GEBR-32A, A NEW PROMISING PDE4D INHIBITOR FOR TREATMENT OF ALZHEIMER'S DISEASE

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Cognitive deficits characterize several neurodegenerative disorders, including Alzheimer's disease (AD). It has been consistently reported that inhibition of type 4 phosphodiesterase (PDE4) and elevation of cyclic adenosine monophosphate (cAMP) is a promising therapeutic approach to treat memory loss. However, PDE4 exists in several isoforms and pan inhibitors such as rolipram cannot be used in humans due to severe emesis.

In previous studies, we have identified novel PDE4D full inhibitors that were able to increase memory performance of healthy rodents in specific behavioural tests and were devoid of emetic-like effects (1,2).

In this study, we present GEBR-32a, a new PDE4D full inhibitor that has been characterized both in vitro and in vivo using biochemical, electrophysiological and behavioural analyses.

GEBR-32a has been characterized for selectivity against a panel of 20 different recombinant human PDEs expressed in baculovirus and it showed good selectivity towards PDE4D isoforms (IC50s ranging from 1.14 to 4.97 □M). Our compound was able to concentration-dependently (0.1-100 □M) enhance forskolin-induced cAMP production in rat hippocampal slices (approx. 4 fold increase at 100 □M). Similar results have been obtained by treating HTLA cells with 100 □M of GEBR-32a for 10 min (approx. 14 fold increase).

Preliminary safety analysis was carried out in vitro by assessing GEBR-32a cytotoxicity and genotoxicity. As a matter of fact, exposure of HTLA cells to 100 □M GEBR-32a for 24 hours at 37 °C did not significantly increase lactate dehydrogenase release (marker of cytotoxicity) or the phosphorylation of the chromatin-bound histone HA2.X (a marker of DNA damage).

In vivo pharmacokinetic analysis was carried out in mice following a subcutaneous administration of 10 mg/kg of our PDE4D inhibitor and it revealed that GEBR-32a was rapidly absorbed in plasma and brain (TMAX=0.33 h) and was also rapidly eliminated (t1/2=0.95 h). Brain penetration was very good, the AUC0-t brain/plasma ratio being 2.71.

From a behavioural point of view, acute administration of GEBR-32a (0.003 mg/kg s.c.) was able to improve consolidation of memory in the object location task (OLT) on a 24 hour-experimental protocol. In the OLT, our inhibitor (0.03, 0.3 mg/kg) was also able to ameliorate cognitive deficits of Tg2576 Alzheimer's disease mice on a 1 hour-experimental protocol. In addition, chronic, but not acute, administration of GEBR-32a (0.03 mg/kg) improved memory performances of Tg2576 mice in the Y-maze continuous alternation test.

Of great interest, GEBR-32a, at doses 100–1000 times higher than the pro-cognitive ones, did not shorten anaesthesia time in the ketamine/xylazine induced alpha2-adrenoceptor-mediated anaesthesia test, which is used to assess drug emetic-like potential in rodents.

Finally, we have also found that GEBR-32a chronic administration (0.003 mg/kg, s.c.) in Tg2576 mice rescued hippocampal long-term potentiation deficits.

In conclusion, GEBR-32a could represent a very promising cognitive-enhancing drug with a great potential for the treatment of Alzheimer's disease and related dementias.

Bruno et al. (2011) Br J Pharmacol. 164: 2054-2063.

Brullo et al. (2016) Eur J Med Chem. 124: 82:102.

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