T-817MA ENHANCED AMYLOID BETA UPTAKE OF IPSC-DERIVED MICROGLIA AND DECREASED NEUROINFLAMMATORY RESPONSE IN MOUSE BRAIN.

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T-817MA BACKGROUND

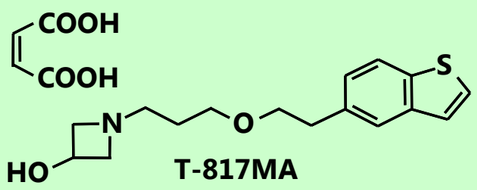
Pharmacological profile of T-817MA

in vitro

- Neuroprotection (ref.1, 2)
  - H_2O_2
  - Amyloid beta (Aβ)
  - Sodium nitroprusside (SNP)
- Neurite outgrowth
  - Hippocampal neurite outgrowth (acute slice)
  - Rat reaggregation cultured neurons (ref.2)

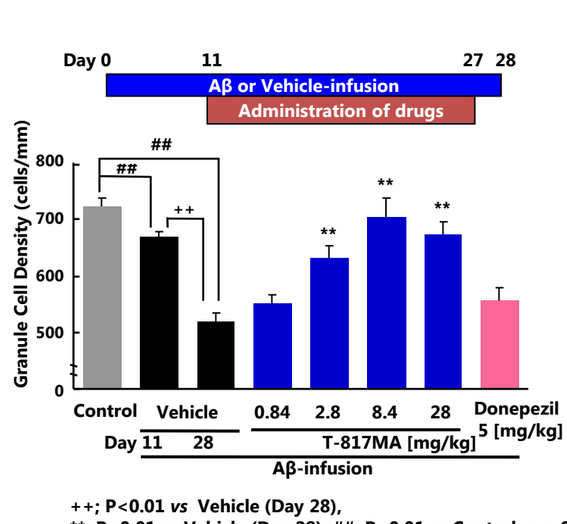
in vivo

- Protection from cognitive impairment and synaptic dysfunction
  - Aβ-infusion rats (ref.3)
  - Tau-P301L mice (ref.4)
- Accelerates motor function recovery from brain damage

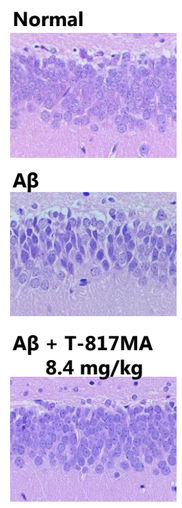


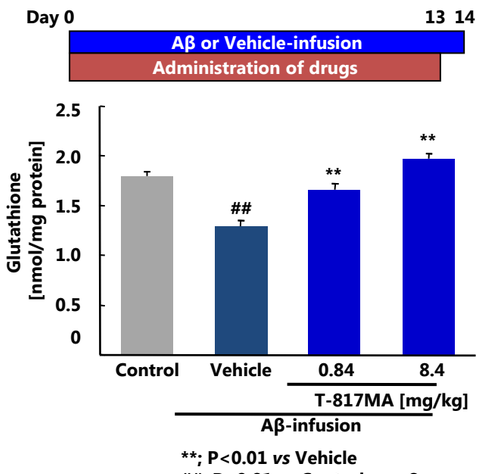
(1-{3-[2-(1-benzothiophen-5-yl) ethoxy] propyl}azetidin-3-ol maleate)

T-817MA prevents granule cell loss and glutathione reduction in Aβ-infusion rats



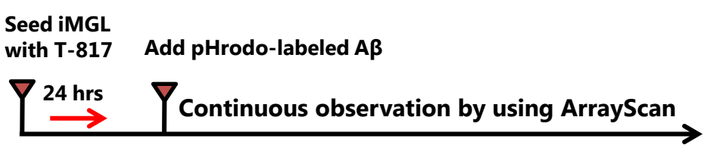
++; P<0.01 *vs* Vehicle (Day 28),
**; P<0.01 *vs* Vehicle (Day 28), ##; P<0.01 *vs* Control, n = 9-10



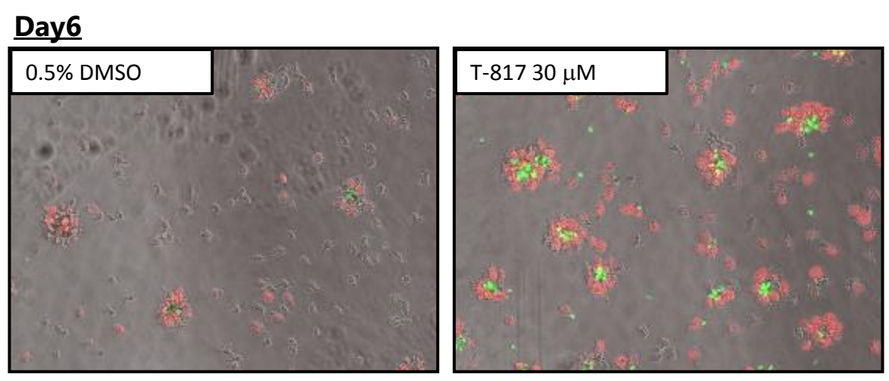


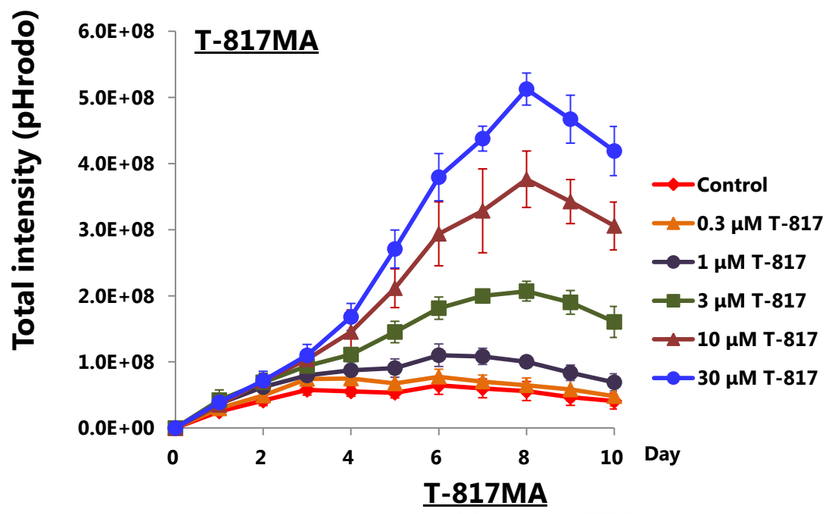
**; P<0.01 *vs* Vehicle
##; P<0.01 *vs* Control, n = 8

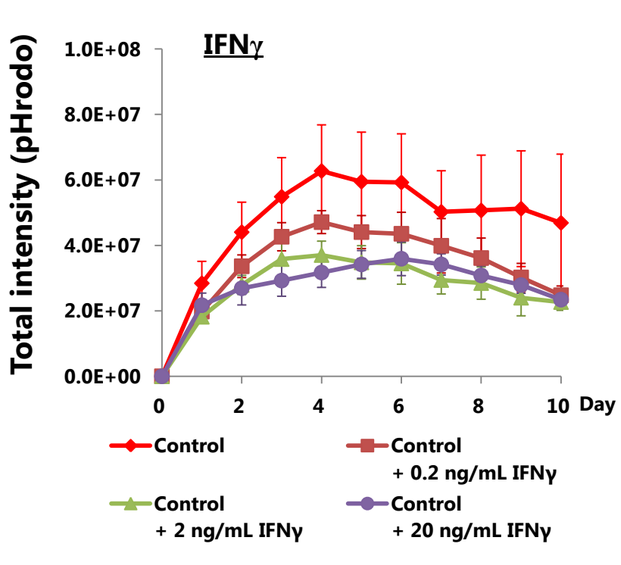
T-817MA enhanced Aβ uptake of human iMGLs and alleviated its inhibition by IFNγ

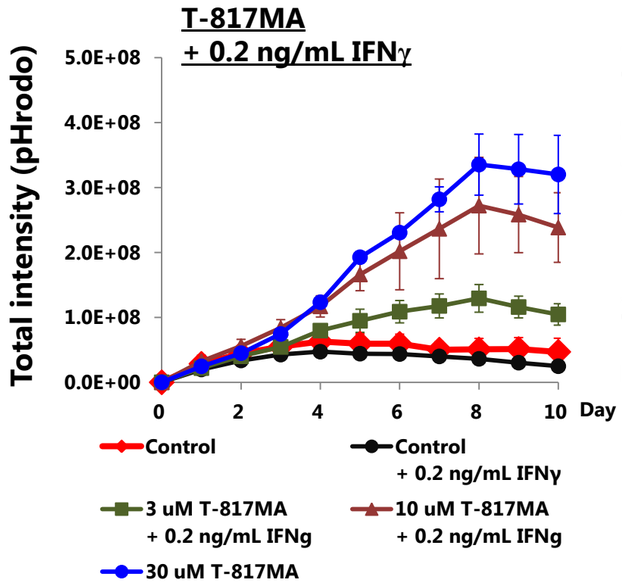


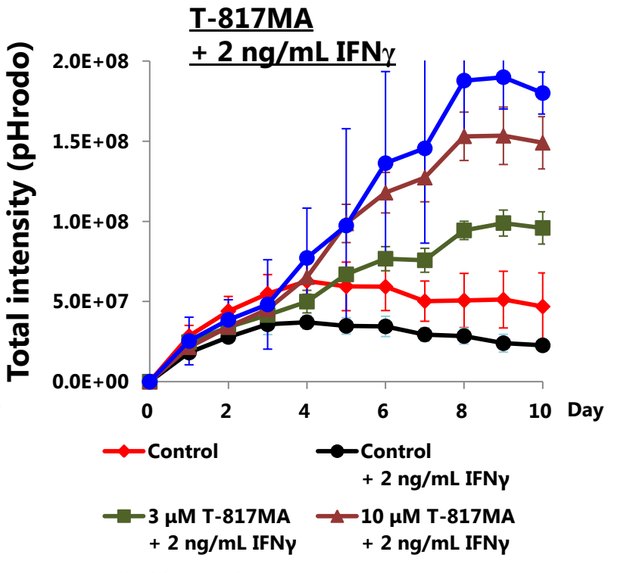
Green: Nucgreen stain (dead cell nuclei)
Red: pHrodo-conjugated fibril Aβ
(pHrodo: pH-sensitive fluorescence dye)

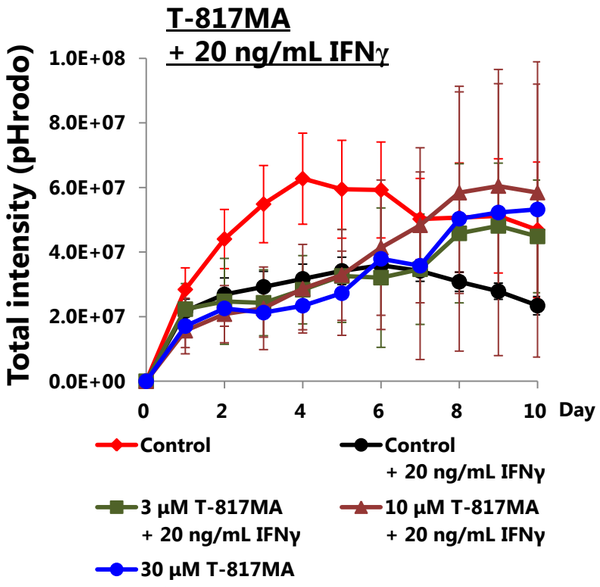












iPSC-derived Microglia (iMGL: Cellular Dynamics) were plated in 384-well plate. T-817MA was treated at the same time with seeding microglia. After twenty four hours, pHrodo (Thermo Fisher Scientific)-labeled Aβ with/without IFNγ were treated. Phagocytosis of Aβ was detected using ArrayScan system.

T-817MA had inhibitory effect on LPS-induced neuroinflammation in vivo.

*: P<0.05 vs Control by Dunnett multiple comparison test n=7

Nine-week-old male Balb/c mice were administrated with T-817MA (p.o.) twice a day. One hour following the last administration, mice were injected *Escherichia coli* LPS (0.5 mg/kg, serotype O127:B8, i.p.) and whole brain tissue were collected at 4 hours after LPS injection and total RNA samples were prepared. Gene expression was detected by quantitative real-time PCR.

Summary

T-817MA has efficacy on human microglial function *in vitro* and on neuroinflammation *in vivo* mice model. These results further support that T-817MA has a potential to be a disease modifier via neuroprotection and anti-neuroinflammatory efficacy.

Reference

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