Stress and the Gender Differences of Depression: Role of Social, Environmental or Biological Factors

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Abstract: Stress is the major predisposing and precipitating factor in the onset of depression which is the most significant mental health risk for women. A role of socio economical, environmental or biological factors in the greater occurrence of depression in women than men has often been a matter of debate. This review accumulates evidence from clinical and preclinical research to delineate potential importance of these factors and to understand whether life stresses are more for women than men or biological mechanism needed for adaptation is more vulnerable to stressors in the female sex. Clinical studies are relevant that women are particularly vulnerable to mood disturbances at key periods in their reproductive life cycle while consistent historically and across cultures, depression occurs twice as frequently in women than men suggesting that socio cultural/ environmental factors are less important. Studies in animal models show that female sex is less affected by an acute stressor but exposure to repeated stressors induces coping deficits to impair adaptation in them. Gender differences also occur in hormones and other agents that mediate adaptation to stress. It is also well established that exposure to mild stressors prepares body to cope severe stressors. It is therefore possible that a protected life style in young girls prevents biological adaptation to severe stressors in women and is the socio cultural cause of gender differences of depression. The present review emphasizes that the issue of sex related differences of depression is not less important because it may provide ways to understand novel mechanisms of adaptation to stress.

Key Words: Adaptation to stress, Gender differences, Socio economical factors Biological factors, Clinical/preclinical research.

1. STRESS AND DEPRESSION

Major Depression, is a psychiatric syndrome characterized by pervasive disturbances in mood, sleep, appetite, energy, motivation and thinking. It is widely accepted that its etiology is influenced by genetic environmental and neurobiological factors. One of the features of a state of depression is the lack of ability to feel sense of pleasure and this state is often accompanied by heightened sensitivity towards unpleasant events. One may describe depression as a decreased capacity for coping stress [1].

The hypothesis that stress is the major precipitating factor in the onset of depression is consistently supported by clinical and preclinical studies [2,3] showing the relationship between previous traumatic stressful event (predisposing factor) and subsequent other stressor (precipitating factor). Depressed patients, at the time, report themselves to be strongly upset by recent stressful event in life [4] and the frequency of occurrence of unpleasant stimuli has been shown to correlate with the severity of depressed mood.

In a study of the role of chronic stress in the precipitation of depression has been reported [5] that onset of first episode of major depression in mothers of children with disabilities (chronic stress sample) was at lower age. Numbers of episodes in life time were also greater in these mothers than diagnostically comparable controls. The authors suggested that chronic stress may not necessarily increase the severity of an episode but the numbers of episodes are increased. Gilbert et al. [6] reported that both men and women patients with symptoms of depression did not blame themselves for many severe life events. These studies suggested that uncontrollable chronic life event stresses may have a role in the pathogenesis of depression.

Both physical and psychological stressors have been shown to lead to the onset of depressive episodes [7]. Some studies have shown that, at least for recurrent depression, stressful life events are more common in "non-endogenous depression" [8]. Other studies reported that stressful life events significantly correlated with the first episode of psychotic/endogenous depression [9]. Stress is very likely interacting with an endogenous genetic predisposition [10], such that in some vulnerable individuals, a stressor can precipitate depression.

Studies in female twins have shown a clear interaction between genetic loading and exposure to a recent stressful life event in the precipitation of depressive episode [11,12]. In some cases genetic influence is so high that an episode of depression may occur in the absence of any apparent precipitating factor. In addition there has been a growing appreciation that stressors and inflammatory immune system, particularly immune-signaling molecules (cytokines), may act synergistically to contribute to major depression [2]. All together these studies suggest that endogenous and environmental health factors may exacerbate

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effects of stressors to make an individual susceptible to an episode of depression (Fig. **1**).

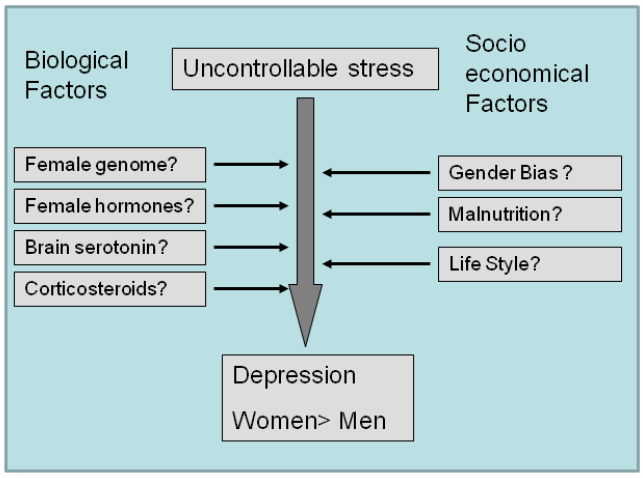

Fig. (1). Factors that may exaggerate the effects of stress to decrease the ability of women to cope stress.

2. GENDER DIFFERENCES OF DEPRESSION

Female sex, the personality trait of neuroticism and depressogenic adversity are the three risk factors for depression [12,13]. Consistent historically and across cultures, depression, the leading cause of disease related disability among women in the world, occurs twice as frequently in women than men [14-16]. Women have higher rates of recurrent depression compared to men and are more likely than men to develop depression in response to stress [12]. This prominent gender difference in depression begins in adolescence, prior to which the rates of major depression are equal in girls and boys, suggesting the potential role of female sex hormones in female depression vulnerability [17]. Similarly, it has been shown that women more often than men suffer from anxiety disorders [18] and that the sexes differ in suicidal behavior [19].

Women have been shown to be particularly vulnerable to mood disturbances at key periods in their reproductive life cycle, i.e. the premenstruum, puerperium and perimenopause [20]. These observations have led investigators to explore the relationship between hormonal cycling and the expression of psychiatric disorders in women. Increased incidence of depression at the time of menstruation and the puerperium in women has been linked with the fall of plasma oestradiol concentration [21,22]. In a study of 4,856 individuals (53% female) experiencing depressive symptoms it has been seen that different types of adverse life events are associated with different depressive symptoms profile [23]. In a follow-up study of over 7 years in 266 mid-life women, without a history of major depression at base line, 15.8% women met criteria for major depression [24]. These researchers reported that lifetime history of anxiety disorder and very stressful life event are important contributing factors in the onset of first episode of major depression in mid-life women.

3. STRESSOR CONTROLLABILITY AND LEARNED HELPLESSNESS IN ANIMAL MODELS

Based upon the clinical evidence that links stressful life events with depressive episodes several animal models exhibiting stressor controllability and learned helplessness have been developed [25-28]. Regarding the presentation of inescapable foot shock a 'learned helplessness' hypothesis was developed [29] which assumed that animals previously treated with this kind of stress will subsequently show some behavioral disturbances when placed in other stressful situation, for example a decrease in escape response to shock presentation in a non stressful situation in which the performance of some learned behavior is measured. It was recognized that such animals perform worse in aversively motivated paradigms and show the lack of pleasure seeking behavior e.g. a decreased responding to electrical brain stimulation, reduced response to attractive food and performance to positively reinforced instrumental learning tasks [30,31].

Animal models of depression should fulfill three major criteria [27]. The first criterion "face validity" assesses how well the symptoms observed in animals resemble those in human patients. The second criterion "predictive validity addresses the question how well animals in the model respond favorably to the same drugs as human do under the same treatment conditions. The third criterion "construct validity" assesses to what extent the model is consistent with the theoretical rationale. Although some animal models are better characterized as models to predisposition to depression [28] but have been extremely useful in understanding the neurochemistry and neurobiology of depression and elaborating and screening of novel compounds for potential antidepressant activity1 [26-32].

Animals exposed to other unpredictable and uncontrollable stressor e.g restraint stress, elevated platform and forced swimming also show coping deficits for aversive but escapable situations [33,34]. Chronic mild stress also causes behavioral changes in animals that parallel symptoms of depression. These models show good face and predictive validity [35-37]. Validity of various animal models of depression has been a subject of discussion in many reviews [27,32,38].

The learned helplessness paradigm was not developed to provide an animal model of depression or anxiety but it was shown in later studies that the model is sensitive to both antidepressants [39,40] and anxiolytics [41-44]. Implications for the learned helplessness paradigm as an animal model of either depression or anxiety have been discussed by [25]. The paradigm is widely used to understand neural mechanism and degree of behavioral adaptation to a stress-inducing situation particularly an uncontrollable stressor.

4. SEX RELATED DIFFERENCES IN STRESS-INDUCED BEHAVIORAL DEFICITS

Although learned helplessness is an established model for clinical depression and anxiety, and has been investigated for

about 40 years, only few studies have used female animals in the learned helplessness paradigm. The female preponderance of depression is also, heretofore, not been consistently reflected in animal models. Presentation of inescapable shock has been reported to induce either more escape impairment in male animals [45] or no sex based difference [46]. Male rats were more vulnerable to restraint stress than that of the female rats because open field behavior of female rats was less affected by a single 2h restraint stress than that of the male rats, though food intake was comparably decreased [47]. Male animals exhibited more immobility than females in the forced swimming test [48-51] but young female rats were more vulnerable than males in a novel open space swim test [52].

In striking contrast female but not male rats exhibited deficits of open field behavior after exposure to repeated restraint stresses [47,53]. Female rats were more vulnerable to chronic mild stress as depicted by the disruption of sucrose intake and decreases of open field activity [54]. But in response to an additional forced swim test, females previously exposed to chronic mild stress, were found to cope better than males.

In general sex related studies on animal models show that female performance though better than males if exposed to an acute stressor but repeated or chronic exposure induces coping deficits to impair adaptation making female sex more vulnerable to depression. Data in Fig. (**2**) (Haleem unpublished data), similar to previously reported studies [47,53] also shows that male and female rats exposed to 2h restraint stress exhibited a decrease in open field activity monitored on the following day but the decreases were smaller and not significant in female rats. These differences were not attributable to the effects of entrained oestrus cycles in females as these were randomly distributed [47,53]. Conversely, following repeated (2h/day for 5 days) exposure to restraint stress the deficits of open field exploration were present in female but not male rats.

Few studies have investigated the influence of estrous cycle on animal behavior analogs of depression. Alonso et al. [48] reported no difference in the duration of immobility in the forced swimming test between female rats during different stages of estrous cycle. Marven et al. [51] found increased immobility in the forced swim test during diestrus compared to estrus while exposure to inescapable shock further increased immobility in diestrus but not estrus females [55]. These studies suggest that vulnerability to stress-induced behavioral depression is modulated by gonadal hormones. Thus male hormones reduced vulnerability to stress in females while female hormones increased it in males [56].

5. CONCLUSION

Although a role of genetic and socio cultural/ environmental factors in the inability to adapt a stressor is well established but how these factors may impair ability to cope more in women than men is not clear. Clinical research suggest a potential role of female sex hormones in the greater vulnerability to depression in women because the prominent gender difference in depression begins in adolescence, prior to which the rates of major depression are equal in girls and boys. Moreover, the gender differences are seen in different countries, races and cultures, suggesting that socio cultural/ environmental factors are less important. Studies on animal models are relevant that female sex is less affected by an acute stressor but adaptation to repeated stressor is impaired to lead to depression (Fig. **2**). Because there are few environmental or socio-cultural factors to consider in preclinical research, it may be argued that biological rather than socio cultural/ environmental factors are more important in the gender differences of depression (Fig. **1**).

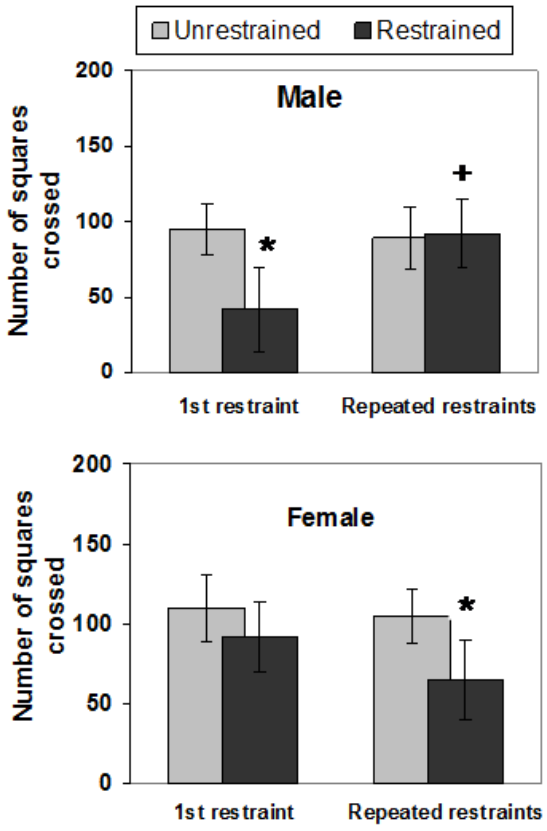

Fig. (2). Activity of male and female rats in an open field 24 h after a single (2h) or repeated (2h/day for 5 days) restraints. Male (body weights 200-250 gm), female (body weights 190-230) animals were restrained for 2h on wire grids and activity in an open field was monitored 24 h after the termination of the 1st or 5th restraint period as described by Haleem & Parveen (1994). Values are means ± S. D. (n=6). Significant differences by Newman Keuls test: *P<0.01 from respective unrestrained animals; +P<0.01 from 1st day (2h/day) restrained animals, following two way ANOVA. (Haleem unpublished data)

In the quest of how female sex hormones may impair adaptation, a role of brain serotonin and circulating corticosteroids may not be excluded (Fig. **3**). Indeed, gender differences occur in brain serotonin as well as stress-induced increases of circulating corticosteroids. A number of studies

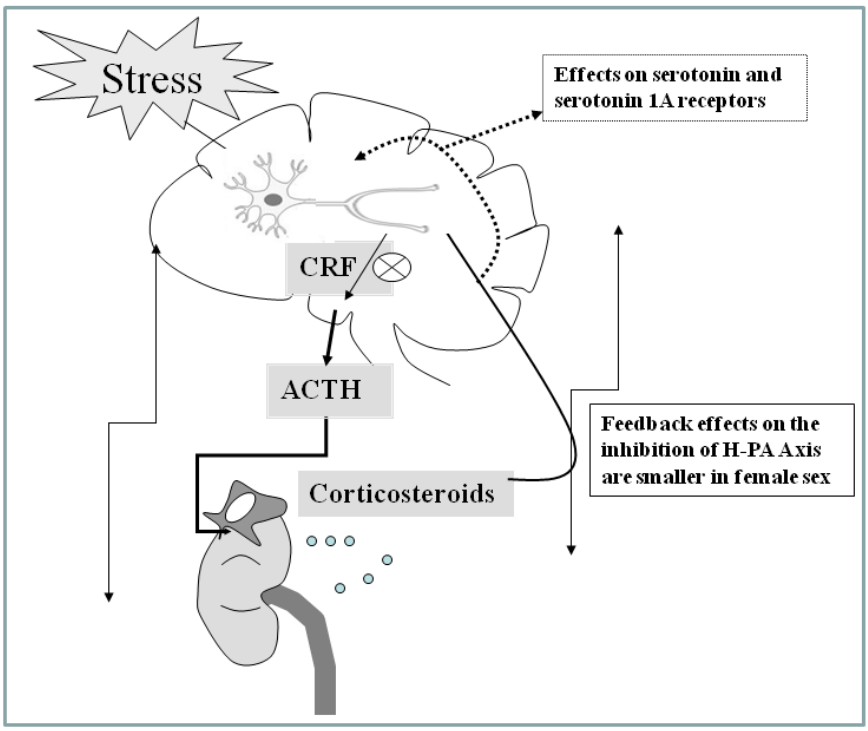

Fig. (3). Gender differences in the effects of stress on brain serotonin and the activity of hypothalamo-pituitary adrenocortical axis (H-PA) axis.

show that stress-induced increases of corticosteroids have adaptive effects in the short term and yet may be damaging when they are over produced. Depressed patients exhibit higher levels of circulating corticosteroid, while selective serotonin reuptake inhibitors (SSRIs) are to date most effective treatment for depression particularly in women. It is therefore possible that a more secured life style in women prevents the initiation of corticosteroid-induced reactions needed for adaptation to sever stressors in adults and is the socio cultural cause of gender difference of depression. It would suggest that the issue of sex related differences of depression is not less important because it may provide ways to understand novel mechanisms of adaptation to stress.

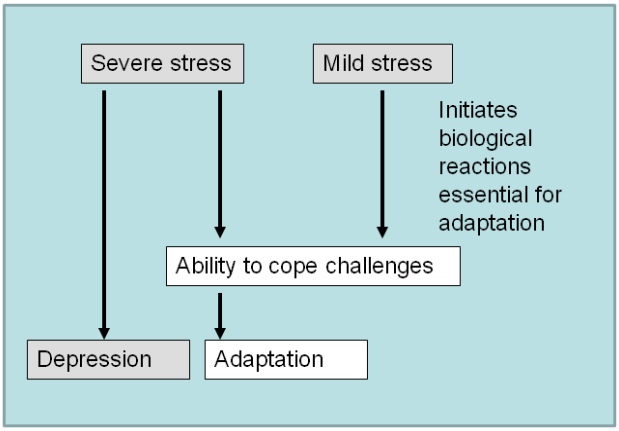

Fig. (4). Schematic view of how prior exposure to mild stress initiates adaptation to cope severe stresses.

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