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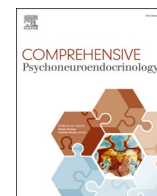
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ABSTRACT

Love and fear were forged by the same fundamental evolutionary processes that permitted life on Earth. Both love and fear are deeply interwoven with the adaptive management of stress and disease. Love and fear share common roots and both can play a role in reproduction, survival, perceived safety and wellbeing. This special issue of *Comprehensive Psychoneuroendocrinology* focuses specifically on the causes and consequences of love from the interactive perspectives of evolution, neurobiology and culture.

1. Background for this special issue

The origins of this special issue of *Comprehensive Psychoneuroendocrinology* (cPNEC) can be traced back over a quarter of a century to a small conference held in Stockholm, Sweden in 1996. It was at that meeting that Drs. Carter and Dantzer first became acquainted. At the invitation of Dr. Dantzer, the Stockholm meeting eventually resulted in a special issue, published in the parent journal, *Psychoneuroendocrinology* in 1998, and entitled "Is there a Neurobiology of Love?" That volume of PNEC created a forum for evidence supporting the notion that what humans experience psychologically and emotionally as "love" is based on an ancient neurobiology.

Research in the 21st century has continued to affirm the hypothesis that love is a legitimate topic for scientific research. It is also become increasingly clear that the evolutionary and neuroendocrine origins of love extend beyond sex or reproduction. Knowledge of the biological origins of both love and fear has broad consequences for individual and global health and wellbeing. The success of that earlier effort led to a decision by Dantzer and Carter to revisit the neurobiology of love in a special issue of the newly launched journal, cPNEC.

Consistent with the expanded focus of cPNEC, a few senior scientists were invited to provide broad perspectives on "big questions" surrounding human evolution and wellbeing. We also invited younger scientists to provide fresh thoughts on the challenges associated with contemporary life. Finally, offers to be included in this issue also were extended to empirical papers that were submitted independently to cPNEC while this issue was in progress; these are used here to illustrate both the potential and problems associated with considering the neurobiology of love and safety as a lens on human wellbeing.

2. The natural history of love and fear

We live in an uncertain world - sometimes inundated with fear and threats to survival. Fear can be protective as living organisms anticipate and defend against danger. Fear, anxiety, vigilance and related states involve primitive responses. In response to chronic threats or disease, prolonged or intense reactivity can overwhelm the capacity to cope [1]. Moreover, chronic or unchecked fear and anxiety can be deadly. In this context, social solutions to the stresses of life are presumed to have evolved because the benefits of sociality outweighed the costs [2]. Individuals and as well as species capable of coregulation with others are gifted with an improved potential for survival, reproduction and longevity [3].

Embedded in positive social relationships are complex emotions and behavioral experiences that came to be known as "love" [4]. The word love has various meanings, but the formation of selective connections and resultant perceptions of safety or trust are found at the core of most biobehavioral definitions of love. The same biological systems that supported social bonds and reproduction enhanced the capacity to overcome fear, stress and disease [1,4]. The absence of supportive social connections leaves social mammals, and especially humans, vulnerable to neuroendocrine and autonomic dysfunctions [2] and virtually every type of physical and emotional illness [1,5].

3. Love as medicine

Embedded in ancient biological systems are specific neuroendocrine, autonomic and immune pathways supporting the capacity to both produce offspring and to survive. In mammals these dynamic processes are necessary for sexual behavior, pregnancy, birth, lactation and maternal behavior [6]. Social bonds and dependency on others can improve individual survival, longevity and genetic fitness [3]. Across time and in

the larger scheme of things the deep biology of love has the capacity to protect and heal. Awareness of how and why this occurs offers a unique portal to understanding human wellbeing and to overcoming chronic fear and disease.

4. The evolution of the capacity for love

Patterns of sociality in primates, canids and other social mammals emerged as consequences of the properties of the mammalian system [2]. Oxytocin, the most recently evolved component of this system [4], has a broad capacity to regulate endocrine, autonomic and immune systems and even cellular inflammation across the lifespan [3]. In contemporary mammals oxytocin has unique functions and biochemical properties that parallel those of love [4]. Of course, oxytocin and the chronic features of love act within a context of other molecules and physiological systems, including those that support fear.

The oxytocin system is regulated across the lifespan, but its patterns of function seem especially sensitive to early nurture or its absence [7]. The oxytocin system and especially the oxytocin receptor serves as an epigenetic “rheostat,” capable of being adaptively tuned by experiences, including interactive and endocrine experiences associated with pregnancy, birth, lactation and parental behavior [6]. The oxytocin receptor is altered by social experiences and love, versus fear and uncertainty especially in early life, and with effects that may extend across generations [7,8].

Timelines for the evolution of hormones of the oxytocin system are being gradually pieced together using genomic methods, including research on samples of ancient DNA. For example, DNA variants regulating oxytocin-like molecules in modern humans are being compared to those found in the genome of archaic humans and other primates [9]. Specific variants in oxytocin pathways are shared with Denisovans and Neanderthals, while others are shared among humans and bonobos. Currently, it is only possible to speculate regarding the functional significance of these shared systems. However, these emerging findings will have profound implications for discovering the origins of well-being sociality, language, consciousness and eventually what it means to be “human.”

Humans not only depend on other humans, but also on other living organisms. The oxytocin system has been being implicated in domestication, a process that supported human evolution and was at the origin of beneficial interactions with domestic animals and especially canids [8]. The same neuroendocrine systems that allowed selective sociality continue to be expressed in the mutual affection experienced between humans and their pets. Domestication and human animal bonds also allowed the development of multispecies relationships and families. For example, it is estimated that 60% of families in the United States have pets. Domestic species can assist in regulating emotions and reducing fear. However, coexisting with other species, including pets, brings not only benefits but also costs, that often have been underestimated in contemporary culture [10].

5. Regulation of love, the endogenous oxytocin system and unresolved questions

Both love and oxytocin offer promise for interventions that can benefit human health [5,7], including improving the birth experience for mother and child [6], encouraging lactation, facilitating a healthy physiology, and protecting neonates against adversities [11]. However, the specific factors regulating the oxytocin pathways [4] and the physiological benefits of oxytocin, including its role as an anti-inflammatory/anti-oxidant [3] are only now being recognized.

Birth and lactation were functions originally associated with oxytocin. However, naturally occurring factors that induce the release of oxytocin, birth and lactation have been difficult to identify, leaving a

myriad of basic questions unresolved [4]. We know in general that birth and experiences in early childhood have effects on the mental and physical health of the baby and mother [5], yet the mechanisms and especially the positive consequences of these have received shockingly little attention. For example, modern obstetrics often relies on interventions including cesarian section and medications intended to reduce the pain or dangers associated with labor or postpartum blood loss, the long-term consequences of which are largely unstudied [6]. In addition, maternal use of addictive drugs, even when given by prescription, has become an increasing concern; this puts the baby at immediate risk for neonatal abstinence syndrome (NAS), which when left untreated can be deadly [11]. All of these impact the endogenous oxytocin system. Intriguing studies in rodents suggest that exogenous oxytocin may reduce the impact for the offspring of NAS.

Arguably less complex than birth, but still poorly understood, are specific factors that regulate oxytocin in nonreproductive contexts in the face of both positive or negative experiences [4]. Oxytocin and vasopressin and their receptors are functional in both sexes; however, their regulation is steroid-dependent and may be sexually dimorphic across the life-span. Both of these systems influence every tissue in the body, and especially the autonomic and immune systems [2–4].

6. Nature via nurture

It is challenging to create psychological safety in a world plagued by war and disease. The problems faced by humanity demand a global perspective based on a solid foundation of biological knowledge. Love and psychological safety are critical not only to survival, but also to the capacity for a peaceful world. The biological foundations for love were set in place by evolution, but require constant nurture [5]. Through awareness of the biological and developmental foundations of human health and resilience we are beginning to identify those aspects of experience that are most essential. Especially critical among these are pregnancy, birth, lactation [6], development during early childhood [5], all of which set the stage for the capacity for a sense of safety and the opportunity for love and nurture across the lifespan [3,10].

The search for processes regulating the release of endogenous oxytocin has been particularly frustrating, in part because of myths and misunderstandings [4]. The basic factors responsible for the release of oxytocin are not well understood. Oxytocin can be difficult to measure with marked individual differences in its release [12] and its effects on both the oxytocin and vasopressin receptors. Failure to recognize the importance of early nurture can have disastrous and lasting consequences, including reduced capacity to manage later traumas, adversities and all aspects of health [2].

The absence of safety nets normally woven into loving relationships sets the stage for structural inequity and discrimination for not only parents and children, but also for access to pets [10]. Acknowledging the importance of early childhood development is essential and requires the full support of families, societies and governments [5]. The adaptive properties of oxytocin-like molecules and their receptors require awareness of the dynamic molecular biology of this system [7]. These kinds of problems in turn have allowed the emergence of controversies and myths [4], that have slowed both awareness and understanding of this molecule that is so pivotal to health [2], disease [1] and even the future of our planet [5].

Love and safety are components of the body's allostatic systems. Humans are inherently more attentive to danger than to safety. Love and other positive experiences, as topics for scientific study have been historically trivialized. However, secure social bonds and love are central to good health [2] and the avoidance of illness [1]. Understanding the neurobiology of love, including its evolution and the specific physiology that allows love to exist, offers a critical scientific perspective that is not apparent when science focuses only on disease and fear.

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Conflicts of interest

CSC declares no conflicts of interest.

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Author contributions

CSC and RD contributed equally to the development of this special issue and this overview.

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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