Reduced Biological Effectiveness of Orally Administered L-Thyroxine In the Rat in the Presence of Blood Plasma. (31787)

T. R. BAUMAN, L. S. SRIVASTAVA, AND C. W. TURNER*†
Department of Dairy Husbandry, University of Missouri, Columbia

The relatively poor oral effectiveness of L-thyroxine (L-T_4) in the rat has been shown previously(1). Recently Chung and Van Middlesworth(2) studied the absorption of L-T_4 from intestinal loops of the rat. They found that within the first hour after introduction of L-T_4-I^{131} into the ligated intestinal loop, 50% of it was absorbed, but there was little further absorption during 3 subsequent hours. They suggested that the L-T_4 remaining in the intestinal lumen appeared to be bound to a large molecule, possibly plasma albumin. It was observed further that when plasma was added to the L-T_4 only 5% was absorbed from ileum loops in one hour.

The object of this study was to determine if rat plasma, added to orally administered L-T_4, inhibited the absorption of the hormone to the same extent as when the hormone was placed directly into the intestine.

Materials and methods. The thyroid secretion rate (TSR) of 30 male rats was determined by a method previously described (3) in which graded doses of L-T_4 were injected to suppress TSH release, thus inhibiting release of thyroidal I^{131}. In this study, 0.4 mg of methimazole/100 g bw was injected daily to prevent recycling of I^{131} from metabolized thyroxine I^{131}(4). It has been reported that methimazole appears to have no extrathyroidal effects in the rat(5). The dose of L-T_4 that inhibited thyroidal I^{131} release (95-100% of previous count) was used as the animals' estimated TSR. This end-point was used in all of the assays using the same group of rats.

For assay of its oral effectiveness, L-T_4 was dissolved in a slightly alkaline saline solution and administered at the rate of 0.1 ml/100 g bw through a stainless steel tube designed for oral administration. Doses were started at the level of 1.5 μg/100 g bw and methimazole was injected at the level of 0.4 mg/100 g bw, and raised 0.25 μg/100 g bw every other day.

For assay of rat plasma plus L-T_4, the L-T_4 was diluted to 5 ml in a slightly alkaline saline solution (to dissolve L-T_4) and added to 45 ml of plasma. The doses given orally (0.1 ml/100 g bw) were started at 2.00 μg/100 g bw every other day. Methimazole was administered daily by subcutaneous injection.

For oral assay of the effect of plasma alone on TSR, it was given at the rate of 0.1 ml/100 g bw and TSR was determined by injecting L-T_4 and methimazole concurrently as in the normal TSR.

L-T_4 (as the sodium salt) was dissolved in 0.1 N NaOH, precipitated with HCl, brought up to volume and stored in the refrigerator. This was then used as a stock solution. Subsequent dilutions for injections were made slightly alkaline (pH 7.5-8.0) with NaOH to redissolve the precipitate.

Plasma used for oral administration was collected as whole blood in heparinized syringes from normal rats of the same strain. The blood was then centrifuged and cells separated from plasma. All plasma was pooled, then frozen in 45 ml aliquots until time for use. Before injections were made, the 45 ml of plasma was thawed and L-T_4 added, then shaken for 30 seconds, and allowed to stand in the refrigerator for 30 minutes.

The rats were maintained at 78° ± 1°F, fed Purina Lab Chow and given water *ad libitum*.

Results. The normal TSR of this group of 30 mature, male Sprague-Dawley-Rolfsmeyer rats (380-480 g) was found to be 1.21 ± .24 μg L-T_4/100 g bw, with a range from 0.75 to 1.50 μg/100 g bw.

L-T_4, given orally, required a mean dose of 2.51 ± .30 μg L-T_4/100 g bw to block

* Contribution from Missouri Agr. Exp. Sta. Journal Series 4039. Approved by Director.

† Aided in part by a grant from U.S. Atomic Energy Commission, Contract At(11-1)-301-131.

thyroidal I^{131} release rate. A range of doses from 2.00 to 3.00 μg/100 g bw was found to be effective, giving the oral doses a mean efficiency of 48.2% of the injected L-T_4.

Rat plasma mixed with L-T_4, administered orally, required a mean dose of 3.55 ± .49 μg/100 g bw to block thyroidal I^{131} release rate. A range of doses from 2.50 to 4.25 μg/100 g bw was found to be effective, giving the oral dose of L-T_4 plus plasma an efficiency of 34.1% of the injected L-T_4. This represents a highly significant 30% reduction in biological effectiveness as compared to oral L-T_4 ($P<.001$).

Rat plasma given orally, during a normal TSR determination (where L-T_4 and tapazole were injected subcutaneously) had no significant effect on TSR. The mean TSR during this trial was 1.24 ± .20 μg L-T_4/100 g bw, with a range in doses from 1.00 to 1.75 μg/100 g bw.

Discussion. It has been shown that the biological effectiveness of L-T_4, L-T_3 and thyroprotein is markedly reduced when administered orally as compared to subcutaneously(1). Since L-T_4 is an amino acid, its absorption from the digestive tract would be expected to be very efficient as is the absorption of other amino acids. A possible explanation of the reduced absorption of L-T_4 by the digestive tract was suggested by Chung and Van Middlesworth(2) who reported that L-T_4 was absorbed rapidly during the first hour when placed in an intestinal loop but that little further absorption took place due to its binding to a large molecule, possibly albumin, secreted into the lumen. They reported further that, when plasma was mixed with the L-T_4 introduced into a loop, the absorption was reduced to 5%.

The present experiment was initiated to determine if rat plasma administered orally with L-T_4 would have an effect upon the biological effectiveness of the hormone as measured by the TSR technique in the same group of rats. The study showed that when L-T_4 was administered orally in saline, the L-T_4 was 48% as effective as by subcutaneous administration whereas when administered orally with rat blood plasma, the effectiveness was reduced to 34%, a significant reduction of 30%. These data suggest that while the absorption of L-T_4 in the digestive tract may be impeded by the normal secretion of plasma proteins into the intestine, the presence of increased amounts of plasma proteins introduced orally with the L-T_4 further decreases L-T_4 absorption.

Summary. The efficiency of absorption of an orally administered dose of L-thyroxine (L-T_4) in saline was found to be 48% compared to subcutaneous administration using the thyroid secretion rate (TSR) as an index. The addition of rat blood plasma to the L-T_4 before oral administration reduced its biological effectiveness to 34%, a significant reduction of 30% in comparison to oral L-T_4. These data suggest that the reduced biological effectiveness of oral L-T_4 may be due, in part, to a plasma-binding protein (TBP) in the intestines to which the L-T_4 becomes bound and fails to be absorbed.

1. Bauman, T. R., Turner, C. W., Proc. Soc. Exp. Biol. and Med., 1966, v123, 9.

2. Chung, S. J., Van Middlesworth, L., Endocrinology, 1964, v74, 694.

3. Bauman, T. R., Pipes, G. W., Turner, C. W., ibid., 1965, v76, 537.

4. Hendrick, C. E., Turner, C. W., Proc. Soc. Exp. Biol. and Med., 1965, v119, 174.

5. Grosvenor, C. E., Endocrinology, 1962, v70, 934.

Received September 30, 1966. P.S.E.B.M., 1967, v124.