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# BRIEF COMMUNICATION

# Effect of Adrenalectomy and Dexamethasone Treatment on Circadian Running in the Rat[1]

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MOBERG, G. P. AND C. R. CLARK. *Effect of adrenalectomy and dexamethasone treatment on circadian running in the rat.* PHARMAC. BIOCHEM. BEHAV. 4(5) 617–619, 1976. – Although adrenalectomy resulted in a marked decrease in total wheel running activity in male rats, the circadian rhythm of the running was not altered. Contrary to what has been previously observed in animals with intact adrenal glands, administration of the synthetic glucocorticoid dexamethasone to adrenalectomized animals resulted in an immediate increase in the amount of running with no effect on the circadian distribution of running. It was concluded that the adrenal axis had an influence on an animal's ability to express running behavior, but the adrenal axis had no influence on the neural control of the circadian rhythm of running.

Circadian rhythm  Corticosteroids  Running  Dexamethasone  Adrenalectomy

IT has been previously demonstrated that the pituitary-adrenal axis is involved in the expression of normal running behavior in the rat. Adrenalectomy will almost totally eliminate the running behavior in rats [4]. As would be expected, if corticosteroids are administered to the adrenalectomized animals, the running behavior will be restored [3]. Conversely, when rats with normally functioning pituitary-adrenal axis are treated with supraphysiological amounts of corticosteroids the amount of running markedly exceeds normal levels of activity [2,3].

The running behavior in rats shows a marked diurnal distribution with the bulk of the activity occurring during the evening. When an examination is made of the diurnal distribution of the increased running following the treatment of normal rats with corticosterone, it is found that the exogenous corticosterone in these animals increased the amount of nighttime running activity without any significant effect on the amount of daytime activity. In keeping with the selective effect on the diurnal distribution of running activity was the finding that following surgical isolation of the basal hypothalamus the amount of running was markedly reduced by an apparent selective effect of the amount of nighttime running [1]. This same surgical preparation abolished the diurnal rhythm of the pituitary-adrenal axis. Whether or not in this latter experiment the effect of the diurnal distribution on running was the result of the modified rhythm of plasma corticosterone is unknown, however, in both of these studies experimental manipulations of the adrenal axis also resulted in a selective effect on the diurnal distribution of running activity.

On the basis of these findings this study was undertaken to determine whether the reduction of running following adrenalectomy was the result of a selective effect on the nighttime running and, therefore, resulted in an alteration of the circadian rhythm of running. In addition, it was determined whether or not administration of dexamethasone in the adrenalectomized rat would, in the absence of endogenous corticoid, be effective only on nighttime running activity.

## METHOD

### *Animals*

Male Sprague-Dawley rats weighing 150 g at the beginning of the experiment were accustomed to standard Wahmann activity wheels for 10 days. Each wheel was housed in an individual chamber which was open at the top and lined with accoustical tile to attenuate sound. The animals were maintained on 14 hr light:10 hr dark (lights on from 0500 until 1900 hr) under controlled temperature. Food and water were ad lib throughout the experiment.

### *Procedure*

Running activity was continuously recorded on both a digital counter and by an Esterline event recorder to allow

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visual inspection of the distribution of running. In rats, wheel running occurs primarily during the dark period with this activity terminating in a final burst of running around the time lights come on in the colony and, in many instances, extending for a short time into the light period. Following this last running, the animals generally become inactive as is characteristic for the light period with little wheel running occurring during this time. For data analysis, it was decided that the running occurring at the beginning of the light period actually represents the conclusion of the major activity period and thus should be included within that period's activity. Therefore, the daily wheel running activity was divided into two 12 hr periods with the evening period (p.m.) extending from lights off through the first 2 hr of light (1900 until 0700 hr) and the light period (a.m.) consisting of the remaining 12 hr of light beginning at 0700 and ending at 1900 hr.

After the adjustment period, the mean of the next 10 days of running served as the control level of daily running activity. The animals were then either adrenalectomized (Adr-X) under pentobarbital anesthesia (45 mg/kg) or underwent laparotomy (sham). The Adr-X rats received 0.9% saline drinking water for the remainder of the experiment. After 10 days of postoperative recovery, the testing procedure was repeated.

To test the effect of dexamethasone (DEX) on running activity in the absence of endogenous cortocosteroids, Adr-X animals were injected intraperitoneally with 0.8 or 1.2 mg of dexamethasone-21-phosphate (Decadron) at 0700 or they were treated with 0.8 or 1.6 mg of DEX at 1900 hr. In addition, one group of animals was injected with 0.8 mg of DEX at both 0700 and 1900 hr to study the effect of a more prolonged administration. For all treatments the running activity for a 24 hr period following the injection was monitored. The inter-group differences in activity was testing for significance by the Student's *t* test.

## RESULTS

As illustrated in Fig. 1A the Adr-X animals had only 10% of the total activity of that observed during the control period. Analysis of the distribution of the running activity occurring during the control period (Fig. 1A) indicated that approximately 95% of the running activity occurred during the evening period as opposed to 5% occurring during the light period. When the distribution of control activity in Fig. 1A is compared with the distribution of Adr-X activity in Fig. 1B it can be seen that although Adr-X markedly reduced total running activity the loss of endogenous corticosteroids did not influence the diurnal distribution of the activity. The sham adrenalectomized animals showed no difference in the total amount of running or in the circadian distribution of that running between the preoperated control period and the test period following surgery.

Unlike the effects of supraphysiological doses of DEX in normal animals, the data in Table 1 indicate that the stimulatory effect of DEX on running behavior in the adrenalectomized animals was noted in the period immediately following administration. DEX was effective in increasing the amount of running whether the drug was administered in the morning or evening, however, the data do indicate that the 1900 hr injections were more effective in increasing total activity during both the daytime and evening phases. The acute administration of DEX in the absence of endogenous corticosteroids did not significantly effect the daily distribution of running regardless of the time of administration.

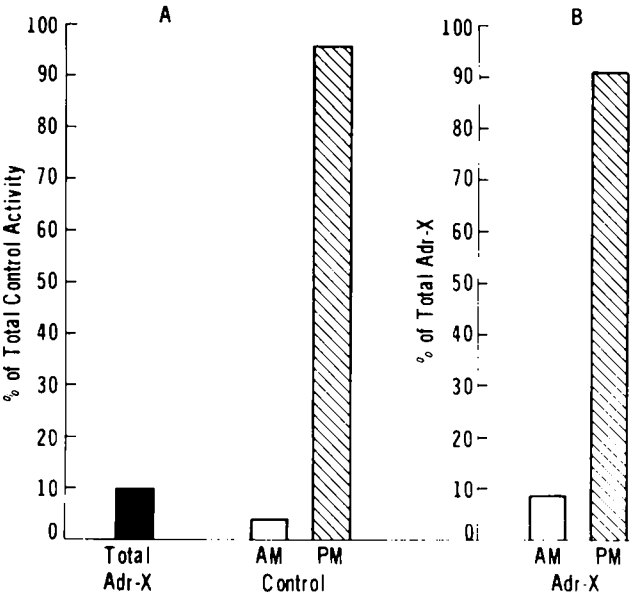


FIG. 1. (A) Total Adr-X activity in relation to total control running activity and depicts the percentage of the total control activity exhibited during the a.m. and p.m. phase. (B) Percentage of total Adr-X activity exhibited during the a.m. and p.m. phase. N = 10.

## DISCUSSION

Although the affect of adrenalectomy in reducing the total amount of running behavior has been demonstrated, suprisingly no one has previously investigated the effect of adrenalectomy on the distribution of running behavior. This information is especially relevant in view of studies on running behavior which utilize drugs that also alter the normal functioning of the pituitary-adrenal axis. The findings of this study show that exogenous corticoids have no effect on the circadian distribution of running activity. Therefore, the decreased running in the absence of endogenous corticosterone probably results from the loss of the steroid's effect on metabolism and the resulting effect on muscular activity [3]. However, the absence of corticosteroids in the adrenalectomized animals does not appear to effect the neural systems controlling the circadian expression of running behavior.

The acute administration of dexamethasone in the Adr-X animal had an entirely different effect from administration of the drug in animals with intact adrenals in respect to latency of action and behavioral response. Previous investigations found that supraphysiological amounts of DEX administered orally increased only the nighttime running following a latency of one to three days. In the current study it was found that, in the absence of exogenous glucocorticoids, the effect of DEX treatment was immediate and increased both daytime and evening running without any significant effect on the distribution of the running. Why the administration of DEX in the evening had a more marked effect on running is unclear, but this difference may result from a circadian difference in the metabolism of the drug.

TABLE 1

EFFECT OF DEXAMETHASONE TREATMENT ON RUNNING ACTIVITY OF ADR-X RATS

| Treatment | Time of injection | N | Mean number of revolutions AM | PM | AM | % of total daily running AM | PM |
|---|---|---|---|---|---|---|---|
| None | — | 9 | 62† | 603† | — | 9 | 91 |
| 0.8 | 0700 | 13 | 181 | 1986 | — | 8 | 92 |
| 1.2 | 0700 | 7 | 112 | 1402 | — | 7 | 93 |
| 0.8 | 1900 | 5 | — | 3372 | 581 | 15 | 85 |
| 1.6 | 1900 | 9 | — | 3139 | 405 | 11 | 89 |
| 0.8 | 0700 & 1900 | 6 | 231 | 2424 | — | 9 | 91 |

*Mg of DEX administered per rat.
†Mean revolutions for 10 day control period.

Although corticosteroids released from the adrenal cortex are essential for the animal to exhibit the normal total amount of running, the corticosteroids do not appear to influence the neural control of the daily rhythm of the expression of this behavior. Indeed, only if the animal is exposed to pharmacological doses of glucocorticoids for an extended period of time is the distribution of running altered [2].

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