**Objective** — There is growing evidence to indicate that somatostatin could be added to the list of natural antiangiogenic factors that exist in the vitreous fluid. In addition, a deficit of intravitreous somatostatin-like immunoreactivity (SLI) has been found in diabetic patients with proliferative diabetic retinopathy (PDR). In the present study, we have determined the main molecular variants of somatostatin (somatostatin-14 and somatostatin-28) in the vitreous fluid and plasma of nondiabetic control subjects and diabetic patients with PDR. In addition, the contribution of cortistatin, a neuropeptide with strong structural similarities to somatostatin, to SLI and its levels in vitreous and plasma in both nondiabetic and diabetic patients has also been measured.

**Research Design and Methods** — Plasma and vitreous fluid from 22 diabetic patients with PDR and 22 nondiabetic control subjects were analyzed. Somatostatin-14, somatostatin-28 and cortistatin were measured by radioimmunoassay but separation by high-performance liquid chromatography was required to measure somatostatin-14.

**Results** — The predominant molecular form of somatostatin within the vitreous fluid was somatostatin-28 (fivefold higher than somatostatin-14 in control subjects and threefold higher in patients with PDR). Cortistatin significantly contributed to SLI and its intravitreous levels were higher than those detected in plasma (nondiabetic control subjects: 147 [102–837] vs. 78 [24–32] pg/ml; patients with PDR: 187 [87–998] vs. 62 [24–472] pg/ml; P = 0.01 for both). Intravitreous somatostatin-14 was similar in both subjects with PDR and the control group (P = 0.87). By contrast, somatostatin-28 concentration was lower in patients with PDR than in nondiabetic control subjects (350 ± 32 vs. 595 ± 66 pg/ml; P = 0.004).

**Conclusions** — Somatostatin-28 is the main molecular variant in the vitreous fluid. The intravitreous SLI deficit detected in patients with PDR is mainly due to somatostatin-28. Cortistatin is abundant in the vitreous fluid and significantly contributes to SLI. These findings could open up new strategies for PDR treatment.

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**Somatostatin Molecular Variants in the Vitreous Fluid**

A comparative study between diabetic patients with proliferative diabetic retinopathy and nondiabetic control subjects

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Proliferative diabetic retinopathy (PDR) represents a highly prevalent cause of visual loss in western countries and is the leading cause of new-onset blindness among people of working age (1). There is now ample evidence to suggest that the development of diabetic retinopathy is a multifactorial process in which it is not just the angiogenic factors alone but the balance between angiogenic and antiangiogenic factors that is crucial. Inhibition of angiogenesis has therefore become a target for the treatment of retinal neovascularization.

Several pilot studies using the somatostatin analog octreotide in patients with early proliferative and severe non-PDR have revealed decreased incidence of progression into proliferative retinopathy needing panretinal laser treatment (2,3). In addition, the incidence of vitreous hemorrhage and the need for vitreoretinal surgery was also significantly reduced in octreotide-treated patients (4). A large-scale, multicenter, randomized, placebo-controlled clinical trial with a long-acting somatostatin analog, octreotide (SOM 201-995, Sandostatin LAR; Novartis), is currently ongoing in patients with severe nonproliferative and early PDR.

It is suggested that the inhibition of retinal vascularization by somatostatin agonists is mediated by the lowering of growth hormone levels, resulting in a subsequent decrease in IGF-I levels. However, somatostatin and its receptors are found in the retina of various species including humans (5,6), and data support a direct antiangiogenic action of somatostatin. In this regard, it has been demonstrated that somatostatin analogs might inhibit angiogenesis directly through somatostatin receptors present on endothelial cells (7,8) and also indirectly through the inhibition of postreceptor signaling events of peptide growth factors such as IGF-I, vascular endothelial growth factor, epidermal growth factor, platelet-derived growth factor, and basic fibroblast growth factor (9–11). Therefore, the antiangiogenic...
Somatostatin variants in vitreous fluid

GENERIC PROPRIETIES OF SOMATOSTATIN CAN BE ACHIEVED INDEPENDENTLY OF THE MODULATION OF SYSTEMIC GROWTH HORMONE AND IGF-1 LEVELS. Moreover, we have observed a decrease of somatostatin-like immunoreactivity (SLI) in the vitreous fluid of patients with PDR, thus suggesting that the deficit of retinal synthesis of somatostatin could be involved in the process of retinal neovascularization (12). Taken together, it seems reasonable to postulate that PDR treatment using somatostatin analogs could be contemplated as an antiangiogenic replacement treatment. For this reason, the characterization of retinal molecular variants of somatostatin might be useful in the design of new somatostatin analogs for PDR treatment.

Somatostatin-14 and somatostatin-28 are the two principal bioactive products cleaved from the C-terminus of prosomatostatin. Prosomatostatin is produced in the retina of all the species studied until now, but a differential expression of somatostatin-14 and somatostatin-28 has been observed (13–19). However, to the best of our knowledge there have been no reports on this issue concerning the human retina or the vitreous fluid.

Vitreous fluid obtained from diabetic patients undergoing vitreoretinal surgery is currently used for indirectly exploring the synthesis of several peptides by the retina. However, several confounding factors such as vitreous hemorrhage and the unspecific increase of vitreal proteins due to serum diffusion that occurs in PDR could lead to misinterpretation of the results. In a previous study (12) that took these confounding factors into account, we demonstrated a higher concentration of SLI in the vitreous fluid than in plasma in nondiabetic control subjects, thus supporting the concept that somatostatin plays a relevant role in retinal homeostasis. However, in this study the antibody used was not specific and, as a consequence, a pool of molecular variants was assessed.

In the present study, we have determined specifically both somatostatin-14 and somatostatin-28 in the vitreous fluid of nondiabetic control subjects and diabetic patients with PDR to evaluate: 1) the predominant molecular variant of somatostatin that exists in the vitreous fluid, and 2) the main somatostatin molecular form accounting for the reduction of SLI observed in the vitreous fluid of diabetic patients with PDR. Finally, the contribution of cortistatin, a neuropeptide with strong structural similarities to somatostatin (20), to SLI and its levels in vitreous and plasma in both nondiabetic and diabetic patients has also been measured for the first time.

RESEARCH DESIGN AND METHODS — The study included 22 consecutive diabetic patients with PDR (7 patients with type 1 diabetes and 15 patients with type 2 diabetes) on whom a vitrectomy was performed. Twenty-two age-matched nondiabetic patients with other conditions requiring vitrectomy, but in whom the retina was not directly affected by neovascularization (idiopathic epiretinal membrane, n = 7; macular hole, n = 8; and rhegmatogenous retinal detachment without associated proliferative vitreoretinopathy, n = 7) served as a control group. Both venous blood and vitreous samples were collected at the time of vitreoretinal surgery. Patients with previous vitreoretinal surgery, those with recent vitreous hemorrhage (<2 months), and those who had received photocoagulation in the preceding 3 months were excluded.

Vitreectomy and collection of specimens

In all cases, a classic three-port pars plana vitrectomy was performed. Undiluted vitreous samples (0.5–1 ml) were obtained at the onset of vitrectomy by aspiration into a 1-ml syringe attached to the vitreous cutter (Alcon Model, Accurus 800 × S4; Irvine, CA) before intravitreal infusion of balanced salt solution was started. The vitreous samples were transferred to a sterile tube, placed immediately on ice, and centrifuged at 16000 g for 5 min at 4°C. Supernatants were frozen at −80°C until assayed. For serum determinations, blood samples were collected simultaneously with the vitrectomy, then centrifuged at 3,000 g for 10 min at 4°C to obtain serum, aliquoted and stored at −80°C until assayed.

The research followed the tenets of the Declaration of Helsinki. The protocol was approved by the hospital ethics committee and written informed consent was obtained from all patients.

Vitreous hemoglobin

Apart from excluding patients with recent vitreous hemorrhage, we also excluded those in whom intravitreous hemoglobin was detected. For this purpose, vitreous hemoglobin levels were measured by spectrophotometry (Uvikon 860; Kontron Instruments, Zurich, Switzerland) using the classic method of Harboe (21) for measuring plasma hemoglobin at micromolar concentration. This method has been further validated (22), and in our studies the lowest limit of detection was 0.03 mg/ml.

Protein assay

Vitreal proteins were measured by a previously validated microturbidimetric method with an autoanalyzer (Hitachi 917; Boehringer, Mannheim, Germany). This method, based on the benzethonium chloride reaction, is a highly specific method for the detection of proteins and has a higher sensibility and reproducibility than the classic method of Lowry. The lowest level of proteins detected was 0.02 mg/ml. Coefficients of variation intra and interassay were 2.9 and 3.7%, respectively.

Somatostatin and cortistatin measurements

SLI was determined by radioimmunossay (RIA) (Euro-Diagnostica, Malmo, Sweden) using an antiserum to synthetic cyclic somatostatin-14 as previously described (12). Apart from somatostatin-14, this antibody cross-reacts significantly with several molecular forms of somatostatin, and therefore a pool of somatostatin isoforms rather than somatostatin-14 is actually measured.

Somatostatin-14 and somatostatin-28 were measured by RIA (Euro-Diagnostica and Phoenix Pharmaceutical, Belmont, CA, respectively). However, due to the high cross-reaction detected for the somatostatin-14 antibody, a previous separation of this molecular form by means of reverse-phase high-performance liquid chromatography (HPLC) was required (see below). The RIA lower detection limits were 10 pg/ml for somatostatin-14 and 20 pg/ml for somatostatin-28. Cortistatin was also determined by RIA by means of an antibody against cortistatin-29 and a detection limit of 24 pg/ml.

To avoid nonspecific interference from class G γ-globulins that may bind to somatostatin antibodies, somatostatin and cortistatin were extracted from both plasma and vitreous fluid before being assayed. For this purpose, 1-ml aliquots of
plasma were acidified (0.1 ml 1 M HCl per ml) and filtered through cartridges containing octadecylsilica (Sep Pak; Waters, Milford, MA) and then washed with 20 ml of 4% acetic acid in H2O. The retained peptides were eluted with 2.0 ml methanol and were then evaporated to dryness and dissolved in 200 µl assay diluent. The mean recoveries of somatostatin-14, somatostatin-28, and cortistatin-29 were 83, 67, and 45%, respectively. When using this method for processing vitreous fluid samples, a very low recovery was obtained, and therefore, a method based on HCl-acetone precipitation was used. Briefly, 1 ml humor vitreous plus 500 µl RIA buffer. With this precipitation method, the mean recovery from vitreous fluid was 87% for somatostatin-14, 92% for somatostatin-28, and 88% for cortistatin-29.

For antibody cross-reactivity studies, pure standards were used. Somatostatin-14 (Euro-Diagnostica), somatostatin-28, cortistatin-17, and cortistatin-29 (Phoenix Pharmaceutical) were prepared at concentrations between 12.5 and 300 pg/ml.

Reverse-phase HPLC
The purification of molecular forms of somatostatin and cortistatin was achieved by HPLC using a Waters chromatography system (Waters, Cerdanyola, Barcelona, Spain) equipped with two 510 HPLC pumps, an automatic gradient controller AGC560, an automatic injector WISP 717, and a ultraviolet detector W-2747, set at 254 or 280 nm as required. Data were analyzed by means of the software package Turbo-Chrom (Perkin-Elmer, Madrid, Spain). The column used was a reversed-phase Symmetry C-18, 300 Å (large pore size silica), 25 × 0.46 cm, particle size 5 µm (Waters).

Mobile phase A was 0.14% trifluoroacetic acid in water and mobile phase B was 40% H2O–60% CH3CN–0.1% trifluoroacetic acid. Separation was run at 37°C. Flow rate was 1 ml/min, and the linear gradient used is presented in Table 1. Column eluates were monitored by for ultraviolet absorbance at 254 nm.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Phase A (%)</th>
<th>Phase B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>20</td>
<td>50</td>
<td>50</td>
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<tr>
<td>75</td>
<td>48</td>
<td>52</td>
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<tr>
<td>80</td>
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<td>70</td>
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<tr>
<td>85</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>90</td>
<td>60</td>
<td>40</td>
</tr>
</tbody>
</table>

Statistical analysis
SLI concentrations and ratios were compared by a Student’s t test. Because of their skewed distribution, the statistical comparisons of cortistatin and intravitreal protein were performed using a nonparametric test (Mann-Whitney U test). SLI concentrations and ratios were compared by a Student’s t test. The Spearman rank correlation coefficient was used to examine correlations. Levels of statistical significance were set at P < 0.05. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS). Results are expressed as means ± SEM or median (range).

RESULTS — The antiserum against somatostatin-14 recognized 100% of somatostatin-14 form but also cross-reacted 31.3% with somatostatin-28 and 30.8% with cortistatin (Fig. 1 A). The antiserum against somatostatin-28 recognized 100% of somatostatin-28 and did not have a cross-reaction with either somatostatin-14 or cortistatin (Fig. 1B). The antibody against cortistatin was highly specific and recognized 100% of cortistatin and did not show any cross-reaction with the other peptides (Fig. 1C). Therefore, somatostatin-28 and cortistatin concentrations could be directly assessed by RIA, although somatostatin-14 measurement required a previous purification by reverse-phase HPLC.

Results for SLI, somatostatin-14, somatostatin-28, and cortistatin concentrations (picograms per milliliter) obtained in the vitreous fluid and plasma are summarized in Table 2. We did not detect any differences in plasma levels between patients with PDR and control subjects for SLI, somatostatin-14, somatostatin-28, and cortistatin. Somatostatin-28 was the most abundant molecular form detected in plasma (sevenfold higher than somatostatin-14 in the control group and almost ninelofd higher in PDR patients).

Notably, plasma levels of cortistatin were higher (more than twofold) than those obtained for somatostatin-14, both in the control group and patients with PDR. In the vitreous fluid, somatostatin-28 was also the predominant molecular variant, but it was again more abundant in the control group (fivefold higher than somatostatin-14) than in PDR patients (threelfold higher than somatostatin-14). Intravitreous levels of cortistatin were also higher than those obtained for somatostatin-14 both in the control group and in patients with PDR.

The somatostatin-14 concentration was significantly higher in the vitreous fluid than in plasma in both control subjects (113.5 ± 23.2 vs. 31 ± 9.4 pg/ml; P = 0.07) and patients with PDR (107 ± 28.6 vs. 28.1 ± 4.3 pg/ml; P = 0.03). Intravitreous levels of somatostatin-28 were also significantly higher than those observed in plasma from control subjects (595.4 ± 66.3 vs. 217.6 ± 49.6 pg/ml; P < 0.001). However, in patients with PDR, although intravitreous levels of somatostatin-28 were higher than those obtained in plasma, the difference was not statistically significant (350.8 ± 32.3 vs. 248.4 ± 47.2 pg/ml; P = 0.086). Intravitreous cortistatin concentrations were higher than those detected in plasma in both nondiabetic control subjects (median 146.5 [range 102–837] vs. 77.7 [24–132] pg/ml; P = 0.01) and patients with PDR (186.7 [87–998] vs. 61.9 [24–472] pg/ml; P = 0.01). No correlations were found between plasma and vitreous levels for any of the peptides analyzed.

Intravitreous levels of SLI and somatostatin-28 were significantly lower in diabetic patients than in the control group both in absolute terms and after adjusting by intravitreal proteins (Table 2). By contrast, intravitreous somatostatin-14 concentrations were similar in patients with PDR and the control group in absolute terms. Although lower values were obtained in patients with PDR after correcting for intravitreal proteins, the differences were without statistical significance. Finally, we could not observe any difference for intravitreal concentrations of cortistatin between PDR patients and nondiabetic control subjects in absolute terms, although after adjusting for vitreal proteins, lower levels were found in patients with PDR.
CONCLUSIONS — The results reported here confirm and reinforce our previous finding that somatostatin is abundant in the vitreous fluid (12) and provide the first evidence that somatostatin-28 is the main molecular variant accounting for this enhancement. Although somatostatin-14 seems to be the predominant molecular form synthesized by the retina in goldfish (13), frog (14), rat (15,16), and rabbit (17), somatostatin-28 is the major form in the bovine retina (18) and also in the guinea pig retina (19). There is no information available concerning the molecular forms of somatostatin synthesized by the human retina. However, in the human brain, somatostatin-14 is primarily secreted by cortical neurons, whereas somatostatin-28 is the predominant form in cells at the subcortical and hypothalamic levels (23,24). In the retina, somatostatin is synthesized in GABAergic amacrine cells, which are localized in the neuroretina (5,25). Because the neuroretina and hypothalamus have the same embryologic origin (26,27), it is comprehensible that in both tissues, as well as in the vitreous fluid, the predominant somatostatin form is somatostatin-28.

In patients with PDR, a deficit of SLI was observed, thus supporting our previous observation on this issue. In addition, we have shown that somatostatin-28 is mainly responsible for this deficit. The efficacy of somatostatin analogs in the treatment of advanced diabetic retinopathy has been largely attributed to their effectiveness in lowering the serum levels of IGF-1. However, the relationship between circulating IGF-1 and the development of diabetic retinopathy remains controversial (28,29). In recent years, growing evidence has accumulated to indicate that somatostatin analogs have an angiostatic effect (30), and it therefore seems reasonable to suppose that this effect could be the main mechanism accounting for their effectiveness in diabetic retinopathy treatment. In this regard, it should be noted that the intravitreal concentrations of somatostatin here reported lie within the same range as those showing antiangiogenic effects in experimental studies (7,10,11). Therefore, the decreased concentration of SLI observed in the vitreous fluid of diabetic patients might facilitate the retinal neovascularization process.

Apart from the lower concentrations...
Table 2—Vitreous and plasma values of the laboratory variables determined in age-matched diabetic patients with PDR and control subjects

<table>
<thead>
<tr>
<th></th>
<th>PDR group</th>
<th>Control group</th>
<th>P value</th>
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<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Plasma (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLI</td>
<td>159.7 ± 20.8</td>
<td>85.2 ± 17.2</td>
<td>0.09</td>
</tr>
<tr>
<td>Somatostatin-28</td>
<td>248.4 ± 47.2</td>
<td>217.6 ± 49.6</td>
<td>0.53</td>
</tr>
<tr>
<td>Somatostatin-14</td>
<td>28.1 ± 4.3</td>
<td>31 ± 9.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Cortistatin</td>
<td>61.9 (24–472)</td>
<td>77.7 (24–132)</td>
<td>0.49</td>
</tr>
<tr>
<td>Vitreous fluid (pg/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLI</td>
<td>155.2 ± 31.3</td>
<td>314.7 ± 48.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Somatostatin-28</td>
<td>350.8 ± 32.3</td>
<td>595.4 ± 66.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Somatostatin-14</td>
<td>107 ± 28.6</td>
<td>113.5 ± 23.2</td>
<td>0.87</td>
</tr>
<tr>
<td>Cortistatin</td>
<td>186.7 (87–998)</td>
<td>146.5 (102–837)</td>
<td>0.49</td>
</tr>
<tr>
<td>Ratio to intravitreous proteins (pg/mg)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>SLI</td>
<td>51.7 ± 10.3</td>
<td>356.4 ± 50.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>Somatostatin-28</td>
<td>123.3 ± 48.9</td>
<td>815.6 ± 90.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Somatostatin-14</td>
<td>51.9 ± 15.2</td>
<td>157 ± 96.5</td>
<td>0.09</td>
</tr>
<tr>
<td>Cortistatin</td>
<td>86.1 ± 20.1</td>
<td>292.2 ± 59.2</td>
<td>0.005</td>
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</table>

Data are means ± SEM or median (range).

of somatostatin-28 in patients with PDR, we also provide the first evidence of cortistatin presence in the vitreous fluid. Cortistatin shares 11 of 14 residues with somatostatin, including those that are essential for binding to the five somatostatin receptor subtypes (SSTRs) (31). Like somatostatin, cortistatin levels were higher in the vitreous fluid than in the plasma and a lack of relationship between plasma and vitreous cortistatin concentrations was observed. In addition, lower cortistatin intravitreous levels were detected in patients with PDR in comparison with the control group. This findings suggest not only that cortistatin is intraocularly synthesized but also that it has a possible role in retinal homeostasis. It could be predicted that cortistatin has actions similar to those of somatostatin in the retina because it has been demonstrated that cortistatin binds with high affinity to all five SSTRs (32). In fact, it has been shown that cortistatin inhibits insulin and growth hormone secretion in humans to the same extent as somatostatin (33,34). In addition, cortistatin possesses other classical somatostatin activities including neurotransmission, neuromodulation, and inhibition of tumor growth (20,35,36). However, the possibility of other actions common to somatostatin, such as inhibition of angiogenesis, deserves further study. In addition, specific studies to evaluate the physiological function of cortistatin in the human retina and whether or not its deficit could be involved in the pathogenesis of diabetic retinopathy are required.

Because somatostatin-14, somatostatin-28, and cortistatin share the same receptors, one might wonder whether the knowledge of the predominant form accounting for the deficit of SLI in the vitreous fluid could be of any consequence in the management of diabetic retinopathy. In this regard, it should be noted that the different molecular variants of somatostatin could operate through distinct intracellular mechanisms, thus contributng to the selective regulation of cell function in tissues where more than one isofom is present (37). In fact, somatostatin-14 is the main bioactive molecular form of somatostatin regulating the inhibition of endocrine secretion from the gut, whereas somatostatin-28 rather than somatostatin-14 is the physiological regulator of postprandial insulin secretion (38) and pituitary hormones (39). Radioligand binding studies on cells expressing individual SSTRs have demonstrated that although somatostatin-14 and somatostatin-28 interact with SSTR1–4 with similar affinity, this is not the case for SSTR5, which displays up to a 10-fold higher affinity for somatostatin-28 (40,41). Indeed, somatostatin activation of SSTR5 modulates inhibition of protein kinase C (42), a key mediator in the pathogenesis of diabetic retinopathy.

In the human retina, there is agreement on the expression of SSTR1, SSTR2, and SSTR3 receptor subtypes, but there is a discrepancy in the existence of the SSTR4 and SSTR5 receptors (43,44). In addition, although cortistatin and somatostatin interact with the same receptors, cortistatin has central activities that are not shared by somatostatin. For instance, cortistatin, unlike somatostatin, reduces locomotor activity and induces slow-wave sleep (35). These differences may be explained by different postreceptor signaling pathways or by the existence of a selective cortistatin receptor. Recently, a novel receptor, the MrgX2, for which cortistatin has the highest affinity, has been cloned (45). Furthermore, somatostatin showed a low binding affinity to this receptor. At present, it is still unknown whether there is a different pattern of somatostatin receptor expression in the retina of diabetic patients, and there is no information concerning the presence of a specific cortistatin receptor in the retina. Nevertheless, our findings might contribute not only to the design of more appropriate somatostatin analogs that could be administered by intravitreous injection as a replacement treatment but also could open new strategies for gene therapy.

Regarding systemic circulation, our results confirm previous data reporting that somatostatin-28 is the predominant form (46,47). Somatostatin-28 is the terminal peptide processed from prosomatostatin in the epithelial cells of the ileum and colon, whereas somatostatin-14 is the final product in most gastric, duodenum, and proximal jejunum D cells (48,49). We have measured plasma cortistatin for the first time, and its levels were higher than those obtained for somatostatin-14. This is not surprising because although cortistatin expression was initially detected in the cerebral cortex (20), a much broader expression pattern in the human body has recently been demonstrated (50). It should be noted that, as occurs in the vitreous fluid, cortistatin significantly contributes to SLI measured by RIAs employing somatostatin-14-based antibodies. Therefore, the accurate assessment of somatostatin levels requires careful characterization of the specificity of the assays used and whether or not they cross-react with cortistatin.

In summary, we have demonstrated...
that somatostatin-28 is the main somatostatin molecular variant in the vitreous fluid, and it is also the main factor accounting for the SLI deficit detected in the vitreous fluid of PDR patients. In addition, cortistatin is abundant in the vitreous fluid and significantly contributes to SLI. These findings could help encourage the design of more rational approaches to PDR treatment.

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