3. Liang, X., Madrid, J., Gartner, R., Verbavatz, J.M., Schiklenk, C., Wilsch-Brauninger, M., Bogdanova, A., Stenger, F., Voigt, A., and Howard, J. (2013). A NOMPC-dependent membrane-microtubule connector is a candidate for the gating spring in fly mechanoreceptors. Curr. Biol. *23*, 755–763.

4. Moe, P., and Blount, P. (2005). Assessment of potential stimuli for mechano-dependent gating of MscL: effects of pressure, tension, and lipid headgroups. Biochemistry *44*, 12239–12244.

5. Guo, Y.R., and MacKinnon, R. (2017). Structure-based membrane dome mechanism for Piezo mechanosensitivity. eLife *6*, e33660.

6. Saotome, K., Murthy, S.E., Kefauver, J.M., Whitwam, T., Patapoutian, A., and Ward, A.B. (2018). Structure of the mechanically activated ion channel Piezo1. Nature *554*, 481–486.

7. Zhao, Q., Zhou, H., Chi, S., Wang, Y., Wang, J., Geng, J., Wu, K., Liu, W., Zhang, T., Dong, M.-Q., *et al*. (2018). Structure and mechanogating mechanism of the Piezo1 channel. Nature *554*, 487–492.

8. Coste, B., Mathur, J., Schmidt, M., Earley, T.J., Ranade, S., Petrus, M.J., Dubin, A.E., and Patapoutian, A. (2010). Piezo1 and Piezo2 are essential components of distinct mechanically activated cation channels. Science *330*, 55–60.

9. Howard, J., Roberts, W.M., and Hudspeth, A.J. (1988). Mechanoelectrical transduction by hair cells. Annu. Rev. Biophys. Biophys. Chem. *17*, 99–124.

10. Corey, D.P., and Holt, J.R. (2016). Are TMCs the mechanotransduction channels of vertebrate hair cells? J. Neurosci *36*, 10921–10926.

11. Maksimovic, S., Nakatani, M., Baba, Y., Nelson, A.M., Marshall, K.L., Wellnitz, S.A., Firozi, P., Woo, S.H., Ranade, S., Patapoutian, A., *et al*. (2014). Epidermal Merkel cells are mechanosensory cells that tune mammalian touch receptors. Nature *509*, 617–621.

12. Kim, S.E., Coste, B., Chadha, A., Cook, B., and Patapoutian, A. (2012). The role of Drosophila Piezo in mechanical nociception. Nature *483*, 209–212.

13. Zarychanski, R., Schulz, V.P., Houston, B.L., Maksimova, Y., Houston, D.S., Smith, B., Rinehart, J., and Gallagher, P.G. (2012). Mutations in the mechanotransduction protein PIEZO1 are associated with hereditary xerocytosis. Blood *120*, 1908–1915.

14. Li, J., Hou, B., Tumova, S., Muraki, K., Bruns, A., Ludlow, M.J., Sedo, A., Hyman, A.J., McKeown, L., Young, R.S., *et al*. (2014). Piezo1 integration of vascular architecture with physiological force. Nature *515*, 279–282.

15. Evans, J., Gratzer, W., Mohandas, N., Parker, K., and Sleep, J. (2008). Fluctuations of the red blood cell membrane: relation to mechanical properties and lack of ATP dependence. Biophys. J. *94*, 4134–4144.

16. Tinevez, J.Y., Schulze, U., Salbreux, G., Roensch, J., Joanny, J.F., and Paluch, E. (2009). Role of cortical tension in bleb growth. Proc. Natl. Acad. Sci. USA *106*, 18581–18586.

17. Syeda, R., Florendo, M.N., Cox, C.D., Kefauver, J.M., Santos, J.S., Martinac, B., and Patapoutian, A. (2016). Piezo1 channels are inherently mechanosensitive. Cell Rep. *17*, 1739–1746.

18. Ge, J., Li, W., Zhao, Q., Li, N., Chen, M., Zhi, P., Li, R., Gao, N., Xiao, B., and Yang, M. (2015). Architecture of the mammalian mechanosensitive Piezo1 channel. Nature *527*, 64–69.

19. McMahon, H.T., and Gallop, J.L. (2005). Membrane curvature and mechanisms of dynamic cell membrane remodelling. Nature *438*, 590–596.

Behavior: Oxytocin Promotes Fearless Motherhood

Lior Cohen[1], Mouna Maroun[1,2], and Shlomo Wagner[1,2,*]
[1]Sagol Department of Neurobiology, University of Haifa, Haifa 3498838, Israel
[2]The Integrated Brain and Behavior Research Center (IBBR), University of Haifa, Haifa 3498838, Israel
*Correspondence: shlomow@research.haifa.ac.il
https://doi.org/10.1016/j.cub.2018.02.063

In mammals, lactating mothers show reduced fear and anxiety. A new study reveals the way by which the lactation-inducing neuropeptide oxytocin attenuates social fear in lactating female mice by inhibiting activity in a single brain area.

Oxytocin is a nine amino acid neuropeptide, the synthesis of which is parsimoniously restricted to two adjacent areas of the hypothalamus, the paraventricular (PVN) and supraoptic (SON) nuclei [1]. Oxytocin is unique among brain neuropeptides (besides its 'twin' neuropeptide arginine-vasopressin, produced in the same areas) in its duality of action: magnocellular oxytocin neurons in these nuclei send one axonal terminal to the posterior pituitary, from where they secrete oxytocin to the peripheral blood system [2], and most, if not all of these neurons also send axonal collaterals to specific brain areas and release oxytocin in these targets [3,4]. Thus, oxytocin released by the same cells acts both as a neurohormone in the periphery and as a neuromodulator within the brain. The precise relationship between these two seemingly separate modes of oxytocin activity is not known. In a new paper published in a recent issue of *Current Biology*, Menon *et al.* [5] provide new information that begins to clarify this issue.

The best established role of oxytocin in the periphery is related to maternal functions, e.g. labor and lactation [6]. Oxytocin release into the blood plays a pivotal role in uterus contractions during labor and is crucial for the milk ejection reflex during lactation. It is therefore not surprising that the level of oxytocin receptor (OXTR) expression in the uterus and mammary glands, as well as oxytocin level in the blood rise dramatically before labor and stay high in lactating mothers. In parallel, OXTR level in many brain areas, including limbic areas linked to emotions, is also increased before labor [7], suggesting an enhanced involvement of oxytocin in regulating the emotional behavior of mothers.

Earlier studies showed that lactating rats are more aggressive towards conspecifics and less fearful than virgin

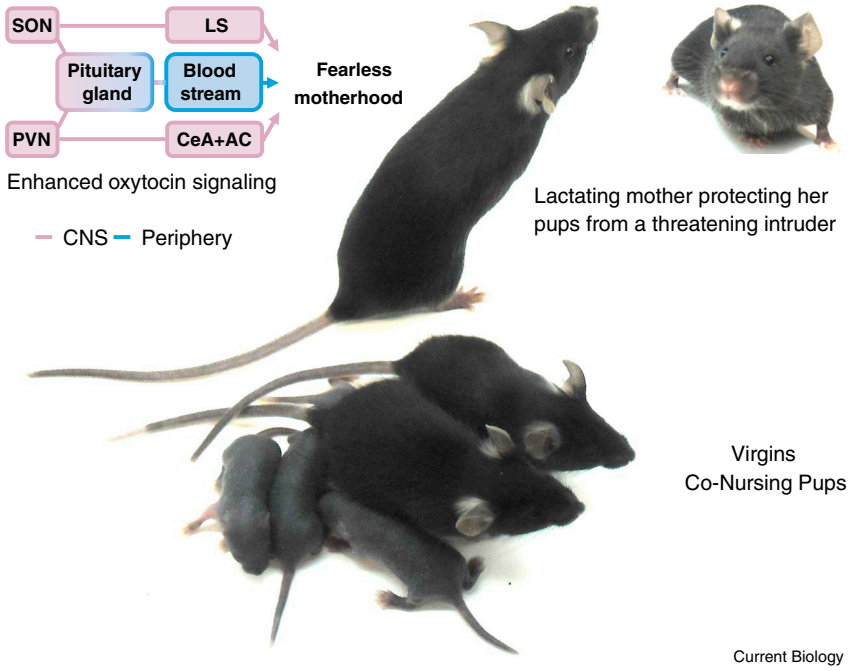

Figure 1. Oxytocin, social fear, and maternal behavior.
Increased oxytocin activity in both the brain and periphery during lactation promotes pup protection and nursing by attenuating social fear in mothers and by stimulating maternal behavior in virgins, thus enhancing colony survival. SON, supraoptic nucleus; PVN, paraventricular nucleus; LS, lateral septum; AC, auditory cortex; CeA, central amygdala. (Photography by Lior Cohen).

rats [8]. For example, lactating mothers showed reduced time in fear-induced freezing postures in response to an aversive auditory tone than virgins [9]. These motherhood-induced behavioral adaptations are thought to be mediated by oxytocin [10,11], signifying a coordination between central and peripheral actions of oxytocin.

In the current study, Menon *et al.* unravel a novel mechanism mediating the tempering effect of oxytocin on social fear responses of lactating mice. They used a behavioral paradigm called social fear conditioning, which pairs, on day 1, foot shocks and a specific social stimulus. On day 2, the animals performed an extinction protocol comprising three exposures to a control non-social stimulus followed by six exposures to the social stimulus from the previous day. On day 3, the animals underwent a recall protocol comprising six exposures to the same social stimulus. This paradigm, previously used with male mice only [12], reports both the level of induced social fear and its time course of extinction during repeated exposures to the conditioned social stimulus.

Surprisingly, while virgin females showed a profound social fear response on day 2, which was gradually extinguished during the extinction protocol, lactating mothers behaved similarly to unconditioned animals and showed no social fear response.

The authors then used immunostaining against the neural-activity marker cFos to identify brain areas exhibiting differences in neural activation during social fear responses, between virgin and lactating female mice. They revealed a lactation-specific significant reduction in cFos expression only in the lateral septum (LS), where oxytocin activity was previously found to enhance extinction of social fear responses of male mice [12]. The authors then employed genetically modified mice in which the fluorescent marker GFP is specifically expressed in OXTR-expressing cells, to probe which neurons in the LS express this receptor. They revealed specific OXTR expression in a population of calbindin-positive, inhibitory interneurons of the LS. Using microdialysis to monitor the levels of oxytocin release in the LS before, during and after social fear response, the authors found a significant increase in oxytocin levels measured in lactating mothers during fear responses, while no such increase was observed in virgin females. These results suggest that enhanced oxytocin release in the LS of lactating mothers reduces their social fear response by activating inhibitory interneurons in this brain area.

To validate this suggestion, Menon *et al.* manipulated the oxytocin system in the LS in various ways, and found that injection of oxytocin into the LS, as well as overexpression of the OXTR in this brain region, of virgin females significantly reduced their social fear response. In contrast, infusion of OXTR antagonist to the LS, as well as a knockout of the OXTR gene, elevated the fear response of lactating mothers, to a level that was similar to virgin females. These experiments confirmed that oxytocin release in the LS does reduce social fear in lactating mothers. Next, the authors aimed to identify the source of oxytocin innervation in the LS and to understand why it is more active in lactating mothers than in virgin females. Prior to the new study from Menon *et al.*, most if not all behavioral effects of oxytocin were found to emerge from PVN neurons [13], and the SON was traditionally neglected as a source of forebrain innervation by oxytocinergic fibers, despite evidence for such innervation [3]. Surprisingly, Menon *et al.*, using retrograde viral-vectors to trace oxytocin neurons that innervate the LS, found that the main source of oxytocin fibers in the LS is the population of oxytocin neurons in the SON. Indeed, inhibition of neural activity in these neurons using pharmacogenetic manipulation strongly augmented the social fear response of lactating mothers and prevented any extinction of this fear response. Moreover, the authors found a two-fold increase in the number of oxytocin-expressing fibers in the LS of lactating mothers as compared to virgin females, suggesting a proliferation of these axonal terminals in lactating mothers.

Thus, the results of this study lead to a double breakthrough. First they demonstrate a clear behavioral role for the innervation of the LS by oxytocin fibers from the SON, indicating that not only the PVN, as previously thought, but also the SON plays an important role in oxytocin-mediated regulation of social behavior.

Second, they show that this innervation is augmented in lactating mothers, a plastic process leading to enhanced release of oxytocin in the LS. By activating local inhibitory interneurons, the enhanced release of oxytocin inhibits neural activity in the LS, subsequently attenuating fear responses of mothers.

The study of Menon *et al.* echoes a recently published study in rats [14], where the authors used odor fear conditioning to show that oxytocin acts in the central amygdala to prevent fear-induced freezing response in lactating mothers, thus enabling them to actively protect their pups. Together, both of these studies show how oxytocin modulates brain activity to prevent an adaptive fear response, such as freezing, in situations where it could possibly be maladaptive, such as when mothers protect their offspring. These findings also reveal a clear match between the physiological role of elevated peripheral oxytocin during lactation and the behavioral consequences of its enhanced brain activity during this precarious period (Figure 1). Thus, these studies are a step forward in understanding that the dichotomy between brain and periphery is artificial and that they should be conceived and explored as one gestalt.

From a broader perspective, social rodents, like humans, live in multigenerational colonies containing females in all stages of the reproductive cycle, including virgins. Previously, it has been reported that oxytocin release in the auditory cortex of virgin female mice co-housed with lactating mothers and their pups accelerates the emergence of maternal behavior displayed by the virgin females [15]. Together, all of these studies suggest that the extended oxytocin system in the central nervous system affects group dynamics beyond the individual, and modulates complex social networking, thus increasing colony fitness (Figure 1).

REFERENCES

1. Grinevich, V., Knobloch-Bollmann, H.S., Eliava, M., Busnelli, M., and Chini, B. (2016). Assembling the puzzle: pathways of oxytocin signaling in the brain. Biol. Psychiatry *79*, 155–164.

2. Leng, G., Pineda, R., Sabatier, N., and Ludwig, M. (2015). 60 years of neuroendocrinology: the posterior pituitary, from Geoffrey Harris to our present understanding. J. Endocrinol. *226*, T173–T185.

3. Knobloch, H.S., Charlet, A., Hoffmann, L.C., Eliava, M., Khrulev, S., Cetin, A.H., Osten, P., Schwarz, M.K., Seeburg, P.H., Stoop, R., *et al.* (2012). Evoked axonal oxytocin release in the central amygdala attenuates fear response. Neuron *73*, 553–566.

4. Landgraf, R., and Neumann, I.D. (2004). Vasopressin and oxytocin release within the brain: a dynamic concept of multiple and variable modes of neuropeptide communication. Front Neuroendocrin. *25*, 150–176.

5. Menon, R., Grund, T., Zoicas, I., Althammer, F., Fiedler, D., Biermeier, V., Bosch, O.J., Hiraoka, Y., Nishimori, K., Eliava, M., *et al.* (2018). Oxytocin signalling in the lateral septum prevents social fear during lactation. Curr. Biol. *28*, 1066–1078.e6.

6. Russell, J.A., and Leng, G. (1998). Sex, parturition and motherhood without oxytocin? J. Endrocrinol. *157*, 343–359.

7. Gimpl, G., and Fahrenholz, F. (2001). The oxytocin receptor system: structure, function, and regulation. Physiol. Rev. *81*, 629–683.

8. Erskine, M.S., Denenberg, V.H., and Goldman, B.D. (1978). Aggression in the lactating rat: effects of intruder age and test arena. Behav. Biol. *23*, 52–66.

9. Hansen, S., and Ferreira, A. (1986). Food-intake, aggression, and fear behavior in the mother rat - control by neural systems concerned with milk ejection and maternal-behavior. Behav. Neurosci. *100*, 64–70.

10. Bosch, O.J., and Neumann, I.D. (2012). Both oxytocin and vasopressin are mediators of maternal care and aggression in rodents: from central release to sites of action. Horm. Behav. *61*, 293–303.

11. Francis, D.D., Champagne, F.C., and Meaney, M.J. (2000). Variations in maternal behaviour are associated with differences in oxytocin receptor levels in the rat. J. Neuroendocrinol. *12*, 1145–1148.

12. Zoicas, I., Slattery, D.A., and Neumann, I.D. (2014). Brain oxytocin in social fear conditioning and its extinction: involvement of the lateral septum. Neuropsychopharmacology *39*, 3027–3035.

13. Lee, H.J., Macbeth, A.H., Pagani, J.H., and Young, W.S., 3rd (2009). Oxytocin: the great facilitator of life. Prog. Neurobiol. *88*, 127–151.

14. Rickenbacher, E., Perry, R.E., Sullivan, R.M., and Moita, M.A. (2017). Freezing suppression by oxytocin in central amygdala allows alternate defensive behaviours and mother-pup interactions. eLife *6*, e24080.

15. Marlin, B.J., Mitre, M., D'Amour, J.A., Chao, M.V., and Froemke, R.C. (2015). Oxytocin enables maternal behaviour by balancing cortical inhibition. Nature *520*, 499–504.

Microbial Genomics: The Expanding Universe of Bacterial Defense Systems

Kevin J. Forsberg[1] and Harmit S. Malik[1,2,*]
[1]Division of Basic Sciences
[2]Howard Hughes Medical Institute
Fred Hutchinson Cancer Research Center, Seattle, WA 98109, USA
*Correspondence: hsmalik@fhcrc.org
https://doi.org/10.1016/j.cub.2018.02.053

Bacteria protect themselves against infection using multiple defensive systems that move by horizontal gene transfer and accumulate in genomic 'defense islands'. A recent study exploited these features to uncover ten novel defense systems, substantially expanding the catalog of bacterial defense systems and predicting the discovery of many more.

Bacteria are at risk for both cell death and genomic invasion by a variety of genetic parasites including phages and plasmids. To protect against these threats, bacteria employ three general strategies for defense. These include: preventing cell entry (via receptor masking or variation); abortive infection (altruistic suicide and/or dormancy of infected cells to protect kin from