*Proc. Natl. Acad. Sci. USA*
Vol. 94, pp. 4823–4824, May 1997

# Commentary

# Serotonin, sex, and psychiatric illness

*George R. Heninger*

*Laboratory of Molecular Psychiatry, Department of Psychiatry, Yale University School of Medicine, 34 Park Street, New Haven, CT 06508*

> The omnipresent process of sex, as it is woven into the whole texture of our man's or woman's body, is the pattern of all the process of our life.—Havelock Ellis (1)

Numerous examples in medicine illustrate that different rates of illness between men and women (based on biologic differences) usually reflect important aspects of the underlying pathophysiology. This can be important for psychiatry, since several psychiatric illnesses have large sex differences in incidence rates. However, after nearly half a century of increasingly sophisticated research on the biologic basis of these illnesses, we still do not have a clear picture of the specific biochemical events that lead to symptom formation in patients. The paper by Nishizawa *et al.* (2), in the current issue of the *Proceedings*, reporting a reduced serotonin [5-hydroxytryptamine (5-HT)] synthesis rate in women compared with men, now provides an opportunity to investigate the role of this important neurobiologic system in those psychiatric conditions differentially affecting males and females.

Since the advent of modern neuropharmacologic research in the 1950s, the brain 5-HT system has been a major focus of intense investigation. The reasons for this high level of sustained interest include: (*i*) The demonstrated widespread distribution of 5-HT axons and multiple 5-HT receptor systems in the brain and the extensive evidence of the importance of 5-HT in maintaining normal brain function; (*ii*) drugs that alter behavior, affect, and cognition produce changes in the 5-HT system and, conversely, drugs that alter 5-HT function are effective treatments for a wide range of psychiatric and medical conditions; and (*iii*) abnormalities in 5-HT function have been shown in many psychiatric illnesses, and depletion of plasma tryptophan (TRP) (the precursor for 5-HT) produces symptoms in several psychiatric conditions.

The wide range of phenomena involving 5-HT including cognition, affect, endocrine regulation, neurotrophic effects, pain, appetite, emesis, sex, sleep, aggression, perception, sensory-motor function, vascular regulation, and GI regulation, can be related to the anatomy, physiology, and biochemistry of the system. The cell bodies located in brain stem nuclei project diffusely to almost all areas of brain (3), and up to 60–70% of the varicosities seen in cortical 5-HT axons are nonjunctional (4). This raises the possibility of more widespread global and sustained paracrine–neurotrophic effects of 5-HT, in addition to the more classical localized actions as a neurotransmitter. The 5-HT neurons have a rather slow constant firing rate (5), which is not generally sensitive to changes in the behavioral state of the animal, except that firing rates decrease in slow wave sleep and almost cease in rapid eye movement sleep (6). However, biochemical studies have clearly shown that 5-HT is a stress responsive system with increases in 5-HT turnover during both acute and longer term stress (7).

Because 5-HT synthesis is dependent on the availability of the essential amino acid TRP, presynaptic function of the 5-HT system can be regulated by any one of several factors including plasma TRP levels, transport of TRP into brain, synthesis of TRP into 5-HT, and 5-HT storage, release, reuptake, and degradation. One of the two essential synthetic enzymes, converting TRP to 5-HT, TRP hydroxylase, is normally only 50% saturated. In the paper by Nishizawa *et al.* (2), the authors used a method where radiolabeled α-[$^{11}$C]methyl-L-tryptophan was injected and the rate of formation of radiolabeled α-[$^{11}$C]methylserotonin was measured in the brains of the subjects by positron emission tomography scanning. α-[$^{11}$C]methylserotonin accumulates in serotonin neurons because it is not a substrate for monoamine oxidase and does not cross the blood brain barrier. Using this method, the authors found that the 5-HT synthesis rate for healthy male volunteers was 50% higher than for females volunteers. In addition, following a TRP-deficient amino acid drink, they reported 72% and 89% reductions in plasma-free TRP for males and females, respectively, which reduced serotonin synthesis by a factor of 9.5 for males and 40 for females. Since the calculation of synthesis rate is directly proportional to plasma-free TRP levels, and the female TRP levels in the study were only one-half the level of the males, the study will need replication in male and female samples with similar baseline TRP levels. If validated, these findings will have major implications for the study of differing sex-related incidence rates of psychiatric illness.

In contrast to the reduced 5-HT synthesis rate in human females, female laboratory rats have an increased 5-HT synthesis rate. Female rats have higher brain 5-HT levels and levels of the 5-HT metabolite 5-hydroxyindole-3-acetic acid than males (8). Following L-amino acid decarboxylase inhibition, 5-hydroxytryptophan accumulation is more pronounced in the female rat brain, which indicates an increased 5-HT synthesis rate in females (9). This is consistent with reports of greater brain TRP hydroxylase capacity in female rats (10). In addition, female rats show less immobility in the Porsolt Test—an animal model of depression (11). Thus, these laboratory animal studies are not consistent with the reported findings in humans of decreased 5-HT synthesis rate and increased vulnerability to depression in human females.

Since there may be important species differences, human studies will be required to fully answer this question; however, human studies directly measuring differences in 5-HT metabolism between males and females are more limited. Lumbar cerebralspinal fluid 5-hydroxyindole-3-acetic acid concentrations have been reported to be higher in females in some studies, but many other studies do not find sex differences in cerebrospinal fluid 5-hydroxyindole-3-acetic acid or postmortem brain 5-HT levels (12, 13).

There is a large sex difference in lifetime rates of depression; three females are affected for every one male (14), and the question of whether impaired 5-HT function contributes to this difference is important. Because drugs that increase 5-HT are effective antidepressants, many clinical studies on the 5-HT system have been conducted in depressed patients (15). However, few of the many demonstrations of altered 5-HT function in depression have shown a clear difference between males and females. Plasma-free and total TRP levels do not differ between healthy male and female controls, but it does appear that plasma-total TRP levels are lower in depressed females


0027-8424/97/944823-2$2.00/0
PNAS is available online at **http://www.pnas.org**.

than depressed males (16–18). As would be expected because of the differences in reproductive endocrinology, the prolactin response to a number of prolactin-stimulating drugs (including 5-HT agonists) is greater in females than males, but the relative effect of depression in altering the response is mostly the same between males and females. One exception is the finding that with sleep deprivation, the prolactin response to infused TRP is increased much more in depressed females than depressed males (19).

Eating disorders are another psychiatric illness having a large increase in incidence in women compared with men; up to 10 women for every 1 man (20). Serotonin is critically involved in the regulation of eating, and abnormalities in 5-HT function have been demonstrated in patients with eating disorders. Dieting can progress into an eating disorder, and a 3-week low caloric diet in healthy controls reduced plasma TRP concentrations and increased the prolactin response to both infused TRP and oral D-fenfluramine in women but not men (21, 22). This is a specific effect on the 5-HT system, since dieting did not alter the response to thyrotrophin releasing hormone in either men or women. In addition, there is evidence for sex differences in 5-HT receptor systems between women and men since compared with men, women have a reduced hypothermic response following administration of the 5-HT precursor 5-hydroxytryptophan or the 5-HTIA type receptor agonist buspirone (23, 24), and women have fewer 5-HT 2 type receptors on positron emission tomography scanning than men (25).

The report by Nishizawa *et al.* (2) that women have a lower 5-HT synthesis rate than men, suggests that women may have impaired 5-HT function, which could relate to an increased incidence of illness. The lower plasma TRP in depressed women and increased prolactin response to TRP following sleep deprivation in depressed women, in addition to the decreased plasma TRP levels and increased sensitivity to infused TRP in normal females with dieting, is consistent with this idea. The findings of decreased hypothermic response to 5-HT agonists and decreased 5-HT receptor number in females are more complex and difficult to interpret, but they do illustrate important sex differences in the human 5-HT system. As stated by Ellis (1), sex differences are the "pattern of all the process of our life" and it is of interest in this regard that even cognitive changes following brain injury are related to sex (26). If specific defects in the 5-HT system of women can be discovered, this will provide powerful and critically needed information with which to clarify the pathophysiology of those psychiatric conditions where sex makes a difference.


1. Ellis, H. (1980) in *Familiar Quotations*, ed. Bartlett, S. (Little, Brown and Company, Boston), p. 689.
2. Nishizawa, S., Benkelfat, C., Young, S., Leyton, M., Mzengeza, S., de Montigny, C., Blier, P. & Diksic, M. (1997) *Proc. Natl. Acad. Sci. USA* **94,** 5308–5313.
3. Azmitia, E. & Whitaker-Azmitia, P. (1995) in *Psychopharmacology: The Fourth Generation of Progress*, eds. Bloom, F. E. & Kupfer, D. J. (Raven, New York), p. 443.
4. Seguela, P., Watkins, K. C. & Descarries, L. (1989) *J. Comp. Neurol.* **289,** 129–142.
5. Aghajanian, G. (1995) in *Psychopharmacology: The Fourth Generation of Progress*, eds, Bloom, F. E. & Kupfer, D. J. (Raven, New York), p. 451.
6. Jacobs, B. L. & Fornal, C. A. (1995) in *Psychopharmacology: The Fourth Generation of Progress*, eds. Bloom, F. E. & Kupfer, D. J. (Raven, New York), p. 461.
7. Vahabzadeh, A. & Fillenz, M. (1994) *Eur. J. Neurosci.* **6,** 1205–1212.
8. Carlsson, M. & Carlsson, A. (1988) *Prog. Neuro-Psychopharmacol. Biol. Psychiatry* **12,** 53–61.
9. Haleem, D., Kennett, G. & Curzon, G. (1990) *J. Neural Transm.* **79,** 93–101.
10. Carlsson, M. & Carlsson, A. (1988) *Arch. Pharmacol.* **338,** 345–349.
11. Alonso, S. J., Castellano, M. A., Afonso, D. & Rodriguez, M. (1991) *Physiol. Behav.* **49,** 69–72.
12. Gottfries, G., Gottfries, L., Johansson, B., Olsson, R., Persson, T., Roos, B. & Sjostrom, R. (1971) *Neuropharmacology* **210,** 665–672.
13. Arato, M., Tekes, K., Tothfalusa, L., Magyar, K., Palkovits, M., Frecska, E. & Falus, A. (1991) *Biol. Psychiatry* **29,** 699–702.
14. Weissman, M. & Olfson, M. (1995) *Science* **269,** 799–801.
15. Maes, M. & Meltzer, H. (1995) in *Psychopharmacology: The Fourth Generation of Progress*, eds, Bloom, F. E. & Kupfer, D. J. (Raven, New York), p. 933.
16. Anderson, I., Parry-Billings, M., Newsholme, E., Poortmans, J. & Cowen, P. (1990) *J. Affective Disord.* **20,** 185–191.
17. Maes, M., DeRuyter, M., Claes, R. & Suy, E. (1988) *J. Affective Disord.* **15,** 119–125.
18. Cowen, P. J., Parry-Billings, M. & Newsholme, E. A. (1989) *J. Affective Disord.* **16,** 27–31.
19. Salomon, R., Delgado, P., Licinio, J., Krystal, J., Heninger, G. & Charney, D. (1994) *Soc. Biol. Psychiatry* **36,** 840–846.
20. Szmukler, G. I. (1985) *J. Psychiatr. Res.* **19,** 143–153.
21. Anderson, I., Parry-Billings, M., Newsholme, E., Fairburn, C. & Cowen, P. (1990) *Psychol. Med.* **20,** 785–791.
22. Walsh, A., Oldman, A., Franklin, M., Fairburn, C. & Cowen, P. (1995) *J. Affective Disord.* **33,** 89–97.
23. Lacoste, V., Wirz-Justice, A., Graw, P., Puhringer, W. & Gastpar, M. (1976) *Pharmakopsychiatie* **9,** 289–294.
24. Cowen, P., Power, A., Ware, C. & Anderson, I. (1994) *Br. J. Psychiatry* **164,** 372–379.
25. Biver, F., Lotstra, F., Monclus, M., Wikler, D., Damahauat, P., Mendlewicz, J. & Goldman, S. (1996) *Neurosci. Lett.* **204,** 25–28.
26. Inglis, J. & Lawson, J. (1981) *Science* **212,** 693–695.