Sex-related differences: Do they matter?

Pavel Hrdina, MD, PhD

Institute of Mental Health Research, Royal Ottawa Hospital, Ottawa, Ont.

Sex differences in the incidence of psychiatric disorders have been well recognized and documented. It is known that depression, anxiety disorders and eating disorders occur more commonly in women.1 Sex-specific syndromes such as post partum depression and premenstrual dysphoric disorder have recently been characterized as distinct psychiatric disorders. Yet, until the early 1990s, women were often excluded from clinical trials of new psychotropic drugs. Women of child-bearing age were generally not included in the testing of new drugs, particularly in the early stages of drug development, because of potential harm to the fetus. In addition, the menstrual cycle was thought to complicate the results of the trials. Since the US Congress mandated the inclusion of women in clinical trials in 1993, regulatory agencies require that the make-up of patient samples for clinical trials of new drugs reflect that of the intended target population.

Most of the preclinical studies on the efficacy and safety of new agents, as well as on neurochemical correlates of behaviour and the mode of action of psychotropic drugs, have been done with male animals. Again, the reason was the concern that the estrus cycle might complicate experimental results. Some of the currently prevailing theories of the mode of action of antidepressants were based on the results of experiments with male rats only.2 Research in biological psychiatry and psychopharmacology is now focusing more on the analysis of sex influences.

New evidence emerging from these studies indicates that sex differences at biological and genetic levels may have an important impact on our understanding of brain functioning and on the clinical use of psychopharmacological agents. A recent study on the forced swimming test,3 which is widely used in screening of antidepressants, showed that sex differences exist in some of the behaviours scored in the test. For instance, duration of immobility and head shake frequency were much lower in female than in male animals. These differences will obviously have to be taken into account when analyzing the effect of tested drugs. Another recent study4 suggests that sex differences in the prevalence of attention deficit with hyperactivity disorder (ADHD) may be attributable to sex differences in dopamine receptor density. In male rats, striatal dopamine D2-receptor density increases 144% between 25 and 40 days of age (the onset of puberty), whereas the increase in females is only 31%. The rise of male, but not female, striatal dopamine receptor density parallels the early developmental appearance of motor symptoms of ADHD and may explain why prevalence rates are 2- to 4-fold higher in boys than in girls.

Serotonergic mechanisms are thought to be involved in the etiology of some psychiatric disorders, particularly major depression and anxiety, in impulsivity and suicidal behaviour, as well as in the action of antidepressant, antianxiety and some newer antipsychotic drugs. There are several reports in the literature of sex differ-
ences in the serotonergic system. For example, cerebral spinal fluid concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid and of whole blood serotonin were shown to be higher in women than in men. In this issue, Okazawa and colleagues report significant differences between men and women in the synthesis of brain serotonin. Employing positron emission tomography imaging in living brain, the authors found that these sex-related differences in serotonin synthesis were region dependent. This observation complements a previous finding of this group that global brain serotonin synthesis is 40%–50% higher in men than in women and emphasizes the need to include sex as a factor in the analysis of results of similar investigations. Sex differences have also been found in the serotonin 5-HT2 receptor-binding capacity in living human brain; using positron emission tomography and the selective radiotracer, 18F-labelled altanserin; Biver and colleagues9 found that binding capacity in the frontal and cingulate cortices was lower in women than in men.

Recent research also shows that sex differences exist in the contribution of genetic factors to personality traits. A significant association between higher neuroticism scores and the short allele of the serotonin transporter gene has been detected in male but not female test subjects.10

In a recent review of the literature, Godfroid11 summarizes important sex differences in the pharmacokinetics of psychotropic drugs. For instance, plasma levels of fluvoxamine and sertraline are 40% lower in men than in women. The tricyclic antidepressant amitriptyline produces, at the same dosage, higher plasma levels in women than in men, and the half-life of imipramine is longer in women than in men, even in the absence of oral contraceptives. After adjusting for age and body weight, female inpatients with schizophrenia had 35% higher steady-state plasma levels of clozapine and 36% higher levels of its metabolite, norclozapine, per unit of dose than male inpatients.12 Obviously, more research in this area is needed — treatment strategies could be optimized by taking sex differences in drug disposition and effectiveness into account.

The identification of biological, genetic and environmental factors involved in the regulation of the serotonergic and other neuronal systems may help to advance both our understanding of sex-related differences in normal behaviour and psychiatric disorders and our diagnostic and treatment modalities.

References


