THE IODIDE CONCENTRATING MECHANISM OF THE THYROID GLAND IN YOUNG ADULT RATS INJECTED WITH MELATONIN FOR 10 AND 30 DAYS

Stephen P. Naber, Max Goldman, and Margaret H. Peaslee
Department of Biology
University of South Dakota, Vermillion, S. Dak. 57069

Introduction

Considerable evidence has been presented showing inhibitory effects on the gonads produced by pineal extracts and the pineal hormone, melatonin. Wakida (1) showed that pituitary and pineal extracts injected together in female rats reduced the number of corpora lutea observed. Decreased ovarian weights of female rats treated with aqueous pineal extracts was also reported by Kitay and Altschule (2).

Wurtman and colleagues (3) reported that daily injections of small amounts of melatonin decreased the incidence of estrous and reduced ovarian weight in female rats. In 1964, Chu et al., (4) observed that small doses of melatonin decreased the incidence of vaginal smears that demonstrated estrous phases in rats.

The pineal gland and its hormone, melatonin, have been shown to exert effects at target organs other than the gonads. Recent reports have suggested that melatonin has an inhibitory effect on thyroid function, however, the site of action of melatonin has not been elucidated. Baschieri et al., (5) suggested that melatonin may have an inhibitory effect on the secretion of thyroid stimulating hormone, or on thyrotropin's action on the thyroid gland since melatonin prevented the hyperplasia due to the goitrogenic action of methyl-thiouracil. Baschieri et al., (5), Reiter et al., (6), and De Prospro et al., (7) have reported that administration of melatonin to rats reduces the thyroidal uptake of radioactive iodide. In our laboratory, Goldman et al., (8) have reported that injection of melatonin into neonatal rats did not modify the organization and functioning of the hypothalamic-pituitary regulation of thyrotropic secretion.

Ishibashi et al., (9) reported that administration of melatonin to rats decreased the thyroid hormone secretion rate. Similarly, Narang et al., (10) found that the reduction in thyroid hormone secretion rate observed when melatonin is administered appears to be reduced with advancing age of the rats. A reduction in thyroid hormone secretion rate would result in decrease in circulating thyroid hormone which would stimulate the thyrotropic function of the anterior pituitary. The increased secretion of thyroid stimulating hormone would influence the iodide concentrating mechanism. T/S ratio represents the

gradient of radioiodide maintained by the thyroid gland against the serum, and is a sensitive indicator of thyroid stimulating hormone activity. Therefore, we decided to investigate the action of melatonin on the iodide concentrating mechansim of the thyroid gland.

MATERIALS AND METHODS

One group of female, Sprague-Dawley rats, 57-60 days old received 150 μg melatonin injected intraperitoneally, daily for 10 days. A second group of 60-70 day old rats received the same injection for a period of 30 days.

At termination, all rats received an injection of Tapazole, an antithyroid drug which prevents the organification of iodine by inhibiting the oxidation of iodide to elemental iodine. One hour later the rats received a carrier-free injection of ^{131}I and were autopsied an hour after ^{131}I injection. The thyroid glands were dissected, homogenized and an aliquot of homogenate counted to determine the radioactivity in 1 g of thyroid tissue. Blood was obtained from the dorsal aorta and an aliquot of serum was counted to determine the radioactivity in 1 ml of serum. The samples were counted in a Nuclear-Chicago, well-type, scintillation counter and the T/S ratios calculated. The T/S ratio being the ratio of radioiodide in 1 g of thyroid tissue to the radioiodide in 1 ml of serum.

RESULTS

Body weights of the rats injected with melatonin for 10 days did not differ significantly from the control value (Table I). Reduction of thyroid weight shown in the melatonin injected group is significant (Table I). The 24 hour ^{131}I uptake is significantly reduced in the melatonin injected group (Table I) and is consistant with the findings of Baschieri et al., (5), Reiter et al., (6), and De Prospro et al., (7) who also reported decreased ^{131}I uptakes in rats injected with melatonin. The T/S ratio of the melatonin injected rats is lower than the control value, however, the difference is not significant (Table I).

Table I. Body weights, thyroid weights and 24 hr. ^{131}I uptakes, and T/S ratios in female, 57-60 day old, Sprague-Dawley rats injected with melatonin daily for 10 days.

Group		Body g	Thyroid Weight mg	Thyroid ^{131}I uptake %	T/S
Control	(10)	201 ± 6	15.0 ± 1.0	8.2 ± 1.0	27.7 ± 5.1
Melatonin	(10)	183 ± 11	11.8 ± 1.0*	4.3 ± 0.5**	23.4 ± 3.2

Results are expressed as mean ± standard error of the mean.
Significantly different from control value: *P⟨0.05
**P⟨0.001

Body weights of the rats injected with melatonin for 30 days did not differ significantly from the control value (Table II). Thyroid weight is significantly decreased in the melatonin injected rats (Table II). The 24 hour ^{131}I uptake is significantly increased in the melatonin injected group (Table II). T/S ratio of the melatonin treated rats is markedly increased over the control value (Table II), indicating an increased capacity to trap iodide.

It is of interest to note that the marked functional change of increased T/S ratio is not accompanied by a similar morphological change in the thyroid gland. Greer (11) reported an increase in T/S ratio in response to propylthiouracil treatment in rats with hypothalamic lesions although the thyroids failed to show any stimulation. Halmi (12) reported that hypophysectomized rats on a low iodine diet showed a marked increase in T/S ratio without a concommitant effect on thyroid weight after injection of thyroid stimulating hormone.

Table 2. Body weights, thyroid weights and 24 hr. ^{131}I uptakes, and T/S ratios in female, 60-70 day old, Sprague-Dawley rats injected with melatonin daily for 30 days.

Group		Body g	Thyroid		T/S
			Weight mg	^{131}I Uptake	
Control	(10)	195 ± 5	13.2 ± 0.7	4.2 ± 0.3	27.5 ± 2.5
Melatonin	(10)	184 ± 5	11.4 ± 0.6*	6.3 ± 0.6*	36.8 ± 1.3**

Results are expressed as mean ± standard error of the mean.
Significantly different from control value: *P<0.05
**P<0.01

Comparing the groups of rats treated with melatonin for 10 and 30 days it is noted that the body weights of the two groups were similar (Table III). The thyroid weights of both groups were lower than the corresponding control values (Table III). Twenty-four hour ^{131}I uptakes were depressed in the 10 day group and elevated in those rats injected with melatonin for 30 days (Table III). A large difference in T/S ratios was noted between the two groups (Table III). In the 10 day group, the T/S ratio showed a slight, non-significant decrease, while in the 30 day group the T/S ratio was elevated markedly.

Table 3. Comparison of body weights, thyroid weights, and 24 hr. ^{131}I uptakes and T/S ratios in female, 57-70 day old, Sprague-Dawley rats injected with melatonin daily for 10 and 30 days.

Melatonin		Body g	Thyroid		T/S
			Weight g	^{131}I Uptake	
10 Days	(10)	183 ± 11	11.8 ± 1.0	4.3 ± 0.5	23.4 ± 3.0
30 Days	(10)	184 ± 5	11.4 ± 0.6	6.3 ± 0.6*	36.8 ± 1.3**

Results are expressed as mean ± standard error of the mean.

Significantly different from 10 Day value: *P<0.05
**P<0.01

DISCUSSION

Panda and Turner (13) have suggested that melatonin acts as an antithyroid agent. If melatonin exerts an antithyroid action similar to that of propylthiouracil, organification of iodine should be blocked. If melatonin exerts an antithyroid action similar to that of thiocyanate, this could result in a decreased rate of entry of iodide and be reflected as a decreased rate of thyroid hormone secretion. Narang et al., (10) have reported that melatonin caused a decrease in thyroid hormone secretion rate. A decrease in the level of circulating thyroid hormone would result in an increase in thyroid stimulating hormone secretion due to the operation of the negative feedback control system.

Our results seem to indicate that the action of melatonin is similar to that of thiocyante in inhibiting the active transport of iodide into the thyroid gland. This would be reflected as a decrease in T/S ratio. Although a slight decrease is indicated in the rats injected with melatonin for 10 days, the decrease was not significant. It was noted, however, that the uptake of radioiodide was significantly depressed in the 10 day group which might reflect a decrease in the rate of entry of iodide into the thyroid gland. In those rats injected with melatonin for 30 days a significant increase in T/S ratio was observed. The increased uptake of radioiodide in the 30 day group appears to support the increased T/S ratio.

Our data suggest that melatonin may be acting as an antithyroid agent to inhibit the active transport of iodide by the thyroid gland, as noted by the slight, but non-significant decrease in T/S ratio. The subsequent elevation in T/S ratio indicates an increased capacity to concentrate iodide which is a reflection of the increased thyrotropin released in response to the decreased circulating thyroid hormone.

Further studies in our laboratory investigating the organification of iodine and the release of thyroid hormone appear to support the results presented in this paper.

LITERATURE CITED

1. Wakida, K. 1944. Shoka-sen ni kan-sura jikken-teki narabi-ni rinsho-teki kenk-yu; shoka-sen hormone no seibutsugaku-teki kenkyu (Experimental and clinical research on the pineal gland; Part 4 - Biological studies on the pineal gland hormone). Nippon fujinkagakkai zasshi 39: 433-450.

2. Kitay, J. I. and Altschule, M. D. 1954. Effects of pineal extract administration on ovary weight in rats. Endocrinology 55: 782-784.

3. Wurtman, R. J., Axelrod, J., and Chu, E. W. 1963. Melatonin, a pineal substance: Effect on rat ovary. Science 141: 277-278.

4. Chu, E. W., Wurtman, R. J., and Axelrod, J. 1964. An inhibitory effect of melatonin on the estrous phase of the estrous cycle of the rodent. Endocrinology 75: 238-242.

5. Baschieri, L., de Luca, F., Cramarossa, L., de Martino, C., Oliverio, A., and Negri, M. 1963. Modifications of thyroid activity by melatonin. Experentia 19: 15-17.

6. Reiter, R. J., Hoffman, R. A., and Hester, R. J. 1967. Inhibition of ^{131}I uptake by thyroid glands of male rats treated with melatonin and pineal extract. Amer. Zool. 5: 727-728.

7. De Prospro, N. D., de Martino, L. J., and McGuinness, E. T. 1968. Melatonin's effect on ^{131}I uptake by the thyroid glands in normal and ovariectomized rats. Life Sciences 7: 183-188.

8. Goldman, M., Peaslee, M. H., and Naber S. P. 1969. The iodide concentrating mechanism of the thyroid gland in weanling Long-Evans rats injected with melatonin soon after birth. Proc. S. D. Acad. Sci. 48: 33-38.

9. Ishibashi, T., Hahn, D. W., Srivastava, L., Kumaresan, P., and Turner, C. W. 1967. Effect of pinealectomy and melatonin on feed consumption and thyroid hormone secretion rate. Proc. Soc. Exp. Biol. Med. 122: 644-647.

10. Narang, G. D., Singh, D. V., and Turner, C. W. 1967. Effect on melatonin on thyroid hormone secretion rate and feed consumption of female rats. Proc. Soc. Exp. Biol. Med. 125: 184-188.

11. Greer, Monte A. 1951. Evidence of hypothalamic control of the pituitary release of thyrotrophin. Proc. Soc. Exp. Biol. Med. 77: 603-608.

12. Halmi, N. S. 1954. Regulation of the rat thyroid in short-term iodine deficiency. Endocrinology 54: 216-224.

13. Panda J. N. and Turner, C. W. 1968. The role of melatonin in the regulation of thyrotrophin secretion. Acta Endocrinologica 57: 363-373.