Acute Effects of Insulin-like Growth Factor-1 and Recombinant Growth Hormone on Liprotein(a) Levels in Baboons

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Elevated lipoprotein(a) [Lp(a)] is an established factor for coronary artery disease (CAD) that acts possibly by increasing cholesterol deposition in arterial wall and promoting thrombosis. The only known Lp(a)-lowering agents, niacin and neomycin, often produce intolerable side effects. We observed that administration of growth hormone (GH) increases but insulin-like growth factor-1 (IGF-1) decreases Lp(a) levels in patients with GH deficiency. To explore the mechanisms for the hormonal effects and to search for an effective pharmaceutical agent, we examined the suitability of the baboon as an animal model by investigating the effects of GH and IGF-1 on Lp(a). We selected 5 baboons with high (group 1) and 5 with low (group 2) Lp(a) levels. Group 1 baboons first received a bolus subcutaneous injection of IGF-1 (300 μg/kg body weight). After a period of 7 days, they were given a bolus infusion of recombinant human (rh)GH (300 μg/kg body weight). For group 2 baboons, the order of injection was reversed, and rhGH was given first and followed by IGF-1. Blood samples were collected during the day before and for 3 days following each injection. Levels of plasma Lp(a), insulin, GH, and IGF-1 were measured for each time point. While rhGH appeared not to raise Lp(a) levles among baboons with extremely low levels (6.8 ± 1.1 mg/dL at baseline *v* 6.6 ± 0.9 mg/dL, n = 5), IGF-1 significantly reduced Lp(a) levels among those with high levels within 2 hours of injection (57.0 ± 6.6 mg/dL *v* 37.4 ± 6.2 mg/dL, or a 34% reduction, n = 3, *P* = .013). Our study for the first time demonstrated that IGF-1 can lower plasma Lp(a) levels by more than 30% within 2 hours in baboons and the effects are sustained for at least 1 week. The effect is likely mediated through increased Lp(a) degradation, but the responsible organs remain to be identified. On the other hand, rhGH appeared to have no effect on those animals with very low Lp(a) levels.

LIPOPROTEIN(a) [Lp(a)] is an atherogenic low-density lipoprotein (LDL)-like cholesterol ester–rich plasma lipoprotein particle,[1,2] and elevated Lp(a) levels are associated with an increased risk for coronary artery disease (CAD), as well as cerebrovascular and peripheral vascular disease.[1-3] Based on its LDL-like feature, it has been postulated that Lp(a) delivers cholesterol to the arterial wall during atherogenesis. Indeed, both apolipoprotein(a) [apo(a)] and apoB have been demonstrated immunohistochemically in atherosclerotic lesions of the vascular wall.[4,5] By virtue of its close resemblance to plasminogen, a possible role of apo(a) in disturbances of thrombolysis has also been proposed.[1,2] Recent studies have further demonstrated that Lp(a) competitively inhibits the action of plasmin in activating transforming growth factor-β1 (TGF-β1), which is a major inhibitor of vascular smooth muscle cell proliferation.[6]

Lp(a) is unique among lipoproteins because its levels may vary more than 1,000-fold among normal healthy individuals. Population genetic studies have ascribed up to 90% of the variance in circulating Lp(a) levels in both humans and baboons to the *LPA* gene.[7,8] Metabolic studies have established that Lp(a) concentrations are largely determined at the level of biosynthesis, specifically, the biosynthesis of the unique apo(a) protein.[9] Cell culture studies suggest that differences in endoplasmic reticulum residence times may be responsible for the different biosynthetic rates.[10] The liver is the major site for the synthesis of circulating Lp(a)[11]; however, the route for Lp(a) clearance from the circulation remains to be established, although both liver and kidney have been proposed.[12-14]

Unlike other circulating lipoproteins, Lp(a) levels are not readily affected by life-style changes or lipid-lowering drugs. Nicotinic acid in high dose is the only pharmaceutical agent that consistently lowers Lp(a) levels by an average of 15% to 20%.[1,15] However, hormones[16] may affect circulating Lp(a) levels to a much greater extent than lipid-lowering drugs, and may be largely responsible for periodic variations in Lp(a) levels within individuals. Hypothyroidism increases plasma Lp(a) and thyroxine therapy rapidly lowers Lp(a) levels as well as apoB and LDL levels.[17] Administration of tamoxifen and estrogen also lowers circulating Lp(a) levels in healthy postmenopausal women,[18] and insulin decreases Lp(a) levels.[19,20] Recently, we[21] and others[22-24] have shown in children and adults that recombinant human growth hormone (rhGH) infusion both long-term (up to 12 months) and short-term (from the first day up to 7 days) can dramatically increase circulating Lp(a) levels. We[25] and others[23,26] have also shown that administration of recombinant insulin-like growth factor-1 (IGF-1) decreases circulating Lp(a) to less than half of the baseline levels both long-term and short-term.

We hypothesize that the rhGH-induced increases of Lp(a) and IGF-1–induced decreases of Lp(a) are mediated by 2 independent pathways. The effect of rhGH on Lp(a) is directly through GH regulatory roles in lipid metabolism. The Lp(a)-lowering phenomenon by IGF-1, on the other hand, could result from either a direct effect on hepatic cell production or degradation, or an indirect effect by suppressing GH secretion through a negative feedback pathway. If the inhibiting effect of IGF-1 is mediated by suppression of GH, it would indicate that the basal GH is essential in maintaining Lp(a) production. This is an unlikely hypothesis. We therefore favor the first mechanism whereby IGF-1 reduces Lp(a) directly. Since GH also

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Table 1. Schedules for the IGF-1 or rhGH Injections

	Group 1 [5 baboons with high Lp(a)]	Group 2 [5 baboons with low Lp(a)]
Initial phase		
SC injection	IGF-1, 300 μg/kg body weight at 24 h	rhGH, 300 μg/kg body weight at 24 h
Blood collection	0, 4, 8, 24, 26, 28, 32, 48, 72, 96 h	0, 4, 8, 24, 26, 28, 32, 48, 72, 96 h
Crossover phase		
SC injection	rhGH, 300 μg/kg body weight at 168 h	IGF-1, 300 μg/kg body weight at 168 h
Blood collection	144, 148, 152, 168, 170, 172, 176, 192, 216, 240 h	144, 148, 152, 168, 170, 172, 176, 192, 216, 240 h

increases intracellular IGF-1 levels, we further hypothesize the functional domain(s) of IGF-1 that reduces Lp(a) levels may act differently from its role as a growth hormone. This might afford an opportunity to design a modified IGF-1 with only the Lp(a)-lowering effect. To test the hypothesis and facilitate the design of IGF-like reagents, it would be valuable to develop a suitable animal model. Given that only old world primates naturally express the *LPA* gene, we selected the baboon model, which is probably the best-characterized model of human Lp(a). We designed the current pilot study to explore whether we can reproduce in baboons the effects of IGF-1 and rhGH on Lp(a).

MATERIALS AND METHODS

Experimental Design

We administered IGF-1 and rhGH to tethered baboons identified as having either high or low Lp(a) concentrations.[8] We observed only acute effects of rhGH and IGF-1 on Lp(a) levels after a single injection, since we were interested in direct effects of these hormones on Lp(a) synthesis. Since ketamine may interfere with the insulin metabolism, the effects of rhGH and IGF-1 cannot be properly assessed with the confounding effect of this agent. Therefore, baboons were cannulated during the experiment, which permitted blood sampling without the necessity of immobilization.[27] As shown in Table 1, initial injection for group 1 baboons was IGF-1, and for group 2, rhGH. At the end of 7 days (96 hours after the final blood collection), we then administered a single-dose treatment of either IGF-1 to the group 2 baboons that received rhGH during the first week, or rhGH to the group 1 baboons that received IGF-1 in the first week. The total experimental period was 10 days. Body weight and the amount of hormones used in the experiments are shown in Table 2.

Table 2. Characteristics of Individual Baboons in the Experiment

Animal ID	Body Weight (kg)	Plasma Lp(a) (mg/dL)*	IGF-1 or rhGH (mg), Injected
Group 1, high Lp(a)			
9581	21.8	41.6	6.5
9711	16.5	39.4	4.9
9774	17.0	31.4	5.1
9963	18.0	27.8	—
9976	26.2	23.9	—
Group 2, low Lp(a)			
8027	25.9	3.2	7.8
8667	14.1	3.2	4.2
8589	13.1	4.1	3.9
10504	15.5	4.3	4.7
7052	31.0	4.5	9.3

*Lp(a) levels reported in this column were initial survey levels, which were measured more than 12 months earlier.

The dosages of IGF-1 and rhGH were based on therapeutic doses with significant effects on Lp(a) levels from human studies. The IGF-1 and rhGH were obtained from Genentech, Pty Ltd (San Francisco, CA) under the reagent support program. Human IGF-1 is a recombinant polypeptide containing 70 amino acid residues. Human GH is produced by recombinant DNA technology, and contains 191 amino acid residues. Both IGF-1 and rhGH are highly purified preparations and have been approved for therapeutic usage in human subjects. A subcutaneous (SC) administration route was chosen to prolong the pharmacological effects and to minimize the possible acute reaction by intravenous bolus injection, such as a hypoglycemic reaction to IGF-1. Blood samples (2 mL, collected at 2, 4, 8, 24, 48, and 72 hours after each injection) were obtained on the same schedule as the first week with 4 baseline collections followed by a serial collection postinjection. The experimental protocol was approved by the Institutional Animal Care and Use Committee Southwest Foundation for Biomedical Research.

Plasma was prepared by low-speed centrifugation of blood and stored at -80°C in single-use aliquots.[28] Plasma Lp(a) levels were determined with a commercial kit that used a "sandwich" style assay similar to that described previously.[29] The plasma levels of IGF-1, GH, and insulin were determined using enzyme-linked immunosorbent assay (ELISA) methods (Diagnostic Systems Laboratories, Inc, Webster, TX).

Statistical Analyses

Levels of all biochemical variables, including Lp(a), GH, IGF-1, and insulin, are presented as the mean ± SEM. We used a paired *t* test to compare level changes between different time points before and after GH injection. Two-tailed *P* values are reported and values less than .05 are regarded as statistically significant. The coefficient of variation (CV) was calculated as (SD/mean) × 100.

RESULTS

We started the experiment with 10 baboons, but 2 (ID# 9963 and 9976 in group 1) were withdrawn prior to the first injection after we were unable to clear clots in their canula at the baseline of 4 hours. Searches for alternative canula sites were unsuccessful. Thus, 8 baboons completed the full experimental protocol.

Effects of IGF-1 and rhGH Injection on Plasma Hormone Levels

To monitor the effectiveness of absorption and effects of these hormones on each other and insulin, levels of IGF-1, GH, and insulin were measured at all time points. First, we assessed intraindividual variation during the first 24 hours of the experiment (4 time points) before any hormone injection. While both insulin (CV, 81% ± 24%) and GH (CV, 195% ± 49%) showed very large intraindividual variations during the 24-hour period, IGF-1 levels were relatively stable (CV, 25% ± 5%, n = 8,

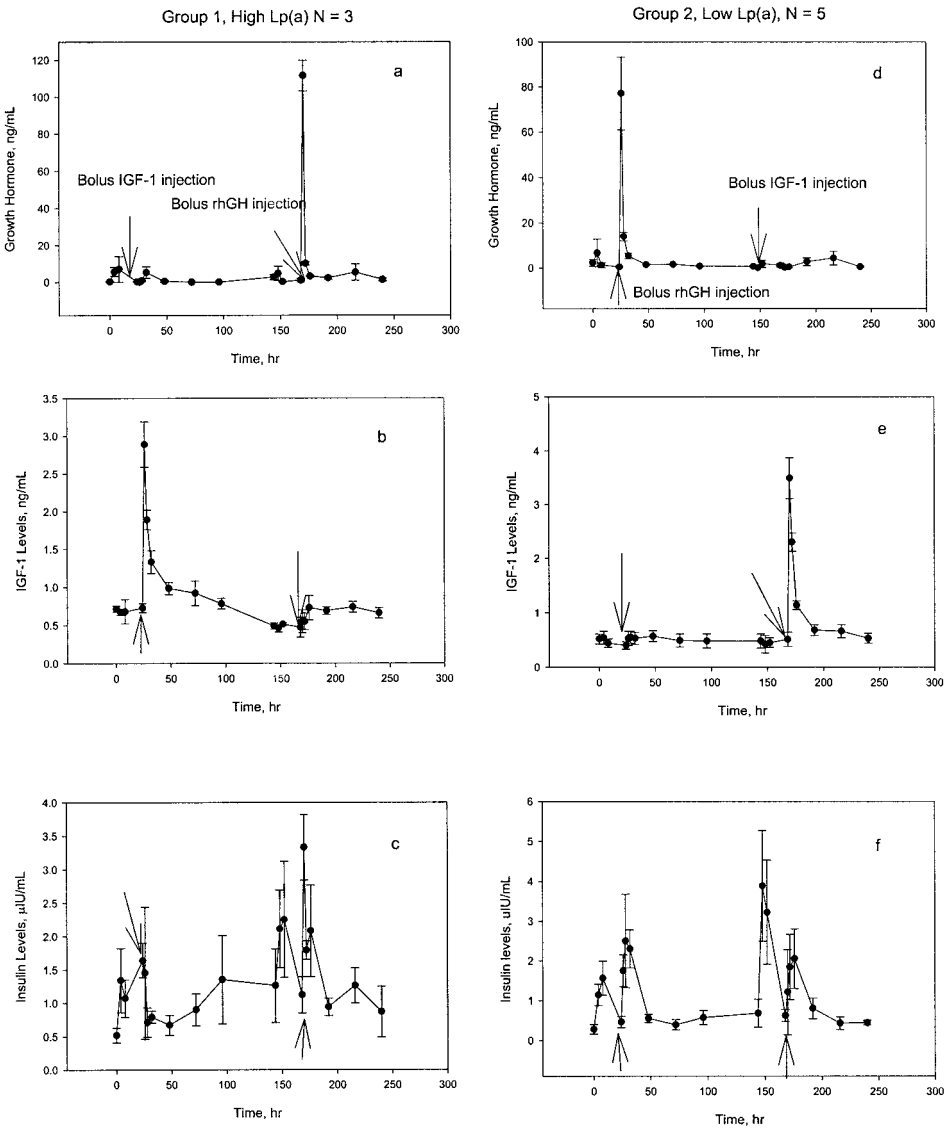

Fig 1. Changes in plasma hormones following subcutaneous (SC) bolus injection of IGF-1 or rhGH to baboons. Graphs on the left are changes in levels of (a) GH, (b) IGF-1, and (c) insulin in group 1 animals given an IGF-1 injection (at 24 hours) followed by an rhGH injection (at 168 hours). Graphs on the right are changes in levels of (d) GH, (e) IGF-1, and (f) insulin in group 2 animals given an rhGH injection (at 24 hours) followed by an IGF-1 injection (at 168 hours). *Significant differences from baseline ($P < .05$).

$P < .001$). There were no associations among levels of GH, IGF-1, or insulin at any time point of the baseline period. Injection of IGF-1 caused little or no change in GH or insulin levels in both experimental groups (Fig 1). In contrast, injection of rhGH tended to induce a minor spike of insulin levels (Fig 1c and f), but the effect of rhGH on circulating IGF-1 was minor (Fig 1b and e). After the bolus injections, it took more than 4 days for IGF-1 to return to baseline levels (Fig 1b and e), but only about 4 hours for GH to do so (Fig 1a and d).

Effects of IGF-1 and rhGH on Lp(a) Levels

We analyzed the hormonal effects on Lp(a) in 2 groups of animals undergoing either IGF-1 or rhGH treatment. The group 1 baboons with high Lp(a) levels were first treated with a single bolus SC injection of IGF-1 followed by a washout period for 7 days before injection of the rhGH bolus. As shown in Fig 1b, plasma IGF-1 levels returned to baseline levels at least 24 hours prior to rhGH injection. We treated the group 2 baboons, which had low Lp(a) levels, with the rhGH bolus first. The levels of GH returned to baseline within 24 hours of injection (Fig 1d). The follow-up bolus IGF-1 injection was given 7 days after the first rhGH injection. While within-animal baseline variation (20.1% $\pm$ 8.8%) in Lp(a) levels within first 24 hours was smaller than that of hormones (Figs 2 and 3), it was much larger than what we expected since a strong genetic control over Lp(a) levels was predicted. Within 2 hours of the IGF-1 injection, we observed a significant decrease in Lp(a) levels (from an average of 57.0 $\pm$ 6.6 mg/dL to 37.4 $\pm$ 6.2 mg/dL, or a 35% reduction, n = 3, $P = .013$; Fig. 2) and this decrease was observed in all 3 baboons of group 1 with high Lp(a) levels. In subsequent hours, Lp(a) levels rebounded somewhat but were maintained for the rest of the week at significantly reduced levels compared to baseline (Fig 2B). Lp(a) never returned to the baseline level during the entire 2-week experimental phase. Injection of rhGH

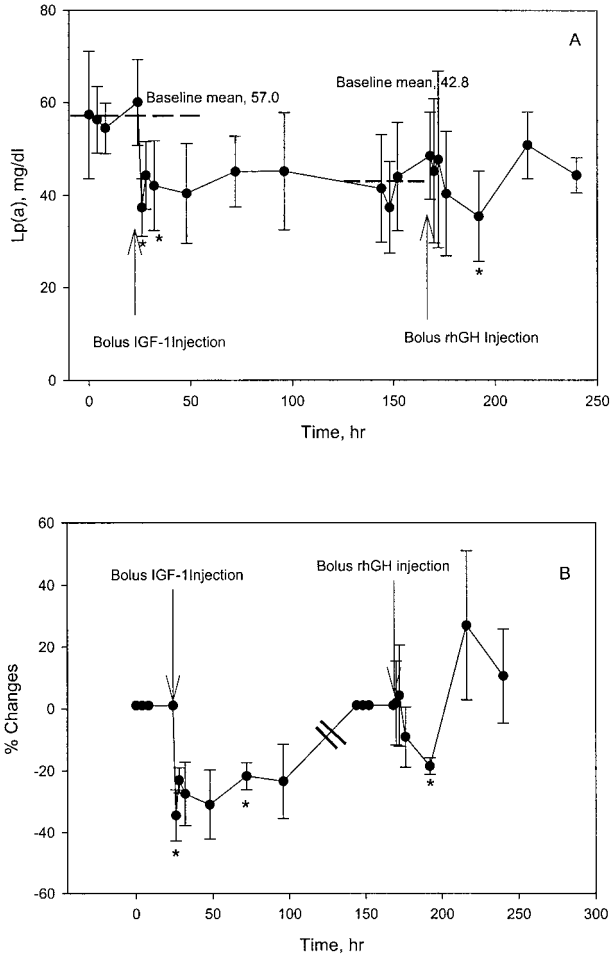

Fig 2. Changes in Lp(a) levels following IGF-1 or rhGH injection in group 1 baboons with high Lp(a) levels. (A) Changes in the actual levels. The first 4 time points (0, 4, 8, 24 hours) are baseline Lp(a) levels prior to IGF-1 injection. The mean level of the 4 measurements is 57.0 ± 6.6 mg/dL. Baseline Lp(a) levels prior to rhGH injection were obtained at 144, 148, 152 and 168 hours. The mean level of the 4 measurements is 42.8 ± 10.4 mg/dL. (B) Lp(a) changes in percentages calculated by comparing the average baseline levels prior to each injection. *$P < .05$.

in the group 1 baboons, on the other hand, did not change Lp(a) levels in a significant manner except for a small reduction, which was followed by an immediate rebound (Fig 2).

For the group 2 baboons with low Lp(a) levels, however, there was a constant increase in the baseline Lp(a) levels prior to rhGH injection (Fig 3). This was followed by a reduction from the time of rhGH injection (Fig 3). Changes in Lp(a) following either rhGH or IGF-1 injection were neither biologically nor statistically significant. The changes were within the range of experimental variations since Lp(a) levels were so low that they were in the lower range of the calibration curve.

DISCUSSION

The present pilot study has demonstrated that Lp(a)-reducing effects of IGF-1 are observed just as previously reported for humans.[23,25,26] This effect is only obvious when one has a high Lp(a) level as demonstrated in group 1 baboons. For those with low Lp(a) levels (group 2), the effect may have been obscured by both the circadian variation and experimental errors. The effect was acute and occurred within 2 hours of the injection. Therefore, it seems likely that this acute effect is mediated through a catabolic pathway, which is not clearly defined currently. A few organs, including liver and kidney, may contribute to Lp(a) degradation. We postulate that liver may be a more likely responsible organ for IGF-1–mediated acute Lp(a) reduction. In vitro studies using primary baboon hepatocytes[30,31] might help distinguish these potential mechanisms. One of the limitations in the current pilot study is the removal of 2 baboons with high Lp(a) levels, making the study statistically less powerful and the results more variable. The tendency of high Lp(a) levels to inhibit fibrinolysis could be the reason we needed to remove these baboons from the study. Nevertheless, the trend and direction of changes in the remaining animals are consistent. Lp(a) reduction after 2 hours averaged of 30%, which is comparable to niacin and neomycin treatment, which often result in intolerable side effects.[32]

On the other hand, the Lp(a) raising effect by rhGH in humans was not reproduced in baboons. This was true in both high (group 1) and low (group 2) Lp(a) baboons. The reasons for the discrepancy between humans and baboons are not clear. It could be that the effects of rhGH on Lp(a) are small, indirect, and long-term. Significant circadian fluctuation in Lp(a) levels and relatively short-term observation in baboons could have contributed to our inability to replicate the effects of rhGH on Lp(a) levels in baboons. However, it is also possible that Lp(a) metabolism is somewhat different in baboons than humans. suggesting baboons may not be a good model of hormone effects on Lp(a).

In our previous studies, we proposed that insulin might be

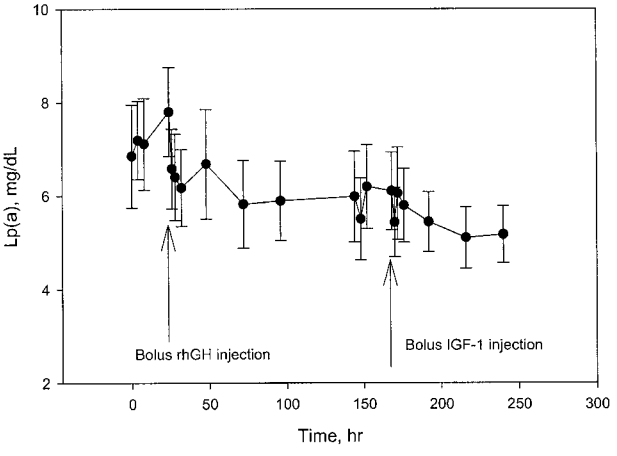

Fig 3. Changes in Lp(a) levels following rhGH or IGF-1 injection in group 2 baboons with low Lp(a) levels. The first 4 time points (0, 4, 8, 24 hours) are baseline Lp(a) levels prior to rhGH injection. The mean level of the 4 measurements is 7.2 ± 0.9 mg/dL. Baseline Lp(a) levels prior to IGF-1 injection were obtained at 144, 148, 152, and 168 hours. The mean level of the 4 measurements is 5.9 ± 0.8 mg/dL. Because the Lp(a) levels were so low that they fell within the lower range of the standard curves and suffered a higher degree of assay variations, percentage changes would not be reliable or informative.

the mediator for the observed effects by IGF-1 or rhGH.[16,21] However, findings from the current study are not consistent with this hypothesis. The within-individual plasma insulin variation is so large that neither rhGH nor IGF-1 injection resulted in any consistently significant shift in plasma insulin levels (Fig 1c and f).

GH has 2 categories of biological effects.[33,34] The first of these is related to growth and is mediated by IGF-1 and, therefore, is considered an indirect effect. The second effect is on carbohydrate and lipid metabolism and it appears to directly affect receptors within the target tissues. IGF-1 has a structure similar to that of proinsulin, hence the name, insulin-like growth factor. IGF-1 is mainly produced in liver and circulates in plasma bound to high–molecular-weight binding proteins. IGF-1 exerts its biological effects via specific receptors, which have little or no affinity for insulin. Blood concentrations of IGF-1 are relatively constant over an extended period, and do not show the extent of fluctuations we found for GH concentrations in baboons.[34] Feedback relationships between pituitary GH, insulin, and IGF-1 are complex. IGF-1, as a secondary messenger for GH, is increased by pituitary GH or exogenous rhGH administration. However, this was not observed in baboon plasma (Fig 1b and e). While IGF-1 administration may inhibit insulin secretion, it also increases insulin sensitivity and therefore improves glycemic profiles, possibly by modulating insulin receptors. This is also not consistent with the reaction profiles in baboons (Fig 1c and f). The effects of rhGH administration on insulin secretion appear to be triphasic with an initial upregulation of insulin secretion, which is true in baboons as well (Fig 1c and f). On the other hand, IGF-1 exerts an effect on pituitary GH by a negative feedback mechanism in that IGF-1 overproduction or exogenous IGF-1 administration inhibits pituitary GH secretion, which was not shown in baboons (Fig 1a and d).

In conclusion, we have found that IGF-1 can directly reduce Lp(a) level to approximately 30% of the baseline levels in baboons, whereas rhGH does not appear to have any effect. Based on the current findings, further in vitro experiments can be designed to explore the molecular mechanisms explaining how IGF-1 affects Lp(a) degradation and possibly production as well.

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