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The intertwining of oxytocin's effects on social affiliation and inflammation

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1. Oxytocin as a master regulator of social affiliation, social connection, and adaptive reproductive behaviors

When I entered graduate school at Cornell University in 1993, I chose to focus on developmental neurobiology with my graduate advisor, Dr. Barbara Finlay. It was then that I met fellow student James (Jim) Goodson, who was studying a subject that would alter my career and life. His subject was neuropeptide control of social courtship behavior and aggression. Although the subject under study was courtship in finches, this topic coincided with our own courtship. For seven years, I admired his graduate and postdoctoral work on the nonapeptides oxytocin (OT) and vasotocin (VT; vasopressin in mammals) from a distance (fortuitously, not too great a distance). Every morning before dawn during the spring field season in upstate New York, Jim would infuse various neuropeptides into the septal region of the brain of estrildid finches to gain insight as to how neuropeptide hormones control social courtship behavior and aggression in species that differ vastly in their social group size and social affiliation. To me, his most surprising discovery was that OT modulates social behavior (measured as fictive vocalizations in midshipman fish) in a *remarkably similar* fashion in fish morphs that have similar reproductive tactics (females and "type 2" sneaker males) but who are of different gonadal sex [1]. This modulation in females and sneaker males contrasts with the modulation in "type 1" males, who have a different reproductive tactic. These findings, published in Nature, illustrated the evolutionary labile nature of oxytocin function regarding social behavior related to reproductive success and piqued my interest in oxytocin.

In 2000, we married and moved to San Diego, California, where Jim continued to examine the neuropeptide modulation of social behavior as an Assistant Professor at the University of California at San Diego (UCSD). There, I continued my study of developmental neurobiology in the laboratory of Dr. Jerold Chun as a postdoctoral fellow. Jim's desire to understand how brain hormones modulate social affiliation in asocial (territorial) versus social (gregarious) species took him to Africa to collect estrildid finches, and because I was always up for an adventure, I tagged along to assist in the fieldwork. We collected asocial violet-eared waxbills and melba finches, which existed as territorial male-female pairs (group size n = 2), as well as moderately gregarious Angolan

blue waxbills, whose typical group size is between 8 and 40 individuals. Together with the highly gregarious zebra finches (group size of ~100 individuals) and spice finches (group size of ~1000 individuals) already in his laboratory, the collection of African estrildid finches allowed us to delve deeper into how the brain distribution of the nonapeptides OT and vasopressin (AVP), and their receptors, allowed for the rich variation in behavior between individuals, sexes, and species. I was hooked.

In 2007, Jim was offered a position at Indiana University as part of the Ecology, Evolution, and Behavior division in the Department of Biology and home to the Center for the Integrative Study of Animal Behavior (CISAB), which made the offer incredibly attractive. My career and life course were forever altered that same month when tragedy struck, and Jim was diagnosed with an incurable indolent lymphoma. This diagnosis was all that was needed to finally propel me into the study of OT and AVP. As we were simultaneously sorting out our career trajectories, Jim's treatment options and prognosis, and a manageable work-life balance with a two-year-old and a baby on the way (also discovered that same month), I made the decision to join forces with Jim so that we could co-run a laboratory together at Indiana University studying the nonapeptide regulation of social behavior. In doing so, I accepted a Research Scientist position at IU, and while this was not exactly a step forward for my career, it allowed us to focus on a research program together while managing his disease and a busy family life with two infants.

Joining forces with Jim proved very fruitful and exciting, as we were incredibly productive as a team. I was told by many, both scientists and non-scientists alike, that not everyone can work *and* live with their spouse, but we must have had the right OT/AVP balance to help us succeed. Over the course of 7 years, we published 3 formative reviews [2–4] and 11 primary manuscripts, including 4 OT manuscripts, in which we detailed how the neuropeptides OT, VT, and vasoactive intestinal polypeptide modulate sociality, aggression, pair-bonding, anxiety-like behavior, and parental care in finches and sparrows that differ in their species-typical group size or social affiliation [5–8]. Some of the primary questions we sought to address were, "What drives an individual to socially engage with others?" and "Do nonapeptides in the brain control whether an individual wants to be by themselves versus affiliate with just a few individuals versus join a large group?" In 2008,

we published our seminal paper on how OT regulates social affiliation in zebra finches titled "Mesotocin and nonapeptide receptors promote flocking behavior in zebra finches" [5]. Our primary finding from this paper was that activation of nonapeptide receptors by OT (mesotocin is the avian homologue of OT) promotes sociality and the preference to affiliate with larger groups of individuals. Another finding was that OT promotes the preference for familiar social partners as opposed to novel social partners. Most of OT's effects were female-specific or stronger in females and were likely mediated by receptors in the lateral septum, an area where nonapeptide receptor density correlates with a species group preference size [5]. In 2004, our close colleague, Rick Thompson, showed that isotocin (OT homologue in fish) acting in goldfish promotes social approach to a novel individual while VT inhibits this social approach [9]. Based on our data that OT modulates sociality in birds [5] and the findings that OT regulates social communication and social approach in fishes [9,10], we suggested that "OT-like peptides have influenced social groupings for most of vertebrate history [5]."

I began to wonder if OT's promotion of social affiliation in flocking and schooling species could also be interpreted as OT's promotion of safety, in that the choice to socially affiliate with your conspecifics may be adaptive and protective. Additional papers that were published from our laboratory at this time supported the idea. The first was a paper published in 2013 by our graduate student, James Klatt, who showed that OT promotes pair bonding in zebra finches, a socially flocking species. While many species are socially monogamous, the relevant neural mechanism that supports pair-bonding had only been thus described for prairie voles, based on the seminal findings of Sue Carter and her colleagues of OT's promotion of partner preference and pair bonding in prairie voles [11]. In his paper, James Klatt showed that blocking OT signaling reduced the ability of zebra finches to pair bond, remain pair bonded, and engage in behaviors that maintain and strengthen pair bonds, such as allopreening, with effects in both males and females, yet stronger in females [12]. Thus, OT regulates not only sociality but also fitness, as reproductive success is influenced by the ability to obtain a mate and maintain that relationship within a socially monogamous species. Furthermore, OT's promotion of allopreening, a social behavior that reduces parasite load, can also confer a fitness advantage.

The graduate dissertation of another one of our students, Leah Wilson, supported the idea that OT may promote social affiliation for safety. Leah showed that species of Emberizid sparrows characterized as "seasonal switchers" (i.e., species that facultatively change from asocial territoriality during spring/summer to social flocking during the fall/winter) show an upregulation in OT in the lateral septum, in contrast to species of sparrows that remain asocial and do not flock during the fall/winter [13], consistent with early findings that OT signaling in the lateral septum promotes sociality [5]. We believe this switch to flocking in the winter could provide safety from predators, enhance thermoregulation, and assist in the discovery of food resources during harsh winter conditions. Leah also showed that OT receptors are specifically upregulated in the rostral arcopallium of seasonal switchers that winter flock [8]. Based on the function of this area, we proposed that the upregulation of OT receptors in this brain region reduces winter social anxiety, enabling social approach and affiliation for adaptive survival during harsh environmental conditions [7,8].

2. OT's stress-buffering effects via social affiliation in science and real-life

Along the lines that OT may promote fitness, it is well known from a whole host of studies that people who are socially connected (are married, part of a church, have a robust social network) have better health outcomes. A study published in Biological Psychiatry in 2014 by Adam Smith and Zuoxin Wang illustrated the remarkable way that social connections (and the endogenous release of OT from these social interactions) can buffer or mitigate stress responses [14]. This study had a strong impact on my evolving thoughts of OT as a protective hormone. In this study, female prairie voles were exposed to 1 h of restraint stress and allowed to recover alone or with their male pair-bonded partner. Remarkably, female voles recovering with their partner had significantly decreased anxiety-like behaviors and circulating levels of corticosterone, a stress hormone, as compared to females recovering alone, with those recovering with partners characterized by increased release of OT from the paraventricular nucleus (PVN) of the hypothalamus. The social buffering effects due to the presence of the male partner could be recapitulated in females subjected to restraint stress and recovering alone if they received intra-PVN injections of OT, while OT receptor antagonism blocked these effects.

In adult mice subjected to focal cerebral ischemia as a model of ischemic stroke, mice that were socially housed had reduced infarct size and lower brain oxidative stress than those housed alone [15]. The protective effects of social housing were attributed to the release of endogenous OT as they could be blocked with an OT receptor antagonist administered in socially housed animals and induced with pretreatment of OT in socially isolated animals. While the first study highlighted OT's mitigation of psychological stress via a reduction in the stress hormone corticosterone [14], the second demonstrated OT's protection from a physical stressor via the enhancement of brain antioxidant activity and the dampening of microglial-mediated inflammatory cascades [15]. Together, these two studies greatly expanded my thinking on how OT (and the social interactions that mediate its endogenous release) can mitigate different types of stressors by acting via different mechanisms [hypothalamic-pituitary-adrenal (HPA) axis, cellular stress pathways, immune system signaling, etc.].

The same month that Adam Smith's paper was published, Jim lost his long eight-year battle with cancer. As I was reeling from this loss, I met Sue Carter, a researcher and expert on oxytocin and a dear colleague of Jim's. Sue had just joined IU as The Director of the Kinsey Institute. I had no idea at the time what a blessing this would be for me. During the renovation of Sue's laboratory space at IU, I invited the Carter lab members into my lab space in the interim. Our lab had plenty of room as The Kingsbury-Goodson lab had been downsizing with Jim's declining health. Little did I know (but Sue did) that being socially engaged and surrounded by her lab members, who quickly became close colleagues of mine, was exactly what I needed to begin to heal. Sue took me under her wing as her mentee to help guide me and provide some hope during my dark period of grief and loss.

One of the final papers that Jim and I published together involved the role of OT in stress responses and aggression in territorial finches [6]. We found that blocking OT signaling reduced aggression in territorial finches, leading us to conclude that aggression is correlated with OT neuronal activation. However, the results from our second experiment were inconsistent with this idea. We found that OT neurons were most strongly activated (as measured by c-Fos induction) in subordinate finches and finches that were "chased," in contrast to dominant finches engaged in aggression, indicating that OT neurons are strongly activated by stressors. Based on what we were learning about OT, we surmised that the resident intruder paradigm induces stress/anxiety and instigates aggression in a territorial finch, with OT release during this task lowering anxiety and allowing territorial finches to feel "safe" while aggressing. This interpretation also agrees with our finding that the defense and subordinate animals upregulate OT in response to stressors (being chased or subjugated) as a form of active stress coping.

Following Jim's death I continued to fulfill our R01. In so doing, I became the supervisor of Leah Wilson, a graduate student in our lab. The idea that oxytocin could be a hormone that mediates stress coping was Leah's central focus and was beautifully illustrated in her thesis. With all this work, I began to understand further the adaptive nature of this hormone and how social affiliation, oxytocin, and stressors (psychological and physiological) are inextricably linked with OT release to promote healing, health, and the pursuit of safety.

3. Oxytocin: not just a birth hormone but a master regulator of the greatest physiological stress of our lifetime (birth)

During this time, Sue encouraged me to consider collaborating with her on the role of OT at birth, as Sue had been awarded an NIH Program Project grant (P01) to study the effects of OT in a labor induction paradigm in prairie voles. Sue was interested in how exogenous regulation of this powerful hormone during birth might interfere with the physiological adaptive roles of OT and alter brain and social behavior development. I decided to write an NIH P01 administrative supplement as part of this NIH Program Grant to obtain funding to begin my collaborations with Sue. While OT had long been known as the "birth hormone" that facilitates labor contractions and milk letdown during lactation, I became interested in OT's functions that might mitigate the physiological stress of labor for the mother and infant.

I was very intrigued by the work of Roman Tyzio and his colleagues, who had shown that OT protects GABAergic neurons against oxidative stress during the hypoxic event of birth by inducing a transient inhibitory switch in GABA signaling, which serves to reduce the metabolic demand of these neurons precisely when the supply of oxygen to the fetus may be limited [16,17]. At this same time, I discovered the work of Jan-Harry Cabungcal and colleagues, who were studying early brain oxidative stress as a neurodevelopmental contributor to schizophrenic pathology [18,19]. They showed that GABAergic neurons expressing parvalbumin are protected against oxidative stress via their encasement in perineuronal nets. Moreover, significant increases in oxidative stress during early brain development can disrupt the formation of perineuronal nets and parvalbumin neuron maturation, leading to a disruption in the balance of excitatory and inhibitory signaling within neuronal networks, thereby impacting social behavior and cognition. Building from the work of these two separate research groups, I wrote a proposal to examine how exogenous OT dosing at birth, via a labor induction model, might modulate cellular oxidative stress and neural circuitry (i.e., the development of parvalbumin GABAergic neurons and perineuronal nets) to alter social behavior. Despite receiving a 3rd percentile score, my NIH P01 supplement went unfunded in 2017 due to federal budgetary cuts. I was undeterred, and I continued to submit this grant proposal, which was finally successfully funded as an NIH R21 in 2020. Work from this grant will soon be submitted for publication as the culmination of Maria Kaltchenko's senior thesis. Maria was a Harvard University undergraduate student who conducted 4 years of research in my laboratory. My exploration of how oxytocin might protect the developing brain from the physiological stress of birth led me to studies describing how OT also suppresses microglial-mediated pro-inflammatory cascades [20,21] and reduces oxidative damage by preserving mitochondrial function [22,23], which I synthesized in a review in 2019 [24].

Around this same time, Sue introduced me to the work of Martha Welch, as Sue knew my interests were expanding to include the role of the microbiome-gut-brain axis and how OT signaling at birth might influence the development of gut-brain signaling and mucosal immune function. Martha's work with her colleagues was fascinating as they showed that OT signaling is crucial for normal gut development [25,26] and can regulate cellular stress through modulation of the unfolded protein response in the endoplasmic reticulum (UPR^{ER}) and the mTORC1 pathway [27–29] within Caco2BB cells (gut epithelial cells *in vitro*). During cellular stress, the UPR^{ER} is activated, and protein translation is halted so that unfolded and misfolded proteins can be cleared. OT acts on various effector molecules within the UPR^{ER} signaling pathway to restore cellular homeostasis before protein translation resumes. OT has similar effects on autophagy, another homeostatic mechanism in which cell components (organelles, proteins, etc.) are degraded and recycled as part of cellular housekeeping or in response to nutrient stress and the need for rebalancing cellular energy. One of their most influential papers for my evolving research demonstrated that OT in colostrum reduces metabolic stress in the intestinal villi of newborns by increasing autophagy, which functions to protect against nutrient insufficiency stress in the interval between birth and an infant's first feeding [30]. Dr. Welch and colleagues followed up by showing that OT-secreting nuclei in the developing brain are subjected to a similar metabolic stress as gut epithelial cells and that this cellular stress in the brain can be attenuated if newborn intestinal epithelial cells are exposed to colostrum [31], thus highlighting an early communication between the developing gut and brain that is likely OT-mediated. I was also influenced by the work of Dr. Susan Erdman and her colleagues, who showed that *Limosillactobacillus reuteri (formerly Lactobacillus reuteri; L. reuteri)*, a commensal microbe found in breast milk and the gut, stimulates OT release from the PVN of the hypothalamus and increases peripheral OT to accelerate wound healing through the activation of CD4 + Foxp3 + CD25+ immune T regulatory cells [32–34]. Together, this research suggests that maternal OT released during birth and within colostrum and breastmilk reduces cellular stress in the infant gut epithelium (and brain) caused by gut microbial colonization [30], likely allowing for the building of immune tolerance during antigen (microbial) stimulation [24]. Furthermore, *L. reuteri* in the breast milk and intestinal epithelium likely contribute to a positive feedback loop where the upregulation of central and peripheral OT by *L. reuteri* keeps inflammation in check and promotes cellular homeostasis in the brain and gut, allowing for healthy gastrointestinal and nervous system development. Not surprisingly, the stimulation of central OT by *L. reuteri* in the gut also promotes social affiliation through actions on the dopaminergic system [35], thereby reinforcing the endogenous release of OT for long-term health and the maintenance of social bonds [36]. Thus, moving beyond a lactation hormone, OT was a master regulator of brain and gut inflammation during the stress of birth and lactation and likely facilitated the building of mucosal immune tolerance in early life. I was fortunate to join a project being conducted at Northeastern University in Dr. Craig Ferris's laboratory, a site involved in the NIH P01 grant directed by Sue. As part of this project, I collected intestinal tissue and stool from offspring born to prairie vole dams that were treated with different doses of OT at birth. My goals were to determine how the administration of exogenous OT to pregnant voles at birth influences the gut microbiome and the development of the gastrointestinal tract of offspring. Our experimental findings will soon be under peer-review. I was also thrilled to be part of a project with Wil Kenkel to examine how pre-labor cesarean sections, which remove the aspect of OT-assisted labor, influence offspring gastrointestinal development [37].

Through my research of OT's protective effects on the developing brain and gastrointestinal system at birth and beyond (reviewed in Refs. [24,38]), I discovered several other remarkable functions of oxytocin at birth for the mother and infant. For the fetus, OT enhances lung maturation, provides analgesia during delivery, and enhances epinephrine production that mobilizes glucose, reduces fetal heart rate, and redirects blood flow to vital organs [39–43], all to mitigate stress to the newborn [44]. For mothers, a surge of OT post-birth expels the placenta and creates a unique window for mother-infant bonding [45], while OT-mediated post-labor contractions shrink the uterus to prevent hemostasis [46]. Furthermore, skin-to-skin contact between parents and newborns releases OT, thereby reducing the stress hormone cortisol in both parents and infants and promoting favorable outcomes in instances of prematurity [47,48].

From these studies, and the influential work of Sue Carter [49–51] and our collaborations [38,52], I began to see OT as a hormone that comes online to mitigate the effects of major physiological and social stressors, seeks to restore homeostasis, and reinforces affiliative social behaviors to promote healing and health. OT's effects are varied and all-encompassing, from dampening the release of cortisol via the HPA axis to reducing inflammation through actions on immune cells (microglia, macrophages, monocytes, T regulatory cells, etc.) and cellular stress pathways, such as the UPR^{ER}, mTORC1 pathway, and autophagy. Everywhere I looked, it seemed like OT had "its fingers in every pie" to reduce stress and re-establish homeostasis within an

organism.

4. The evolution of stress signaling: a role for oxytocin and social affiliation

In late 2021, Sue approached me and asked if I would join her in writing a review on the relationship between oxytocin and oxygen within the context of an evolutionary framework. I readily accepted the challenge as I love nothing more than to delve into complex topics, research "the heck out of a question," and develop a synthesis. This passion of mine is what likely propelled me toward the sciences in 6th grade and into the field of neuroscience as a sophomore in college. In graduate school and as a research scientist at IU, I discovered that I was drawn to understanding evolutionary adaptations and evolutionary developmental (evo-devo) biology. This started under the mentorship of my graduate advisor, Barbara Finlay, a brilliant scientist and revolutionary thinker, who has researched evo-devo mechanisms of brain development [53–55]. My interest in OT's role in evolution was further developed at IU through my affiliation with the Ecology, Evolution, and Behavior Section within the Department of Biology, my introduction to the research of Rudy Raff, and the comparative neuroanatomical research questions that Jim and I addressed together. The main thesis of my paper with Sue titled "Oxytocin and oxygen: The evolution of a solution to the 'stress of life'" was to explore the evolutionary origins of interactions between oxygen and OT (and OT-like precursors) and how these interactions allowed for the evolution of immune defense, the adaptations to stress, and the emergence of sociality [52].

During this time, I was exploring how oxytocin is an anti-inflammatory molecule, immunomodulator, and regulator of cellular stress. As I began researching the effects of OT and OT-related peptides in early evolutionary time, I uncovered roles for OT in mitochondrial function and basic cellular processes that facilitate recovery from cellular stress. For our manuscript thesis, I discovered how cellular stress pathways changed with the evolutionary emergence of oxygen, particularly with the transition from anaerobic to aerobic respiration. Whereas anaerobic respiration uses sulfur-based compounds and occurs in the cell cytoplasm of unicellular organisms, the bacterial invasion of unicellular organisms permitted the development of oxygen-based aerobic respiration at the mitochondrial membrane, with mitochondria evolving from aerobic bacterial cells that had taken up residence inside anaerobic eukaryotes. Oxygen is required during the final stage of aerobic respiration for the generation of ATP for cellular energy, and this requirement of oxygen during oxidative phosphorylation allowed for the expansion of oxygen-based chemistry, including the generation of oxygen-based compounds such as free radicals known as superoxides (O_2^- and H_2O_2). I was fascinated to learn that the generation of these O_2 molecules drives essential adaptive cellular homeostatic processes, such as the UPR^{ER}, autophagy, and even immune system defense through the packaging of superoxides in phagocytes for bacterial killing during phagocytosis. I had always thought of free radicals as "bad actors," but here were functions for these molecules for cellular housekeeping tasks. However, excessive levels of these superoxides generated by a significant acute stressor or prolonged chronic stress can have damaging effects on cells [24]. I was delighted to discover that alongside the development of oxygen-based aerobic respiration at the mitochondrial membrane, OT functions to alleviate cellular stress and protect mitochondrial function through 1) increases in glutathione (GSH), a potent antioxidant, and 2) increases in cellular ATP (reviewed in Refs. [38,52, 56]). Under conditions of high metabolic demand and limited oxygen supply, such as the hypoxic event of birth [44], there are increases in reactive oxygen species (ROS) production that can be damaging to cells unless ROS are reduced (such as the reduction of H_2O_2 to H_2O). An increase in GSH reduces more ROS during an inflammatory event, alleviating oxidative stress load, while increases in ATP provide more cellular energy, with both processes facilitating cell recovery. One of my current research avenues is to investigate how endogenous maternal OT

during labor may protect cellular mitochondrial function and ensure cellular recovery from the stress of birth, thereby preventing alterations to mitochondrial respiratory capacity that render cells vulnerable to future cellular stressors.

Until recently, I had been thinking about OT and its role in acute stress. However, one recent paper on OT expanded my interest in OT, social connection, and OT's potential protection against chronic stress over one's lifetime. In "Love and Longevity: A Social Dependency Hypothesis," Alex Horn and Sue Carter propose that the evolution of longer lifespans is due to the cumulative actions of oxytocin, which mitigates extrinsic mortality threats through the promotion of social bonds, social relationships, and reproductive behaviors, as well as intrinsic cellular threats through its anti-inflammatory and anti-oxidative actions [36]. They further surmise that natural selection favors increased longevity in individuals who engage in caregiving across the lifespan and later in life to promote the survival of the next generation of offspring. According to this hypothesis, the expression of the mammalian caregiver phenotype and the physiological changes that accompany this phenotype (i.e., enhanced OT signaling) likely contribute to the health and longevity of socially connected individuals who are delivering care later in life, such as grandparents and elderly community members. For instance, the more caregiving behavior and social connectedness an individual experiences, the greater their cumulative exposure to OT throughout life, with OT acting at the cellular level to reduce oxidative stress and inflammation and at an extrinsic level to reduce environmental harshness to promote longer lifespans. As we learned from the COVID-19 pandemic, humans are inherently a social species that suffers when socially isolated and socially disconnected. As Alex and Sue conclude in their synthesis of the Social Dependency Hypothesis, maximizing human health and longevity may likely be found in our instincts to love and care for each other [36], as social connectedness releases OT to dampen cellular stress. One question that remains elusive to me is whether OT's regulation of social affiliation evolved from its regulation of immune signaling and cellular stress pathways.

5. Conclusions

When I began my study of OT with Jim, I discovered the deep evolutionary history of this peptide in the regulation of social affiliation and reproductive behavior with the exciting discovery of OT's ability to promote sociality in birds. Later studies that emerged from the Kingsbury-Goodson lab with asocial finches gave me insight into the complexity of OT's role in stress coping, from facilitating "coping" in subordinate individuals to promoting aggression in dominant individuals via its anxiolytic actions. In my early collaborations with Sue, I learned of OT's anti-inflammatory actions for the developing brain and gut and began to see it as a hormone with remarkable healing properties, particularly within the context of stress. I have moved from the level of the individual to the level of the cell, with my current research focused on how OT may promote mitochondrial and cellular recovery from physiological and psychological stressors during developmental windows to decrease cellular vulnerabilities to future trauma, immune challenges, and stress. As I moved from the study of OT as a social affiliation hormone to the study of OT as an anti-inflammatory molecule, I developed a complex understanding of how OT's social and cellular stress functions are inextricably linked.

CRediT authorship contribution statement

Marcy A. Kingsbury: Writing – original draft, Conceptualization.

Declaration of competing interest

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

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