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Research report

Estrogen-mediated effects on depression and memory formation in females

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Abstract

Women are twice as likely to suffer from depression as men. It has been proposed that the ovarian hormones estrogen and progesterone contribute to the higher incidence of this potentially debilitating disorder. Depression can also be accompanied by a loss of cognitive performance. Here we review estrogen-mediated effects on depression and memory formation in females. We propose that changes in levels of estrogen are associated with sex differences in learning as well as changes in affect prior to menses, immediately after pregnancy and during perimenopause and the menopausal transition. Finally, we discuss the animal model of depression known as 'learned helplessness' and describe research from our laboratory demonstrating that exposure to an acute stressful experience compromises a female's later ability to acquire certain types of new memories. This response to stressful experience is opposite to that observed in males and is dependent on the presence of estrogen, and more specifically—changing levels of estrogen. This observation indicates that females and males can use different hormonal and neural mechanisms to respond to the same emotional event and underscore the importance of studying the unique and changing biology of females, especially when considering treatment strategies for depression and stress-related illness.

Keywords: Sex; Stress; Learning; Ovarian steroids; Serotonin; Mood

1. Introduction

Depression is a mood disorder known to many, with up to 20% of the population experiencing some type of depression in their lives (Kessler et al., 1994). One of the more striking features of depression is the fact that twice as many females experience some form of depression when compared to males (Earls, 1987). In addition to increased incidence, their depressive episodes can last longer, be more severe and often recur (Nolen-Hoeksema, 1987). It is recognized that some environmental and sociocultural factors contribute to the sex difference

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in depression. For example, females are more likely to seek treatment for depression and thus their numbers can appear higher. Moreover, males often use alcohol or illegal drugs to self-medicate. As such, they are often times diagnosed as substance abusers or antisocial rather than depressive. Also, females often appear more depressed because they tend to ruminate more about their mood (Nolen-Hoeksema, 1987). Finally, the changing role of women in the workplace seems to contribute to the sex difference. For example, women who work outside the home have a reduced incidence of depression (Nolen-Hoeksema, 1991) and in communities where both sexes work, as in the Amish community, there are no reported sex differences in depression (Egeland and Hostetter, 1983). However, there is ample evidence that the high incidence of depression in females is attributable or at least exacerbated by their unique biology and specifically by the presence of the ovarian hormones estrogen and progesterone.

2. The neurobiology of depression

As with many psychological disorders, an appreciation for the underlying mechanisms of depression arose from the development of treatments. Nearly 40 years ago, it was observed that depression could be treated with drugs that enhance monoamines in the brain. The most effective antidepressants were those that enhanced either serotonergic or noradrenergic systems. From these observations, it was assumed that depression was caused by or at least accompanied by a decrease in effectiveness of these systems. This hypothesis has been called the 'monoamine hypothesis of depression'. The hypothesis was strengthened by the discovery that drugs that enhance both the serotonergic and noradrenergic systems, the so-called monoamine oxidase (MOA) inhibitors, were effective in the treatment of unipolar depression. Because many of the initial drugs developed for the treatment of depression carried unwanted side-effects, a great deal of effort went into developing drugs that selectively targeted the noradrenergic or the serotonergic systems. Those that have been most effective are known as the selective serotonin reuptake inhibitors (SSRIs) which function to increase the bioavailability of serotonin in the synapse. The SSRIs have become the most widely prescribed treatment for depression primarily because they often relieve the depression without side effects such as headache, nausea and drowsiness, although many patients do present with sexual dysfunction. Interestingly, these drugs are also effective in the treatment of other psychiatric disorders such as panic and obsessive-compulsive disorder, even bulimia nervosa.

Given the usefulness of serotonergic drugs for treating depression, it is assumed that depressed patients would have reduced levels of serotonin. Indeed, there are reports of reduced concentrations of 5HT and its metabolite 5HIAA in the cerebrospinal fluid of depressed patients, as well as reduced serotonin uptake, transporter binding sites and concentration of tryptophan, the serotonin precursor (Nemeroff, 1998). However, the connection between reduced serotonin and depression is not direct. For example, a reduction in monoamines including serotonin does not necessarily result in behavioral depression in undepressed people nor does reduction in monoamines in depressed patients worsen their symptoms (Delgado, 2000). Also, only about 30% of depressed patients respond to serotonergic therapy (Nemeroff, 1998). Thus, a reduction in serotonin is not sufficient to induce depression but may be permissive in some individuals.

In addition to serotonergic dysfunction, depression has been associated with disturbances in the hypothalamic–pituitary–adrenal axis (HPA) in humans. Drug-free depressed patients have enhanced levels of adrenal hormones and corticotropin-releasing factor (CRF) in the blood (Banki et al., 1987). CRF and its receptors are prevalent in brain regions associated with affect such as the amygdala, the bed nucleus of the stria terminalis, the cerebellum and the dorsal raphe nuclei. Interestingly, it is reported that an injection of CRF into laboratory animals can induce similar responses as depressed patients such as weight loss, sleep disturbances and fear of novelty (Nemeroff, 1998).

From the previous discussion, it is clear that serotonin and adrenal hormones may contribute to the symptoms of depression. To further complicate the issue, there is evidence that glucocorticoids regulate serotonergic activity from the raphe nucleus

and that under chronic conditions of elevated corticosteroids, as under stressful conditions, serotonin is reduced (Meijer and de Kloet, 1998). Also, there are reports that treatment with antidepressants can reduce the activity of CRF-containing neurons (Nemeroff, 1998). These results emphasize the need to view depression as a set of behavioral symptoms that are manifest by interactions of hormonal and neurotransmitter systems in numerous brain regions. It is unlikely that any one molecule will be responsible for such a complex phenomenon as depression.

3. Female depression and the role of ovarian hormones

As discussed, females present with depression much more than males. The higher incidence and in some cases, severity of depression is associated with the presence or absence of ovarian hormones. In fact, female depression often occurs during periods of hormonal perturbation such as prior to menses, immediately after pregnancy, as well as during and shortly after menopause. It is important to note that these conditions are often associated with changes in hormone levels rather than an absolute level. Consider the case of postpartum depression, which occurs in the weeks to months following birth. This disorder is evident in up to 10% of new mothers, with 30% of those still depressed 6 months later (Buckwalter et al., 2001). During pregnancy, estrogen levels are very high and decline precipitously after birth. Thus, it could be proposed that depression is associated with the decrease or 'change' in levels of gonadal steroids. In order to test whether the change in hormone levels is indeed responsible for postpartum depression, one study treated females with the very high levels of estrogen associated with pregnancy followed by treatment with low levels associated with postpartum. Females either had a history of postpartum depression or did not (Bloch et al., 2000). As expected, treated females with a history developed dysphoric mood consistent with depression whereas those treated without a history did not. These results indicate that fluctuations in estrogen contribute to depression after pregnancy but other factors are contributing to its etiology. Thus, changes in ovarian hormones are likely necessary but not sufficient for inducing this type of depression.

Another type of female depression associated with changing hormone levels is referred to as premenstrual syndrome (PMS), or in more severe cases as premenstrual dysphoric disorder (PMDD), which occurs in ~5% of women of reproductive age (Rubinow, 1992). The mood-related symptoms of PMS, including depression, anxiety and irritability, vary in accord with the different patterns of ovarian hormone secretion during the menstrual cycle. The symptoms of PMS occur when estrogen and progesterone levels decrease during the late leuteal phase of the menstrual cycle and disappear at or soon after the onset of menses. Thus, PMS may be triggered by hormonal changes occurring during the leuteal phase of the menstrual cycle. However, the symptoms of PMS can occur despite the elimination of the leuteal phase by administration of the progesterone antagonist mifepristone (Schmidt et al., 1991). These results suggest that hormonal changes before the leuteal phase may be responsible for the onset of PMS symptoms (Schmidt et al., 1998). In addition, the interaction between the gonadal steroid and serotonergic systems may regulate mood and affect during the menstrual cycle. Serotonin function is altered in women with PMS (Steege et al., 1992) and serotonergic compounds such as fluoxetine can be used to treat PMS and PMDD (Romano et al., 1999).

As emphasized, the incidence of depression is higher in women than men. However, this sex difference tends to diminish after menopause which occurs at an average age of 51 years in the United States (Sonnenberg et al., 2000). The postmenopausal period is characterized by the virtual absence of ovarian steroids as well as decreased serotonergic function (Halbreich et al., 1995). Because older females do not menstruate nor experience changing levels of ovarian hormones, this may constitute further support for the hypothesis that sex differences in depression are associated with changing rather than absolute levels of female hormones. As with postpartum depression, menopause is a time when depressive symptoms reoccur in women with a history of the disorder (Pearlstein, 1995; Richardson and Robinson, 2000).

Perimenopause corresponds to the period preceding menopause and is characterized by irregular

cycle lengths, reduced fertility and decreased estrogen production. Higher rates of depressive symptoms occur in about 10% of perimenopausal women (Avis and McKinlay, 1995; Burt et al., 1998). It has been suggested that mood disturbances associated with perimenopause may be attributable to the hot flashes, insomnia and fatigue commonly experienced during this period. The various subtypes of female depression clearly indicate that women are particularly susceptible to depression at discrete points in their reproductive life cycle. This increased vulnerability corresponds to changes in circulating levels of ovarian hormones.

4. Interactions between serotonin and ovarian hormones

Serotonin's widely recognized role in depression and the ability of estrogen and progesterone to modulate different aspects of serotonergic function implicate ovarian hormones as a factor underlying depression and its treatment (Joffe and Cohen, 1998; McEwen and Alves, 1999). However, the mechanisms by which ovarian hormones modulate the central serotonin system, and ultimately mood, are unknown. The raphe nuclei have been suggested as the site of action for ovarian hormone regulation of serotonergic function despite the inability to detect the classic alpha subtype of estrogen receptor in this region. The recent discovery of the beta subtype estrogen (Kuiper et al., 1996) and the localization of ER-beta mRNA in the dorsal raphe (Shughrue et al., 1997) provides a potential explanation of the interactions between estrogen and serotonergic systems. Serotonergic neurons in the raphe of the rhesus macaque have also been found to contain estrogen inducible progestin receptors thus providing a direct target for the regulation of serotonergic function by ovarian hormones (Bethea, 1993). Ovarian hormones have also been shown to affect numerous factors regulating serotonin synthesis and serotonin levels in the central nervous system (see Bethea et al., 1999 for review). For example, ovarian hormones promote the induction of tryptophan hydroxylase, the rate-limiting enzyme in the synthesis of serotonin, and reduce serotonin reuptake transporter (SERT) mRNA expression in the raphe nuclei. In addition, numerous serotonergic receptor subtypes are reportedly regulated by ovarian steroids, as well as implicated in depression. For example, expression of the 5HT1A autoreceptor in the dorsal raphe is decreased by estrogen and progestin (Pecins-Thompson and Bethea, 1998). Estrogen has also been shown to increase the density of 5HT2A receptors in brain regions associated with mood (Fifa and Fillion, 1992). Taken together, these findings suggest that estrogen can facilitate serotonergic transmission by enhancing serotonin synthesis and/or decreasing serotonin reuptake thereby alleviating depressive symptoms (Bethea et al., 1999). Consistent with this, clinical studies have demonstrated estrogen treatment to have antidepressant effects when administered alone (Klaiber et al., 1996) or in combination with serotonergic antidepressants (Halbreich et al., 1995). Thus, it is evident that in women, ovarian hormones can interact with serotonergic function to influence affect.

5. Estrogen and the treatment of female depression

The pivotal role of ovarian hormones in the etiology of female depression suggests a potential role of estrogen and progesterone in the treatment of affective disorders in women. The available research indicates that estrogen may be pharmacologically effective in ameliorating depressive symptoms. For example, estrogen treatment repeatedly improves the physical and psychological symptoms of PMS (Epperson et al., 1999) and may be effective for postpartum depression (Gregoire et al., 1996; Sichel et al., 1995). There is widespread use of hormone replacement therapy (HRT) following cessation of menses with an estimated 10 to 30% of postmenopausal women receiving HRT for at least some time during and after menopause (Halbreich, 1997). Clinical studies indicate that estrogen replacement improves mood and increases the sense of well-being in post-menopausal women with no or mild depressive symptoms. However, in postmenopausal women with major depression, estrogen alone is not sufficient, although it may be useful as an augmentation strategy (Derman et al., 1995). Interestingly, estrogen can remedy the symptoms of perimenopausal

depression providing support for the idea that ovarian hormones are involved in the expression of the disorder (Rubinow et al., 1998; Burt et al., 1998). Recently, Schmidt et al. (2000) demonstrated the beneficial effects of estrogen replacement in perimenopausal depression to be independent of its ability to reduce the sleep disturbances and the distress of hot flushes.

Despite these findings, further research is needed to elucidate the role of ovarian hormones in female depression. Particularly, the determination of effective doses and treatment duration for the different subtypes of female depression must be addressed as well as the potential prevention strategies during susceptible times in a woman's life. It has recently been determined that there are at least two types of estrogen receptors, the alpha and the beta-receptor. The beta-receptor is highly localized in the brain, while the alpha is more highly localized in reproductive tissue such as the ovaries. Because of the dangers of inducing cancer via activation of the alpha receptor, there is much emphasis now in finding ways to selectively activate one receptor and not the other (Kuiper et al., 1996). Although promising, those involved in these studies remain cautious since estrogen has many effects on other organ systems including heart and bone (Roussouw et al., 2002).

6. Helplessness behavior in the female rat

In order to understand the neurobiology of depression or other disorders of affect, it is useful to have an animal model and numerous animal models have been proposed (Willner, 1990; Porsolt, 2000 for review). Surprisingly, however, there has been minimal research on the neurobiology of depression in females and no apparent attempt to establish an animal model. The reluctance to study this issue arises from a number of factors. Foremost is the difficulty in studying any phenomenon with a changing baseline, such as occurs across an estrous cycle of a laboratory animal. For example, the rat transitions through at least four stages of estrus (proestrus, diestrus 1, diestrus 2, estrus) in a 4–5-day period. Thus, for each experiment, 4–5 times as many groups are necessary than when studying only males and results in a much more laborious and expensive effort on the part of the researcher. More critically, it has been assumed that the neurobiology of depression in females is simply an extension of that observed in males, and therefore a model specific to females was unnecessary. In the following section, we review the most common animal model of depression and its incompatibility with some symptoms of female depression.

The most common animal model of depression is known as 'learned helplessness'. This model developed from a series of experiments conducted by Overmier, Seligman and Maier in the mid-1960s (Overmier and Seligman, 1967; Seligman and Maier, 1967). In the experiments, animals were exposed to aversive shocks or other stressors and tested later on their ability to learn a new task in which escape from a mild footshock was possible. They found that animals exposed to inescapable stress were severely impaired in their ability to perform while animals exposed to the same amount of escapable shock were not impaired. These experiments provided evidence that an emotional state induced by exposure to uncontrollable events could later retard an animal's capacity to respond when control was possible. The impaired performance in response to inescapable stress was most often evident during operant conditioning, in which an animal must elicit an overt response to earn some reinforcer. Because it appeared as if the animals had 'given-up', the phenomenon was promoted as an animal model for depression in humans (Seligman, 1975, 1997). In the model, it was proposed that exposure to uncontrollable and stressful life events led to a feeling of 'loss of control' which ultimately led to depression. Adding to its usefulness as an animal model of depression, treatment with standard antidepressants such as the SSRIs and lesions to the serotonergic system ameliorated some if not all of the performance deficits (Maier et al., 1993). Although compelling, there is concern that some of these effects of stress on learning are attributable to nonspecific effects on performance (Maier and Jackson, 1979; Weiss and Glazer, 1975). For example, exposure to stressful events as used in these studies can induce neophobia and a decrease in activity, both of which can impair learning when activity is necessary. This is not to say that the effects are not similar to those

observed with depressed patients. To the contrary, some would argue that the behavioral depression exemplified by inactivity in the laboratory animal is of the type observed in depressed humans and reflects their lack of interest in daily life. The primary concern for the present review is that this phenomenon of 'learned helplessness' reportedly does not occur in female animals (Steenbergen et al., 1990; Kirk and Balmpied, 1985) despite the fact that females have a much higher incidence of depression. A recent study has demonstrated that female mice of some strains exhibit moderate helplessness behavior whereas others are less or not disrupted by the effects of inescapable shock (Caldarone et al., 2000). Findings from these various studies suggest that helplessness may not be a useful animal model for depression in females. Minimally, they suggest that an appropriate model for depression in males may not be appropriate for depression in females.

7. A stress-induced performance deficit in the female rat

Recently, we observed a very different effect from the traditional 'helplessness' effect. In our studies we use a classically conditioned response known as eyeblink conditioning. In the learning task, an auditory conditioned stimulus (CS) is preceded by and predicts the occurrence of an unconditioned stimulus (US), which is a periorbital shock to the eyelid. The stimulation to the eyelid elicits a blink, which is the unconditioned response (UR). When repeatedly paired with and preceded by the auditory stimulus, the auditory stimulus itself comes to elicit an eyeblink conditioned response (CR). In the male rat, we observed that exposure to an acute inescapable stressor of either swim stress or tailshocks (a similar protocol to that used in the learned helplessness studies) greatly facilitated this type of associative learning. Exposure to the stressful experience enhanced delay conditioning in which the two stimuli are associated in time (Fig. 1A) and trace conditioning in which the stimuli are discontiguous in time (Fig. 1B) (Shors et al., 2000 for review; Shors, 2000, 1998; Beylin and Shors, 1998; Servatius and Shors, 1994; Shors et al., 1992). In contrast, exposure to the very same stressor dramatically impaired conditioning in females (Wood and Shors, 1998; Shors et al., 1998; Wood et al., 2000) (Fig. 1A and 1B). Thus, in response to the very same environmental event, males and females responded in opposite

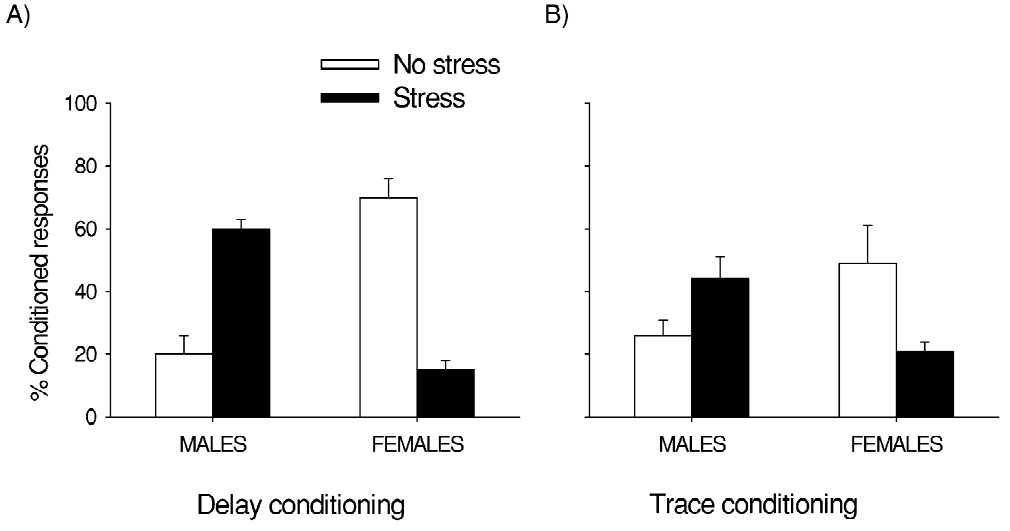

Fig. 1. Effects of stress on learning in males versus females. Figure depicts the percent conditioned responses across 300 trials of delay (A) and trace (B) classical eyeblink conditioning in the rat. Unstressed females in proestrus conditioned more than unstressed males. Exposure to an acute stressor of restraint and brief intermittent tail-shocks facilitated classical conditioning in males 24 h later, whereas in females exposure to the same stressor during diestrus impaired conditioning 24 h later during proestrus.

directions, with females being severely compromised in their ability to perform. As illustrated, the females were virtually unresponsive to the association between environmental events.

Although unresponsive to acquiring new associations, it is not the case that the female could not respond (Wood and Shors, 1998). Neither stress nor gender altered the number of spontaneous blinks or blinks in response to auditory stimuli prior to training. Neither stress nor gender altered responding to the conditioning stimuli when they were presented in an explicitly unpaired manner. We also observed no difference in activity or measures of gross pain sensitivity 24 h after stressor exposure, at the time of training. Rather, the data suggest that exposure to stressful experience induces dramatic, persistent and diametrically opposed effects on memory formation in the male versus female animal.

As discussed, many of the instances of depression in females are associated with levels of reproductive hormones and their fluctuations across time. The effect of stress on conditioning in females is sensitive to both these factors. First of all, the effect of stress is prevented by removal of ovarian hormones via ovariectomy (Wood and Shors, 1998) (Fig. 2A). Secondly, the effect can be prevented by administration of the estrogen antagonist, tamoxifen (Fig. 2B). In contrast, it does not appear that progesterone is as critical to the effect of stress on conditioning in that administration of a progesterone antagonist did not prevent the impaired performance (Wood and Shors, unpublished data). We also have data to suggest that the *change* in level of estrogen is critical. Firstly, it is noted that unstressed females acquire the response faster than do unstressed males (Fig. 1). Thus, there is a difference in the baseline response that is dependent on sex and moreover, dependent on the stage of estrus (Shors et al., 1998). Specifically, females acquire the CR faster during proestrus when estrogen levels are high relative to females in estrus or diestrus, when estrogen levels are relatively low (Fig. 3). Importantly, the impaired performance in response to stress is most evident when levels of hormones change from diestrus to proestrus. That is, the effect of stress on conditioning is most apparent when estrogen levels are rising.

From these data, one can propose two hypotheses. The first is that levels of estrogen and conditioning are linearly related. In this scenario, high levels of estrogen as observed during proestrus would be associated with high performance and low levels as observed during diestrus and estrus would be associated with low levels of performance (Fig. 4A). In addition, this scenario would predict that stress would decrease estrogen levels and thereby impair performance. The second hypothesis would propose an inverted-U shaped function between levels of estrogen and performance (Fig. 4B). In this scenario, low levels of estrogen as observed during estrus and diestrus would be associated with poor performance, moderate levels of estrogen would be associated with moderate levels of performance and very high levels of estrogen in response to stress would be associated with poor performance. In order to test which of these hypotheses was correct, one would need to know whether stress elevated or reduced endogenous levels of estradiol. We conducted this experiment and determined that exposure to the stressor of either tailshock or swim stress *increases* estrogen (Shors et al., 1999). Thus, it appears that there is an inverted-U shaped relationship between levels of estrogen and performance of the classically conditioned eyeblink response. In the presence of very low and very high levels of estrogen, as in diestrus and after stress, respectively, performance is poor, but in the presence of moderate levels of estrogen, performance is optimal. However, it should be noted that administration of stress-induced levels of estrogen does not impair learning in females (Leuner and Shors, unpublished data). Thus, although extreme changes in estrogen are associated with poor performance, estrogen by itself is not sufficient to produce these effects. Exactly how changes in estrogen can influence behavior to such a degree and what it interacts with is unknown at this time.

As discussed, there is some evidence that a disruption in the HPA activity is associated with depression, at least in males. Interestingly, we have found that adrenal glucocorticoids are necessary for the enhancing effect of stress on conditioning in males (Fig. 5A), yet they do not contribute significantly to the impairment in females (Wood et al., 2000) (Fig. 5B). That adrenal steroids do not contribute is somewhat surprising since females under both stressed and unstressed conditions have much higher levels than males (Shors et al., 1999). None-

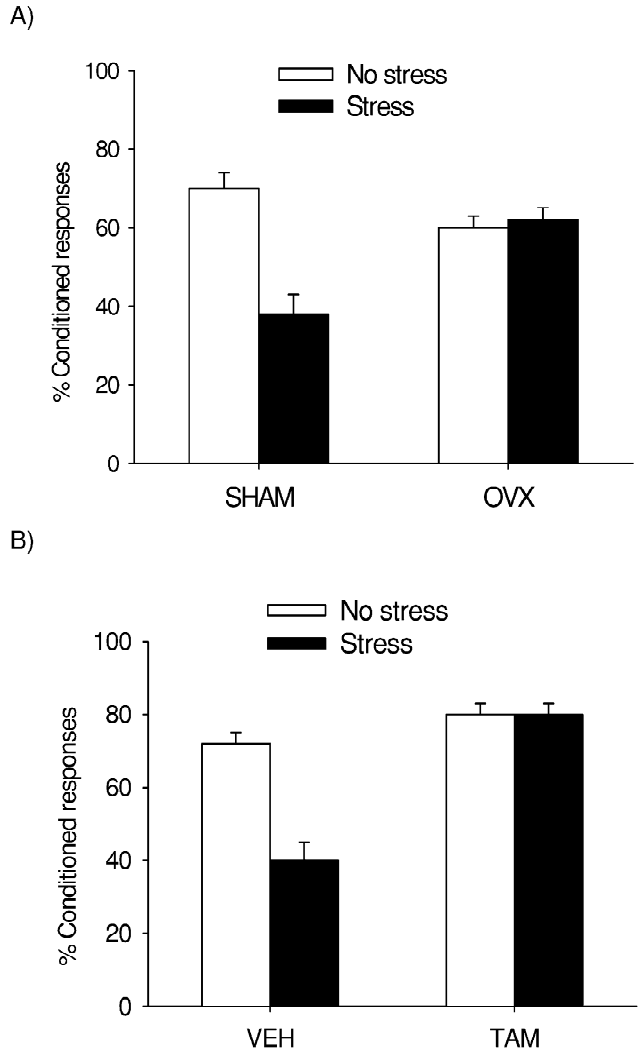

Fig. 2. Contribution of ovarian hormones to the stress-induced impairment of learning. (A) Females exposed to sham surgery were impaired in their ability to acquire the classically conditioned eyeblink response 24 h after exposure to the stressor. Removal of ovarian hormones (OVX) prevented the stress-induced impairment of classical eyeblink conditioning in females. (B) Effect of estrogen receptor antagonist on the stress-induced impairment of learning in females. Stressed females receiving the vehicle (VEH) were impaired relative to unstressed controls injected with VEH. After receiving injections of the estrogen antagonist, tamoxifen (TAM), females were not impaired by stressor exposure.

theless, these results suggest that the sexually dimorphic effects of stress on conditioning are mediated by differing hormonal substrates—by adrenal hormones in males and ovarian hormones in females. Minimally, the data illustrate why we cannot assume that female expression of a disorder is simply the same as a male with the addition of ovarian hormones.

Whether or not the phenomenon just described has potential as a model for depression in females remains to be determined. If so, several contributing factors would have to be shown. For example, the ability to control the stressful event should ameliorate the deficit in performance. Also, the effect should be lessened in females treated chronically with serotonergic drugs such as Prozac (Leuner et al.,

Fig. 3. Stages of estrus influence learning. Percentage conditioned eyeblink responses for female rats in different stages of their cycle: proestrus, estrus and diestrus. Rats in each stage were exposed to a stressor of intermittent tailshock and trained 24 h later. Female rats in proestrus, when estrogen levels are relatively high, emitted more conditioned responses in 300 trials than females in other stages.

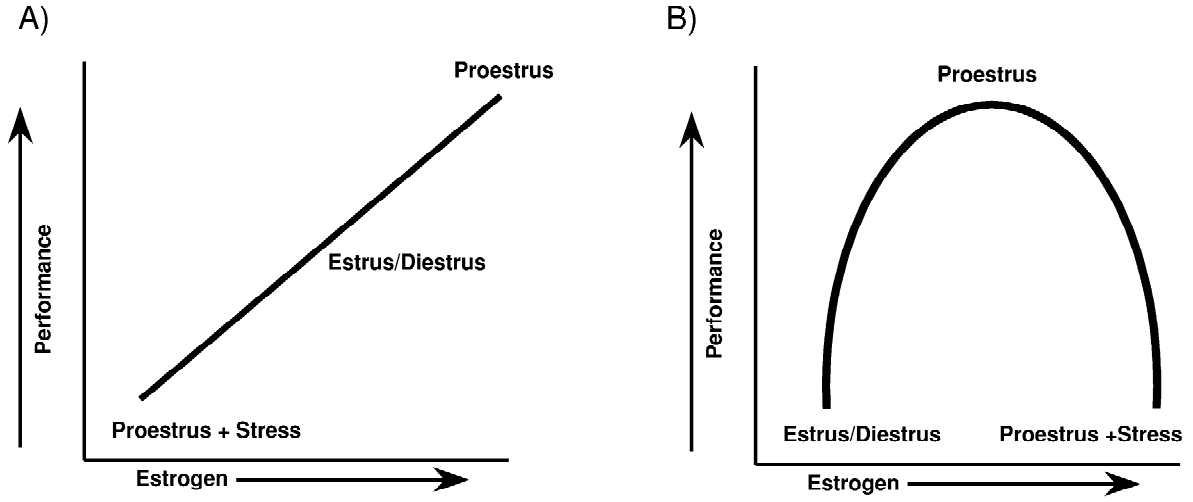

Fig. 4. Relationships between estrogen and learning. Two hypotheses regarding the relationship between levels of estrogen and performance are diagrammed. (A) A linear relationship between estrogen and performance would suggest that elevated levels of estrogen (proestrus) are associated with enhanced performance whereas reduced levels of estrogen (diestrus and estrus) are associated with poor performance. (B) An inverted U relationship would suggest that when estrogen levels are very low and very high, performance is poor, and when estrogen levels are moderate, performance is optimal. Stressor exposure that impairs conditioning in female rats enhances the release of estrogen (Shors et al., 1999) consistent with an inverted-U shaped relationship.

2002). Nevertheless, we should not avoid studying females simply because a particular phenomenon does not exactly model a particular behavior in the human female. This approach (or lack thereof) contributes to our lack of knowledge about the female in general, her tendency towards depression, as well as her response to stressful experience. Rather, we should study the female as a matter of course and as a consequence will gain a greater understanding of her unique and changing biology and how it contributes to disorders such as depression and stress-related illness.

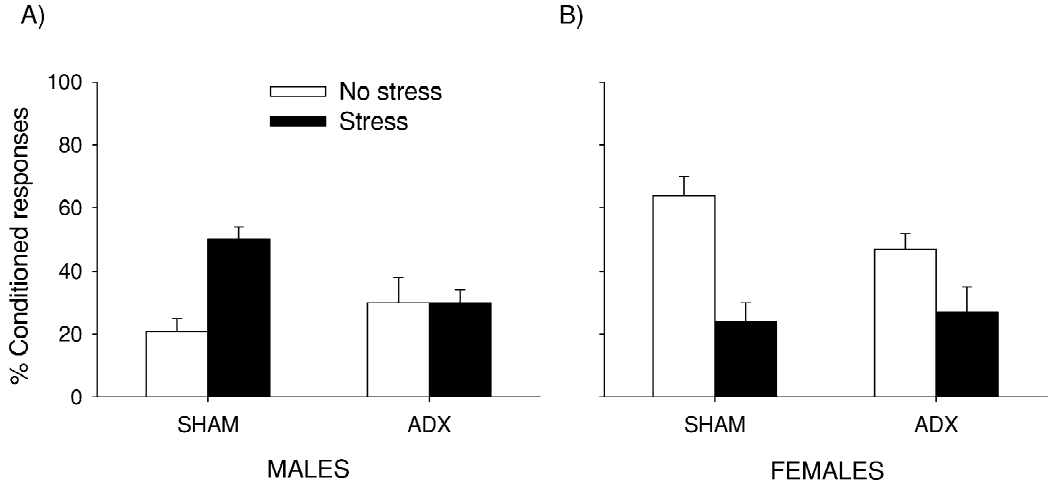

Fig. 5. Contribution of adrenal hormones to the stress effects on learning. (A) Males exposed to sham surgery emitted more conditioned responses 24 h after stressor exposure than unstressed males. ADX prevented the stress-induced facilitation in males. (B) Females exposed to sham surgery exhibited the stress-induced impairment of conditioning. ADX did not prevent the impairment of conditioning in females 24 h following stressor exposure.

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References

Avis, N.E., McKinlay, S.M., 1995. The Massachusetts Women's Health Study: an epidemiologic investigation of the menopause. J. Am. Med. Assoc. 50, 45–49.

Banki, C.M., Arato, M., O'Connor, L., Nemeroff, C.B., 1987. Cerebrospinal fluid corticotropin-releasing factor-like immunoreactivity in depression and schizophrenia. Am. J. Psychiatry 144, 873–877.

Bethea, C.L., 1993. Colocalization of progestin receptors with serotonin in raphe neurons of macaque. Neuroendocrinology 57, 1–6.

Bethea, C.L., Pecins-Thompson, M., Schutzer, W.E., Gundlah, C., Lu, Z.N., 1999. Ovarian steroids and serotonin neural function. Mol. Neurobiol. 18, 87–123.

Beylin, A.V., Shors, T.J., 2003. Glucocorticoids are necessary for enhancing the acquisition of associative memories after acute stressful experience. Horm. Behav., In press.

Bloch, M., Schmidt, P.J., Danaceau, M., Murphy, J., Nieman, L., Rubinow, D.R., 2000. Effects of gonadal steroids in women with a history of postpartum depression. J. Psychiatry 157, 924–930.

Buckwalter, J.G., Buckwalter, D.K., Bluestein, B.W., Stanczyk, F.Z., 2001. Pregnancy and postpartum: changes in cognition and mood. Prog. Brain Res. 133, 303–319.

Burt, V.K., Altshuler, L.L., Rasgon, N., 1998. Depressive symptoms in the perimenopause: prevalence, assessment, and guidelines for treatment. Harv. Rev. Psychiatry 6, 121–132.

Caldarone, B.J., George, T.P., Zachariou, V., Picciotto, M.R., 2000. Gender differences in learned helplessness behavior are influenced by genetic background. Pharmacol. Biochem. Behav. 66, 811–817.

Delgado, P.L., 2000. Depression: the case for a monoamine deficiency. J. Clin. Psychiatry 61, 7–11.

Derman, R.J., Dawood, M.Y., Stone, S., 1995. Quality of life during sequential hormone replacement therapy. Int. J. Fertil. Menopaus. Stud. 40, 73–78.

Earls, F., 1987. Sex differences in psychiatric disorders: origins and developmental influences. Psychiatr. Dev. 5, 1–23.

Egeland, J.A., Hostetter, A.M., 1983. Affective disorders among the Amish. Am. J. Psychiatry 140, 56–61.

Epperson, C.N., Wisner, K.L., Yamamoto, B., 1999. Gonadal steroids in the treatment of mood disorders. Psychosom. Med. 61, 676–697.

Fifa, E., Fillion, G., 1992. 5-Hydroxytryptamine receptors. Pharmacol. Rev. 44, 401–458.

Gregoire, A.J.P., Kumar, R., Everitt, B., Henderson, A.F., Studd, J.W.W., 1996. Transdermal oestrogen for treatment of severe postnatal depression. Lancet 347, 930–933.

Halbreich, U., Rojansky, N., Palter, S., Tworek, H., Hissin, P., Wang, K., 1995. Estrogen augments serotonergic activity in postmenopausal women. Biol. Psychiatry 37, 434–441.

Halbreich, U., 1997. Role of estrogen in postmenopausal depression. Neurology 48, S16–S20.

Joffe, H., Cohen, L.S., 1998. Estrogen, serotonin and mood disturbance: where is the therapeutic bridge? Biol. Psychiatry 44, 798–811.

Kessler, R.C., McGonagle, K.A., Zhao, S., Nelson, C.B., Hughes, M., Eshleman, S., Wittchen, H.U., Kendler, K.S., 1994. Lifetime and 12 month prevalence of DSM-III-R psychiatric disorders in the United States. Arch. Gen. Psychiatry 51, 8–19.

Kirk, R.C., Balmpied, N.M., 1985. Activity during inescapable shock and subsequent escape and avoidance learning: female and male rats compared. N.Z. J. Psychol. 14, 9–14.

Klaiber, E.L., Broverman, D.M., Vogel, W., Peterson, L.G., Snyder, M.B., 1996. Individual differences in changes in mood and platelet monoamine oxidase (MAO) activity during hormonal replacement therapy in menopausal women. Psychoneuroendocrinology 21, 575–592.

Kuiper, G.G., Carlsson, B., Grandien, K., Enmark, E., Haggblad, J., Nilsson, S., Gutafsson, J.A., 1996. Comparison of the ligand binding specificity and transcript tissue distribution of estrogen receptors alpha and beta. Endocrinology 138, 863–870.

Leuner, B.L., Mendolia, S., Falduto, J., Shors, T.J., 2002. Serotonergic antidepressants protect females from the adverse effects of stress on learning. Society for Neuroscience Abstracts, 380.1.

Maier, S.F., Jackson, R.L., 1979. Learned helplessness: all of us were right (and wrong): inescapable shock has multiple effects. In: Bower, B. (Ed.), Advances in Learning and Motivation. Academic Press, New York, pp. 155–215.

Maier, S.F., Grahn, R.E., Kalman, B.A., Sutton, L.C., Wiertelak, E.P., Watkins, L.R., 1993. The role of the amygdala and dorsal raphe nucleus in mediating the behavioral consequences of inescapable shock. Behav. Neurosci. 107, 377–388.

McEwen, B.S., Alves, S.A., 1999. Estrogen action in the central nervous system. Endocr. Rev. 20, 279–307.

Meijer, O.C., de Kloet, E.R., 1998. Corticosterone and serotonergic neurotransmission in the hippocampus: functional implications of central corticosteroid receptor diversity. Crit. Rev. Neurobiol. 12, 1–20.

Nemeroff, C.B., 1998. Psychopharmacology of affective disorders in the 21st century. Biol. Psychiatry 44, 517–525.

Nolen-Hoeksema, S., 1987. Sex differences in unipolar depression: evidence and theory. Psychol. Bull. 101, 259–282.

Nolen-Hoeksema, S., 1991. Responses to depression and their effects on the duration of depressive episodes. J. Abnorm. Psychol. 100, 569–582.

Overmier, J.B., Seligman, M.E.P., 1967. Effects of inescapable shock on subsequent escape and avoidance learning. J. Comp. Psychol. 63, 23–33.

Pearlstein, T.B., 1995. Hormones and depression: what are the facts about premenstrual syndrome, menopause, and hormone replacement therapy? Am. J. Obstet. Gynecol. 173, 646–653.

Pecins-Thompson, M., Bethea, C.L., 1998. Ovarian steroid regulation of 5HT1A autoreceptor messenger ribonucleic acid expression in the dorsal raphe of rhesus macaques. Neuroscience 89, 267–277.

Porsolt, R.D., 2000. Animal models of depression: utility for transgenic research. Rev. Neurosci. 11, 53–58.

Richardson, T.A., Robinson, R.D., 2000. Menopause and depression: a review of psychologic function and steroid neurobiology during the menopause. Prim. Care Update Ob. Gyns. 7, 21–223.

Romano, S., Judge, R., Dillon, J., Schuler, C., Sundell, K., 1999. The role of Fluoxetine in the treatment of premenstrual dysphoric disorder. Clin. Ther. 21, 615–633.

Roussouw, J.E., Anderson, G.L., Prentice, R.L., La Croix, A.Z., Kooperberg, C., Stefanick, M.L., Jackson, R.D., Beresford, S.A., Howard, B.V., Johnson, K.C., Kotchen, J.M., Ockene, J., Writing Group for the Women's Health Initiative Investigators, 2002. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 288, 321–333.

Rubinow, D.R., 1992. The premenstrual syndrome: new views. J. Am. Med. Assoc. 268, 1908–1912.

Rubinow, D.R., Schmidt, P.J., Roca, C.A., 1998. Estrogen–serotonin interactions: implications for affective regulation. Biol. Psychiatry 44, 839–850.

Schmidt, P.J., Nieman, L.K., Grover, G.N., Muller, K.L., Merriam, G.R., Rubinow, D.R., 1991. Lack of effect of induced menses on symptoms in women with premenstrual syndrome. N. Engl. J. Med. 324, 1171–1179.

Schmidt, P.J., Nieman, L.K., Danaceau, M.A., Adams, L.F., Rubinow, D.R., 1998. Differential behavioral effects of gonadal steroids in women with and in those without premenstrual syndrome. N. Engl. J. Med. 338, 209–216.

Schmidt, P.J., Nieman, L., Danaceau, M.A., Tobin, M.B., Roca, C.A., Murphy, J.H., Rubinow, D.R., 2000. Estrogen replacement in perimenopause-related depression: a preliminary report. Am. J. Obstet. Gynecol. 183, 414–420.

Seligman, M.E.P., Maier, S.F., 1967. Failure to escape traumatic shock. J. Comp. Psychol. 74, 1–9.

Seligman, M.E.P., 1975. Helplessness. Freeman, San Francisco.

Seligman, M.E.P., 1997. Learned helplessness as a model of depression. Comment and integration. J. Abnorm. Psychol. 87, 165–179.

Servatius, R.J., Shors, T.J., 1994. Exposure to inescapable stress persistently facilitates associative and nonassociative learning in rats. Behav. Neurosci. 108, 1101–1106.

Shors, T.J., Weiss, C., Thompson, R.F., 1992. Stress-induced facilitation of classical conditioning. Science 257, 537–539.

Shors, T.J., 1998. Stress and sex effects on associative learning: for better or for worse. Neuroscientist 4, 353–364.

Shors, T.J., Lewczyk, C., Paczynski, M., Mathew, P.R., Pickett, J., 1998. Stages of estrous mediate the stress-induced impairment of associative learning in the male rat. Neuroreport 9, 419–423.

Shors, T.J., Pickett, J., Wood, G.E., Paczynski, M., 1999. Acute stress enhances estrogen levels in the female rat. Stress 3, 163–171.

Shors, T.J., 2000. Acute stress rapidly and persistently enhances classical conditioning in the male rat. Neurobiol. Learn. Mem. 74, 1–20.

Shors, T.J., Beylin, A.V., Wood, G.E., Gould, E., 2000. The modulation of Pavlovian memory. Behav. Brain Res. 110, 39–52.

Shughrue, P.J., Lane, M.V., Merchenthaler, I., 1997. Comparative

distribution of estrogen receptor-α and -β mRNA in the rat central nervous system. J. Comp. Neurol. 388, 5007–5025.

Sichel, D.A., Cohen, L.S., Robertson, L.M., Ruttenberg, A., Rosenbaum, J.F., 1995. Prophylactic estrogen in recurrent postpartum affective disorder. Biol. Psychiatry 38, 814–818.

Sonnenberg, C.M., Beekman, A.T., Deeg, D.J., Tilburg, W., 2000. Sex-differences in late-life depression. Acta Psychiatr. Scand. 101, 286–292.

Steege, J.F., Stout, A.L., Knight, D.L., Nemeroff, C.B., 1992. Reduced platelet tritium-labeled imipramine binding sites in women with premenstrual syndrome. Am. J. Obstet. Gynecol. 167, 168–172.

Steenbergen, H.L., Heinsbroek, R.P.M., van Hest, A., van de Poll, N.E., 1990. Sex dependent effects of inescapable shock administration on shuttle-box escape performance and elevated plus maze behavior. Physiol. Behav. 48, 571–576.

Weiss, J.M., Glazer, H.I., 1975. Effects of acute exposure to stressors on subsequent avoidance–escape behavior. Psychosom. Med. 37, 499–521.

Willner, P., 1990. Animal models of depression: an overview. Pharmacol. Ther. 45, 425–455.

Wood, G.E., Shors, T.J., 1998. Stress facilitates classical conditioning in males but impairs conditioning in females through activational influences of ovarian hormones. Proc. Natl. Acad. Sci. 95, 4066–4071.

Wood, G.E., Beylin, A.V., Shors, T.J., 2000. The contribution of reproductive and adrenal hormones to the sexually-opposed effects of stress on trace conditioning. Behav. Neurosci. 115, 1–13.