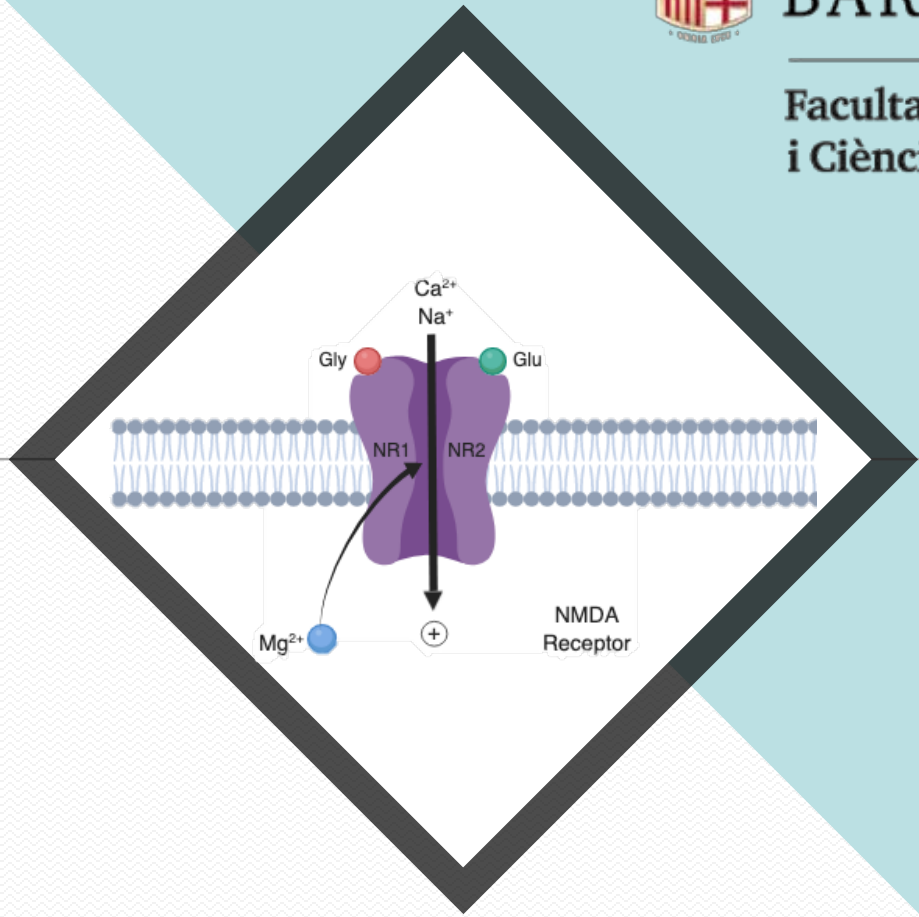
UNIVERSITAT DE BARCELONA

Facultat de Farmàcia i Ciències de l'Alimentació



Novel NMDA receptor antagonist: mechanisms of action in murine models of Alzheimer's disease.

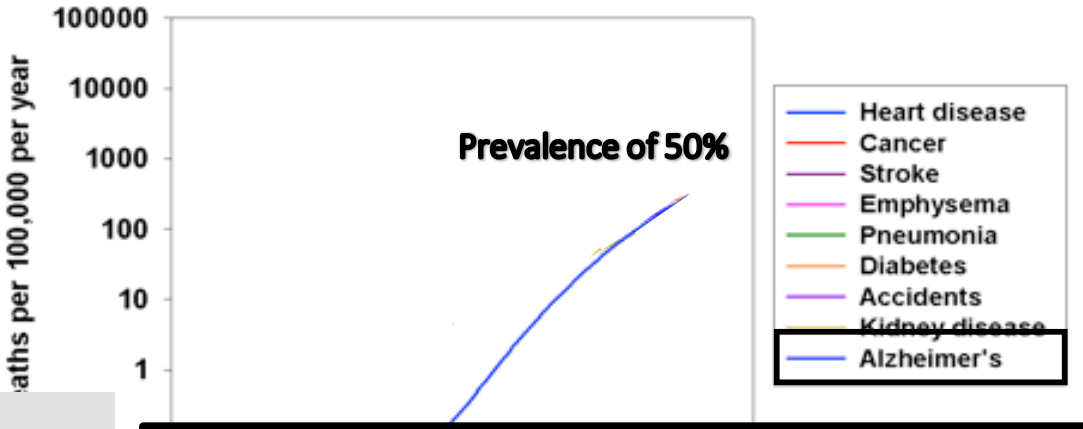
Júlia Companys Alemany

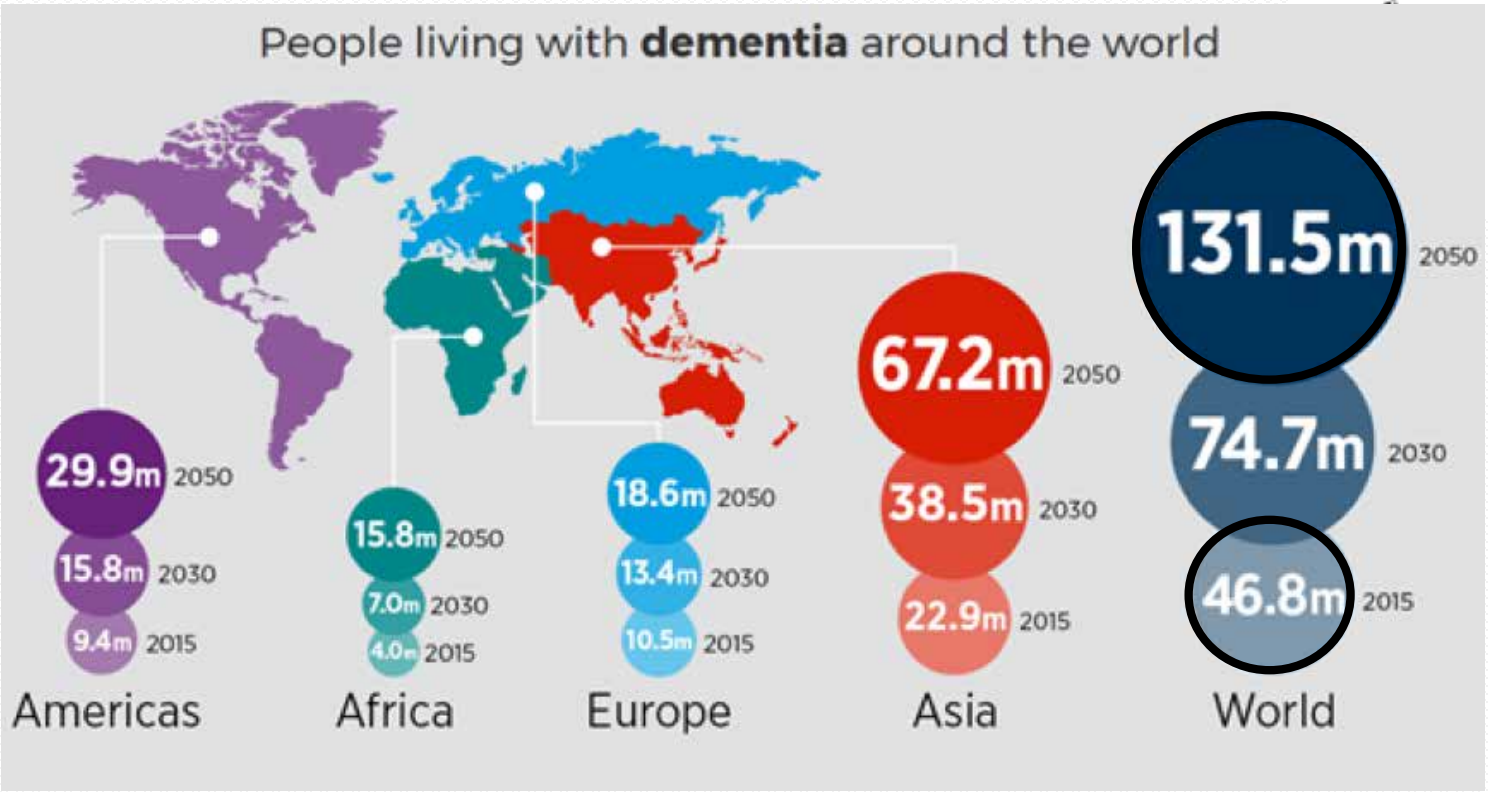
PhD Student

Department of Pharmacology, Toxicology and Medical Chemistry

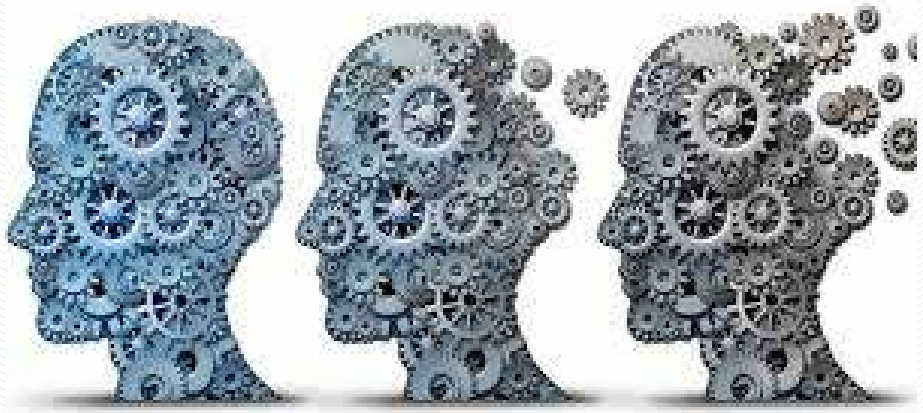
Universitat de Barcelona

Age Related Diseases



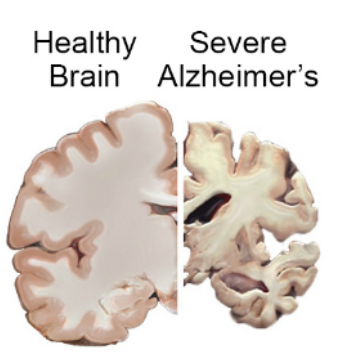


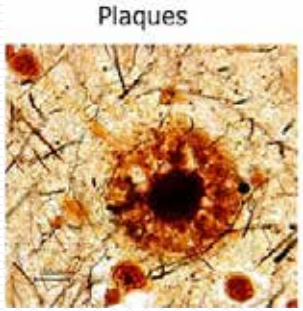
The greatest risk factor for AD is advanced age



Projected growth of Dementia in the world in several areas. (Alzheimer's Disease International, 2015)

Introduction. Alzheimer's Disease





Alzheimer's disease (AD) is a progressive age-dependent **neurodegenerative disease** characterized by cognitive decline and memory loss

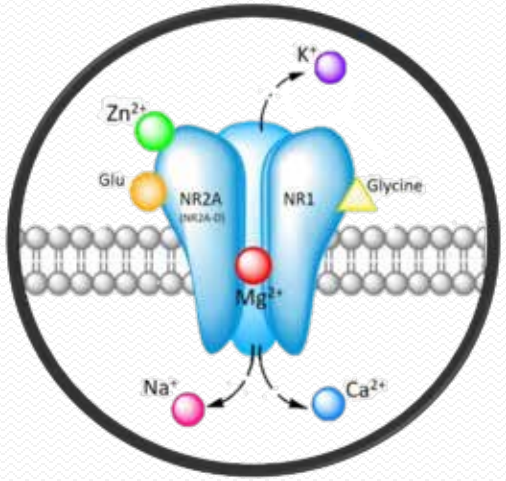
Neuropathological alterations: β-amyloid, Tau hyperphosphoryation, **neurotransmitter deficits** and cell death.

Characteristics	DONEPEZIL	RIVASTIGMINE	GALANTAMINE	MEMANTINE
Chemical class	piperidine	carbamate	phenanthrenea lkaloid	Similar to amantadine
Primary mechanism	AchE inh	AchE inh	AchE inh	NMDA antagonist
Other mechanism	None	None	Nicotine modulator	HT3 receptor antagonist
Half life	70 h	90 min	7 h	70 h

Nowadays the available treatments for AD neither prevent nor reduce the progression of the disease. Therefore, new therapies are urgently needed

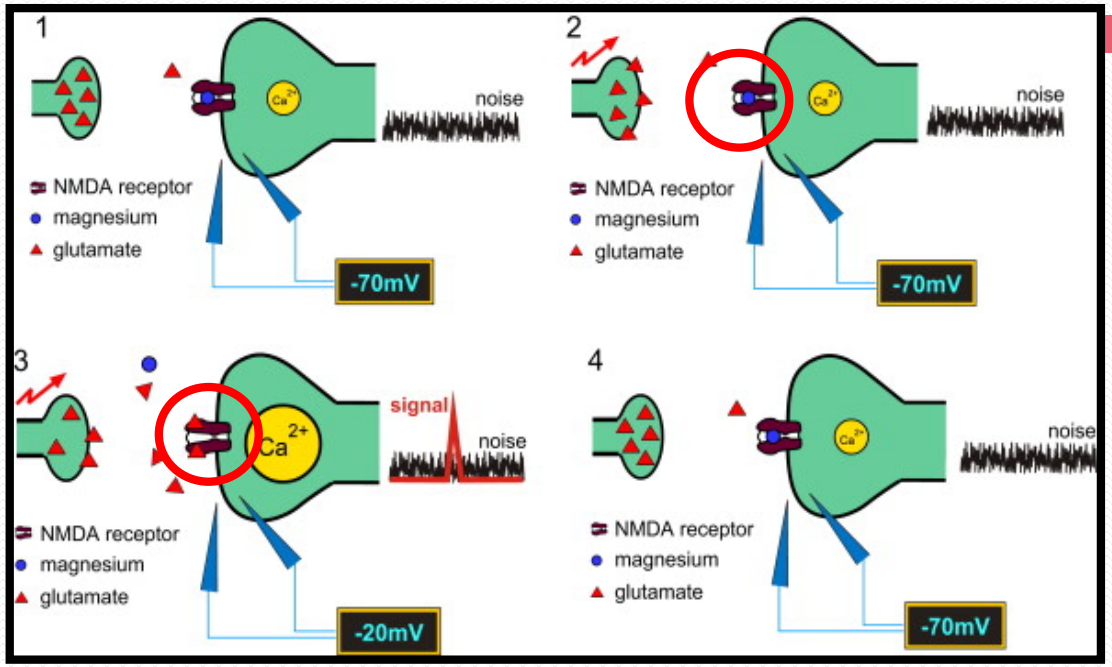
Unmet medical need

Introduction



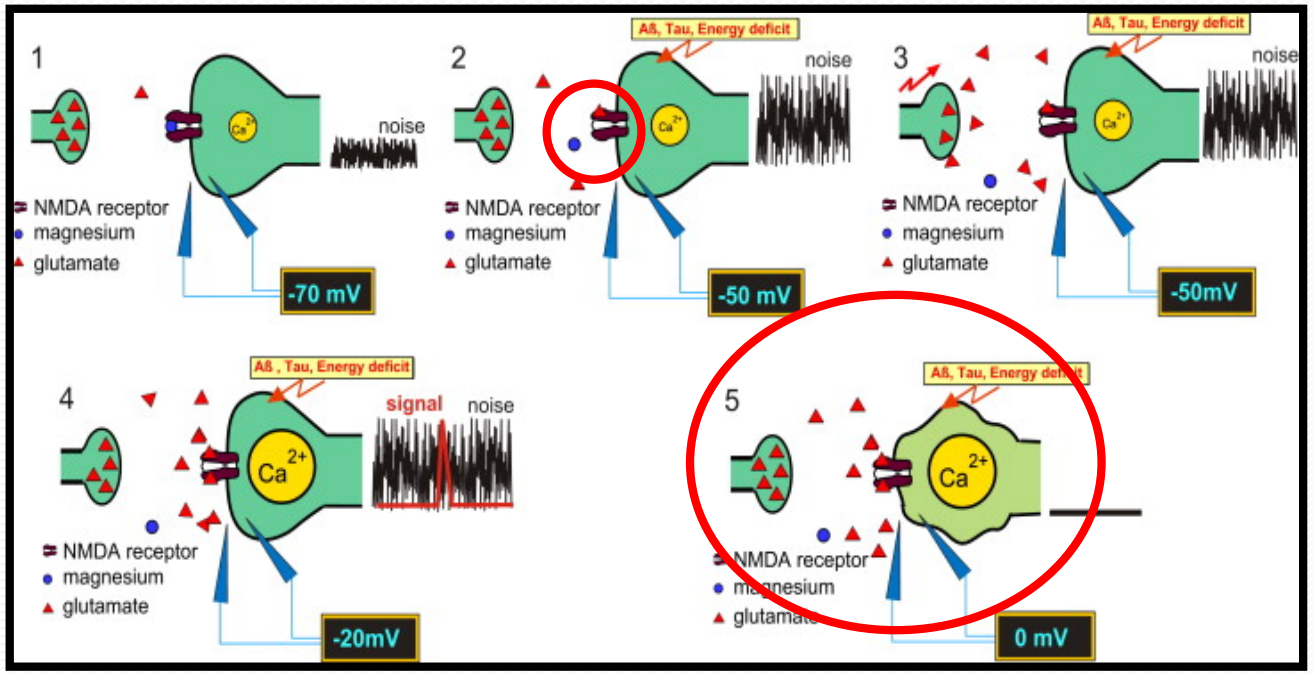
NMDA Receptor

Healthy



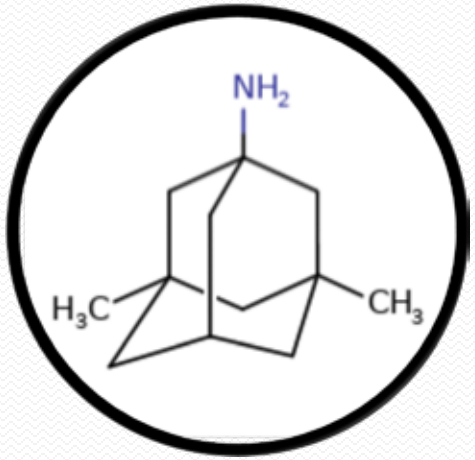
C.G. Parsons et al. / Neuropharmacology 53 (2007) 699-723

Alzheimer's Disease



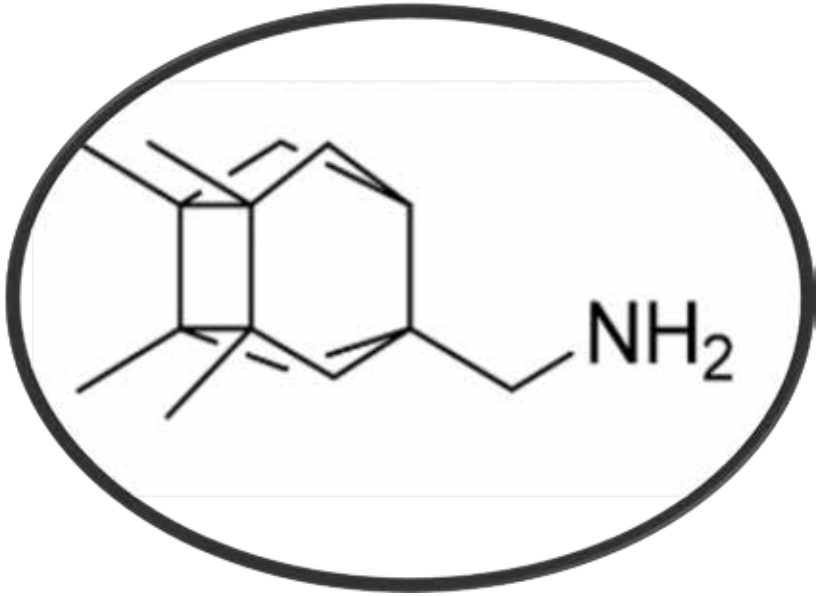
C.G. Parsons et al. / Neuropharmacology 53 (2007) 699-723

Introduction



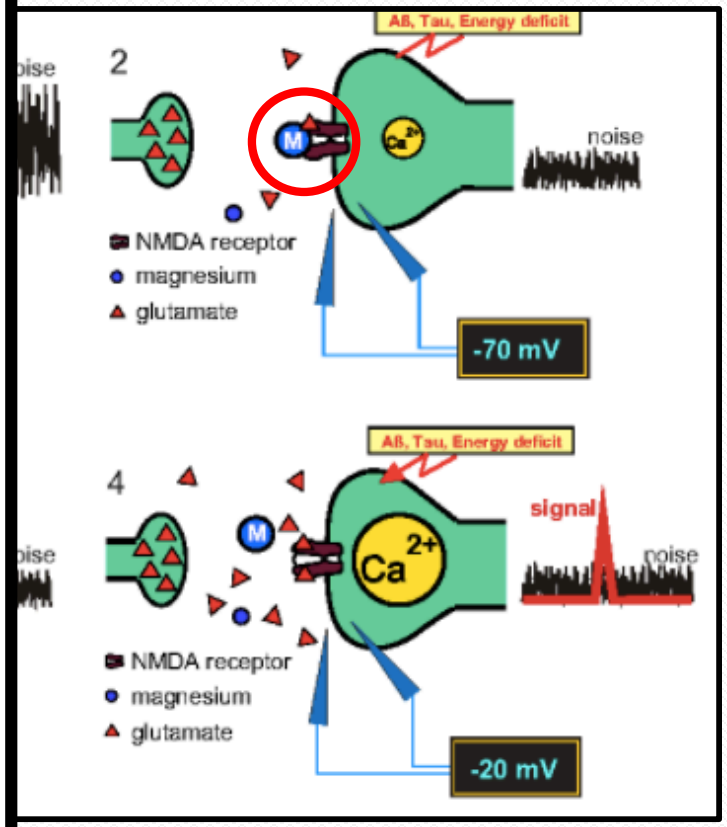
Memantine

Memantine, a NMDAR antag
showed an improvement in cognition and molecular alterations.



RL-208

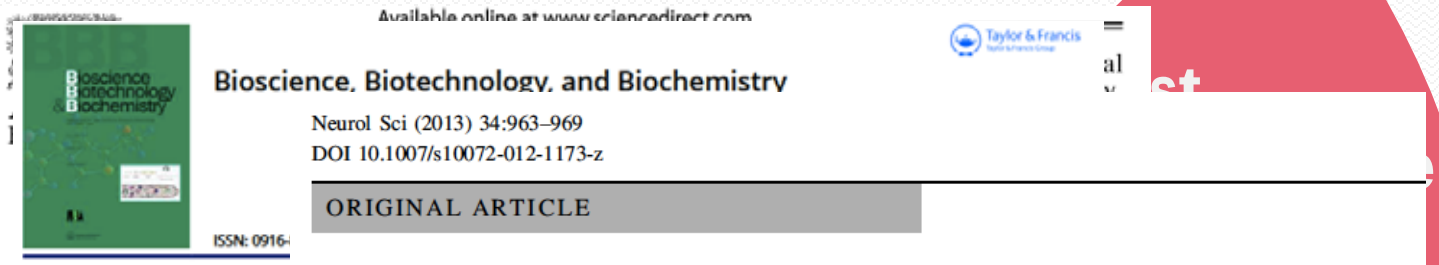
Pharmacological evaluation of a new NMDAR antagonist, RL-208.



3 (2007) 699-723

R. Leiva et al. / ACS Chem. Neurosci. 9, 11 (2018) 2722-2730

Senescence Accelerated Mouse Prone 8 (SAMP8)



Available online at www.sciencedirect.com

Taylor & Francis

Bioscience, Biotechnology, and Biochemistry

Neurol Sci (2013) 34:963–969
DOI 10.1007/s10072-012-1173-z

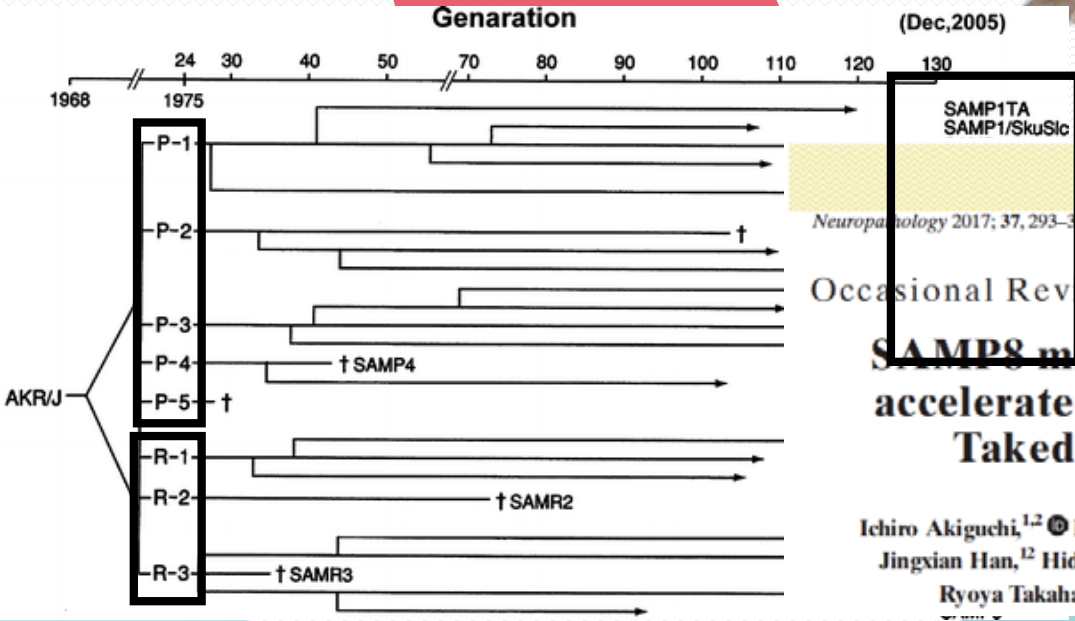
ORIGINAL ARTICLE

Aβ induc
accelerat

Hippocampal neuron loss is correlated with cognitive deficits in SAMP8 mice

Kurara Takag
Yanagihara, I
Ishiura

Guomin Li · Haiyan Cheng · Xuezhu Zhang · Xuemei Shang · Hui Xie · Xin Zhang · Jianchun Yu · Jingxian Han



Dr. Takeda 1968

NEUROPATHOLOGY

Neuropathology 2017; 37, 293–305 doi:10.1111/neup.12373

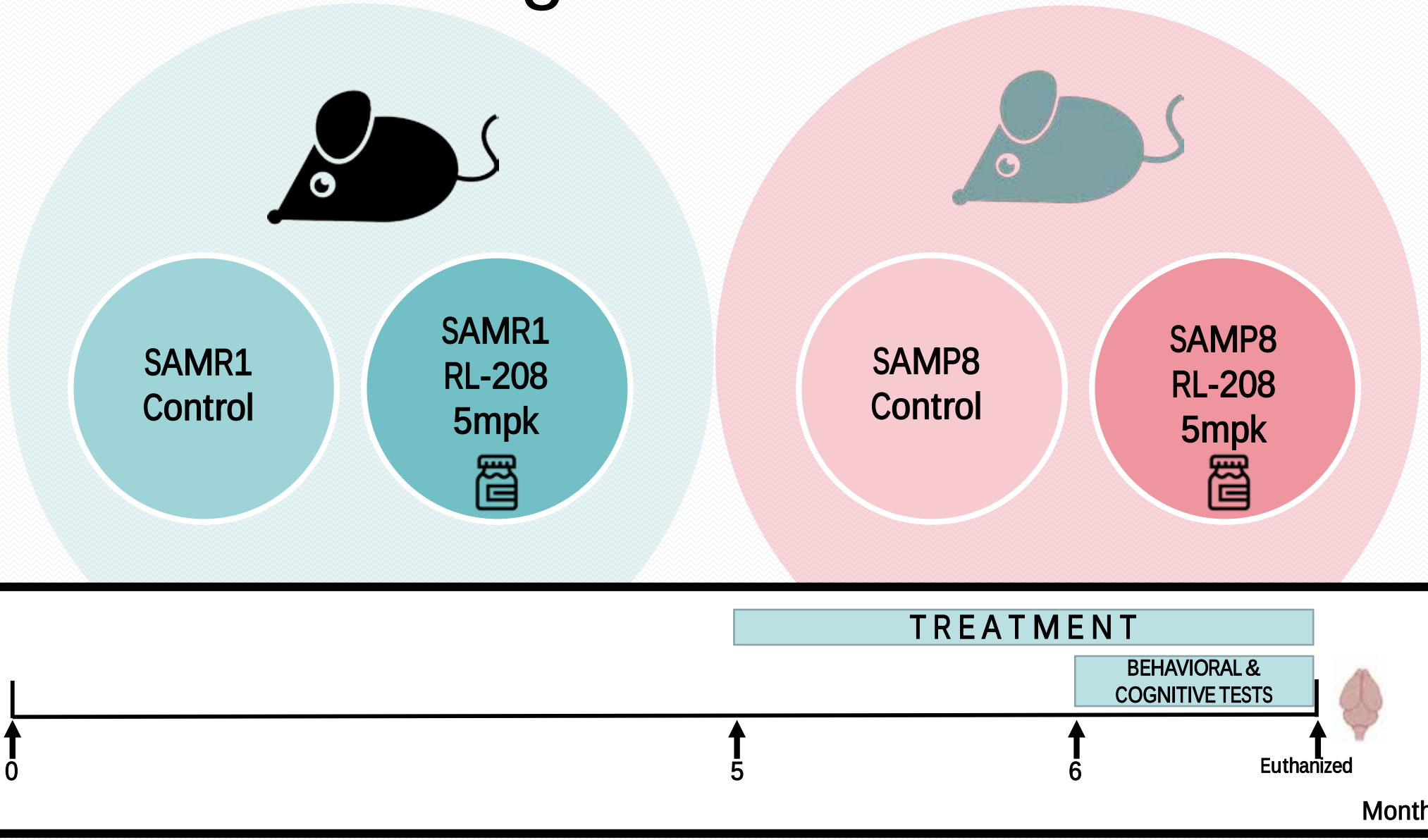
Occasional Review

SAMP8 mice as a neuropathological model of accelerated brain aging and dementia: Toshio Takeda's legacy and future directions

Ichiro Akiguchi,[1,2] Mercè Pallàs,[10] Herbert Budka,[11] Haruhiko Akiyama,[4] Masaki Ueno,[5] Jingxian Han,[12] Hideo Yagi,[1] Tomohumi Nishikawa,[2] Yoichi Chiba,[5] Hiroshi Sugiyama,[3] Ryoya Takahashi,[6] Keiko Unno,[7] Keiichi Higuchi[8] and Masanori Hosokawa[9]

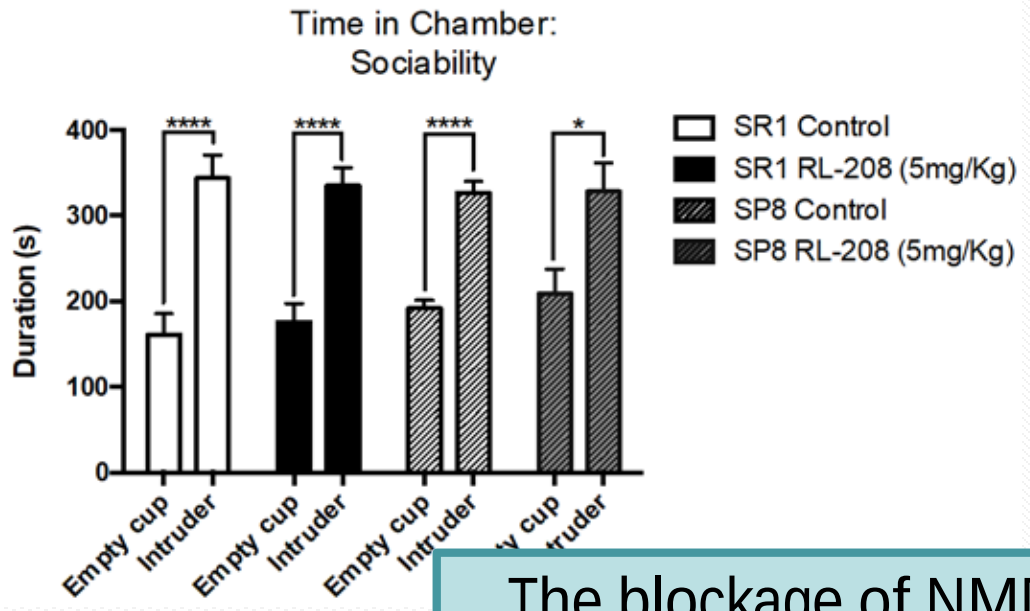
T. Takeda / Neurochem Res 34 (2009) 639–659

Experimental Design



Behavioral Results

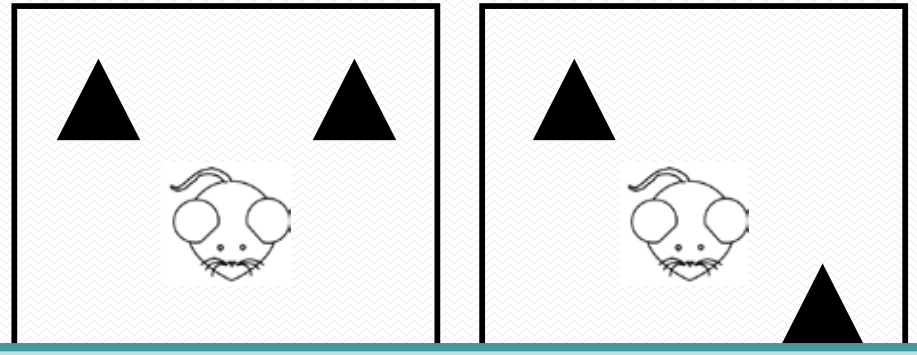
Three Chamber Test

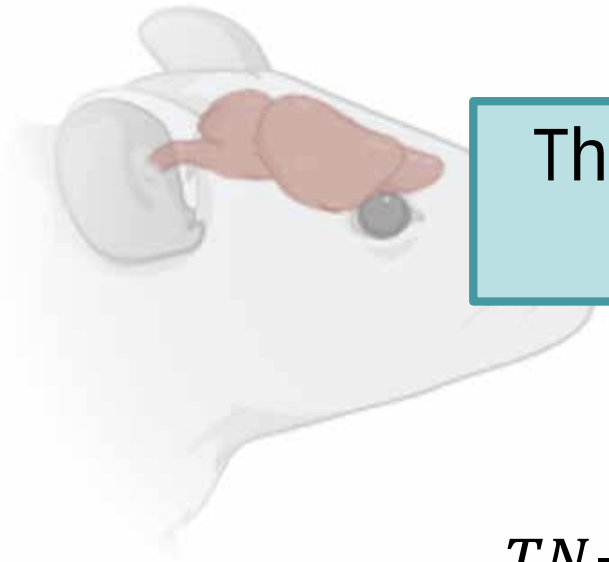


The blockage of NMDAR by RL-208 **increased motivation for social behaviour** in SAMP8

Cognitive Results

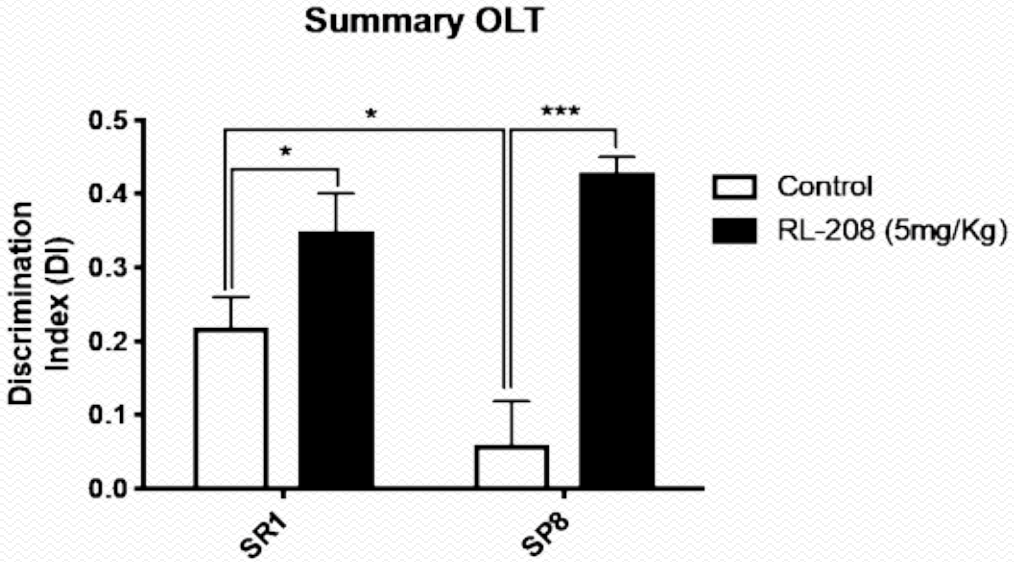
Object Location Test





The blockage of NMDAR **improved spatial memory** in SAMR1 and SAMP8 mice

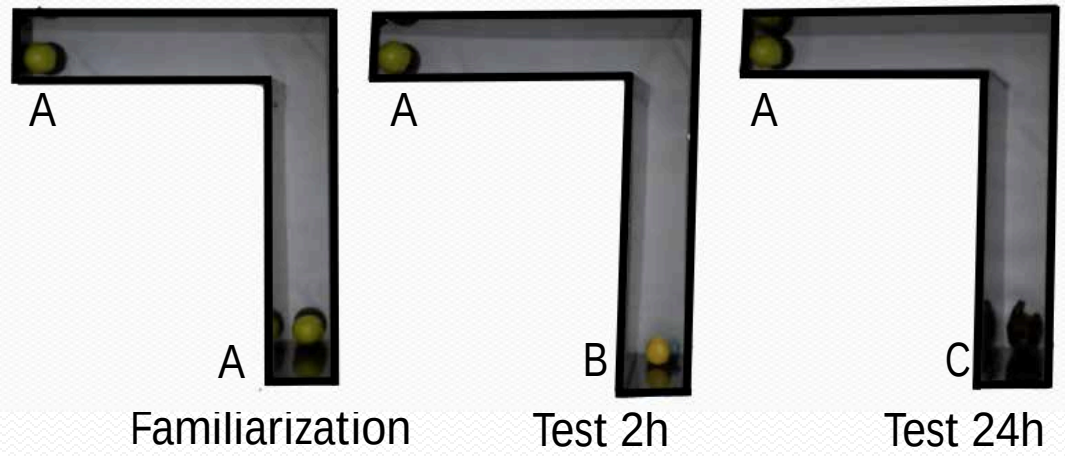
$$DI = \frac{TN - TO}{TN + TO}$$



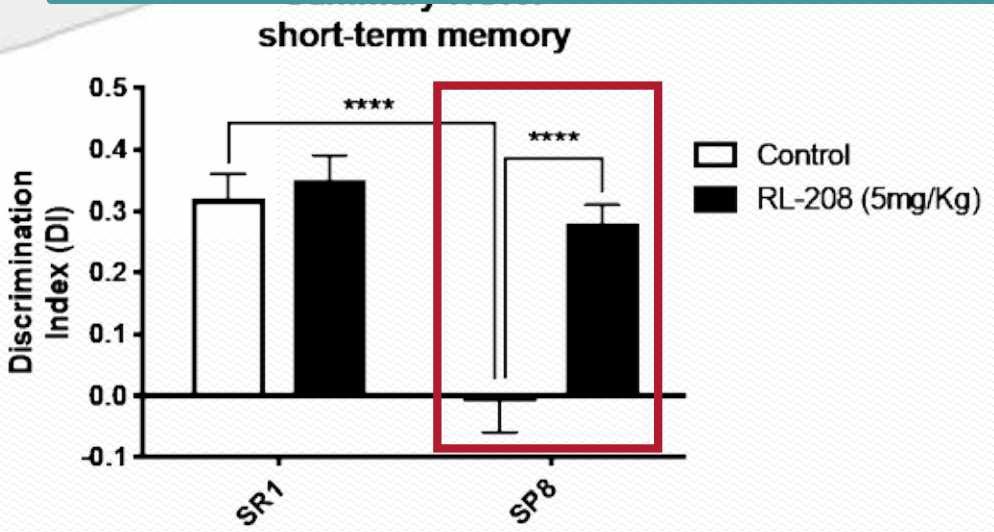
Cognitive Results

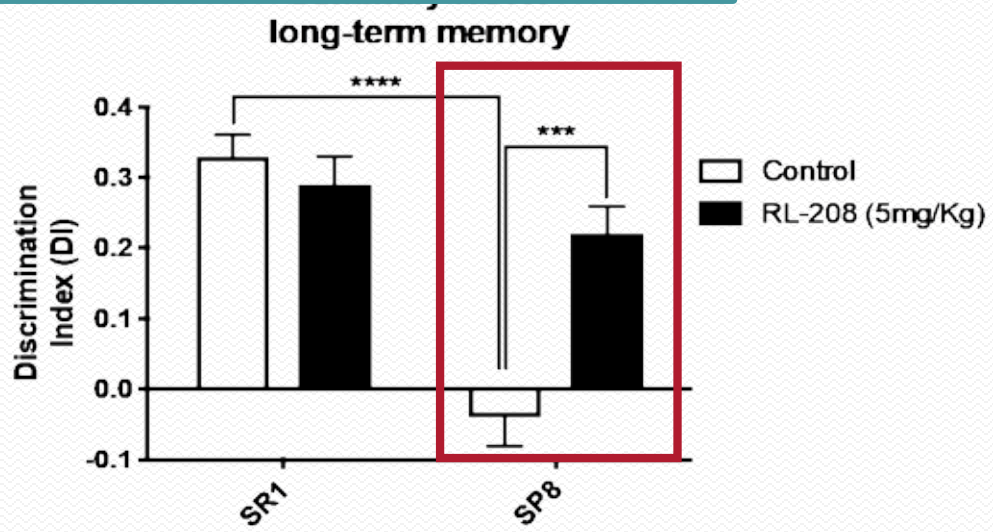
Novel Object Recognition Test

$$DI = \frac{TN - TO}{TN + TO}$$



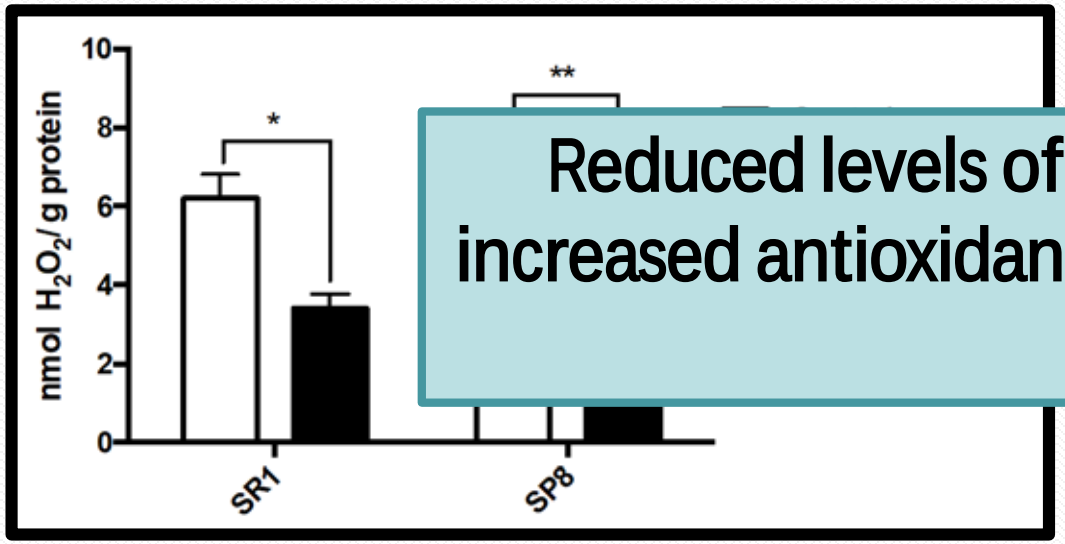
The blockage of NMDAR **improved working memory** in SAMP8

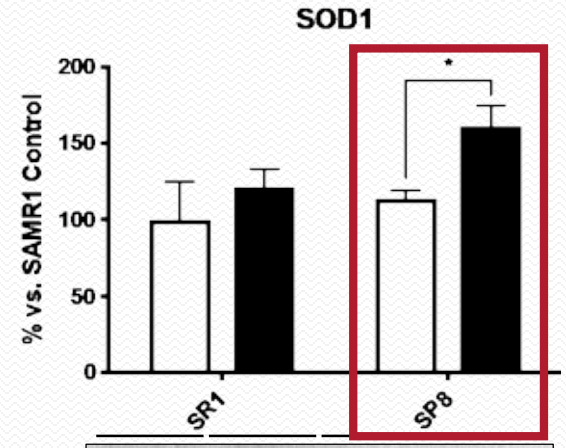


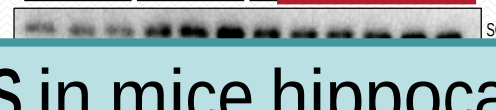


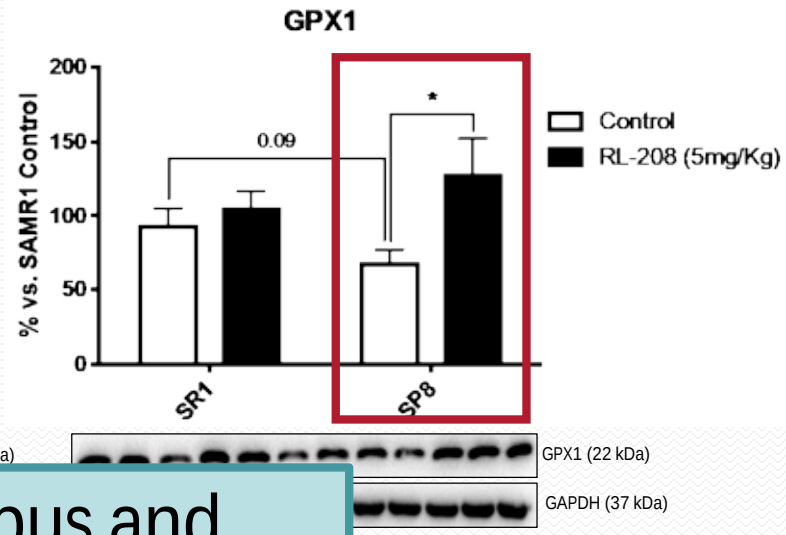
Molecular Results

Oxidative Stress

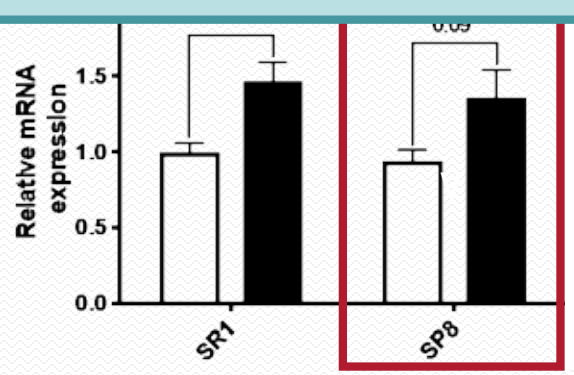


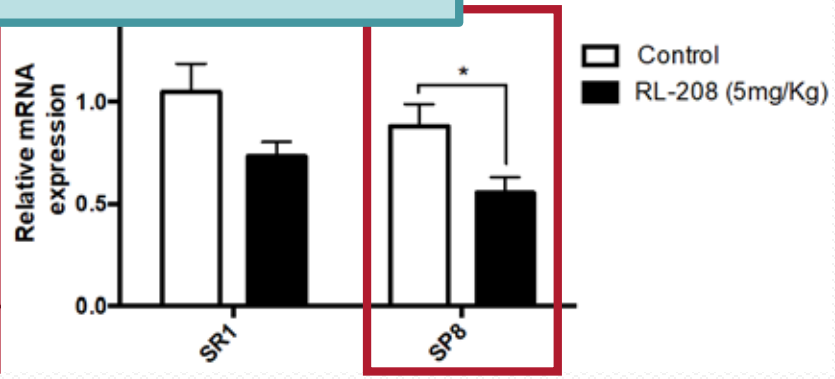






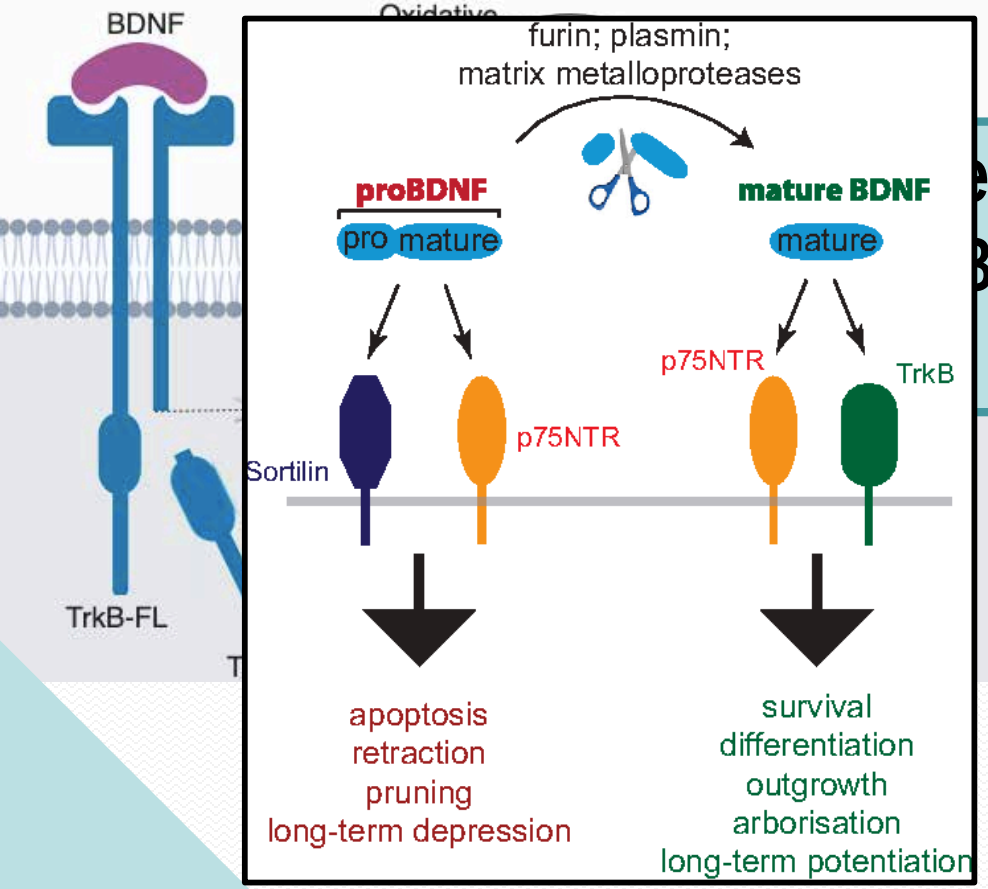
Reduced levels of ROS in mice hippocampus and **increased antioxidant markers** were induced by RL-208 treatment

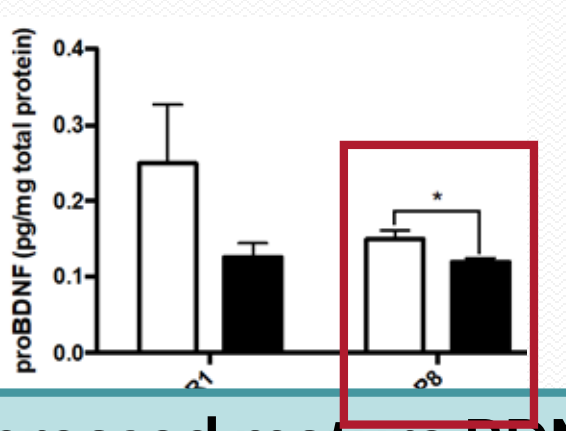


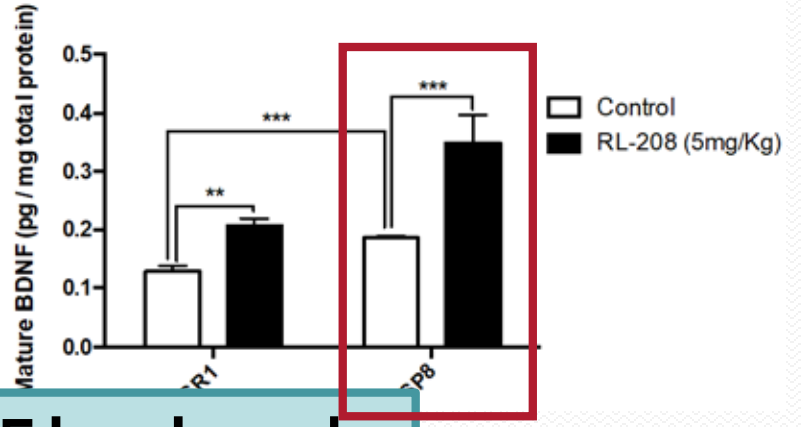


Molecular Results

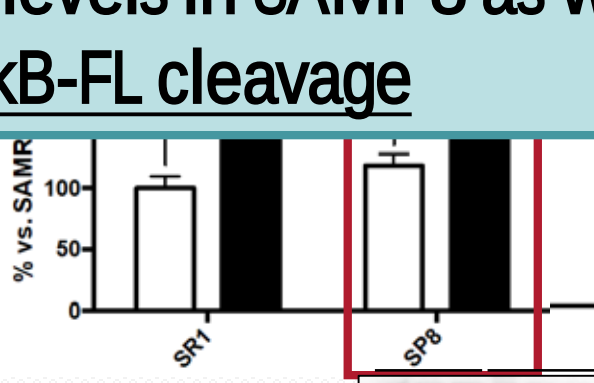
BDNF/TrkB Signaling pathway

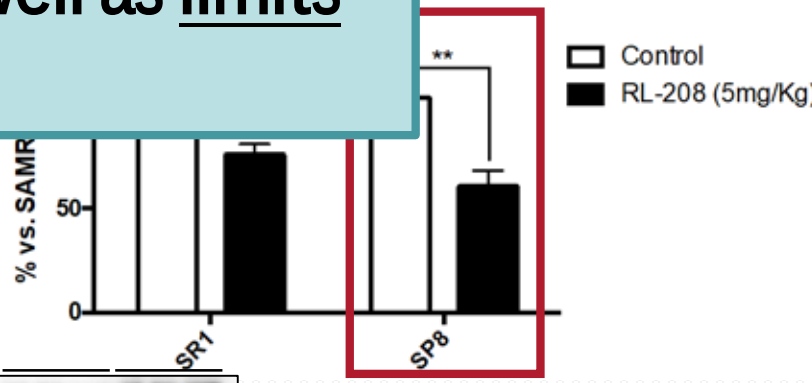


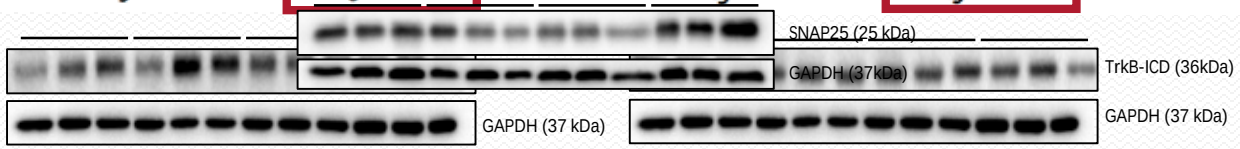




ent increased mature BDNF levels and
BDNF levels in SAMP8 as well as limits
TrkB-FL cleavage





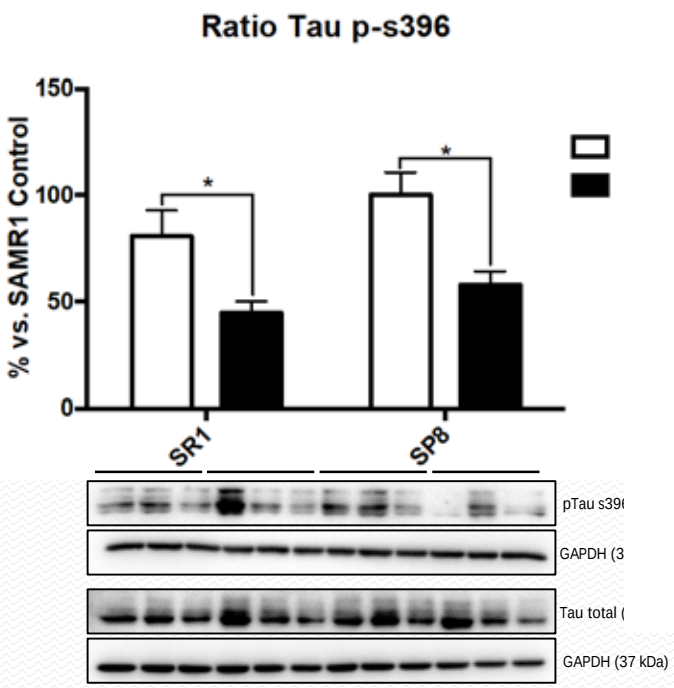


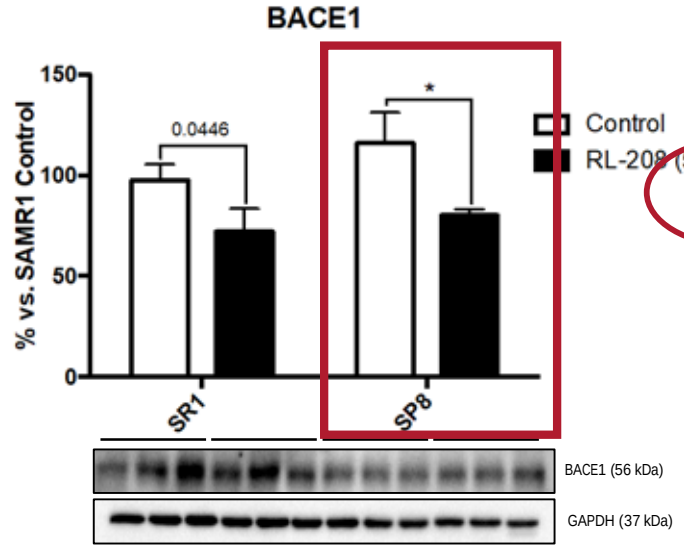
Deinhardt, K., & Chao, M.V. (2014). *Neuropharmacology, 76*, 603-609.

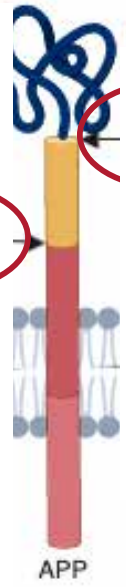
Molecular Results

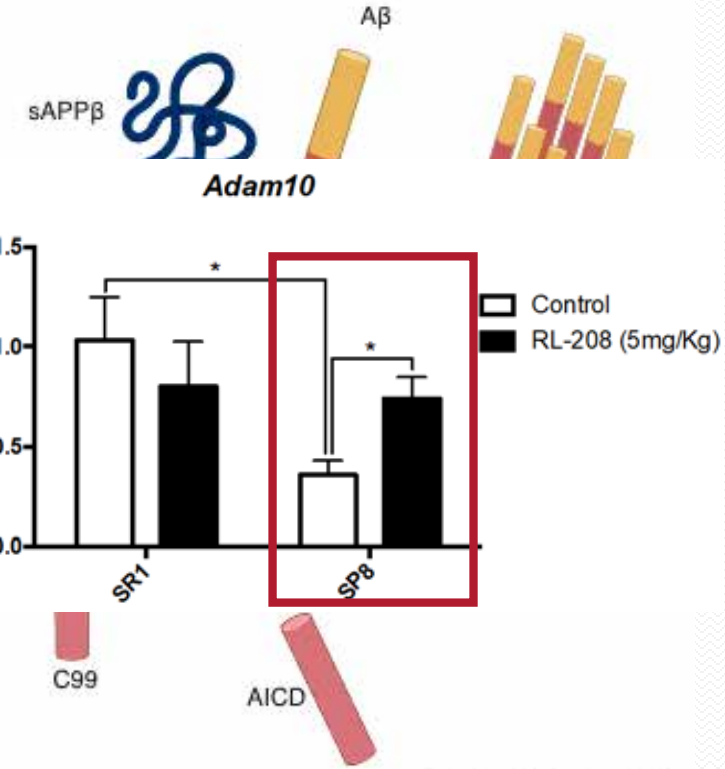
Alzheimer Disease Hallmarks

Proteolytic processing of the **Amyloid Precursor Protein APP**









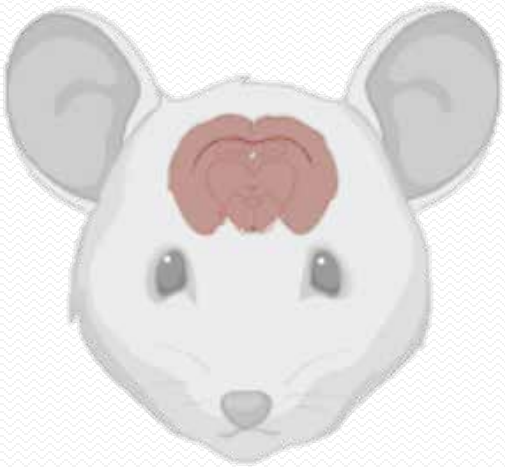
Non- Amyloidogenic pathway

Amyloidogenic pathway

Conclusions

- SAMP8 mice treated with RL-208 **improved the sociability, spatial and working memory.**
- RL-208 treatment decreased ROS levels and showed increased protein levels and mRNA expression of antioxidant enzymes.
- RL-208 treatment induced synaptic plasticity by the increase of mBDNF levels and the inhibition of BDNF Receptor (TrkB) truncation. Furthermore, increased SNAP25 protein levels were demonstrated
- The blockage of NMDA receptor induced a **decrease in Tau hyperphosphorylation** and **decreased β-secretase** protein levels

These results demonstrate the neuroprotectant role of RL-208 treatment in SAMP8 mice, improving their behaviour and cognitive performance as well as molecular pathways involved in the neurodegeneration.



Acknowledgments

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