Title

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Publication Date

2024-11-01

DOI

10.1016/j.cpnec.2024.100273

Peer reviewed

Comprehensive Psychoneuroendocrinology 20 (2024) 100273

Contents lists available at ScienceDirect

Comprehensive Psychoneuroendocrinology

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

Oxytocin: Not "just a female hormone": A very special issue and a very special molecule

A B S T R A C T

For decades it was believed that oxytocin was "just a female hormone." This was a mistake. In the 21st century it has become clear that oxytocin arose from ancient roots, and acquired dozens of diverse functions throughout the mammalian body. This Special Issue of *Comprehensive Psychoneuroendocrinology* brings together a series of fifteen papers describing different facets and functions of oxytocin. Each author was invited to describe her perspectives on oxytocin, as well as to share experiences that led them to study this remarkable molecule. Many of these stories are highly personal and set in the context of what it means to be a female and to be an academic scientist. Oxytocin is not "just" a female hormone and these articles are not "just" routine descriptions of scientific facts. The readers are invited to join us in a celebration of the molecule that made us human.

1. Introduction

Oxytocin was traditionally viewed as a "female reproductive hormone." This is only partially correct. In fact, oxytocin is a pleiotropic peptide that affects virtually every bodily tissue and system in both males and females. However, both this original reputation of its importance **only** in females, and an underestimation of the remarkable extent of oxytocin's functions may have discouraged and mislead research on oxytocin. This is changing and much of that change has been driven by women scientists who entered this field over the last half century.

Oxytocin was the first polypeptide to be isolated and synthesized, an accomplishment which earned the 1955 Nobel Prize in Chemistry for Vincent du Vigneaud. The oxytocin receptor was identified by Kimura and colleagues in 1992. A number of important physiological studies began to appear, albeit slowly at first. However, in the 21st century interest in oxytocin increased dramatically and at present, a search of PubMed reveals almost 32,000 articles that include oxytocin as a keyword. Most of those studies are **not** dealing simply with "female reproduction."

2. Unique features of this special issue

The purpose of this Special Issue of *Comprehensive Psychoneuroendocrinology* is to bring together a set of articles that offers personal perspectives and experiences drawn from women scientists who have studied different facets and functions of oxytocin. The papers in this Special Issue are sole-authored, narrative reviews that describe the author's personal and professional journey. Authors were invited to write in candid terms, describing their strategies for success and challenges encountered along the way. The authors also were encouraged to use bold or personal titles and to tell their story in the first-person.

Each author was asked to describe their own history in the context of the scientific discoveries and frontiers they found most relevant or exciting to the neurobiology that has developed around the study of oxytocin. Authors were invited to merge their personal history with highlights of the scientific context, discoveries and applications that have arisen, or that they project may arise in the future. In so doing we hoped to create an accessible archive that is filled with scientific insights, and that we hope will encourage younger scientists, and especially women who are from different cultures and traditions, to enter Science.

3. If oxytocin is not "just a female hormone," then what is it?

The origins of genes responsible for oxytocin, its receptors [1,2] and its functions [3] also challenge the notion that "oxytocin is a mammalian hormone." Oxytocin, as a peptide, evolved over 200 million years ago at around the time that mammals first appeared. However, vasotocin - the ancestor of oxytocin, and oxytocin homologues, such as isotocin and mesotocin - have many parallel physiological and behavioral functions in species that emerged before mammalian evolution. These oxytocin-like precursor molecules can be traced from cartilaginous and bony fishes to mammals [2]. It is argued that precursors to oxytocin were present before the division between vertebrate and invertebrate species. Functions of these early VT and OT-like peptides include the modulation of cellular stress and homeostatic mechanisms, satiation, and mitochondrial function [1].

4. Is oxytocin "Nature's" medicine?

Early research of oxytocin focused on birth, lactation, maternal behavior and social bond formation [3,4]. Studies followed in the 1980s and 1990s documenting a role for oxytocin in other forms of social behavior, group formation and social cognition [1,4–8]. The characteristics of oxytocin and related peptides are only now being fully appreciated in physiology and medicine [3,9,10]. There is increasing evidence that oxytocin has a role both in behavioral and physical

https://doi.org/10.1016/j.cpnec.2024.100273
Received 28 October 2024; Accepted 29 October 2024
Available online 31 October 2024

development, as well as health and longevity [5,6,8,11]. Hundreds of studies are now revealing a major role for oxytocin in the management of challenge, stress and pain [4,5,8,10–13], including potentially preventing the events associated with birth from developing into "birth trauma." However, in general oxytocin, seems capable of preventing or healing traumas of various kinds.

There is a growing literature implicating oxytocin in the regulation of cellular stress and immunity [1,11,12], food intake and metabolism [9], while maintaining the integrity of bone and muscle. Several of these functions can be traced back to oxytocin's ancient role as an anti-inflammatory agent, with direct consequences for mitochondrial functions, involved in providing energy for almost every bodily tissue [1].

The hypothalamus is the primary, but not exclusive source of oxytocin. Oxytocin plays a major role in healthy social development [11], improving the capacity to cope with adversity especially in early life [4,5,8]. Lactation is a uniquely mammalian function and also is uniquely dependent on oxytocin. Systems responsible for lactation involve physiological adaptations that help the mother care for her young and also manage the stress of rearing offspring, maintaining maternal and infant health and even pacing reproduction through lactation amenorrhea. Nursing and the novel and adaptive components of milk provide altricial mammalian offspring with, not only nutrients, but also antibodies, as well as critical support and programming for the developing immune system, including the mucosal immune system that upregulates oxytocin receptors during lactation [14]. Oxytocin, though specific rhythmic actions on muscle and other aspects of behavior, assists in the development of social synchrony [2] and parental-child bonding [4,5,11]. Oxytocin also plays an essential role in the regulation of the symbiotic microbiome, which are now understood to have effects on essentially every aspect of health and well-being [14].

Oxytocin was essential for the evolution of the human nervous system [4], which in turn was necessary for speech and complex cognition [2]. Oxytocin also may support emotional development [11], consciousness, language development and is being tested in the treatment of speech, movement [2] and cognitive pathologies [7].

Atypical expression of oxytocin has been discovered in a vast array of human disorders including autism [5,6,8,11], Williams syndrome [7], schizophrenia, anxiety, depression [15] and especially PTSD [4]. There are correlations with endogenous oxytocin levels in several forms of mental illness, generally suggesting a beneficial role for oxytocin [15]. However, oxytocin can be elevated in some diseases, possibly as part of an adaptive and healing process [7].

5. Methodological challenges

Methods for releasing **endogenous** oxytocin are surprisingly poorly understood. These are questions of particular concern in the optimization of the health of premature and full-term infants [11]. Perhaps, most remarkable and least understood is emerging evidence for a role for oxytocin in mystical and religious experiences [7].

Measurement of the oxytocin receptor also has presented important technical obstacles to the study of oxytocin. Significant species and individual variations occur in the expression of the oxytocin receptor [4–6, 8]. In fact, the existence of a functional oxytocin receptor in brain regions implicated in social and emotional behavior has been challenged by data from tissue from old world primates and humans, creating concern over the generality of mechanisms through which oxytocin functions.

6. Oxytocin as a pharmaceutical?

Findings such as those described in this Special Issue have led to interest in the medical application of oxytocin or oxytocin-like molecules. Pituitary extracts and then synthetic oxytocin (Pitocin/Syntocinon) were used to facilitate birth and lactation beginning in the 20th century. Oxytocin is still widely applied in childbirth to facilitate and manage labor and may also prevent postpartum hemorrhage - which remains a major factor in postpartum maternal health [10].

Oxytocin and oxytocin-like molecules, especially in the context of positive social experiences, also are being suggested and implemented in therapeutic applications and may support good health. These are being tested as treatments in a diverse range of disorders including mental illnesses [15], autism spectrum disorders [6,8,11], excess inflammation [1], pain and stress relief [11,12], substance abuse [13], dysfunction of speech and movement [2], and more. However, there is at present a lack of consensus concerning the usefulness of such treatments. In part this may be because current methods for administering exogenous oxytocin do not deliver adequate amounts of the molecule to relevant neural tissues and/or may not model endogenous release. Current methods are simultaneously exploring how to enhance endogenous release of oxytocin for better physiological efficacy. And importantly, as described throughout this special issue oxytocin does not act alone [3,4].

Under ideal conditions, oxytocin, like most other essential hormones, would be routinely measured and perhaps even supplemented. However, the novel physiology and chemistry of oxytocin has created technical issues and controversies that have challenged the usefulness of measurements of oxytocin or treatments involving oxytocin. Oxytocin measurements are not, at present, components of most physiological testing, and standardized methods that allow comparisons across laboratories remain to be established [4].

7. Oxytocin and vasopressin: an integrated system

Among the most serious challenges in studying oxytocin is the presence of adaptive interactions of oxytocin with vasopressin. Vasopressin is the more ancient molecule, having preceded the evolution of canonical oxytocin, by hundreds of millions of years [12]. However, the receptors for oxytocin and vasopressin are also ancient and interactive, with a major role in the management of challenges [3,12]. This was not understood in the original naming of these systems. In fact, it has been argued that the nomenclature associated with the system that involves oxytocin, vasopressin and their receptors should be altered to reflect this history [2].

In addition to issues around nomenclature, there is increasing evidence for significant and functional cross-talk between oxytocin, vasopressin and their receptors [4]. The early tendency to attribute separate and distinct functions to oxytocin and vasopressin and the failure to understand that oxytocin and vasopressin are part of a functional system, has further contributed to misunderstandings and controversy. Sophisticated tools, at present primarily used in *ex vivo* tissue or animal models, are slowly untangling this mystery. To fully appreciate interactions among peptides (including both oxytocin and vasopressin), future studies will need to extend to other relevant molecules. For example, endogenous opioids, dopamine, corticotropin-releasing hormone and serotonin (and their receptors) have functionally important interactions with oxytocin [3,12]. Knowledge of these systems will be essential to the development of a deeper appreciation of the complex regulation of mammalian biology and behavior and may lead to greater insight as to the evolutionary underpinnings of oxytocin-like peptides.

8. Who are the authors?

The individuals who contributed to this Special Issue represent scientific disciplines from clinical and translational research to molecular and genomic biology. Over time, many individuals, even some of the youngest authors in our (admittedly nonrandom) sample, have covered this gamut of perspectives (Table 1).

To extend the inclusiveness of our approach, the authors invited to participate in this Special Issue also ranged from very senior scientists to individuals still in training. Of our authors, 8 of 15 were trained in clinical or veterinary medicine. All but two have PhDs. Over half of the authors originated their careers in the United States, but among the authors are individuals who spent significant parts of their lives in Canada, East Germany, Greece, Italy, India and the Caribbean.

Table 1
Backgrounds and demographics of authors.

AUTHOR	MD or Other Clinical Training	PhD	Year - First OT Publication	# of years working on OT	Webpage
Bales, Karen		+	**2003**	**21**	https://bales.faculty.ucdavis.edu/.
Carter, Sue		+	**1990**	**44**	https://kinseyinstitute.org/about/profiles/cscarter.php
Erdman, Susan	+	+	**2013**	**10**	https://erdmanlab.us/about.php
Erickson, Elise	+	+	**2014**	**16**	www.mumhlab.com
Jacob, Suma	+	+	**2004**	**20**	https://capfellowship.semel.ucla.edu/faculty-member/jacob-suma/
Kingsbury, Marcy		+	**2009**	**15**	https://researchers.mgh.harvard.edu/profile/15814685/Marcy-Kingsbury
Korenberg, Julie	+	+	**2006**	**20**	https://neuroscience.med.utah.edu/faculty/korenberg.php
Lawson, Elizabeth	+		**2011**	**16**	https://researchers.mgh.harvard.edu/profile/26762/Elizabeth-Lawson
Marazziti, Donatella	+	+	**2012**	**22**	https://www.donatellamarazziti.com/en/
Neumann, Inga		+	**1988**	**36**	Prof. Dr. Inga D. Neumann - Universität Regensburg (uni-regensburg.de)
Nisbett, Khalin		+	**2023**	**6**	www.kayenisbett.com
Parker, Karen		+	**2001**	**28**	https://med.stanford.edu/parkerlab.html
Theofanopoulous, Constantina		+	**2016**	**10**	https://www.constantinatheofanopoulou.com/
Uvnas-Moberg Kerstin	+	+	**1985**	**43**	kerstinuvnasmoberg.com
Welch, Martha	+		**2000**	**24**	https://www.columbiapsychiatry.org/profile/martha-g-welch-md

9. The heroine's journey

Details were not always provided, but none of the authors describe being reared by mothers who were scientists or doctors (although several mothers were nurses). In contrast, several of our authors had academically educated fathers who were successful scientists or engineers. Co-incidentally two authors had fathers who worked for Bell Labs and another's father was a chief chemist at Union Carbide.

A striking version of following in a parent's footsteps is found in the biography of the most senior author in this volume and a true pioneer in the study of oxytocin. Kerstin Uvnas Moberg [3] trained at the Karolinska Institute, where she obtained an MD and PhD (in a department created by and chaired by her father). Kerstin's father later became Dean of the Karolinska Institute and Chair of the Nobel Committee, but this heritage did not spare her from a career filled with academic and political drama.

It is common for our authors to express gratitude to their families for the support that allowed them to become scientists. In various ways, either as models or through overt encouragement, the parents of most of our authors seem to have supported their daughters to follow careers in science and/or medicine. The demands of family life, including having children and/or partners, are not always described, but clearly created issues for many of our authors. However, in several cases the experience of loving relationships, including giving or receiving parenting, was a specific motivation toward their interest in oxytocin.

Despite parental support, when queried privately, many – perhaps most – of these women experienced serious obstacles to having and maintaining careers in science. Obstacles came in the form of a need to adapt to the "two-career" problem, loss of a partner, finding the time and energy to care for families, dealing with life-threatening illnesses, or in one case working under restrictions imposed by an authoritarian government. In several cases, overt discrimination and/or harassment were experienced. However, none of these issues were able to deter these women from careers that continue to the present to be driven by both intellectual curiosity and in many cases heroic determination.

CRediT authorship contribution statement

C. Sue Carter: Writing – review & editing. **Rose-Marie Bluthé:** Writing – review & editing. **Jessica J. Connelly:** Writing – review & editing. **Marcy A. Kingsbury:** Writing – review & editing.

Funding

The research studies of CSC, JJC and MAK have been repeatedly funded by the National Institute of Health and other agencies and foundations. But that funding was not directly relevant to this editorial.

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.

Acknowledgements

We are grateful to the authors of this special issue who graciously shared both their scientific knowledge and their personal experiences. We are also grateful to the Elsevier staff who made this publication possible. We are particularly indebted to Dr. Robert Dantzer and the officers of the International Society for Psychoneuroendocrinology who supported the notion of creating a special issue devoted to oxytocin and featuring a few of the women scientists who have worked so hard to bring this molecule out of the shadow of "female reproduction."

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