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Voluntary Ethanol Intake of Individually- or Pair-Housed Rats: Effect of ACTH or Dexamethasone Treatment

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WEISINGER, R. S., D. A. DENTON AND P. G. OSBORNE. *Voluntary ethanol intake of individually- or pair-housed rats: Effect of ACTH or dexamethasone treatment.* PHARMACOL BIOCHEM BEHAV 33(2) 335–341, 1989.—The effect of ACTH or dexamethasone treatment on ingestion of 10% ethanol, 0.5 M NaCl and water was studied in individually- and pair-housed rats. Crowding or decreasing the amount of space per rat by increasing the number of rats per cage from 1 to 2, together with the associated increase in social interactions caused a large increase in ethanol intake. In pair-housed rats and in rats housed alone, ACTH treatment caused a large increase in Na intake but no change in ethanol intake. In pair-housed rats and in rats housed alone, dexamethasone treatment caused no change in either ethanol or Na intake. Thus, it would appear that the induction or maintenance of a high ethanol intake of rats during crowding, a presumed social stressor, can not be attributed entirely to either an increase in blood ACTH levels with the subsequent increase in glucocorticoid hormones or to a decrease in blood ACTH and natural glucocorticoid hormone levels. However, the possibility that ACTH and/or adrenocorticoid hormones, combined with other physiological or environmental factors, causes stressor-induced ethanol intake cannot be excluded.

Crowding Social stress ACTH Ethanol NaCl Drinking Isolation Group housing

STRESS may be defined as the constellation of physiological responses of an animal in response to a threatening situation. Increased ingestion of ethanol (11, 16, 17, 20, 24) and NaCl (5, 10, 22) are two of the many responses induced by a variety of stressors. Increased secretion of ACTH and subsequently, increased adrenocortical hormone levels (8, 15, 29) are usually associated with stress. It has been shown that ACTH treatment causes enhanced Na intake (6, 27, 28). The increased Na intake caused by ACTH treatment is partially (6) or completely (27,28) dependent on the adrenocortical hormones, as this enhanced appetite is partially or completely eliminated by adrenalectomy. Thus, there is evidence consistent with the possibility that ACTH or adrenocortical hormones are involved in stressor-induced Na intake. At present, however, there is conflicting evidence regarding the role of ACTH or adrenocortical hormones in stressor-induced ethanol intake. For example, it has been reported that adrenalectomy, and, presumably, the subsequent elevation in ACTH had no effect (30) or decreased (23) ethanol intake of rats. Also, administration of glucocorticoid hormones increased the ethanol intake of rats (30) but decreased the ethanol intake of mice (14).

In the first experiment, we attempted to define the NaCl/ethanol intake patterns of socially stressed rats. To this end, rats were crowded by increasing the number of rats per cage from one to two, i.e., from isolation to paired housing. With the increase in the number of rats per cage, the space per rat was decreased (from 450 to 225 cm^2) and the number of social interactions was increased. The crowding procedure used in the present experiments is a very mild stressor relative to earlier studies where crowding was defined as 6 or more rats per cage (16, 17, 20) and where space per rat was reduced to as little as 61.2 cm^2 (17). In the second, third, fourth and fifth experiments, we evaluated the effect of altering blood ACTH levels (by administration of ACTH or dexamethasone) on the NaCl/ethanol intake patterns of individual and pair-housed rats. By comparison of the results of these experiments, the role of ACTH in stressor-induced ethanol intake could be evaluated.

METHOD

Experiment 1. Crowding by Pair Housing after Individual Housing

Twenty-four naive male Sprague-Dawley rats weighing 270–400 g (90–120 days of age) at the start of the experiment were used. The animals had free access to 10% v/v ethanol, 0.5 M NaCl, water and rat chow (Clark-King GR2+, Na content 35–70 mmol/kg) during adaptation and experimental housing regimes. The liquids were available from containers hung on the front of the cage. The position of the containers was changed daily on a random basis.

After an adaptation period when rats were housed alone (14 days), the experiment began. The experiment consisted of two periods: baseline (8 days) and treatment (8 days). During the adaptation and baseline periods, the animals were housed individ-

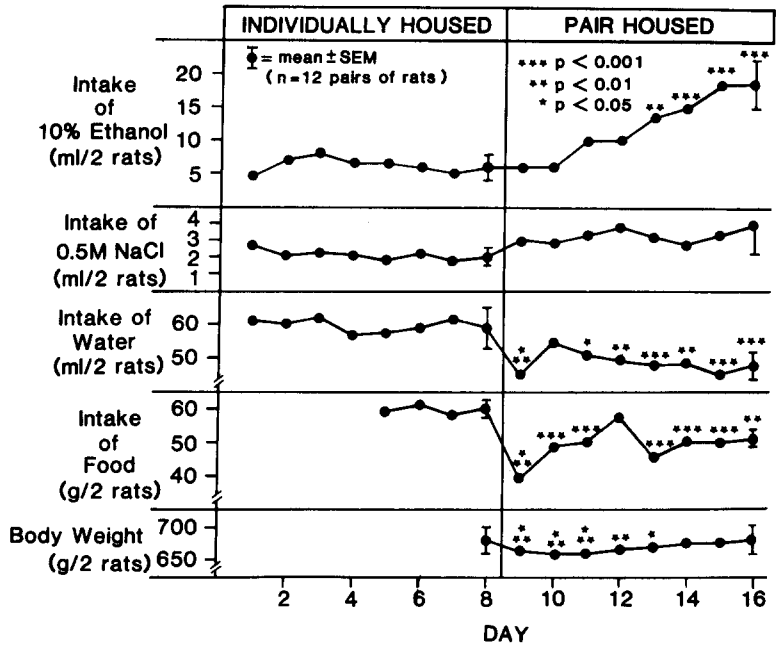

FIG. 1. The effect of paired housing on intakes of 10% v/v ethanol 0.5 M NaCl, water and food and body weight of rats. Statistical analysis described in text.

ually in stainless steel metabolism cages (i.e., 18 × 25 × 18 cm high). During the treatment period, the animals were housed two per metabolism cage. Animals with similar alcohol intakes and body weights were selected for pairing. The cage and drinking bottles used during the treatment period were thoroughly cleaned and not used by either of the two animals previously. For all animals, intakes of 10% ethanol, 0.5 M NaCl and water were measured daily. In addition, in 4 of the animals, intake of food and in 8 of the animals, body weight was measured prior to and during the treatment period. All measurements were made between 1100 and 1200 hr.

Experiment 2. ACTH Treatment of Individually-Housed Rats

Ten naive male Sprague-Dawley rats weighing 300–400 g (90–120 days of age) at the start of the experiment were used. The animals were housed individually in stainless steel cages (18 × 25 × 18 cm high). One group of animals (n = 5) had free access to 10% ethanol, water and rat chow. The second group of animals (n = 5) had free access to 10% ethanol, 0.5 M NaCl, water and rat chow. The liquids were available from containers hung on the front of the cage. The position of the containers was changed daily on a random basis.

After an adaptation period (7 days), the experiment began. The experiment consisted of three periods: baseline (6 days), treatment (8 days) and posttreatment (6 days). During the treatment period, all rats received one intraperitoneal injection of long-acting, synthetic 1–24 ACTH (Synacthen Depot, 10 μg/I.U. CIBA) daily. The dose of ACTH (50 μg/day ≈ 143 μg/kg) was chosen such that the decrease in body weight did not exceed 20%—a level which could stimulate ethanol intake for its caloric value (14,30). This dose of ACTH has been previously shown (28) to cause a large appetite for Na in the rat. Administration of long-acting ACTH in doses as low as 80–100 μg/kg has been shown to cause large and sustained increases in plasma corticosterone level (1,13). Similar to the adaptation period, during the baseline and posttreatment periods, no injections were given. Intakes of 10% ethanol and 0.5 M NaCl were measured daily. In addition, intakes of food and water and body weight were measured occasionally. All measurements (and injections when required) were made between 0900 and 1000 hr.

Experiment 3. Dexamethasone Treatment of Individually-Housed Rats

Eight male Sprague-Dawley rats weighing 400–600 g (120–150 days of age) at the start of the experiment were used. The animals were housed individually in stainless steel cages with free access to 10% ethanol, 0.5 M NaCl, water and rat chow.

An adaptation period of 14 days was followed by a baseline period of 6 days and a treatment period of 6 days. During the treatment period, all rats received a daily intraperitoneal (IP) injection of dexamethasone (Decadron, Merck, Sharpe and Dohme): 250 μg/kg body weight for the first 2 days of the treatment period and 100 μg/kg body weight for the remaining 4 days. The dose of dexamethasone was chosen such that the loss of body weight was similar to that caused by ACTH in Experiment 2. Administration of dexamethasone in doses as low as 10–60 μg/kg daily has been shown to prevent increases in plasma ACTH in stressed rats (12,25). Intakes of 10% ethanol, 0.5 M NaCl, water and food and body weight were measured daily. All measurements (and injections when required) were made between 0900 and 1000 hr.

Experiment 4. ACTH Treatment of Pair-Housed Rats

Eight male Sprague-Dawley rats weighing 615–740 g (150–180 days of age) at the start of the experiment were used. Initially the rats were housed individually in stainless steel cages with free access to 10% ethanol, 0.5 M NaCl, water and rat chow. Rats of similar body weight and ethanol intake (less than 2 ml/day) during the baseline period were housed two per cage for 3 weeks (adaptation period). After the adaptation period, the experiment

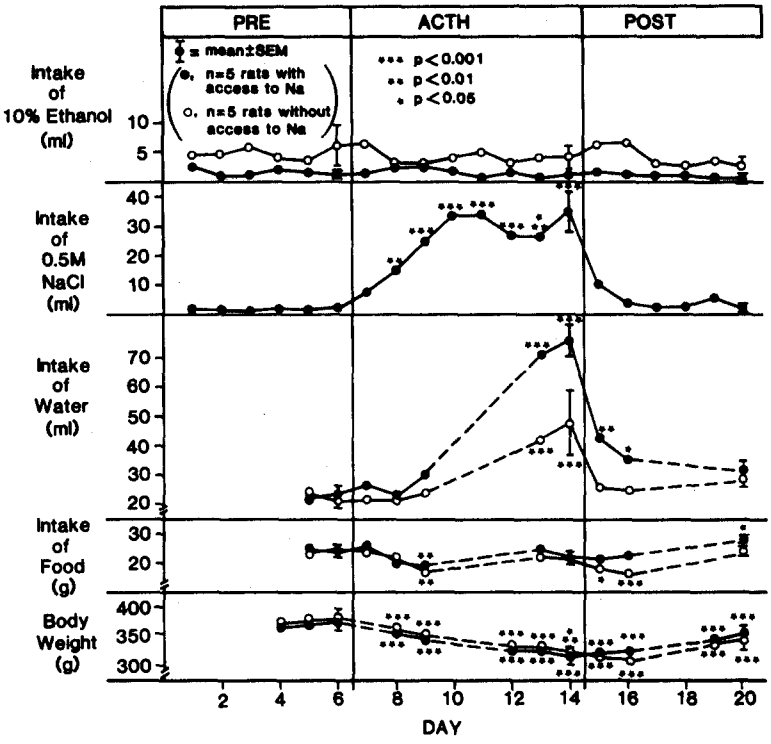

FIG. 2. The effect of intraperitoneal injection of ACTH (50 μg ~ 143 μg/kg daily) on ingestive behavior and body weight. The rats had access to 10% ethanol, food and water (○, n = 5) or to 10% ethanol, food, water and 0.5 M NaCl (●, n = 5). Statistical analysis described in text.

was begun. The experiment consisted of three periods: baseline (6 days), treatment (7 days) and posttreatment (6 days). During the treatment period, each rat received one intraperitoneal injection of ACTH (Synacthen Depot, CIBA) daily. The dose of ACTH used was 25 μg/kg body weight on the first two days of the treatment period and 60 μg/kg body weight for the remaining five days of the treatment period. Intakes of 10% ethanol, 0.5 M NaCl, water and food and body weight were measured daily. All measurements and injections (when required) were made between 0900 and 1100 hr.

Experiment 5. Dexamethasone Treatment of Pair-Housed Rats

Twenty male Sprague-Dawley rats weighing 440–600 g (120–150 days of age) at the start of the experiment were used. Initially the rats were housed individually in stainless steel cages with free access to 10% ethanol, 0.5 M NaCl, water and rat chow. Rats of similar body weight and ethanol intake (less than 2 ml/day) during the baseline period were housed two per cage for two weeks (adaptation period). After the adaptation period the experiment was begun. The experiment consisted of three periods: baseline (6 days), treatment (6 days) and posttreatment (3 days). During treatment period, each rat received one intraperitoneal injection of dexamethasone (Decadron, Merck, Sharpe and Dohme) daily. The dose of dexamethasone was less than that used in Experiment 3, i.e., the dose of dexamethasone used was 25 μg/kg body weight for the first 2 days of the treatment period and 20 μg/kg body weight for the remaining days of the treatment period. Intakes of 10% ethanol, 0.5 M NaCl, water and food and body weight were measured daily. All measurements and injections (when required) were made between 0900 and 1100 hr.

Data Analysis

For each of the measured variables (e.g., ethanol intake) except body weight, the values obtained on the two to eight days prior to treatment were used as baseline values. For body weight, the value obtained on the day prior to treatment was used as a baseline value. For each of the measured variables, a two-way analysis of variance (repeated measures design; animals by days) and subsequent *t*-tests (using the error mean square from the ANOVA as the estimate of variance; df = degrees of freedom of the error mean square; two-tailed test) were used to compare the mean baseline value with the mean daily value obtained during the treatment or posttreatment period. In no instance was there a significant difference between values obtained on the different baseline days. Data are presented in the text as mean ± standard error of the mean.

RESULTS

Experiment 1. Paired Housing after Individual Housing

Figure 1 shows the results of this experiment. During the treatment period two rats were housed in each individual cage (n = 12 pairs). For comparison, the sum of the intakes for the 2 animals to be paired (pretreatment) are shown even though the animals were housed individually during the pretreatment period. The results indicated that relative to the intake of ethanol during the baseline period (6.0 ± 2.0 ml/day; n = 96 observations on 12 pairs of rats), the daily intake of ethanol was increased, $F(8,88) =$

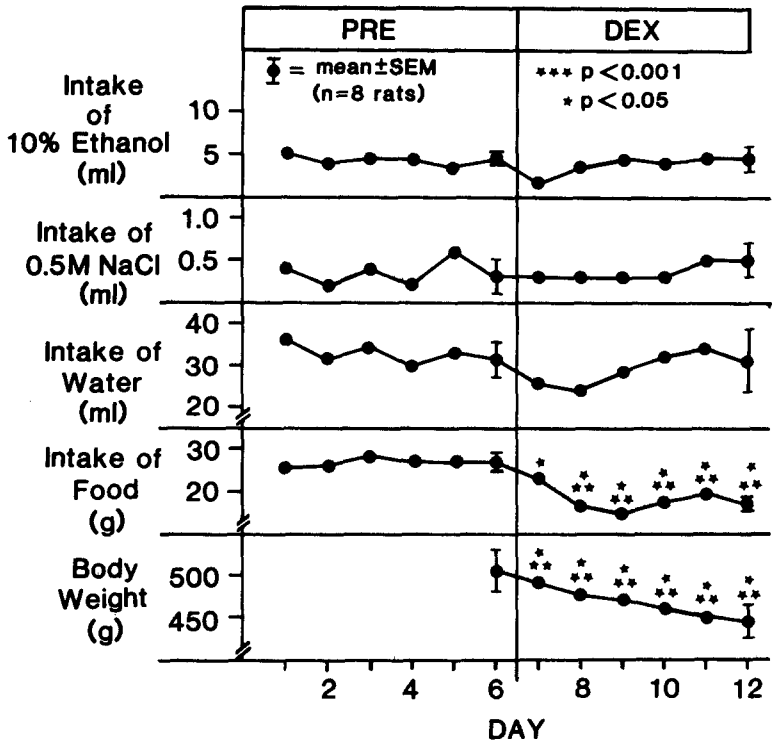

FIG. 3. The effect of intraperitoneal injection of dexamethasone (250 μg/kg, days 1 and 2 of the treatment period; 100 μg/kg, days 4, 5 and 6 of the treatment period) on ingestive behavior and body weight. The rats had access to 10% ethanol, food, water and 0.5 M NaCl. Statistical analysis described in text.

8.36, $p<0.001$, during the last 4 days, with the maximum intake of 18.7 ± 3.2 ml achieved on the last day of the crowding period. The daily NaCl intake was not significantly changed by crowding, $F(8,88)=0.87$.

Relative to baseline values, intake of water and food and body weight were decreased during crowding. The intake of water was decreased, $F(8,88)=3.60$, $p<0.001$, on 7 of the 8 days of the treatment period. Food was continuously available, but intake of food was measured in only 4 of the 12 pairs of rats. Similar to the intake of water, the intake of food was decreased, $F(8,24)=11.27$, $p<0.001$, during 7 of the 8 days of the treatment period. Body weight was measured in 8 of the 12 pairs of rats. Body weight was decreased, $F(8,56)=7.65$, $p<0.001$, during the first 5 days of the treatment period, falling from 678 ± 23 g to a minimum value of 660 ± 23 g on the second day of treatment, and was at baseline or above thereafter.

Experiment 2. ACTH Treatment of Individually-Housed Rats

The results are shown in Fig. 2. During the baseline period, the daily intake of ethanol by animals with (closed circles) or without (open circles) access to NaCl was 1.5 ± 0.4 ml/day and 4.8 ± 1.5 ml/day, respectively. During ACTH treatment, the daily intake of ethanol was unaltered in either group, $F(14,56)=0.65$ and 0.43, respectively for animals with and without NaCl available.

ACTH treatment caused a marked increase in the intake of NaCl, $F(14,56)=14.56$, $p<0.001$. The increase was evident by the second day and was maximal [25–35 ml vs. 1–2 ml (baseline)] during the last 5 days of treatment. Intake of NaCl returned to baseline level on the first day after cessation of treatment.

Under baseline conditions, water intake was similar for animals with (closed circles) and without Na (open circles) available, 23.0 ± 2.5 ml and 22.2 ± 2.4 ml, respectively. During ACTH treatment, water intake was increased in both groups, $F(8,32)=22.99$ and 6.13, p's<0.001, respectively. The increase in water intake was not evident during the first 3 days of ACTH treatment and the maximum increase in intake was greater in animals with access to Na (e.g., 76.0 ± 5.6 ml vs. 47.8 ± 11.1 ml, respectively, for animals with and without access to Na, day 8 of treatment). In addition, in animals with access to Na, water intake was elevated during the first 2 days of the posttreatment period.

Intake of food was decreased, $F(8,32)=5.05$, $p<0.001$ and 4.07, $p<0.002$, respectively for animals with (closed circles) and without (open circles) access to NaCl, on the third day of the treatment period. In addition, intake of food was decreased on the first and second days of the postperiod in animals without access to Na. Intake of food was increased on the last day of the posttreatment period in animals with Na available. Body weight was decreased during each day (when measured) of the treatment and posttreatment period in animals with, $F(9,36)=73.88$, $p<0.001$, or without Na available, $F(9,36)=54.84$, $p<0.001$.

Experiment 3. Dexamethasone Treatment of Individually-Housed Rats

The results are shown in Fig. 3. The results indicated that dexamethasone did not alter the daily intake of ethanol, $F(6,42)=0.58$, NaCl, $F(6,42)=0.37$, or water, $F(6,42)=0.85$.

Intake of food and body weight were decreased, $F(6,42)=18.67$, $p<0.001$; $F(6,42)=71.78$, $p<0.001$, respectively, on all 6

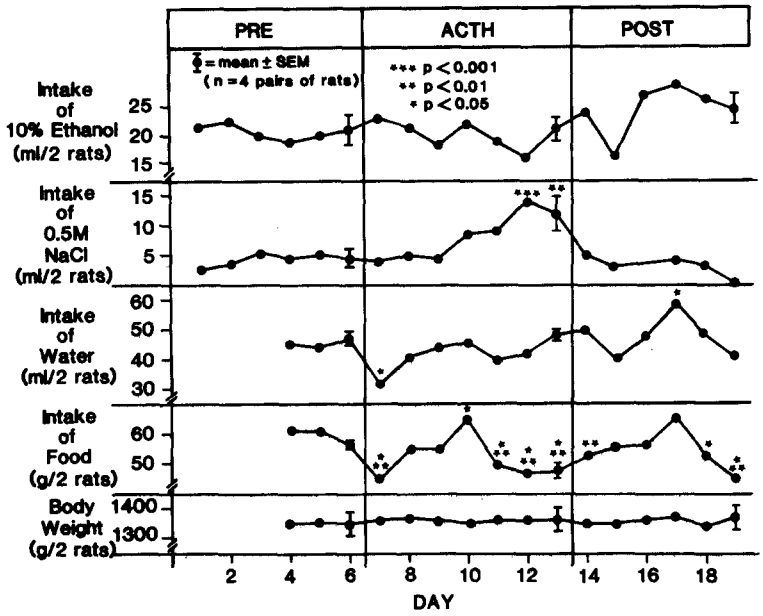

FIG. 4. The effect of intraperitoneal injection of ACTH (synacthen depot, 25 μg/kg days 1 and 2 of the treatment period: 60 μg/kg remaining days of the treatment period) on ingestive behaviour and body weight of pair-housed male rats. The rats had access to 10% ethanol, food, water and 0.5 M NaCl. Statistical analysis described in text.

days of the treatment period.

Experiment 4. ACTH Treatment of Pair-Housed Rats

The results are shown in Fig. 4. The dose of ACTH used in this experiment was smaller than that used in Experiment 2. The major effects of this lower dose were to 1) eliminate, $F(13,39)=0.77$, the decrease in body weight previously observed (Experiment 2) and 2) attenuate the increase in NaCl intake previously observed (Experiment 2). The increase, $F(13,39)=3.73$, $p<0.001$, in Na intake did not occur until the 6th day of treatment with the maximal intake being 12–14 ml (baseline intake $=4.3\pm1.6$ ml).

As in Experiment 2, ACTH treatment did not alter the daily intake of ethanol, $F(13,39)=1.8$. However, the baseline ethanol intake in this experiment was elevated compared to that in Experiment 2. For example, prior to ACTH treatment, the daily ethanol intake of the paired rats was 20.8 ± 2.5 ml/pair while in Experiment 2, the intake was 1.5 ± 0.4 ml/individual $\approx$ 3.0 ml/pair (with Na available).

Intake of water was only minimally changed, $F(13,39)=2.2$, $p<0.05$, being decreased on the first day of ACTH treatment and increased on the fourth day of the posttreatment period. Intake of food was, in the main, decreased, $F(13,39)=12.03$, $p<0.001$. During the ACTH treatment period food intake was decreased on days 1, 5, 6 and 7 but increased on day 4. During the posttreatment period food intake was decreased on day 1, 5 and 6, $F(13,39)=12.03$, $p<0.001$.

Experiment 5. Dexamethasone Treatment of Pair-Housed Rats

The results are presented in Fig. 5. Although the dose of dexamethasone used in this experiment was smaller than that used in Experiment 3, the results of the present experiment were very similar to those obtained in Experiment 3. For example, neither intake of ethanol nor intake of NaCl were altered by dexamethasone treatment, $F(9,81)=1.68$ and 1.55, respectively. Also, both food intake and body weight were reduced during the treatment period, $F(9,81)=13.5$ and 24.87, p's<0.001, respectively. However, in contrast to Experiment 3 where water intake was unaltered, water intake was decreased, $F(9,81)=4.14$, $p<0.001$, during the first 4 days of dexamethasone treatment in this experiment.

DISCUSSION

Experiment 1 demonstrated that ethanol intake was increased when the number of rats per cage was changed from one to two, without increased cage size. Increased ethanol intake under similar circumstances has been observed previously (16,17) and is presumably due to changes induced in neural and/or hormonal mechanisms which occurred as a consequence of crowding (i.e., a decrease in amount of space per animal) and of an involuntary increase in social interactions. The subsequent experiments evaluated the possibility that crowding-induced increase in ethanol intake is mediated via changes in the activity of the pituitary-adrenal axis. In this regard, the profiles of voluntary ingestion of 10% v/v ethanol, 0.5 M NaCl and water of individually or pair-housed rats were compared to the intake profiles for these same solutions in individually or pair-housed rats which had been treated with ACTH or dexamethasone. That is, although not measured in the present experiments, increased secretion of ACTH from the anterior pituitary and subsequent increased secretion of various adrenal steroids (8) and adrenal hypertrophy (8,16) have been reported to occur with either high (e.g., crowding) or low (e.g., isolation) population density with the consequent increase or decrease in social interaction between conspecifics (7,18).

Regardless of the initial blood levels of ACTH or adrenocorticoid in the animals, based on evidence noted earlier (1,13) and/or on the fact that Na intake is increased and that this response is mediated by adrenal hormones (28), it can be assumed that both ACTH and endogenous glucocorticoid hormone levels were ele-

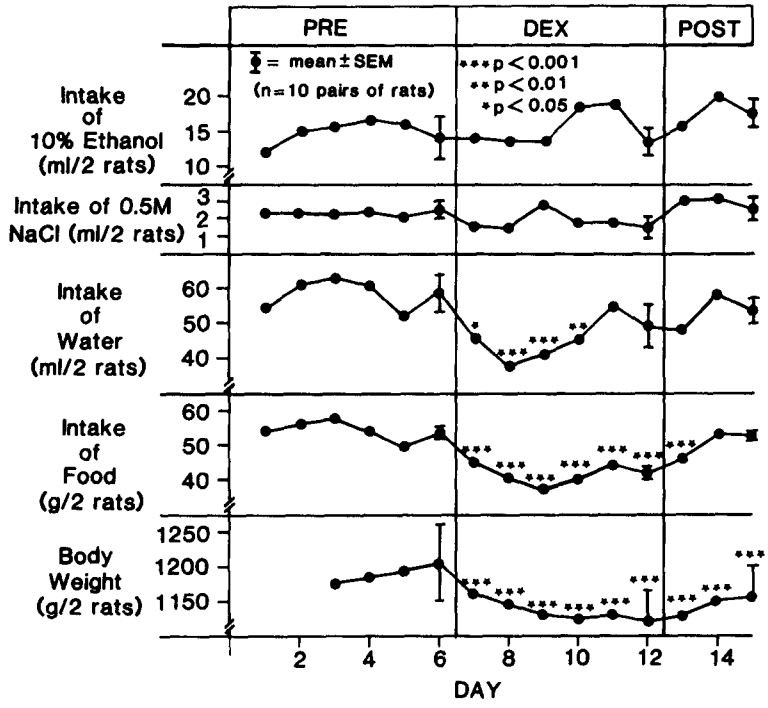

FIG. 5. The effect of intraperitoneal injection of dexamethasone (25 μg/kg days 1 and 2 of the treatment period: 20 μg/kg remaining days of the treatment period) on ingestive behaviour and body weight of pair-housed male rats. The rats had access to 10% ethanol, food, water and 0.5 M NaCl. Statistical analysis described in text.

vated during ACTH treatment in Experiment 2 and 4. Thus, although only a small number of animals were used, given that ACTH treatment failed to alter the ethanol intake of either individually- or pair-housed rats, the results are suggestive that the enhanced ethanol intake that occurred during crowding could not be attributed entirely to a crowding-induced increase of ACTH or to the subsequent increase in glucocorticoid hormones. On the other hand, based on evidence noted earlier (12,25), it can be assumed that during dexamethasone treatment, ACTH, and subsequently, endogenous glucocorticoid hormone levels were decreased although synthetic glucocorticoid hormone levels were elevated. Thus, given that dexamethasone treatment failed to alter the ethanol intake of either individually- or pair-housed rats, the results are suggestive that the enhanced intake of ethanol that occurred during crowding could not be attributed entirely to a crowding-induced decrease in ACTH or endogenous glucocorticoid hormones, i.e., other factors seem to be involved.

Several other points are worth noting. Firstly, it has been suggested (21) that the maximum amount of ethanol that will be ingested is determined, in part, by the amount of ethanol that can be metabolized. Given that elevation of glucocorticoid hormone levels can cause increased ethanol metabolism, by increasing the rate of ethanol oxidation to acetylaldehyde in the liver (9,19), it would seem that the reason that neither ACTH nor dexamethasone causes increased ethanol intake was not the animals inability to metabolize any more ethanol. Secondly, the observation that rats did not alter their ethanol intake when body weight loss was up to 17% of their initial body weight (Experiments 2–5) suggests that crowding-induced ethanol intake is not caused by body weight loss or the need for calories. Thirdly, a possible explanation for crowding-induced ethanol intake that cannot be eliminated at present is that the additional ethanol intake was not stressor-induced but was, in fact, socially motivated—i.e., social drinking. Finally, since both β-endorphin and ACTH are secreted together in various stressful situations and secretion of both hormones is suppressed by dexamethasone treatment (15), it would appear that β-endorphin is not involved in crowding-induced ethanol intake.

Pair-housed rats, relative to individually-housed rats, exhibited no increase in Na intake. By comparison, the ACTH-treated rats, as reported previously (28), had a very large increase in Na intake. This finding may suggest that crowding did not substantially increase circulating levels of ACTH, that crowding induced increase in ethanol intake prevented the usual rise in ACTH or, that by some interaction between elevated ACTH and elevated ethanol intake an increase in Na intake was prevented. The observation that dexamethasone did not cause increased Na intake suggests that elevation of glucocorticoid activity alone is insufficient to cause Na appetite. Thus, while ACTH-induced Na appetite is dependent on the adrenal hormones (28), it would appear that if the glucocorticoid hormones are involved, they must work in conjunction with other adrenal hormones in order to stimulate Na intake [e.g., (28)].

Food intake was decreased, at least transiently, in all experiments. Decreased food intake during crowding has been reported previously (3,4) and maybe due to any of a number of factors, e.g., increased environmental temperature, decreased activity, decreased eating time due to conflict between animals, some hormonal change. Decreased food intake during dexamethasone treatment has been previously reported (26) and may be due to increased blood glucose or free fatty acid levels and their subsequent effect on central neural systems involved in feeding and satiety (26,28). ACTH treatment can (13) but does not always cause a decrease in food intake [present experiments, (2, 26, 28)]. It is conceivable that the elevation of adrenal hormones other than the glucocorticoids caused by ACTH or other metabolic affects of ACTH interfere with the glucocorticoid hormone induced de-

crease in food intake.

Body weight was decreased, at least transiently, in all experiments except Experiment 4. Decreased body weight is due, presumably, to decreased food intake, increased protein catabolism or decreased growth hormone levels (27,30). The observation that body weight was decreased only during the early part of the crowding period could be that the elevated caloric intake which occurred as a consequence of the elevated ethanol intake was sufficient to restore body weight to baseline level. The observation that the high dose but not the low dose of ACTH caused a decrease in body weight is consistent with previous observations (2, 13, 26, 28) and is presumably due to the greater stimulation of glucocorticoid secretion by the large dose of ACTH.

Changes in water intake, when observed, seem to be secondary to changes in other ingestive behaviours. For example, the decreased water intake that occurred during crowding could be due to the increased ethanol intake (which is 90% water) or to the decreased food intake (i.e., requirement for water is decreased). Increased water intake, as previously reported (28) occurred during ACTH treatment (Experiment 2) when intake of hypertonic NaCl was markedly elevated. At present, it is not clear why water intake did not decrease during dexamethasone treatment (Experiment 3) when food intake was decreased or why water intake did not change during ACTH treatment (Experiment 4) when intake of hypertonic NaCl was elevated (i.e., days 6 and 7 of treatment). It is conceivable that the increased need for water caused by increased Na intake was offset by the decreased need for water due to the decreased food intake.

In summary, the present data indicate that by increasing the number of rats per small cage—with the consequent increase in social interaction or conflict—an increase in ethanol intake is produced. Furthermore, at present, it would appear that this enhanced appetite for ethanol is not altered by either an increase or a decrease of blood ACTH with an increase of glucocorticoid hormones (synthetic or natural) as manipulated in abovementioned experiments.

ACKNOWLEDGEMENTS

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