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In Vivo and *In Vitro* Effects of Human Growth Hormone on Rat Intestinal Ion Transport

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ABSTRACT

It has been reported that: *1*) ovine growth hormone stimulates intestinal water, sodium, and chloride absorption and *2*) specific growth hormone receptors are present in the rat intestine. Aims of this work were to investigate the effects of acute administration of hGH on water and ion transport in the rat ileum *in vivo* and *in vitro*. *In vivo*, the absorption rates of water, sodium, chloride, and potassium were determined in the rat perfused ileum, during a basal period and after i.v. administration of 6 μg/kg recombinant DNA-derived hGH. *In vitro*, electrical parameters were measured before and after the hormone addition to the mucosal or the serosal side of rat ileal mucosa mounted in Ussing chambers. *In vivo*, growth hormone induced a rapid increase in the absorption rates of water, sodium, chloride, and potassium. *In vitro*, the serosal, but not the mucosal, addition of growth hormone induced a rapid decrease of transepithelial potential difference and of short-circuit current. The effect was time- and dose-dependent, saturable, but not reversible in the short time. The electrical effect was abolished in the absence of chloride, indicating that it was related, at least in part, to inhibition of basal active chloride secretion. Growth hormone also reduced the short-circuit current increase induced by the secretagogues *Escherichia coli* heat-stable enterotoxin, theophylline, and calcium ionophore A23187. These results indicate that hGH has a rapid absorptive effect that is related, at least in part, to a direct intestinal antisecretory mechanism. It also reduces active intestinal secretion induced by various secretagogues. (***Pediatr Res* 37: 576–580, 1995**)

Abbreviations

GH, growth hormone
r-hGH, recombinant DNA-derived hGH
Isc, short-circuit current
PD, transepithelial potential difference
G, tissue conductance
ST, *Escherichia coli* heat-stable enterotoxin

The ability of GH to induce fluid retention is well established, but the mechanisms of this effect are not well understood (1). Most studies have focused on the interrelationships between various hormones taking part to the complex network that regulates Na^+ balance and on the renal effects of GH (1).

It is now known that the intestine plays an important role in the regulation of body fluid homeostasis (2). GH has several effects at the intestinal level. In fact, it stimulates intestinal growth and differentiation (3, 4), vitamin D-dependent Ca^{2+} binding protein synthesis (5), and Ca^{2+} absorption (6). Furthermore, GH increases the gastrin and somatostatin contents of rat stomach (7). Finally, it has been previously shown that high doses of ovine GH, given to rats for 2 d *in vivo*, increased the absorption rates of H_2O and electrolytes as measured by intestinal everted sacs (8). The effects of GH have been traditionally believed to be mediated by GH-dependent production of mediators such as IGF-I (9, 10). However, it has been reported that IGF-I does not cause fluid retention (11). Recently GH has been shown to inhibit the production of the atrial natriuretic peptide (12). Inasmuch as atrial natriuretic peptide is capable of directly inducing H_2O and electrolyte secretion in the rat intestine (13), the inhibition of its production could be an indirect mechanism of a proabsorptive effect by GH.

However, the recently reported evidence of GH receptors in the rat gastrointestinal tract (14) raises the hypothesis that GH exerts its effect through a direct mechanism. We have investigated the effects of GH administration on intestinal H_2O and electrolyte transport *in vivo* by the rat perfused intestine and *in vitro* by exposing the isolated intestine to the hormone and studying its electrical parameters, which reflect the modifications of transepithelial ion transport.

METHODS

Animals. Wistar male rats, weighing 230–280 g and fed Purina Rat Chow (Ralston-Purina, St. Louis, MO), were starved for 12 h before the experiments, but allowed tap water *ad libitum*.

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In vivo intestinal perfusion. On the day of the experiment, the animal was anesthetized with intraperitoneal sodium thiopental (6.25 mg/100 g of body weight). The rectal temperature was maintained at 37°C throughout the experiment by overhead electric lamps. The abdomen was opened with a midline incision and a 10- to 20-cm segment of distal ileum was prepared. Fecal material was removed from the loop by washing with isotonic saline at 37°C. Influx and efflux catheters were placed into the loop, which was perfused at a constant rate of 0.2 mL/min. Perfusion fluid consisted of (in mmol/L): NaCl 115, $NaHCO_3$ 25, K_2HPO_4 2.4, KH_2PO_4 0.4, $CaCl_2$ 1.2, and mannitol to a final osmolality of 290 mosmol/kg, [14C] polyethylene glycol (molecular weight 4000), and unlabeled polyethylene glycol 3 g/L, as a nonabsorbable water marker. Recoveries of polyethylene glycol ranged from 95 to 105%. The pH was maintained at 7.4 by gassing with 95% O_2-5% CO_2.

Each experiment lasted 120 min and consisted of two periods. The first was a 60-min equilibration period, during which perfusate was collected for three consecutive 20-min periods to establish baseline values of H_2O, Na^+, Cl^-, and K^+, as previously described (15). The second 60-min period was started by giving GH in the form of recombinant DNA-derived human GH (r-hGH), as a bolus of 6 μg/kg of body weight in 150 μL of saline solution by the i.v. route. Intestinal effluent was collected for three consecutive 20-min periods to determine the absorption rates upon stimulation with r-hGH. Control animals received r-hGH–free saline solution.

The rats were killed at the end of the experiment, and the loops were dissected, stripped of mesentery, and weighed. The collected samples were analyzed, as previously described (15), for Na^+ and K^+ content by flame photometer (Instrumentation Laboratory 243, ILSUD SpA, Ascoli Piceno, Italy), for Cl^- by a chloride analyzer (Corning 926, Corning Ltd., Halstead, Essex, UK), and for polyethylene glycol by liquid scintillation analyzer (Packard 1600 TR, Packard Instrument Co., Downers Grove, IL).

Ussing chamber studies. Animals were killed by cervical dislocation. Four paired fragments of rat ileal unstripped mucosa were mounted in Ussing chambers containing Ringer's solution, as previously described (16). The bathing solution had the following composition (in mmol/L): NaCl 53, KCl 5, Na_2SO_4 30.5, mannitol 30.5, Na_2HPO_4 1.69, NaH_2PO_4 0.3, $CaCl_2$ 1.25, $MgCl_2$ 1.1, and $NaHCO_3$ 25. It was maintained at 37°C with water-jacketed reservoirs connected to a thermostated circulating pump and constantly gassed with 95% O_2-5% CO_2. PD, Isc, and G were measured as previously described (16), before and after the mucosal or serosal addition of various doses (ranging from 2 to 400 ng/mL, *i.e.* 10^{-7} to 8×10^{-6} M) of r-hGH. Control tissues were treated with the same volumes of r-hGH–free Ringer's solution. Variations between baseline electrical parameters of tissues mounted in the Ussing chamber did not exceed 10%. In the experiments performed to study the reversibility of r-hGH effect, the hormone-containing Ringer's solution was rapidly removed from the chamber and substituted by r-hGH–free Ringer's solution. To test the role of Cl^- in the effects of r-hGH, experiments were performed in Cl^--free Ringer's solution. In these experiments Cl^- was replaced by an equimolar concentration of SO_4^{2-}.

The viability of intestinal specimens mounted in each Ussing chamber was checked at the end of each experiment by adding 10 mmol of glucose/L to the mucosal side to obtain an Isc response. In cases in which this was less than 50% of that of controls at 0 time, the result was not considered.

To investigate the effects of r-hGH on active intestinal secretion, secretion was induced by ST, theophylline, or the Ca^{2+} ionophore A23187 (17). In these experiments, intestinal tissues were incubated with r-hGH (at a final concentration of 4×10^{-6} M); 20 min later the secretagogue to be tested was added, and the resulting peak increments of Isc were recorded in the next 60 min. Each secretagogue was used at its maximally effective concentration, as determined in prior dose-response studies (18). ST was added to the mucosal side at the final concentration of 10^{-7} M. Theophylline was added to the serosal side at the final concentration of 5×10^{-3} M. Ca^{2+} ionophore A23187 was added to the serosal side at the concentration of 5×10^{-7} M. Control tissues were either those not pretreated with r-hGH but exposed to the same concentration of each of the secretagogues used or those receiving r-hGH only.

The research project was approved by the Ethical Committee of the 2nd School of Medicine, University Federico II of Naples.

Chemicals. r-hGH was obtained from Serono (Industria farmaceutica Serono, Rome, Italy). All chemicals were of reagent grade and were purchased from Sigma Chemical Co. (St. Louis, MO).

Statistics. Each experiment was performed at least three times. Results are expressed as means ± SEM. Results of perfusion studies are expressed as microliters of H_2O or microequivalents of electrolyte·min·g of wet tissue weight. Results of Ussing chamber studies are expressed as follows: Isc as $\mu A/cm^2$, G as mS/cm^2, and PD as mV. Isc values of dose-response experiments and of those investigating the effects of secretagogues are expressed as the difference of Isc between basal and stimulated tissues. The significance of the differences was calculated using the *t* test for paired data.

RESULTS

Effects of r-hGH in the in vivo perfused ileum. Net fluxes of H_2O and electrolytes during *in vivo* perfusion in experimental and control animals are shown in Figure 1. There were no differences in the absorption rates of H_2O (Fig. 1*A*), Na^+ (Fig. 1*B*), Cl^- (Fig. 1*C*), and K^+ (Fig. 1*D*) between the two groups during the equilibration period (0–60 min). In control animals the absorptive pattern did not change in period 2, whereas in animals receiving i.v. administration of r-hGH, a significant increase in H_2O absorption was observed (Fig. 1*A*). The effect was prompt, reaching its peak within 20 min from administration of r-hGH and then slowly declining toward baseline levels. However, the difference between animals receiving r-hGH and controls maintained its statistical significance throughout the duration of the experiment (Fig. 1). The pattern of absorption of Na^+ (Fig. 1*B*), Cl^- (Fig. 1*C*), and K^+ (Fig. 1*D*) paralleled that of H_2O.

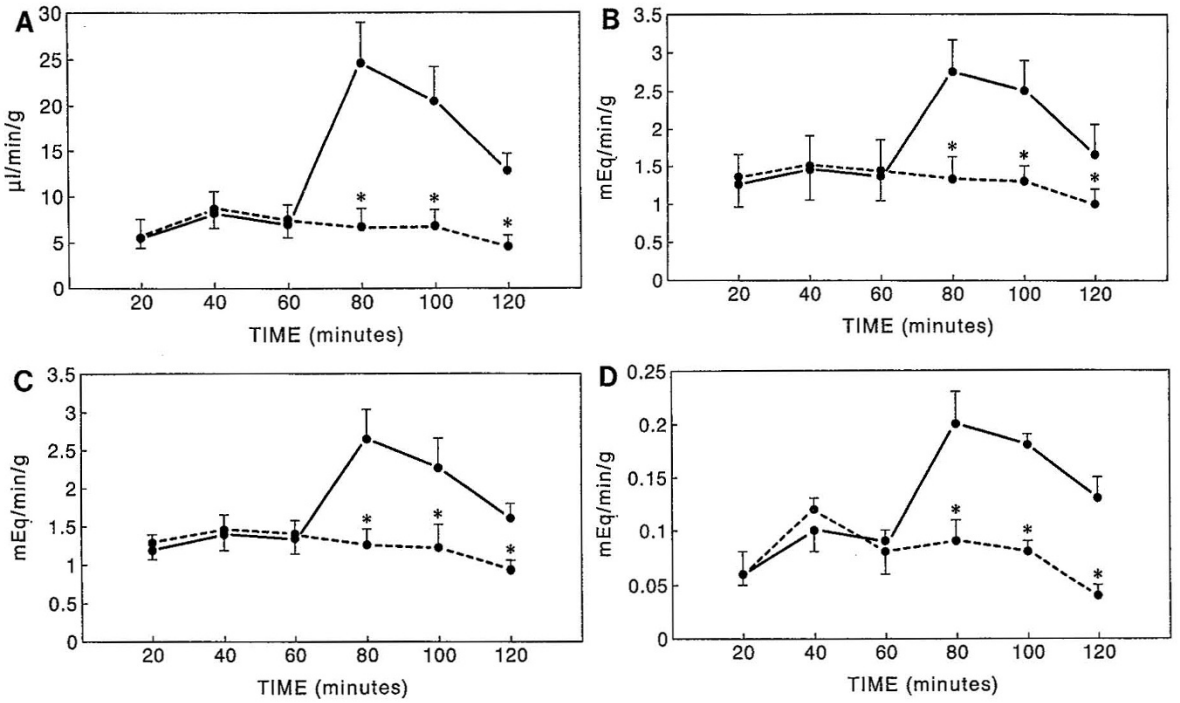

Figure 1. Effect of r-hGH on *in vivo* ileal absorption of H_2O (*A*), Na^+ (*B*), Cl^- (*C*), and K^+ (*D*). After 60 min of equilibration r-hGH (6 µg/kg) was administered by i.v. route (*continuous line*), and absorption rates were determined each 20 min. Control animals (*dotted line*) received r-hGH–free saline solution. $*p < 0.01$ ($n = 15$).

Effects of r-hGH in the in vitro ileal mucosa mounted in Ussing chambers. The mucosal addition of r-hGH did not induce modifications of electrical parameters. The serosal addition of r-hGH induced a rapid fall in Isc. Isc decrease was time-dependent, reaching its maximum in 40 min and remaining stable thereafter (Fig. 2). The serosal effect was entirely due to a decrease of PD, because no modifications of G values were observed (Fig. 2).

To determine whether the effect of r-hGH was dose-dependent, increasing amounts of r-hGH were added to the serosal side of rat ileal specimens mounted in Ussing chambers, and Isc values were recorded after 60 min of incubation with each dose. Results are shown in Figure 3. The r-hGH–induced decrease of Isc was dose-dependent, and the calculated half-maximal effect was achieved with 10^{-6} M or 50 ng/mL r-hGH. Concentrations higher than 4×10^{-6} M r-hGH did not induce any further decrease of Isc, indicating a saturation pattern of the effect.

Lack of reversibility of r-hGH effect. To determine whether r-hGH effect was reversible, intestinal tissue was incubated in the presence of the hormone for 35 min. r-hGH–containing Ringer's solution was then rapidly removed from the Ussing chamber, and the tissue was washed twice and rapidly reincubated with r-hGH–free Ringer's solution. Results are reported in Figure 4.

A slight rise in Isc was observed shortly after removal of r-hGH. However, no significant difference with Isc of tissues constantly exposed to r-hGH was observed.

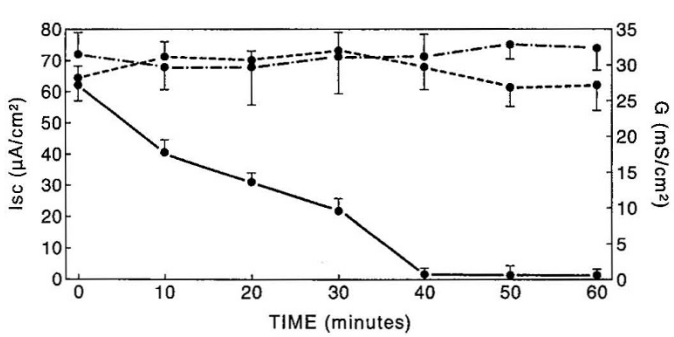

Figure 2. Time course effect of r-hGH on Isc and G in rat ileal mucosa mounted in Ussing chambers. r-hGH was added at 0 time ($n = 6$). (——) Isc of tissues treated with 4×10^{-6} M r-hGH to the serosal side (Isc scale is expressed as µA/cm² on the left side of the figure). (- - - - -) Isc of tissues treated with 4×10^{-6} M r-hGH to the mucosal side. (—·—) G of tissues receiving r-hGH to serosal side (G scale is expressed as mS/cm² on the right side of the figure).

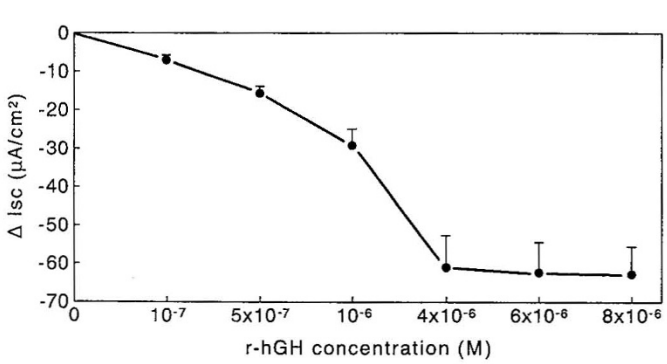

Figure 3. Dose-response of Isc to r-hGH administration. Each dose was administered to a single intestinal specimen mounted in Ussing chamber, and Isc was recorded 60 min after hormone addition. The effect is reported as the difference between baseline Isc and hormone-stimulated Isc. Half-maximal effect was achieved with 10^{-6} M ($n = 5$ for each data point).

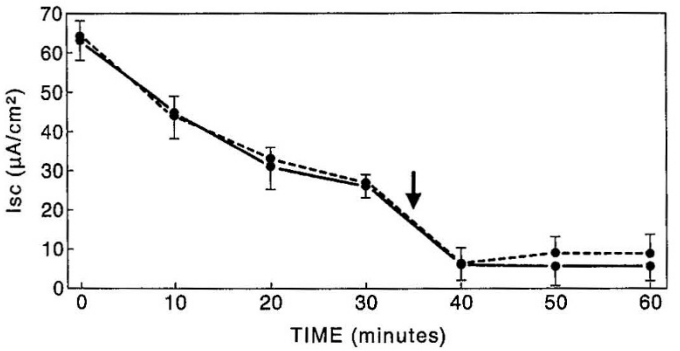

Figure 4. Effect of r-hGH withdrawal on r-hGH–induced decrease of Isc. Ileal mucosa was exposed to r-hGH for 35 min (*arrow*). The hormone was then rapidly removed (*dotted line*) and the electrical parameters were recorded during the next 25 min. No significant difference was observed with tissue constantly exposed to r-hGH (*continuous line*) ($n = 4$).

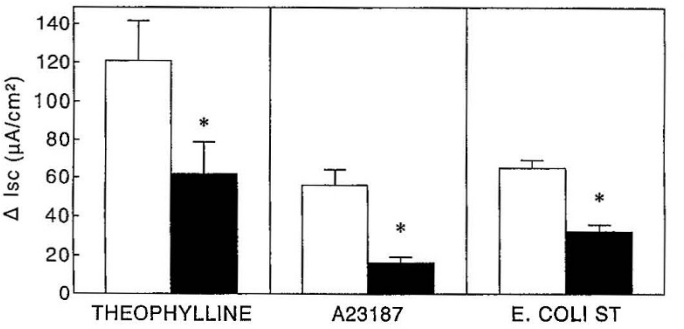

Figure 6. Peak increments in Isc produced by intestinal secretagogues in the absence (*white columns*) or in the presence (*black columns*) of r-hGH. All secretagogues were added 20 min after serosal addition of r-hGH (4×10^{-6} M), and Isc values were recorded in the following 60 min ($n = 8$ for each secretagogue tested). *$p < 0.01$.

Chloride dependency of r-hGH effect. To test the hypothesis that *in vitro* r-hGH action was related to Cl^- movements, the addition of r-hGH to ileal specimens was examined in Cl^--free buffer. Results are reported in Figure 5. The decrease in Isc induced by r-hGH was abolished in the absence of Cl^-, thus indicating that the electrical effect of r-hGH was Cl^--dependent.

Effects of r-hGH on secretagogue-induced changes in Isc. Active intestinal secretion can be induced by an increase in intracellular concentration of *1*) cAMP, *2*) cGMP, or *3*) Ca^{2+}. To test whether r-hGH also affects active intestinal secretion, the effects of the hormone on the secretory pattern induced by agonists of cAMP, cGMP, or Ca^{2+} were examined, as detailed under "Methods." Results are shown in Figure 6. r-hGH was able to reduce the secretory effects of all three mediators.

DISCUSSION

It has been previously reported that hypophysectomy causes a decrease in water and electrolyte absorption in the rat jejunum and this can be prevented by pretreatment with bovine GH (19). An intestinal proabsorptive effect has been previously reported in normal rats, receiving ovine GH by s.c. route (8).

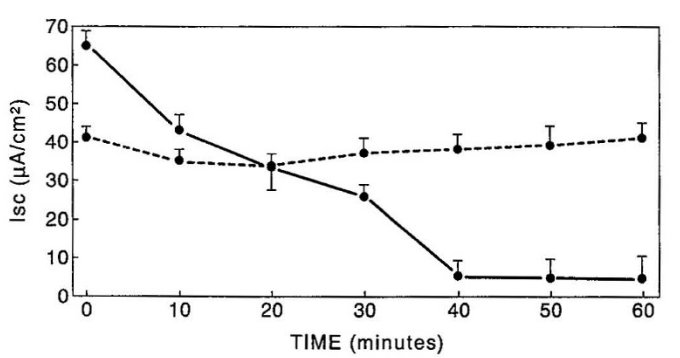

Figure 5. Cl^- dependency of r-hGH–induced electrical effect. Ileal mucosa was exposed to r-hGH in standard Ringer's solution (*continuous line*) and in Cl^--free Ringer's solution (*dotted line*). In the absence of Cl^-, the addition of r-hGH did not induce electrical modifications. A significant difference in Isc basal values was also observed in the presence or absence of Cl^- ($n = 4$).

Our results demonstrate *1*) that human recombinant DNA-derived GH is able to rapidly promote intestinal absorption of water and electrolytes, *2*) that this effect is, at least in part, related to a direct interaction between the hormone and the intestinal epithelium, and *3*) that r-hGH is also capable of reducing active intestinal secretion induced by various mechanisms.

The first observation confirms and extends the previously reported proabsorptive effect of animal GH (8, 19) to recombinant DNA-derived human GH. Furthermore, this work first shows that the effect on intestinal transport has a rapid onset, being observed within minutes from a single i.v. dose of r-hGH. The apparently transient nature of the proabsorptive effect *in vivo* is well explained by the half-life of r-hGH, which is reported to be 18 min after i.v. administration (20). It should be noted that the pharmacokinetic features of r-hGH change, depending on the administration route, and more sustained concentrations may be achieved by intramuscular or s.c. compared with the i.v. administration (20). This could allow an absorptive effect of longer duration compared with that observed by i.v. administration of r-hGH, should alternative routes be used. The ileal proabsorptive effect consisted of an enhanced absorption of H_2O, Na^+, Cl^-, and K^+, resembling that seen in the kidney of animals treated with GH (1).

The antinatriuretic effect of GH in the kidney is thought to be, at least in part, indirect and probably mediated by the activation of the renin-angiotensin system and by an increase of aldosterone (21). However, other evidence suggest a role for IGF-1 and even the possibility of a direct effect of GH has been proposed, because receptors for GH have been identified on renal tubular cells (1). The *in vitro* experiments gave us the opportunity to better characterize the intestinal effects of r-hGH.

The observed decrease of Isc in response to r-hGH addition may be due either to an increase in net movement of an anion from mucosal to serosal compartment (increased absorption or decreased secretion) or an increase in net movement of a cation from serosal to mucosal compartment (decreased absorption or increased secretion). Several lines of evidence support the hypothesis that the r-hGH–induced decrease in Isc was related to a proabsorptive and/or antisecretory effect. First, GH has been known for several decades to cause fluid retention (1). Second, our data from *in vivo* perfusion studies clearly showed an

intestinal proabsorptive effect after GH administration. It should be noted that such an effect was obtained in a range of hormone concentrations which are well below those previously administered to human volunteers (20). Third, the dependency on Cl^- of the electrical response to r-hGH represents clear-cut evidence in favor of the antisecretory nature of the hormone effect.

Indeed, it is now known that Cl^- secretion continues in the absence of externally applied forces (22), and it is responsible for lumen-negative electrical potential difference (23). The latter can be controlled by voltage clamp, generating a positive value of Isc. In fact, in our experiments performed in Cl^--free Ringer's solution, basal Isc values were lower than those obtained in normal Cl^--containing Ringer's solution. The loss of GH ability to induce Isc decrease in the absence of Cl^- strongly suggests that r-hGH inhibits basal active Cl^- secretion.

The *in vitro* experiments showed that the effect of r-hGH was of direct type. A direct GH-enterocyte interaction is consistent with the presence of GH specific receptors on the enterocytes (14). The effect of r-hGH was seen when it was added on the serosal, but not the mucosal, side; it was time- and dose-dependent, saturable, and not reversible (at least within the time frame of our experiment).

The time course of r-hGH, either in the *in vivo* and the *in vitro* experiments, showed a rapid onset of the effect. The *in vitro* effect was longer than that seen *in vivo*, which can be explained by the intervention of homeostatic mechanisms to balance an excessive fluid retention in the *in vivo* rat. The dose response represents the first evidence of such a feature of the effect of GH on fluid retention, because a clear dose response was not obtained in previous work describing the influence of animal GH on intestinal transport (19).

The lack of reversibility of r-hGH effect, upon its removal from the incubation medium, is not surprising, as it is well known that the interaction of growth factors with cell surface receptors involves their binding, the redistribution of hormone-receptor complex at the cell surface, and the internalization and degradation and/or recycling of hormone and/or receptor (24). Overall these data represent evidence of a direct role of GH in the regulation of the homeostasis of water and electrolytes at the intestinal level.

The capability of r-hGH to inhibit secretagogue-stimulated Isc was also investigated. r-hGH inhibited by about 50, 48, and 68% the Isc changes induced by theophylline, by ST and by Ca^{2+} ionophore A23187, respectively. This suggests that the mechanism r-hGH activity is relatively nonspecific. It is possible that the effect of GH is related to inhibition of basal, rather than to stimulated Cl^- secretion. Indeed, at least for ST and Ca^{2+} ionophore, the final Isc values could be interpreted as the average of initial GH-induced decrease and subsequent secretagogue-induced increase.

Treatment strategies for secretory diarrhea include drugs that stimulate absorption, those that inhibit secretion, and those that have both effects (25). Our data suggest that r-hGH exerts a proabsorptive effect *in vivo*, stimulating water and ion absorption.

Data from the *in vitro* experiments indicate that the proabsorptive effect observed *in vivo* is related, at least in part, to the inhibition of basal electrogenic Cl^- secretion. In most cases diarrhea is the result of both impaired absorption and enhanced secretion (26). Therefore, this work discloses a potential use of r-hGH as treatment of diarrhea. The lack of side effects, even by the i.v. administration (20), together with the availability of r-hGH, make it an attractive tool to be used in the treatment of protracted and/or severe diarrhea.

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