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# Glucagon and Gastrointestinal Motility in Relation to Thyroid-Parathyroid Function

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## ABSTRACT

Gastrointestinal propulsive motility was studied after intragastric deposition of a non-absorbable isotope in rats after subcutaneous glucagon injections. Glucagon administration was followed by retardation of gastric emptying. The results indicated that the retarding effect of glucagon on gastrointestinal propulsion was independent of the presence of both thyroid and parathyroid tissue. The hypocalcemic effect of glucagon was exerted independently of the presence of thyroid tissue, i.e. thyrocalcitonin.

## INTRODUCTION

Glucagon is known to influence gastrointestinal motility. In man, Dotevall & Kock (2) observed that glucagon retarded gastrointestinal motility independently of the hyperglucemia. In dogs, glucagon retarded motility of the stomach and of the colon but not of the ileum (7). Nor in rats was any influence by glucagon found on small intestine (11).

Parathyroid hormone and glucagon were assumed to act antagonistically in pancreatitis in man, where glucagon-induced hypocalcemia presumably elicited a secondary hyperparathyroidism (9). Parathyroid hormone accelerated and parathyroidectomy retarded gastric emptying in rat experiments performed in our laboratory (10, 6). Thus, opposite effects of parathyroid hormone and glucagon seem to exist both on serum calcium level and on gastrointestinal propulsive motility. However, changes in parathyroid function in rats did not alter the pancreatic islet cells neither quantitatively nor qualitatively (3).

The aim of the present study was to test experimentally the effect of glucagon on gastrointestinal propulsive motility in relation to thyroid and parathyroid function.

## MATERIAL

The material consisted of 109 male albino rats (Sprague-Dawley) fed on laboratory food and with free access to water. The animals were distributed at random in following series:

### Series I

The influence of glucagon on gastrointestinal motility in intact rats. The observation period was 7 days.

1. Intact rats given 1.2 mg glucagon/kg body weight (GN-A,  $n=6$ )
2. Intact rats given 4.8 mg glucagon/kg body weight (GN-B,  $n=5$ )
3. Intact rats given 9.6 mg glucagon/kg body weight (GN-C,  $n=12$ )
4. Intact rats given glucine buffert (GLY,  $n=10$ ).

### Series II

The influence of glucagon on gastrointestinal motility in parathyroidectomized rats. The animals were given 4.8 mg glucagon/kg body weight. The observation period was 90 days.

1. Parathyroidectomized rats with a verified parathyroidectomy (V,  $n=11$ )
2. Parathyroidectomized rats with a non-verified parathyroidectomy (NV,  $n=9$ )
3. Intact rats used as controls (C,  $n=8$ )

### Series III

The influence of glucagon on gastrointestinal motility in thyroparathyroidectomized rats. The observation period was 14 days.

1. Thyroparathyroidectomized rats with a verified reduction of serum calcium level given 4.8 mg glucagon/kg body weight (TP-V-GN,  $n=19$ )
2. Thyroparathyroidectomized rats with a verified serum calcium reduction given glucine buffert (TP-V-GLY,  $n=18$ )
3. Thyroparathyroidectomized rats with a non-verified serum calcium reduction given 4.8 mg glucagon/kg body weight (TP-NV-GN,  $n=6$ )
4. Thyroparathyroidectomized rats with a non-verified serum calcium reduction given glucine buffert (TP-NV-GLY,  $n=5$ )

The groupings and the mean weights of the animals in the three series are shown in Table I.

Table I. Characteristics of the groups

Group	No. of rats	Mean initial weight, g		Mean weight change, %, after 7 days		14 days		35 days		85 days		90 days	
		M	S.E.M.	M	S.E.M.	M	S.E.M.	M	S.E.M.	M	S.E.M.	M	S.E.M.
<i>Series I</i>													
GN-A	6	270	5.2	-6.5	0.4								
GN-B	5	217	1.8	11.6	0.5								
GN-C	12	222	1.7	10.5	0.6								
GLY	10	233	8.2	6.7	2.3								
<i>Series II</i>													
V	11	242	4.9	3.5	1.3					62.6	6.9	53.3	9.4
NV	9	246	4.9	3.7	1.4					49.0	12.9	51.8	11.0
C	8	238	5.8	6.2	1.4					48.8	15.8	51.9	14.5
<i>Series III</i>													
TP-V-GN	19	235	3.0	7.8	0.9	12.2	0.8						
TP-V-GLY	18	234	1.9	9.9	0.7	11.8	0.5						
TP-NV-GN	6	240	3.2	9.6	2.2	13.2	2.3						
TP-NV-GLY	5	238	4.2	5.0	3.7	7.4	2.4						

Glucagon Novo® (Novo Industri A/S, Copenhagen), lot B 66, was administered subcutaneously in doses of A 1.2 mg, B 4.8 mg and C 9.8 mg glucagon/kg body weight. The injections were given 45 min before recording gastrointestinal motility, i.e. 15 min before deposition of the radioactive test meal (see below).

Gastrointestinal motility was studied according to the method of Derblom et al. (1). This gave a graphic recording of the quantitative distribution of a known absorbable radioactive ( $\text{Na}_2^{51}\text{CrO}_4$ ) test meal in the gastrointestinal tract. The recordings were carried out 30 min after deposition of the radioactive dose into the stomach by gavage. The curve representing the distribution of the radioactivity was divided into 11 parts, one for the stomach and 10 equal parts for the small bowel. Each fraction was analysed planimetrically. The value for each fraction was expressed as a percentage of the given dose.

Serum calcium level was consecutively determined by spectrophotometry (Eppendorph). Peripheral blood was used except at the end of the experiments, when blood was taken from the heart. The coefficient of variation of the calcium determinations calculated on 131 duplicate readings was found to be 5.1%.

Parathyroidectomy was performed by coagulation of the parathyroids with a fine diathermy needle (5). The parathyroidectomy was considered "verified" if the serum calcium concentration, 1 week postoperatively, was reduced to  $\leq 4.1$  mEq/l, which implicates the one-sided confidence limit of 95%.

#### Statistical methods

Data concerning serum calcium level for the different groups were compared in pairs and subjected to Student's *t*-test. Gastric retentions for the different groups were

similarly compared in pairs and subjected to Student's *t*-test.

## RESULTS

### Serum calcium level (Table II)

In series I, when the three doses (1.2 mg, 4.8 mg and 9.6 mg/kg body weight) of glucagon were compared with glucine buffert injections, only the last two doses were followed by significant hypocalcemia ( $p < 0.001$ ).

In series II, neither in intact (group C) nor in parathyroidectomized rats (groups V and NV) was any significant change ( $p > 0.05$ ) in serum calcium level found despite administration of glucagon in a dose of 4.8 mg/kg body weight.

In series III, glucagon administration to thyro-parathyroidectomized rats with a verified serum calcium reduction (TP-V-GN) did not induce a further serum calcium decrease than after glycine buffert treatment (TP-V-GLY). However, the serum calcium reduction was highly significant in group TP-V-GN ( $p < 0.001$ ) but almost significant in group TP-V-GLY ( $p < 0.05$ ). In rats subjected to a combined thyro-parathyroidectomy but without verified serum calcium reduction (TP-NV-GN), administration of glucagon was followed by an almost significant serum calcium decrease ( $p < 0.05$ ) but no significant decrease ( $p > 0.05$ ) was seen in glycine buffert treated controls (TP-NV-GLY).

Table II. Serum calcium level

Group	No. of rats	Mean initial serum calcium level		Mean serum calcium level after										
		M	S.E.M.	7 days		14 days		35 days		85 days		90 days		
				M	S.E.M.	M	S.E.M.	M	S.E.M.	M	S.E.M.	M	S.E.M.	
Series I														
GN-A	6	5.3	0.06	5.3	0.11	NS								
GN-B	5	5.2	0.08	4.1	0.04	***								
GN-C	12	5.1	0.05	4.6	0.06	***								
GLY	10	5.2	0.07	5.0	0.15	NS								
Series II														
V	11	5.1	0.06	2.9	0.14			2.8	0.20	3.5	0.18	3.5	0.15	NS
NV	9	5.1	0.09	4.4	0.25			4.8	0.08	4.9	0.09	4.8	0.06	NS
C	8	5.2	0.10	4.8	0.08			4.7	0.07	4.8	0.18	4.6	0.21	NS
Series III														
TP-V-GN	19			2.9	0.04	2.7	0.04	***						
TP-V-GLY	18			2.9	0.07	2.7	0.06	*						
TP-NV-GN	6			5.0	0.04	4.7	0.10	*						
TP-NV-GLY	5			5.1	0.13	4.8	0.07	NS						

The levels of significance are indicated in the table with NS= $p>0.05$ , \*= $p<0.05$ , \*\*= $p<0.01$  and \*\*\*= $p<0.001$  after the last one of the two compared values. Glucagon was given 45 min before the last readings.

### Gastric emptying

In series I (Fig. 1), glucagon was followed by retardation of gastric emptying in intact rats, and the retardation was more pronounced in rats given a larger dose of glucagon (GN-A, GN-B, GN-C with gastric retention of 52, 57 and 61 %, respectively) compared with corresponding controls given glycine buffert (GLY with gastric retention of 28 %). The difference from the control group GLY was significant ( $p<0.01$ ) for groups GN-A and GN-C and almost significant ( $p<0.05$ ) for group GN-B.

In series II (Fig. 2), glucagon treatment induced retardation of gastric emptying independently whether the rats were intact (C with gastric retention of 67 %) or parathyroidectomized (groups NV and V with gastric retention of 74 and 70 %, respectively), and no significant difference was found between the three groups ( $p>0.05$ ).

In series III (Fig. 3), glucagon was followed by pronounced retardation of gastric evacuation in rats subjected to thyroparathyroidectomy (TP-V-GN with gastric retention of 66 %) when compared with glycine buffert treatment of rats submitted to a combined thyroparathyroidectomy and with a verified serum calcium reduction (TP-V-GLY with gastric retention of 35 %) ( $p<$

0.001). The difference in gastric retentions between the groups TP-NV-GN (44 %) and TP-NV-GLY (23 %) was not statistically significant ( $p>0.05$ ).

### Intestinal propagation

In series I (Fig. 1), the percentual distribution of the radioactive dose in the small intestine in intact rats given glucagon was harmoniously accumulated in the middle of the small bowel and it seemed to be due to the amount delivered from the stomach (groups GN-A, GN-B, GN-C and GLY).

In series II (Fig. 2), the percentual distribution of the radioactive dose in the small intestine of intact (C), parathyroidectomized rats (V and NV) following glucagon administration showed no marked relation to the degree of parathyroid dysfunction.

In series III (Fig. 3), glucagon treatment in rats with combined thyroparathyroidectomy and with a verified serum calcium reduction (TP-V-GLY) was followed by an extensive intestinal distribution of the small amount delivered from the stomach which did not differ principally from that seen in controls given glycine buffert (TP-

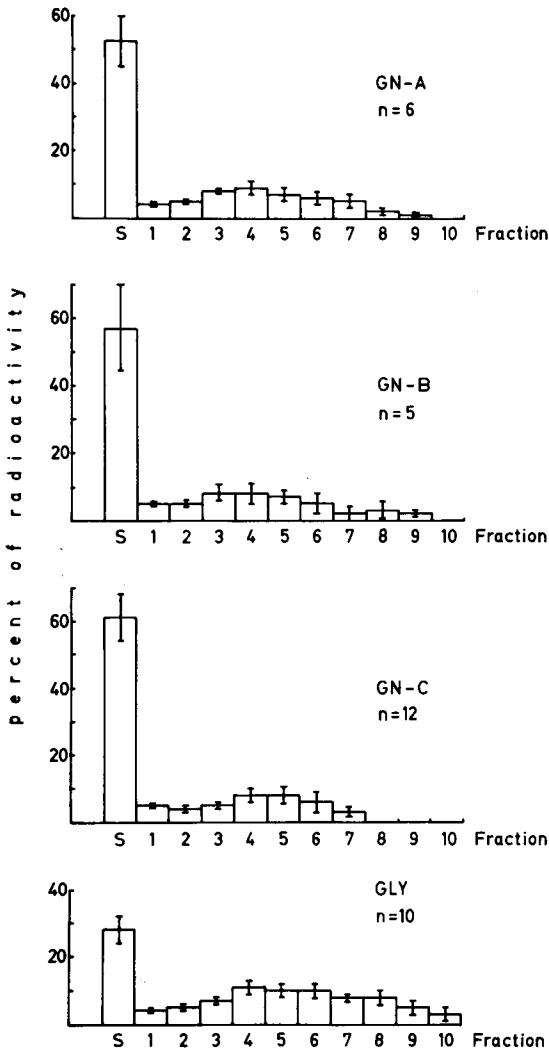


Fig. 1. Histograms showing the percentile distribution of the radioactive test meal in the stomach and fractions of the small bowel for the groups in Series I. The top bars represent the S.E.M. For the symbols of the different groups, see text.

V-GLY). The intestinal propagation in group TP-NV-GN was similar with that of group TP-NV-GLY.

## DISCUSSION

Two of the employed three doses of glucagon in the present study are larger than the doses (0.4 mg and 1.6 mg/kg body weight) used by Hattner et al. (4) in rat studies on the hypocalcemic effect of glucagon. The retardation of gastroin-

testinal motility after glucagon administration was exerted essentially on gastric emptying. The glucagon influence on the small bowel seemed to depend only on what was delivered from the stomach and this finding is consistent with the results of Stickney et al. (11) who found no glucagon influence on small bowel motility in the rat. Analogous results were found when the influence of parathyroid hormone on small bowel motility was studied by Nilsson & Segerström (8).

In the present study (series II) the retardation after glucagon administration was independent of different states of parathyroid function and of different serum calcium levels. The retardation

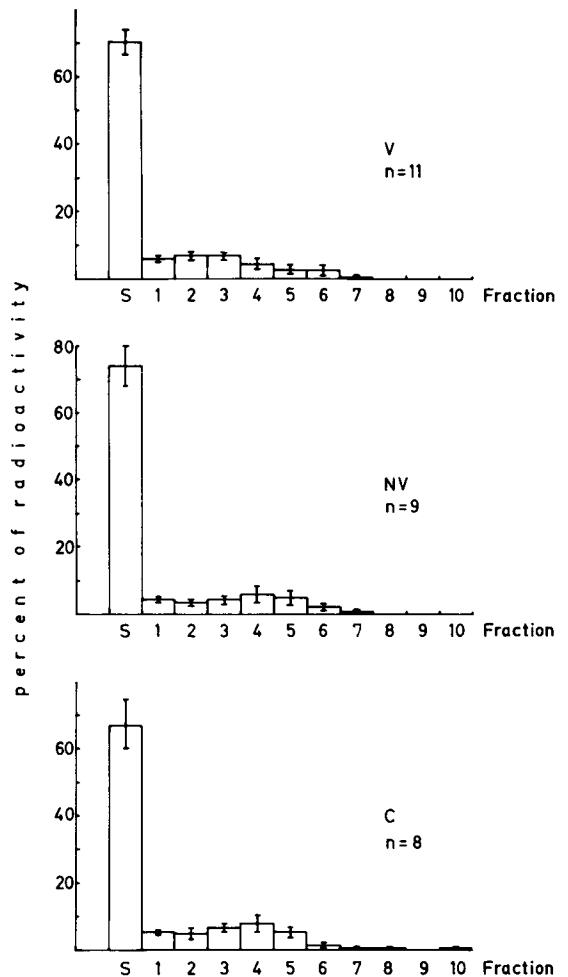


Fig. 2. Histograms showing the percentile distribution of the radioactive test meal in the stomach and fractions of the small bowel for the groups in Series II. The top bars represent the S.E.M. For the symbols of the different groups, see text.

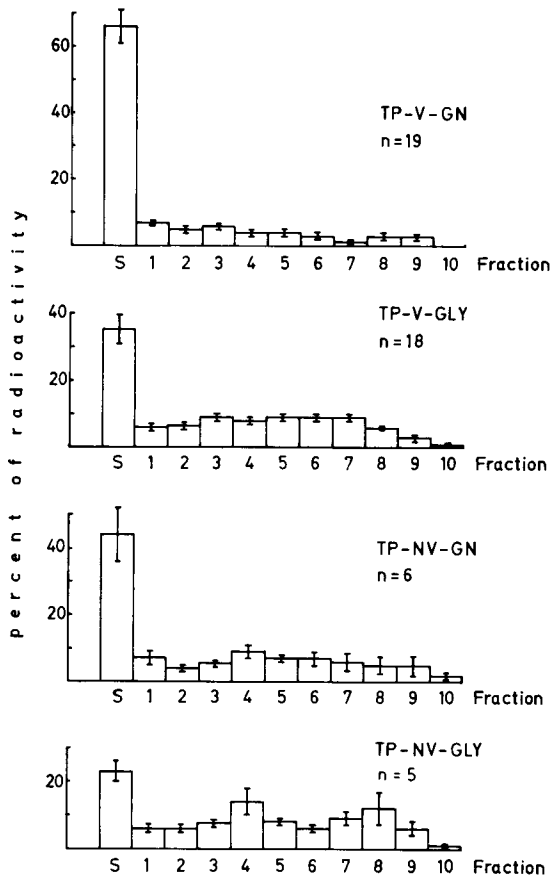


Fig. 3. Histograms showing the percentile distribution of the radioactive test meal in the stomach and fractions of the small bowel for the groups in Series III. The top bars represent the S.E.M. For the symbols of the different groups, see text.

in series II found 12 weeks after parathyroidectomy must completely be due to administration of glucagon when earlier results (6) are considered. These results showed that parathyroidectomized rats 12 weeks postoperatively had identical gastrointestinal motility when compared with propagation in intact animals.

In contrast to the effect of glucagon on gastrointestinal propulsion in rats with parathyroidectomy alone, the hormonal influence in animals with combined thyroparathyroidectomy was dependent of different serum calcium levels. Thus, when parathyroidectomy was combined with simultaneous thyroidectomy the effect of glucagon was dependent upon the degree of the parathyroid function. This was evident from the findings in

series III, where the results showed that the glucagon effect on gastrointestinal motility in hypothyroidism was more pronounced in the presence of a verified parathyroidectomy (66%) than in a combination with a non-verified parathyroidectomy (44%). Furthermore the retarding effect of glucagon was not statistically significant in glucagon treated thyroparathyroidectomized rats with a non-verified serum calcium reduction when compared with corresponding glycine treated controls.

Hattner et al. (4) concluded that thyrocalcitonin is unnecessary for the hypocalcemic effect of glucagon. Despite the fact that the hypocalcemic effect of the glucagon in a dose of 4.8 mg/kg body weight was not uniform in the present study, our results confirmed their finding that thyrocalcitonin was unnecessary for the hypocalcemic action of glucagon.

In the present study the retarding effect of glucagon was recorded 45 min after its administration. In pilot studies when glucagon was given 90 min before recording of gastrointestinal motility we did not observe any hypocalcemic or retarding effect despite the fact that similar doses of glucagon were used as in the present investigation. These findings indicate that the glucagon action has a short duration.

In conclusion, our results showed that glucagon retards gastrointestinal propulsion regardless of the presence of the thyroid or parathyroid tissue. This does not necessarily exclude a relationship between pancreatic and thyro-parathyroid function but not even these experiments provide any proof of such a possibility.

## ACKNOWLEDGEMENTS

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