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Sex Differences and Stress Response of WKY Rats

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PARÉ, W. P. AND E. REDEI. *Sex differences and stress response in WKY rats.* PHYSIOL BEHAV **54**(6) 1179–1185, 1993.— Wistar Kyoto (WKY), Fischer-344 (F-344), and Wistar male and female rats during either proestrus-estrus or diestrus phases of the estrus cycle were exposed to the ulcerogenic procedure of water restraint. Both male and female WKY rats revealed significantly more stomach ulcers as compared to Wistar and F-344 rats of the same sex. No persistent sex difference was observed, but ulcer severity was more pronounced during the proestrus-estrus phase as compared to the diestrus phase of the estrus cycle particularly in WKY female rats. In the second study, WKY females were observed as more active in the open-field test (OFT), but more immobile in the forced swim test (FST), as compared to WKY male rats. In addition, proestrus-estrus WKY females were less active in the OFT and significantly more immobile in the FST as compared to diestrus females. Thus, proestrus-estrus WKY females were judged as more emotional in the OFT and as exhibiting more signs of behavioral depression according to the FST. These studies suggest that the steroid hormone milieu in WKY rats may be responsible for these behavioral changes as well as the stress responsiveness in this stress-susceptible rat strain.

Stress Ulcer Rat WKY Open-field test Forced swim test Estrus cycle Sex differences Behavioral depression

SEX differences in various behavioral paradigms have previously been observed. Female rats generally exhibit superior performance in a variety of active avoidance tasks (10,16,24,59). Female rats are also more active in the open-field test (24,40,63) and, consequently, are judged as less emotional. Because these behavioral tests represent stressful situations (52,53,65), these data would suggest that female rats are less vulnerable to the effects of stressors as compared to male rats. In contrast, sex-related mood disorders are more prevalent in women than in men (18,67).

In the experimental stress literature, the results are not always consistent. The application of ulcerogenic procedures do not provide results that reflect a specific sex-dependent vulnerability to stress ulceration. Male rats develop more stomach ulcers after being subjected to conflict stress (55), whereas female rats are more vulnerable to restraint-induced ulcer (3,20,27,35,50,58,61) and activity-stress ulcer (46). The human clinical literature suggests that gastrointestinal ulceration was more prevalent in women at the beginning of this century (30). Some studies have reported that this difference has diminished in contemporary Western countries (34), but other studies have noted that ulcer incidence depends on the particular country studied (62).

The inconsistencies in the animal stress-ulcer literature may be attributable to three factors. First, different ulcerogenic stressor techniques have been used and, consequently, the results are difficult to compare. Second, different rat strains have been used. Finally, the gender differences may not have emerged because the estrus cycle status of the female rats was ignored and, consequently, not considered as a contributing factor regarding sex differences in stress reactivity.

We have reported that differences in stress-ulcer vulnerability may depend, in part, on the rat strain (44) and that Wistar Kyoto (WKY) rats, in particular, are more susceptible to restraint-induced stress ulcer (42,43). Sex differences in ulcer vulnerability within WKY rats have not been reported, and the one study which did compare male and female rats (42) did not determine the estrus cycle phase of the female rats and, consequently, this study is subject to the same criticisms outlined above.

The present paper reports on two studies that addressed sex and strain differences to certain environmental stressors. In the first study, strain and sex differences in stress-ulcer vulnerability was evaluated, and the estrus status of female rats was taken into consideration. WKY rats were compared to Fischer-344 (F-344) and Wistar rats. These two strains were selected for comparison purposes because we had previously observed that Wistar rats were resistant to stress ulcer and F-344 rats were more susceptible to stress-induced gastric ulcer. In the second study, the effect of gender and phase of estrus cycle on stress reactivity was further evaluated in WKY rats employing two behavioral tests that involved relatively mild stressors.

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EXPERIMENT 1

Method

Subjects. This study used 119 rats. These consisted of 30 male rats and 89 female rats. The male rats included 10 Wistar, 10 F-344, and 10 WKY rats. The female rats included 30 Wistar, 30 F-344, and 29 WKY rats. The F-344 and Wistar rats were acquired from Charles Rivers (Kingston, NY). The WKY rats were bred in our colony from breeding stock obtained from Taconic Farms (Germantown, NY) and represented first-generation animals. Rats were 70–86 days old at the beginning of the study. Animals were housed in our animal facility with ad lib food and water and daylight conditions maintained artificially between 0600 and 1800 h.

Apparatus. The immobilization-stress technique utilized a device fabricated from PVC tubing 23 cm long and 7.7 cm in diameter (inside dimensions). These tubes had four rows of 1 cm holes drilled along the length of the tube. Once the animal was in the tube, it was closed with a piece of 5 mm hardware cloth at one end and two bolts at the other end. The tube, containing the rat, was placed in 18.5°C water and suspended so that the water surface was level with the rat's neck.

Procedure. The estrus cycle of all female rats was determined by taking daily vaginal smears for at least 14 days. Eleven female rats were discarded because their cycle was not predictable. On their last cycle, female rats were exposed to the water-restraint ulcerogenic procedure during either diestrus, proestrus-estrus, or metestrus. Because rats were smeared in the late morning for a stressor intervention that would take place 20 h later, rats starting to exhibit proestrus smears were included in a group designated as proestrus-estrus. After analyzing the data, we combined the diestrus and metestrus groups because they failed to show any significant differences between any of the dependent variables. Therefore, the diestrus group designation included rats in metestrus as well as diestrus. Once a female had been assigned to an estrus cycle group, it was then scheduled for the water-restraint procedure. Both male and female rats scheduled for restraint had food removed from their cages at 1100 h. Drinking water was always available. The next day, at 0700 h, the rats were individually inserted into the PVC tubes and these were placed in the water for 2 h. After the 2-h water-restraint period, the rats were released and returned to their home cages for a 2-h postrestraint rest period. After the rest period, rats were sacrificed with carbon dioxide. The stomach was immediately removed and cut along the greater curvature. It was rinse with water, spread and pinned, and covered with 10% formalin to fix the stomach in a flat attitude. The stomach was examined with a binocular microscope. One eyepiece of the scope was fitted with a reticle permitting ulcers to be measured in terms of millimeters of ulcerated tissue. Most ulcers were oblong in configuration. Thus, the cumulative length of all ulcers, in millimeters, for each subject was recorded and this cumulative score represented the measure of ulcer severity. All stomachs were inspected by a technician who was unaware of the rat's strain.

Results

The ulcer data are illustrated by Fig. 1. For the initial data analysis the estrus cycle condition was collapsed within each rat strain. An analysis of these data revealed that male and female rats did not differ from one another with respect to ulcer severity, $F(1, 114) = 0.25$. However, ulcer severity scores were significantly different between strains, $F(2, 114) = 23.60$, $p < 0.01$, and this difference was attributable to the greater ulcer scores of WKY rats as compared to the other two strains, Tukey HSD test, $p < 0.05$. WKY female rats also had significantly more ulcers as compared to F-344 and Wistar female rats, $F(2, 83) = 24.68$, $p < 0.01$. When the data for female rats was analyzed with estrus phase as a factor, we noted that proestrus-estrus females had more ulcers as compared to diestrus females, $F(1, 83) = 4.89$, $p < 0.05$, but, within strain, this estrus cycle difference was significant only for the WKY rats, Tukey HSD test, $p < 0.05$. As noted above, the mean ulcer score for female WKY rats (30.75 mm) was not significantly greater than the mean ulcer score for male WKY rats (28.61 mm). Even the higher mean ulcer score for proestrus-estrus female WKY rats (35.16 mm) was not significantly greater than the mean WKY male score.

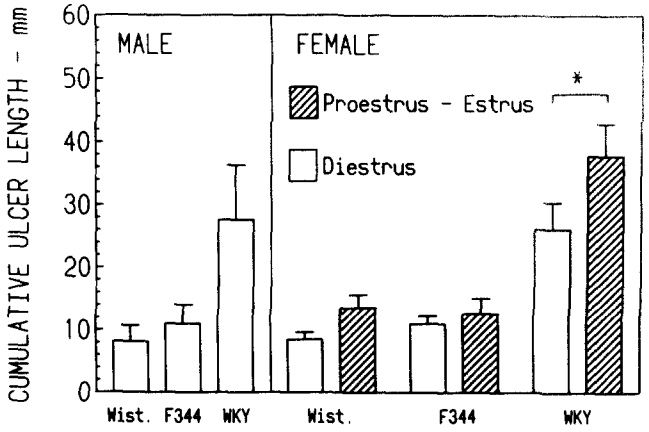

FIG. 1. Mean (±SE) cumulative ulcer length (mm) for Wistar, Fischer-344, and WKY male and female rats. Female rats were tested during either proestrus-estrus or the diestrus phases of the estrus cycle. *$p < 0.05$.

WKY rats developed significantly more ulcers as compared to Wistar and F-344 rats. These data confirmed our earlier observations (43,44), as well as reports from other laboratories (9,56,57). There were no sex differences, but the proestrus-estrus females were more vulnerable to stress ulcer. However, this vulnerability to stress ulcer by proestrus-estrus females was significant only with WKY female rats. These data imply that there are at least two risk factors for stress ulcer. One is the WKY strain characteristic, and the other is the proestrus-estrus period of the estrus cycle for the WKY female rats. Apparently the WKY proestrus-estrus female rat is hyperresponsive to stress stimulation. To further delineate this vulnerability, we questioned whether there were other behavioral characteristics of the WKY proestrus-estrus female rat, which either were associated with or contributed to their hyperresponsiveness to stress. Our previous work with male rats (43) revealed that WKY rats were more active in the open-field test (OFT) and quite immobile in the forced swim test (FST). The OFT behaviors have been proposed as major indices of emotional reactivity (2,7,29,51). Similarly, the FST is considered as one of the more valid animal models of behavioral depression (68,69). Given that WKY male rats are more emotionally reactive and behaviorally depressed as compared to other rat strains, was it possible that these behavioral characteristics also contributed the WKY proestrus-estrus female rat's hyperresponsiveness to stress? In the second study we tested the hypothesis that WKY proestrus-estrus females, as compared to WKY diestrus females, would be judged as more emotionally reactive in the OFT and more behaviorally depressed in the FST. To investigate this hypothesis, male WKY rats, as well as proestrus-estrus and diestrus females WKY rats, were exposed to the OFT and the FST.

EXPERIMENT 2

Method

Subjects. Twenty female and 12 male WKY rats (86–100 days old) were used in this study. The animal source and the housing conditions were described in Experiment 1.

Apparatus. The open-field test (OFT) arena was designed after the unit described by Broadhurst (14). The arena was round with a diameter of 82 cm. The circular wall was 30-cm high and was constructed of aluminum sheeting. The arena was situated on a plywood floor. The floor and the wall were painted with black enamel paint. The arena was divided by three concentric circles. The smallest inner circle had a diameter of 20 cm; the second circle had a diameter of 50 cm, and the outside circle was defined by the arena wall. The number of areas in the inner, middle, and outer circles were 1, 6, and 12, respectively. A ceiling light was situated 132 cm above the arena floor. Five 100-watt bulbs were mounted in the ceiling. Cheese cloth was draped from the ceiling and dropped outside the arena wall. The cloth served to diffuse the light and function as a one-way vision screen.

The forced-swim test (FST) was adapted from the procedure reported by Porsolt and his colleagues (48,49). This consisted of a large water tank which was 30 cm in diameter and 45 cm tall. The water level was 15 cm from the top. Water temperature was maintained at 25°C.

Procedure. Vaginal smears were obtained daily at 0800 h from 20 female WKY rats for at least 20 days and cycles determined. The cycle phases were determined as proestrus (i.e., beginning), estrus, metestrus, and diestrus. However, because the tests were performed in the morning and not the afternoon, determination of true proestrus was not possible. After analysis, data for proestrus and estrus, as well as diestrus and metestrus, were collapsed into two major phases because there were no differences between proestrus and estrus, nor between metestrus and diestrus. Half of the proestrus-estrus females were exposed to the OFT at 1000 h and the FST at 1400 h, whereas the other half received the FST at 1000 h and the OFT at 1400 h. This same counterbalanced procedure was also applied to the diestrus females and the male WKY rats.

For the OFT, the rat was placed in the inner circle. Three behaviors were measured: latency (in s) to leave the inner circle, number of field segments entered, and the number of rearings. The OFT lasted 5 min, after which the rat was returned to its home cage. The arena was washed with soap and water after each individual trial.

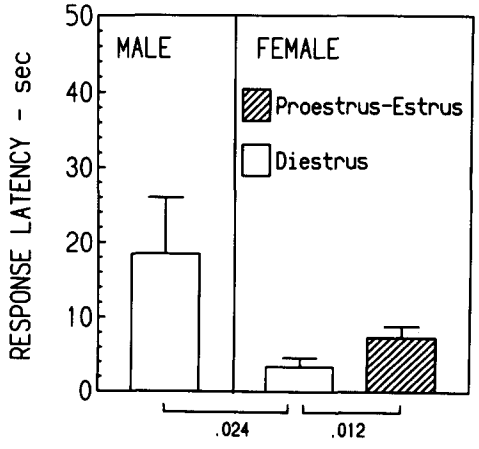

FIG. 2. Mean (±SE) response latency scores from the open field test for male and proestrus-estrus or diestrus female WKY rats. Differences between groups are indicated by the *p*-values below the x axis.

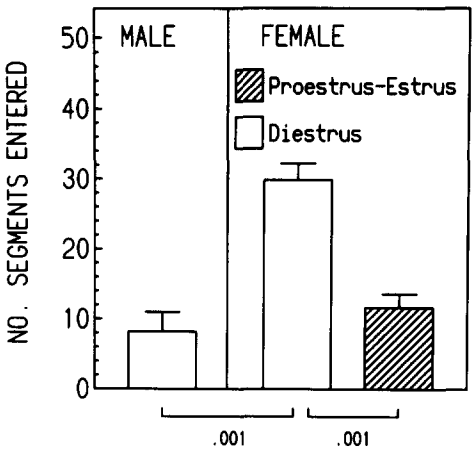

FIG. 3. Mean (±SE) number of floor segments crossed in the open-field test for male and proestrus-estrus or diestrus WKY female rats. Significant differences between groups are identified by the *p*-values below the x axis.

For the FST rats were individually placed in the water tank and three behaviors were recorded. These included time (in s) spent floating, time spent struggling, and the number of bobbings. These were defined as follows: floating—motionless without moving front or rear legs; struggling—vigorously breaking the water surface with head and forepaws; bobbing—paddling with forepaws and/or rear paws with head moving above and below water surface. Animals remained in the water tank for 15 min during which time these three behaviors were recorded. To determine if significant differences occurred between male and female rats, with regard to any of the dependent variables, the estrus cycle condition was collapsed for female rats and a simple *t*-test was conducted between male and female rats. To further probe the source of other group differences, *t*-tests were conducted between all three groups.

Results

The a.m. data for each dependent variable was compared with its p.m. counterpart, and no significant differences emerged, thereby indicating that a sequence effect was not a factor in this study. Therefore, the a.m. and the p.m. data were pooled for each dependent variable.

Female rats had significantly shorter response latency scores as compared to male rats, $t(30) = 2.63$, $p < 0.013$, and the response time of proestrus-estrus females was significantly slower than diestrus females, $t(18) = 2.59$, $p < 0.012$. These data are illustrated by Fig. 2. Female rats were also more active in the OFT as compared to male rats, $t(30) = 4.04$, $p < 0.001$, but this difference was attributable to the significantly greater activity of the diestrus females as compared to the male rats, $t(20) = 7.73$ $p < 0.001$. Proestrus-estrus females were not more active than males. These data are shown in Fig. 3. This affinity for greater activity in the OFT by female rats was also reflected by the significantly greater number of rearing behaviors by female rats as compared to males, $t(30) = 3.20$, $p < 0.003$. As Fig. 4 reveals, diestrus female emitted more rearing responses than proestrus-estrus females, but this difference was not significant. If emotionality in the OFT is operationally defined in terms of high latency scores and low activity scores (2,7,29,51), then these

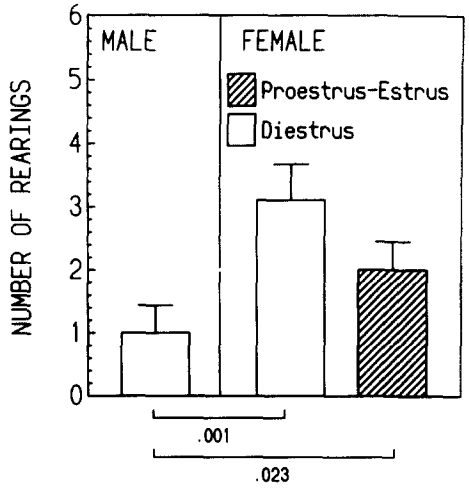

FIG. 4. Mean (±SE) number of rearing responses in the open field test for male and proestrus-estrus or diestrus WKY female rats. Significant differences between groups are identified by the *p*-values below the x axis.

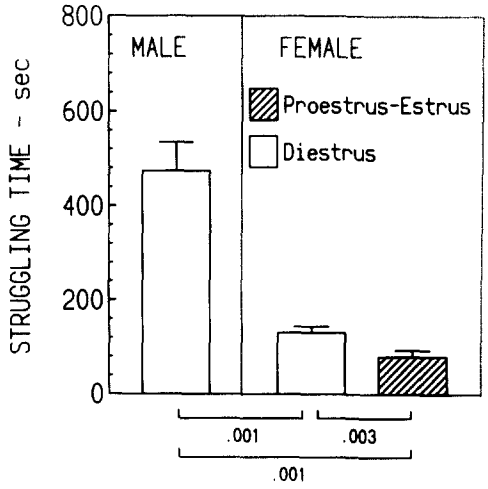

FIG. 6. Mean (±SE) struggling time (s) in the forced swim testfor male and proestrus-estrus or diestrus WKY female rats. Significant differences between groups are identified by the *p*-values below the x axis.

data indicate that male WKY rats were more emotional than females, and that proestrus-estrus females were more emotional than diestrus females.

Female rats were significantly more immobile in the FST. As Fig. 5 indicates, floating time scores were significantly greater for female rats, $t(30) = 6.50$, $p < 0.001$, and the floating scores were significantly greater for proestrus-estrus females as compared to diestrus rats, $t(18) = 3.43$, $p < 0.005$. Female rats spent significantly less time struggling (see Fig. 6), $t(30) = 6.46$, $p < 0.001$, and proestrus females struggled significantly less than diestrus females, $t(18) = 3.21$, $p < 0.003$. In addition, significantly fewer bobbing responses were recorded for female rats, $t(30) = 4.90$, $p < 0.001$, and proestrus-estrus females had fewer bobbing responses as compared to diestrus females, but this difference was not significant. These data are illustrated by Fig. 7. In summary, female rats were significantly more immobile in the FST and when females were compared, on the basis of estrus cycle phase, the proestrus-estrus females were more immobile as compared to diestrus females.

GENERAL DISCUSSION

The first study demonstrated that WKY rats were more ulcer prone than F-344 or Wistar rats, and that ulcer vulnerability for WKY female rats was greater in proestrus-estrus as compared to diestrus females. In the second study, emotionality was operationally defined in terms of the OFT behaviors and behavioral depression was operationally defined by the behaviors in the FST. According to these two behavioral tests, WKY proestrus-estrus females were judged as more emotionally reactive and more behaviorally depressed as compared to WKY diestrus fe-

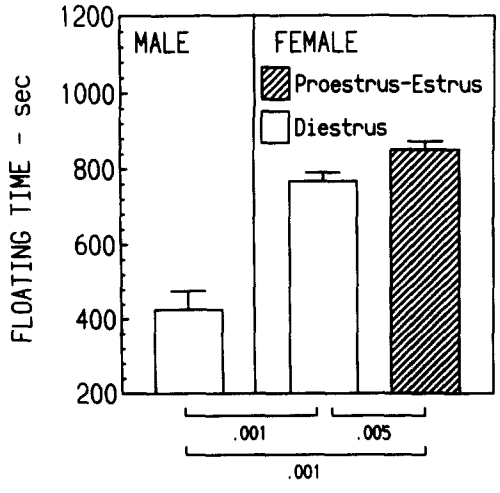

FIG. 5. Mean (±SE) floating time (s) scores in the forced swim test for male and proestrus-estrus and diestrus WKY female rats. Significant differences between groups are identified by the *p*-values below the x axis.

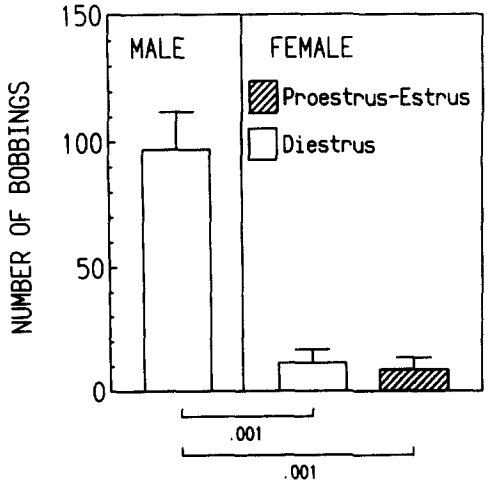

FIG. 7. Mean (±SE) number of bobbing responses in the forced swim test for male and proestrus or diestrus WKY female rats. Significant differences between groups are identified by the *p*-values below the x axis.

males. We recognize that these behavioral characterizations have theoretical limitations, but these data, nevertheless, support our earlier reports wherein WKY males, as compared to F-344, Wistar, and spontaneously hypertensive rats (SHR), were shown to be ulcer prone and also judged as more emotional in the OFT (43) and more depressed according to the FST (43,45). Hence, a similar relationship has been revealed for female WKY proestrus-estrus rats. Consequently, we can reasonably consider that the emotional reactivity and behavioral depression are related to the greater stress response of WKY female rats during proestrus-estrus.

The data from these two studies can also be evaluated on the basis of sex differences and hormonal mechanisms. There are sex differences in a number of nonsexual behaviors that are either organizationally programmed early in development (33) or are activated by steroids in adulthood; some of these behaviors are influenced both organizationally and activationally. Among these are rotational behavior (12), food intake (64), locomotion (28), and reactivity to foot shock (11,19). However, the organizational and activational effects of sex steroids on stress-related behavior are not at all clear. On the one hand, ovarian hormones have been shown to modulate the impact of stressors on endogenous pain inhibition (53), whereas sex differences in adaptation to chronic restraint stress have been reported to be independent of the estrus cycle (31). These reports would suggest that sex differences in the response to stress may be dependent on either organizational or activational factors, or both.

In Experiment 1 WKY rats were more susceptible to restraint-induced stress ulcer. There were no significant sex differences, but WKY proestrus-estrus female rats had significantly more ulcers than WKY diestrus females. Our data support the assertion by other investigators (6,32,37,38,60) that the female gonadal hormone milieu does influence susceptibility to stress ulcer and suggest that ulceration, as a response to stress, is not controlled by organizational factors but does respond to activation by circulating gonadal steroids.

In Experiment 2 we hypothesized that sex differences would emerge if WKY rats were exposed to other mild stress-inducing behavioral tests such as the OFT and FST. Indeed, we found that female WKY rats were more active in the OFT—an observation that concurs with similar studies in other rat strains (8,22,23,25,39,41,64). But what is new about the present data is the fact that reactivity to the OFT was contingent not only on sex but on the estrus status of the female WKY rat. The data indicated that emotionality was associated with the proestrus-estrus period in the WKY rat. This agrees with the previous report by Diaz-Veliz, and colleagues (17), that hyperactivity of female Sprague-Dawley rats in the open field occurs during diestrus as compared to proestrus and estrus. Thus, the OFT is organizationally programmed according to sex and also modulated by cyclical changes in ovarian hormones.

Because female rats are more active in the OFT, we might expect, if we disregard estrus stages, similarly high levels of activity in the FST by female rats. Indeed, some investigators have reported that female rats are more active than male rats in the FST (22,23). Accordingly, when the OFT and FST are compared, one assumption is that high activity in the OFT will lead to high activity in the FST (1,4,5). However, our data did not support that assumption, if the data were compared only on the basis of sex. Female rats were more active in the OFT but female rats were also more immobile in the FST as compared to male rats. This suggested that activity in one test is not necessarily predictive of activity in the other test, and that the two test were relatively independent. Support for this assertion is found from studies where antidepressant drugs produced different outcomes in the OFT and the FST (10,13,47). Electric foot shock also modifies the two behaviors in different ways (4,5,36,67). These studies imply that OFT and FST behaviors are controlled by different mechanisms. When Alonso and his colleagues studied both the OFT and the FST, they found that the two procedures were not correlated (4,5). However, if our data are analyzed, not on the basis of gender alone, but considering the phase of the estrus cycle, we noted that proestrus-estrus females, which were less active in the OFT, were also less active in the FST. Proestrus-estrus females, as compared to diestrus females, were judged as more emotional in the OFT and more depressed in the FST. Thus, if we extend our organizational-activational analysis to the FST, we can propose that behavioral differences in this test can be attributed to both organizationally programmed factors and activated by circulating ovarian hormones associated with estrus.

Proestrus-estrus WKY rats had more ulcers and were more depressed according to the FST scores. These data would imply that proestrus-estrus WKY rats were more reactive to acute stress stimulation as compared to diestrus females or males. Other investigators (31,59) have suggested that male rats, as compared to female rats, are more vulnerable to acute stress, but these studies did not use the stress-responsive WKY rat. Our data with this stress-vulnerable strain may well reflect the human clinical picture wherein women, probably genetically predisposed, have a higher risk for depression (18,67). We suggest that questions pertaining to sex differences in reactivity to stress will yield answers if genetic or strain factors are taken into consideration. In addition, sex differences in reactivity to stress cannot be adequately addressed unless estrus cycle phases are identified.

In these studies we have observed a) greater susceptibility to stress ulcer in WKY rats as compared to F-344 and Wistar rats; b) greater ulcer susceptibility in proestrus-estrus female rats, and this relationship was significant in WKY female rats; and c) higher emotionality and depression in proestrus-estrus, as compared to diestrus, WKY female rats. Therefore, we propose that attempts to define the organism's response to stress is best accomplished with a model such as the stress-susceptible WKY rat, and that the greater vulnerability of the proestrus-estrus WKY female rat indicates that the steroid hormone milieu may be responsible for these behavioral sex differences in addition to the ones programmed in early development.

ACKNOWLEDGEMENTS

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