volved in the manifestation of ASDs, because maternal stress associates with the prevalence rates of ASDs in humans [2, 21, 36]. Further more, maternal glucocorticoids modulate the developing HPA-axis and ASDs-like behaviors in rodents [10, 15, 22, 25, 37, 38] and primates [32, 33]. For example, maternal adrenalectomy increases maladaptive behavior in the forced swim test [38], and maternal stress alters social behavior and the oxytocinergic system in the adult offspring of rodents [22]. The removal of, or an increase in, maternal glucocorticoids leads to similar consequences: immobility in the forced swim test and hypothalamic glucocorticoid receptor expression in adult offspring [38]. Impairment in social recognition behavior may reflect a decrease in plasma corticosterone concentration in IBP-exposed dams [19]; however, further studies are, necessary to confirm this.

Previously, we showed that maternal exposure to IBP decreased uterine sensitivity to estrogen, which may be reflected in estrogen receptor (ER) expression in adult female offspring [19]. Similarly, previous works have shown that ER expression in animals treated with other estrogenic compounds is significantly lower than that in control animals [20, 35]. Interestingly, ER plays a role in mediating social recognition in female mice, as *ERα* and *ERβ* knockout mice have specifically impaired social recognition [6]. In addition, ERα and ERβ play a crucial role in oxytocin-dependent social recognition [6]. Therefore, impairment of social recognition may reflect low sensitivity to estrogen from fat, adrenal and brain in IBP-exposed female rats, though puberty, estrous cycle, plasma estradiol and gonadotropin appear normal [19].

In conclusion, this study represents the first investigation of the effects of endocrine-disrupting chemicals on social recognition. Social recognition in rodents has been implicated in oxytocin, vasopressin and cell adhesion molecule 1 [3, 27, 34], and impairment of these chemicals' function is associated with human ASDs [16, 40]. One of the prominent social dysfunctions in autism is abnormal social recognition. Environmental factors including exposure to chemicals are likely to account for a major proportion of the increased prevalence of autism. Early exposure to chemicals may have played a role in the increasing prevalence of ASDs, through changes in the HPA-axis or estrogen sensitivity.

Acknowledgments

We are grateful to Professors M. Sadamatsu and K. Watanabe for giving us fruitful advice on behavioral analysis of social behaviors. We thank Yukiko Okada for her experimental assistance. This work was partially supported by the "High-Tech Research Center" Project for Private Universities: matching fund subsidy from Ministry of Education, Culture, Sports, Science and Technology, Japan and by the Smoking Research Foundation (to T. H.).

References

1. American Psychiatric Association. 2000. Diagnostic and statistical manual of mental disorders, Fourth Edition, Text Revision: DSM-IV-TR, American Psychiatric Publishing, Inc., Arlington.
2. Beversdorf, D.Q., Manning, S.E., Hillier, A., Anderson, S.L., Nordgren, R.E., Walters, S.E., Nagaraja, H.N., Cooley, W.C., Gaelic, S.E., and Bauman, M.L. 2005. *J. Autism Dev. Disord.* 35: 471–478.
3. Bielsky, I.F., Hu, S.B., Szegda, K.L., Westphal, H., and Young, L.J. 2004. *Neuropsychopharmacology* 29: 483–493.
4. Burgess, L.H. and Handa, R.J. 1992. *Endocrinology* 131: 1261–1269.
5. Cashman, A.L. and Warshaw, E.M. 2005. *Dermatitis* 16: 57–66.
6. Choleris, E., Gustafsson, J.Å., Korach, K.S., Muglia, L.J., Pfaff, D.W., and Ogawa, S. 2003. *Proc. Natl. Acad. Sci. U.S.A.* 100: 6192–6197.
7. Clarke, A.S., Wittwer, D.J., Abbott, D.H., and Schneider, M.L. 1994. *Dev. Psychobiol.* 27: 257–269.
8. Colborn, T., vom Saal, F.S., and Soto, A.M. 1993. *Environ. Health Perspect.* 101: 378–384.
9. Darbre, P.D. and Harvey, P.W. 2008. *J. Appl. Toxicol.* 28: 561–578.
10. Darnaudéry, M. and Maccari, S. 2008. *Brain Res. Rev.* 57: 571–585.
11. Deth, R., Muratore, C., Benzecry, J., Power-Charnitsky, V.A. and Waly, M. 2008. *Neurotoxicology* 29: 190–201.
12. Engell, M.D., Godwin, J., Young, L.J., and Vandenbergh, J.G. 2006. *Neurotoxicol. Teratol.* 28: 103–110.
13. Golden, R., Gandy, J., and Vollmer, G. 2005. *Crit. Rev. Toxicol.* 35: 435–458.
14. Grandjean, P. and Landrigan, P.J. 2006. *Lancet* 368: 2167–2178.
15. Halasz, I., Rittenhouse, P.A., Zorrilla, E.P., and Redei, E. 1997. *Brain Res. Dev. Brain Res.* 100: 198–204.
16. Insel, T.R. 2010. *Neuron* 65: 768–779.
17. Jaroenporn, S., Furuta, C., Nagaoka, K., Watanabe, G., and Taya, K. 2008. *Endocrine* 33: 205–209.
18. Kawaguchi, M., Irie, K., Morohoshi, K., Watanabe, G., Taya,

K., Morita, M., Kondo, Y., Imai, H., and Himi, T. 2009. *Neurosci. Res.* 65: 136–140.
19. Kawaguchi, M., Morohoshi, K., Masuda, J., Watanabe, G., Morita, M., Imai, H., Taya, K., and Himi, T. 2009. *J. Vet. Med. Sci.* 71: 1027–1033.
20. Khurana, S., Ranmal, S., and Ben-Jonathan, N. 2000. *Endocrinology* 141: 4512–4517.
21. Kinney, D.K., Munir, K.M., Crowley, D.J., and Miller, A.M. 2008. *Neurosci. Biobehav. Rev.* 32: 1519–1532.
22. Lee, P.R., Brady, D.L., Shapiro, R.A., Dorsa, D.M., and Koenig, J.I. 2007. *Brain Res.* 1156: 152–167.
23. Levitt, P. and Campbell, D.B. 2009. *J. Clin. Invest.* 119: 747–754.
24. Morohoshi, K., Yamamoto, H., Kamata, R., Shiraishi, F., Koda, T., and Morita, M. 2005. *Toxicol. In Vitro.* 19: 457–469.
25. Mueller, B.R. and Bale, T.L. 2008. *J. Neurosci.* 28: 9055–9065.
26. Nakagami, A., Negishi, T., Kawasaki, K., Imai, N., Nishida, Y., Ihara, T., Kuroda, Y., Yoshikawa, Y. and Koyama, T. 2009. *Psychoneuroendocrinology* 34: 1189–1197.
27. Neumann, I.D. 2008. *J. Neuroendocrinol.* 20: 858–865.
28. Rastogi, S.C., Schouten, A., de Kruijf, N., and Weijland, J.W. 1995. *Contact Dermatitis* 32: 28–30.
29. Rice, C. 2009. *Morb. Mortal. Wkly. Rep.* 58: 1–20.
30. Román, G.C. 2007. *J. Neurol. Sci.* 262: 15–26.
31. Schaefer, G.B. and Mendelsohn, N.J. 2008. *Genet. Med.* 10: 4–12.
32. Schneider, M.L. 1992. *Dev. Psychobiol.* 25: 529–540.
33. Schneider, M.L., Clarke, A.S., Kraemer, G.W., Roughton, E.C., Lubach, G.R., Rimm-Kaufman, S., Schmidt, D., and Ebert, M. 1998. *Dev. Psychopathol.* 10: 427–440.
34. Takayanagi, Y., Fujita, E., Yu, Z., Yamagata, T., Momoi, M.Y., Momoi, T., and Onaka, T. *Biochem. Biophys. Res. Commun.* 396: 703–708.
35. Varayoud, J., Ramos, J.G., Bosquiazzo, V.L., Muñoz-de-Toro, M., and Luque, E.H. 2008. *Endocrinology* 149: 5848–5860.
36. Ward, A.J. 1990. *Child. Psychiatry Hum. Dev.* 20: 279–288.
37. Weinstock, M. 2008. *Neurosci. Biobehav. Rev.* 32: 1073–1086.
38. Wilcoxon, J.S. and Redei, E.E. 2007. *Horm. Behav.* 51: 321–327.
39. Windham, G.C., Zhang, L., Gunier, R., Croen, L.A., and Grether, J.K. 2006. *Environ. Health Perspect.* 114: 1438–1444.
40. Zhiling, Y., Fujita, E., Tanabe, Y., Yamagata, T., Momoi, T., and Momoi, M.Y. 2008. *Biochem. Biophys. Res. Commun.* 377: 926–929.