Sex differences in depression and anxiety disorders: Potential biological determinants

Margaret Altemus *

Department of Psychiatry, Weill Medical College, Cornell University, New York, NY 10021, USA

Received 29 June 2006; revised 29 June 2006; accepted 29 June 2006
Available online 22 August 2006

Abstract

The phenomenon of higher rates of affective disorders in women illustrates many of the difficulties as well as promises of translating preclinical models to human disorders. Abnormalities in the regulation of the hypothalamic–pituitary adrenal axis and the sympathoadrenomedullary system have been identified in depression and anxiety disorders, and these disorders are clearly precipitated and exacerbated by stress. Despite the striking sex difference in the prevalence of depression and anxiety disorders, attempts to identify corresponding sex differences in stress response reactivity in animal models have met with limited success. Processes which may contribute to increased rates of affective disorders in women are greater fluxes in reproductive hormones across the life span, and increased sensitivity to catecholamine augmentation of emotional memory consolidation.

Keywords: Stress; Depression; Anxiety; Sex differences; HPA axis; Serotonin

Women are at least twice as likely as men to suffer from depression and anxiety disorders, including unipolar depression, dysthymia, panic disorder, post-traumatic stress disorder, generalized anxiety disorder, social anxiety disorder, and phobias (Regier et al., 1993; Kessler et al., 1994). These sex differences are seen in multiple diverse countries and cultures, suggesting a biological basis. However, despite great interest in this area, biological mechanisms that may contribute to this striking sex difference have remained elusive.

Sex differences in stress responses

Abnormalities in the regulation of the hypothalamic–pituitary adrenal axis and the sympathoadrenomedullary system have been identified in depression and anxiety disorders, and these disorders are clearly precipitated and exacerbated by stress (Gold and Chrousos, 2002). Surprisingly, evidence from animal studies to date suggests that females are relatively resistant to the behavioral and neurobiological effects of acute and chronic stress. For example, although chronic stress over 21 days produces reversible atrophy of apical dendrites of hippocampal pyramidal neurons in males (Conrad et al., 1999), this effect is not seen in females (Galea et al., 1997). Similarly, repeated swim stress over 30 days decreased CA3 and CA4 pyramidal cell number in gonadectomized male rats, but not in females (Mizoguchi et al., 1992). Parallel results were found in a study of male and female vervet monkeys subjected to chronic social stress (Uno et al., 1989). Males also had higher stress-induced c-fos gene expression in several brain areas compared to proestrus and diestrus females (Figueiredo et al., 2002). Consistent with these sex differences in structural responses to chronic stress, female rats do not show the impairment of spatial memory or object recognition memory after chronic restraint stress that is characteristic of males (Luine, 2002). In addition, an acute stressor enhances fear behaviors and impair escape learning (learned helplessness) in males, but less so in females (Steenbergen et al., 1990; Heinsbroek et al., 1991). Moreover, in males, acute stress enhances eyelid conditioning (a reflex learning that does not involve fear), but in females it impairs eyelid conditioning in proestrus and has no effect in...
A similar sex difference in stress-induced enhancement of fear conditioning was recently reported in humans (Jackson et al., 2005). In humans, males seem to have greater HPA axis responses to stress (reviewed in Kudielka et al., 2004) and when circulating gonadal steroids are removed, men also have higher HPA axis responses than women (Roca et al., 2005). Female rats have higher ACTH and total corticosterone responses to stress (Kant et al., 1983; McCormick et al., 2002), but it remains to be determined whether free corticosterone responses are higher in female rats. High levels of corticosterone binding globulin (CBG) in female rats (McCormick et al., 2002) may blunt the free corticosterone response and require more ACTH release than males to generate the same free corticosterone response. Animal and human data are concordant in suggesting that physiological doses of estradiol suppress HPA axis responses to stress (Redei et al., 1994; Komesaroff et al., 1999; Young et al., 2001). For more information on sex differences in the regulation of the HPA axis, see the companion paper by Bale in this volume.

One way to reconcile relative resistance of females to neurobiological effects of stress with increased prevalence of affective illness in women is to consider the stress-induced neurobiological changes in males as adaptive, potentially preventing subsequent development of depression and anxiety symptoms. For example, relatively impaired memory in response to 3 weeks of restraint stress may enable males to forget the stress and its associations more quickly.

Problems and promises of animal models

A major problem with animal models of affective disorders that involve behavioral measures reminiscent of depression in humans is that the core clinical features of the disorders are subjective experiences, rather than observable behaviors. Several of the classic animal models of depression, such as learned helplessness, separation, the forced swim test, and chronic restraint stress, could be argued to be equally good models of anxiety disorders, based on the behavioral features of the models. It is difficult to know whether failure of adaptive behaviors in these models is due to hopelessness and helplessness, or fear and uncertainty. Similarly, it is difficult to know whether repetitive circling or licking behavior in a dog is a better model of a motor tic or Tourette’s disorder vs. a compulsive response to an obsession, as occurs in obsessive compulsive disorder. Although related, and sometimes co-morbid, these disorders respond very differently to treatment, generate different subjective experiences, and typically segregate in different families (Eapen et al., 1997).

Another obstacle to developing animal models is that current diagnostic criteria for depression and anxiety disorders are based on symptom clusters rather than underlying neurobiology (APA, 1994). Charney and colleagues (2002) (Charney et al., 2002) in A Research Agenda for DSM-V, provide a comprehensive overview of how neuroscience research should be applied to longer-term efforts to refine our current psychiatric diagnostic system as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Version IV (DSM-IV). Although the knowledge base is inadequate at this time, neurobiology and genetics are expected to play an increasingly important role in defining and validating diagnostic categories. New diagnostic categories are likely to be based on biobehavioral dimensions of psychopathology that cut across the current diagnoses. At this time, depression and anxiety disorders are split into multiple diagnoses with overlapping clinical features, based on the most prominent symptom such as panic attacks or worrying or onset following trauma. One consequence is that individuals with different pathophysiology, but similar clinical features, are lumped into the same diagnostic category. For example, episodic obsessive compulsive disorder (OCD) that is associated only with pregnancy and the postpartum period may arise from biological processes distinct from the more common chronic form of OCD and may respond to distinct treatments. Another consequence of the symptom-based diagnostic system is that individuals with similar pathophysiology can be split into different diagnostic categories. For example, a bipolar patient is diagnosed with unipolar depression until the first manic episode occurs. Although earlier hints may come from poor antidepressant response, family history, and chronic insomnia, these features are not diagnostic criteria. Another problem is that individuals with affective disorders commonly receive multiple diagnoses. It is rare to carry a diagnosis of a single anxiety disorder, and anxiety disorders are highly co-morbid with depressive disorders (Goldenberg et al., 1996). Diagnoses based on neurobiological characteristics should lead to more targeted psychological, pharmacological, and other biological treatments. In addition, a more pathophysiologically based diagnostic system will improve translation of investigations from animal to human studies and animal studies could play a greater role in definition of diagnostic categories. For example, girls with conduct disorder demonstrate more impulsive sexual behavior and boys engage in more interpersonal violence. If these behaviors are linked to similar biological processes, it would strengthen the argument for one diagnosis incorporating both behavioral profiles.

An advantage of animal models is the opportunity to control sex-specific environmental variables that may contribute to the sex differences in prevalence, symptom patterns, and treatment response of psychiatric disorders. In humans, culturally determined behaviors and experiences such as dieting, social subordination, and sexual abuse may promote development of affective disorders in women. For example, food restriction is known to suppress thyroid hormone activity and to alter brain serotonergic function (Attenburrow et al., 2003) both of which may increase risk of depression in women who diet. Women are more susceptible to sexual abuse in childhood, which is associated with anxiety and increased hormonal responses to stress in adulthood (Heim et al., 2000). More sex differences in the consequences of food restriction are discussed in the paper by Sodersten and Berg in this volume. These sex differences in factors that may trigger depression suggests that sex differences should be considered systematically in developing appropriate animal models.
Sex differences and hormonal modulation of affective disorders as a window into pathophysiology

Sex differences can be a window that provides new perspectives on biological mechanisms in affective illness. For example, the finding that increased risk of depression at puberty is limited to girls with a family history of depression, and only presents as they reach Tanner stage III of puberty (Angold et al., 1999), begs the question as to how depression-related genetic polymorphisms could contribute to systems that are differentially sensitive to estrogen or other reproductive hormones that emerge at Tanner stage III.

Premenstrual Dysphoric Disorder (PMDD) provides the clearest example of a hormonally based mood disorder. Women with PMDD have the same types of premenstrual symptoms experienced by most women, including irritability, mood swings, poor concentration, and bloating. However, their symptoms are particularly severe, always involve a mood component, and significantly interfere with social and occupational functioning. Under current diagnostic criteria, PMDD affects 3–8% of reproductive aged women (Cohen et al., 2002; Wittchen et al., 2002). Research to date indicates that women with PMDD have normal levels of circulating adrenal and sex hormones across the menstrual cycle but they respond much stronger physically as well as emotionally to changes in gonadal steroids across the cycle, particularly to the increase in progesterone in the luteal phase (Rubinow et al., 1988). Although PMDD occurs only in women, the biological mechanism underlying PMDD may shed light on PMDD-like symptoms that occur in men, and in other psychiatric disorders. For example, several lines of evidence suggest that androgenic neurosteroids, produced from the luteal surge in circulating progesterone, may play a critical role in PMDD. Although PMDD has been considered a form of depression, close examination of symptom profiles reveals that irritability and hostility are more prominent in PMDD than is depressed mood (Hartlage and Arduino, 2002). In addition, a new oral contraceptive containing drospirenone, an androgen receptor antagonist, has demonstrated efficacy for treatment of PMDD (Pearlstein et al., 2005; Yonkers et al., 2005). Earlier studies also suggested that spironolactone, a similar androgen receptor antagonist, could relieve premenstrual mood symptoms (Aslaksen and Falk, 1991; Wang et al., 1995). Finally, androgens reduce the osmotic threshold for vasopressin release (Crowley and Amico, 1993; Stachenfeld et al., 2001), possibly contributing to bloating symptoms.

Of all of the anxiety disorders, OCD is exacerbated most during the perimenstrual period. In addition, blockade of gonadal steroids can ameliorate symptoms of OCD (Casas et al., 1986; Chouinard et al., 1996). Both OCD and PMDD are distinguished from other affective disorders by a differential response to serotonin-reuptake inhibiting antidepressants (Eriksson et al., 1995; Greist et al., 1995; Freeman et al., 1999). There is also preliminary evidence that postpartum depression, which usually has prominent OCD features, responds better to SSRI antidepressants (Wisner et al., 2001, 2004). Other anxiety disorders and depression syndromes are equally responsive to SSRIs and non-SSRI antidepressants. In summary, these observations point to a particular role for serotonin in the pathophysiology of hormonally modulated affective disorders.

Various other biological factors that may influence depression vary in men and women. For example, an intriguing example of sex differences in psychopathology is the tendency of women to ruminate more than men (Nolen-Hoeksema et al., 1999). Rumination is a risk factor for depression and the increased tendency to ruminate shows up in girls by age nine, prior to puberty (Nolen-Hoeksema and Girdus, 1994). There is evidence that blood pressure and pulse are more reactive to anxiety in women compared to men (Kario et al., 2001) and that women are more sensitive to the effects of catecholamines on memory consolidation (Cahill, 2003). Together, these characteristics may increase stress sensitivity and suggest a potential biological pathway to disproportionate generation of affective disorders in women.

Effects of reproductive hormone fluxes

Compared to men, women are subject to greater fluxes in reproductive hormones across the life span. Changes in reproductive hormones in utero, during puberty, the estrus cycle, pregnancy, and menopause clearly alter brain structure and function, and are likely to play a role in the increased prevalence of affective disorders in women. HPA axis responsiveness increases (Altemus et al., 1997b; Kirschbaum et al., 1999) and glucocorticoid feedback sensitivity (Altemus et al., 1997a) and brain GABA content decreases (Epperson et al., 2002) in the luteal phase of the menstrual cycle, potentially destabilizing these homeostatic systems in vulnerable women (Epperson et al., 2002; Roca et al., 2003). In addition, both catecholamine and HPA axis stress response systems are suppressed during pregnancy (Barron et al., 1986; Schulte et al., 1990; Matthews and Rodin, 1992) and lactation (Altemus et al., 1995; Heinrichs et al., 2001; Mezzacappa et al., 2003). Several brain neurochemical systems known to modulate anxiety and fear, including oxytocin, prolactin, norepinephrine, and GABA, appear to be altered in parallel during pregnancy and lactation (Altemus et al., 2004) (see also paper by Toufexis and Davis in this volume). Rapid weaning or lack of breastfeeding postpartum may precipitate more rapid decreases in these anxiolytic hormones, destabilizing stress responses and exacerbating anxiety and depression symptoms. Behavioral studies have demonstrated suppression of multiple fear behaviors and stress-induced gene responses in lactating rats and mice (Hansen and Ferreira, 1986; Abdou et al., 1993; DaCosta et al., 1996; Toufexis et al., 1999) and decreased anxiety and depression in breastfeeding compared to bottle-feeding mothers (Lane et al., 1997; Yonkers et al., 2001; Mezzacappa and Katkin, 2002). Until relatively recently, women spent much of their adult lives either pregnant or lactating, raising the possibility that longer life span, and reduced frequency of pregnancy have exposed modern-day women to relatively more activated stress response systems for much of their adult lives.
Conclusion

Better understanding of the pathophysiology of affective disorders will point the way to better treatment and prevention of these disorders. Advancement toward this goal has been limited by the symptom-based diagnostic system in psychiatry. Psychiatry has been the last of the medical specialties to move to an biologically based diagnostic system, primarily due to the inaccessibility of the brain. However, in the near future, neurobiology is expected to play an increasing role in the definition and validation of diagnostic categories and biobehaviorial dimensions of psychopathology. Animal models will be crucial to the success of this effort, providing a way to study functioning human brain tissue (see companion paper by Bale in this volume). Although animal models of psychiatric disorders have limited ability to model psychiatric symptoms, the potential to demonstrate the neurobiological consequences of genetic, developmental, and postnatal environmental variables is great. Sex differences in affective disorders and hormonal modulation of affective disorders are likely to provide an important window into the pathophysiology of anxiety and depression.

References


