Better together – Novel dual-acting and disease-modifying approach to combat Alzheimer's

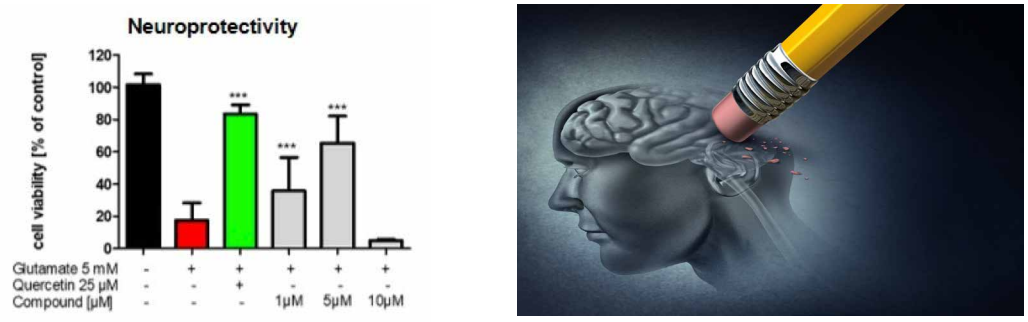
Reference No: B79080

CHALLENGE

Alzheimer's disease (AD) is a neurodegenerative disorder with cognitive, functional, and behavioral alterations. AD is progressive and memory loss and personality changes pose a great burden for the more than 25 million patients and their families worldwide. Despite all efforts to identify the cause and halt the fast progression, only 5 drugs are currently approved in the US for treating the cognitive decline with no new therapies in over a decade. The cholinesterase (ChE) inhibitor tacrine raises levels of the neurotransmitter acetylcholine (ACh). However, the compound exhibits dose-dependent hepatotoxicity and acts only symptomatically, like all approved drugs. Due to the complex pathophysiology of AD, multi-target strategies may be the way forward[1] . Here, tacrine can pose a promising start for developing a multitarget drug. The last years have yielded evidence that activating the human cannabinoid receptor subtype 2 receptor reduces overall AD-like pathology by attenuating associated neuroinflammation and improving cognitive impairment in animal models[2] .

INNOVATION

Here, we present **hybrids** of tacrine and an hCB_2R agonist connected by different linkers. All synthesized hybrids showed pronounced **inhibition of human ChEs** compared to tacrine alone and **interfered with overall β-amyloid aggregation**. The most promising hybrids showed **pronounced anti-neuroinflammatory effects *in vitro* on microglia cells and neuroprotection *in vivo*** as evidenced by attenuation of short- and long-term memory in a murine Alzheimer's model[3] . Importantly, even high doses of hybrid compounds (3mg/kg) **lacked hepatotoxicity** seen with tacrine alone.



Glutamate-induced **oxidative stress test in a neuronal cell line** confirms hybrids to have a pronounced neuroprotective effect comparable to positive control quercetin but already at much lower concentration.

COMMERCIAL OPPORTUNITIES

- Stronger **inhibition** of ChEs compared to tacrine alone
- Efficient crossing of **blood-brain barrier** despite high molar mass
- High *in vivo* efficacy even at low dosages (0.1 mg/kg) and **no liver toxicity**

DEVELOPMENT STATUS

Proof of concept *in vitro* and *in vivo* Alzheimer's model.

REFERENCES:

1. doi: 10.3233/JAD-180766
2. doi: 10.3389/fnins.2016.00243
3. doi: 10.1021/acs.jmedchem.9b00623

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