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RAPID COMMUNICATION

Thyroparathyroidectomy Produces a Progressive Escape Deficit in Rats

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LEVINE, J. D., L. R. STRAUSS, L. R. MUENZ, M. B. DRATMAN, K. T. STEWART AND N. T. ADLER. *Thyroparathyroidectomy produces a progressive escape deficit in rats.* PHYSIOL BEHAV **48**(1) 165–167, 1990.—Abnormal thyroid status and affective disorders have been associated in the human clinical literature. It has recently been shown that pretreatment with thyroid hormone can prevent escape deficits produced by inescapable shock in an animal analogue of depression. In this report we provide evidence that hypothyroid status can produce an escape deficit in rats. While sham-operated rats improved their performance on a simple escape task over three days of testing, thyroparathyroidectomized rats showed a pronounced decrease in their responses. Markov transition analysis was used to obtain conditional probabilities of escaping given a prior escape or failure to escape for the two groups. This analysis shows that the structure of the data set may be similar for the two groups. These results suggest that if intact rats learn to escape, then hypothyroid rats may learn not to escape.

Thyroid Escape Rat Learning Depression

BOTH clinical observation and experimental evidence suggest a relationship between thyroid-axis abnormalities and affective disorders. Altered thyroid function is commonly found in affective illness and hypothyroidism has been associated with rapid-cycling bipolar depression (1,2). Thyroid hormone potentiates the effects of conventional antidepressants in humans and rats otherwise refractory to their benefits (3, 8, 15). Moreover, Martin *et al.* (4) have demonstrated that supraphysiologic doses of T_3 can prevent avoidance and escape deficits in a purported animal analogue of depression.

These data support the idea that hypothyroidism itself might produce depression-like behavioral deficits in rats. As a first step in examining this possibility, hypothyroid, thyroparathyroidectomized (TPX) rats were run in a simple escape task. Along with measures of escape behavior per se, Markov transition probabilities were used to analyze the organization of escape responding in TPX and sham-operated (SHAM) rats.

METHOD

Subjects

Six male, TPX, albino rats were procured from Zivic-Miller (Allison Park) at approximately 75 days of age; surgery had been performed when they were approximately 60 days of age. Only TPX rats showing the characteristic hypothyroidism-induced plateau in body-weight (250–325 grams when tested) were used in these experiments (7). Because of the potential confounding effects of large weight differences between age-matched experimental and control animals, SHAM rats were matched for weight rather than age. Six SHAM rats were procured from Zivic-Miller when the TPX rats were five months of age and both groups were tested one month later. All of the animals were maintained on Purina rat chow and a 0.5% $CaCl_2$ solution ad lib and housed individually in a large colony room (LD 16:8).

Testing Apparatus

The test chambers were constructed of stainless steel with Plexiglas walls. They measured 23.0 × 20.0 × 20.0 cm with 0.2-cm stainless steel grid bars spaced 2.0 cm apart forming the floor. An aluminum lever 2.5 cm wide extended 3.0 cm into the cage and 3.0 cm above the floor on one side of the box. Scrambled footshock (1.0 mA) was supplied to the floor of each cage by

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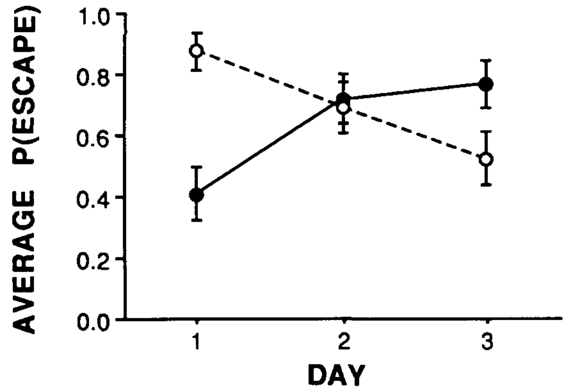

FIG. 1. The average probability of escape [p(escape)] as a function of day for the two groups on the FR2 trials. Probabilities for the SHAM rats are given by solid lines and filled circles (—●—). Probabilities for the TPX rats are given by dashed lines and open circles (--O--). The bars around each point denote 95% confidence intervals for the probabilities.

TABLE 1

TABLE OF MARKOV TRANSITION PROBABILITIES

	Probability		
Treatment	Day 1	Day 2	Day 3
SHAM			
p(escaping after escaping)	0.74	0.92	0.90
p(not escaping after escaping)	0.26	0.08	0.10
p(escaping after not escaping)	0.18	0.16	0.41
p(not escaping after not escaping)	0.82	0.84	0.59
TPX			
p(escaping after escaping)	0.88	0.77	0.77
p(not escaping after escaping)	0.12	0.23	0.23
p(escaping after not escaping)	0.79	0.49	0.24
p(not escaping after not escaping)	0.21	0.51	0.76

In the text, the daily average probability of escaping after escaping or not escaping on the previous trial for SHAM rats is compared with the average probability of not escaping after escaping or not escaping on the previous trial for TPX rats. See text for discussion.

shock generators. Shocks were generated and lever presses recorded by computer.

Procedure

After one month in the colony, TPX and SHAM subjects were randomly paired and assigned to one of two lever-press boxes (one rat per box). Each TPX/SHAM pair was tested in three sessions over three consecutive days at the same time each day. In the interval between testing successive pairs of rats, each box was wiped clean with a deodorizing cleanser and fresh bedding was provided to minimize odor cues (5). Each session consisted of 30 trials separated by random intertrial intervals lasting an average of 60 sec and ranging from 10 to 110 sec. In order to facilitate responding, during the first ten trials of each session one lever press immediately terminated the shock (FR1). During the remaining 20 trials, two such responses constituted the escape task (FR2). The maximum shock duration on each trial was 20 sec.

For each day we estimated the escape probability as the proportion of successful attempts among the six animals in a group. Because the same animals were tested repeatedly each day, the standard error of the daily average escape probability, necessary for comparisons, is not the same as in the usual binomial theory (16). We used a Markov chain model to estimate this standard error following the formulae of Appendix A of Muenz and Rubinstein (6).

RESULTS AND DISCUSSION

As seen in Fig. 1, the escape test revealed differences due to thyroid status, with the probability of escape increasing in SHAM rats and decreasing in TPX rats over the three days of testing. There was a highly significant difference between the SHAM and TPX groups on Day 1 (two-sided p-value = 0.0035), but not on Days 2 and 3. Furthermore, both SHAM and TPX groups showed significant trends in opposite directions and the difference of the trends (slopes) is highly significant; the upward trend for SHAM rats is marginally significant (two-sided p-value = 0.055); the downward trend for TPX rats is significant (two-sided p-value = 0.033); and the comparison of the trends is highly significant (two-sided p-value = 0.0042). Thus, SHAM rats improved their performance while performance in the TPX group declined.

The initial high probability of escape [p(escape)] for TPX rats may have been due in part to TPX-induced hyperactivity (9,10). The subsequent decrease in escape responses suggested to us that some other process, such as learning, might be overtaking the effects of hyperactivity.

TPX rats exhibited escape deficits resembling those produced by inescapable shock. The notion that learning about responses to aversive stimuli can lead to behavioral depression has been used to account for escape deficits following exposure to inescapable shock (11). We employed a statistical approach in an attempt to illustrate that an orderly process might account for the TPX-induced decrement in p(escape).

Specifically, a Markov chain model was used to test for behavioral persistence (i.e., a high probability of repeated escaping on successive trials). This analysis produced conditional probabilities of escaping within each session to yield a more fine-grained view of the data set. We reasoned that if the increase in p(escaping) for SHAM rats and the increase in p(not escaping) for TPX rats were similar, TPX rats might have learned not to escape just as SHAM rats might have learned to escape.

Table 1 summarizes this analysis for the FR2 data. For SHAM rats, the probability of an escape following an escape increased during the experiment, and the probability of an escape after a failure to escape more than doubled from Day 1 to Day 3. For TPX rats, on the other hand, the probability of not escaping [$1 - p$(esc)] following an escape, while low over all sessions, nearly doubled, and the probability of not escaping after not escaping increased more than three-fold. Thus, while not identical, the processes underlying the increase in p(escaping) for SHAM rats and the increase in p(not escaping) for TPX rats behave as if they were similar. In other words, thyroparathyroidectomy seems to have produced a learning deficit that superseded the hyperactivity. A more robust confirmation would require a larger data set.

CONCLUSION

The results reported here suggest that thyroparathyroidectomy may produce an escape deficit in rats similar to that produced by inescapable shock, supporting a link between thyroid status and depression in an animal model. Pharmacological intervention with antithyroid drugs or antibodies or with selective deiodinase inhibitors such as propylthiouracil and ipodate may provide further insights into the role of iodothyronines in the deficit reported here.

Such methods might additionally permit an examination of the proposition that altered CNS thyroid economy may play a role in depression (2).

A relationship between thyroid status and circadian rhythms has been hypothesized. Schull *et al.* (9,10) have demonstrated an effect of thyroparathyroidectomy on activity and on wheel-running circadian rhythms in rats. In addition, Stewart *et al.* (12,13) have shown a positive correlation between stress-induced effects on wheel-running rhythms and escape responding in rats. These studies along with the present report suggest the possibility that thyroid status, circadian rhythms, and depression are linked.

In addition, we believe that Markov models might prove to be generally useful for the analysis of escape phenomena. A general Markov model could be used to generate hypotheses about the basis for escape deficits. For example, Theios (14) has described a general Markov model for aversive conditioning that could be exploited to analyze the relative contributions of parameters such as fear and memory to the effects of thyroid status on learning.

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