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A COMPARATIVE STUDY OF THE RENAL ACTIONS OF GROWTH AND LACTOGENIC HORMONES IN RATS

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INTRODUCTION

Single injections of bovine growth hormone diminish the rates of the urinary excretion of sodium, potassium and water by normal rats (Lees, Lockett & Roberts, 1964), but increase the rates of the urinary excretion of sodium and potassium by rats which have been pretreated with propylthiouracil (Lockett & Nail, 1964). Our first interest has been to compare the renal effects of human, bovine and ovine growth hormone in normal rats and in rats pretreated with propylthiouracil.

Secondly, since the human growth hormone and the lactogenic hormone appear electrophoretically similar (Ferguson & Wallace, 1961; Barrett, Friesen & Astwood, 1961) we have compared the renal actions of the bovine and ovine growth hormones sent us by the Endocrine Study Group of the U.S.A. with those of ox and sheep prolactin prepared by Dr K. A. Ferguson and Mr A. L. C. Wallace.

METHODS

Female Wistar rats, 150–210 g, drank water freely and were fed *ad libitum* on a pellet diet manufactured as follows: premix 4 g calcium pantothenate, 4 g riboflavin, 26 g (Apac) vitamin A and D_2, 30 g vitamin E and add to each ton of a mixture containing wheat, 999; barley, 250; lucerne, 100; whalemeal, 100; rock phosphate, 40; salt, 10; oyster flour, 10; milk powder, 150; brewers' yeast, 30, and molasses, 112 parts (Wesfarmers Pty., Perth W.A.).

All rats were accustomed to handling and to stomach tubes before use and were maintained at a room temperature of 22–24° C. Each assay was designed as a series of cross-over tests in which each animal afforded individual data. Equal numbers of each treatment were allocated to each day. Tests were made every third day and began with a 2 hr period during which rats were deprived of solid food. The oral water load, equivalent to 2·5 % body weight, was given at the end of this period immediately before each animal was put into a separate cage for the collection of all urine formed in the next hour. Since, after practice, almost every rat micturated spontaneously when held gently and firmly under restraint for the administration of the water load, suprapubic pressure was used to empty rat bladders solely to terminate urinary collections. Since the rate of excretion of sodium has been shown to fall throughout the day (Lees *et al.* 1964), all cross-over tests which have constituted a single assay were made at a time of day fixed for each separate assay.

Time-effect curves

In the first series of experiments (Fig. 1) rats were deprived of solid food for 2 hr before and throughout the experiment, which began with the oral administration of the standard water load (2·5 % body weight) and collection of all urine entering the bladder in the following hour. Solutions of hormones or of alkaline saline were injected intraperitoneally as the animals were removed from the metabolism cages. Further similar water loads preceded subsequent 1 hr periods of urine collection. The effect of the hormone was measured as a percentage change in the initial rate of excretion of sodium; the animals injected with saline alone were used to measure the extent of the diurnal variation in urinary sodium. In later experiments (Fig. 2) single groups of twelve to sixteen rats were used to determine a series of curves by multiple cross-over tests in which each rat received each hormone and equal numbers of each treatment were allocated to each day. The animals used for these experiments were pretreated with propyl thiouracil because this treatment reduced diurnal variation in the urinary excretion of sodium. Time-effect curves for the action of hormones given intramuscularly were also made by multiple cross-over tests. The rats used had not, however, received propylthiouracil (Fig. 3).

Hormones and drugs

Pure bovine and ovine growth hormone (Endocrine Study Group, U.S.A.) and also human growth hormone (Dr K. A. Ferguson, C.S.I.R.O., Prospect, N.S.W.) and bovine (Dr K. A. Ferguson) and ovine (Dr K. A. Ferguson and Mr A. L. C. Wallace) lactogenic hormones (Ferguson, 1964; Harris, Rubenstein, Ferguson & Beck, 1965) were dissolved in 0·9 % NaCl which had been brought to pH 9·0–9·5, 100 μg/ml.: these solutions were stored at 7° C, and were used within 18 days. Dilutions were made immediately before intraperitoneal injection in a volume of 0·1 ml. per rat. Propylthiouracil, 10 mg/100 g rat per day, was given orally, suspended in 0·1–0·2 ml. olive oil for 3 weeks before and throughout experiments requiring this pretreatment. The hypothyroid state of rats so treated was confirmed in the absence of significant weight change, by highly significant bradycardia and reduction in respiratory rate as shown by a small animal plethysmograph (Electronic Medical Specialties, Cleveland, Ohio) coupled to an Offner Dynograph (Lockett & Nail, 1964).

Chemical procedures

Concentrations of sodium and potassium in urine were determined by flame photometry. The influence of hormones on creatinine clearance was measured as previously described (Botting, Farmer & Lockett, 1961). All mean values shown in tables and figures are accompanied by their standard errors.

RESULTS

Assays of the renal actions of human, bovine and ovine growth hormone, in rats

Three assays were made to compare the effects of single intraperitoneal injections of human (HGH) and bovine (BGH) growth hormone on the rates of urinary excretion of water, sodium (Na) and potassium (K) in the third hour after injection of hormone into normal rats (Table 1, Expts. I–III). HGH was, weight for weight, approximately twice as active as BGH in reducing the rate of the urinary excretion of Na in each of these experiments. Similarly, the increase in the rate of urinary excretion of Na caused by 2·5 μg HGH equated with that caused by 5·0 μg BGH in rats

TABLE 1. Comparison of changes induced in the rates of urinary excretion of water, sodium and potassium by single I.P. injections of human, ovine and bovine growth hormone. All measurements were made in rats during the third hour after injection of hormone

Expt.	Body weight (g)	Excretion rates per 100 g rat per hour				Growth hormone per rat
		Water (ml.)	Na (μ-equiv)	K (μ-equiv)	Na/K	
Normal rats						
I	150 ± 3·1 (12)	1·68 ± 0·26	10·2 ± 3·15	22·2 ± 3·16	0·44 ± 0·11	Nil
		1·57 ± 0·25	5·2 ± 1·22**	17·9 ± 4·93	0·31 ± 0·07*	2·5 μg human
		1·73 ± 0·22	9·3 ± 1·94	22·7 ± 5·37	0·39 ± 0·07	5·0 μg bovine
		1·78 ± 0·24	6·0 ± 1·21**	15·5 ± 2·82*	0·46 ± 0·13	10·0 μg bovine
II	190 ± 5·7 (10)	1·74 ± 0·20	18·5 ± 4·41	20·8 ± 5·01	0·95 ± 0·16	Nil
		1·57 ± 0·25	5·2 ± 1·22**	17·9 ± 4·93	0·31 ± 0·07**	2·5 μg human
		1·69 ± 0·24	3·9 ± 0·74**	15·2 ± 2·81	0·23 ± 0·05**	5·0 μg human
		1·73 ± 0·22	9·3 ± 1·94*	22·7 ± 5·37	0·39 ± 0·07**	2·5 μg bovine
		1·78 ± 0·24	6·0 ± 1·21**	15·5 ± 2·82	0·46 ± 0·13**	5·0 μg bovine
III	206 ± 3·1 (10)	2·20 ± 0·13	11·9 ± 1·38	16·3 ± 1·82	0·75 ± 0·06	Nil
		1·87 ± 0·24	10·2 ± 1·03	12·0 ± 2·44	0·93 ± 0·07	2·5 μg human
		2·14 ± 0·16	7·2 ± 1·50*	20·2 ± 2·34	0·35 ± 0·05**	5·0 μg human
		2·30 ± 0·13	7·0 ± 1·38*	17·8 ± 1·97	0·42 ± 0·09**	10·0 μg bovine
IV	188 ± 3·3 (10)	1·99 ± 0·15	14·1 ± 3·55	22·7 ± 4·52	0·71 ± 0·05	Nil
		1·64 ± 0·09	10·4 ± 2·68	18·4 ± 3·55	0·57 ± 0·04	5·0 μg bovine
		2·06 ± 0·22	4·9 ± 1·79**	12·7 ± 2·78*	0·39 ± 0·06*	10·0 μg bovine
		1·87 ± 0·21	6·3 ± 2·17**	13·9 ± 3·31*	0·45 ± 0·03*	7·5 μg bovine
V	198 ± 2·8 (9)	2·07 ± 0·18	10·6 ± 1·42	16·1 ± 1·84	0·67 ± 0·03	Nil
		1·91 ± 0·21	9·3 ± 1·52	17·4 ± 2·24	0·52 ± 0·04	5·0 μg ovine
		1·83 ± 0·17	5·7 ± 0·96**	11·9 ± 1·76*	0·49 ± 0·03	10·0 μg ovine
		1·86 ± 0·09	6·8 ± 1·77**	12·2 ± 1·58*	0·57 ± 0·05	7·5 μg bovine
Rats pretreated with propylthiouracil						
VI	174 ± 3·9 (10)	1·90 ± 0·22	14·8 ± 1·60	24·2 ± 1·66	0·57 ± 0·16	Nil
		1·58 ± 0·20	21·8 ± 3·39*	16·8 ± 2·09	1·40 ± 0·22**	2·5 μg human
		1·82 ± 0·22	23·7 ± 3·51**	20·9 ± 2·78	1·18 ± 0·12**	5·0 μg human
		1·78 ± 0·23	16·3 ± 2·91	19·6 ± 2·30	0·78 ± 0·08	2·5 μg bovine
		1·59 ± 0·25	21·7 ± 3·12*	24·6 ± 4·14	1·22 ± 0·18**	5·0 μg bovine
VII	185 ± 3·2 (11)	1·82 ± 0·19	6·9 ± 1·77	11·8 ± 2·14	0·56 ± 0·036	Nil
		1·73 ± 0·16	10·6 ± 1·78*	18·7 ± 2·67*	0·55 ± 0·042	2·5 μg ovine
		1·30 ± 0·16*	30·5 ± 4·54**	28·7 ± 4·74**	1·15 ± 0·125**	5·0 μg ovine
		1·56 ± 0·18*	28·1 ± 6·13**	26·3 ± 6·00**	1·15 ± 0·203**	5·0 μg bovine

The significance of differences between means was examined by t tests in which each rat served as its own control. Significant changes induced by hormones are indicated by asterisks: *, $P < 0.05$; **, $P < 0.01$.

pretreated with propylthiouracil (Table 1, Expt. VI). In these particular experiments, both hormones had only a small effect on the rate of urinary excretion of K, and hence marked influence on Na/K. The time-effect curve for HGH differed markedly from that for BGH. Figure 1 shows rectangles relating the percentage decrease in the rate of urinary excretion of Na (as ordinates) to the time in hours (as abscissae) caused by I.P. injection of 5 μg HGH and 10 μg BGH into normal rats. The maximum intensity of the action of HGH was reached in the third hour but that of BGH was delayed until the sixth hour. Whereas the effect of HGH had disappeared, that of BGH was still strongly apparent in the ninth hour after injection.

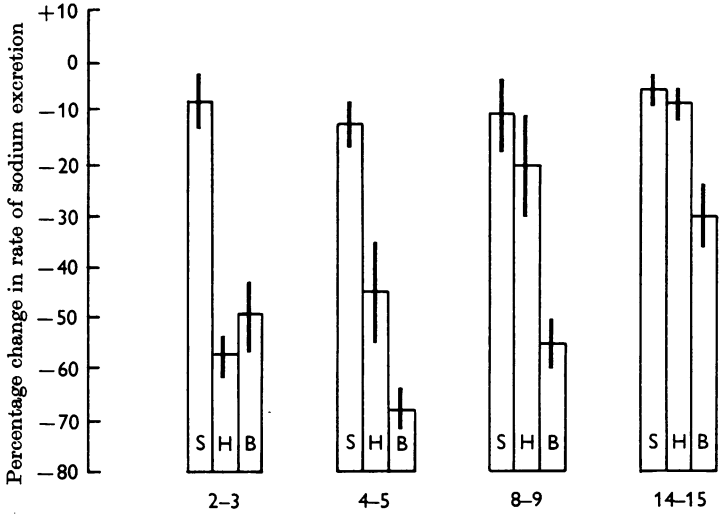

Fig. 1. Time-effect curves for the actions of 5 μg human growth hormone (H) and of 10 μg bovine growth hormone (B) rate of urinary excretion of sodium by rats. Hormones injected I.P. The heights of the rectangles indicate mean percentage changes as compared with pre-injection control values in the rate of excretion of urinary sodium caused by I.P. injections of 0·1 ml. 0·9 % NaCl (S), or of saline containing growth hormone. Black inset rectangles depict S.E. of means in this and the following figures.

There were no significant differences between the urinary changes induced by BGH and ovine growth hormone (OGH) in the third hour after injection, either in normal (Table 1, Expts. IV and V) rats or in those pretreated with propylthiouracil (Expt. VII). The influence of the growth hormones on K excretion was more evident in these experiments; hence their effect on Na/K was proportionately lessened.

Comparison of the renal actions of bovine and ovine growth and lactogenic hormones (LH) in rats

No qualitative or quantitative differences were found (Table 2) between the renal actions of BGH and BLH (Expts. VIII and XII), OGH and OLH (Expts. IX, XIII and XIV) or between BGH and OLH (Expts. X and XI) in the third hour after intraperitoneal injection into normal rats or into rats pretreated with propylthiouracil. Over-all, these hormones caused equivalent reductions, weight for weight, in the rates of urinary excretion of Na by normal rats, and equivalent increases in the urinary Na of rats pretreated with propylthiouracil. Like but lesser changes in the rates of urinary excretion of K varied in intensity from one experiment to the next. Hence the Na/K of the urine from normal rats was reduced and the Na/K of the urine from the pretreated rats was raised by these hormones, to variable extent.

The time-effect curves for the renal actions of the growth and lactogenic hormones given either intraperitoneally (Fig. 2) or intramuscularly (Fig. 3) were not significantly different (Fig. 2). This observation was confirmed by comparison of the urinary changes induced by these hormones in the sixth hour after their intraperitoneal injection (Table 3). No significant differences were found between the actions of OLH and OGH (Expts. XV, XVII and XVIII) or between those of BLH and BGH (Expts. XVI and XIX) either in normal rats or in rats which had been pretreated with propylthiouracil.

The doses of ovine and bovine growth and lactogenic hormones used did not modify rates of the urinary excretion of creatinine (Figs. 2 and 3) significantly.

DISCUSSION

Demonstration of the ability of bovine, ovine and human growth hormones (Table 1) to cause sodium retention in rats accords with the growth-promoting actions of the human, monkey, whale and bovine hormones in hypophysectomized animals of this species (Li, Papkoff & Jordan, 1959) despite differences in the molecular structure of these hormones (Li, 1960).

The intense but short-lasting action of the human hormone injected I.P. (Fig. 1) should probably be related to its relatively small molecular weight and hence to its more rapid absorption, for Li (1960) has given the molecular weight of the human hormone as 27,000 and of the bovine hormone as 45,000.

The urinary changes caused by the hormones resemble and should, without doubt, be ascribed to direct renal actions which have been demonstrated on the perfused cat kidney (Lockett & Roberts, 1963; Lockett, 1964). Lack of precision in estimates made on whole animals

TABLE 2. Comparison of changes induced in the rates of urinary excretion of water, sodium and potassium by single I.P. injections of growth hormone (Endocrine Study Group U.S.A., prepared by Wilhelmi's method) and lactogenic hormone prepared by Dr K. A. Ferguson (Prospect, N.S.W.). All measurements were made in rats during the third hour after injection of hormone

Expt.	Body weight (g)	Excretion rates per 100 g rat per hour: Water (ml.)	Na (μ-equiv)	K (μ-equiv)	Na/K	Hormone per rat
Normal rats						
VIII	193 ± 2·4 (11)	1·46 ± 0·21	14·1 ± 3·16	23·5 ± 4·23	0·68 ± 0·08	Nil
		1·64 ± 0·16	10·5 ± 1·60	28·4 ± 3·49	0·48 ± 0·12*	7·5 μg bovine growth
		1·58 ± 0·235	8·8 ± 4·70**	16·9 ± 2·32*	0·46 ± 0·08*	10·0 μg bovine lactogenic
		1·48 ± 0·117	4·7 ± 0·87**	13·8 ± 1·61*	0·33 ± 0·06**	5·0 μg bovine lactogenic
IX	193 ± 2·2 (10)	1·49 ± 0·20	14·0 ± 2·30	19·0 ± 3·27	0·76 ± 0·07	Nil
		1·66 ± 0·16	3·6 ± 0·84**	13·7 ± 1·27*	0·30 ± 0·08**	10·0 μg ovine growth
		1·55 ± 0·20	7·3 ± 1·41*	17·0 ± 3·06	0·47 ± 0·01*	5·0 μg ovine growth
		1·99 ± 0·21	4·9 ± 1·08**	14·6 ± 1·39	0·36 ± 0·09**	7·5 μg ovine lactogenic
X	163 ± 2·0 (12)	2·02 ± 0·19	15·1 ± 1·63	28·3 ± 3·10	0·56 ± 0·79	Nil
		1·89 ± 0·24	8·3 ± 1·35**	22·3 ± 2·93	0·43 ± 0·08	5·0 μg bovine growth
		1·92 ± 0·18	6·2 ± 0·71**	20·8 ± 3·40	0·26 ± 0·06*	10·0 μg bovine growth
		1·79 ± 0·18	6·1 ± 0·86**	19·4 ± 5·08*	0·25 ± 0·06*	10·0 μg ovine lactogenic
XI	149 ± 3·2 (11)	1·89 ± 0·23	21·4 ± 3·83	42·6 ± 7·02	0·55 ± 0·10	Nil
		2·09 ± 0·18	8·7 ± 2·19**	29·8 ± 3·88*	0·39 ± 0·30*	10·0 μg bovine growth
		1·83 ± 0·17	8·3 ± 2·01**	30·0 ± 4·52*	0·34 ± 0·07*	10·0 μg ovine lactogenic
		2·30 ± 0·16	10·3 ± 1·81**	29·9 ± 2·55*	0·45 ± 0·06	5·0 μg ovine lactogenic
Rats pretreated with propylthiouracil						
XII	207 ± 2·5 (12)	1·81 ± 0·15	6·9 ± 0·83	16·8 ± 1·97	0·47 ± 0·23	Nil
		1·74 ± 0·16	15·4 ± 1·73**	18·8 ± 1·82	0·93 ± 0·13*	2·5 μg bovine growth
		1·51 ± 0·17	19·0 ± 2·02**	18·2 ± 2·23	1·14 ± 0·20**	5·0 μg bovine growth
		1·60 ± 0·22	14·8 ± 1·55**	19·6 ± 2·14	0·97 ± 0·12*	2·5 μg bovine lactogenic
		1·83 ± 0·20	21·0 ± 2·19**	26·8 ± 2·66*	0·81 ± 0·08**	5·0 μg bovine lactogenic
XIII	185 ± 1·4 (10)	1·46 ± 0·28	9·9 ± 2·01	19·9 ± 4·38	0·48 ± 0·02	2·5 μg ovine growth
		1·36 ± 0·25	18·4 ± 5·52††	26·6 ± 8·91	0·88 ± 0·27†	5·0 μg ovine growth
		1·32 ± 0·20	10·5 ± 3·03	21·0 ± 5·87	0·49 ± 0·08	2·5 μg ovine lactogenic
		1·27 ± 0·26	29·6 ± 5·91††	39·3 ± 1·84†	0·80 ± 0·15†	5·0 μg ovine lactogenic
XIV	208 ± 2·7 (8)	1·38 ± 0·17	10·9 ± 0·73	22·2 ± 0·97	0·64 ± 0·11	2·5 μg ovine growth
		1·33 ± 0·20	20·3 ± 1·41††	27·5 ± 1·45†	0·88 ± 0·17†	5·0 μg ovine growth
		1·32 ± 0·19	10·4 ± 0·70	22·3 ± 1·44	0·72 ± 0·15	2·5 μg ovine lactogenic
		1·40 ± 0·20	23·6 ± 1·44††	32·2 ± 1·41†	0·86 ± 0·17†	5·0 μg ovine lactogenic

The significance of differences between means was examined by t tests in which each animal served as its own control. Asterisks are used to indicate significant differences caused by the use of a hormone; daggers indicate significant changes caused by an increase in the dose of a hormone: *, $P < 0{\cdot}05$; **, $P < 0{\cdot}01$.

TABLE 3. Comparison of the changes induced in the rates of the urinary excretion of water, sodium and potassium by I.P. injections of growth hormone (Endocrine Study Group) and of lactogenic hormone (Ferguson). All measurements were made 5–6 hr after injection of hormone

Expt.	Body weight (g)	Excretion rates per 100 g rat per hour: Water (ml.)	Na (μ-equiv)	K (μ-equiv)	Na/K	Hormone per rat
Pretreated with propylthiouracil						
XV	161 ± 4·2 (12)	2·35 ± 0·17	6·4 ± 2·01	16·4 ± 2·70	0·41 ± 0·24	Nil
		2·52 ± 0·14	16·9 ± 1·33**	25·9 ± 5·14*	0·63 ± 0·12*	10·0 μg ovine lactogenic
		2·31 ± 0·26	14·6 ± 2·89**	21·8 ± 2·93*	0·65 ± 0·14*	10·0 μg ovine growth
XVI	159 ± 3·9 (16)	1·71 ± 0·17	10·2 ± 1·55	16·9 ± 1·83	0·70 ± 0·11	Nil
		1·83 ± 0·11	16·4 ± 2·16**	17·2 ± 1·62	0·97 ± 0·15*	10·0 μg bovine lactogenic
		1·92 ± 0·18	15·2 ± 1·10**	18·8 ± 2·95	0·91 ± 0·13*	10·0 μg bovine growth
Normal rats						
XVII	209 ± 2·3 (8)	1·28 ± 0·26	18·2 ± 0·27	28·2 ± 5·75	0·79 ± 0·13	Nil
		1·56 ± 0·22	10·5 ± 1·93**	21·3 ± 3·83*	0·50 ± 0·05*	10·0 μg ovine lactogenic
		1·67 ± 0·27	8·3 ± 1·25**	19·7 ± 4·20*	0·46 ± 0·06*	10·0 μg ovine growth
XVIII	194 ± 4·0 (7)	1·53 ± 0·11	16·3 ± 2·76	26·2 ± 3·64	0·63 ± 0·12	Nil
		1·52 ± 0·09	8·1 ± 2·47**	16·5 ± 2·77*	0·47 ± 0·09*	10·0 μg ovine lactogenic
		1·36 ± 0·08	6·4 ± 0·77**	13·1 ± 1·17*	0·53 ± 0·08*	10·0 μg ovine growth
XIX	207 ± 5·1 (9)	1·61 ± 0·23	11·2 ± 2·31	17·6 ± 2·21	0·63 ± 0·12	Nil
		1·49 ± 0·21	6·8 ± 1·97**	12·4 ± 1·75*	0·55 ± 0·08	10·0 μg bovine lactogenic
		1·52 ± 0·18	6·2 ± 2·13**	10·8 ± 1·92*	0·59 ± 0·10	10·0 μg bovine growth

The significance of differences between means has been examined by t test. Asterisks denote significant effects of hormones. *, $P < 0·05$; **, $P < 0·01$.

(Tables 1–3) may have hidden any small difference between intensities of the renal effects of these hormones. Hence inability to distinguish between the renal actions of bovine and ovine growth hormone (Table 1) is not evidence of the absence in rats of the slightly greater renal effect of the ovine hormone as shown by the perfused cat kidney (Lockett, 1964).

Inability to distinguish between the renal actions of pure preparations of ovine and bovine growth hormones prepared by Wilhelmi's technique

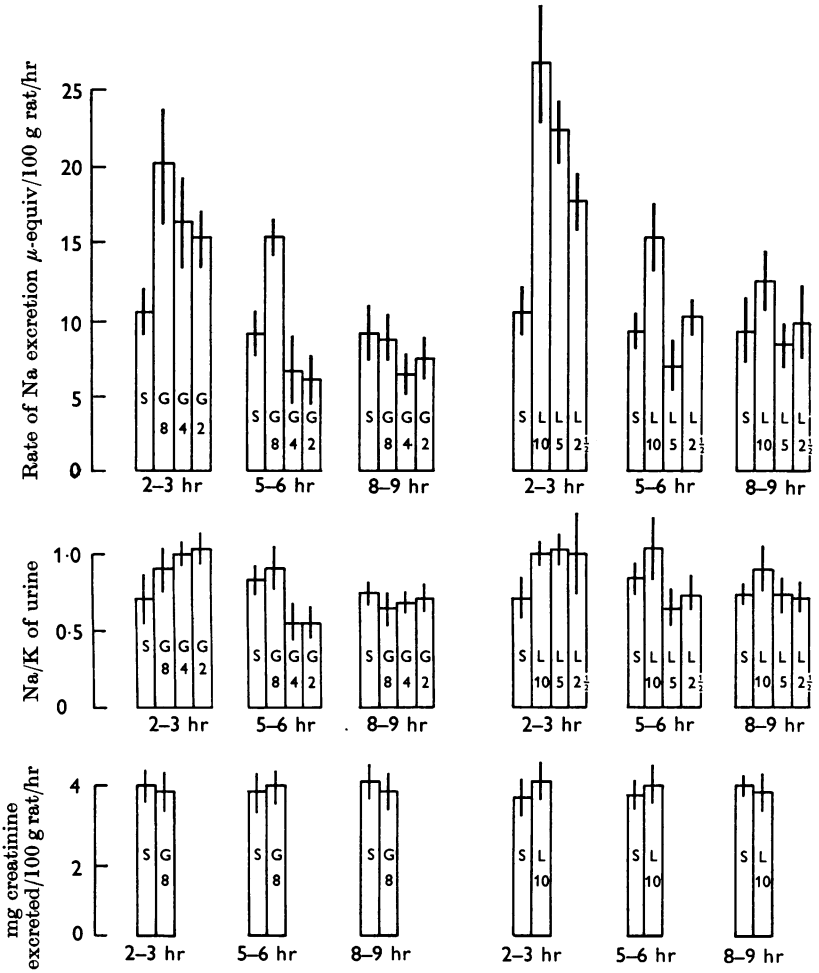

Fig. 2. Time-effect curves for the actions of ovine growth (G) and lactogenic (L) hormones on urinary sodium, Na/K and creatinine in rats pretreated with propylthiouracil. Hormones injected I.P. The heights of the rectangles show mean rates of Na excretion (above) and mean value for Na/K (centre) and mean rates of creatinine excretion (below). On the left, control (S) values, and effects of 8, 4 and 2 μg ovine growth hormone per rat; on the right, control (S) values and effects of 10, 5 and 2·5 μg ovine lactogenic hormone.

(1956) and corresponding prolactins prepared by Sephadex filtration and DEAE cellulose chromatography (Ferguson & Wallace, 1961; Harris *et al.* 1965) demonstrates (Table 3) a great similarity between the renal actions of these hormones. The similarity of the human growth and lactogenic hormones has already been demonstrated, for Irie & Barrett (1962) found them immunologically identical and Ferguson & Wallace (1961) could not separate them electrophoretically.

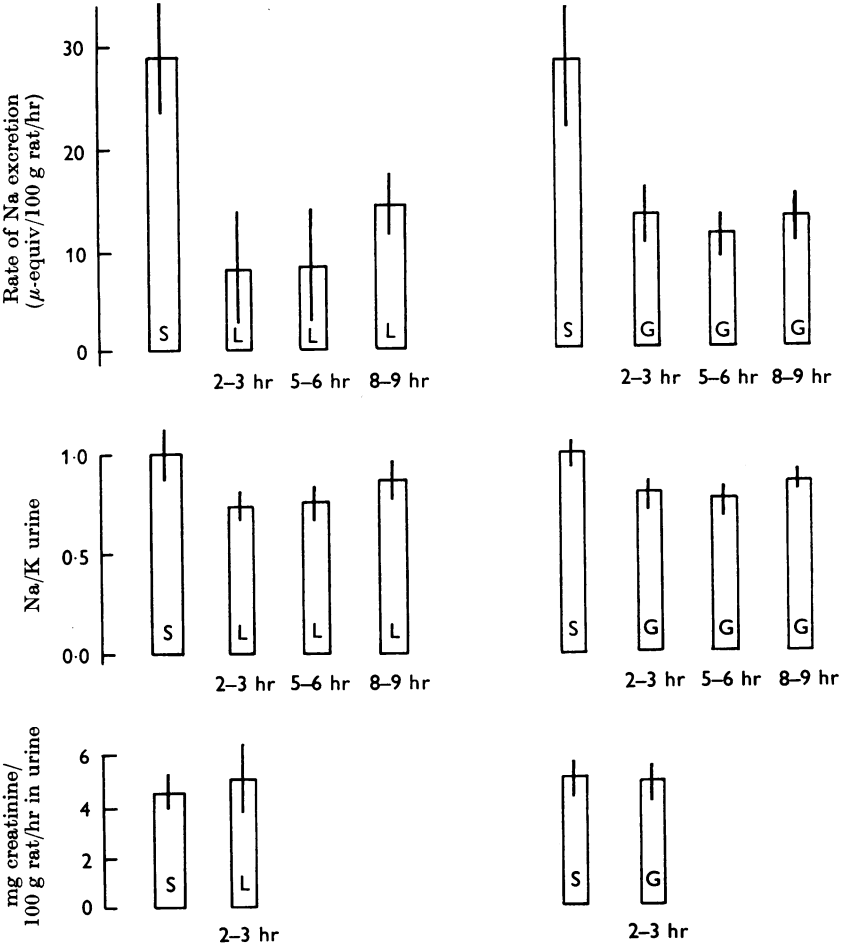

Fig. 3. Time-effect curves for the actions of ovine growth (G) and lactogenic (L) hormones on urinary sodium, Na/K and creatinine in normal rats. Hormones injected I.M. The heights of the rectangles show mean rates of Na excretion (above), mean values for Na/K (centre) and mean rates of creatinine excretion (below). On the left, control values and the effects of 60 μg ovine lactogenic hormone per rat; on the right, control values and the effects of 60 μg ovine growth hormone per rat.

SUMMARY

1. Single intraperitoneal injections of 2·5–10 μg human, bovine and ovine growth hormone reduced the urinary excretion of sodium by normal rats, but increased the urinary sodium of rats pretreated with propylthiouracil, during water diuresis.

2. Human growth hormone had twice the activity of the bovine hormone in the third hour after injection, but had shorter duration of effect.

3. Single intraperitoneal injections of pure bovine and ovine lactogenic hormones produced changes in urinary sodium indistinguishable in intensity and in duration from those caused by the corresponding growth hormones.

4. Single intraperitoneal injections of these growth and lactogenic hormones caused no measurable changes in the urinary excretion of creatinine.

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