Introduction

The anti-inflammatory benefits of the melanocortin system suggest that melanocortin receptor (MC) agonists have great promise in the treatment of inflammatory diseases.1,2 The synthetic selective MC1 agonist, PL8177, and the synthetic MC1/M3r/MC4r/M5r pan-agonist PL8177A and PL8654 and PL8664 have been investigated in distinct settings of experimental pathologies.1,3 To demonstrate the value of investigating the melanocortin system in inflammatory diseases, we determined the effects of these melanocortin agonists as potential treatments for diabetic retinopathy (DR), multiple sclerosis (MS), and rheumatoid arthritis (RA).

Methods

PL8177/PL8654 Streptozotocin (STZ)-Treated Rat Model of DR

Potential beneficial effects of PL8177 and PL8654 on visual function in an STZ-impaired rat model of DR were investigated in a 114-day study. Rats were randomly assigned to 5 separate study arms (Table 1) and dosed on Days 4 – 114.

Table 1. Study Arms for PL8177/PL8654 STZ-Treated Rat Model of DR

<table>
<thead>
<tr>
<th>Group</th>
<th>Dosing</th>
<th>Study Day</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>0.05 mg/kg</td>
<td>4 – 114</td>
</tr>
<tr>
<td>PL8177 0.05 mg/kg</td>
<td>1 mg/kg</td>
<td>4 – 114</td>
</tr>
<tr>
<td>PL8177 1 mg/kg</td>
<td>10 mg/kg</td>
<td>4 – 114</td>
</tr>
<tr>
<td>PL8177 10 mg/kg</td>
<td>100 mg/kg</td>
<td>4 – 114</td>
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Vehicle (PBS) was dosed daily or intraperitoneally (IP), whereas B- and T-lymphocyte populations remained unchanged, whereas B- and T-lymphocyte populations remained unchanged.

Results

Figure 1. Study Design for PL8654 MOG-Induced EAE Mouse Model

Figure 2. Changes in Visual Acuity Over Days 4–113

Figure 3. Changes in Visual Acuity Over Days 4–113

Figure 4. Changes in Visual Acuity Over Days 4–113

Figure 5. Changes in Cataract Scores Over Days 4–113

Figure 6. EAE Clinical Score Changes and AUC Over Days 8–35

Figure 7. Changes in Clinical Score, AUC, and Body Weight Over Days 0–7 of IP Treatment

Figure 8. Changes in Paw Volume and AUC Over Days 0–7 of IP Treatment

Conclusions

Subcutaneous BID administration of PL8654 or PL8177 showed efficacy in reducing vision loss in a rat model of DR. PL8654 (0.3 mg/kg), administered orally, was effective in reducing the clinical score of EAE in a mouse model of MS. PL8654 (30.0 and 3 mg/kg) also showed efficacy in reducing vision loss in a rat model of DR. PL8654 (0.3 mg/kg) showed a dosedependent reduction of the signs of arthritis, with a lower AUC value of 0.05 mg/kg vs vehicle. PL8177 (1 mg/kg) also showed a reduction in paw volume in a dose-dependent manner, with a lower AUC value of 0.05 mg/kg vs vehicle. In the preclinical model systems, these melanocortin agonists showed promise in the treatment of DR, MS, and RA by reducing inflammation and by providing protection from or amelioration of symptoms.

Acknowledgments

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