The Influence of the Thyroid on the Acute Toxicity of a Dynamite-Sensitizing Mixture (36135)

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(Introduced by H. E. Stokinger)

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Ever since the development, by Nobel, of a relatively safe method of preparing and handling nitroglycerine and its analogs, those who are required to come into close contact with it have complained of ensuing headaches (1). This is especially true of certain production plant workers who have coined the name "Monday morning headaches" for the phenomenon which, because of loss of acquired tolerance on Saturday and Sunday, usually occurs on Monday morning.

Occasionally these headaches are preceded by severe anginal attacks which may end in sudden death (2). The exact mode of action is not known nor is there any knowledge of any biochemical parameter which could portend an imminent attack.

Raab (3) has shown that thyroidectomy gives dramatic relief from angina pectoris. He explains this on the grounds that thyroid hormone sensitizes the myocardium to epinephrine, and therefore, removal of the thyroid gland lowers the level of hormone and the resultant desensitization reduces the frequency of anginal attacks.

Our purpose in this experiment was to investigate the influence of thyroid hormone on the acute toxic response to a dynamite-sensitizing mixture.

Materials and Methods. Male CFN (Wistar-derived) rats (weighing 100 g upon receipt) were used in all cases including the hypothyroid study where the supplier performed thyroidectomy prior to delivery. One week was allowed for acclimatization prior to any treatment.

The LD_{50} for a mixture (mix) of organic nitrates (83% ethylene glycol dinitrate, 17% glyceryl trinitrate) was determined by injecting the rats intraperitoneally with a 10% (w/v) solution in peanut oil. The percentage response (death) was converted to probits and plotted against the logarithm of the dose on rectangular coordinate graph paper. The dose level corresponding to a probit of 5 was accepted as the LD_{50}.

The 60 animals selected for the hyperthyroid study were subdivided into three groups: (a) 15 which received thyroxine (T_4); (b) 15 which received tri-iodothyronine (T_3); and (c) 30 which received 0.1 ml of 0.01 *N* NaOH. In the first two groups, the free acid forms of hormone were dissolved in 0.01 *N* NaOH and injected ip daily for 17 days; and the concentrations were adjusted so that 0.1 ml was injected in all cases. The T_4 group received 100 γ per animal, and the T_3 group received 20 μg/animal daily. On day 18, the animals were all challenged with an LD_{50} of mix.

Sixty additional rats were obtained for hypothyroid studies, 30 of which were thyroidectomized and were maintained on 1% calcium lactate in their drinking water. These animals were weighed every Monday, Wednesday, and Friday while we allowed 4 weeks for depletion of residual systemic hormone. On day 28, 22 controls and 30 thyroidectomized animals were challenged with an LD_{50} of mix.

Results. Table I shows the percentage response, in terms of death, of rats to ip injections of serially increased doses of mix. The response (ordinates) is expressed as probits. After the probits (as ordinates) were plotted against log dose (as abscissa) and the curve was eyed in, the LD_{50} was extrapolated by dropping a perpendicular line to the abscissa from the point where the probit 5 intersected the curve. The derived $LD_{50} = 304$ mg/kg.

Pretreating rats with thyroid hormone re-

TABLE I. Acute LD_{50} of Dynamite Mixture in Rats.[a]

Group	No.	Dose (mg/kg)	Deaths No.	Deaths %	Probit
1	11	200	0	0	0.0
2	11	250	0	2.5	3.04
3	11	275	2	18.2	4.08
4	11	300	3	27.3	4.39
5	11	350	11	97.5	6.96

[a] LD_{50} = 304 mg/kg.

sulted in increased sensitivity (Table II) to dynamite mix to the point that the LD_{50} became an LD_{95}. On the other hand, rendering the animals hypothyroid with thyroidectomy followed by a depletion period, made the rats resistant (Table II). There was 100% protection; therefore, the LD_{50} became an LD_0.

TABLE II. Posttreatment Response in Rats to LD_{50}.

Group	No.	Deaths	% Response
Part I. Hyperthyroid phase			
Controls	30	15	50
Hyperthyroid (T_4)	15	14	93
Hyperthyroid (T_3)	15	15	100
Part II. Hypothyroid phase			
Controls	22	14	64
Thyroidectomized	30	0	0

Discussion. The finding that hyperthyroidism potentiates the toxicity of dynamite mix and that hypothyroidism protects against it, is not surprising when one considers the work of Zarrow, *et al.* (4), who demonstrated a similar effect on rats which were subjected to anoxia, and the description by Clark and Litchfield (5) of the mode of death due to propylene glycol dinitrate which was identical to the death due to anoxia.

In 1945, Raab (3) studied the feasibility of using a goitrogen (thiouracil) to treat angina pectoris. His rationale was based on the facts that: (a) epinephrine has an anoxiating effect on heart muscle; (b) epinephrine injections can cause angina; (c) there is an abnormally high level of epinephrine in heart muscle following an anginal attack; and (d) angina pectoris has already been effectively treated by thyroidectomy. In time, 7 of the 10 patients whom he treated with thiouracil became entirely symptom free. In the animal phase of his study, rats which were pretreated with thyroid hormone, making them hyperthyroid, were sensitized to epinephrine by a factor of 6; whereas, those rats pretreated with thiouracil became resistant by a factor of 6.

From the cited studies and from the results of the present work, it is evident that the thyroid system has a profound influence on the acute toxicity of organic nitrates. While this gives us no specific information about chronic intoxication from organic nitrates, it does give us a logical approach to future chronic investigations.

Summary. The effects of hyperthyroidism and hypothyroidism on the acute toxicity of a dynamite-sensitizing mixture were studied in rats. Hyperthyroidism was shown to potentiate the mix while conversely, hypothyroidism antagonized it.

The author is grateful to Dr. Emil Cristofano and Mr. H. A. Read of Hercules Powder Company for the contribution of dynamite-sensitizing mixture and also to Drs. E. J. Fairchild II and H. E. Stokinger and Mr. John T. Mountain of the National Institute for Occupational Safety and Health for their professional guidance.

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Received Sept. 13, 1971. P.S.E.B.M., 1972, Vol. 139.