EVALUATION OF THE ANTIDIABETIC EFFECT OF NOVEL SELECTIVE GLUCOCORTICOID ANTAGONISTS IN A MODEL OF CORTISONE-INDUCED DIABETES

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INTRODUCTION

A considerable amount of evidence indicates that, in both animals and man, elevated circulating levels of glucocorticoids are associated with the development of insulin resistance and type 2 diabetes1-3. Mifepristone has been shown to ameliorate or reverse many of the symptoms of glucocorticoid excess, but because of its actions to antagonise progesterogen receptors, it is not ideal for the long-term treatment of metabolic disorders. The development of selective antagonists of glucocorticoid receptors may have a role in the treatment of diabetes.

The aim of this study was to develop a sub-chronic model of insulin resistance using cortisone which would be suitable for screening novel selective glucocorticoid receptor antagonists. Mifepristone was used as the positive reference comparator.

METHODS

Two cohorts of male Sprague Dawley rats (Charles River, 225-275g, n=8 and 10 at start) were group housed on a normal light/dark cycle and maintained on a standard pelleted rat diet and tap water. After a 3 day baseline period, during which rats were dosed orally with vehicle once daily, rats were administered cortisone (30 mg/kg sc qd) or vehicle for 6 days. Rats were weighed every day at the time of dosing throughout the study and at termination (Day 7). In addition to cortisone, vehicle or the novel glucocorticoid receptor antagonists, CORT125134, CORT125281 and CORT108297 were dosed orally b.i.d and compared to the non-selective glucocorticoid/progesterogen receptor antagonist mifepristone (30 mg/kg po qd). A terminal freely feeding blood sample was collected on Day 7 (tail vein) for determination of plasma glucose and insulin. CORT125134 and CORT125281 were group housed on a normal light/dark cycle and maintained on a standard pelleted rat diet and tap water. After a 3 day baseline period, during which rats were dosed orally with vehicle once daily, rats were administered mifepristone (30 mg/kg po qd) or vehicle for 6 days. Rats were weighed every day at the time of dosing throughout the study and at termination (Day 7). In addition to cortisone, vehicle or the novel glucocorticoid receptor antagonists, CORT125134, CORT125281 and CORT108297 were dosed orally b.i.d and compared to the non-selective glucocorticoid/progesterogen receptor antagonist mifepristone (30 mg/kg po qd). A terminal freely feeding blood sample was collected on Day 7 (tail vein) for determination of plasma glucose and insulin. CORT125134 and CORT125281 were dosed b.i.d.

RESULTS (1)

Table 1 Affinity for Glucocorticoid and progesterogen receptors

<table>
<thead>
<tr>
<th>Glucocorticoid receptor</th>
<th>Progesterogen receptor</th>
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<tr>
<td>Ki values (nM)</td>
<td>Ki values (nM)</td>
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<tr>
<td>CORT125134</td>
<td>0.15</td>
</tr>
<tr>
<td>CORT125281</td>
<td>0.51</td>
</tr>
<tr>
<td>CORT108297</td>
<td>0.27</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>0.09</td>
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</table>

Mifepristone exhibits high affinity for both the glucocorticoid and progesterogen receptors in vitro (see Table 1). In contrast, CORT125134, CORT125281 and CORT108297 demonstrate high affinity for the glucocorticoid receptor with no significant affinity for the progesterogen receptor in vitro (Table 1). Thus, CORT125134, CORT125281 and CORT108297 are potent and selective antagonists of the glucocorticoid receptor.

RESULTS (2)

- CORT125134, CORT125281 and CORT108297 all exhibited a similar profile to mifepristone exhibiting inhibition of the effects of cortisone on bodyweight and insulin resistance (Figures 1A and 2A).

- Mifepristone (30 mg/kg po) partially reversed cortisone-induced weight loss and fully blocked the corresponding increases in plasma glucose and insulin (Figures 1A - B, 2A –B).

- These data support the concept that selective glucocorticoid antagonists are effective in ameliorating or reversing cortisone-induced weight loss and insulin resistance and may therefore be of value in the treatment of disease states where glucocorticoid activity is excessive.

CONCLUSION

- These data support the concept that selective glucocorticoid antagonists are effective in ameliorating or reversing cortisone-induced weight loss and insulin resistance and may therefore be of value in the treatment of disease states where glucocorticoid activity is excessive.

REFERENCES

4. Balanoff JK, Blasey CM, Clark RD, Roe RL. Selective glucocorticoid receptor (type II) antagonist prevents and reverses olanzapine-induced weight gain. Diabetes Obesity & Metabolism 2010,12,545-547.

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