Alzheimer’s disease (AD) model

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SMC Laboratories, Inc.

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Ver. 2021.1

Drug development in AD

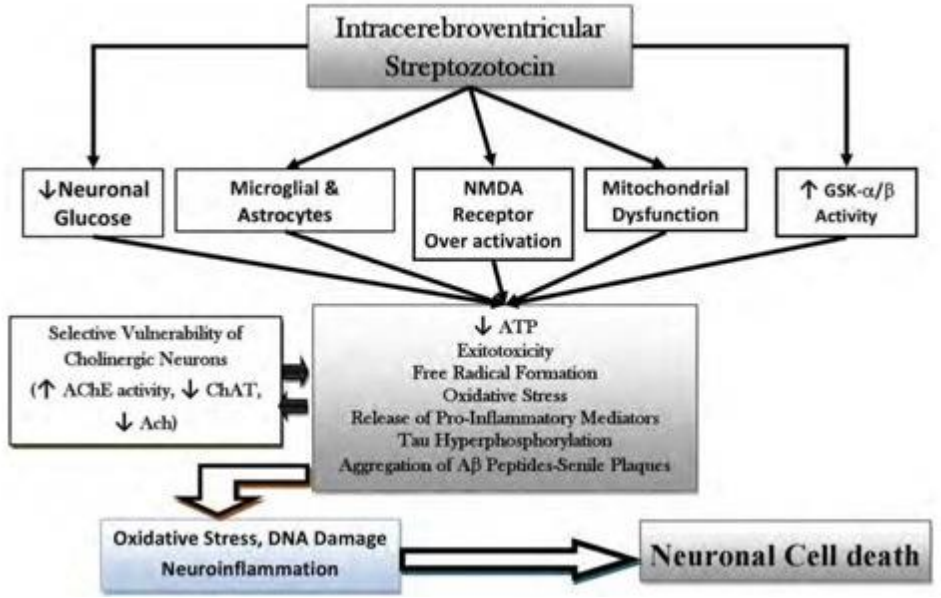
Compound	Current or recent clinical phase (s)	Preclinical research supporting clinical trials		Treatment scheme
		Reference	Animal model	
PBT-2	Phase Ⅱ	Adlard et al. (2008)	a) APP/PS1 mouse model expressing human APP with Swedish mutation and human PS1-dE9 deletion	a1) 11 or 35 days p.o. treatment at age 8 months (10 or 30 mg・kg-1・day-1) a2) single p.o. dose (30 mg・kg-1) prior to microdialysis at age 22 months a3) single p.o. dose (30 mg・kg-1) prior to microdialysis at age 3-4 months
			b) Tg2576 mouse model ($hAPP_{695}$Swedish)	b1) 11 days p.o. treatment at age 13.5 months (30 mg・kg-1・day-1) b2) single p.o. dose (30 mg・kg-1) prior to microdialysis at age 18 months
IVIg	Phase Ⅲ	Magga et al. (2010)	APP/PS1 mouse model expressing human APP with Swedish mutation and human PS1-dE9 deletion	i.v. administration of 1.0 g・kg-1 of 10% IVIg starting at age 4 months with twice weekly injections for 1-3 weeks (short-term) or long-term study with weekly injection for 14 weeks
Lithium	Phase Ⅱ	Leroy et al. (2010)	Tg30tan mice expressing human 4R1N doub l e-mutant tan (P302S and G272V)	a) 8 month treatment starting at age 3 montha with lithium carbonate supplemented in food (2.4 g・kg-1 chow) b) 1 month treatment starting at age 9 months with daily gavage (350 mg・kg-1)
Donepezil	Phase Ⅰ-Ⅱ	Meunier et al. (2006)	Mouse i.c.v. aggregated Aβ25-35 infusion model causing learning deficits on day 7-8	Dose range 0.12-1 mg・kg-1: a) i.p. injection 20 min before behavioural testing (antiamnestic) b) i.p. injection 20 min before $Aβ_{25-35}$ infusion (neuroprotective) c) i.p. injection 20 min before $Aβ_{25-35}$ infusion and daily until behavioural testing (neuroprotective)
Memantine	Phase Ⅲ	Martinez-Coria et al. (2010)	3 × Tg AD mouse model ($hAPP_{695}$Swedish; human tan P301L; human PS1 M146L)	a) 3 month p.o. treatment starting at age 6 months (30 mg・kg-1・day-1), mild pathology group b) 3 month p.o. treatment starting at age 9 months (30 mg・kg-1・day-1), moderate pathology group c) 3 month p.o. treatment starting at age 15 months (30 mg・kg-1・day-1), severe pathology group
Ibuprofen	Phase Ⅰ	Van Dam et al. (2010)	APP23 mouse model ($hAPP_{751}$Swedish)	2 month treatment (50 mg・kg-1・day-1) starting at age 6 weeks, followed by 3 weeks wash-out period
α-Tocopherol	Phase Ⅲ	Nishida et al. (2009)	Ttpa-APPsw	a) 18-month-old α-tocopherol transfer protein knockout mice crossed with Tg2576 model b) α-tocopherol supplementation (750 mg・kg-1)
Semagacestat	Phase Ⅲ	Ness et al. (2004)	PDAPP mouse model ($hAPP_{695}$Indiana)	5 month p.o. treatment starting at age 5 months (3, 10 or 30 mg・kg-1・day-1)
CDA-106	Phase Ⅱ	Staufenbiel et al. (2006)	APP23 mouse model ($hAPP_{751}$Swedish)	10 month s.c. treatment with monthly administration starting at age 3-4 months

Van Dam D and De Deyn PP. Br J Pharmacol; 164:1285-300, 2011

Animal model for AD:

Intracerebroventricular (icv) administration of streptozotocin (STZ)-induced AD model

■ Central mechanism of action of icv-STZ



Sidharth Mehan et al., Inflammatory Diseases - Immunopathology, Clinical and Pharmacological Bases, (2002), ISBN: 978-953-307-911-0,

■ Neuronal cell death is induced by icv-STZ through the generation of oxidative stress, DNA damage and neuroinflammation.

Icv-STZ

↓

GLUT2^{+} neurons

↓

1)Insulin signaling alteration:
PI3K and MAPK pathways.
2)Glucose metabolism changes:
Brain insulin concentration↑
3)Oxidative stress:
MDA↑. TBARS↑・・・
4)Neurotransmission deficits:
Cholinergic deficit, ChAT↓, AChE↑,
5)Behavioral alterations:
Learning, memory, and cognitive disorders.
6)Structural changes, inflammation and neurodegerenation.
7) Aβ and Tau hyperphosphorylation.

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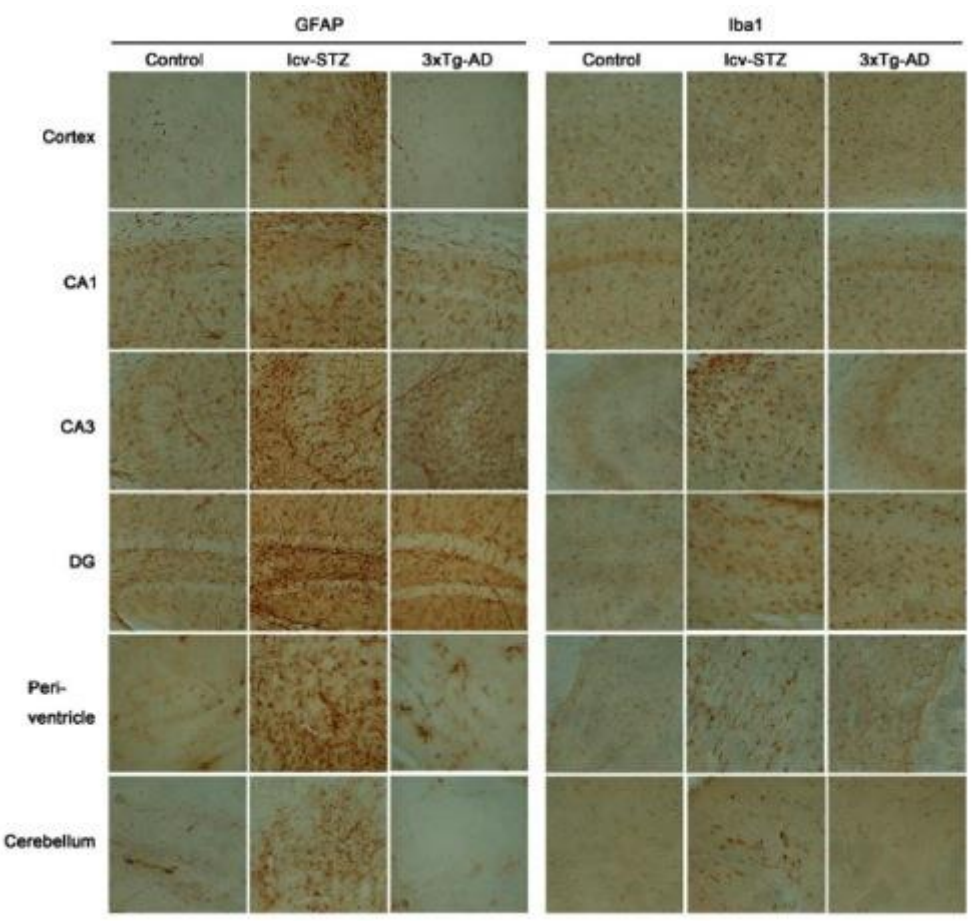
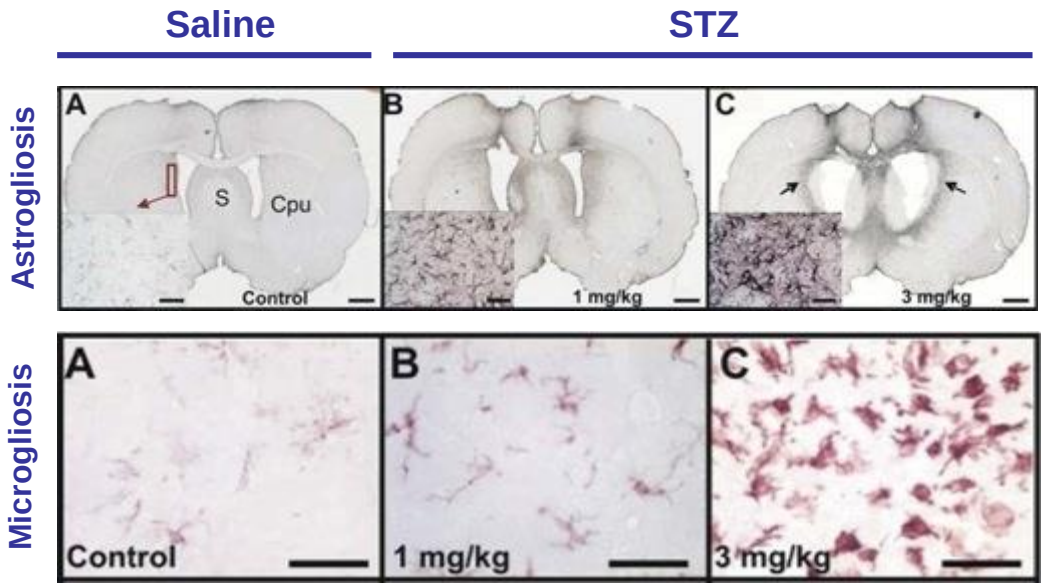
Intracerebroventricular (icv) administration of streptozotocin (STZ)-induced AD model



Chen Y et al., Mol Neurobiol 47(2): 711,2013

Histopathological features of icv-STZ AD model



Kraska A et al., PLoS ONE 7(9): e46196,2012

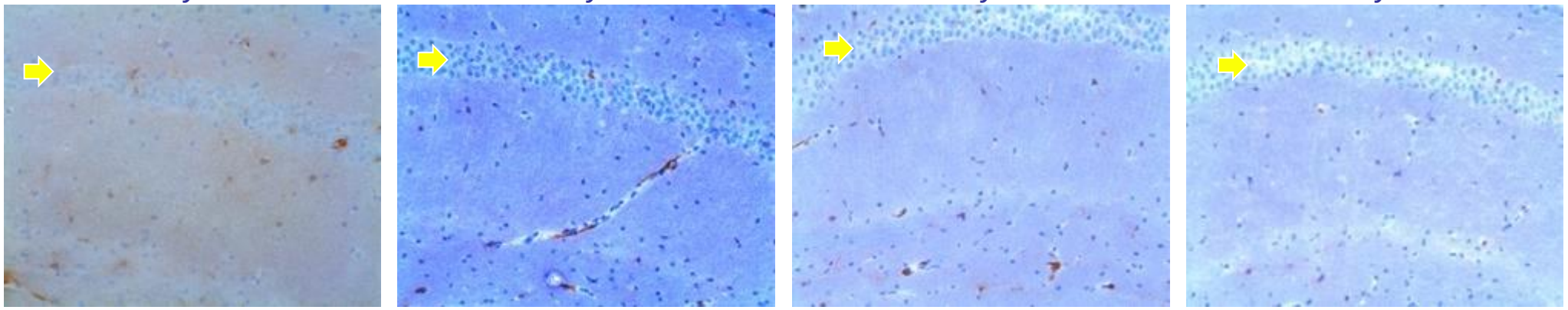
Histopathology one week after icv-STZ injection (brain section): Astro- and microgliosis are observed one week after icv-STZ injection, suggesting the induction of inflammatory responses. Upper panel: glial fibrillary acidic protein; lower panel: Iba-1 (immunohistochemistry).

icv-STZ model:

Sequential histological changes (Hippocampus (CA1))

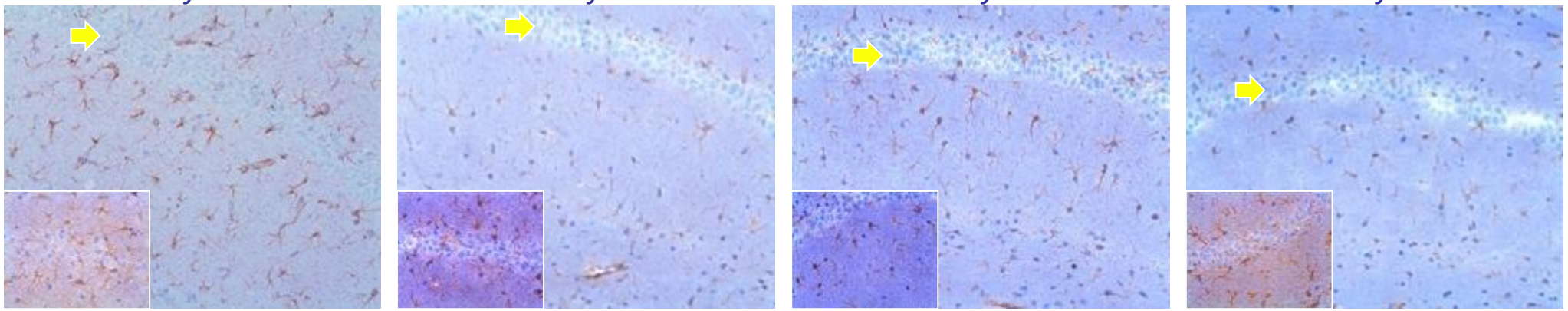
F4/80

Day 0 | Day 3 | Day 7 | Day 15



GFAP

Day 0 | Day 3 | Day 7 | Day 15



- Neuronal loss was observed in the pyramidal layer ( ) at Day 3
- Activated astrocytes were observed in the CA1 region at Day 3 as judged by GFAP immunostaining.

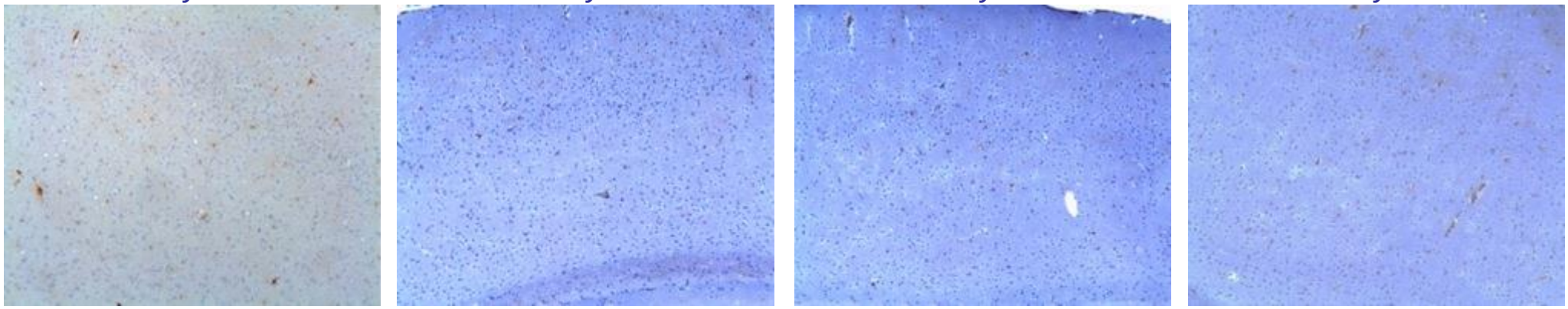
x200

icv-STZ model:

Sequential histological changes (Cortex)

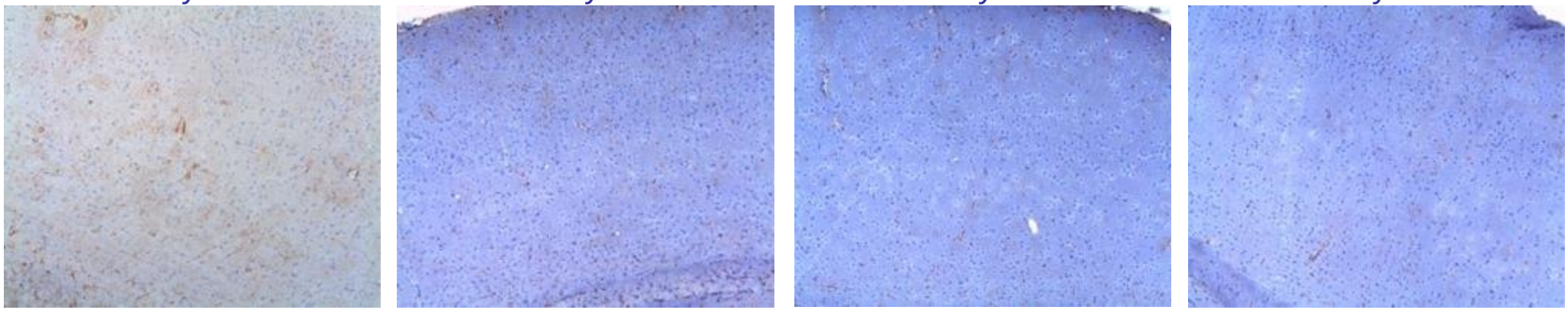
F4/80

Day 0 | Day 3 | Day 7 | Day 15



GFAP

Day 0 | Day 3 | Day 7 | Day 15



- Activated microglia were observed in the cortex at Day 15 as judged by F4/80 immunostaining.
- Activated astrocytes were observed in the cortex at Day 3 as judged by GFAP immunostaining.

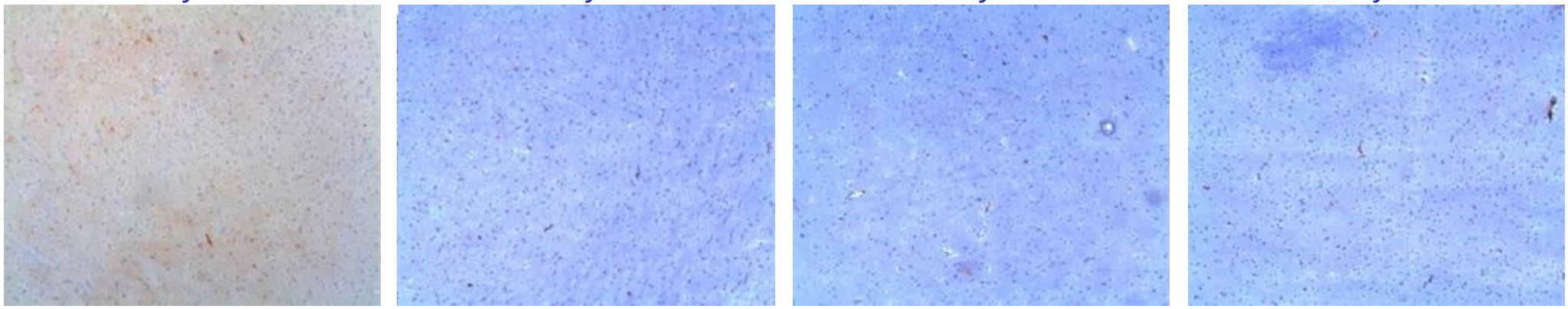
x100

icv-STZ model:

Sequential histological changes (Diencephalon)

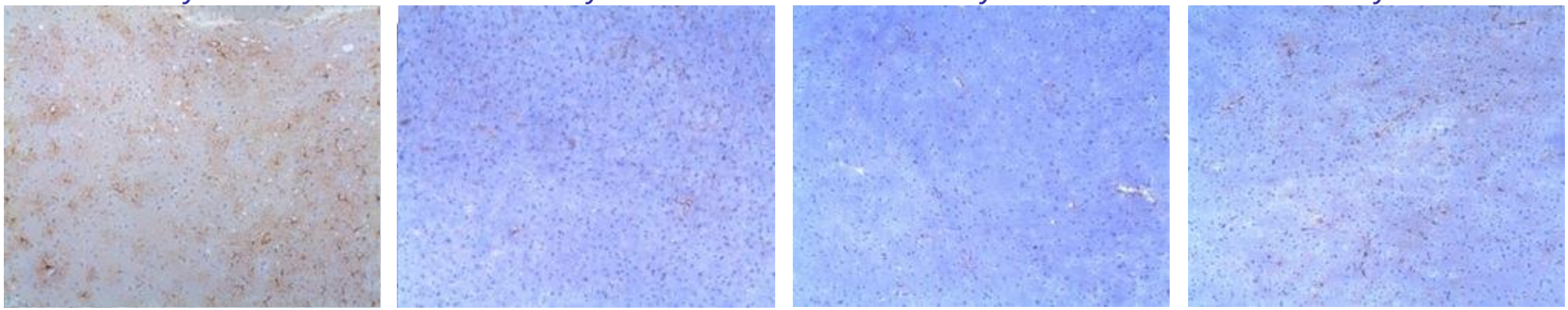
F4/80

Day 0 | Day 3 | Day 7 | Day 15



GFAP

Day 0 | Day 3 | Day 7 | Day 15



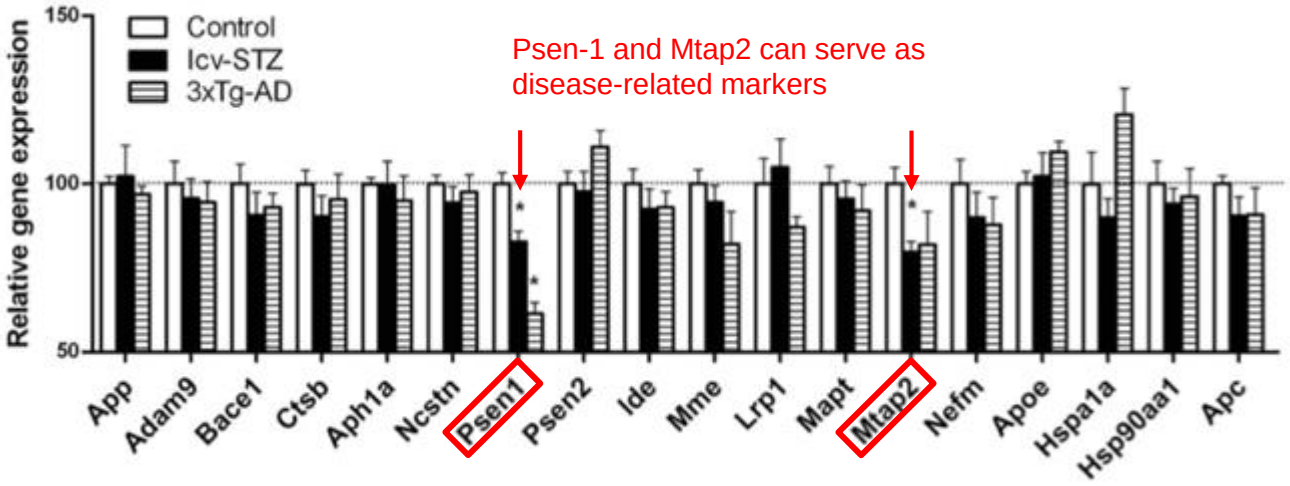
- Activated microglia were observed in the diencephalon at Day 15 as judged by F4/80 immunostaining.
- Activated astrocytes were observed in the diencephalon at Day 15 as judged by GFAP immunostaining.

x100

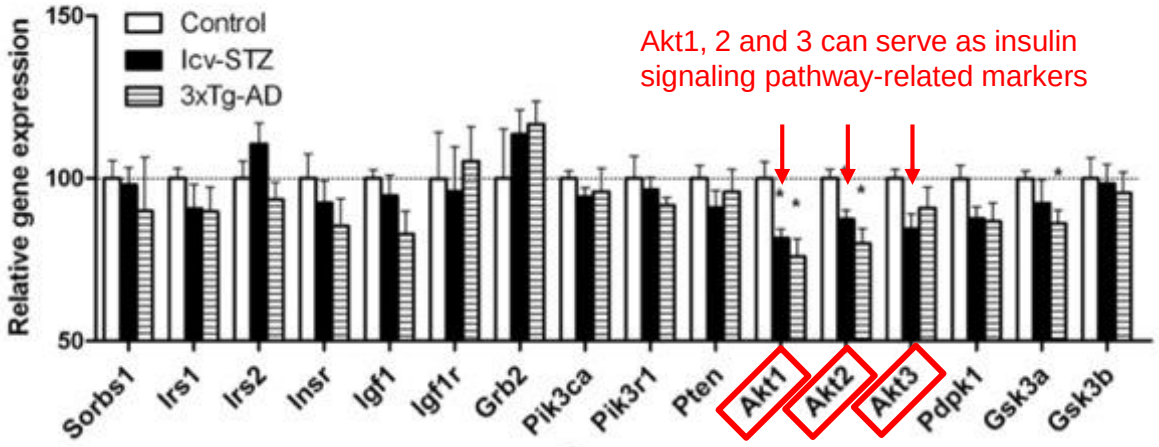
icv-STZ model:

Gene expressions

- APP- and tau related gene expressions of icv-STZ mice



- Insulin signaling-related gene expressions in the hippocampus of icv-STZ mice

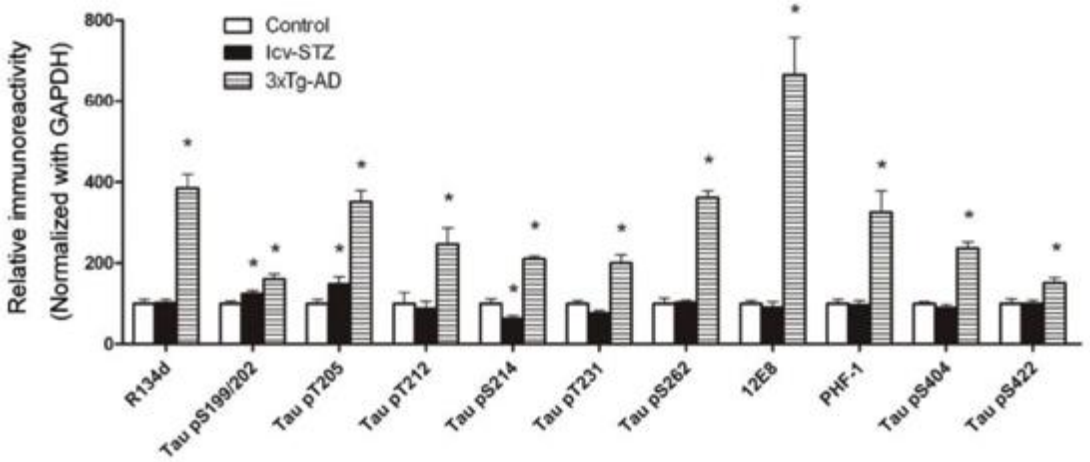


C Yanxing et al., PLoS ONE 7(12): e51432, 2012

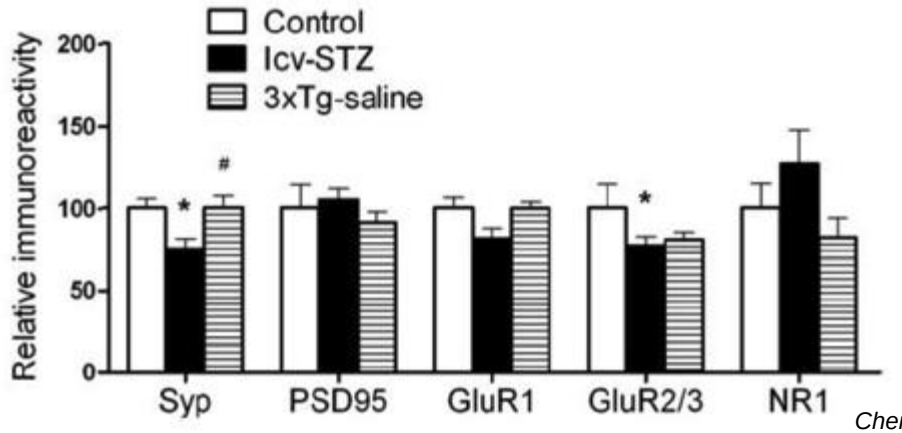
icv-STZ model:

Protein expressions

- Tau phosphorylation in the hippocampus of icv-STZ mice



- Insulin signaling and synapitc loss in the hippocampus of icv-STZ mice



Chen Y et al., Mol Neurobiol 47(2): 711,2013

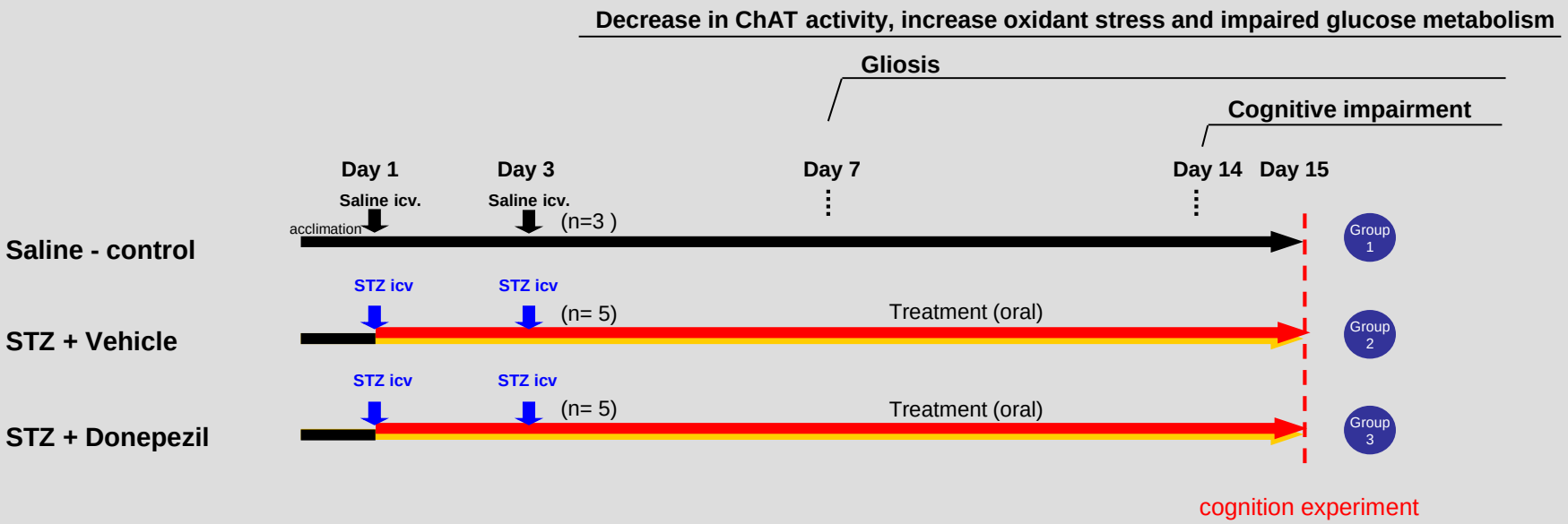
Advantages of icv-STZ model:

The model reflects the heterogeneity of sporadic AD

Compound	Dose (mg/kg)	Biochemical effect	Behavior evaluation	Regimen	Refferences
Acetylcholinesterase inhibitors and other chlinergic-related drugs					
Donepezil	1 and 3	Ach E activity	memory test	-	Sonkusare et al., 2005
tacrine	5	Ach E activity, GSH, MDA	PAT, MWMT	-	Saxena et al 2008
NMDA receptor antagonist					
Memantin	5	-	memory test	-	Ponce-Lopez et al., 2011
Antioxidative activity					
Alpha-lipoic acid	50, 100 ,200	MDA	memory test	21 days	Sharma and Gupta, 2003
Acetl-L-carnitine	75	CAT actvity	MWMT	pre 2 weeks	Terwel et al., 1995
Acetl-L-carnitine	-	Ach E activity, GSH, MDA	-	14 days	Prickaerts et al., 1995
Coenzyme Q10	-	Ach E activity	memory test	-	Ishrat et al., 2006
Vitamin E	100	GSH, TBARS	PAT, MWMT	21 days (pre) + 14 days(post)	Ishrat et al., 2009
Anti-inflammatory activity					
COX inhibitors	-	GSH, MDA, SOD	neuron death , cognitive impaired	5 days (pre) + 5 days (post)	Dhull et al, 2012a
Insulin sensitizer					
Pioglitazone	30	GSH, MDA, SOD	neuron death , cognitive impaired	2 weeks	Ponce-Lopez et al., 2011
	10, 20 30	GSH, MDA, cerebral glucose utilization	MWMT	5 days (pre) + 2 weeks	Pathan et al., 2006, Kaur et al., 2009
Eexedine-4	-	-	MWMT	-	Chemet al., 2011
Antihypertensive drug					
Candesartan	-	MDA, GSH	-	-	Tota et al. 2009

- A variety of drugs has shown effects in the icv-STZ model and can serve as a positive control.

Donepezil as positive control



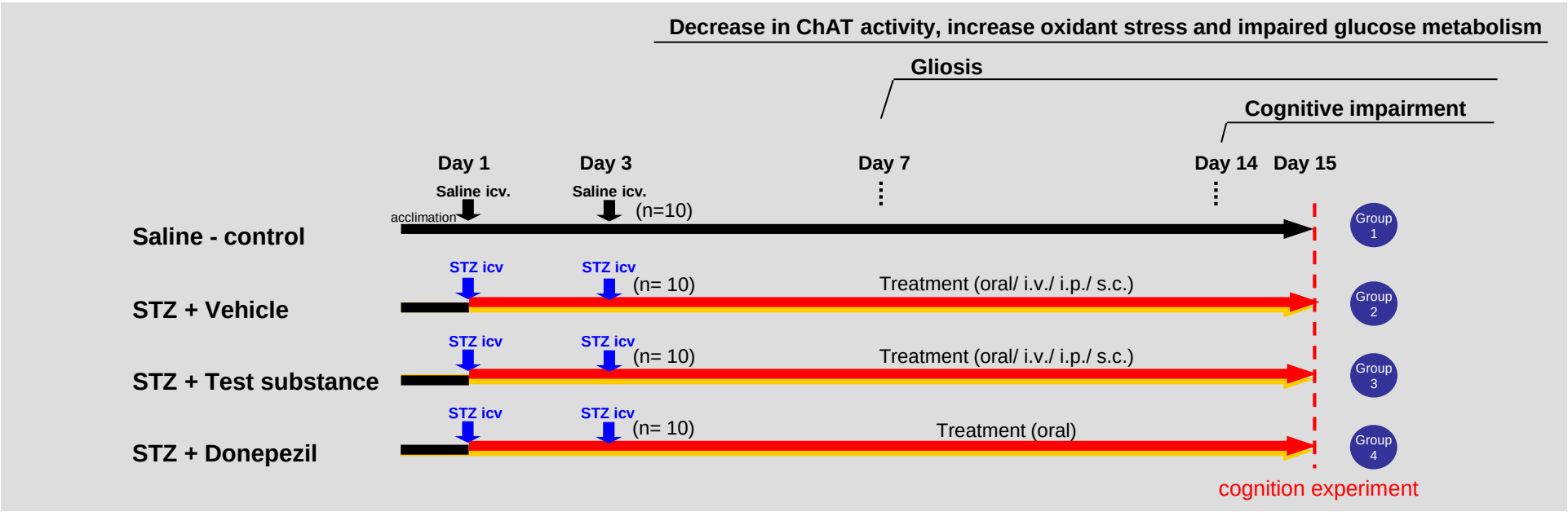
Animal model: icv-STZ induced AD model

- Animal: C57BL/6J mice, male, week 7-8
- Induction of AD: intracerebroventricularly injection of STZ

Study design

- Aim of the study: To investigate the preventive efficacy of test substance on AD
- Route of administration: oral
- Arm: 3
  control, vehicle, positive control (Donepezil)
- The number of mice/group before dosing: n=3 or n=5
- Baseline: day 1 (just prior to STZ administration)
- Randomization: Body weight at day 0
- Treatment period: 2 weeks
- Endpoints (day 15):
  behavioral test: Y-maze

Study design example



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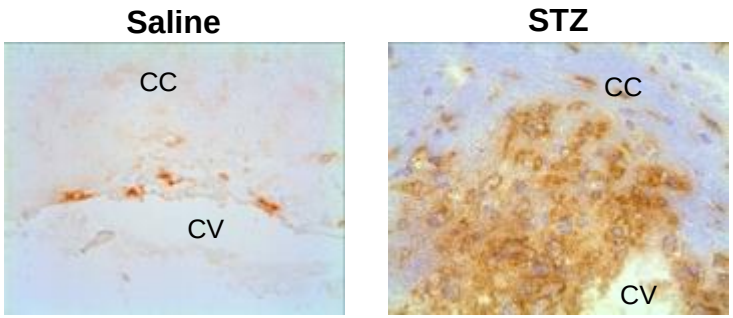
- Animal: C57BL/6J mice, male, week 7-8
- Induction of AD: intracerebroventricularly injection of STZ

Study design

- Aim of the study: To investigate the preventive efficacy of test substance on AD
- Route of administration: oral/ i.p./ i.v./ s.c.
- Arm: 4
  control, vehicle, test substance, positive control (Donepezil)
- The number of mice/group before dosing: n=10
- Baseline: day 1 (just prior to STZ administration)
- Randomization: Body weight at day 0
- Treatment period: 1 or 2 weeks
- Endpoints (day 15):
  behavioral test: Y-maze
  <Analytical items>
  Immunohistochemistry
  Acetylcholine activity
  Gene expression

Immunohistochemistry: Neuralinflammation (day 15)



CV: cerebral ventricle, CC: corpus callosum