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The Pituitary-Adrenocortical System Is Not Involved in the Sex Difference in Passive Avoidance

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HEINSBROEK, R. P. W., H. G. VAN OYEN AND N. E. VAN DE POLL. *The pituitary-adrenocortical system is not involved in the sex difference in passive avoidance.* PHARMACOL BIOCHEM BEHAV **20**(5) 663–668, 1984.—The hypothesis that sex differences in passive avoidance are related to the sex difference in the pituitary-adrenocortical system was studied. A high dose of dexamethasone (500 microg/kg body weight) was injected in male and female rats in order to suppress the activity of the pituitary-adrenocortical system. Dexamethasone treated animals and controls were tested for retention of passive avoidance at one of 4 different intervals after punishment. The percentage of females re-entering the compartment in which they were previously shocked was significantly higher than the percentage of males, after a retention interval of 60 minutes, but not after an interval of 0 minutes or 15 minutes (Experiment 1). Dexamethasone did not affect this pattern of sex differences. The same sex difference was found after an interval of 24 hours (Experiment 2), and again dexamethasone had no effect on it. However, in males a state-dependent effect of dexamethasone treatment was found in Experiment 2 when animals were given two injections of either dexamethasone or saline, one before the learning trial and one before the retention trial. Within the groups of males given two different injections (Dex-Sal and Sal-Dex) a higher percentage re-entered the shock compartment, when compared with the groups of males given the same injection twice (Sal-Sal and Dex-Dex). Conclusions: (1) A sex difference in passive avoidance apparently occurs after a certain interval during which the animals are not disturbed. (2) This sex difference does not depend on the integrity of the pituitary-adrenocortical system. (3) State-dependency was observed in males only, indicating that changes in the pituitary-adrenocortical system, as a consequence of dexamethasone treatment, may have a more important stimulus value in males.

Passive avoidance Sex differences Dexamethasone

A reliable sex difference has been found, when rats were tested for the passive avoidance of a compartment in which they were shocked 24 hours before. Compared to females, males consistently showed more suppression of the previously punished entry-response [8, 10, 20, 25, 26]. The manifestation of this sex difference has been found to be less consistent when shorter intervals between punishment and retention testing were used. Drago *et al.* [10] found longer response latencies in males for entering a dark compartment in which the animals were previously shocked when they used retention intervals as short as 30 minutes, but no sex difference was apparent when the animals were tested 1 minute after the learning trial. When tested directly upon shock presentation, however, male rats avoided the shock compartment more than female rats [26]. The results of other punishment procedures using short retention intervals are equally inconsistent concerning the occurrence of sex differences. When retesting male and female rats 1 hour after punishment of a food rewarded approach response, Beatty *et al.* [4] found stronger response inhibition of males. When, however, the tendency to emit a drink-response was measured immediately after the punishment of this response, females were found to show more inhibition [28]. On the whole, the literature on sex differences in passive avoidance offers a rather confusing picture as far as short intervals after punishment are concerned.

The performance of rats in an avoidance situation is influenced by the time intervals which elapse between original avoidance learning and retesting [14, 15, 16, 23]. It has been suggested that the effect of the duration of the retention interval could be related to the activity of the pituitary-adrenocortical system in response to the stress of the original training [5, 13, 18]. Hormones of the pituitary-adrenocortical system indeed affect active as well as passive avoidance behaviour [9] and it is plausible that changes in hormonal concentrations as a consequence of the stress of original training result in differences in performance at different retention intervals. The activity and reactivity of the pituitary-adrenocortical system is quite different in male and female rats. Females have a larger pituitary and a larger adrenal, a greater output of ACTH and corticosterone and a faster turnover of corticosterone [6,12]. Therefore, the occurrence and the direction of sex differences in passive avoidance at different retention intervals may very well be related to sex

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differences in the reactivity of the pituitary-adrenocortical system. Scouten and Beatty [22] and also Heinsbroek *et al.* (submitted) investigated whether or not the sex difference in the activity of the pituitary-adrenocortical system could explain the observed female superiority in active avoidance. These experiments yielded negative results, i.e., the sex difference in active avoidance was found not to be abolished by pharmacological suppression of this system by means of dexamethasone administration. The synthetic glucocorticoid dexamethasone is a very potent blocker of the ACTH release from the pituitary thereby completely suppressing the activity of the pituitary-adrenocortical system ([2, 3, 7] Heinsbroek *et al.*, submitted).

In the present experiment we used dexamethasone to investigate the putative role of the pituitary-adrenocortical system in the manifestation of sex differences in passive avoidance. It was hypothesized that, if complete suppression of the activity of the pituitary-adrenocortical system would lead to the disappearance of sex differences in passive avoidance, found at one or more intervals after punishment, the involvement of this hormone system in sex differences in passive avoidance would be established. If, however, suppression of the activity of the pituitary-adrenocortical system would not result in the disappearance of the sex differences, other factors have to be involved in the occurrence of this phenomenon. The effects of dexamethasone treatment on the sex difference in passive avoidance procedures were studied in a step-through passive avoidance situation using 3 retention intervals, i.e., immediately after shock presentation, 15 minutes or 60 minutes after shock presentation. Dexamethasone suppresses the ACTH release from the pituitary for a period of 2–6 hours after subcutaneous injection [21]. Therefore, one injection of dexamethasone 3 hours before the experimental session, would have been sufficient to inhibit the activity of the pituitary-adrenocortical system during both the learning and the retention trial.

EXPERIMENT 1

METHOD

Subjects

Ninety male and 90 female naive Wistar rats were obtained from the Animal Supply House, TNO in Zeist (The Netherlands). The animals were approximately 12 weeks old at the start of experimentation. The average weight of the males was 273 g, the females weighed 184 g. All subjects were housed in a single-sex group of 6 animals per cage. Each one of the 6 experimental or control groups was represented in one cage. Lights were on from 8.15 a.m. till 20.15 p.m. Water and food were available ad lib. The animals were handled daily, beginning one week before the start of the experiment.

Apparatus

The apparatus used has been described in detail elsewhere [1]. It consisted of a cubical dark compartment (40 cm per side) from which an elevated runway of 25 cm protruded. This runway was illuminated by a 25 W lamp and was connected to the dark compartment via a square opening of 64 cm^2. Scrambled footshocks were delivered from Grason Stadler shock generators (model 700) through the grid floor in the dark compartment.

Procedure

On Day 1 each animal was adapted to the dark compartment for 2 minutes. Subsequently one adaptation trial was run, in which the animal was placed on the runway with its back to the dark compartment. Latency for entering the dark compartment was measured. The animal was allowed to stay in the dark compartment for about 10 seconds. On Day 2 three adaptation trials were run at intervals of 30–45 minutes. After entering the dark compartment on the third trial a guillotine door was lowered and a footshock of 1.0 mA was delivered through the grid floor for 2 seconds. Animals were replaced on the runway after one of the following intervals: immediately after (0 minutes), 15 minutes or 60 minutes after the shock. Each animal was allowed a maximum of 300 seconds on the runway before the retention trial was ended. All animals were housed in individual cages during the interval of testing. All tests were run during the first hours of the animals' light period.

Hormonal Treatment

Three hours before the shock trial, animals were subcutaneously injected with dexamethasone (500 microg/kg body weight) or its equivalent volume of saline. This dose is approximately 3 times the dose used in a comparable experiment in which suppression of the corticosterone level in male rats was found for a period of 2–6 hours after injection [21] and equal to the dose used in the experiment of Heinsbroek *et al.* (submitted). Compared to the experiment of Pappas and Gray [21], a substantially higher dose of dexamethasone was used because female rats were also included in the present experiment. Dexamethasone phosphate was delivered in capsules of 4 mg/ml (Decadron, Merck) and diluted to 1 mg/ml with saline. Animals were weighed after testing on Day 1 and Day 2 and on Day 3.

RESULTS

Table 1 shows the number of animals entering the dark compartment within the maximum test duration (300 seconds), and the median and range of their latencies, for the shock trial and the retention trial. Entering latencies of females were shorter than those of males at the shock trial (Mann Whitney: $z=-3.40$; $p<0.001$). The retention data were dichotomized based on whether or not subjects entered the dark compartment within the maximum test duration. These dichotomized data were subjected to a three-way analysis of variance [19] involving the factors "sex," "treatment" and "retention interval." Only the factor "sex" was significant, a lower number of males entering the dark compartment, $F(1,168)=5.18$, $p<0.05$. Subsequent analysis of the separated retention intervals using a two-way analysis of variance with "sex" and "treatment" as main factors revealed that this sex difference was only significant at the 60 minutes interval, $F(1,56)=4.61$, $p<0.05$. No effect of dexamethasone treatment nor any interaction involving this factor were found to be significant.

Body weight on the second and third day is expressed as a percentage of the body weight on Day 1. Dexamethasone treatment resulted in a considerable loss of body weight in both males and females. On Day 2, when animals were weighed 7 hours after injection average weights of the control groups were reduced 0.5%, whereas the dexamethasone-treated animals lost 3% of their body weight. Day 3 revealed a further loss of weight in the

TABLE 1

NUMBER OF ANIMALS RE-ENTERING (Nr.) WITHIN THE MAXIMUM TEST DURATION (300 SEC) AND MEDIAN AND RANGE (L) FOR THESE ANIMALS

		Males				Females			
		Sal		Dex		Sal		Dex	
		Nr.	L	Nr.	L	Nr.	L	Nr.	L
	shock-trial	45:	4 1- 58	45:	6 1- 58	45:	4 1- 25	45:	4 1- 25
retention intervals	0	9:	148 2–212	10:	20 3–160	12:	14 3–237	10:	9 1- 59
	0,25	9:	138 4–253	7	93 38–175	12:	37 3–222	10:	10 1–111
	1	9:	168 3–286	6:	80 1–255	14:	20 1–288	14:	20 1–229

All groups n=15; in the shock-trial n=45.

dexamethasone-treated groups, reaching 4% of their original weight on Day 1. Body weight of the male and female control groups showed an *increase* on the third day compared with the second day. In order to see whether these effects of treatment were equal in males and females, percentage of body weight on Day 2 and Day 3 was analyzed using a two-way analysis of variance with the factors "treatment" and "sex." As expected Day 2 and Day 3 revealed a significant effect of "treatment," $F(1,179)=104.90$, $p<0.001$ and $F(1,179)=208.72$, $p<0.001$ respectively. No interactions involving the factors "sex" and "treatment" were found, indicating that dexamethasone equally reduced body weight in males and females.

DISCUSSION

The hypothesis that sex differences in passive avoidance behaviour are related to sex differences in the activity of the pituitary-adrenocortical system was investigated in a step-through passive avoidance situation, using three different retention intervals shortly after shock presentation. Superior passive avoidance behaviour of males was only apparent when an interval of 60 minutes elapsed between shock trial and retention trial. Blocking the activity of the pituitary-adrenocortical system with a sufficient dose of dexamethasone did not affect differences in performance between males and females. This study, therefore, seems to exclude the significance of sexual dimorphism in pituitary-adrenocortical functioning for the sex difference in step-through passive avoidance learning.

EXPERIMENT 2

Whether this result could be extended to a retention interval of 24 hours was investigated in Experiment 2. It has been found that in a passive avoidance situation, the pituitary-adrenocortical system is activated both during the learning and during the retention trial [27]. Therefore a factorial design was used in which animals were injected with dexamethasone both before the learning and before the retention trial. This design permitted independent analysis of effects of dexamethasone treatment on the learning trial and on the retention trial.

METHOD

Subjects

Seventy-two male and 72 female naive Wistar rats were obtained from the Animal Supply House, TNO in Zeist (The Netherlands). The animals were nearly 15 weeks of age at the start of experimentation, average weight of the males was 394 g, and of the females 223 g. All subjects were housed in single-sex groups of 6 animals per cage. Lights were on from 12.30 p.m. till 0.30 a.m. Water and food were available ad lib. Animals were handled daily, beginning one week before experimentation.

Apparatus

The apparatus described in Experiment 1 was used.

Procedure

The same passive avoidance training as in Experiment 1 was used. After the shock trial the animals were replaced in their home cage and tested for retention after an interval of 24 hours. Tests ended after the animals had re-entered the dark compartment or after the maximum test duration of 300 seconds. All tests were conducted at the end of the dark period and the beginning of the light period.

Hormonal Treatment

Three hours before the learning trial animals were subcutaneously injected with dexamethasone in a dose equal to the one used in Experiment 1 (500 microg/kg body weight). Control animals were injected with saline.

On the next day all animals received a second injection three hours before the retention trial. Half of the dexamethasone treated group was again injected with dexamethasone (Dex-Dex), the other half was injected with a control injection of saline (Dex-Sal). The animals originally injected with saline were also divided in two groups, one receiving a dexamethasone injection (Sal-Dex), the other a

TABLE 2

NUMBER OF ANIMALS RE-ENTERING (Nr.) WITHIN THE MAXIMUM TEST DURATION (300 SEC) AND MEDIAN AND RANGE (L) FOR THESE ANIMALS

	Males								Females							
	DD		DS		SD		SS		DD		DS		SD		SS	
	Nr.	L	Nr.	L	Nr.	L	Nr.	L	Nr.	L	Nr.	L	Nr.	L	Nr.	L
shock-trial	18:	5 1– 35	18:	4 1– 84	18:	5 1– 16	18:	6 1– 21	18:	4 1– 14	18:	3 1– 20	18:	3 1– 12	18:	3 1– 9
retention trial	3:	104 7–238	8:	19 2–234	6:	36 11–287	4:	29 25–271	10:	41 3–293	11:	58 4–252	13:	50 3–299	12:	14 2–238

All groups n=18.

second injection of saline (Sal-Sal). Body weights were determined on Days 1, 2 and 3 after behavioural testing.

RESULTS

The results of this experiment are shown in Table 2. As in Experiment 1, females entered the shock compartment with shorter latencies on the shock trial than did males (Mann Whitney: $z=-3.64$; $p<0.001$).

The results obtained on the retention test were dichotomized dependent on whether or not the animals entered the dark compartment. These dichotomized data were analyzed using a three-way analysis of variance involving the factors "sex," "treatment on the shock trial" and "treatment on the retention trial." As can be seen in Table 2, more females than males re-entered the dark compartment in which they were shocked 24 hours earlier resulting in a significant effect of the factor "sex," $F(1,136)=16.12$, $p<0.01$. The factors "treatment on the shock trial" and "treatment on the retention trial" separately did not influence the number of animals re-entering within 300 seconds. The interaction between these two factors was not significant, $F(1,136)=2.09$, $p<0.25$. Separate *post hoc* analysis of males and females using a two-way analysis of variance with "treatment on the shock trial" and "treatment on the retention trial" as main factors, revealed that the interaction between these two factors was significant in males, $F(1,68)=6.67$, $p<0.05$, but not in females, $F(1,68)=0.13$, n.s. Figure 1 shows that the number of animals re-entering the dark compartment within 300 seconds in males is smaller in the Dex-Dex and Sal-Sal treated groups as compared with the Dex-Sal and Sal-Dex groups. However, differences among treatment groups were not significant, except between the Dex-Dex and Dex-Sal treated groups, $F(1,35)=5.99$, $p<0.05$. Differences between the Dex-Dex and Sal-Dex treated groups and between the Sal-Sal and the Dex-Sal treated were only marginally significant, $F(1,35)=3.50$, $p<0.10$ and $F(1,35)=3.50$, $p<0.10$ respectively.

Percentage of body weight on Day 2 and Day 3 was expressed as described in Experiment 1 and the data of Day 2 and Day 3 were analyzed using a three-way analysis of variance involving "sex," "treatment on the learning trial" and "treatment on the retention trial" as factors. Dexamethasone injected 3 hours before the learning trial (Day 2) again greatly reduced the body weight, $F(1,136)=33.00$, $p<0.001$. No interaction was found between the factor "sex" and the factor "treatment on the learning trial." The effect of dexamethasone on the body weight was therefore equally strong in males and females.

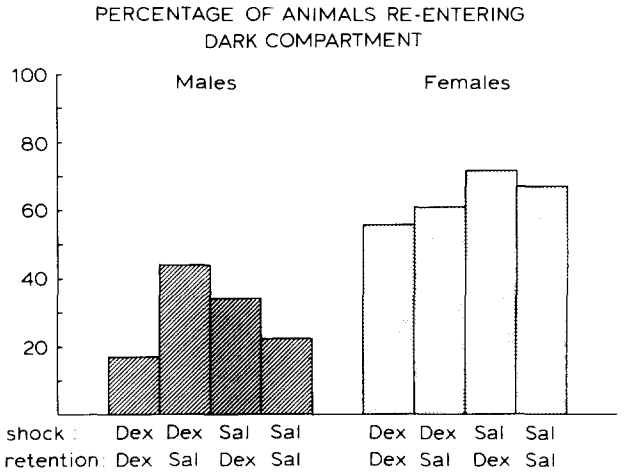

FIG. 1. Passive avoidance of a compartment in which the animals were shocked 24 hours earlier (1.0 mA, 2 sec) expressed as the percentage of animals re-entering the compartment within 300 seconds (n=18). Animals were injected with dexamethasone (500 microg/kg body weight) or physiological saline 3 hours before the shock and 3 hours before the retention trial.

Analysis of the body weight on Day 3 revealed significant effects of both treatment on the preceding Day, $F(1,136)=135.87$, $p<0.001$, and treatment on the third Day, $F(1,136)=18.71$, $p<0.001$. On Day 2 and Day 3 no significant interactions were found between the "treatment" factors and the factor "sex." Dexamethasone therefore did not have a sex dependent effect on the body weight of rats.

In both Experiments 1 and 2, however, the main factor sex did reveal significant effects. Irrespective of treatment, female rats were found to lose a larger amount of their body weight as compared with male rats. In Experiment 1 this effect was significant on Day 3, $F(1,179)=6.14$, $p<0.02$, and in Experiment 2 on Day 2, $F(1,136)=22.74$, $p<0.001$.

GENERAL DISCUSSION

The possibility of a sex difference in passive avoidance was studied after abolishment of the activity of the pituitary-adrenocortical system, using a number of different

retention intervals. In the first experiment, 3 short retention intervals after the shock were used. At the 60-minute interval, the percentage of males re-entering the shock compartment was significantly lower than the percentage of females. For the intervals immediately after the shock and 15 minutes after shock presentation, the results were in the same direction; however, sex differences were not significant. In the first experiment sex differences were not affected by dexamethasone treatment. This result was extended to an interval of 24 hours. The sex difference found in the second experiment was not influenced by dexamethasone treatment during the learning trial, nor by dexamethasone treatment during the retention trial. In conclusion, these results make it unlikely that the sex difference in the pituitary-adrenocortical system is in some way related to sex differences in passive avoidance.

In earlier experiments, in our laboratory, superior passive avoidance learning of males was found also for the short intervals (0 and 15 minutes) [26]. The discrepancy between these results and the present findings can not be explained by procedural differences, as both experiments were conducted at the same laboratory using the same highly standardized procedure. The only significant difference between the present experiment and the earlier experiment was the administration of an injection per se a few hours before testing, which could interfere with the occurrence of a sexual dimorphism. It could be suggested that in passive avoidance paradigms using retention intervals shortly after punishment, the performance of male and female rats is rather susceptible to procedural details and therefore the manifestation of sex differences in passive avoidance behaviour is variable at these intervals [4, 10, 26, 28].

In the second experiment, separate analysis of the males revealed a significant interaction between dexamethasone treatment during the learning trial and dexamethasone treatment during the retention trial. When males were given the same injection twice (Dex-Dex and Sal-Sal groups), more response suppression was observed compared with males receiving two different injections (Dex-Sal and Sal-Dex groups). This may be interpreted as a state-dependent effect, i.e., when an animal is retested under conditions equal to the conditions under which the animal acquired a certain task, its performance is better as compared with animals conditioned and retested under different conditions. Pappas and Gray [21] used the same design for dexamethasone treatment in a passive avoidance paradigm in which a drink response was punished. A retention interval of 24 hours revealed a similar effect of dexamethasone treatment as described in the present experiment, animals treated with the same substance during both the learning and the retention trial showed a stronger suppression of the drink-response.

In the present experiment no state-dependent effect of dexamethasone treatment was found in females. This finding may indicate that dexamethasone or alterations in pituitary-adrenocortical functioning as a consequence of dexamethasone treatment have a more important stimulus value in male rats as compared with female rats. Pappas and Gray [21], using male rats, did not consider sex differences in passive avoidance. Hennessy *et al.* [11], however, observed a considerably stronger correlation between the corticosterone plasma level and strength of taste aversion in males than in females, a finding which supports the hypothesis that male rats are more susceptible to differences in hormone levels of the pituitary-adrenocortical system.

The sex difference in sensitivity to the presence of hormones in the pituitary adrenocortical system may have important implications for sex differences in agonistic behaviour. While aggressive behaviour is primarily influenced by ACTH, the manifestation of submissive behaviour has been found to be related to corticosterone release and to be facilitated by the corticosterone elevation as a consequence of defeat [17]. Recent results of our laboratory clearly indicate that male rats, as compared with female rats, are more readily affected by the experience of defeat and show submissive behaviour [24]. This difference may be a consequence of the fact that males are more sensitive to the elevation of the corticosterone level that is concurrent with an experience of defeat. Taken together, it might very well be that, especially in males, the rise in adrenal hormone levels more readily affect subsequent behaviour.

An important finding of the present paper is the fact that elimination of the substantial differences in pituitary-adrenocortical hormone levels between male and female rats did not affect the sexual dimorphism in passive avoidance learning, thereby giving no support to the hypothesis that the sex difference in passive avoidance results from sex differences in pituitary-adrenocortical activity. A comparable result has been obtained in an investigation of the role of the pituitary-adrenocortical system in the sex differences in active avoidance ([22] Heinsbroek *et al.*, submitted).

The results of the present paper should encourage further investigations searching for alternative processes involved in the sexual dimorphic avoidance behaviour, and confirming the notion that male rats are more easily conditionable to alterations in hormone levels of the pituitary-adrenocortical system as compared with female rats.

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