The sustained release of the acetylcholinesterase inhibitor ZT-1 confers the potential for a more efficient neuroprotection in rats

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Introduction
ZT-1 (Figure 1) is a prodrug of huperzine A, a quinolizidine alkaloid originally isolated from the club moss Huperzia serrata, and one of the most potent and selective acetylcholinesterase inhibitors¹. ZT-1 administration induces an increase in cerebral acetylcholine making it a candidate for symptomatic Alzheimer's disease (AD) treatment.

Neuroprotective effects were evidenced in in-vitro and in-vivo models² studying the protective effect of huperzine A from organophosphate-induced convulsions³, hypoxic-ischemic brain injury⁴, neuronal glutamate5 and β-amyloid⁶ induced toxicity. An inconvenient aspect of a huperzine A treatment is its frequent intolerance due to organophosphate-induced convulsions and β-amyloid induced toxicity. To avoid this inconvenient aspects, an injectable sustained-release implant formulation of ZT-1 was developed, aiming at achieving a prolonged liberation over several weeks of the active metabolite.

Methods

Material
ZT-1 was obtained by hemi-synthesis from (-)-huperzine A. Biodegradable polymeric implants of ZT-1 were prepared by Debio R.P. (Martigny, Switzerland).

Animal study
Several types of implants were tested. For each batch, a group of six 10-11 week-old Sprague-Dawley male rats were given a single subcutaneous (s.c.) administration of an implant of ZT-1 (dose: ca. 15 mg/kg of ZT-1) under the neck skin (see Figure 2). The day before ZT-1 administration, a reference plasma sample was collected. Plasma samples for drug measurement were then collected at 2h, 6h, 8h, 10h post-dosing and then twice a week from day 2 to day 35 after administration.

Results & Discussion

Among the tested batches, two types of implants were of particular interest, with the following characteristics (see Figure 3):

- A progressive release of huperzine A in plasma was observed within 7-14 days after administration.
- Sustained plasma levels were achieved over a 3 week-period, while ZT-1 plasma levels were negligible.
- Inter-individual variability was low.
- No clinical signs were observed throughout the study and no signs of local intolerance were reported.

- Implants were almost completely degraded within 35 days after administration.

As compared to oral administration, the ZT-1 implant offers the following advantages:

- Injectable sustained-release ZT-1:
  - once-a-month dosing
  - implant-controlled progressive increase in huperzine A plasma levels
  - no influence of food or variability in drug absorption
  - sustained plasma levels

- Oral ZT-1:
  - daily dosing
  - escalating dosing schedule required for tolerance establishment
  - bioavailability influenced by food / variability in drug absorption

The potential neuroprotective benefits of the sustained release implant of ZT-1 will be further evaluated in a transgenic amyloid precursor protein mouse model of Alzheimer’s Disease.

Conclusion & Perspectives

An injectable sustained-release formulation of ZT-1 for monthly dosing was administered to rats in this study. Biocompatibility of the implant and a prolonged liberation over several weeks of the active metabolite huperzine A was achieved after a single injection.

We speculate that the sustained release pattern could have a favorable effect on amyloid deposits as compared to the oral route. To validate these results, further models will be used.