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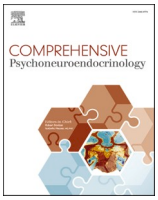

Oxytocin: A developmental journey

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ABSTRACT

The neuropeptide hormone oxytocin is involved in many processes in our bodies, linking our social lives to our internal states. I started out my career studying primate families, an interest that expanded into the role of oxytocin in family-oriented behaviors such as pair bonding and parenting in prairie voles, humans, and other primates. Starting as a post-doc with Dr. C. Sue Carter, I also became interested in the role of oxytocin during development and the way that we manipulate oxytocin clinically. During that post-doc and then as a faculty member at the University of California, Davis, I have worked on a number of these questions.

1. Introduction

Oxytocin (OXT) is an ancient and foundational hormone that has seemingly diverse functions – in labor and birth, lactation, feeding behavior, heart function, muscle composition, and more [1–4]. All of these functions are necessary and integrated into the role of OXT in social bonds – which reciprocally affect the rest of our physiology, and enable us to connect our social lives to our internal states. And just as social bonds are critical to human health as we age [5], the actions of OXT during development are crucial to establishing the substrates for its effects during adulthood [6–8].

As far as my own development, I don't remember wanting to be a primatologist as a child, although in a childhood "memory book", I wrote that my favorite animals were monkeys. In fact, I went off to college with the goal of becoming a cultural anthropologist; I wanted to understand families and how they varied in humans. I quickly realized that I found animals, particularly primates, far more interesting than people. I had not yet identified the desire to understand hormones or the brain; I found it sufficient to ask questions about behavior and evolution. I was particularly interested in other primates that had families that resembled human families, and in which we could identify factors that predicted their parental investment. As an undergraduate, I volunteered in the primate and reptile sections of the Audubon Zoo in New Orleans – cementing my determination to work with primates, particularly monkeys. While great apes are usually the stars of the non-human primate world, and their behavior and social structures are both complicated and interesting, their social relationships are quite unlike human families in many ways. At least, they do not routinely display the capacity for shared parenting – both male parenting and alloparenting - which characterize a number of platyrrhine (Central and South American) monkey species, as well as humans. This willingness to allow allomothering may have been key in the evolution of modern humans [9].

2. Watching monkey families

I conducted my Master's research studying common marmosets (*Callithrix jacchus*) at the University of Tennessee with Dr. Suzette Tardif. At the time, there were many things that we did not yet know about these tiny anthropoid primates; for instance, that they have germ-line chimerism [10], and importantly, that they have a different form of OXT than humans, having a proline amino acid instead of a leucine in position eight [11]. My thesis focused on parental investment and what predicted it – characteristics of the offspring such as sex or size, characteristics of the parents, or both. But the common marmosets that I worked with in the laboratory had all the food they could eat and no predators. I was sure that I needed to study these relationships in monkeys that had no such convenient props. So for my Ph.D. work, I decided to study golden lion tamarins (*Leontopithecus rosalia*) in the wild in Brazil.

Between 1996 and 1999, I spent many months in Brazil, in the Atlantic coastal rainforest at the Reserva Biológica Poço das Antas, following golden lion tamarins around. My big question about maternal investment was, if you had helpers to do everything for you except for lactation, why do we still see variation in maternal behavior? And there *was* a lot of variation in maternal behavior – wild golden lion tamarin mothers ranged from carrying their infants from less than 10% of observations to nearly 80% of observed time [12]. In studying these sixteen mothers and 32 infants, I identified several axes along which early

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investment in infants varied. Mothers that weighed more carried their infants more; mothers that had more helpers carried their offspring less. And mothers that received outside provisioning (as part of a conservation program run by the Brazilian conservation organization Associação Mico-Leão-Dourado), allowed their offspring more time on the nipple. Levels of steroid hormones (particularly estrogen conjugates and cortisol) also predicted prenatal investment as measured by neonatal weights. Unfortunately, the easiest samples to get in wild primates are fecal samples – and OXT, like many peptides, is likely destroyed in the gut; so I was not able to measure OXT in this study, even though it seems like a natural target when studying maternal investment. The other way in which this experience led me to OXT was that Dr. Sue Carter, a pioneer in the study of OXT and the prairie vole model, was on my dissertation committee at the University of Maryland, and a huge influence on my thinking.

3. Into the brain with OXT

Watching these monkeys live their lives, and measuring their peripheral hormones, I became more and more interested in the mechanisms behind the behavior. But a critically endangered wild primate was not the best species in which to study the brain! In moving to a postdoctoral position with Sue, I started working with prairie voles (*Microtus ochrogaster*), the scientific poster child for pair-bonding and male parenting. At the time, Sue had an NIH grant to study the developmental effects of OXT in female prairie voles. This research was exciting in its implications for human clinical practice; asking the question of how neonatal exposure, potentially via labor induction, might have long-term effects on the social and reproductive behavior of female offspring. For updates on that question, see Refs. [13–15]. Although at the time much of the focus in OXT research was in females, Sue and I thought that the OXT exposures in male offspring might have even larger effects, thus my post-doc focused on the male offspring from these same OXT-treated litters – and the results were very interesting.

Male prairie voles display extremely strong pair bonds; i.e. they show a strong preference for their pair-mate [16], distress upon separation [17–19], and their pair-mate buffers them against stress [20]. They are also very good fathers, and even before they are paired, they are very good alloparents [21]. In males, we found that early exposure to an OXT antagonist reduced alloparenting [23], while exposure to OXT itself speeded up pair bonding [22]. Males treated with either OXT OR an OXT antagonist neonatally experienced reduced reproductive potential, either behaviorally or through alterations in sperm production and transport [23]. Treatment with OXT and OXT antagonists had significant effects on central vasopressin receptors, in complicated, sex-dependent ways [39,73]. Over the years, we would find that many types of early experiences profoundly affected variation in the display of pair bonding and parenting as an adult.

3.1. Development and the OXT system

In 2004 I accepted a faculty position in the Psychology department at the University of California, Davis, where I am still located today. Many of my vole studies here centered on various types of early experience, how they affected adult pair bonding and parenting, and how they affected the OXT and vasopressin systems. In addition to pharmacological manipulations, we have looked at the effects of individual variation in parental behavior [24–27]; family composition [28,29]; prenatal stress [30]; and perinatal exposure to fluoxetine [31].

Throughout these studies, we struggled with sometimes unexpected results. Why did early exposure to OXT have dose-dependent effects on adult behavior? Allison Perkeybile (then a graduate student) and I attempted to predict what the general results of various types of early experience would be on OXT receptor regulation [6]. In Fig. 1, we took available information and summarized our thoughts as to what might happen to OXT receptors as the result of various early experiences.

It has now been over ten years since we developed those hypotheses. How have they held up? A full review is outside the scope of this article, with a slew of new data and review articles having been published since 2012 [32–34], and more being published every day. However, we now know that epigenetic methylation of the OXT receptor is a major mechanism in later behavioral effects [7,8,35,36]. In a recent review of epigenetic regulation of the OXT receptor, the authors summarized the literature showing that decreased parental behavior in voles, decreased maternal engagement in infancy in humans, and childhood trauma in humans all led to increased DNA methylation of the OXT receptor at the MT2 site (a specific region around the promoter) [7]. Thus, presumed low physiological OXT (from neglect or low parenting) appears to have had a similar effect to what might be high physiological OXT with a negative valence (from trauma or abuse). Danoff and co-authors give a more nuanced view of OXT receptor as an epigenetic method for allostatic adjustments [7]. The field has also added other valuable measures on top of changes in receptor binding – for instance, examining the effects of early exposure to OXT via labor induction in prairie voles for its effect on fractional anisotropy and functional connectivity [13].

4. Back to monkeys (along with voles, mice, etc.)

At UC-Davis, I had the opportunity to integrate my prairie vole research with study of another socially monogamous, pair-bonding species, the titi monkey (*Plecturocebus cupreus)*. The titi monkey colony at the California National Primate Research Center (CNPRC) had been studied by Drs. William Mason and Sally Mendoza for several decades before I arrived [37]. Titi monkeys, along with owl monkeys and humans, provide the best examples of strong pair-bonds and extensive fathering in the Primate Order [38]. With the use of functional imaging, we have been able to study the neurobiological effects of pair-bond formation [39–41], separation distress [42], jealousy [43], reactions to partners and strangers [44] and other aspects of the adult pair-bond in

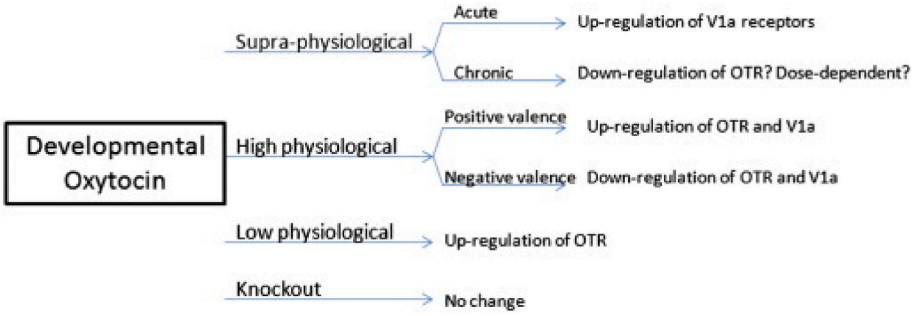

Fig. 1. Hypothesized relationships between developmental exposure to OXT and outcomes for oxytocin (OTR) and vasopressin receptors (V1a). Reprinted from Ref. [6].

this primate model [45].

While we were able to study neurobiological measures such as changes in glucose uptake and dopamine receptors, the study of OXT in primates poses particular challenges. Ligands for OXT receptor binding that worked well in rodents were non-specific in primates, also binding to vasopressin receptors, and causing Toloczko, Young and Insel to ask, "Are there OXT receptors in primate brain?" [46]. Dr. Sara Freeman, while still a graduate student at Emory in Larry Young's lab, was able to map OXT receptor in titi monkey brain tissue (collected from animals that had been euthanized for health reasons) [47]. However, OXT remains a difficult problem for imagers, because of the lack of an OXT receptor imaging ligand that crosses the blood-brain barrier [48].

However, pharmacology has allowed us another window into the role of OXT and vasopressin [as well as opioids [49–51] and serotonin [52]] in primate pair bonds, parenting, and development. In 2002 Born and colleagues published a paper in which they showed that a number of peptides, if given intranasally, reach the cerebrospinal fluid in humans (implying that the peptides had entered the brain and then been cleared into the CSF) [53]. OXT was not actually one of the neuropeptides in this paper (although vasopressin was); but it set off a renewed interest in using OXT to alter social behavior in humans.

After some initial studies in adults, public interest very quickly turned to using intranasal OXT as a therapeutic for social deficits in autism spectrum disorder [54]. My concern for the use of OXT as a therapeutic was specific to its use in children, whose developing brains might realistically be expected to be the most plastic. What if they developed tolerance? What if the chronic effects were the opposite of the acute effects [6]? Funded by NICHD, and in a collaboration between behavioral endocrinologists, reproductive endocrinologists, psychiatrists and child psychologists, we embarked on our most ambitious study of the role of OXT in development. This study involved three species (prairie vole, mouse, and titi monkey) and extensive developmental exposures, all with the main question: How does a chronic developmental exposure to OXT affect social behavior, anxiety-like or repetitive behaviors, and reproductive variables in the long term? We treated each species with OXT daily during its peri-adolescent period. For voles and mice, this meant exposures of approximately three weeks; for the titi monkeys, they received OXT every day for six months.

Our first data were from the voles, and they were quite worrying: male voles that had received the same dose of OXT (weight-adjusted) as was being used in clinical trials, or an even lower dose, did not form normal pair bonds as adults. This negative long-term result was in direct opposition to the acute effects of OXT in the same males, which had increased their levels of affiliation. As is often the case with OXT, female voles responded differently, with the same doses causing an increase in preference for the partner rather than a decrease [55]. In follow-up studies, we found that the intranasal OXT treatments had decreased numbers of vasopressin cells in the paraventricular nucleus of the hypothalamus in males; while increasing OXT receptor binding in the nucleus accumbens of females [56]. But these prairie voles were neurotypical animals – they were not an "autism model". We were excited to see what happened in an animal that had social deficits.

At the time, the best characterized mouse with social deficits, and high levels of repetitive behavior, was the BTBR T+ltpr3tf/J mouse. In social interaction tests, these mice preferred to be alone over interacting with a novel mouse [57]; they also displayed repetitive self-grooming [58]. These behavioral characteristics align with core diagnostic symptoms of autism [59]. Testing intranasal OXT with the BTBR mouse therefore meant that we had no ceiling effect – we were actually able to test whether social behavior would go up. However, there were no effects of intranasal OXT at all – it did not decrease the social deficits or the repetitive self-grooming [60]. This result was both unexpected and unsettling.

Finally, we tested chronic developmental exposure to intranasal OXT in titi monkeys. We recorded behavioral data immediately after their treatments, at which time they were still living with their parents [61]. At 2.5 years of age, one year since they had received any treatment, we removed them from their natal groups and paired them with a reproductively experienced mate. In addition to examining behaviors related to pair bonding such as partner preference [62] and separation distress [63], we also examined whether or not OXT treatment had affected pubertal maturation in either sex. An intranasal saline control group went through the same procedures.

Both sexes of juvenile titi monkeys showed increased affiliation with their families in the home cage immediately following treatment [61]. In a preference test comparing the juvenile's preference for its parents vs. a strange adult pair, OXT-treated females showed an enhanced preference for their parents (compared to saline-treated females). For OXT-treated males, they did not spend less time near their parents, but they did increase the amount of time near the strange pair. They also displayed increased anxiety-like behavior in a novel pattern test, suggesting that the increased attraction to strangers was not caused by a reduction in anxiety. At this point (up to 20 months of age), we found no significant differences in gonadal hormones. We predicted that as adults, we would probably see a pattern similar to that in the voles, with males impaired in their formation of a pair bond.

After pairing them a year later, the results were rather surprising [62]. OXT-treated animals of both sexes spent more time tail-twining (a highly intimate measure of affiliation) with their pair mate. OXT-treated males, after just one week of pairing, preferred their partner more than a stranger (a preference not displayed by saline males); while OXT-treated females did not prefer their partner (unlike saline females). After four months, OXT-treated males also displayed more contact with their partner than saline males, and responded more than saline males to a simulated intruder. In these tests of affiliation and preference, there were very few differences between OXT- and saline-treated females, except for the initial delay in formation of a preference.

However, not all aspects of pair bonds are "positive". One psychological mechanism for maintaining a bond is distress upon separation from the partner. After having been paired for five months, we tested the effects of both subjects' chronic intranasal treatment, as well as acute treatment with OXT or saline, on separation distress [63]. In summary, chronic treatment in both sexes resulted in a dampened response to separation, although the effect was larger in females. OXT-treated females gave fewer contact calls and shorter long calls when separated from their pair mate, and engaged in less contact with him when reunited. These results suggest that the pair bond was altered in both males and females, but in different ways from each other and from the prairie vole results.

Finally, we also examined the effects of OXT on reproductive maturation in both sexes [64], based on the role of OXT as a reproductive hormone and the rodent literature on effects of developmental exposure [23,65,66,74]. All subjects in the study were eventually able to either get pregnant or impregnate their mate. However, both sexes experienced some effects of OXT treatment on puberty. OXT-treated females had earlier (although not regular) cycles than saline-treated females; while the androgen rise in males was later for OXT-treated animals.

Altogether, the results for this experiment, using the same dosages of OXT (adjusted for weight), in the same lab and often administered by the same personnel, were different in every species we examined. What does this mean for translation to human work? Rather than shake my belief in the necessity of using animals in research, these results reaffirmed for me both the necessity of studying basic processes in multiple species [67], and the value of primate research [68]. Choosing the right species for the right question is important, and so is studying certain questions in our closest relatives, other primates.

5. What does it all mean?

Many of the big questions about the neurobiology, development, and evolution of pair bonding remain to be answered. How do our own

results inform us about the mechanisms and evolution of pair bonding? Have we been able to identify pathways and mechanisms that are conserved across species, or is every pair-bonding species solving this evolutionary puzzle in a different way? How does development fit into the picture?

While still leaving much to future research, there are some consistent threads throughout our projects which contribute to the larger OXT picture. OXT, along with the closely related hormone vasopressin, are like twin conductors that lead to the coordination between social signals, physiology and behavior, throughout the body and brain [69,70]. This has been true throughout the evolutionary history of animal life [3,70–72]. We find this relationship in many of our results, which often show effects of manipulation of the OXT system on the vasopressin system, and vice versa [56,73]; affecting both the brain and the body simultaneously [62,64,73,74]. The OXT system is coordinated with other systems as well, including the opioid and serotonin systems [49,52]. Studying changes in energy balance that male prairie voles experience across pairing and parenting [75], led us to suggest that OXT also coordinates parenting behavior with energy balance, another theme that is reflected in more recent discoveries regarding the role of feeding hormones in social behavior [76,77].

As with many systems [78], developmental processes utilize alterations in OXT and OXT receptor gene expression to produce traits that may be better adapted to the current environment [79]. While regulation of OXT and the OXT receptor is complex [69,80], our results highlight the multiple sensitive periods during which OXT can affect social development, including the immediate postnatal and peri-pubertal periods [6,55,62].

Utilizing comparative research designs in our own research has also helped us to identify potential new directions in understanding common mechanisms for pair bonding and parenting. For instance, in our comparison of how gene expression changes with pair bonding in lined seahorses (*Hippocampus erectus*) with prairie voles, we found that cilia-related genes changed across both species [81].

6. Strategies for success

In the description of the articles for this special issue, one suggestion is that authors discuss their strategies for success. I only have one to share: make sure that you work with the right people. And by "right", I mean collaborators who share your joy in your topic, share your principles regarding scientific rigor, and have your best interests at heart. Some of my best friends, both professionally and personally, are other women who are interested in either OXT or monkeys or both.

7. The present and future

My lab, my collaborators, and I have continued to ask questions about the basic neurobiology of pair bonding and parenting across species [82], including of our most recent addition, lined seahorses, another species which convergently evolved pair bonding [81]. We are particularly interested in interactions between OT and other systems, such as the kappa opioid system, that also underlie pair bonding [49]. We have also expanded our developmental focus past the prenatal to adult period, to include aging [83]. As we continue our own lifelong development and growth, we hope to continue to make new discoveries about pair bonding, parenting, friendship and the role of oxytocin in it all.

Declaration of competing interest

None.

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