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### Thyroid inhibition by $\gamma$ -amino- $\beta$ -hydroxybutyric acid

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BENEDETTI *et al.* (1964) have found that in patients affected by Grave's disease the neuro-psychic symptoms improve following administration of  $\gamma$ -amino- $\beta$ -hydroxybutyric acid (GABOB). They believe this improvement is due to a central action of GABOB. We have resolved to investigate if this drug may modify thyroid activity too. The results shown in this preliminary paper point out that large doses of GABOB depress the function of thyroid gland both in animals and in men.

### EXPERIMENTAL AND RESULTS

In the rat 600-1000 mg/kg per day of GABOB orally administered for 5 days decreased the thyroid uptake of  $^{131}$ iodine ( $I^{131}$ ). A similar result was obtained in the rabbit by s.c. daily administration of 600 mg/kg during 23 days (Table 1).

TABLE 1. EFFECT OF GABOB ON  $I^{131}$  THYROID UPTAKE IN THE ANIMAL. THE DIFFERENCE FROM THE NORMAL IS ALWAYS SIGNIFICANT

Species	No	Drug	mg/kg/day	Route	$I^{131}$ uptake after 24 hr (%)	
					mean	S.D.
rat	10	—	—	—	30.53	7.34
rat	10	GABOB	600	oral	21.76	8.72
rat	10	propyl-thiouracil	10	oral	7.49	3.17
rat	10	—	—	—	30.79	6.09
rat	10	GABOB	1000	oral	20.73	5.29
rat	10	propyl-thiouracil	3	oral	2.27	1.33
rabbit	10	—	—	—	20.04	3.53
rabbit	9	GABOB	600	s.c.	9.18	4.11
rabbit	9	propyl-thiouracil	0.5	s.c.	4.96	1.87

Rats were given a single i.p. injection of  $0.1 \mu\text{C}$  of  $\text{I}^{131}$ \*, while rabbits were injected with  $1 \mu\text{C}$  by the same route. All the animals, along with control groups, were killed 24 hr later. Their thyroids were carefully dissected, rinsed with saline, and counted in a well-type scintillation counter, and the percent  $\text{I}^{131}$  uptake was calculated in comparison to a standard (Money *et al.*, 1959). The histologic picture of the thyroids from rats treated with GABOB showed changes qualitatively very close to those of a group treated with 5-propyl-2-thio-uracil, but less marked; namely, follicles appeared reduced, colloid very scanty, epithelium thickened and somewhere polystratified.

Other experimental results can be considered as effects of the thyroid depression produced by GABOB; for instance, the inhibition of body growth in the young rabbit. Fig. 1 shows the average

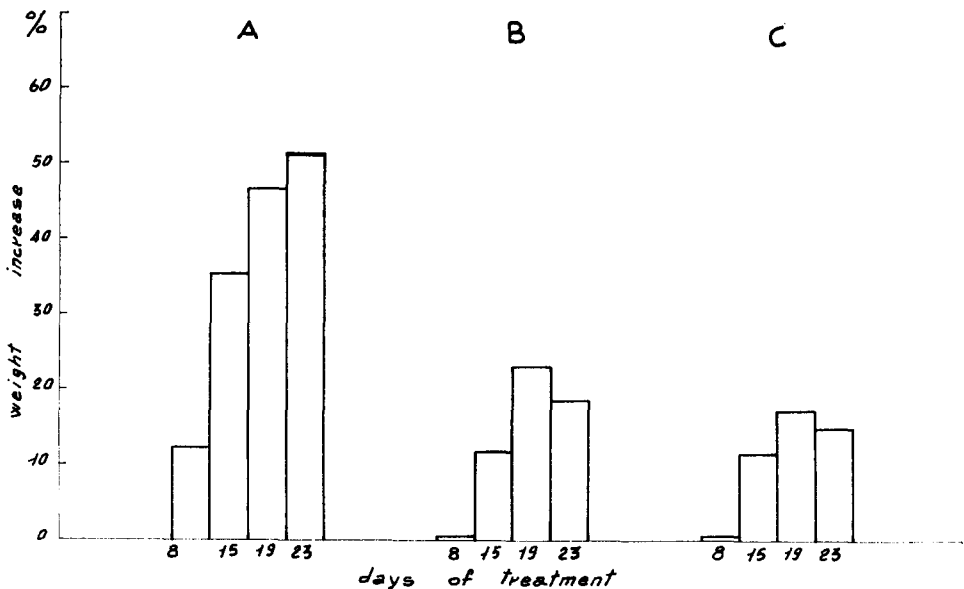


FIG. 1. A = untreated. B = GABOB. C = propyl-thiouracil

body weight increase in rabbits after 23 days of daily s.c. injections of GABOB (600 mg/kg) and, for comparison, the values of quite like animals either untreated or injected with propyl-thiouracil (0.5 mg/kg).

Moreover, GABOB i.p. injected to rats (600 mg/kg/day, for 7 days) reduced their  $\text{O}_2$ -consumption.

In this experiment, two groups of 12 animals each were set aside and placed in an air-conditioned room at  $24^\circ$  of temperature with a relative humidity of 55 per cent. After 4 days, during which the animals were acclimatized, the oxygen consumption of each animal was measured three times on three different days. Next, one group of animals was given 600 mg/kg of GABOB per day by stomach tube; the other group was given 0.5 mg of propylthiouracil per kg and per day, by the same route of administration, for a period of seven consecutive days. At the end of treatment, oxygen consumption were again assessed.

The oxygen consumption of rats was measured with the electrolytic metabolimeter of V. Capraro (Italian patent No. 161117; U.S.A. patent No. 414816) made by the Carlo Erba Company in Milan. Each animal remained in the measuring apparatus for 30 min: the first 10 min for adjustment, and remaining 20 min for actual measuring of oxygen consumption. Because the weight of the animals was very uniform, the oxygen consumption was calculated per animal and per hour.

As shown in Table 2, it was found that treatment with GABOB reduced the oxygen consumption from  $283.83 \pm 17$  ml/hr to  $225.86 \pm 58$  ml/hr, the difference being statistically significant (Student's *t* test).

\* IBS.2P supplied by "The Radiochemical Centre", Amersham, England.

TABLE 2. CHANGES OF OXYGEN CONSUMPTION IN RATS AFTER ADMINISTRATION OF GABOB

Treatment	Oxygen consumption (ml/animal/hr)				no. of observations	Average wt. of animals in g	After treatment	Average wt. of animals in g	No. of observations
	Before treatment	Average wt. of animals in g	no. of observations	After treatment					
GABOB (600 mg/kg/7 days) per os	283.83 ± 17	153.64 ± 12	36	225.86 ± 58*	36	153.75 ± 14			12
PTU (0.5 mg/kg/7 days) per os	285.06 ± 13	152.83 ± 13	36	184.52 ± 33†	36	159.41 ± 16			12

\* P > 0.001, < 0.01.  
† P 0.001.

TABLE 3. EFFECT OF  $\gamma$ -AMINO- $\beta$ -HYDROXY-BUTYRIC ACID (GABOB) ON HUMAN THYROID

No	Age	Days of oral treatment	Total dose (g)	$I^{131}$ Thyroid uptake				PBI-conversion ratio after 24 hr	
				Before treatment		After treatment		Before treatment	After treatment
				6 hr	24 hr	6 hr	24 hr		
1	43	9	27	34.81	60.86	39.86	52.20	37.12	29.24
2	32	9	27	56.47	76.36	56.07	67.75	36.18	31.49
3	47	12	36	38.94	51.32	25.55	42.49	48.24	20.56
4	71	12	36	38.46	58.01	27.69	41.47	35.20	28.75

With propylthiouracil the consumption of oxygen dropped from  $285.06 \pm 13$  ml/hr to  $184.52 \pm 58$  ml/hr, the difference being again statistically significant.

Considering that GABOB is widely used in therapeutics and has low toxicity, we have tried to ascertain if the inhibitory action upon thyroid gland found in the animal would be demonstrated in the human too. For this research we employed four female volunteers, in normal hormonal balance (except No. 2 who showed moderate thyroid hyperfunction), that had not been receiving any treatment since 2-3 months. In order to evaluate the basal level of thyroid activity, first we performed the  $I^{131}$  uptake test 6 and 24 hr after oral administration of  $25 \mu\text{C}$ , and the test of PBI-conversion ratio in plasma after 24 hr.\* Then the four subjects were orally given 3 g a day of GABOB for 9-12 days. After determining the extent of any residual radioiodine over the thyroid and on the plasma, the  $I^{131}$  uptake and PBI-conversion ratio studies were repeated as above. The data are reported in Table 3.

### CONCLUSION

The results obtained suggest that high doses of  $\gamma$ -amino- $\beta$ -hydroxybutyric acid depresses the thyroid function in the animal; this effect seems to be observed also in man.

\* For  $I^{131}$ iodine uptake studies we used a single channel gamma ray spectrometer; the PBI-conversion ratio was determined by the zinc sulfate method.

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