

---

The following resources related to this article are available online at <http://stke.sciencemag.org>.  
This information is current as of 10 December 2008.

---

- Article Tools** Visit the online version of this article to access the personalization and article tools:  
<http://stke.sciencemag.org/cgi/content/full/sigtrans;2007/406/pe55>
- References** This article cites 13 articles, 5 of which can be accessed for free:  
<http://stke.sciencemag.org/cgi/content/full/sigtrans;2007/406/pe55#otherarticles>
- Glossary** Look up definitions for abbreviations and terms found in this article:  
<http://stke.sciencemag.org/glossary/>
- Permissions** Obtain information about reproducing this article:  
<http://www.sciencemag.org/about/permissions.dtl>

# Gene-Hormone-Environment Interactions in the Regulation of Aggressive Responses: Elegant Analysis of Complex Behavior

Donald Pfaff<sup>1\*</sup> and Rae Silver<sup>2,3,4\*</sup>

(Published 2 October 2007)

These are exciting times for aspects of neuroscience that address the relationship between genes and behavior. Early successes in this field often required the choice of extremely simple neural systems and reduced behavioral paradigms (1). However, success is no longer constrained to limited behaviors in simple organisms. Social behaviors such as aggressive interactions have become increasingly accessible to analysis and can be well understood in mechanistic terms (2).

Ask most neuroscientists how aggression is controlled, and they will likely snap back an answer that has to do with testosterone and aggression in males. However, it is clear that one causal route whereby testosterone influences aggression is through its chemical conversion by aromatase enzymes to estradiol. Now, Trainor *et al.* (3) report that the effects of testosterone aromatization to estrogen on aggression in mice depend on the duration of exposure to daylight during each 24-hour day. Remarkably, estrogen has opposite effects according to whether days are long, mimicking summer (16 hours of light per day), or short, like winter (8 hours of light per day). Using fadrozole (a nonsteroidal aromatase inhibitor that blocks the conversion of testosterone to estradiol), they showed that during long days treatment increases aggression, but during short days, the same treatment decreases aggression in the Oldfield mouse, *Peromyscus polionotus* (Fig. 1).

How might this work? Are the behaviorally important effects based on genomic or nongenomic mechanisms? The answer apparently is “yes” to both types of mechanism, depending on day length. No one ever said that connecting genetic functions with behaviors would be easy!

Modern neuroscience has taken many steps beyond the classic work of George Beadle and Edward Tatum on *Neurospora* metabolism, in which they inferred the one-gene one-enzyme principle. We now know that in mammals, patterns of genes’ activities lead to patterns of behavior (4). With respect to genomic mechanisms, there are well-known pleiotropic effects in which an individual gene can have several distinct functions, especially at different developmental stages. Complications in analyzing the contribution of any particular gene to behavior derive from redundancy, in which diminished activity from one gene may be compensated by overlapping functions with another gene. Also, variations in penetrance of dominant alleles in heterozygotes of different genes can lead to different phenotypes.

Genomic actions on behavior may be direct or indirect. For

example, altering a gene’s expression might affect overall central nervous system (CNS) arousal mechanisms, thus altering the force of expression of aggressive responses. Some gene activities important for behavior may not even take place in the brain. For example, disruption of the gene encoding leptin, expressed in fat cells, affects feeding behavior. Additional lessons in the relationships between genes and behaviors have cropped up in studies of the effects of hormones on brain and behavior. For example, the effect of the gene encoding estrogen receptor- $\alpha$  (ER- $\alpha$ ) on aggressive behavior is diametrically opposite, depending on whether it is acting in a male or female mouse (5). Knocking out ER- $\alpha$  reduces aggression in the male but increases it in the female. Additionally, the effect of a given gene on aggression can depend on the age at which the animal is tested (6) and the type of aggression tested (for instance, maternal aggression versus testosterone-facilitated aggression).

Given these subtleties, the findings of Trainor and colleagues in Randy Nelson’s lab at Ohio State University—following up on their initial microarray analyses of genes regulated by estrogen response elements—are all the more impressive. They found 11 genes that were differently expressed during long days than during short days. Among those, the expression of one estrogen-dependent gene, *XRCC1*, was reduced in the bed nucleus of the stria terminalis (a forebrain cell group known to be involved in hormonal effects on aggression) by exposure to the estrogen synthesis inhibitor fadrozole during long days but not short days. No such effect was seen in brain areas that are not involved in aggression. This finding posed the problem of explaining how estrogen could increase aggression in the absence of changes in estrogen-driven gene expression.

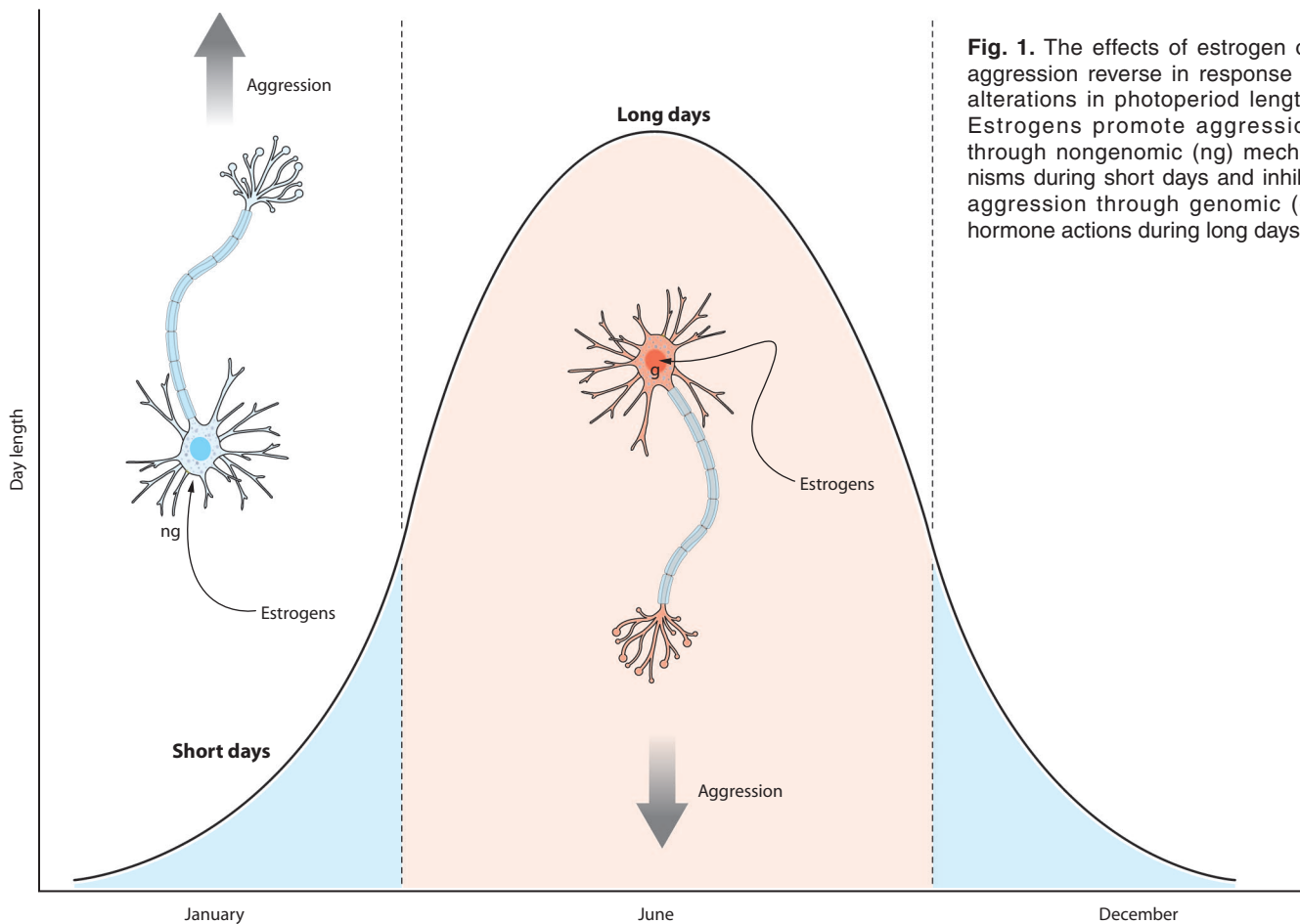
For almost 40 years, molecular endocrinologists have focused on nuclear mechanisms of steroid hormone action, with the greatest emphasis placed on the promotion or prevention of gene transcription. There have long been hints, however, that some of the effects of steroid hormones are very rapid and do not depend on transcriptional events (7). Recent work supports the view that such rapid effects occur in the CNS (8, 9), as well as outside it. At first, slower genomic and faster nongenomic actions were seen as functionally opposing each other. However, results with transient transfections in a neuroblastoma cell line have made it clear that membrane-initiated actions of estrogens can enhance later transcriptional effects (10).

Trainor and his colleagues exploited the time-course differential between genomic and nongenomic effects to investigate this aspect of estrogen action. They used a conjugated estrogen, which, if it is not cleaved, should not be able to enter the cell nucleus; most important, they assayed the animals for aggressive behavior at various intervals after treatment.

Indeed, for animals maintained on a short-day schedule, a behavioral effect of estrogen treatment was seen after 15 min,

<sup>1</sup>Laboratory of Neurobiology and Behavior, Rockefeller University, New York, NY 10021, USA. <sup>2</sup>Department of Psychology, Barnard College, New York, NY 10027, USA. <sup>3</sup>Department of Psychology, Columbia University, New York, NY 10027, USA. <sup>4</sup>Department of Anatomy and Cell Biology, College of Physicians and Surgeons, Columbia University, New York, NY 10032, USA.

\*Corresponding authors. E-mail, pfaff@rockvax.rockefeller.edu (D.P.); qr@columbia.edu (R.S.)



**Fig. 1.** The effects of estrogen on aggression reverse in response to alterations in photoperiod length. Estrogens promote aggression through nongenomic (ng) mechanisms during short days and inhibit aggression through genomic (g) hormone actions during long days.

with increased numbers of offensive attacks. During long days, this rapid effect did not occur. This fits with previous findings of different effects of long and short days on reproductive responses (11).

Within one paper, therefore, the Nelson lab has encompassed several of the themes of modern endocrinology: the functional genomics of behavior and environmental effects on social behavior. The work also raises questions about the mechanisms whereby photoperiod acts. Intriguingly, the nervous system distinguishes identical day lengths when responding to the increasing day lengths of spring versus the decreasing day lengths of fall (12). One wonders how this takes place and whether the estrogen effects reported here are a consequence of exposure to melatonin (12). Does photoperiodic history affect these responses, or are they acute effects of the increased duration of light during a given day? What are the crucial sites of action in the brain for decoding day-length information? At a more reductionistic level, what are the intracellular signaling cascades produced by estrogen exposure, and how do these differ in long and short days? Finally, there is evidence that photoperiodic effects occur in humans in both health (13, 14) and illness (15). We are on the way to unraveling their mechanisms of action and, hopefully, translating such information into medical applications.

#### References

1. D. Pfaff, Precision in mouse behavior genetics. *Proc. Natl. Acad. Sci. U.S.A.* **98**, 5957–5960 (2001).
2. R. Nelson, *Biology of Aggression* (Oxford, New York, 2006).
3. B. Trainor, S. Lin, S. Finy, M. Rowland, R. Nelson, Photoperiod reverses the effects of estrogens on male aggression via genomic and nongenomic pathways. *Proc. Natl. Acad. Sci. U.S.A.* **104**, 9840–9845 (2007).

4. D. Pfaff, S. Ogawa, K. Kia, N. Vasudevan, C. Kregs, J. Frohlich, L.-M. Kow, Genetic mechanisms in neural and hormonal controls over female reproductive behaviors. In *Hormones Brain and Behavior*, D. Pfaff, A. Arnold, E. Etgen, S. Fahrbach, R. Rubin, Eds. (Academic/Elsevier, San Diego, CA, 2002), vol. 3, pp. 441–510.
5. S. Ogawa, E. Choleris, D. W. Pfaff, Genetic influences on aggressive behaviors and arousability in animals. *Ann. N.Y. Acad. Sci.* **1036**, 257–266 (2004).
6. M. Nomura, L. Durbak, J. Chan, O. Smithies, J. A. Gustafsson, K. S. Korach, D. W. Pfaff, S. Ogawa, Genotype/age interactions on aggressive behavior in gonadally intact estrogen receptor beta knockout (betaERKO) male mice. *Horm. Behav.* **41**, 288–296 (2002).
7. M. Schumacher, Rapid membrane effects of steroid hormones: An emerging concept in neuroendocrinology. *Trends Neurosci.* **13**, 359–362 (1990).
8. O. K. Ronnekleiv, M. J. Kelly, Diversity of ovarian steroid signaling in the hypothalamus. *Front. Neuroendocrinol.* **26**, 65–84 (2005).
9. N. Vasudevan, D. W. Pfaff, Membrane initiated actions of estrogens in neuroendocrinology: Emerging principles. *Endocr. Rev.* **28**, 1–19 (2007).
10. N. Vasudevan, L. M. Kow, D. W. Pfaff, Early membrane estrogenic effects required for full expression of slower genomic actions in a nerve cell line. *Proc. Natl. Acad. Sci. U.S.A.* **98**, 12267–12271 (2001).
11. B. J. Prendergast, L. J. Kriegsfeld, R. J. Nelson, Photoperiodic polyphenisms in rodents: Neuroendocrine mechanisms, costs, and functions. *Q. Rev. Biol.* **76**, 293–325 (2001).
12. B. D. Goldman, Pattern of melatonin secretion mediates transfer of photoperiod information from mother to fetus in mammals. *Sci. STKE* **2003**, pe29 (2003).
13. F. H. Bronson, Are humans seasonally photoperiodic? *J. Biol. Rhythms* **19**, 180–192 (2004).
14. T. Roenneberg, The decline in human seasonality. *J. Biol. Rhythms* **19**, 193–197 (2004).
15. C. A. McClung, Circadian genes, rhythms and the biology of mood disorders. *Pharmacol. Ther.* **114**, 222–232 (2007).

**Citation:** D. Pfaff, R. Silver, Gene-hormone-environment interactions in the regulation of aggressive responses: Elegant analysis of complex behavior. *Sci. STKE* **2007**, pe55 (2007).