From the results in the table it is apparent that there is a linear relationship between the dose and enrichment factor of 5-PD, suggesting no major alterations in clearance or metabolism at the higher doses. Total urinary steroid profiles[3] for the pre and post collections were almost identical again implying that no pharmacological affect was manifested because of the administered steroid.

The close agreement of the enrichment factors from the sulphate and glucuronide fractions of 5-PD (table) confirms previous findings[8] and suggests that the endogenous secretion of pregnenolone sulphate is low[10]. Expectedly, the enrichment factor for PD in most cases is considerably lower than that of 5-PD (table) since it is formed from other sources as well as via peripheral conversion of pregnenolone to progesterone[8]. Substitution in equation (1)[11] gives an average urinary pregnenolone production rate of 5.5 ± 1.3 mg $\cdot$ 24 h^{-1} which is in agreement with prior reports using radioactive isotopes[8].

Enrichment factors for 5-pregnene-3β,20α-diol (5-PD) and 5β-pregnane-3α,20α-diol (PD)

Steroid dose (mg)	Enrichment factors* (atom %) 2.0	3.6	6.0
5-PD			
Sulphate	7.9 ± 1.2**	21.0 ± 1.7	31.1 ± 2.1
Glucuronide	9.3 ± 1.0	19.4 ± 0.8	27.7 ± 1.4
PD			
Glucuronide	3.1 ± 0.5	14.2 ± 0.9	27.0 ± .18

* Mean ± SD based on ion ratio measurements (n = 8) corrected for background. ** Intra-assay CV = 5.0% (n = 4).

$$\text{Production rate} = \frac{a \cdot m}{ef \cdot t} - \frac{m}{t} \quad \ldots (1)$$

a = isotopic purity (%), m = mass (mg), t = days of collection

Extension of this work to more complicated systems in which the use of more than one labelled steroid is required[12] is presently under consideration.

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Oxygen consumption in the rat following neonatal thyrotoxicosis

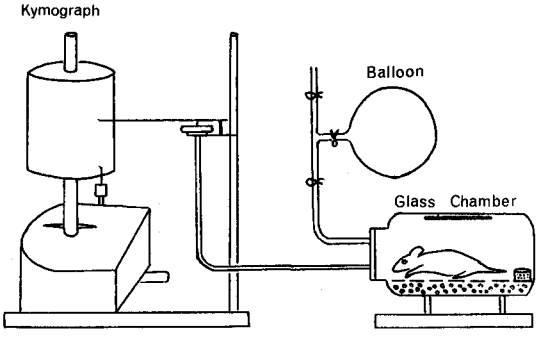
Y.C. Toh

Department of Physiology, The University of New England, Armidale (NSW 2351, Australia), 27 November 1978

Summary. Adult rats made thyrotoxic with large doses of thyroxine during the neonatal period had a lower oxygen uptake as compared with neonatal controls and those of neonatal calorically-deprivated ones.

Rats treated with large doses of thyroxine during the first few days of life (neonatal thyrotoxicosis) results in permanent dysfunction of the hypothalamus-hypophyseal-thyroid system. Adult animals with neonatal thyrotoxicosis exhibit a lower level of protein bound iodine and free thyroxine plasma concentration, smaller thyroid glands, and the pituitary thyrotropin content is diminished[1,2]. Since the hormone influences oxidative metabolism in tissues[3,4], changes in the activity of the gland will be reflected directly by changes in the amount of oxygen utilized. The present investigation is concerned with the effect of an excess thyroxine at birth on the adult oxygen consumption.

Materials and methods. Litters of an inbred colony of Sprague-Dawley rats were randomly divided into different groups, each containing males and females. One third of rats in each litter were injected s.c. with 28 µg of L-thyroxine in 0.05 ml of 0.1 N sodium hydroxide on day 1 and continuing through the 7th day of age. An additional third served as controls, received only the alkaline diluent. Since newborn rats given excess doses of thyroxine lose weight, the effects of neonatal thyrotoxicosis and of neonatal weight loss produced by restricting food intake were compared. For the first week one third of the rats in each litter were removed from their mother for about 8 h daily and were injected as described above with alkaline diluent. After weaning at 4 weeks of age, the animals were fed a laboratory diet and water ad libitum. At the age of 60 days, the oxygen consumption of rats was measured in a glass metabolic chamber (figure) in which carbon dioxide was absorbed by a layer of soda lime on the floor, thus creating a fall in pressure within the chamber as oxygen was consumed. Water vapour produced by the animals were absorbed by calcium chloride in a small container in the glass chamber. The drop of pressure in the chamber was recorded on a Kymograph. The time for the volume of gas in the chamber to fall 40 ml was the time taken for the rat



Apparatus for determination of oxygen consumption in the rat.

The effect of thyroxine treatment in neonatal life on heat production in adult male and female rats

	Sex	Number of rats	Body weight (g)	Heat production/h kJ	kJ/m^2	J/g
Control	M	10	232.09± 9.51	9.44±0.47	17.74±0.80	40.91±1.94
	F	11	168.76± 4.50[f]	8.64±0.49	20.40±1.22[g]	51.41±3.10[f]
Neonatal thyrotoxicosis	M	8	212.75± 8.47	7.90±0.16[ad]	15.81±0.40[ce]	37.40±1.21[e]
	F	6	131.80±14.11[bef]	5.70±0.49[adf]	16.57±1.51[ce]	44.80±4.35
Neonatal caloric deprivation	M	6	223.53± 6.86	9.63±0.52	18.63±1.14	43.30±2.71
	F	7	167.63± 5.49[f]	8.26±0.27[g]	19.71±0.68	49.47±1.87[g]

[a] $p<0.001$–0.005
[b] $p<0.01$ –0.02
[c] $p<0.025$–0.05
} Comparison between control and neonatal thyrotoxicosis.

[d] $p<0.001$–0.005
[e] $p<0.025$–0.05
} Comparison between neonatal caloric deprivation and neonatal thyrotoxicosis.

[f] $p<0.001$–0.005
[g] $p<0.025$–0.05
} Comparison between males and females.

to use 40 ml oxygen. A correction was made for the temperature rise during the measurement. The volume of oxygen consumed was converted to standard condition and the result expressed in terms of international energy unit, joule (J), on the basis of per square meter of surface area and body weight. The square meter of surface area of the animals was calculated from the formula: (Animal weight$^{0.73}\times 10$) : 1000. Statistical evaluation of the data was done with Student's t-test.

Results. The results are summarized in the table. There was no statistically significant differences of body weights in male rats between control, neonatal thyrotoxicosis, and neonatal calorie deprivation. However, the b.wt of female rats treated with thyroxine at birth was smaller as compared with controls ($p < 0.02$) and neonatal rats undergoing caloric deprivation ($p < 0.025$). There was a significant sex difference of b.wt irrespective of treatments, with greater in the male than in the female ($p < 0.001$). The oxygen consumption was significantly reduced in rats made thyrotoxic with large doses of thyroxine during the neonatal period as compared with the control and the neonatal caloric deprivation.

Discussion. The administration of large doses of thyroxine into rats during the first few days of life produces many abnormalities in adults[1,2,5]. These usually include impaired body, pituitary and thyroid growth, diminished pituitary and serum thyrotropin concentrations, and a diminished serum thyroxine. Although the hypothalamic thyrotropin-releasing hormone is increased, its concentration in the circulating blood was found to be significantly reduced, suggesting that thyroid hypofunction secondary to decreased thyroid-stimulating hormone secretion may be the consequence of an impaired hypothalamic secretion of thyrotropin-releasing hormone[2]. This influence of the thyroid gland secretions can be measured readily by determining the rate of oxygen uptake in the animals. The present experiments clearly indicate a reduction of oxygen consumption in rats with neonatal thyrotoxicosis as compared with the controls.

Since in rats neonatal thyrotoxicosis is associated with early weight loss, it might be predicted that caloric deficiency or some factor related thereto, rather than excess of thyroid hormone, is responsible for the abnormalities seen in these rats later in the life. However, Azizi et al.[1] reported that food deprivation during the neonatal period sufficient to produce early growth curves comparable to those seen in thyroxine-treated pups failed to produce subsequent abnormalities in either thyroid-stimulating hormone secretion or thyroid ^{131}I metabolism. In addition, the present investigation shows that there was no difference in oxygen uptake between neonatal calorically-deprived rats and normal control ones (table). On the other hand, the amount of oxygen utilized in rats with neonatal thyrotoxicosis was significantly decreased as compared with calorically-deprived rats.

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DISPUTANDUM

A simple theoretical criterion of chemical carcinogenicity?

E. Ch. Herrmann*

Research Laboratories, Schering AG, Müllerstrasse 178, D-1000 Berlin 65/West, 26 October 1978

Summary. The simple theoretical criterion for chemical carcinogenicity based on the 'average quasi-valence number' is discussed and shown to be inappropriate as a reliable indicator of carcinogenicity of any organic compound.

V. Veljković and D.I. Lalović[1] claim that the 'average quasi-valence number Z*' of an organic compound is a 'simple theoretical criterion for chemical carcinogenicity'. They define

$$Z^* = \left(\sum_i^m N_i Z_i\right) \Big/ \left(\sum_i^m N_i\right) \qquad (1)$$

where N_i is the number of atoms of the i-th type in the given organic compound, Z_i is the number of valence electrons in atom i, and m is the number of different elements in the molecule. For $Z^* > 3.20$, the compound will definitely be a 'noncarcinogen', since this condition is necessary and sufficient. On the other hand for $Z^* < 3.20$,