CNS Pharmacology Platform

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Animal Models of Ischemic Stroke

OVERVIEW

Rodent models of ischemic stroke
- Intraluminal suture MCAO model (acute:1~3 days; chronic: 28 days)
- Photothrombosis model

Non-human primate models
- Middle cerebral artery occlusion by endovascular micro-coil placement
- Craniotomy model
- Transient（ischemia-reperfusion) or permanent ischemia

Clinical Assessment:
- Body weight
- Infarct volume: TTC Staining or MRI scanning
- Neurological defect test: Bederson Scale & Modified Neurological Severity Scores (mNSS) for rodents, specialized neurological evaluation scale for non-human primates
- Cognitive function/Anxiety-like behaviors: Morris Water Maze/Elevated Plus Maze Test, only for rodents

▲ Angiographic X-ray system from GE Healthcare

Case Study

■ Intraluminal Suture MCAO Model of Rats

·Animals: SD rats, male, 270~280 g
·Induction: occlusion of the middle cerebral artery for 2h, inclusion criteria: Bederson's scale≥3,1h after ischemia
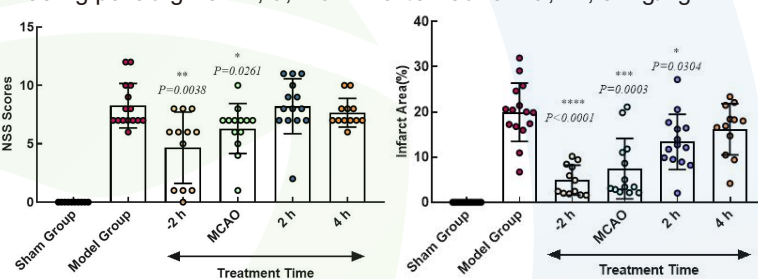·Clinical Assessment: behavioral deficits and infarct volume (TTC staining), 24h after MCAO

<u>A 24-hour pharmacodynamics study</u>

Dosing paradigms: 0, 2h after ischemia

▲ TTC staining
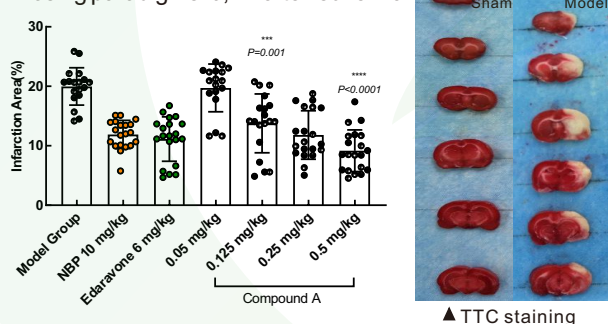
<u>A therapeutic time-window study</u>

Dosing paradigms: -2, 0, 2 or 4h after ischemia, iv., 3 mg/kg


■ Non-Human Primate Model

·Animals: Rhesus monkeys, male, 4~8 kg
·Induction: the M1 segment of the middle cerebral artery was occluded with a custom microcoil for 2h, MCAO and reperfusion were confirmed by digital subtraction angiography (DSA)
·Dosing Paradigms: qd.×21d, the first dosage was given 2h after reperfusion
·Clinical Assessment:
   ·Body weight: qw;
   ·Neurologic deficit score: pre,1,3,7,14,21 days after MACO;
   ·infarct volume: determined by MRI, pre,1,7,14,21 days after MACO.

Before occlusion   After ischemia   After reperfusion
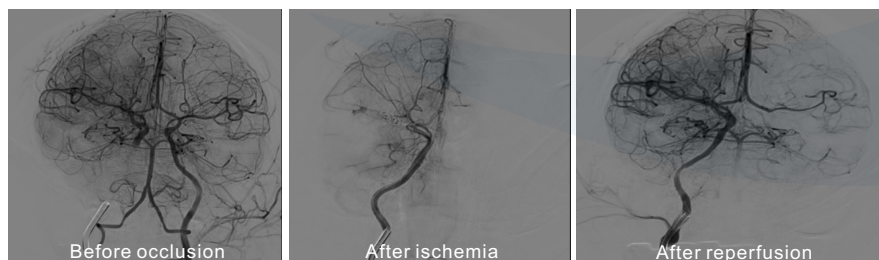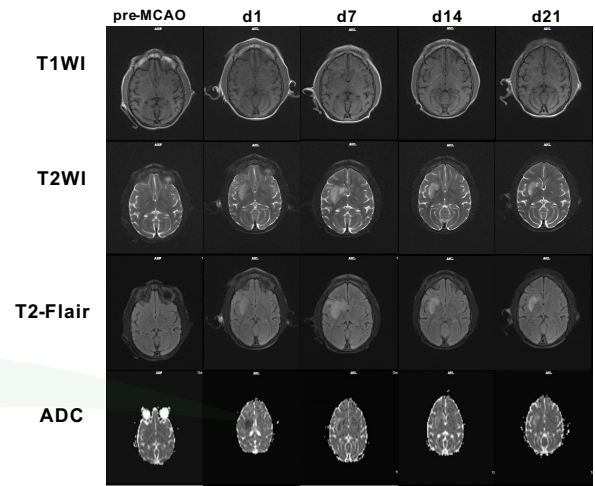
▲ Digital subtraction angiography (DSA) imaging
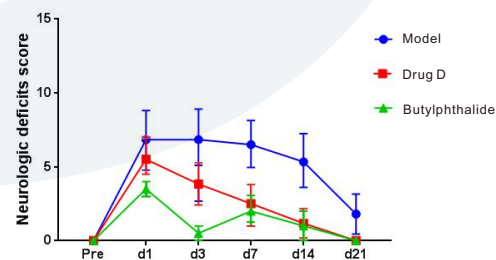
▲ Neurological evaluation scale specialized for NHP

Journal of Neuroscience Methods 105 (2001) 45–53;
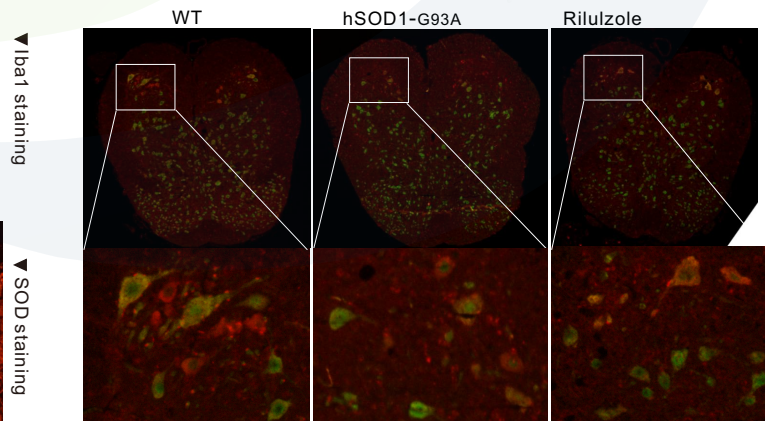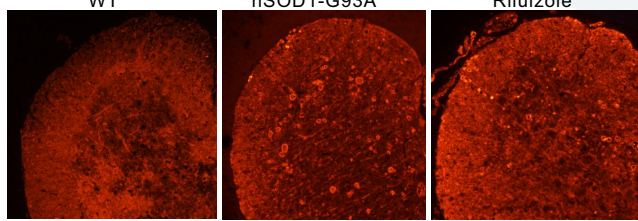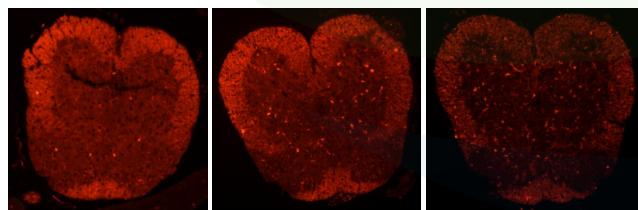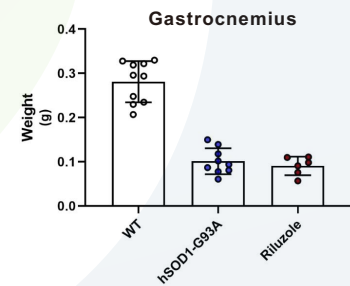Journal of Cerebral Blood Flow & Metabolism (2011) 31, 448–456
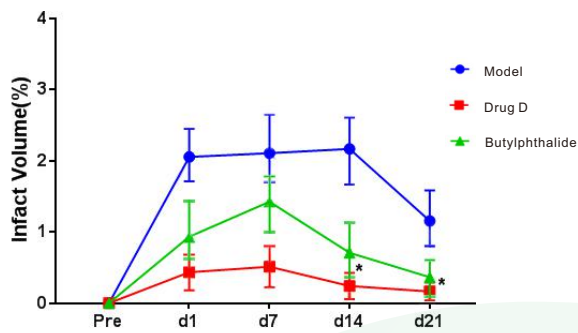
▲ Infarct volume, determined by MRI examination using a 3.0-T MRI before & after MCAO

* represents P<0.05 vs. Model group

Legend: Model, Drug D, Butylphthalide

MRI rows: T1WI, T2WI, T2-Flair, ADC
Columns: pre-MCAO, d1, d7, d14, d21

Animal Models of Amyotrophic Lateral Sclerosis (ALS)

■ hSOD1-G93A Transgenic Mouse Model

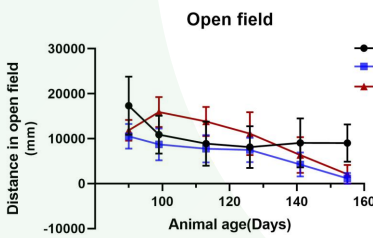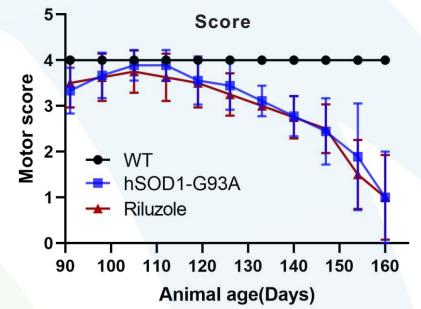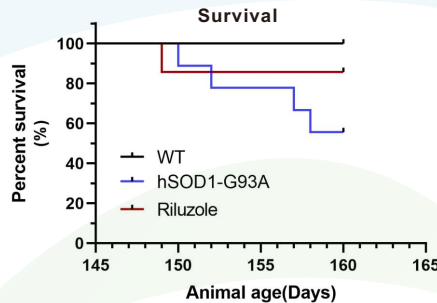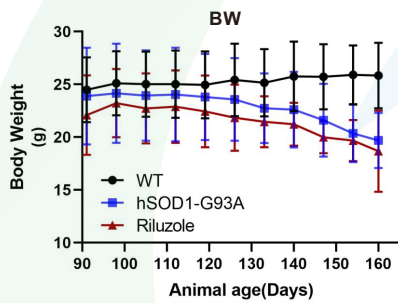BW — Body Weight (g) vs Animal age (Days); WT, hSOD1-G93A, Riluzole

Survival — Percent survival (%) vs Animal age (Days); WT, hSOD1-G93A, Riluzole

Score — Motor score vs Animal age (Days); WT, hSOD1-G93A, Riluzole

Open field — Distance in open field (mm) vs Animal age (Days); WT, hSOD1-G93A, Riluzole

Suspension test — Retention time (s) vs Animal age (Days); WT, hSOD1-G93A, Riluzole

Rotarod — Retention time (s) vs Days; WT, hSOD1-G93A, Riluzole

Gastrocnemius — Weight (g); WT, hSOD1-G93A, Riluzole

WT   hSOD1-g93A   Rilulzole

WT   hSOD1-G93A   Rilulzole
▲ Iba1 staining

WT   hSOD1-G93A   Rilulzole
▲ SOD staining

WT   hSOD1-G93A   Rilulzole
▲ NeuN&ChAT staining

Animal Models of Alzheimer's Disease (AD)

OVERVIEW

Non-transgenic animal models

1. Naturally-aged rats
   Readouts: behavior tests (memory and learning)
2. Senescence-accelerated mouse (SAM) model（SAMP8 mice）
   Readouts: behavior tests(memory and learning), Aβ deposits
3. Scopolamine-induced models
   Readouts: behavior tests (memory and learning), cholinergic function

Transgenic animal models

- APP/PS1, APP/tau/PS1, 5xFad transgenic mice
- Readouts: Behavior tests , Aβ deposits, tau hyperphosphorylation, microglial activation, neuropathology.

Case Study

■ APP/PS1 Transgenic Mouse Model

- **Animals**: APP/PS1 mice, male, 9-month old (n=11)
- **Treatment**: Po., qd.×15 weeks
- **Clinical Assessment**: body weight, behavior tests , Aβ40 & Aβ42 expression in cortex and hippocampus, TNFα, IL-1β mRNA expression in cortex

*P<0.05 vs. Model group

▲ Water maze

▼ Cortex

▼ Hippocampus
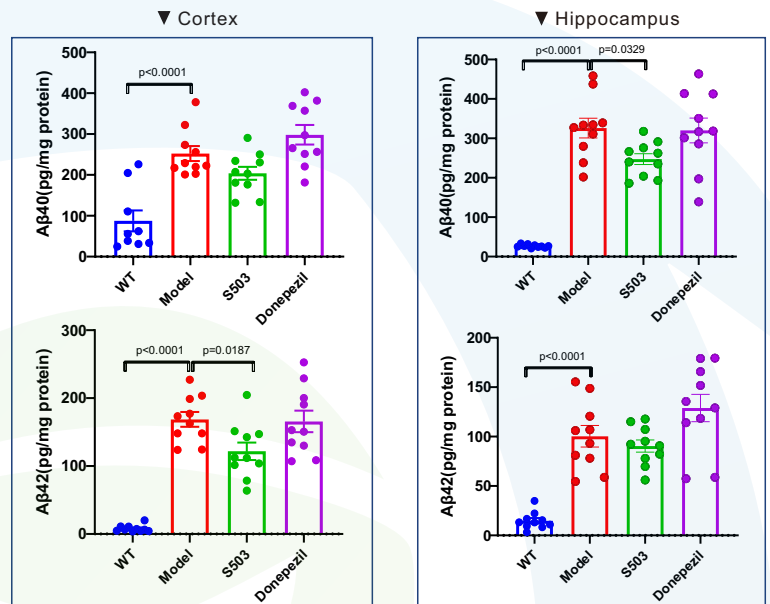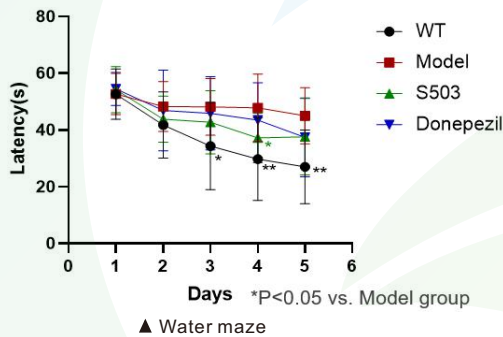
Animal Models of Parkinson's Disease (PD)

OVERVIEW

- **α-synuclein (A53T) transgenic mice**
  Readouts: Behavior tests, nigral dopaminergic neurodegeneration, α-syn pathology, and neuroinflammation
- **MPTP-induced induced PD model (mice)**
  Readouts: neuron loss, gliosis, behavioral dysfunction and dopamine secretion.
- **6-OHDA-induced PD model (rats)**
  Readouts: neuron loss, gliosis, behavioral dysfunction and dopamine secretion
- **Pilocarpine-induced tremulous jaw movements (rats)**
  Readouts: frequency and intensity of tremor

Case Study

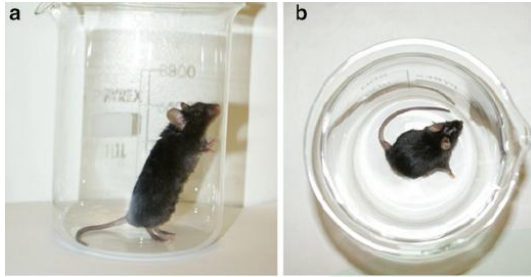### ■ Pilocarpine-Induced Tremulous Jaw Movements (Rats)

The number of TJMs was counted after the treatment of HB or L-DOPA treatment (qd×7d for HB, and qd×1d for L-DOPA) on rats received intraperitoneal administration of pilocarpine (4.0 mg/kg).

► Number of tremulous jaw movements (5 min)
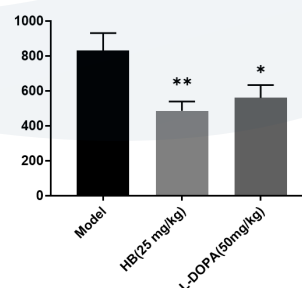
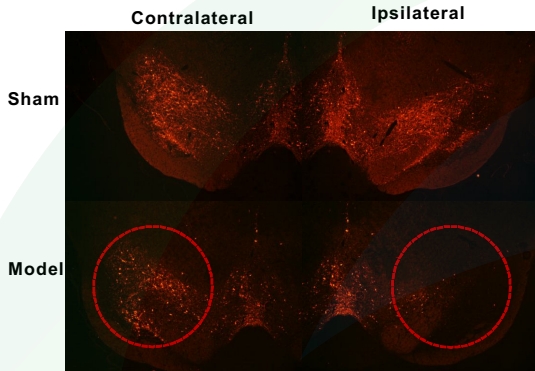*P<0.05 vs. Model group(n=12)
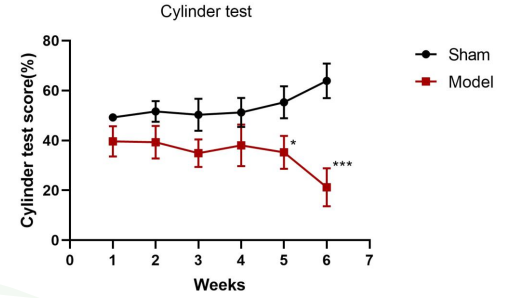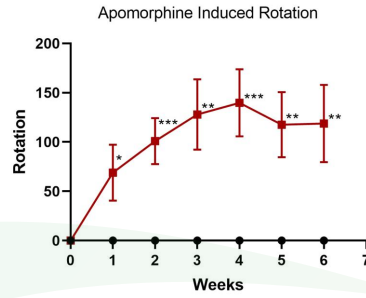**P<0.01 vs. Model group(n=12)
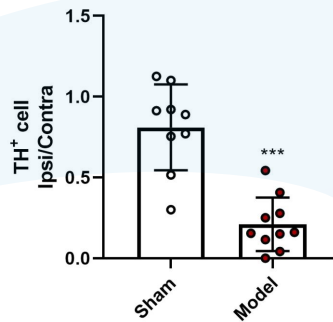
■ 6-OHDA-Induced PD model (Rats)

▲ Behavioral test

▲ Tyrosine hydroxylase (TH) immunostaining in substantia nigra

CONTACT US

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