal humans (Burris et al., 1992). These findings suggested that reflexes and pathways necessary for sexual reflexes or even orgasm did not require high levels of gonadal steroids.

Physiological links between reproduction and behavior were less controversial than the construct of instinct, but came with their own issues. Although reflexes were still present, removing the gonads reduced mate seeking, sometimes call sexual motivation (Pfaff & Baum, 2018). Reproductive behaviors, including sexual and maternal behaviors, had seemed particularly likely to have a neuroendocrine basis. However, in studies focused on steroid hormones, this was surprisingly difficult to establish. Even the role of the nervous system, or at least the neocortex, also was open to question. For example, it was discovered early on that some components of sexual behavior continued even after ovariectomy or castration, and Beach had shown that decorticate female rats were capable of showing not just maternal behavior, but also lordosis. Beginning in the 1970s, there also were studies suggesting a central role for a decapeptide, known as gonadotropin releasing hormone (GnRH) in the control of female sexual behavior (Moss et al., 1975)(Sakuma & Pfaff, 1980). Nonsteroidal molecules were beginning to enter the field of reproductive endocrinology.

Decades later, I was offered an opportunity to help conduct a study of the biological basis of steroid hormones in human males. In that study we tested the response of hypogonadal or castrated men to tactile stimulation. This study was initiated by Julian Davidson, who had predicted that androgens would make men more sensitive to genital stimulation. The results of our study were remarkably clear and (of course) the opposite of Davidson’s prediction. Androgens actually reduced sensitivity to tactile and vibratory stimulation (Burris et al., 1991). Furthermore, even when untreated, several of the hypogonadal men in our study, who had no measurable levels of testosterone, reported being sexually active and capable of orgasm. Genitally-stimulated male rats, even after castration, retained ejaculatory reflexes, although their sexual motivation was impaired by the absence of gonadal steroids (a deficit also seen in humans) (Pfaff & Baum, 2018). These findings confirmed historical legends concerning the continuing capacity of male eunuchs to engage in sexual behavior.

If gonadal hormones were not essential for sex, what did that mean for neuroendocrine theories, which up to that point had been primarily focused on steroids? In this context, research on hypogonadal humans and rodents repeatedly supported the notion that there was more to sexual behavior than sex steroids. Furthermore, it was not just the causes, but also the consequences of sexual activity that began to suggest the possible importance of nonsteroidal hormones in reproduction. Testing these hypotheses would require exploring yet another animal model.

11. Lowell and the monogamous vole

In the late 1970s I was introduced to the prairie vole by Lowell Getz. Lowell was my colleague at the University of Illinois, where I held my first academic position. He was a field biologist studying population dynamics. Prairie voles were small rodents that could be studied in the laboratory and in the context of their natural history. In fact, within the field of ecology the booms and crashes in the abundance of microtine rodents (including voles and lemmings) were considered models for population dynamics (Carter et al., 1995).

Based on over 25 years of field research, as well as his early experience finding families of voles under haystacks on his family farm, Lowell had become convinced that prairie voles were living in monogamous pairs. Lowell's field research and the laboratory studies we conducted indicated that - among those animals that survived long enough to reproduce - prairie voles of both sexes were sharing a nest and raising offspring with their mates until one member of the pair died (Carter & Getz, 1993). Strangers of either sex were not welcome to join an established family group. Females of this species did not have ovarian cycles. In prairie voles reproduction in both sexes was not controlled by light cycles, but instead was regulated by social stimuli. Fathers were fully involved in care of the offspring, and about 70% of older siblings of both sexes remained as alloparents in the natal nest, eventually allowing the development of extended families. Alloparents were reproductively suppressed and also avoided incest. Males and females were similar in body size and hard to tell apart, even based on genital anatomy. Many behaviors of males were identical to those of females (Carter et al., 1995). From my perspective all of these traits were suspicious indicators that factors other than, or at least in addition to, gonadal hormones were at play in this species (Carter & Perkeybile, 2018).

Long-lasting social preferences and biparental care are rare among mammals, occurring in fewer than 5% of mammalian species and are more common in larger mammals, including canids and New World primates. The notion that prairie voles were monogamous was not well-received by other mammologists. After all, in nature voles were prey for many other species - as someone once said, "voles are the potato chips of the prairie." Over 90% of infant prairie voles did not survive to weaning and in the wild adults rarely lived more than a few months. Why would these small mammals bother to form long-lasting relationships?

We had discovered early in our work that if female prairie voles were exposed to a stranger of the opposite sex, a chemosensory pathway allowed a neuroendocrine cascade leading to ovarian or testicular activation. Stimuli from the male could triggered release of GnRH in the olfactory bulb and eventually the onset of estrus (Dluzen 1981) (Carter & Getz, 1993). But this socially-regulated reproductive system did not explain the formation of pair bonds. Ovariectomy or castration did not prevent the development of social preferences. It was social bonding that fascinated me. Exploring pair bonding would require a focus on species differences in sociality and also pointed us toward nongonadal hormones.

12. A “real” animal

Organismic biologists are expected to consider whatever they do in light of ecology and evolution. However, in the early part of my career I studied domesticated species. I became increasingly concerned that behaviors I saw in laboratory animals might simply be products of human intervention or domestication. Initially most of what was believed to be true about hormones and behavior was based on rats, mice and hamsters. Data that did not fit the patterns reported in laboratory species were generally ignored. But the relationships between physiology and behavior that we later observed in prairie voles were not only different from species like rats and hamsters, but the prairie voles often responded in directions that were opposite to those predicted by the literature based on more commonly studied rodents.

Here at last I thought was an authentic organism. Wild-caught voles came with parasites, unique dietary requirements and so forth. But at least they were the product of natural selection and not domestication. Furthermore, a variety of related voles existed within the genus *Microtus*, and some of these species did not seem to be monogamous (Dewsbury, 1981) (Parker & Lee, 2001). Even better, from my perspective, if prairie voles really had life-long pair bonds, perhaps they could be used to explore the biology of social attachment.

We tried various ways of asking voles questions about their social or sexual preferences (Carter & Getz, 1993). The systematic study of prairie vole preferences became possible because of a careful behavioral analysis by my postdoctoral fellow, Jessie Williams. Jessie developed a behavioral preference test that allowed animals to make choices between a familiar partner, a stranger or spending time alone. After living together both females and males showed strong behavioral preferences for familiar partners and, if they mated, in a matter of hours became aggressive toward strangers (Williams et al., 1992).

When we brought prairie voles into the lab we assumed, based on Lowell’s field data, that females and males also would show a sexual preference for their established partners. However, in 1985, the early days of these studies, DNA fingerprints became possible. Like a bad outcome on a TV reality show, DNA from offspring in our studies revealed that prairie voles were voluntarily having sex outside of the pair bond, even when they appeared to be aggressive toward intruders, including members of the opposite sex (Carter et al., 1995).

13. Social monogamy

Our studies in voles clearly indicated that the traits associated with monogamy were based on species differences in physiology. Furthermore, we discovered that monogamy was a social system, not simply a mating system. At the core of the prairie vole version of monogamy were social preferences, measured by social contact, but not by sexual preferences (Carter & Perkeybile, 2018).

I realized that what we were seeing in prairie voles was more accurately described as “social monogamy” – a set of behaviors characterized by selective social behaviors and lasting pair bonds. The capacity for social monogamy of prairie voles also was associated with unique patterns of physiology that affected the entire body. The monogamy of prairie voles actually included a coordinated set of features that resembled a “syndrome,” with both endocrine and

anatomical adaptations. Studies of prairie voles guided us into research on the importance of neuropeptides that would have been difficult to identify in animals that were less social and more dependent on the geophysical environment and gonadal steroids. As this work continued it would also become apparent that there were remarkable parallels between prairie voles and the behavior of postnatal women (Carter & Altemus, 1997), especially with regard to the capacity to form lasting relationships and to use those relationships to cope with stress. As explained below, my awareness of these similarities was heightened by concurrent events in my personal life, all of which led me to focus on oxytocin.

14. Life as a laboratory

On the morning of July 26, 1980 I was admitted to a birthing room at Christie Clinic in Champaign, Illinois. Although I had taught reproductive biology and had taken standard prenatal courses, I was not prepared for what happened next. After I failed to progress in the birth process - in what was considered a timely manner - my obstetrician was awaken from his sleep by the delivery-room nurses. The doctor seemed even more disoriented than I was, and told me I had to deliver my child within 24 hours of the time I had entered the hospital and before 6 am. (He had to attend his son's swim meet that morning.) My doctor also gave me three choices: labor induction with an infusion of oxytocin, being sliced open for a surgical birth, or (and I am serious) the potential that my child would die from a hospital infection. Before that day I had never been in a hospital as a patient, much less experienced surgery. I am reasonably certain that fear of a cesarian section and the insensitive management of my labor slowed the birth. I reluctantly accepted the oxytocin-induction alternative, rejected pain medications, and experienced a first-hand introduction to the contemporary birth experience.

A second pregnancy and lengthy bouts of lactation would become a major initial impetus for my personal obsession with oxytocin. However, as described elsewhere, my determination to study oxytocin was primarily driven by my concern over the consequences for infants of exposure to exogenous oxytocin (Pitocin), now widely used as a mechanism for facilitating labor (Harris & Carter, 2013).

15. Molecules and motherhood

Parenting is not generally a science-based process. Google and social media - for better or worse - are now major sources of education for modern parents. When my children were born, opinions on how to manage both the child and mother were either based on culture and tradition or, in some cases, books written by male pediatricians. My own experiences of motherhood were informed primarily by trial and error and a naïve notion that "mother nature" and biology would help guide me.

Prior to 1980, there was little scientific literature on the biology of human "motherhood." Based primarily on my own experience, I became convinced that the biology of lactation was in some way protective against the stresses associated with birth and childrearing. I began to search for an understanding of endogenous hormones associated with birth and

lactation that might help women and babies cope with stressful experiences (Carter & Altemus, 1997).

At that time, birth had been studied primarily from the perspective of delivery. The behavioral and physiological consequences of lactation were not well identified and still are not well understood. It was known that women who nursed their infants often and especially at night, would experience lactational amenorrhea. This natural and inherently "social" form of contraception was not perfect, but across millennia had helped humans space fertility and also gave mothers more time to rear their children (Short, 1984). Lactation created a unique physiological state that historically dominated the lives of postpubertal females. Modern living allowed a different endocrinology across the lifespan and it is that physiology that we have come to consider "normal" (Grant & Erickson, 2022). Imposed on top of this contemporary shift in human biology are hormonal manipulations, including hormonal contraception and postmenopausal hormone replacement therapies which first began to be widely available in the 1960s (Wilson, 1966) and still need to be better understood.

16. Oxytocin

Oxytocin, both as a molecule and in some cases a metaphor for safety, has been described in detail elsewhere (Hurlemann & Grinevich, 2018) (Jurek & Neumann, 2018) (Carter et al., 2020) (Carter, 2022). The unique chemistry of oxytocin, including its role as an anti-inflammatory, may explain many of its beneficial functions (Uvnas Moberg et al., 2019) (Carter & Kingsbury, 2022). However, the same structure that makes oxytocin biologically active, also made it difficult to study, helping to stir controversy around the molecule and concern over the value of measuring oxytocin, especially in bodily fluids. Several of these issues have been resolved as explained elsewhere (MacLean et al., 2019) (Gnanadesikan et al., 2021) (Gnanadesikan et al., 2022), and with the help of Evan MacLean and Hans Nazarloo we are continuing to improve our capacity to accurately measure endogenous oxytocin.

17. Historical context

Genes for oxytocin and its' receptor have an ancient lineage. Precursors can be traced back to the last common ancestor of both vertebrates and invertebrates, over 500 million years ago. A specific mammalian physiology emerged roughly 200 million years ago coincident with the evolution of the specific oxytocin molecule (Knobloch & Grinevich, 2014). The ligands and receptors for these systems have been influenced by whole genome duplications, subsequent evolutionary pressures and the continuing capacity of genes to be modified by mutations and epigenetic changes (Theofanopoulou, 2021) (Torday, 2022) (Danoff, Connelly, et al., 2021).

Oxytocin's effects on the nervous system and behavior have repeatedly been associated with sociality. Through various interactions with more primitive survival and reproductive strategies oxytocin supports selective social connections, cooperation and perceived safety (Carter, 1998). In a sense oxytocin is very old, but compared to other biologically active molecules it is also very modern (Carter & Kingsbury, 2022) (Carter, 2022)

Recognition of the role of oxytocin in birth and lactation began in the early 20th century. However, because oxytocin initially was discovered in the context of female reproduction and thought to have no role in males (Murphy et al., 1987) (Carter, 1992), other functions were slow to be recognized. Oxytocin is now described as a pleiotrophic molecule, with effects on the capacity for sociality and reproduction in both sexes. Oxytocin also has a central role in the management of virtually all aspects of health and disease, including major functions in the regulation of the immune and autonomic nervous systems (Carter et al., 2020). But this awareness would take over 40 years to emerge.

In the 1990s, in collaboration with Margaret Altemus and Laura Redwine we conducted a series of human experiments comparing stress-reactivity in lactating, versus bottle feeding mothers (Carter et al., 2001). We found that lactating women were better adapted to both physical and psychological challenges than bottle feeding mothers (Altemus et al., 1995). Among the differences we saw were higher levels of parasympathetic control of the heart and larger lymphocyte responses to a mitogen. These studies of the immune system were done in blood samples. Remarkably, even the blood of lactating women was different than their bottle-feeding counterparts (Redwine et al., 2001). This research of course was not based on randomized studies. Mothers were not assigned to groups and group differences might have been due to processes unrelated to lactation. However, our findings were consistent with my personal experience of lactation as well as a slowly expanding scientific literature (Carter & Altemus, 1997).

During the 1980s, two childbirths and a total of almost four years of lactation had given me first-hand opportunities to experience the functions of exogenous and endogenous oxytocin. The birth of my sons aligned with the time when I was beginning my earliest studies in prairie voles. Among the recurrent parallels between the endocrinology of prairie voles and motherhood were high levels of oxytocin, low levels of sex steroids and an exaggerated capacity to form long-lasting relationships.

Having a career and a family also offered a unique opportunity to experience the consequences of acute and chronic stressors, both with and without high levels of oxytocin. The coincidence of these pulled me deeply into the study of oxytocin in the context of the capacity to cope with stress and reinforced my long-term concern regarding the lasting consequences of early experience. Furthermore, embedded in the data we collected from lactating women were early hints implicating oxytocin in the regulation of the autonomic and immune systems (Altemus et al., 2001) - topics that I would return to decades later (Carter et al., 2020).

Looking back we can see that early studies attempting to find highly specific functions for oxytocin were misguided. There was evidence that oxytocin did improve the capacity of mammals, including humans, to manage stress, autonomic responses, and to overcome fears, including those associated with attending to infants. But behavior does not appear in a vacuum. Understanding the adaptive nature of the effects of the oxytocin system in the face of stressors requires a sense of physiological and behavioral context as well as knowledge of development and evolution (Berendzen & Manoli, 2022). Those complex perspectives are still emerging.

Based on lessons from rodents and my personal experiences as a mother, I was repeatedly drawn toward the hypothesis that both social attachments and oxytocin were involved in stress and coping. The capacity to cope with stress, not just during lactation, but also across the lifespan was likely related to oxytocin (Carter, 1998) (Neumann, 2002) (Feldman, 2021) and its critical role in sociality. However, studies of endocrine mechanisms underlying responses to challenge historically were focused on hormones in the HPA axis and there was little awareness of oxytocin in the field of stress biology. From 1985–2001 I was a guest researcher in the pediatric endocrinology branch at the National Institutes of Health (NIH) in Bethesda. George Chrousos, who directed that laboratory was dedicated to understanding the HPA axis, including CRF and glucocortiocoids (Chrousos & Gold, 1992). Several of my students worked at NIH and George and his colleagues taught us a great deal about how neuroendocrinologists viewed stress and measured hormones. However, with a few exceptions, oxytocin was not yet included as a major factor in stress research.

18. Oxytocin: A missing link - or not?

An early backlash had been directed toward the idea that oxytocin was involved with either the brain or behavior. Oxytocin was believed to be made in the brain and released at the pituitary, primarily acting on peripheral target tissues, including the uterus and breast. It was not initially accepted as a behaviorally active molecule. It took years before evidence accumulated showing that oxytocin was not simply a pituitary hormone, but was acting in the brain (Bridges, 2015) (Rosenblatt et al., 1988).

For example, in 1979 Cort Pedersen published high profile papers implicating oxytocin in the onset of maternal behavior in rats (Pedersen, 2004). However, these studies had proven difficult to replicate. Subsequent research by Susan Fahrbach and Donald Pfaff suggested that the functions of oxytocin in maternal behavior were most easily detected against a background of stressful experiences and HPA axis hormones (Fahrbach et al., 1986). An adaptive role for oxytocin in stress-coping was later reinforced in studies by Liberzon, who showed that treatment with glucocorticoids increased expression of the oxytocin receptor in brain areas involved in managing stress (Liberzon & Young, 1997). The importance of steroid hormones in regulating the oxytocin system was overlooked at first, especially by neuroscientists and is still often ignored (Jirikowski et al., 2018).

Beginning in the late 1990s researchers in Japan (Nishimori et al., 1996) and at the NIH in Bethesda (Caldwell et al., 2017) had begun to create mice that were mutant for oxytocin or for the oxytocin receptor. These mice gave birth and, although they were sometimes slow to respond, did show some parental behavior to their pups. Studies in oxytocin knock-out mice indicated that the oxytocin peptide was not “essential” for maternal behavior. Early studies, especially based on knock-out mice, seemed to indicate that oxytocin might have only one unique function – milk ejection. This apparently narrow functional niche reduced interest in oxytocin within neurobiology. However, earlier studies by Janet Amico and colleagues, had also revealed that oxytocin knock-out mice had deficits in their capacity to manage various kinds of stress and were autonomically overreactive (Amico et al., 2008).

The first evidence in prairie voles specifically implicating oxytocin in positive social behaviors had appeared in the 1980s, arising from the thesis research of my graduate student Diane Witt. Diane's studies showed that voluntary social contact was increased by intracranial injections of oxytocin - even in the absence of positive effects on reproductive behavior (Witt et al., 1990). This led to a series of other studies in prairie voles and later in rats suggesting direct neural effects of oxytocin in the capacity for social approach.

It is difficult to differentiate reactions to social stimuli, but in general healthy animals with comparatively high levels of oxytocin may be better able to manage most kinds of stressors, including those associated with infant care or approach by another adult (Carter, 2022). When we started our vole research there was already evidence that sexual behavior was associated with the release of oxytocin into blood. This had been reported in several species, including male rats and rabbits and male and female humans (Carter, 1992). Our partner preference paradigm revealed that exogenous oxytocin, injected into the ventricles of the brain, could facilitate selective social behavior in both male and female prairie voles. Conversely, blocking the oxytocin receptor prevented the development of partner preferences and other selective social behaviors. However, if oxytocin receptors were available, oxytocin, when given alone, stimulated - not social preferences - but high levels of *nonselective* social contact and possibly a reduction in autonomic reactivity in both sexes (Cho et al., 1999).

19. Vasopressin

Obviously, it would have been easier to study the traits of social monogamy if oxytocin were acting alone. This was not the case. Many molecules and neural systems, especially the vagus nerve, were working behind the scenes to support sociality in general and social bonds in particular. If animals were allowed to mate the formation of a partner preference occurred more quickly. Once again, as with rats and hamsters, something associated with sexual interactions was changing behavior. That "something" would turn out to include not just oxytocin, but also vasopressin.

Vasopressin, oxytocin and their receptors work together as part of a highly evolved system. The implications of these interactions are sometimes overlooked. These are beyond the scope of the present review, but are of particular relevance to the dynamics of mammalian social behaviors and attachment (Carter, 2017a) (Carter, 2017b).

Particularly dramatic in male prairie vole behavior was the fact that within a few hours after mating males began to show aggression toward strangers (Carter, 2017a). Postcopulatory aggression did not seem to be "oxytocin talking" or at least not the voice of an abundance of oxytocin receptors, which were generally associated with positive sociality and calm states. Females also would attack strangers, but not with the vigor shown by males. In a scene ripped from the post-coital playbook of golden hamsters, generally good-natured prairie voles turned into killers (Getz et al., 1981). The capacity to form and defend social bonds in voles required both oxytocin and vasopressin. We now understand that these two molecules and their receptors are components of a finely tuned system with a central role in the willingness of animals engage in social behavior – and with many other functions.

In the 1980s vasopressin had been implicated in hamster aggression and territoriality by Craig Ferris and Elliot Albers (Ferris et al., 1986). During this period, Geert De Vries had shown that central vasopressin was androgen-dependent, specifically in a neural axis involved in agonistic behaviors, including the medial amygdala, bed nucleus of the stria terminalis and lateral septum (De Vries, 2004). To my endocrine-tuned eye vasopressin seemed a likely candidate for male post-copulatory aggression toward unfamiliar strangers. Our experiments in prairie voles supported this hypothesis (Winslow et al., 1993). The onset of post-copulatory aggression required access to a specific vasopressin (V1a) receptor found in brain (and different from the vasopressin V2 receptors found in the kidney). Furthermore, the onset of post-mating aggression was not prevented by blocking the oxytocin receptor. Vasopressin was an essential ingredient in an endogenous cocktail capable of converting prairie voles into lethal weapons that were aimed selectively at intruders.

The most important clues that would lead us out of the “vole hole,” away from steroids and toward peptides, came from studying the effects of sexual experience on subsequent social behaviors. Gonadal steroids (at the time of testing) were not essential for partner preferences to form. There was more to pair bond formation than simply selecting a partner. Social bonds could occur without mating, but sexual interactions significantly speeded up the process (Williams et al., 1992). Sexual activity released oxytocin (Carter, 1992), which reinforced my interest in this peptide as a causal candidate in the induction of partner preferences. After mating, as in hamsters, we observed aggression, and we were later able to show that vasopressin, acting on the V1a receptor, was essential for the onset of postcopulatory aggression (Winslow et al., 1993).

20. Vasopressin: Fear or bravery?

Taken together our studies of vasopressin and oxytocin suggested that aggression and positive social behaviors were independently regulated by a coordinated process that involved both peptides (Cho et al., 1999). These studies implicated oxytocin-vasopressin interactions in emotional regulation. The androgen-sensitivity of both vasopressin and its receptors encouraged investigators studying vasopressin to focus on males (De Vries, 2004). But both males and females needed vasopressin to form pair bonds.

One of my graduate students, John Stribley, also looked at the developmental consequences of vasopressin (Stribley & Carter, 1999). Aggression increased in both sexes following exposure during the first week of life to exogenous vasopressin and was reduced in animals that received a vasopressin antagonist. However, the treatments that affected aggression did not affect the capacity to form a pair bond. Research in other various rodents has since suggested that adversity, especially in early life, is associated with increases in both vasopressin and sensitivity of vasopressin receptors (Kompier et al., 2019). However, the developmental consequences of vasopressin in both sexes needs to be studied in more detail, since both vasopressin and the vasopressin receptor can be both context- and steroid-dependent.

The link between vasopressin and aggression is still not fully understood. For example, using gene-editing techniques to eliminate the expression of the vasopressin V1a receptor

in hamsters does not eliminate aggression, but instead produces animals that are more aggressive than normal (Taylor et al., 2022). This finding suggests that it is too early to assume that vasopressin is simply a hormone capable of inducing overt aggression. It takes courage for a naïve animal to mate, defend a partner (Winslow et al., 1993), or approach offspring (Bales et al., 2004). Perhaps vasopressin, especially in conjunction with oxytocin, is better conceptualized as a component of a neural system that helps overcome fear and especially in males permits "bravery," and behavioral exploration – necessary for various forms of sociality and defensive behaviors to be expressed.

The neural systems that regulate sociality also are tuned in early life. Severe stressors, trauma or neglect are increasingly considered important factors in the capacity to show sociality and to regulate emotions across the lifespan. More subtle effects of different amounts of early maternal stimulation have been detected in rodent models, where it has been possible to describe physiological mechanisms underlying both positive experiences and varying degrees of social deprivation. Studies in nonhuman mammals have revealed that the effects of early experience can have different consequences in males and females, possibly through differential effects on oxytocin and/or vasopressin receptors (Bales & Carter, 2003) (Bales et al., 2007) (Bales et al., 2011). Possible interactions among the effects of either developmental exposure to exogenous peptides or to early adversity remain largely unresolved. However, these findings, even when limited to rodents, are helping to direct attention to the epigenetic and sexually-dimorphic developmental roles of oxytocin and vasopressin (Perkeybile & Bales, 2017) (Perkeybile et al., 2019) (Ellis et al., 2021).

21. Peptide receptors

The actions of both oxytocin and vasopressin depend on receptors for these molecules. Studies in voles provided a novel model for beginning to understand peptide receptors. The first analysis of prairie vole oxytocin receptors had been conducted by Diane Witt (Witt et al., 1991). Diane compared oxytocin receptor distributions in prairie voles to those in rats. Striking differences were apparent, especially in brain networks that were implicated in social or aggressive behaviors in other species. In that time period, it was assumed that in general peptide receptor distributions were highly conserved across species; in this context the dramatic differences we saw in brain receptors between rats and voles were especially unpredicted.

Our observations in prairie voles triggered later peptide receptor comparisons in other species. The brain regions that differed in peptide receptors were not necessarily identical across species or even among individuals. However, closely related and highly social species (such as prairie and pine voles) differed dramatically from nonmonogamous voles (meadow and montane voles) (Wang et al., 1998). In subsequent research, Miranda Lim, Larry Young, Zuoxin Wang and their colleagues were able to transfer peptide receptor genes from one species to another, eliciting at least some of the traits of "monogamy" in less social species (Lim et al., 2004). Taken together, these findings brought voles as well as oxytocin, vasopressin and their receptors to the attention of the emerging field of molecular neurobiology.

Exciting ongoing studies in several laboratories are now using both natural species variation and genetically engineered animals to probe the molecular and evolutionary origins of sociality (Kelly & Ophir, 2015) (Phelps et al., 2017) (Donaldson & Manoli, 2020). For example, in prairie voles CRISPR mutations that blocked the expression of the oxytocin receptor did not prevent the formation of partner preferences (Berendzen et al., 2022). Our prior pharmacological studies in prairie voles had revealed that either oxytocin or vasopressin alone were not sufficient to explain pair bond formation (Cho et al., 1999). Furthermore, pair bonding required interactions among oxytocin, vasopressin, hormones of the HPA axis, including glucocorticoids and CRF (DeVries, 2002) as well as dopamine (Aragona & Wang, 2009) and opioids (Burkett et al., 2011). These molecules allow relationships to be rewarding (Dölen & Malenka, 2014) and also help to regulate reactivity to stress in a manner that is both adaptive and sexually dimorphic (DeVries et al., 2007) (DeVries et al., 1996). At present, even in voles the physiology and benefits of social attachment remain only partially understood. However, these findings are forcing new interpretations of the biology of social attachment (Berendzen & Manoli, 2022) (Carter, 2022), and continuing to suggest that the actions of oxytocin alone are not sufficient to explain pair bonding in voles.

22. Epigenetics and the capacity for sociality

Among the possible mechanisms mediating the effects of early experiences are changes in the availability or sensitivity of peptide receptors. For example, in prairie voles we discovered that a brief perinatal exposure to oxytocin, acting on the oxytocin receptor alters behavioral phenotypes (Bales & Carter, 2003) (Kenkel et al., 2019). In general, prairie voles receiving extra oxytocin are more social and pair bond more quickly. When given exogenous oxytocin they also show an increase in oxytocin receptors in early life. Conversely, blocking oxytocin receptors on the first day of life, leaves prairie voles unable to form adult pair bonds and less likely to show paternal and alloparental behavior. Our findings continue to support the hypothesis that the consequences of early nurture (or its absence) are registered in and possibly mediated by epigenetic changes in the oxytocin system. Findings such as these suggest that perinatal exposure to oxytocin has lasting effects on sociality. Furthermore, oxytocin is rarely used alone, the effects of oxytocin can be dose-dependent and, depending on other factors, could influence other systems. For example, during labor oxytocin is often used in conjunction with opioids and may be associated with a cesarian delivery (Kenkel, 2020). The widespread use of oxytocin in the perinatal period supports the continuing need for a deeper analysis of behavioral consequences for the offspring and mother of these treatments (Harris & Carter, 2013).

In addition, early neglect or trauma might have particularly long-lasting consequences for the capacity to release or respond to oxytocin or could upregulate the vasopressin system. Physiological studies of the consequences of differential experiences were initially focused on hormones of the HPA axis and adverse effects of early “stress.” However, HPA effects are difficult to describe dynamically. The HPA axis also does not always provide a clear link between early experiences and subsequent sociality (Hostinar et al., 2014). At least part of the process that permits selective social behavior involves oxytocin-vasopressin pathways.

23. Love lost

The most compelling evidence for the importance of sociality and connection in humans comes from studies of isolation (Holt-Lunstad, 2018) or perceived loneliness (Cacioppo & Cacioppo, 2018)(de Lange et al., 2021). Social relationships affect all aspects of existence, and play a major role in human health and well-being. Social support and other forms of positive relationships, including helping and caring for others, benefits health and longevity in both those who give (Brown & Brown, 2015) (Chen et al., 2021) and those who receive (Horn and Carter, 2021). It is now well accepted that social isolation, disconnection and perceived loneliness can induced a sense of fear and physical and mental dysfunction, while social co-regulation has the power to protect and heal, processes that are in many cases managed by the autonomic nervous system and a perception of safety (Porges, 2021) (Carter et al., 2020) (Ludwig & Welch, 2022).

In the absence of relationships and a sense of safety, even when other basic needs are met, and especially in early life, individuals may fail to flourish (Harlow & Harlow, 1966) (Bowlby, 1978). In humans, the benefits of positive social experiences have been examined primarily through descriptive or epidemiological studies (Ryff et al., 2004) (Holt-Lunstad, 2018). However, the limitations inherent in human research left us dependent on animal models for the discovery of mechanisms for both sociality and the consequences of its absence. Prairie voles have proven a fertile testing ground for uncovering the biology of social isolation and love lost. These studies have implicated low levels of oxytocin and immune and autonomic reactivity in the behavioral symptoms, suggestive of anxiety and depression seen during social isolation (Grippo et al., 2009) (Smith & Wang, 2014) (Pohl et al., 2019). Furthermore, social isolation also is followed by reductions in telomere length, which is associated with aging and longevity (Stevenson et al., 2019). Of particular importance is the finding that these effects often can be prevented by treatments with exogenous oxytocin (Abdelwahab et al., 2021).

24. Sex differences

Sex differences in neural responses to early experiences have been repeatedly detected in both rodents and humans, with increasing evidence that steroid-peptide interactions in early life might explain at least some of the many sex differences that have been reported. For example, in rats, steroid-peptide interactions may play an important role in individual differences in the expression of social behavior. Virgin females given exogenous estrogen showed an increase in oxytocin receptor binding, but this effect was limited to female rats that were showing high levels of nurture and not seen in the low licking and grooming mothers (Champagne et al., 2001). Champagne and colleagues also discovered an association between endogenous oxytocin receptors and individual variation in maternal behavior. Females that showed higher levels of nurture toward their pups had high levels of oxytocin receptors in regions of the hypothalamus and amygdala that have been implicated in maternal behavior and aggression. Group differences in licking/grooming behavior were no longer seen when mothers were treated centrally with an oxytocin antagonist.

25. Steroids

Based on research in rats, it was initially assumed that the expression of oxytocin receptors would be regulated by estrogen and that the relationship between oxytocin and estrogen would be duplicated in other mammals. As we began to anticipated, this did not turn out to be the case in prairie voles. An initially unexpected feature of hypothalamic oxytocin receptors in voles was their comparative lack of dependence on sex steroids. Estrogen, whether produced in the ovaries or given as an exogenous treatment brought female voles into behavioral estrus. However, Witt had shown that in contrast to rats, estrogen had a remarkably small effect on the abundance of oxytocin receptors (Witt et al., 1991).

My earlier studies of rodent sexual behavior also had focused on steroids and especially interactions between estrogen and progesterone. However, once more prairie voles were different. Females of this species did not use progesterone to induce sexual receptivity, apparently depending entirely on estrogen (Carter et al., 1989). Ovarian steroids also were not necessary for female prairie voles to form pair bonds, which could occur after ovariectomy and in reproductively naïve animals. However, mating – probably through the release of oxytocin and vasopressin – did facilitate the formation of partner preferences (Williams et al., 1992). Furthermore, the capacity of oxytocin to increase sociality did not require estrogen priming.

This seemed to fit with the natural history of prairie voles. As a species prairie voles were induced-ovulators finely tune to use social behavior, rather than ovarian cycles, to adaptively regulate their physiology. As described above, this was not consistent with theories at that time that had been constructed primarily on data collected from cycling rodents. Relationships among peptides, including both oxytocin and vasopressin and their receptors, and gonadal steroids are still incompletely described. The link between steroids and peptides that had drawn me into this field is still not well defined. These may be regulated in part through species and sex-specific epigenetic effects on peptide receptors during early life (Perkeybile et al., 2019) (Kenkel et al., 2019).

26. Prairie voles seem insensitive to androgens

Prairie voles, like many other socially monogamous species, tend to have less sexual dimorphism in anatomy and behavior, possibly because they are less sensitive to androgens than polygynous species. Despite a relatively small sex difference in body size and genital appearance, male prairie voles have comparatively high levels of testosterone in early life (Lansing et al., 2013). We have proposed that this may be due to androgen-receptor insensitivity, which in turn might leave socially monogamous mammals more dependent on peptides, including oxytocin and vasopressin, and also generally more social than their polygynous counterparts.

This hypothesis has been detailed in an earlier paper (Carter & Perkeybile, 2018), but remains to be empirically tested. The developmental functions of oxytocin and vasopressin in sexual differentiation are not fully understood. However, moving away from androgens as the primary mechanism for sex differences may be of particular importance in highly social

species, such as prairie voles (Bales et al., 2011), with exceptionally high levels of peptides as well as adrenal steroids (Carter et al., 1995).

27. The oxytocin-vasopressin system is designed to be changed

Oxytocin has a central role in behavioral functions while coordinating hormones of the HPA axis including epigenetic control of glucocorticoid receptors (Champagne & Curley, 2016), effects on the vasopressin system (Murgatroyd et al., 2016) and the immune system (Danoff, Wroblewski, et al., 2021). Adaptive consequences of epigenetically modifying oxytocin and its receptors also have been detected across the lifespan, but are especially important around the time of birth, when mammals must anticipate and then cope with life outside of the maternal environment (Ben-Ari, 2018) (Carter & Kingsbury, 2022).

Early experiences, in part through epigenetic change, allows what has been called “adaptive calibration” – the capacity to use experiences to both adjust to differential experiences and to predict the future (Ellis & Del Giudice, 2019) (Ellis et al., 2021). The features of this kind of adaptation might escape detection in complex environments where the amounts of peptide and other experiences are variable, or in species less dependent than prairie voles or humans on oxytocin and/or experiences in early life?

The biological processes that underlie various forms of sociality are remarkably flexible but require updating and adjustment. Successful social interactions depend on moving beyond the present moment, learning from the past and planning for the future. Early life stress or nurture can developmentally adjust the brain and immune system, the entire body and even the microbiota (Sherwin et al., 2019) (Morais et al., 2021). Much of this work has focused on factors in the HPA axis (Champagne, 2009), or systems implicated in reproduction (Crews, 2008). Of course, these are only part of the epigenetic mechanism through which information relevant to social experience is transmitted to future generations.

In other words, love and lasting relationships must be constantly adjusted. Much of our ongoing research is building on the hypothesis that epigenetic changes in the oxytocin receptor offer a mechanism that will explain the important role of early experiences. Among recent examples our studies in prairie voles have revealed developmental effects of oxytocin exposure on the expression of the oxytocin receptor.

These studies take advantage of the discovery by our collaborator, Jessica Connelly that prairie voles and humans share a pattern of CpG sites in a region of the gene regulating the oxytocin receptor (Danoff, Connelly, et al., 2021). In prairie voles there is a *de novo* increase in methylation around the time of birth that regulates (in this case silences) the expression of the oxytocin receptor (Perkeybile et al., 2019). Methylation of specific CpG sites in the oxytocin receptor gene offers a molecular tuning device or rheostat regulating the oxytocin receptor. DNA methylation of these sites is one important mechanism through which early experience can influence the oxytocin system across the lifespan.

We now know that oxytocin-vasopressin pathways are dynamically altered by early experience. For example, a variety of different manipulations, including exposure to oxytocin (Kenkel et al., 2019), different amounts of maternal nurture (Nephew &

Murgatroyd, 2013) (Perkeybile & Bales, 2015)(Perkeybile & Bales, 2017)(Perkeybile et al., 2019) in early life and in social experiences in adulthood (Grippo et al., 2011) (Grippo et al., 2009) (Grippo et al., 2019), can have lasting functional and epigenetic consequences (Danoff, et al., 2021). In the context of cross-talk between oxytocin, vasopressin and their various receptors this dynamic system creates a vast number of permutations that may help to allow individual, species and sex differences in this system, and in the capacity for sociality and coping with stress. Whether methylation of peptide receptors is primarily genetic, or is transmitted to the next generation through epigenetic tuning, or represents a combination of these presents a challenge to our understanding of the relevance of epigenetics as a mechanism for transmitting the effects of early experience. Our ongoing studies with the Connelly laboratory are devising novel ways to use the parallels between humans and prairie voles to address these questions.

28. Oxytocin and “sociostasis”

Oxytocin always functions against an endocrine background of other molecules with relationships that are most easily understood in the context of evolution, survival and reproduction. The biology of sexuality and sociality were forged from primitive elements, providing solutions to the harsh demands of life on early Earth. Molecular mechanisms through which oxytocin supports a “social solution to the stress of life” are detailed elsewhere (Carter & Kingsbury, 2022). However, several of the functions of oxytocin may be overlook if not considered in the context of stress and adversity (Carter et al., 2020) (Carter, 2022).

Oxytocin functions through complex interactions with other protective systems. Key among these are neuroendocrine systems that involve vasopressin and the HPA axis, including corticotropin releasing factors (CRF1 and CRF2) and their receptors (Vuppaladhadiam et al., 2020). Fully appreciating oxytocin and sociality requires awareness of oxytocin’s effects on protective immune and autonomic processes (Carter, 2017a) (Carter et al., 2020) (Porges, 2021) (Carter & Kingsbury, 2022). See Table 1 for a partial list comparing the properties and functions of oxytocin, vasopressin and CRF.

Interactions among these systems can help to explain how and why oxytocin and sociality are repeatedly implicated in dealing with what Walter Cannon described as “homeostasis (Goldstein & Kopin, 2007) (Matthews & Tye, 2019), which Selye (Selye, 1956) called the “stress of life,” and others have called “allostasis” (Schulkin & Sterling, 2019) (Quintana & Guastella, 2020).

Lou Cozolino previously used the term *sociostasis* to describe the reciprocal influence individuals have on one another as they regulate each other’s biology, psychology, and states of mind across what he has termed the social synapse (Cozolino, 2021). Cozolino’s derivation of the term sociostasis was made in a clinical context and was an expansion of the language of Murray Bowen, who created a systemic approach to therapy based on the regulation of anxiety within a family. The role of relationships in emotional and physiological regulation is one example, among many, of the importance of sociality in homeostasis and allostasis. This awareness is now well accepted in psychology, but until

recently was largely missing from “stress” research (Tomova et al., 2019), as well as medicine in general. Consistent with and expanding on Cozolino and Bowen, I suggest here that “sociostasis” be used as a broader term acknowledging the critical role of sociality in physiological and behavioral homeostasis, as well as allostasis – all of which are targets for the functions of oxytocin (Quintana & Guastella, 2020) (Carter et al., 2020).

29. Time matters

Survival depends on the capacity to respond to acute challenges and also chronic conditions. Vasopressin, CRF, glucocorticoids and many other classical stress hormones have benefits in the face of an immediate threat or danger. These molecules may act quickly and are associated with acute stressors and individual defense strategies. Acute responses to behavioral and physiological threats are essential to survival (Quintana & Guastella, 2020). In contrast, chronic or excessive exposure to threats and “stress” hormones and molecules from the immune system can be damaging (Carter & Kingsbury, 2022). However, it is critical to realize that the physiological responses to acute and chronic challenges are often different, (Antoni, 2019) and also may differ between males and females (Bangasser et al., 2019) (Zuloaga et al., 2020).

Social buffering and oxytocin can be of particular importance during chronic conditions. By calibrating physiological and behavioral responses in anticipation of future demands, oxytocin facilitates an accurate sense of safety and thus facilitates survival. Thus, oxytocin could be thought of as a sociostatic molecule, with particularly important consequences during periods of chronic challenge.

There are many points in the mammalian life course where oxytocin is particularly beneficial. Among these are the need to make a safe transition from intra- and extrauterine life and care for altricial young (Kingsbury & Bilbo, 2019). Oxytocin allows a slow reproductive strategy in humans, including the eventual development of a massive cortex, permitting cognition and language, supported by breast feeding and extended parental behavior. Embedded in the success of human evolution is the capacity to develop selective and lasting social attachments and trust (Carter, 2014) – essential components of love (Table 2). A sense of safety also is of importance to survival and longevity across time. The biological properties of oxytocin help to explain the long term physical and emotional benefits of secure relationships (Horn & Carter, 2021) and the value of adding a sense of emotional safety to our awareness of processes that maintained the survival and wellbeing of our species (Cozolino, 2021) (Porges, 2021).

30. The politics of love and sex

Concepts like “love” were outside the mainstream of neuroscience, especially when I began my research, and too esoteric a topic for someone from my practical midwestern background. Eventually studies of the effects of oxytocin in prairie vole pair bonding would become central to the acceptance of the notion that there is a neural basis for social behavior, including the capacity for adult social attachments and love.

In the 1990s - and without my input - our research on vole monogamy was pressreleased by one of my collaborators. This led to several news articles describing the prairie vole work as a study of the hormonal basis of “love.” I was “accused” by the Media and even some other scientists of studying “love.”

The timing of this media coverage coincided (to the exact day) with the review of my pending NIH grant renewal. The summary statement of the review of my grant application went so far as to criticize what was being written about our work by journalists. I was stunned.

The NIH program officer who managed my proposal acknowledged that criticizing my grant application for what had been written by the press was inappropriate. But it was too late; the review panel’s score had been influenced, and the grant was not funded. I also found myself defending what we were doing and eventually trying to explain what pair bonding in prairie voles had to do with love. Within Academia studying love was apparently taboo. My attempts to deal with that criticism forced me to think more deeply about what was meant by love and whether oxytocin did in fact have a role in love (Carter, 2022).

Searching for understanding I began to organize workshops, reviews and books around the topic of the relationship between biology and love (Carter et al., 1997) (Carter & Dantzer, 2022). Although a painful lesson, this experience put me on the path I have followed for the rest of my career.

I was not the first scientist whose work was blocked because it was considered too close to the study of love. The most famous example had appeared in 1975. At that time most research in psychology focused on the individual. Studies by Elaine Hatfield and Ellen Berscheid were pioneering the study of adult social relationships - a topic which is now recognized as foundational to understanding human behavior (Reis et al., 2013).

Berscheid and Hatfield received a $84,000 National Science Foundation grant (big money in those days) and with it a “Golden Fleece Award” for “squandering” federal resources to study “love.” To quote Senator William Proxmire (originator of this dubious Award), the basis for this distinction was the following. *“I object to this not only because no one—not even the National Science Foundation—can argue that falling in love is a science; not only because I’m sure that even if they spend $84 million or $84 billion they wouldn’t get an answer that anyone would believe. I’m also against it because* ***I don’t want the answer****. I believe that 200 million other Americans want to leave some things in life a mystery, and right on top of the things we don’t want to know is why a man falls in love with a woman and vice versa.”*

In an evolutionary sense, oxytocin – an ancient molecule - is older than love - the metaphor. Love was historically treated as an abstract metaphor, perhaps both too frivolous, and at the same time too sacred or vulnerable to be examined with the analytic tools of science. Both love and oxytocin have been misunderstood or in some cases denigrated as topics for serious scientific study. Yet there is a homologous neurobiology below the surface of social bonds, that requires oxytocin and sits at the core of love (Table 2).

31. Wandering in Wonderland

My attempts to understand the biology of sociality began a bit like the adventures of *Alice in Wonderland*. I chased not "white rabbits," but certainly many other creatures into the underworld in a search for the biological basis of sociality and reproductive behaviors. Over time, I gained access to a small zoo of interesting creatures and was able to studied the causes and consequences of social interactions in guinea pigs, rats, mice, hamsters, lemmings, gerbils, marmosets and quail.

However, it was comparing prairie voles to more common laboratory animals, most of which were polygynous, that drew me into an alternative universe. Like Alice chasing the White Rabbit, I found surprises at every turn, especially when I tried to applied endocrine theories based on rats or hamsters to prairie voles. The results of my studies were only rarely what was predicted. In fact, what I found was closer to Alice's adventures in *"Through the Looking-Glass."* When Alice climbed through a mirror, she discovered that, as in a reflection, everything inside the mirror was reversed. This was what happened when I tried to apply accepted theories concerning the endocrinology of behavior to a "real animal," known as the prairie vole. Social behavior is variable and presumably dependent on species, individual and sex differences, with mechanisms at least partially dependent on peptides. However, in some cases the endocrinology of different species appeared to be reversed. Peptides, working through different mechanisms and often in collaboration with classical steroid hormones, provided an alternative or additional behavioral and physiological solution to the "stress of life" (Carter & Kingsbury, 2022).

In comparatively asocial species, such as golden hamsters, cues from the physical environment and gonadal steroids regulate reproduction. In contrast, the behavior of highly social species, including prairie voles depend heavily on social cues and more "modern" peptides including oxytocin. Less social mammals, such as hamsters, may use the same basic molecules, but with genetic and epigenetic programs that depend more strongly on either more ancient neuropeptides (such as vasopressin) or other hormones (such as steroids). Looking across species, we see many examples of roles for peptide hormones in the mediation of rapid and adaptive behavioral changes. For example, even in hamsters the social experience of mating is capable of quickly changing behavioral states from sexual receptivity to aggression, probably through the dynamic actions of peptide hormones including oxytocin and vasopressin (Whitman & Albers, 1995) (Harmon et al., 2002).

Social attachments are hypothetical constructs. No one has ever seen a "social bond" (Carter, 2017b). However, the high levels of sociality and co-regulatory processes found in prairie voles allowed us to explore a natural model for the study of the biology of what humans call "love." Data, collected over more than four decades, reinforced my notion that specific molecules, including oxytocin, would be easier to investigate than metaphorical concepts like sociality or even sex.

The properties of oxytocin offered a potential neurobiological component of mechanisms for positive social behaviors in general and social attachment in particular. Studies of the effects of oxytocin have been primarily conducted in adults, and the developmental consequences

of oxytocin have received less attention. That work is ongoing and has turned toward understanding the epigenetic consequences of oxytocin (Perkeybile et al., 2019) (Kenkel et al., 2019). It is difficult, perhaps impossible, to appreciate the consequences of oxytocin in adulthood, without awareness of the individual's social and developmental history.

32. Summary

From a scientific perspective humans are biological creatures with physical and emotional limitations created by our evolved physiology (Carter, 2014). It is in these contexts that the study of sex, love and oxytocin has much to offer. Of course the study of sex and love, and even the functions of oxytocin, have not always been met with acceptance (Carter, 2022). Vulnerability concerning topics related to reproduction and perhaps life in general stands in the path of a deeper appreciation of these subjects. However, avoidance by science and medicine of sex and love leaves us with blind spots in our awareness of the importance of sociality and co-regulation as a central mechanism for the management of health and wellbeing, which could be termed sociostasis.

Oxytocin exposure is most often associated with increased sociality, however, treatments such as those used to facilitate child birth, are likely to be dose-dependent and depend on the availability of other molecules (Grant & Erickson, 2022). Oxytocin, especially if there has been an alteration in receptor sensitivity, could have unexpected or apparently paradoxical consequences. The capacity of oxytocin and vasopressin to bind to each other's receptors also opens possible dose-sensitive cross-talk between these peptides (Carter, 2017a). Feedback mechanisms between ligands and receptors, common in hormonal systems, contribute to repeated examples of the Goldilock's effect or too much or too little of a good thing. For these reasons, attempts to model or manipulate behavior using a single peptide or receptor are rarely successful (Carter et al., 2020).

Dozens of reviews and hundreds of empirical papers now support the hypothesis that the capacity for social behaviors and many aspects of physiology are programmed by experiences in early life (Ellis et al., 2021). Furthermore, the presence or absence of oxytocin, vasopressin and the expression of their receptors have consequences for this programming. However, this was not known when I began my own attempts to understand the lasting consequences of early experiences.

Social relationships in general and sex and love in particular have been marginalized topics in scientific study (Reis et al., 2013). Contradictory and contentious political pressures surround both sex and love. It has taken decades for science to acknowledge that selective social attachments are not limited to humans, are not simply theoretical constructs, and have a neurobiological reality (Carter, 2017a) (Carter, 2022). Perhaps as we look back on the 20th century, we may be able to give the little prairie vole a bit of credit for offering an exaggerated version of sociality and attachments, and thus highlighting the neurobiological mechanisms that support the capacity for love and the social management of challenges?

Awareness of the behavioral effects of specific chemicals with identifiable neural targets, especially in the second half of the 20th century, suggested paths forward that are helping

to reduce some of the theoretical controversy surrounding the biology of love and sex. As clearly articulated by Senator Proximire, deep and often unappreciated vulnerability is associated with love. Some people would prefer to remain in ignorance of the notion that there is a biological basis for love. If spending money on understanding human love was off-limits, imagine what Senator Proxmire might have thought of federal funding for studies of social bonding in prairie voles?

But the vole is out of the bag, with no way to put it back in. Prairie voles allowed us to study the natural history of the capacity for sociality in general and selective social preferences in particular (Carter & Getz, 1993). Monogamy in prairie voles and oxytocin as a "love drug," became part of pop culture.

> "Can't take it back once it's been set in motion You know I need you for the oxytocin"
>
> By Billie Eilish, 2021

As I became more aware of the functions of oxytocin and the importance of lasting social bonds there was no turning back. Understanding this became my passion as I continued to explore the wonderland that is science. The biology of love and perceived safety are natural medicines. The same deep biology that underlies love protects and heals in the face of all forms of chronic disease (Furman et al., 2019) and adversity (Carter et al., 2020). Looking back on my journey I believe humans are a species in search of, not just love, but also what I am calling here sociostasis – defined as the capacity for social behavior to play a central role in both homeostasis and allostasis.

The price we have paid for the molecular biology revolution, and not taking seriously basic physiology for the last half a century is that we are in considerable ignorance of what happens when the body (from cell to society) is "threatened" (Porges, 2021) (Leckman et al., 2021). Whether this is due to a virus or other challenges, including early adversity or severe trauma the pattern is similar. Why sex, love and oxytocin are not front and center in medicine is a topic in itself worthy of discussion.

Acknowledgement and Dedication

When I started my journey in academics, it was the 1960s and anything seemed possible. Love was in the air. I met a remarkable partner, Stephen Porges. Steve would become my main support through the ups and downs of being a woman in science and the father of our two sons. Everything I do is dedicated to Steve and our sons Seth and Eric.

Over my career I became a member of at least seven different academic societies. Among these was the Society for Neuroscience (SfN), which I joined in 1973. The specific mission of SfN was and remains "to advance the understanding of the brain and the nervous system." Behavior, arguably the most important function of the brain, was never an explicit focus of SfN. Furthermore, SfN became increasingly technology oriented, and the meetings (sometimes with more than 30,000 participants) were impersonal and chaotic.

In 1993 Matthew Wayner founded the International Behavioral Neuroscience Society (IBNS). The transdisciplinary approach to behavioral neurobiology within IBNS filled several gaps. IBNS also welcomed cultural, ethnic and gender diversity and held its meetings in smaller international venues. Matt had anticipated the growing need for journals in behavioral neuroscience and had in 1966 launched *Physiology and Behavior*. Several other journals followed including, in 1977, *Neuroscience and Biobehavioral Reviews*. The survival of IBNS also depended on the organizational skills of Marianne Van Wagner. Marianne began as Matt's assistant on his journals. However, over three decades she transformed herself into a full service conference planner, part time psychotherapist and the emotional glue that has kept IBNS, and several other societies, functional and financially solvent. This paper is respectfully dedicated to both Matt and Marianne.

Funding:

The research described here was funded primarily by the National Science Foundation and National Institute of Health. Additional support for studies of the biology of love came from the Fetzer Foundation and the Templeton Foundation.

References

Abdelwahab LA, Galal OO, Abd El-Rahman SS, El-Brairy AI, Khattab MM, & El-Khatib AS (2021). Targeting the oxytocin system to ameliorate early life depressive-like behaviors in maternally-separated rats. Biological & Pharmaceutical Bulletin. 10.1248/bpb.b21-00247

Ainsworth MDS (1969). Object Relations, Dependency, and Attachment: A Theoretical Review of the Infant-Mother Relationship. Child Development, 40(4), 969–1025. 10.2307/1127008 [PubMed: 5360395]

Altemus M, Deuster PA, Galliven E, Carter CS, & Gold PW (1995). Suppression of hypothalmic-pituitary-adrenal axis responses to stress in lactating women. The Journal of Clinical Endocrinology and Metabolism, 80(10), 2954–2959. 10.1210/jcem.80.10.7559880 [PubMed: 7559880]

Altemus M, Redwine LS, Leong YM, Frye CA, Porges SW, & Carter CS (2001). Responses to laboratory psychosocial stress in postpartum women. Psychosom Med, 63(5), 814–821. [PubMed: 11573030]

Amico JA, Miedlar JA, Cai H-M, & Vollmer RR (2008). Oxytocin knockout mice: A model for studying stress-related and ingestive behaviours. Progress in Brain Research, 170, 53–64. 10.1016/S0079-6123(08)00405-6 [PubMed: 18655871]

Antoni FA (2019). Magnocellular Vasopressin and the Mechanism of "Glucocorticoid Escape." Frontiers in Endocrinology, 10, 422. 10.3389/fendo.2019.00422 [PubMed: 31297096]

Aragona BJ, & Wang Z (2009). Dopamine regulation of social choice in a monogamous rodent species. Frontiers in Behavioral Neuroscience, 3, 15. 10.3389/neuro.08.015.2009 [PubMed: 19707518]

Bales KL, Boone E, Epperson P, Hoffman G, & Carter CS (2011). Are behavioral effects of early experience mediated by oxytocin? Frontiers in Psychiatry, 2, 24. 10.3389/fpsyt.2011.00024 [PubMed: 21629841]

Bales KL, & Carter CS (2003). Sex differences and developmental effects of oxytocin on aggression and social behavior in prairie voles (Microtus ochrogaster). Horm Behav, 44(3), 178–184. [PubMed: 14609540]

Bales KL, Kim AJ, Lewis-Reese AD, & Carter CS (2004). Both oxytocin and vasopressin may influence alloparental behavior in male prairie voles. Horm Behav, 45(5), 354–361. [PubMed: 15109910]

Bales KL, Plotsky PM, Young LJ, Lim MM, Grotte N, Ferrer E, & Carter CS (2007). Neonatal oxytocin manipulations have long-lasting, sexually dimorphic effects on vasopressin receptors. Neuroscience, 144(1), 38–45. 10.1016/j.neuroscience.2006.09.009 [PubMed: 17055176]

Bangasser DA, Eck SR, & Ordoñes Sanchez E (2019). Sex differences in stress reactivity in arousal and attention systems. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology, 44(1), 129–139. 10.1038/s41386-018-0137-2 [PubMed: 30022063]

Beach FA (1955). The descent of instinct. Psychological Review, 62(6), 401–410. 10.1037/h0049138 [PubMed: 13273556]

Beach FA (1976). Sexual attractivity, proceptivity, and receptivity in female mammals. Hormones and Behavior, 7(1), 105–138. 10.1016/0018-506X(76)90008-8 [PubMed: 819345]

Ben-Ari Y (2018). Oxytocin and Vasopressin, and the GABA Developmental Shift During Labor and Birth: Friends or Foes? Frontiers in Cellular Neuroscience, 12, 254. 10.3389/fncel.2018.00254 [PubMed: 30186114]

Berendzen KM, & Manoli DS (2022). Rethinking the Architecture of Attachment: New Insights into the Role for Oxytocin Signaling. Affective Science. 10.1007/s42761-022-00142-5

Berendzen KM, Sharma R, Mandujano MA, Wei Y, Rogers FD, Simmons TC, Seelke AHM, Bond JM, Larios RD, Sherman M, Parthasarathy S, Espineda I, Knoedler JR, Beery A, Bales KL, Shah NM,

& Manoli DS (2022). Oxytocin receptor is not required for social attachment in prairie voles (p. 2022.07.22.501192). bioRxiv. 10.1101/2022.07.22.501192

Bosmans G, Bakermans-Kranenburg MJ, Vervliet B, Verhees MWFT, & van IJzendoorn MH (2020). A learning theory of attachment: Unraveling the black box of attachment development. Neuroscience and Biobehavioral Reviews, 113, 287–298. 10.1016/j.neubiorev.2020.03.014 [PubMed: 32276142]

Bowlby J (1978). Attachment theory and its therapeutic implications. Adolescent Psychiatry, 6, 5–33. [PubMed: 742687]

Bridges RS (2015). PMC4342279; Neuroendocrine regulation of maternal behavior. Front Neuroendocrinol, 36(Journal Article), 178–196. 10.1016/j.yfrne.2014.11.007 [PubMed: 25500107]

Brown SL, & Brown RM (2015). Connecting prosocial behavior to improved physical health: Contributions from the neurobiology of parenting. Neuroscience and Biobehavioral Reviews, 55, 1–17. 10.1016/j.neubiorev.2015.04.004 [PubMed: 25907371]

Burkett JP, Spiegel LL, Inoue K, Murphy AZ, & Young LJ (2011). Activation of μ-opioid receptors in the dorsal striatum is necessary for adult social attachment in monogamous prairie voles. Neuropsychopharmacology : Official Publication of the American College of Neuropsychopharmacology, 36(11), 2200–2210. 10.1038/npp.2011.117 [PubMed: 21734650]

Burris AS, Banks SM, Carter CS, Davidson JM, & Sherins RJ (1992). A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. Journal of Andrology, 13(4), 297–304. [PubMed: 1399830]

Burris AS, Gracely RH, Carter CS, Sherins RJ, & Davidson JM (1991). Testosterone therapy is associated with reduced tactile sensitivity in human males. Hormones and Behavior, 25(2), 195–205. 10.1016/0018-506x(91)90050-r [PubMed: 2066080]

Cacioppo JT, & Cacioppo S (2018). The growing problem of loneliness. Lancet (London, England), 391(10119), 426. 10.1016/S0140-6736(18)30142-9

Caldwell HK, Aulino EA, Freeman AR, Miller TV, & Witchey SK (2017). Oxytocin and behavior: Lessons from knockout mice. Developmental Neurobiology, 77(2), 190–201. 10.1002/dneu.22431 [PubMed: 27513442]

Carcea I, Caraballo NL, Marlin BJ, Ooyama R, Riceberg JS, Mendoza Navarro JM, Opendak M, Diaz VE, Schuster L, Alvarado Torres MI, Lethin H, Ramos D, Minder J, Mendoza SL, Bair-Marshall CJ, Samadjopoulos GH, Hidema S, Falkner A, Lin D, … Froemke RC (2021). Oxytocin neurons enable social transmission of maternal behaviour. Nature. 10.1038/s41586-021-03814-7

Carter CS (1972). Postcopulatory sexual receptivity in the female hamster: The role of the ovary and adrenal. Hormones and Behavior, 3(3), 261–265. 10.1016/0018-506x(72)90039-6 [PubMed: 4681747]

Carter CS (1973). Stimuli contributing to the decrement in sexual receptivity of female golden hamsters (Mesocricetus auratus). Animal Behaviour, 21(4), 827–834. 10.1016/s0003-3472(73)80108-3 [PubMed: 4798200]

Carter CS (1992). Oxytocin and sexual behavior. Neurosci Biobehav Rev, 16(2), 131–144. [PubMed: 1630727]

Carter CS (1998). Neuroendocrine perspectives on social attachment and love. Psychoneuroendocrinology, 23(8), 779–818. [PubMed: 9924738]

Carter CS (2014). Oxytocin pathways and the evolution of human behavior. Annu Rev Psychol, 65, 17–39. 10.1146/annurev-psych-010213-115110 [PubMed: 24050183]

Carter CS (2017a). The Oxytocin-Vasopressin Pathway in the Context of Love and Fear. Frontiers in Endocrinology, 8, 356. 10.3389/fendo.2017.00356 [PubMed: 29312146]

Carter CS (2017b). The Role of Oxytocin and Vasopressin in Attachment. Psychodynamic Psychiatry, 45(4), 499–517. 10.1521/pdps.2017.45.4.499 [PubMed: 29244625]

Carter CS (2022). Oxytocin and love: Myths, metaphors and mysteries. Comprehensive Psychoneuroendocrinology, 9, 100107. 10.1016/j.cpnec.2021.100107 [PubMed: 35755926]

Carter CS, & Altemus M (1997). Integrative functions of lactational hormones in social behavior and stress management. Annals of the New York Academy of Sciences, 807, 164–174. 10.1111/j.1749-6632.1997.tb51918.x [PubMed: 9071349]

Carter CS, Altemus M, & Chrousos GP (2001). Neuroendocrine and emotional changes in the post-partum period. Progress in Brain Research, 133, 241–249. 10.1016/s0079-6123(01)33018-2 [PubMed: 11589134]

Carter CS, & Dantzer R (2022). Love and fear: A special issue. Comprehensive Psychoneuroendocrinology, 11, 100151. 10.1016/j.cpnec.2022.100151 [PubMed: 35967926]

Carter CS, DeVries AC, & Getz LL (1995). Physiological substrates of mammalian monogamy: The prairie vole model. Neurosci Biobehav Rev, 19(2), 303–314. [PubMed: 7630584]

Carter CS, & Getz LL (1993). Monogamy and the prairie vole. Sci Am, 268(6), 100–106. [PubMed: 8516669]

Carter CS, Kenkel WM, MacLean EL, Wilson SR, Perkeybile AM, Yee JR, Ferris CF, Nazarloo HP, Porges SW, Davis JM, Connelly JJ, & Kingsbury MA (2020). Is Oxytocin "Nature's Medicine"? Pharmacological Reviews, 72(4), 829–861. 10.1124/pr.120.019398 [PubMed: 32912963]

Carter CS, & Kingsbury MA (2022). Oxytocin and oxygen: The evolution of a solution to the "stress of life." Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 377(1858), 20210054. 10.1098/rstb.2021.0054 [PubMed: 35856299]

Carter CS, Lederhendler I, & Kirkpatrick B (1997). The integrative neurobiology of affiliation. Introduction. Ann N Y Acad Sci, 807, xiii–xviii. [PubMed: 9071340]

Carter CS, & Perkeybile AM (2018). The Monogamy Paradox: What Do Love and Sex Have to Do With It? 6(202). 10.3389/fevo.2018.00202

Carter CS, & Porges SW (1974). Ovarian hormones and the duration of sexual receptivity in the female golden hamster. Hormones and Behavior, 5(4), 303–315. 10.1016/0018-506x(74)90017-8 [PubMed: 4477151]

Carter CS, Witt DM, Manock SR, Adams KA, Bahr JM, & Carlstead K (1989). Hormonal correlates of sexual behavior and ovulation in male-induced and postpartum estrus in female prairie voles. Physiology & Behavior, 46(6), 941–948. 10.1016/0031-9384(89)90195-9 [PubMed: 2699360]

Champagne FA (2009). Nurturing nature: Social experiences and the brain. J Neuroendocrinol, 21(10), 867–868. 10.1111/j.1365-2826.2009.01901.x [PubMed: 19686450]

Champagne FA, & Curley JP (2016). Plasticity of the Maternal Brain Across the Lifespan. New Directions for Child and Adolescent Development, 2016(153), 9–21. 10.1002/cad.20164

Champagne F, Diorio J, Sharma S, & Meaney MJ (2001). Naturally occurring variations in maternal behavior in the rat are associated with differences in estrogen-inducible central oxytocin receptors. Proc Natl Acad Sci U S A, 98(22), 12736–12741. 10.1073/pnas.221224598 [PubMed: 11606726]

Chen E, Lam PH, Finegood ED, Turiano NA, Mroczek DK, & Miller GE (2021). The balance of giving versus receiving social support and all-cause mortality in a US national sample. Proceedings of the National Academy of Sciences of the United States of America, 118(24), e2024770118. 10.1073/pnas.2024770118 [PubMed: 34099550]

Cho MM, DeVries AC, Williams JR, & Carter CS (1999). The effects of oxytocin and vasopressin on partner preferences in male and female prairie voles (Microtus ochrogaster). Behav Neurosci, 113(5), 1071–1079. [PubMed: 10571489]

Chrousos GP, & Gold PW (1992). The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. Jama, 267(9), 1244–1252. [PubMed: 1538563]

Cozolino L (2021). The Making of a Therapist: A Practical Guide for the Inner Journey. W. W. Norton & Company.

Crews D (2008). Epigenetics and its implications for behavioral neuroendocrinology. Frontiers in Neuroendocrinology, 29(3), 344–357. 10.1016/j.yfrne.2008.01.003 [PubMed: 18358518]

Danoff JS, Connelly JJ, Morris JP, & Perkeybile AM (2021). An epigenetic rheostat of experience: DNA methylation of OXTR as a mechanism of early life allostasis. Comprehensive Psychoneuroendocrinology, 8, 100098. 10.1016/j.cpnec.2021.100098 [PubMed: 35757665]

Danoff JS, Wroblewski KL, Graves AJ, Quinn GC, Perkeybile AM, Kenkel WM, Lillard TS, Parikh HI, Golino HF, Gregory SG, Carter CS, Bales KL, & Connelly JJ (2021). Genetic, epigenetic, and environmental factors controlling oxytocin receptor gene expression. Clinical Epigenetics, 13(1), 23. 10.1186/s13148-021-01017-5 [PubMed: 33516250]

de Lange A-MG, Kaufmann T, Quintana DS, Winterton A, Andreassen OA, Westlye LT, & Ebmeier KP (2021). Prominent health problems, socioeconomic deprivation, and higher brain age in lonely

and isolated individuals: A population-based study. Behavioural Brain Research, 414, 113510. 10.1016/j.bbr.2021.113510 [PubMed: 34358570]

De Vries GJ (2004). Minireview: Sex differences in adult and developing brains: compensation, compensation, compensation. Endocrinology, 145(3), 1063–1068. 10.1210/en.2003-1504 [PubMed: 14670982]

DeVries A (2002). Corticotropin-releasing factor induces social preferences in male prairie voles. Psychoneuroendocrinology, 27(6), 705–714. 10.1016/s0306-4530(01)00073-7 [PubMed: 12084663]

DeVries AC, Craft TK, Glasper ER, Neigh GN, & Alexander JK (2007). 2006 Curt P. Richter award winner: Social influences on stress responses and health. Psychoneuroendocrinology, 32(6), 587–603. [PubMed: 17590276]

DeVries AC, DeVries MB, Taymans SE, & Carter CS (1996). The effects of stress on social preferences are sexually dimorphic in prairie voles. Proc Natl Acad Sci U S A, 93(21), 11980–11984. [PubMed: 8876248]

Dewsbury DA (1981). An exercise in the prediction of monogamy in the field from laboratory data on 42 species of muroid rodents. Biologist, 63, 138–162.

Dölen G, & Malenka RC (2014). The emerging role of nucleus accumbens oxytocin in social cognition. Biological Psychiatry, 76(5), 354–355. 10.1016/j.biopsych.2014.06.009 [PubMed: 25103539]

Donaldson ZR, & Manoli DS (2020). Blueprints for Bonding? New Genetic Tools to Parse the Neural Basis of Pair Bonding in Prairie Voles. Neuroscience, 448, 311. 10.1016/j.neuroscience.2020.08.038 [PubMed: 33092783]

Ellis BJ, & Del Giudice M (2019). Developmental Adaptation to Stress: An Evolutionary Perspective. Annual Review of Psychology, 70, 111–139. 10.1146/annurev-psych-122216-011732

Ellis BJ, Horn AJ, Carter CS, van IJzendoorn MH, & Bakermans-Kranenburg MJ (2021). Developmental programming of oxytocin through variation in early-life stress: Four meta-analyses and a theoretical reinterpretation. Clinical Psychology Review, 86, 101985. 10.1016/j.cpr.2021.101985 [PubMed: 33770582]

Fahrbach SE, Morrell JI, & Pfaff DW (1986). Effect of varying the duration of pre-test cage habituation on oxytocin induction of short-latency maternal behavior. Physiology & Behavior, 37(1), 135–139. 10.1016/0031-9384(86)90396-3 [PubMed: 3737711]

Feldman R (2021). Social Behavior as a Transdiagnostic Marker of Resilience. Annual Review of Clinical Psychology, 17, 153–180. 10.1146/annurev-clinpsy-081219-102046

Ferris CF, Meenan DM, Axelson JF, & Albers HE (1986). A vasopressin antagonist can reverse dominant/subordinate behavior in hamsters. Physiol Behav, 38(1), 135–138. [PubMed: 3786493]

Fleming AS, & Rosenblatt JS (1974). Olfactory regulation of maternal behavior in rats. II. Effects of peripherally induced anosmia and lesions of the lateral olfactory tract in pup-induced virgins. Journal of Comparative and Physiological Psychology, 86(2), 233–246. 10.1037/h0035936 [PubMed: 4590492]

Furman D, Campisi J, Verdin E, Carrera-Bastos P, Targ S, Franceschi C, Ferrucci L, Gilroy DW, Fasano A, Miller GW, Miller AH, Mantovani A, Weyand CM, Barzilai N, Goronzy JJ, Rando TA, Effros RB, Lucia A, Kleinstreuer N, & Slavich GM (2019). Chronic inflammation in the etiology of disease across the life span. Nature Medicine, 25(12), 1822–1832. 10.1038/s41591-019-0675-0

Getz LL, Carter CS, & Gavish L (1981). The mating system of the prairie vole, Microtus ochrogaster: Field and laboratory evidence for pair-bonding. Behavioral Ecology and Sociobiology, 189–194.

Gnanadesikan GE, Hammock EAD, Tecot SR, Carter CS, & MacLean EL (2021). Specificity of plasma oxytocin immunoassays: A comparison of commercial assays and sample preparation techniques using oxytocin knockout and wildtype mice. Psychoneuroendocrinology, 132, 105368. 10.1016/j.psyneuen.2021.105368 [PubMed: 34364024]

Gnanadesikan GE, Hammock EAD, Tecot SR, Lewis RJ, Hart R, Carter CS, & MacLean EL (2022). What are oxytocin assays measuring? Epitope mapping, metabolites, and comparisons of wildtype & knockout mouse urine [Preprint]. Neuroscience. 10.1101/2022.03.03.482682

Goldstein DS, & Kopin IJ (2007). Evolution of concepts of stress. Stress, 10(2), 109–120. [PubMed: 17514579]

Grant AD, & Erickson EN (2022). Birth, love, and fear: Physiological networks from pregnancy to parenthood. Comprehensive Psychoneuroendocrinology, 100138. 10.1016/j.cpnec.2022.100138 [PubMed: 35757173]

Grippo AJ, McNeal N, Watanasriyakul WT, Cacioppo S, Scotti M-AL, & Dagner A (2019). Behavioral and cardiovascular consequences of disrupted oxytocin communication in cohabitating pairs of male and female prairie voles. Social Neuroscience, 14(6), 649–662. 10.1080/17470919.2019.1572031 [PubMed: 30658044]

Grippo AJ, Pournajafi-Nazarloo H, Sanzenbacher L, Trahanas DM, McNeal N, Clarke DA, Porges SW, & Carter CS (2011). Peripheral oxytocin administration buffers autonomic but not behavioral responses to environmental stressors in isolated prairie voles. Stress, 15(2), 149–161. 10.3109/10253890.2011.605486 [PubMed: 21854168]

Grippo AJ, Trahanas DM, Zimmerman RR, Porges SW, & Carter CS (2009). Oxytocin protects against negative behavioral and autonomic consequences of long-term social isolation. Psychoneuroendocrinology, 34(10), 1542–1553. [PubMed: 19553027]

Harlow HF, & Harlow M (1966). Learning to love. American Scientist, 54(3), 244–272. [PubMed: 4958465]

Harmon AC, Huhman KL, Moore TO, & Albers HE (2002). Oxytocin inhibits aggression in female Syrian hamsters. Journal of Neuroendocrinology, 14(12), 963–969. 10.1046/j.1365-2826.2002.00863.x [PubMed: 12472877]

Harris JC, & Carter CS (2013). Therapeutic interventions with oxytocin: Current status and concerns. Journal of the American Academy of Child and Adolescent Psychiatry, 52(10), 998–1000. 10.1016/j.jaac.2013.08.001 [PubMed: 24074464]

Holt-Lunstad J (2018). Why Social Relationships Are Important for Physical Health: A Systems Approach to Understanding and Modifying Risk and Protection. Annual Review of Psychology, 69, 437–458. 10.1146/annurev-psych122216-011902

Horn AJ, & Carter CS (2021). Love and longevity: A Social Dependency Hypothesis. Comprehensive Psychoneuroendocrinology, 8, 100088. 10.1016/j.cpnec.2021.100088 [PubMed: 35757670]

Hostinar CE, & Gunnar MR (2015). Social Support Can Buffer against Stress and Shape Brain Activity. AJOB Neuroscience, 6(3), 34–42. 10.1080/21507740.2015.1047054 [PubMed: 26478822]

Hostinar CE, Sullivan RM, & Gunnar MR (2014). Psychobiological mechanisms underlying the social buffering of the hypothalamic-pituitary-adrenocortical axis: A review of animal models and human studies across development. Psychological Bulletin, 140(1), 256–282. 10.1037/a0032671 [PubMed: 23607429]

Hrdy SB (2009). Mothers and Others: The Evolutionary Origins of Mutual Understanding. Belknap Press of Harvard University Press.

Hurlemann R, & Grinevich V (2018). Behavioral pharmacology of neuropeptides: Oxytocin. Springer.

Jirikowski GF, Ochs SD, & Caldwell JD (2018). Oxytocin and Steroid Actions. Current Topics in Behavioral Neurosciences, 35, 77–95. 10.1007/7854_2017_9 [PubMed: 28812264]

Jurek B, & Neumann ID (2018). The Oxytocin Receptor: From Intracellular Signaling to Behavior. Physiological Reviews, 98(3), 1805–1908. 10.1152/physrev.00031.2017 [PubMed: 29897293]

Kelly AM, & Ophir AG (2015). Compared to what: What can we say about nonapeptide function and social behavior without a frame of reference? Current Opinion in Behavioral Sciences, 6, 97–103. 10.1016/j.cobeha.2015.10.010 [PubMed: 26858966]

Kenkel W (2020). Birth signalling hormones and the developmental consequences of caesarean delivery. Journal of Neuroendocrinology, n/a(n/a), e12912. 10.1111/jne.12912 [PubMed: 33145818]

Kenkel WM, Perkeybile A-M, Yee JR, Pournajafi-Nazarloo H, Lillard TS, Ferguson EF, Wroblewski KL, Ferris CF, Carter CS, & Connelly JJ (2019). Behavioral and epigenetic consequences of oxytocin treatment at birth. Science Advances, 5(5), eaav2244. 10.1126/sciadv.aav2244 [PubMed: 31049395]

Keverne EB, & Kendrick KM (1992). Oxytocin facilitation of maternal behavior in sheep. Ann N Y Acad Sci, 652, 83–101. [PubMed: 1385685]

Kingsbury MA, & Bilbo SD (2019). The inflammatory event of birth: How oxytocin signaling may guide the development of the brain and gastrointestinal system. Front Neuroendocrinol, 55(Journal Article), 100794. 10.1016/j.yfrne.2019.100794 [PubMed: 31560883]

Knobloch HS, & Grinevich V (2014). Evolution of oxytocin pathways in the brain of vertebrates. Frontiers in Behavioral Neuroscience, 8, 31. 10.3389/fnbeh.2014.00031 [PubMed: 24592219]

Kompier NF, Keysers C, Gazzola V, Lucassen PJ, & Krugers HJ (2019). Early Life Adversity and Adult Social Behavior: Focus on Arginine Vasopressin and Oxytocin as Potential Mediators. Frontiers in Behavioral Neuroscience, 13, 143. 10.3389/fnbeh.2019.00143 [PubMed: 31404254]

Lansing SW, French JA, & Lonstein JS (2013). Circulating plasma testosterone during early neonatal life in the socially monogamous and biparental prairie vole (Microtus ochrogaster). Psychoneuroendocrinology, 38(2), 306–309. 10.1016/j.psyneuen.2012.06.003 [PubMed: 22770983]

Leckman JF, Ponguta LA, Pavarini G, Hein SD, McCarthy MF, Staiti H, Hanöz-Penney S, Rubinstein J, Pruett KD, Yazgan MY, Fallon NS, Hartl FJ, Ziv M, Salah R, Britto PR, Fitzpatrick S, & Panter-Brick C (2021). Love and peace across generations: Biobehavioral systems and global partnerships. Comprehensive Psychoneuroendocrinology, 8, 100092. 10.1016/j.cpnec.2021.100092 [PubMed: 35757671]

Lehrman DS (1953). A Critique of Konrad Lorenz's Theory of Instinctive Behavior. The Quarterly Review of Biology, 28(4), 337–363. 10.1086/399858 [PubMed: 13121237]

Leng G, & Leng RI (2021). Oxytocin: A citation network analysis of 10 000 papers. Journal of Neuroendocrinology, e13014. 10.1111/jne.13014 [PubMed: 34328668]

Levine S (2005). Developmental determinants of sensitivity and resistance to stress. Psychoneuroendocrinology, 30(10), 939–946. 10.1016/j.psyneuen.2005.03.013 [PubMed: 15958281]

Liberzon I, & Young EA (1997). Effects of stress and glucocorticoids on CNS oxytocin receptor binding. Psychoneuroendocrinology, 22(6), 411–422. 10.1016/s0306-4530(97)00045-0 [PubMed: 9364620]

Lim MM, Wang Z, Olazabal DE, Ren X, Terwilliger EF, & Young LJ (2004). Enhanced partner preference in a promiscuous species by manipulating the expression of a single gene. Nature, 429(6993), 754–757. [PubMed: 15201909]

Lorenz K (1935). Der Kumpan in der Umwelt des Vogels. Der Artgenosse als auslösendes Moment sozialer Verhaltungsweisen. Journal Für Ornithologie. Beiblatt.(Leipzig).

Lorenz K, Latzke M, & Salzen E (2021). On aggression. Routledge.

Ludwig RJ, & Welch MG (2022). Wired to Connect: The Autonomic Socioemotional Reflex Arc. Frontiers in Psychology, 13. https://www.frontiersin.org/articles/10.3389/fpsyg.2022.841207

MacLean EL, Wilson SR, Martin WL, Davis JM, Nazarloo HP, & Carter CS (2019). Challenges for measuring oxytocin: The blind men and the elephant? Psychoneuroendocrinology, 107, 225–231. 10.1016/j.psyneuen.2019.05.018 [PubMed: 31163380]

Matthews GA, & Tye KM (2019). Neural mechanisms of social homeostasis. Annals of the New York Academy of Sciences, 1457(1), 5–25. 10.1111/nyas.14016 [PubMed: 30875095]

Meaney MJ (2001). Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. Annual Review of Neuroscience, 24, 1161–1192. 10.1146/annurev.neuro.24.1.1161

Morais LH, Golubeva AV, Casey S, Scott KA, Ramos Costa AP, Moloney GM, Dinan TG, & Cryan JF (2021). Early-life oxytocin attenuates the social deficits induced by caesarean-section delivery in the mouse. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 10.1038/s41386-021-01040-3

Moss RL, McCann SM, & Dudley CA (1975). Releasing hormones and sexual behavior. Progress in Brain Research, 42, 37–46. 10.1016/S0079-6123(08)63639-0 [PubMed: 1105666]

Murgatroyd CA, Hicks-Nelson A, Fink A, Beamer G, Gurel K, Elnady F, Pittet F, & Nephew BC (2016). Effects of Chronic Social Stress and Maternal Intranasal Oxytocin and Vasopressin on Offspring Interferon-γ and Behavior. Frontiers in Endocrinology, 7, 155. 10.3389/fendo.2016.00155 [PubMed: 28018290]

Murphy MR (1985). History of the Capture and Domestication of the Syrian Golden Hamster (Mesocricetus auratus Waterhouse). In Siegel HI (Ed.), The Hamster: Reproduction and Behavior (pp. 3–20). Springer US. 10.1007/978-1-4757-0815-8_1

Murphy MR, Seckl JR, Burton S, Checkley SA, & Lightman SL (1987). Changes in oxytocin and vasopressin secretion during sexual activity in men. The Journal of Clinical Endocrinology and Metabolism, 65(4), 738–741. 10.1210/jcem-65-4-738 [PubMed: 3654918]

Nephew B, & Murgatroyd C (2013). The role of maternal care in shaping CNS function. Neuropeptides, 47(6), 371–378. 10.1016/j.npep.2013.10.013 [PubMed: 24210943]

Neumann ID (2002). Involvement of the brain oxytocin system in stress coping: Interactions with the hypothalamo-pituitary-adrenal axis. Prog Brain Res, 139, 147–162. [PubMed: 12436933]

Nishimori K, Young LJ, Guo Q, Wang Z, Insel TR, & Matzuk MM (1996). Oxytocin is required for nursing but is not essential for parturition or reproductive behavior. Proceedings of the National Academy of Sciences, 93(21), 11699–11704.

Numan M (2006). Hypothalamic neural circuits regulating maternal responsiveness toward infants. Behav Cogn Neurosci Rev, 5(4), 163–190. [PubMed: 17099111]

Parker KJ, & Lee TM (2001). Central Vasopressin Administration Regulates the Onset of Facultative Paternal Behavior in Microtus pennsylvanicus (Meadow Voles). Hormones and Behavior, 39(4), 285–294. 10.1006/hbeh.2001.1655 [PubMed: 11374914]

Perkeybile AM, & Bales KL (2015). Early rearing experience is associated with vasopressin immunoreactivity but not reactivity to an acute non-social stressor in the prairie vole. Physiology & Behavior, 147, 149–156. 10.1016/j.physbeh.2015.04.024 [PubMed: 25890274]

Perkeybile AM, & Bales KL (2017). Intergenerational transmission of sociality: The role of parents in shaping social behavior in monogamous and non-monogamous species. J Exp Biol, 220(Pt 1), 114–123. 10.1242/jeb.142182 [PubMed: 28057834]

Perkeybile AM, Carter CS, Wroblewski KL, Puglia MH, Kenkel WM, Lillard TS, Karaoli T, Gregory SG, Mohammadi N, Epstein L, Bales KL, & Connelly JJ (2019). Early nurture epigenetically tunes the oxytocin receptor. Psychoneuroendocrinology, 99, 128–136. 10.1016/j.psyneuen.2018.08.037 [PubMed: 30227351]

Pfaff DW, & Baum MJ (2018). Hormone-dependent medial preoptic/lumbar spinal cord/autonomic coordination supporting male sexual behaviors. Molecular and Cellular Endocrinology, 467, 21–30. 10.1016/j.mce.2017.10.018 [PubMed: 29100889]

Phelps SM, Okhovat M, & Berrio A (2017). Individual Differences in Social Behavior and Cortical Vasopressin Receptor: Genetics, Epigenetics, and Evolution. Frontiers in Neuroscience, 11, 537. 10.3389/fnins.2017.00537 [PubMed: 29085274]

Pohl TT, Young LJ, & Bosch OJ (2019). Lost connections: Oxytocin and the neural, physiological, and behavioral consequences of disrupted relationships. International Journal of Psychophysiology, 136, 54–63. 10.1016/j.ijpsycho.2017.12.011 [PubMed: 29330007]

Porges SW (2021). Polyvagal Theory: A biobehavioral journey to sociality. Comprehensive Psychoneuroendocrinology, 7, 100069. 10.1016/j.cpnec.2021.100069 [PubMed: 35757052]

Quintana DS, & Guastella AJ (2020). An Allostatic Theory of Oxytocin. Trends in Cognitive Sciences, 24(7), 515–528. 10.1016/j.tics.2020.03.008 [PubMed: 32360118]

Redwine LS, Altemus M, Leong YM, & Carter CS (2001). Lymphocyte responses to stress in postpartum women: Relationship to vagal tone. Psychoneuroendocrinology, 26(3), 241–251. 10.1016/s0306-4530(00)00049-4 [PubMed: 11166487]

Reis HT, Aron A, Clark MS, & Finkel EJ (2013). Ellen Berscheid, Elaine Hatfield, and the Emergence of Relationship Science. Perspectives on Psychological Science: A Journal of the Association for Psychological Science, 8(5), 558–572. 10.1177/1745691613497966 [PubMed: 26173214]

Rowold K (2019). What Do Babies Need to Thrive? Changing Interpretations of “Hospitalism” in an International Context, 1900–1945. Social History of Medicine : The Journal of the Society for the Social History of Medicine, 32(4), 799–818. 10.1093/shm/hkx114 [PubMed: 31857744]

Ryff CD, Singer BH, & Dienberg Love G (2004). Positive health: Connecting well-being with biology. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 359(1449), 1383–1394. 10.1098/rstb.2004.1521 [PubMed: 15347530]

Sakuma Y, & Pfaff DW (1980). LH-RH in the mesencephalic central grey can potentiate lordosis reflex of female rats. Nature, 283(5747), 566–567. 10.1038/283566a0 [PubMed: 6986562]

Schulkin J, & Sterling P (2019). Allostasis: A Brain-Centered, Predictive Mode of Physiological Regulation. Trends in Neurosciences, 42(10), 740–752. 10.1016/j.tins.2019.07.010 [PubMed: 31488322]

Selye H (1956). The Stress of Life. McGraw-Hill.

Sherwin E, Bordenstein SR, Quinn JL, Dinan TG, & Cryan JF (2019). Microbiota and the social brain. Science (New York, N.Y.), 366(6465). 10.1126/science.aar2016

Short RV (1984). Breast feeding. Scientific American, 250(4), 35–41. 10.1038/scientificamerican0484-35 [PubMed: 6729428]

Smith AS, & Wang Z (2014). Hypothalamic oxytocin mediates social buffering of the stress response. Biol Psychiatry, 76(4), 281–288. 10.1016/j.biopsych.2013.09.017 [PubMed: 24183103]

Stern JM, Weinberg J, & Hennessy MB (2010). From Freud to a Modern Understanding of Behavioral, Physiological, and Brain Development. Developmental Psychobiology, 52(7), 609–615. 10.1002/dev.20496 [PubMed: 20882587]

Stevenson JR, McMahon EK, Boner W, & Haussmann MF (2019). Oxytocin administration prevents cellular aging caused by social isolation. Psychoneuroendocrinology, 103, 52–60. 10.1016/j.psyneuen.2019.01.006 [PubMed: 30640038]

Stribley JM, & Carter CS (1999). Developmental exposure to vasopressin increases aggression in adult prairie voles. Proc Natl Acad Sci U S A, 96(22), 12601–12604. [PubMed: 10535968]

Tang A, Almas A, Zeytinoglu S, Zeanah CH, Nelson CA, & Fox NA (2021). Long-Term Effects of Institutional Care and Enhanced Attachment Relationships on Close Adolescent Friendships. Child Development, 92(6), 2431–2446. 10.1111/cdev.13592 [PubMed: 33997968]

Taylor JH, Walton JC, McCann KE, Norvelle A, Liu Q, Vander Velden JW, Borland JM, Hart M, Jin C, Huhman KL, Cox DN, & Albers HE (2022). CRISPR-Cas9 editing of the arginine-vasopressin V1a receptor produces paradoxical changes in social behavior in Syrian hamsters. Proceedings of the National Academy of Sciences of the United States of America, 119(19), e2121037119. 10.1073/pnas.2121037119 [PubMed: 35512092]

Theofanopoulou C (2021). Reconstructing the evolutionary history of the oxytocin and vasotocin receptor gene family: Insights on whole genome duplication scenarios. Developmental Biology, 479, 99–106. 10.1016/j.ydbio.2021.07.012 [PubMed: 34329619]

Tomova L, Tye K, & Saxe R (2019). The neuroscience of unmet social needs. Social Neuroscience, 1–11. 10.1080/17470919.2019.1694580

Torday JS (2022). Morphological forms arising from the evolutionary process are topologies. Bio Systems, 214, 104646. 10.1016/j.biosystems.2022.104646

Uvnas Moberg K, Handlin L, Kendall-Tackett K, & Petersson M (2019). Oxytocin is a principal hormone that exerts part of its effects by active fragments. Med Hypotheses, 133, 109394. 10.1016/j.mehy.2019.109394 [PubMed: 31525634]

Vuppaladhadiam L, Ehsan C, Akkati M, & Bhargava A (2020). Corticotropin-Releasing Factor Family: A Stress Hormone-Receptor System's Emerging Role in Mediating Sex-Specific Signaling. Cells, 9(4), E839. 10.3390/cells9040839

Wang Z, Young LJ, De Vries GJ, & Insel TR (1998). Voles and vasopressin: A review of molecular, cellular, and behavioral studies of pair bonding and paternal behaviors. Prog Brain Res, 119, 483–499. [PubMed: 10074808]

Welch MG, & Ludwig RJ (2017). Calming Cycle Theory and the Co-Regulation of Oxytocin. Psychodynamic Psychiatry, 45(4), 519–540. 10.1521/pdps.2017.45.4.519 [PubMed: 29244620]

Whitman DC, & Albers HE (1995). Role of oxytocin in the hypothalamic regulation of sexual receptivity in hamsters. Brain Research, 680(1–2), 73–79. 10.1016/0006-8993(95)00233-g [PubMed: 7663986]

Williams JR, Catania KC, & Carter CS (1992). Development of partner preferences in female prairie voles (Microtus ochrogaster): The role of social and sexual experience. Horm Behav, 26(3), 339–349. [PubMed: 1398553]

Wilson R (1966). Feminine Forever (First Printing edition). W.H.Allen.

Winslow JT, Hastings N, Carter CS, Harbaugh CR, & Insel TR (1993). A role for central vasopressin in pair bonding in monogamous prairie voles. Nature, 365(6446), 545–548. 10.1038/365545a0 [PubMed: 8413608]

Witt DM, Carter CS, & Lnsel TR (1991). Oxytocin Receptor Binding in Female Prairie Voles: Endogenous and Exogenous Oestradiol Stimulation. Journal of Neuroendocrinology, 3(2), 155–161. 10.1111/j.13652826.1991.tb00258.x [PubMed: 19215517]

Witt DM, Carter CS, & Walton DM (1990). Central and peripheral effects of oxytocin administration in prairie voles (Microtus ochrogaster). Pharmacol Biochem Behav, 37(1), 63–69. [PubMed: 2263668]

Zuloaga DG, Heck AL, De Guzman RM, & Handa RJ (2020). Roles for androgens in mediating the sex differences of neuroendocrine and behavioral stress responses. Biology of Sex Differences, 11(1), 44. 10.1186/s13293-020-00319-2 [PubMed: 32727567]

Highlights

- This historical review traces evidence that led to current awareness of the role of oxytocin in the neurobiology of early experience, stress-coping and love.
- Fear and stress are rooted in the same adaptive biology that supports love and sex.
- Sex, love and oxytocin are components of biobehavioral mechanisms coordinating health and wellness with the social environment - here termed “sociostasis.”

Table 1.

HYPOTHESIZED FUNCTIONAL CHANGES IN OXYTOCIN, VASOPRESSIN AND CRF (AND SELECTED RECEPTORS), IN THE CONTEXT OF EVOLUTION AND COPING WITH STRESSORS, (reproduced from Carter and Kingsbury, 2022)

HYPOTHESIZED FUNCTIONS	**Oxytocin (OT) & OT receptors (OTR)**	**Vasopressin (VP) & VP receptors**	**Corticotropin releasing hormone (CRF) and CRF R1**
Evolutionary history	**MODERN - Mammalian** OT 250–200 mya	**PRIMITIVE vertebrates** Vasopressin 300–350 mya (Vasotocin-like much earlier)	**PRIMITIVE** Early vertebrates (Other CRH family peptides were much earlier
Life history strategy	**SLOW**	**FAST**	**FAST**
Survival strategies	**Cooperative - Social**	**Defensive - Individual** Protective Aggression	**Defensive - Individual** Mobilization or Freeze ?
Social behaviors	**Approach** Context-dependent	**Approach or Avoidance** Context-dependent	**Approach or Avoidance** Context-dependent
Mobilization Anxiety or Fear	**Anxiolytic and fear reducing** Immobility without fear	**Anxiogenic (VPRs)**	**Anxiogenic (CRF R1)**
Acute stress	**Increase – OT**	**Increase – VP** Amplifies effects of CRH	**Increase in HPA axis** activity Amplifies effects of VP
Chronic stress	**Increase in OT;** esp in females	**Increase in VP**; esp in males;	**Increase in CRF (and catecholamines)**; esp in females
Autonomic nervous system	**Parasympathetic and Sympathetic Nervous Systems**	**Sympathetic NS**	**Sympathetic NS**
Inflammation	**Anti-inflammatory** primarily	**Pro-inflammatory** primarily	**Anti-inflammatory** initially **Pro-inflammatory** over time
Early life experience; Epigenetic	**Early nurture** Increase OT-OTR	**Early neglect or abuse** i Increase VP- VPRs	**Early adversity** may increase CRF-CRF R1

Abbreviations: OT – oxytocin, OTR – oxytocin receptor, VP – vasopressin, VRP – vasopressin receptors, CRF – corticotopin releasing factor, CRF-R1 – CRF type 1 receptor, mya – million years ago.

Table 2.

PARALLELS BETWEEN FUNCTIONS AND PROPERTIES OF LOVE AND OXYTOCIN, (reproduced from Carter, 2022)

FUNCTIONS (among many)	**LOVE**	**OXYTOCIN**
MODERN (evolutionarily recent)	+	+
Associated with SELECTIVE sociality & bonds	+	+
Supporting parental investment	+	+
Metaphor for SAFETY	+	+
Selectively rewarding	+	+
Anti-inflammatory/Anti-oxidant	+	+
Anxiolytic/Analgesic	+	+
Allows immobilization without fear	+	+
Sexually dimorphic	+	+
Epigenetically tuned and Context dependent	+	+