The Novel Somatostatin Analogue PTR-3173 Inhibits Experimental Diabetic Retinopathy

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Introduction
Diabetic retinopathy (DR) is by far the commonest microvascular damage in patients with both type 1 and type 2 diabetes. The state of the art therapy of proliferative diabetic retinopathy (PDR) is laser photoagulation. However, photoagulation is aggressive with severe side effects and variable success rates. Alternative strategies currently target growth factors involved in neovascularizations in the eye.

Since the early observation that PDR can result from uncontrolled infarction, the GH-IGF-1 axis has been implicated in the pathogenesis of PDR. In this study we investigated the effects of the novel somatostatin analogue PTR-3173, a potent suppressor of growth hormone release, on the development of DR in a streptozotocin (STZ) induced diabetic rat model.

Materials and methods
- Male Wistar rats (20 per group) were rendered diabetic by intravenous STZ injection of 65 mg/kg body weight
- All animals received 3 IU insulin three times a week after reaching >600 mg/dl blood glucose levels
- PTR-3173 (10 or 100 mg/kg), Octreotide (100 mg/kg) or vehicle were administered s.c. once daily
- Eyes were obtained after 13 and 30 weeks treatment period
- Retinal vascular preparations were performed using a peptin-trypsin digestion technique as previously described (Hammes, 1996). Figure 2 represents examples of retinal digest preparations from treatment groups (30 weeks)
- Animals developed stable hyperglycemia upon intravenous STZ-injection. Mean blood glucose over the entire study period was >30 mmol/l (all diabetic) and <8 mmol/l (N) (Fig. 1)
- Neither PTR-3173 nor Octreotide treatment affected glucose levels, HbA1c or body weight development (Tab. 1).
- Therefore retinae in all diabetic animals were exposed to comparable levels of hyperglycemic stress over the entire treatment period

Results
- PTR-3173 significantly reduces the formation of acellular capillaries in the retinae of diabetic animals
- Figure 3B: At 30 weeks of diabetes, PTR-3173 treated groups had significantly fewer acellular capillaries, compared to vehicle-treated diabetic animals: Non-diabetic: 37 +/- 2 AC, diabetic + vehicle 97 +/- 47 AC, diabetic + 100 mg/kg/day PTR-3173 64 +/- 13 AC, diabetic + 100 mg/kg/day PTR-3173 41 +/- 6 AC
- PTR-3173 reduces acellular capillaries by 95 % (p<0.01, high dose) resp. 55 % (p=0.05, low dose), Octreotide reduces acellular capillaries by 72 % (p=0.05, high dose), Fig. 3B
- Figure 3A: After 13 weeks of hyperglycemia only slightly elevated numbers of acellular capillaries were present in the diabetic control group
- PTR-3173 and Octreotide reduced pericyte loss by 55 % (p< 0.001 vs D) after 30 weeks hyperglycemia (Fig. 4B).

Conclusions
- PTR-3173 is a novel Somatostatin analogue with a unique receptor binding profile
- PTR-3173 significantly reduces pericyte drop-out in the diabetic rat retina
- PTR-3173 reverses the hyperglycemia-induced formation of acellular capillaries
- PTR-3173 does not induce vasoregression
- Therefore PTR-3173 inhibits incipient diabetic retinopathy and is a potential drug candidate for diabetic retinopathy

Literature

Table 1: Bodyweight and HbA1c at the end of the study (13 weeks resp. 30 weeks intervention)

<table>
<thead>
<tr>
<th>Group</th>
<th>Bodyweight (g)</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>519 +/- 44</td>
<td>5.7 +/- 0.5</td>
</tr>
<tr>
<td>DC</td>
<td>332 +/- 37</td>
<td>14.7 +/- 1.0</td>
</tr>
<tr>
<td>D=PTR100</td>
<td>238 +/- 39</td>
<td>15.6 +/- 1.3</td>
</tr>
<tr>
<td>D=PTR100</td>
<td>340 +/- 54</td>
<td>14.6 +/- 1.3</td>
</tr>
<tr>
<td>N</td>
<td>341 +/- 51</td>
<td>14.2 +/- 0.7</td>
</tr>
<tr>
<td>DC</td>
<td>324 +/- 54</td>
<td>13.8 +/- 1.1</td>
</tr>
<tr>
<td>D=Oct100</td>
<td></td>
<td></td>
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</tbody>
</table>

Figure 1: Time course of blood glucose levels in the experimental groups

Figure 2: Retinal digest preparation

Figure 3: Formation of acellular capillaries and loss of pericytes in the retinae of diabetic rats 13 (3A, 4A) and 30 weeks (3B, 4B) after STZ treatment

Abbreviations: N: Non Diabetic; DC: Diabetic + vehicle; D=PTR10, D=PTR100: Diabetic + 100 mg/kg, 1000 mg/kg PTR-3173; D=Oct100: Diabetic + 100 mg/kg Octreotide