Stress-Related Psychopathology as a Vulnerability Factor in Drug-Taking: The Role of Sex

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STRESS, STRESS-RELATED PSYCHOPATHOLOGY, AND SUBSTANCE USE

There is a strong empirical relationship between stress or stress-related psychopathology and substance use, abuse, and addiction. Lindenberg and colleagues (1993) reviewed nine relatively large-scale studies of the relationship between magnitude or intensity of social stress and one or more types of substance use and abuse. Of these nine studies, conducted between 1984 and 1991, six showed a significant positive relationship, two showed no significant correlation, and one reported mixed findings—unemployment and part-time employment predicted chronicity of substance use, but stressful life events did not. Examination of studies that failed to find a relationship (e.g., Tennant et al. 1986) between stress and substance use suggests that certain factors may obscure this relationship, including wide variations in the timespan between the stressful experience and the measurement of substance use, possible increased attrition within the sample of individuals showing greater medical or psychiatric psychopathology as a result of the stressful experience, and the use of a control group that also had experienced stress. The term "timespan" refers to the time between the occurrence of the stressful experience and the time when the study measures sequelae. One study (Tennant et al. 1986) examined World War II prisoners of war and other combat veterans with a stress experience-to-measurement interval of more than 40 years. Attrition within this group of veterans included those who had died or become unavailable for evaluation because of negative medical consequences or other reasons. Some studies have noted high rates of substance use or abuse in subgroups that experience unusually high stress levels, such as firefighters (Boxer and Wild 1993), homeless women (Smith et al. 1993), and HIV-positive homosexual men (Atkinson et al. 1988). These groups' extremely divergent characteristics (e.g., social and employment status), other than high

stress levels, suggest that stress is a major common factor in their elevated substance use.

Comorbidity of affective disorders and substance abuse also has been well documented in several studies. A review by Ries (1993) reports comorbid rates of 40 to 80 percent for addictive and psychiatric disorders when patients only in psychiatric settings are considered. In a group of more than 500 patients at an addiction research and treatment facility, 78 percent had a lifetime psychiatric disorder, and 65 percent had a current mental disorder, in addition to substance abuse (Ross et al. 1988). Patients with psychiatric disorders had more severe abuse and addiction problems. Although these psychiatric disorders included some for which a strong link to stress was not apparent, such as antisocial personality disorder, stress- and emotion-linked disorders were well represented. Hesselbrock and associates (1985) reported that major depression was the most common associated disorder among alcoholic women. Primm (1992) reported a substance abuse rate of more than 60 percent in individuals with bipolar I disorders. In a group of veterans referred to an outpatient clinic for posttraumatic stress disorder (PTSD), Behar (1987) found that 54 percent reported cannabis abuse, 49 percent reported alcohol abuse, and 35 percent reported opiate abuse. Keane and coworkers (1988) reviewed studies of Vietnam combat veterans seeking treatment for PTSD and found that 60 to 80 percent had concurrent diagnoses of substance abuse or dependence.

Although these data suggest a strong connection between substance abuse and stress- or emotion-linked psychopathologies, the dynamics of this relationship are difficult to determine in clinical or field studies. One possible indication concerns the onset of behavioral symptoms. In a study of more than 1,000 young adults who abused alcohol and nonprescription drugs, Christie and colleagues (1988) reported rates of depression 2.7 times higher and rates of anxiety disorders 1.7 times higher than that of a cohort group. Anxiety was reported to have preceded substance abuse by about 5 years; the depressive or anxiety disorder preceded the abuse in three-quarters of the cases; and, when depression was a preexisting condition, probability of abuse was doubled. Among those who experience frequent or chronic stress, substance use or abuse is more common for individuals who believe that substance-taking will alleviate distress (Cooper et al. 1992; McKirnan and Peterson 1989), and there is evidence that drug treatment for psychiatric disorders closely associated

with substance abuse also may reduce substance intake (Weiss and Mirin 1989). Thus, although the relationship between substance use and psychiatric disorders is likely to be bidirectional, these reports emphasize the importance of one component of this relationship: Stress-related changes in brain and behavior may be an important factor in the development of substance abuse and addiction.

OVERREPRESENTATION OF WOMEN IN STRESS-RELATED PSYCHOPATHOLOGY

The importance of stress-related psychopathologies in vulnerability to substance use, abuse, and addiction may be particularly important for women because women show much higher rates of these psychopathologies than do men. It has long been acknowledged that women are overrepresented among patients with depression (Silverman 1968; Nolen-Hoeksema 1987). The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* (American Psychiatric Association 1994) indicates that depressive episodes occur twice as frequently in women as in men. Studies of possible mechanisms of gender discrepancy in depression strongly suggest that the difference is not an epiphenomenon and that it remains after factors such as gender-specific diagnostic bias, differential experience with aversive events, income and education level, occupation, and particular response bias have been considered and controlled for (see Nolen-Hoeksema 1987 for a review).

DSM-IV also acknowledges that women are diagnosed with particular anxiety disorders far more frequently than men. Panic disorder (PD) without agoraphobia is diagnosed twice as often, and PD with agoraphobia three times as often, in women as in men, whereas agoraphobia without a history of PD "is diagnosed far more often in females than in males" (American Psychiatric Association 1994, p. 403). Women receive from 55 to 90 percent of the diagnoses for specific phobias, including the animal and natural environment, the situational, and the blood-injection-injury types. Generalized anxiety disorder is diagnosed slightly more often in women (55 to 60 percent of diagnoses), but epidemiological studies show about twice as many women as men. The only codable anxiety disorders for which approximately equal ratios of men and women are noted are obsessive-compulsive disorder and social phobia, although epidemiological and community-based studies of social phobia suggest that it is more common in women. Although *DSM-IV* (American

Psychiatric Association 1994) does not provide information on sex factors in PTSD, one study (Helzer et al. 1987) using data from the National Institute of Mental Health-sponsored Epidemiologic Catchment Area Study (Robins and Regier 1991) found that more than 70 percent of those with PTSD in its large sample were women.

These findings for anxiety and depression suggest a striking gender difference in reactivity to stressful or threatening situations. Because the gender discrepancy for anxiety disorders has only recently been recognized (see Cameron and Hill [1989, pp. 175-186] for a review of previous findings), there have been comparatively few studies analyzing the mechanisms involved. However, Thyer and associates (1985) reported that clinical severity of phobic symptoms were not different for phobic men and women, suggesting that the gender difference for phobic disorder cannot be attributed to a lower threshold for reporting a phobic response, or presenting at a clinic, by women.

STRESS AND SUBSTANCE SELF-ADMINISTRATION: NONHUMAN MAMMALS

A nexus of relationships among stress, psychopathology, and substance-taking—with gender as a potential factor because women show higher rates of stress-related psychopathology—is well documented in human research but difficult to analyze in human populations. Animal studies, in which a wider range of analytic techniques is clearly possible, are complicated by the lack of unequivocal and well-accepted animal models of stress-related psychopathology. However, a body of evidence suggests that stress enhances self-administration of several abusable substances. Stressful rearing conditions have been shown to increase self-administration of cocaine (Schenk et al. 1987), amphetamine, and barbital (Zimmerberg and Brett 1992) by rats, with the latter study also finding a sex difference in the effects of early social isolation on the choice of drug preferred. Offspring of rat mothers stressed by periods of forced immobility in a restraint tube during gestation days 14 to 21 also showed enhanced amphetamine self-administration (Deminiere et al. 1992), suggesting that maternal hypersecretion of corticosterone may have lasting effects on the rat fetus. Consonant with this view, the restraint stress-based enhancement of the locomotor response to amphetamine and morphine was not obtained in adrenalectomized animals with corticosterone implants (Deroche et al. 1992).

Rats vulnerable to amphetamine self-administration, either because of individual differences (Deminiere et al. 1989) or prenatal stress (Deminiere et al. 1992), also showed enhanced locomotor response to amphetamine in a novel but not a familiar environment (Piazza et al. 1990). These animals had stress-induced increases in nucleus accumbens concentrations of dopamine that were longer lasting and of higher magnitude than those of animals not showing the enhanced locomotor response to amphetamine, according to Rouge-Pont and colleagues (1993), who suggest that changes in these brain systems may constitute an important neurobiological substrate of the predisposition to acquire amphetamine self-administration as well as other addictive behaviors. Rats that developed self-administration also tended to be those that showed an enhanced locomotor response in a novel environment and also acquired schedule-induced polydipsia (SIP) (drinking in the context of an intermediate schedule of food delivery). However, when tested for SIP first (an experience that is interpreted as having a coping function), the polydipsic rats subsequently failed to acquire self-administration and had a reduced locomotor response to novelty (Piazza et al. 1993).

Pohorecky and coworkers (1989) presented a somewhat similar picture for caffeine effects: Doses of 10 mg/kg caffeine increased crossover frequency and duration, and rearing frequency and duration in an open field, for 60-day-old rats. Prenatal stress (during gestation days 14 to 21) increased sensitivity to caffeine on measures of locomotor activity in the corners of the apparatus and rearing. Again, individual difference factors may be important, in addition to the effects of prenatal stress: Taylor and colleagues (1990) reported that rats that showed a high plasma catecholamine response to stress showed higher intake of a cocaine solution than did low-catecholamine stress responders.

Stress effects on substance self-administration are not limited to psychostimulants. Although stress enhancement of voluntary alcohol consumption has been demonstrated in rhesus monkeys (Orloff and Masserman 1975), most of the considerable literature in this area has involved laboratory rodents (see reviews by Pohorecky [1981, 1990] and Blanchard and associates [1993*b*]). Briefly, a range of stressors, including shock (Bond 1978; Caplan and Puglisi 1986), grouping (Ellison 1981; Ellison et al. 1983), and subordination (Blanchard et al. 1987, 1992), increase voluntary alcohol consumption in rats and in mice (Hilakivi-Clarke and Lister 1992). Because the literature on human subjects

suggests that psychopathology may be a mediator of stress enhancement of substance-taking, it is interesting to note findings of individual differences' effects on the stress-induced enhancement of voluntary alcohol consumption. High-plasma-catecholamine, stress-responding rats showed more voluntary alcohol consumption than did low-catecholamine, stress-responding rats (Taylor et al. 1990). When male rats were evaluated on a variety of defense measures prior to grouping, pregrouping defense scores were highly (and significantly) correlated with pregrouping to postgrouping increases in voluntary alcohol consumption for subordinates (Blanchard et al. 1992).

Although there are no well-accepted animal models of psychopathology that are homologous to clinical disorders in humans, there is an emerging trend to examine the relationship between specific changes in defensive behaviors in laboratory animals and the target symptoms of emotion-linked psychopathologies in humans. Highly stressed subordinate male rats and tree shrews show a variety of consistent behavior changes, many of which are isomorphic to major symptoms of clinical depression. These include reductions in nondefensive behaviors (eating, drinking, social, sexual, and exploratory), weight loss, changes in resting/activity cycles and circadian rhythm, decreased movement celerity, and longer periods of attention to potential threat stimuli (Von Holst 1986; Blanchard and Blanchard 1990; Blanchard et al. 1993*a*, 1995*a*; Tornatzky and Miczek 1993).

Although female rats generally do not participate in the dominance hierarchies established by males (making it more difficult to study chronic social stress in these animals), analysis of the defensive behaviors of both male and female rats to a natural stressor (a cat predator) provides a foundation for evaluating sex differences in the rat's response to acute stress. Moreover, particular defensive behaviors measured in these studies have been shown to respond selectively to anxiolytic (Blanchard et al. 1993*c*) or antipanic (Griebel et al. 1996) drugs, suggesting that these defensive behaviors to stressful stimuli may provide animal models for some behavioral psychopathologies. Notably, among control animals used in a variety of drug studies, female rats showed consistently different, and often higher, levels of certain defensive behaviors than did males, particularly in situations involving cued or anticipatory (as opposed to present) threat (see Blanchard et al. 1991 for a review). When serotonergic compounds were tested in this defense test battery, female

rats frequently showed patterns of drug response different from males (Blanchard et al. 1993*d*; Shepherd et al. 1992, 1993). In addition, Fernandez-Guasti and Picazo (1990) noted that the anxiolytic action of several serotonergic compounds and ligands appears to be different for male and female rats and for different phases of the estrous cycle. However, sex differences in defense are by no means confined to laboratory rodents. On the basis of a review of sex-specific reactivity profiles to threatening stimuli in a variety of primate species under natural conditions, Crepeau and Newman (1991) suggest that these differences may be related to variations in adaptive outcomes of specific defensive behaviors for males and females, given their different social and reproductive roles.

These findings suggest gender modulation of the biological mechanisms of responsivity to stress and threat, and an emerging literature (see Blanchard et al. 1995*b* for review) attests to a variety of sex-linked differences in neurotransmitter and neuromodulatory systems in both laboratory rodents and humans. Sex differences appear to be particularly notable for the serotonin (5-HT) systems (e.g., Biegon and Israeli 1987; Carlsson and Carlsson 1988; Haleem 1992; Haleem et al. 1990; Simerly et al. 1984, 1985), which are influenced by the estrous cycle in female rats (Biegon et al. 1980; Uphouse et al. 1986) and the menstrual cycle in women (Halbreich 1990). Sex differences in 5-HT systems have been demonstrated to result in physiological (e.g., Uphouse et al. 1991), behavioral (e.g., Uphouse et al. 1991; Cutler 1991), and stress response (Heinsbroek et al. 1988; Albonetti et al. 1994) effects of manipulation of 5-HT systems.

These studies consistently indicate the importance of analyzing gender differences in studies of the biology of defense-related psychopathologies, both for their intrinsic interest and because such studies may provide information crucial in understanding substance abuse and addiction among women. However, such studies are rare and show no sign of becoming more common. An examination (Blanchard et al. 1995*b*) of a database on essentially all preclinical studies of serotonergic compounds in conjunction with tests designed to provide a model of anxiety included about 1,600 studies published between 1960 and early 1994. Although the number of such studies has increased in recent years, the proportion in which only males were used as subjects has remained relatively consistent. Male-only studies constituted about 95 percent of preclinical research on how serotonin affects anxiety, which is much

more common among women than men. In addition, of those studies using females, only a few involved both females and males, as required for meaningful comparisons within each study. Although this review specifically involved serotonin and anxiety, there appears to be little reason to believe that the situation of virtually exclusive use of male subjects for preclinical research on models of psychopathology is different when other biological variables and other models are used.

SUMMARY: RELATIONSHIPS AND RESEARCH STRATEGIES

Stress appears to enhance substance-taking in both humans and laboratory animals. Moreover, recent work on the defensive behaviors of lower mammals suggests that alterations of these systems, like human emotional psychopathologies, may be mediators of the stress/substance-taking relationship. Because women show consistently higher rates of emotional psychopathologies such as anxiety and depression, whereas female laboratory animals also show a greater defensive response to potential threat, this may be a particularly important vulnerability factor in substance abuse by women.

This view suggests that research into the mechanisms of this vulnerability may be important in the development of improved treatment for drug abuse and addiction, for both men and women, but especially for women. Specifically, it suggests that research leading to improved interventions, either pharmacological or experiential, for stress, anxiety, and depression, might be effective in reducing women's vulnerability to substance use and abuse. However, like the effects of stress on drug vulnerability generally, research on gender effects on the biology of the stress response has been neglected. This continuing omission is a substantial barrier to understanding gender modulation of the relationship between stress and drug-taking and to creating more effective treatments for these disorders among women.

Finally, these detailed similarities between animal and human findings provide support for the view that a wide range of human phenomena can be well modeled in laboratory settings incorporating attention to the natural behaviors shown by the subject species, with results that are, in turn, sensitive to the same array of factors that are important on the human level. For all mammals, the relationship between the organism and experience is bidirectional, with the interplay of biological and

experiential factors reflected in a range of important behaviors. For optimum progress in understanding behavioral phenomena common to all mammals, the results of research using human and animal subjects should be used to provide reciprocal enlightenment.

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