RAPID COMMUNICATION

Evidence for Stimulation of Thyroidal Secretion by Iodoaminoacids or Iodide

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Synopsis

Iodoaminoacids or iodide, in a dose containing 50 μ g iodine stimulated intracellular colloid droplet formation and radioactive iodothyronine release in mouse prepared for McKenzie bioassay. Theophyllin enhanced those effects on both aspects. Those results may explain thyroglobulin-induced enhancement of thyroidal secretion currently drawing attention of many investigators.

Thyroglobulin was repeatedly shown to stimulate thyroidal secretion in mice prepared for McKenzie bioassay, enhancing both intracellular colloid droplet formation and prelabelled radioiodine release (Wood *et al.*, 1971; Burke *et al.*, 1972), whereas the mechanism involved has remained unexplored. In the recent publication, Burke stated that the products of degradation of thyroglobulin, namely, iodoaminoacids and iodide were not effective in stimulating the thyroidal secretion, although he did not show any evidences supporting this comment.

Our study examines the acute effect of iodoaminoacids or iodide on thyroidal secretion to add more information on the mechanism of secretion.

Iodide (KI), monoiodotyrosine (MIT), diiodotyrosine (DIT), triiodothyronine (T_3) or thyroxine (T_4) was dissolved in a small amount of 0.1 N NaOH and diluted with saline to a concentration containing 100 μ g iodine per ml. A solution of tyrosine, 100 μ g per ml was

prepared in a similar fashion. Theophyllin was dissolved in saline or in the solution described above to give a final concentration of 1.0 mg/ml. 0.5 ml of each solution was injected into the tail vein of a mouse prepared for McKenzie bioassay as described previously (Shishiba *et al.*, 1973). When the effects on radioiodine release were studied, blood specimens were obtained from orbital sinus before, 3 hr, 8 hr and 24 hr after injecting test substances. Blood radioactivity was counted by a well-type scintillation counter with spectrometer. To know the identity of radioiodine increased in the blood, pooled serum was obtained and applied to a 7×1 cm Dowex resin column. Radioiodine fractionation was performed as described by Pileggi *et al.* (1964). When the effect on thyroidal intracellular colloid droplets was studied, the animal was sacrificed 1 hr after injection of the test substances. Thyroid glands were removed with trachea, fixed with Bouin's solution and stained with PAS. Colloid droplets were counted on the 25 follicles examined without the knowledge of the identity of the slides. Each group consists of 8 animals, five being for radioiodine release study and remaining three for histological examination.

As summarized in Table 1, KI, MIT, DIT, T_3 or T_4 elicited an obvious increase in blood radioactivity showing a peak response 8 hr to the level 3 to 5 times that of control, while tyrosine was not effective in this respect. Theophyllin 0.5 mg, although not effective by itself, exaggerated the effect of iodoami-

Table 1. Stimulation of Thyroidal Secretion by iodoaminoacids or iodide

Test Substance	Response Index (%)			Colloid droplets per 25 follicles
	3 hr	8 hr	24 hr	
Control	96 ± 8	122 ± 6	115 ± 27	9 ± 5
Theophyllin alone	105 ± 23	115 ± 32	118 ± 36	14 ± 2
KI	174 ± 38	276 ± 43	214 ± 18	142 ± 68
KI + T	237 ± 81	448 ± 159	250 ± 37	230 ± 108
MIT	193 ± 49	297 ± 62	172 ± 47	80 ± 66
MIT + T	370 ± 70	675 ± 204	275 ± 24	312 ± 69
DIT	270 ± 133	387 ± 73	202 ± 51	107 ± 38
DIT + T	514 ± 157	692 ± 227	241 ± 33	589 ± 203
T ₃	336 ± 70	520 ± 68	320 ± 24	299 ± 188
T ₃ + T	383 ± 140	545 ± 144	341 ± 57	221 ± 46
T ₄	202 ± 23	369 ± 126	190 ± 98	150 ± 38
T ₄ + T	174 ± 58	338 ± 119	236 ± 80	131 ± 57
Tyrosine	100 ± 22	123 ± 22	125 ± 20	15 ± 9
Tyrosine + T	99 ± 27	133 ± 55	136 ± 58	25 ± 12

noacids or iodide to a various extent. The radioactivity obtained at 8 hr after KI, MIT or DIT combined with theophyllin was more than twice that obtained with the former alone. Theophyllin failed to enhance the effect of T₃ or T₄. When the radioactivity of pooled serum obtained at 8 hr in individual group was analyzed by Dowex resin column method, almost all the radioactivity was recovered in the fraction where iodothyronine was eluted.

Table 1 also summarizes the result of experiments in which the effect of iodoaminoacids or iodide on intracellular colloid droplet formation was studied separately or in combination with theophyllin. Iodoaminoacids or iodide elicited an obvious peak response in terms of intracellular colloid droplet formation at 1 hr, different from TSH or LATS which did so at 1/2 hr or 2 hr respectively. When the effect of iodoaminoacids or iodide was studied in combination with theophyllin, an increase in the response was observed for KI, MIT or DIT. Here again, theophyllin failed to enhance the effect of T₃ or T₄. Tyrosine or theophyllin alone was not effective on both radioiodine release and colloid droplet formation.

The results described demonstrate that

iodoaminoacids or iodide stimulate thyroidal secretion, enhancing intracellular colloid droplet formation and radioiodothyronine release like TSH or LATS does. The similarity suggests that their action is a stimulation of thyroidal secretion (Shishiba *et al.*, 1967; Pinchera *et al.*, 1965). The synergistic effect of theophyllin on the action of MIT, DIT or iodide may suggest that cyclic AMP is participating (Bastomski *et al.*, 1968).

The reason of the failure of theophyllin to enhance the action of T₃ or T₄ is currently undetermined. It is our assumption that if appropriate timing of sampling was adopted, theophyllin might be shown to stimulate the action of T₃ or T₄.

From the fact that tyrosine was not effective in this regard, the stimulation may be elicited by the iodide derived from de-iodination *in vivo*. Relevant to this possibility, Nagataki and his associates reported the enhanced radioiodine release by iodide in McKenzie assay animal in a form of abstract (1972). Our results are in contrast to the comment stated by Burke, who reported that iodoaminoacids or iodide was not effective in inducing intracellular colloid droplets and radio-iodine release, though no data was given. It is not possible for us to explain the

discrepancy except that the preparation of McKenzie assay animal was different especially in the schedule for suppression by T_3 . Administration of T_3 , 4 hr prior to the injection of iodoaminoacids or iodide may well mask the response because of the possible thyroid effect of T_3 *per se* here described (Shishiba *et al.*, 1973 abstract).

References

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