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Anti-inflammatory and protective effects of MT-031, a novel multitarget MAO-A and AChE/BuChE inhibitor in scopolamine mouse model and inflammatory cells

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ABSTRACT

Previous study demonstrated that the novel multitarget compound, MT-031 preserved in one molecule entity the beneficial properties of its parent drugs, rasagiline and rivastigmine, and exerted high dual potencies of monoamine oxidase-A (MAO-A) and cholinesterase (ChE) inhibition in acute-treated mice and neuroprotective effects against H_2O_2-induced neurotoxicity in human neuroblastoma SH-SY5Y cells. The present study aimed to further investigate the anti-inflammatory and protective effects of MT-031 in scopolamine mouse model and inflammatory cell cultures. Our findings demonstrated that once daily chronic administration of MT-031 (5–10 mg/kg) to mice antagonized scopolamine-induced memory and cognitive impairments, displayed brain selective MAO-A and AChE/BuChE inhibition, increased the levels of striatal dopamine (DA), serotonin (5-HT) and norepinephrine and prevented the metabolism of DA and 5-HT. In addition, MT-031 upregulated mRNA expression levels of Bcl-2, the neurotrophic factors, (e.g., brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF) and nerve growth factor (NGF)), the antioxidant enzyme catalase and the anti-inflammatory cytokine, neurotrophic tyrosine kinase receptor (Ntrk), and down-regulated the mRNA expression levels of the pro-inflammatory interleukin (IL)-6 in scopolamine-induced mice. In accordance, MT-031 was shown to reduce reactive oxygen species accumulation, increase the levels of anti-inflammatory cytokines, IL-10 and decrease the levels of the pro-inflammatory cytokines, IL-1β, IL-6, IL-17 and interferon-gamma (IFN-γ) in activated mouse splenocytes and microglial cells. Taken together, these pharmacological properties of MT-031 can be of clinical importance for developing this novel multitarget compound as a novel drug candidate for the treatment of Alzheimer's disease.

1. Introduction

Alzheimer's disease (AD) is a neurological disease, consider as a progressive disorder of dementia and impaired cognitive and mental functions (Alzheimer's Association, 2015; Katzman, 1986; McCarty, 2006). In addition to the two major neuropathological hallmarks of the disease, namely the neurofibrillary tangles and amyloid beta (Aβ) plaques (Hardy and Selkoe, 2002; Octave, 2005), AD is characterized by a consistent deficit in cholinergic neurotransmission, particularly in the basal forebrain (Schliebs, 2005). Moreover, accumulating evidence indicated that many cytotoxic signals in the AD brain such as, oxidative stress (OS),

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; AChEIs, acetylcholinesterase inhibitors; AD, Alzheimer's disease; Bcl-2, B-cell lymphoma 2; BDNF, Brain-derived neurotrophic factor; GDNF, Glial cell line-derived neurotrophic factor; ChE, cholinesterase; DOPAC, 3,4-dihydroxyphenylacetic acid; DA, dopamine; HPLC, high performance liquid chromatography; HVA, homovanillic acid; 5-HIAA, 5-hydroxyindoleacetic acid; IL, Interleukin; IFN-γ, Interferon-gamma; LPS, Lipopolysaccharide; MAO, monoamine oxidase; 3-MT, 3-methoxytyramine; NE, noradrenaline; NGF, neurotrophic growth factor; Ntrk, neurotrophic tyrosine kinase receptor; OS, oxidative stress; ROS, reactive oxygen species; RT-PCR, real-time reverse transcription polymerase chain reaction; 5-HT, serotonin.

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inflammation and excessive bio-metals (e.g. iron, zinc, and copper) at the sites of the neurodegeneration can initiate neuronal death processes (Aisen and Davis, 1994; Joseph et al., 2005; Octave, 2005; Rogers and Lahiri, 2004). Thus, it is likely reasonable to conclude that novel AD therapeutic strategy will require multitarget drug treatment to address the varied pathological aspects of this disease.

A vast studies considered to develop and design multitarget-directed ligands towards targeting AD complex etiological pathways (Buccafusco and Terry, 2000; Weinstock et al., 2000; Youdim, 2010; Zheng et al., 2005). Recently, we have designed and synthesized a new series of multitarget compounds, by amalgamating the neuroprotective/neurorescue active N-propargyl moiety of the monoamine oxidase (MAO)-B inhibitor/anti-Parkinson's drug, rasagiline (Youdim, 2003) to the methyl-amino-position of the acetylcholinesterase (AChE) inhibitor/anti-AD drug, rivastigmine (Weinstock et al., 1994), aiming to develop new therapy for AD (Liu et al., 2016). The use of the multitarget-directed ligand strategy to combine rasagiline and rivastigmine in order to create a series of rasagiline-rivastigmine hybrids, MT compounds, attained to achieve simultaneously inhibition of MAO/ChE inhibitory activities, antioxidant activity and neuroprotective properties. Among MT series, MT-031 (Fig. 1A) exerted the higher dual potency of MAO-A and ChE inhibition than other compounds and found to increase the striatal levels of dopamine (DA), serotonin (5-HT) and norepinephrine (NE), and prevent the metabolism of DA and 5-HT in acute-treated mice (Liu et al., 2016). Additionally, MT-031 exerted neuroprotective/antioxidant effects against H_2O_2 in human neuroblastoma SH-SY5Y cells (Liu et al., 2016).

In the present study, we have further examined the anti-inflammatory and protective effects of the multitarget ligand, MAO-A/ChE inhibitor, MT-031 in mice-treated with scopolamine-induced amnesia, which is widely referred as a model simulating human dementia in general and AD in particular (Joshi and Parle, 2006). In addition, the anti-inflammatory and protective effects of MT-031 were explored in mouse splenocytes and microglial cells.

2. Materials and methods

2.1. Materials

The MD-TM Mobile Phase, for analysis of monoamines and

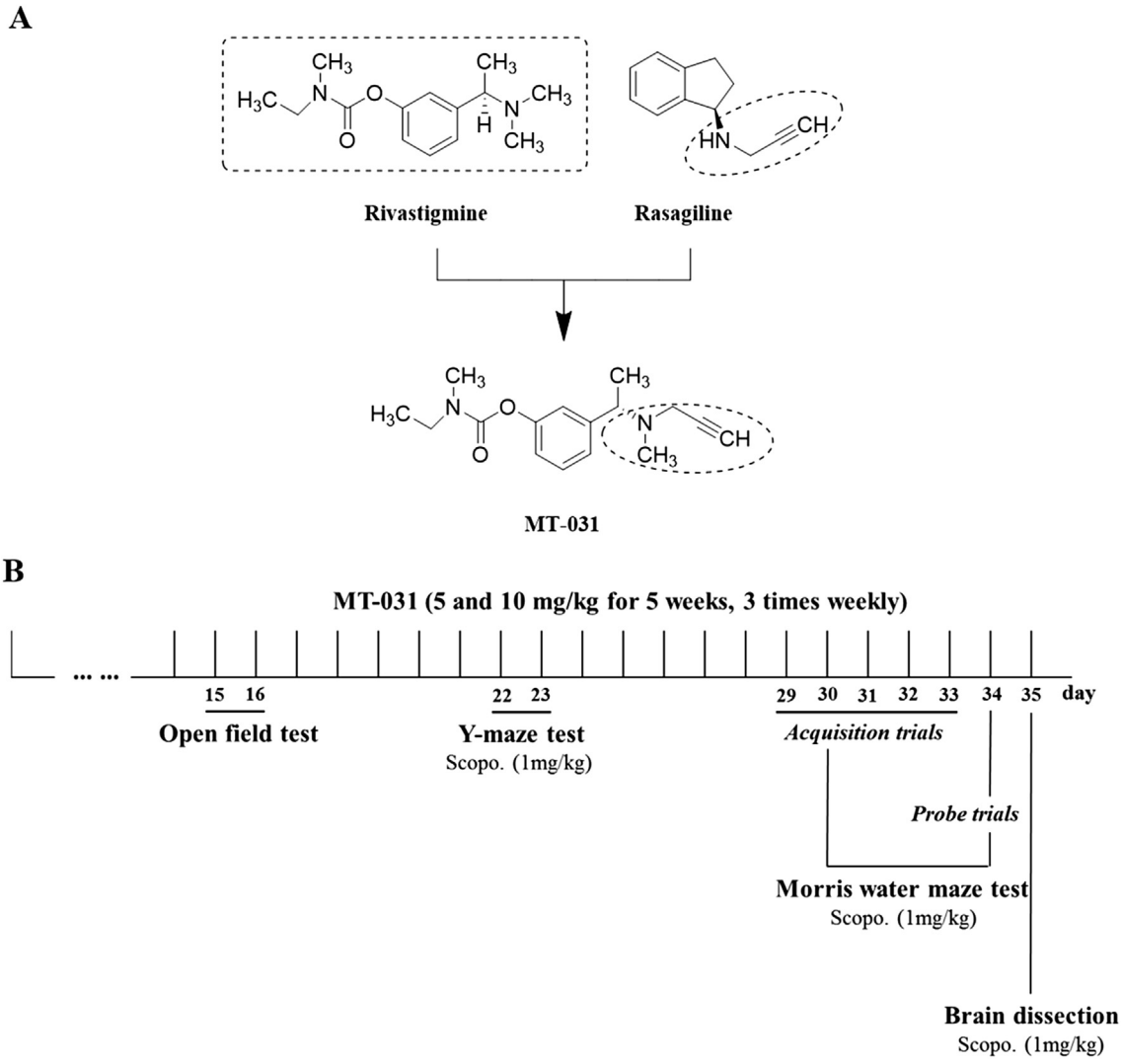

Fig. 1. A) Design and chemical structure of MT-031. MT-031 ((S)-Ethyl-methyl-carbamic acid 3-[1-(methyl-prop-2-ynyl-amino)-ethyl]-phenyl ester) was designed and synthesized by amalgamating the active propargyl moiety of the anti-Parkinsonian drug, brain selective MAO-B inhibitor, rasagiline into the N-methyl position of the anti-AD drug, ChE inhibitor, rivastigmine. **B) Chronic treatment schedule of MT-031 in scopolamine-induced mice**. The experimental protocol is discussed in Material and methods section.