Rationale for ACR16 as a symptomatic treatment for Huntington’s disease

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INTRODUCTION

Huntington’s disease (HD) is assumed to be associated with dysfunction of the neuronal circuits in both the striatum and cerebral cortex.

In animal models of HD, an early indication of neuronal dysfunction is the loss of regulation of the corticostriatal pathway: compromising primary control of the striatum.

Widespread changes in dopamine functions occur, including disruptive regulation of corticostriatal nerve terminals via presynaptic dopamine D2 receptors.

Studies indicate that interventions to reduce or prevent the development of the HD phenotype should:
- begin early to target neuronal dysfunction
- be aimed at abnormalities in the cortex and striatum.

PHARMACOLOGY OF ACR16

ACR16 belongs to a novel class of functional modulators of the dopaminergic system.

- Its primary mechanism of action is to modulate the effects of dopamine via interaction with D2-type receptors.

In vivo, the effect of ACR16 on psychomotor function is a state-dependent stabilization:
- inhibition in states of hyperactivity and stimulation in states of low activity.

The mechanism of action extends beyond the dopaminergic system as it is also active in models of glutamatergic hypofunction (i.e. cortical weakness) (Figure 1).

The mechanisms underlying the ability of ACR16 to modify cortical function presumably rely on its ability to induce release of monoamines in the cerebral cortex.

Figure 2 summarizes the main effects of ACR16 on the corticostriatal pathway.

EXTRASTRIATAL D2 RECEPTORS ARE PRESERVED IN MID-STAGE HD

The hallmark of HD pathology is the loss of medium spiny neurones (MSNs) in the striatum.

Progressive loss of MSNs is paralleled by a loss of D2 receptors in the striatum.

Little is known about the integrity of D2 receptors outside the striatum.

ACR16 acts on D2 receptors to exert its cortical enhancing effects.

- This requires the reasonably intact structural integrity of such receptors in patients with HD.

To assess this receptor integrity, we treated patients with mid-stage HD and age-matched healthy controls with the high-affinity D2 receptor agonist [11C]FLB457.

- Patients were examined by high-resolution positron emission tomography (PET) scan (Figure 3).

Extrastriatal regions were delineated from magnetic resonance imaging (MRI) examinations.

A simplified reference tissue model was used to determine the binding potential for the radiotracer in each region.

RESULTS

Table 1: Dopamine D2 receptor densities measured by [11C]FLB457 binding potential in some extrastriatal regions providing input to the striatum in patients with mid-stage Huntington’s disease (HD; n = 9) and age-matched healthy volunteers (n = 6).

<table>
<thead>
<tr>
<th>Region</th>
<th>Healthy volunteers</th>
<th>Patients with HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal cortex</td>
<td>0.39 ± 0.3</td>
<td>0.39 ± 0.29</td>
</tr>
<tr>
<td>Temporal cortex</td>
<td>0.80 ± 0.39</td>
<td>0.80 ± 0.42</td>
</tr>
<tr>
<td>Ventromedial thalamus</td>
<td>3.59 ± 0.72</td>
<td>4.02 ± 0.86</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.91 ± 0.78</td>
<td>0.72 ± 0.39</td>
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</tbody>
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ACR16 IS WELL TOLERATED IN MID-STAGE HD

ACR16 was well tolerated by most patients:
- no significant differences could be detected in D2 receptor densities in these patients with HD.

ACR16 IN HD: CLINICAL EXPERIENCE

The safety, tolerability and efficacy of ACR16 in patients with HD has been studied in two clinical trials:

- open-label, dose-escalation study in 10 patients
- randomized, double-blind, placebo-controlled study in Scandinavia.

In the double-blind trial:
- 58 patients were randomized to treatment with either ACR16 50 mg (hydrochloride salt) or placebo once daily
- 4 weeks’ treatment.

ACR16 was well tolerated by most patients in both trials:
- clinically significant adverse effects did not occur.

CONCLUSIONS

ACR16 represents a novel class of functional modulators of the dopaminergic system (i.e. dopaminergic stabilizers).

Unlike other compounds acting on D2 receptors (e.g. neuroleptics and partial agonists), the effects of ACR16 extend beyond the dopaminergic system, strengthening cortical control of the striatum.

Early clinical studies with ACR16 have been encouraging in terms of reducing HD symptoms, without producing unwanted side effects.

Further clinical studies are ongoing:
- assessing the effects of different doses and extended treatment durations.

REFERENCES
