Bull. Inst. Zool., Academia Sinica 13(2): 107-110 (1974)

THE EFFECT OF PROPYLTHIOURACIL ON OXYGEN CONSUMPTION OF LIVER IN THYROIDECTOMIZED RATS[1]

SHUN-YOU LI[2] AND W. CHIA-MO WAN

Institute of Zoology, Academia Sinica, Taipei, Taiwan 115, ROC

Received for publication, September 5, 1974

ABSTRACT

S. Y. Li and W. C. M. Wan (1974). *The effect of propylthiouracil on oxygen consumption of liver of thyroidectomized rats.* Bull. Inst. Zool., Academia Sinica 13(2): 107-110. The oxygen consumption (OC) of liver slices of thyroidectomized (TX) male rats of Sprague-Dawley strain pre-treated with the combination of thyroxine (T_4) and propylthiouracil (PTU) was measured. The OC of the liver slices increased with the increase of pre-treated T_4 superimposed on the constant dose of PTU, while decreased with the increase of PTU superimposed on the constant dose of T_4 however, an uniformed OC can be maintained with appropriated combination of T_4 and PTU dosage. The results indicated that without mediation of the thyroid gland, *in situ*, the PTU decreases the total metabolism of liver, and inhibits partially the peripheral metabolism of T_4. The reaction site(s) of T_4 and PTU could be the same or the related "location".

The effect of thyroxine (T_4) on total body metabolism is a well known fact. It is also known that the propylthiouracil (PTU) inhibits the hormone synthesis by inhibiting the activity of the peroxidase of the gland, and in turn, stops the oxidation of iodide.

During the process of the study on the effect of thyroid hormone deficiency on gonadotrophin, the PTU was used to induce the hypothyroidism. Whether any effect on the liver that will influence the metabolism of gonadotrophin remained to be clarified[7]. The present investigation is subjected to understand the PTU effect on the general metabolism of liver with no thyroid gland present.

MATERIALS AND METHODS

Animal Male rats of Sprague-Dawley strain bred from this laboratory with body weight of 180-220 gm were selected for the present investigaton. The rats were housed in a room of regulated temperature (23 ± 1°C) and light (6:00 am - 6 : 00 pm). The rats were fed on chicken feed (Taiwan Sugar Coorp., Taipei. Taiwan) previous to thyroidectomy, and a food mixture, according to the formula of Jolin *et al.*[8], was given after the operation. The supplement of iodide (2.5 mg KI/L) and calcium lactate (1%) were supplied in drinking water. Both food and water were given *ad*

1. Partially supported by a grant from National Science Council, Republic of China to W. Chia-Mo Wan.
2. Research Institute of Zoology, National Taiwn University.
Present address: Department of Anatomy, Chung-Shan Medical College Taichung, Taiwan.

libtum. Thirty μC of ^{131}I (Tsing Hua University, Hsing Chu, Taiwan) were injected to each rat intraperitoneally 4–5 days after the operation.

Treatment After the operation, the rats were then subjected to thyroxine (T_4; L-thyroxine, Sigma Chemical Co.) and propylthiouracil (PTU; 6-propyl-2-thiouracil, Sigma Chemical Co.) treatment simultaneously.

All dosages for T_4 and PTU were on the basis of 100 gm body weight daily. The combination were as fellow: (1) NT-VPTU group; T_4 of the dose of normal secretion rate (2.2 μg)[14] was injected subcutaneously to each rats, and PTU of various dose levels were injected intraperitoneally to different group of rats. The dose levels of PTU were 1, 2, 4, 8 and 16 mg, with 6–9 rats in each group. (2) VT-PTU group; 4 mg of PTU administrated to all rats, but T_4 dose varied for different groups (2.2, 8.8 and 35.2 μg). (3) VT-VPTU groups, three combinations were included, e. g. *a*, 2.2 μg of T_4 and 2 mg of PTU, *b*, 8.8 μg of T_4 and 4 mg of PTU, *c*, 35.2 μg of T_4 and 8 mg of PTU. The period of treatment was of one week for all groups.

The liver was obtained after 24 hr fasting under ether aneathesia, and immediately put into pre-cooled Krebs-Reinger phosphate buffer. The liver slices were prepared in a cool room (4°C) by Stadie-Riggs tissue microtome. The slices with a thickness less than 0.5 mm and weight of 80–120 mg were selected for oxygen consumption (OC) measuring.

Oxygen consumption Warburg manometric apparatus (MRK, Mitomura Riken, Tokyo, Japan) was employed for OC measuring. The tissue slices were put into the main chamber which contained 3 ml of Krebs-Ringer phosphate glucose solution, and a piece of filter paper socked with 0.2 ml of 20% KOH was placed in the center well for CO_2 absorption. The water bath temperature was maintained at 37°C. After 15 min preincubation the system was cut off from the atomosphere, and the reading of the manometer was taken in every 10 min for 1 hr. The reading and calculation for OC were done by the instructions of Umbreit *et al.*[15] The tissue dried weights were obtained after being dried in an oven for 24 hr at 100°C.

RESULTS AND DISCUSSION

It is known that the total body OC of intact rats decreases with the treatment of PTU[1,6]. This is obviously through the blocking effect of the drug on hormonal production of the thyroid. In order to demonstrate the direct effect of the drugs on the metabolism of liver, the gland of the rats were removed in the present investigation. With the supplement of T_4, in accordance with the normal secretion rate[14], the liver preparations of thyroidectomized (Tx) rats demonstrated a similar OC as those of the normal rats, *e. g.*, 3.15 ± 0.07 (n=24) and 3.11 ± 0.07 (n=24), respectively. However, with the increased PTU dose level administrated to T_4-pretreated Tx rats, the NT-VPTU groups, a significant negative correlation between PTU dosage and the OC was observed (Fig. 1). These results are in agreement with the suggestion of

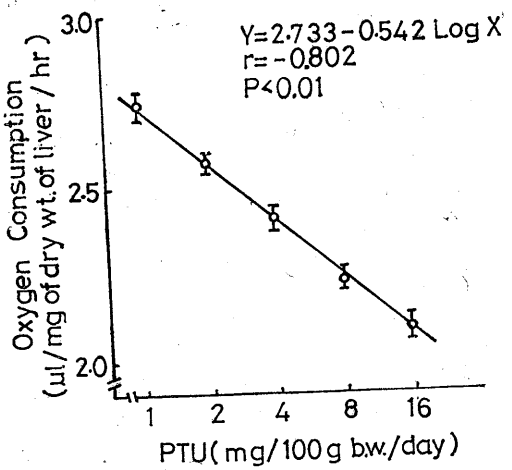

Fig. 1. The dose-response relationship between PTU treatment and oxygen consumption of liver slices of thyroxine (2.2 μg/100 g body weight/day) pre-treated-thyroidectomized rats. Each point represents the mean value (± S.E.) of 24 to 26 observations from 6 rats. The x-axis is in log scale.

previous investigators that PTU inhibits the effect of T_4 at peripheral level[1,6].

It was proposed that the amount of T_4 deiodinated could be used as as an index for the amount of T_4 metabolized, and the inhibitory effect of PTU is mainly on deiodination of T_4[13]. With the treatment of PTU, the metabolites of labelled T_4 in urine excretion decreased, and the metabolites and unmetabolized T_4 increased in feces[11~13]. As shown in Fig. 2, a significant correlation was observed between the OC of liver preparations and the dose of T_4 in VT-PTU groups. This phenomenon implied that only a certain portion of the injected T_4 was under the inhibitory influence of PTU. The effect of T_4 on OC of liver may also determined by its action on the activity of alpha-glycerophosphate dehydrogenase (GPD), and, in turn, on the electron transport mechanism[9,10]. The inhibitory effect of PTU may act on the reaction between T_4 and GPD[5]. However, the machanism of this inhibitory effect was not totally clear[5].

The inhibitory effect of PTU on deiodination of T_4 may lead to the decrease of the T_4 feed back effect of T_4 on TSH secretion[13], however,

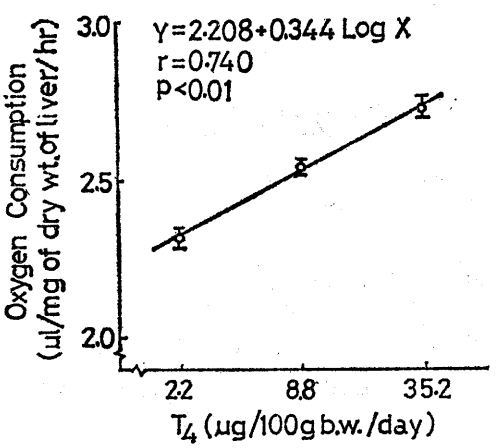

Fig. 2. The dose-response relationship between thyroxine treatment and oxygen consumption of liver slices of PTU (4 mg/100 g body weight/day) pre-treated-thyroidectomized rats. Each point represents the mean value (± S.E.) of 24 observations from 6 rats. The x-axis is in log scale.

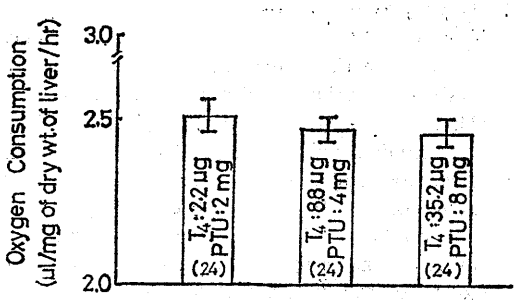

Fig. 3. Oxygen consumption of liver slices of thyroidectomized rats treated with various doses of thyroxine (in µg/100 g body weight/day) and PTU (in mg/100 g body weight/day) in combination. The number of observatians and the mean are shown.

with the thyroid gland removed and with daily supply of constant dose of T_4 in the present experiments, the effect on TSH should be minimized, if not completely disappeared. The deiodination of the drugs, such as tetraprop and triprop, did not increase the GPD activity[5] as that in T_4[1,3,13]. It is possible that the deiodination of T_4 is specific for the activition of T_4. The presence of T_4 is essential to the completion of a certain process which lead to increase OC, and the influence of PTU on this process will only be showed in the presence of T_4[5]. As shown in Fig. 3, there is a dose of PTU for a dose of T_4 that could give a similar OC of liver preparation (VT-VPTU groups). These results, together with that in NT-VPTU groups, may suggest that the inhibitory effect of PTU increased with the increased dose of T_4, and also may imply that the action site(s) for T_4 and PTU could be the same or related "location".

REFERENCES

1. Bray, G. A. and S. Hildreth (1967). Effect of propylthiouracil and methimazole on the oxygen consumption of hypothyroid rats receiving thyroxine or triiodothyroxine. *Endrocrinol.* **81**: 1018-1020.
2. Escobar del Rey, F. and G. Morreale de Escobar (1961). The effect of propylthiouracil on the peripheral metabolism of L-thyroxine in thyroidectomized, L-thyroxine maitained rats. *Endrocrinol.* **69**: 456-465.

3. Galton, V. A. and S. H. Ingbar (1961). The influence of reserpine, serotonin and metabolites of tryptophane on the degradation of thyroxine and its derivatives. *Endocrinol.* **68**: 435-449.
4. Harpor, H. A. (1969). Physiological chemistry, 12th Edition, pp. 155 Lange Medical Publications Los altos, California.
5. Hoffman, W. W., C. A. Richert and W. W. Westerfeld (1966). Effect of thiouracil-type drugs on the α-glycerophosphate dehydrogenase to thyroxine analogs. *Endocrinol.* **26**: 55-63.
6. Hsieh, A. C. L. (1963). The effects of triiodothyroxine and L-thyroxine on the oxygen consumtion and cody weights of rats fed on a diet containing 0.5% propylthiouracil. *J. Endocrinol.* **26**: 55-63.
7. Hwang, J. C., P. H. Li and W. C-M. Wan (1974). Effect of induced hypothyroidism on pituitary luteinizing hormone (LH) concertration in femal rats *J. Formosan med. Assoc.*, **73**: 227-231.
8. Jolin, Y. P., G. Morrdale de Escobar and F. Escobar and F. Escobar del Rey (1968). 6-propyl-2thiouracil vs. $KClO_4$ induced goiters. *Endocrinol.* **83**: 620.
9. Lee, Y. P., A. E. Takemori and H. Lardy (1959). Enhanced oxidation of α-glycerophosphate by mitochondria of thyroid-fed rats. *J. Biol. Chem.* **240**: 1427-1436.
10. Lee, Y. P. and H. A. Lardy (1965). Influence of thyroid hormones on L-glycerophosphate dehydrogenases and other dehydrogenase in various organ of the rat. *J. Biol. Chem.* **240**: 1427-1436.
11. Morreale de Escobar, G. and F. Escobar del Rey (1962). Influence of thiourea, potassiom perchlorate and thiocyanate and of graded doses of propylthiouraicl on thyroid hormone metabolism in thyroidectomized rats, isotopically equilibrated with varying doses of exogenous hormone. *Endocrinol.* **71**: 906-913.
12. Morreale de Escobar, G. and F. Escobar del Rey (1968). Extrathyroid effect some antithyroid drugs and their metabolic consequence. *Recent Prog. Horm. Res.* **23**: 87-137.
13. Mouriz, J., D. Morreale de Escobar and F. Escobar del Rey (1966). Evulation of the peripheral deiodination of thyroxine as an index of its thyrotrophin suppressing effectiveness. *Endocrinol.* **79**: 248-260.
14. Reineke, E. P. and O. N. Singh)1955). Estimation of thyroid secretion rate of intact rat. *Proc. Soc. Exp. Biol. Med.* **88**: 203-207.
15. Umbreit, W. W., R. H. Burros anp J. F. Stauffer (1964). Manometric technique. Minneapolis, Burgess.

丙基硫代二氧嘧啶 (PTU) 對去甲狀腺大白鼠肝臟耗氧量之影響

李 宣 佑　萬 家 茂

大白鼠於甲狀腺切除後，以正常分泌量 (2.2 μg/100 g 體重/天) 之甲狀腺素及不同劑量之 PTU 處理時，在體外測得肝之耗氧量因 PTU 劑量之增加而減少。反之，固定 PTU (4 mg) 而改變甲狀腺素之劑量，則耗氧量因甲狀腺素之劑量增加而增加。若以對等量之甲狀腺素及 PTU (各爲 2.2 μg 及 2 mg；8.8 μg 及 4 mg；35.2 μg 及 8 mg) 所得之耗氧量間無統計上之差異。由此結果似可推論 PTU 有抑制甲狀腺素致使代謝增加之影響，而作用位置或與甲狀腺素同或在相關之處。