グリア細胞から見た神経免疫学

名古屋大学環境医学研究所　神経免疫
錫村　明生

最終講義　3月13日, 2015

グリア細胞

神経膠細胞　　vs　　神経細胞

Glue(膠) → glia

macroglia　　oligodendroglia, astroglia

oligodendrocyte, astrocyte

microglia

免疫学的特権部位としての脳

- 主要組織適合性抗原の欠如
  すべての神経系細胞にClass Ⅰ
  ミクログリアにClass Ⅱ が誘導可
- 血液脳関門の存在
- リンパ組織の欠如
  活性化T細胞はBBBを潜り抜ける
- グリア細胞による免疫性サイトカインの産生

神経系は免疫学的にActiveな部位になり得る

グリア細胞の研究の歴史

- 病理組織学的研究　　1960年以前
- ミエリンの分離、抽出　1960－70年代
- 軸索の分離

DeVries GH, Norton WT, Raine CS. **Axons: isolation from mammalian central nervous system.** Science. 1972.

- グリア細胞の分離、培養　1970－80年代

Poduslo SE, Norton WT. **Isolation and some chemical properties of oligodendroglia from calf brain.** J Neurochem. 1972.

Lisak RP, Pleasure DE, Silberberg DH, Manning MC, Saida T. **Long term culture of bovine oligodendroglia isolated with a Percoll gradient.** Brain Res. 1981

McCarthy KD, de Vellis J . **Preparation of separate astroglial and oligodendroglial cell cultures from rat cerebral tissue.** J Cell Biol. 1980 Jun;85(3):890-902.

グリア細胞の研究の歴史②

- グリア細胞のマーカーの発見　1970－80年

Astrocyte : GFAP

Determination of glial fibrillary acidic protein (GFAP) in human brain tumors. Jacque CM, Vinner C, Kujas M, Raoul M, Racadot J, Baumann NA J Neurol Sci. 1978;35(1):147-55.

Cell-type-specific markers for distinguishing and studying neurons and the major classes of glial cells in culture. Raff MC, Fields KL, Hakomori SI, Mirsky R, Pruss RM, Winter J. Brain Res. 1979;174(2):283-308.

Oligodendrocyte : GalC O1-4

Galactocerebroside is a specific cell-surface antigenic marker for oligodendrocytes in culture. Raff MC, Mirsky R, Fields KL, Lisak RP, Dorfman SH, Silberberg DH, Gregson NA, Leibowitz S, Kennedy MC. Nature. 1978;274(5673):813-6.

Monoclonal antibodies (O1 to O4) to oligodendrocyte cell surfaces: an immunocytological study in the central nervous system. Sommer I, Schachner M. Dev Biol. 1981 Apr 30;83(2):311-27.

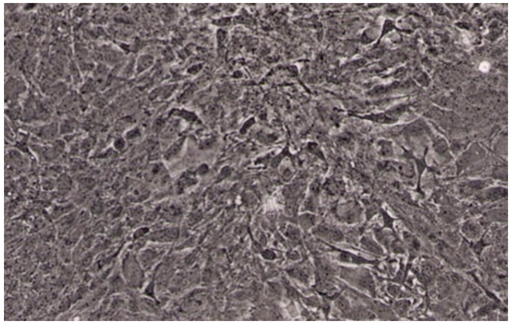
Microglia :lectin-binding, C3R =Mac1,CD11b

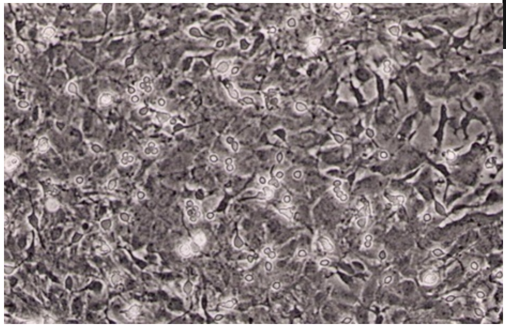
Lectin binding by resting and reactive microglia. Streit WJ, Kreutzberg GW. J Neurocytol. 1987;16(2):249-60.

Axotomy of the rat facial nerve leads to increased CR3 complement receptor expression by activated microglial cells. Graeber MB[1], Streit WJ, Kreutzberg GW. J Neurosci Res. 1988 Sep;21(1):18-24.

グリア細胞とのかかわり

- Suzumura A, Bhat S, Eccleston PA, Lisak RP, Silberberg DH. **The isolation and long-term Culture of oligodendrocytes from newborn mouse brain.** Brain Res. 1984 ;324(2):379-83.





- Suzumura A, Silberberg DH. **Expression of H-2 antigen on oligodendrocytes is induced by soluble factors from concanavalin A activated T cells.** Brain Res. 1985 ;336(1):171-5

- Wong GH, Bartlett PF, Clark-Lewis I, Battye F, Schrader JW. **Inducible expression of H-2 and Ia antigens on brain cells.** Nature. 1984 Aug 23-29;310(5979):688-91.

Reprint Series
23 May 1986, Volume 232, pp. 991–993

SCIENCE

Coronavirus Infection Induces H-2 Antigen Expression on Oligodendrocytes and Astrocytes

AKIO SUZUMURA, EHUD LAVI, SUSAN R. WEISS, AND DONALD H. SILBERBERG

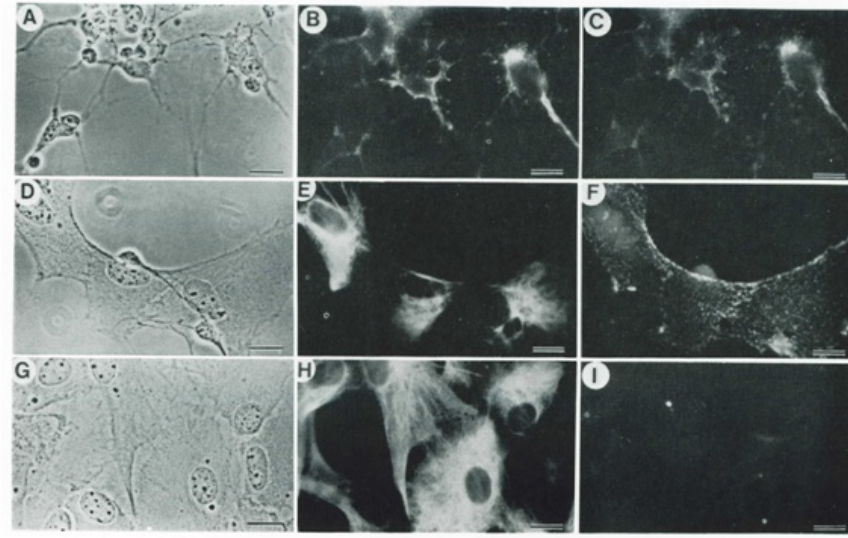


Fig. 1. In vitro induction of H-2 antigen expression on oligodendrocytes and astrocytes by supernatant from mixed brain cell cultures infected with MHV-A59. The expression of MHC antigens was assessed by indirect immunofluorescence of unfixed viable cells. Monoclonal antibodies against mouse H-2 were obtained from Bionetics Laboratory (Charleston, SC) (*3*). Cultures were then double-labeled with antibodies to H-2 and antibodies to GalC or GFAP (*3, 9*). Oligodendrocytes (A–C) and astrocytes (D–F) stimulated with 10% Sup for 2 days. Astrocyte cultures stimulated with supernatant from uninfected mixed brain cell cultures did not express detectable H-2 antigen (G–I). Viewed with phase-contrast (A, D, and G), fluorescein [GalC (B), GFAP (E and H)], and rhodamine [H-$2D^b$ and H-$2K^b$ (C, F, and I)] optics. Bar, 15 μm.

免疫学的特権部位としての脳

- 主要組織適合性抗原の欠如
  すべての神経系細胞にClass Ｉ
  ミクログリアにClass Ⅱ が誘導可
- 血液脳関門の存在
- リンパ組織の欠如
  活性化T細胞はBBBを潜り抜ける
- グリア細胞による免疫性サイトカインの産生

神経系は免疫学的にActiveな部位になり得る

Suzumura A, Mezitis SG, Gonatas NK, Silberberg DH.
MHC antigen expression on bulk isolated macrophage-microglia from newborn mouse brain: induction of Ia antigen expression by gamma-interferon. J Neuroimmunol. 1987;15(3):263-78.

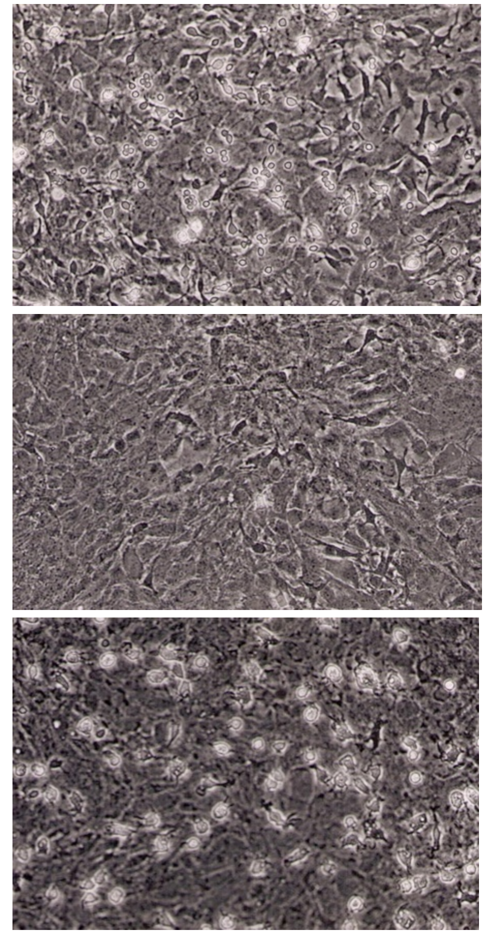


TABLE 2

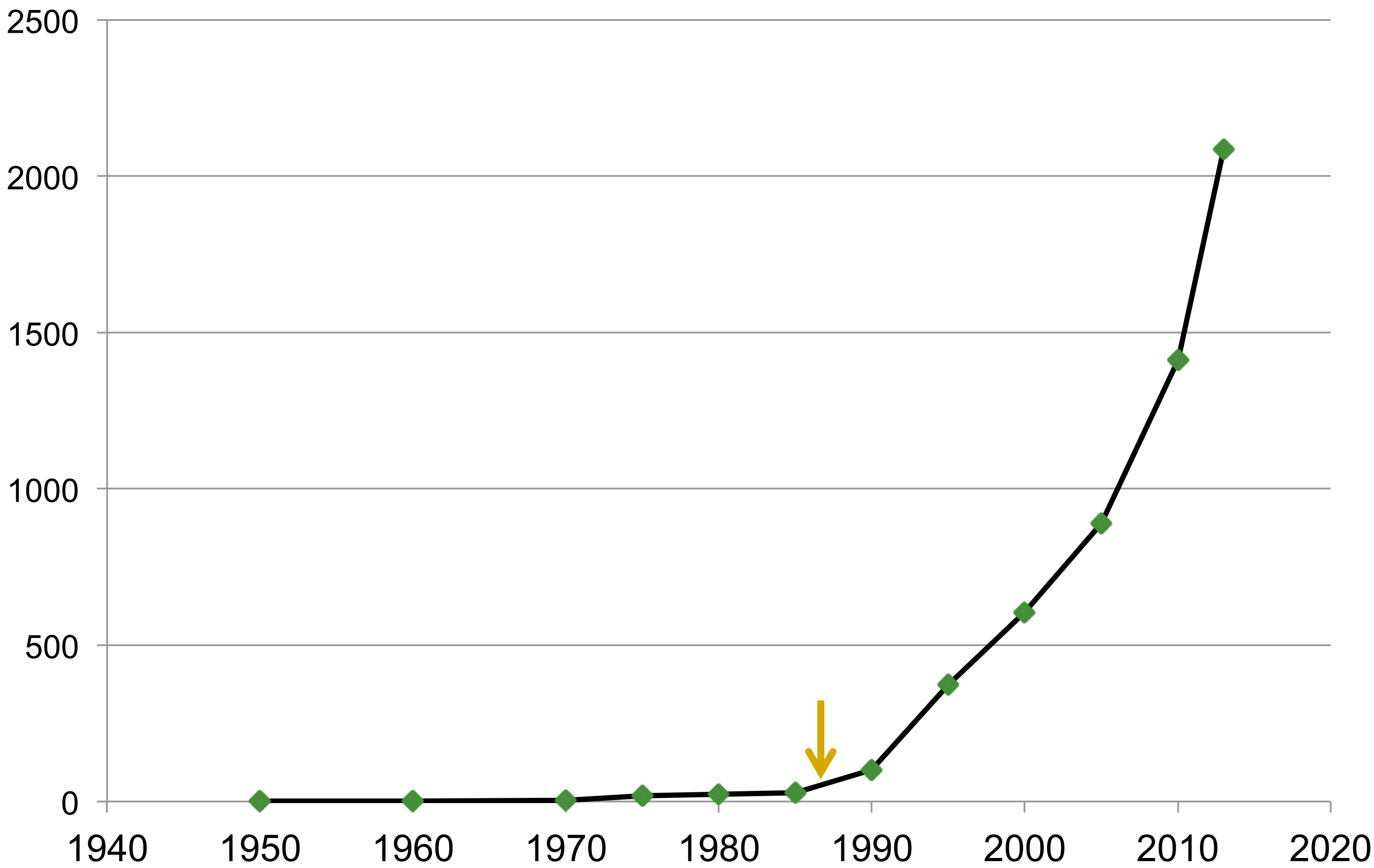
MHC ANTIGEN EXPRESSION ON MACROPHAGE-MICROGLIA: ^{51}Cr RELEASE ASSAY

Each value represent mean ± standard deviation of individual percent ^{51}Cr release ($n = 9$), obtained from three separate experiments using triplicate coverslips.

	H-2D^k,K^k	I-A^k	I-E/C^k	MEM	SP2/0	H-2D^d,K^d	I-A^d
AKR							
γ-IFN	47.3 ± 5.0 *	39.5 ± 6.7 *	28.7 ± 9.0 *	15.5 ± 4.2	17.8 ± 3.3	14.5 ± 6.2	16.4 ± 4.2
(−)	31.2 ± 10.9 *	14.9 ± 1.0	15.5 ± 6.1	13.7 ± 2.6	17.3 ± 3.2	14.8 ± 2.2	16.8 ± 4.2
BALB/c							
γ-IFN	14.8 ± 6.8	18.5 ± 4.7	16.9 ± 3.5	13.9 ± 6.1	14.7 ± 2.7	39.4 ± 11.3 *	13.8 ± 7.7
(−)	15.5 ± 3.3	14.2 ± 3.1	13.7 ± 1.7	16.7 ± 1.9	17.9 ± 1.8	35.6 ± 5.4 *	12.9 ± 2.1

* $P < 0.001$ when compared to spontaneous release with MEM.

ミクログリア論文数の推移



（PubMed　n/year)

1. Suzumura A, Bhat S, Eccleston PA, Lisak RP, **Silberberg** DH.
The isolation and long-term culture of oligodendrocytes from newborn mouse brain. Brain Res. 1984 ;324(2):379-83.

2. Suzumura A, **Silberberg** DH.
Expression of H-2 antigen on oligodendrocytes is induced by soluble factors from concanavalin A activated T cells. Brain Res. 1985 ;336(1):171-5

3. Suzumura A, Lisak RP, **Silberberg** DH.
Serum cytotoxicity to oligodendrocytes in multiple sclerosis and controls: assessment by 51Cr release assay. J Neuroimmunol. 1986 ;11(2):137-47.

4. Suzumura A, **Silberberg** DH, Lisak RP.
The expression of MHC antigens on oligodendrocytes: induction of polymorphic H-2 expression by lymphokines. J Neuroimmunol. 1986 ;11(3):179-90

5. Suzumura A, Lavi E, Weiss SR, **Silberberg** DH.
Coronavirus infection induces H-2 antigen expression on oligodendrocytes and astrocytes. Science. 1986 ;232(4753):991-3

6. Lavi E, **Suzumura** A, Lampson LA, Siegel RM, Murasko DM, **Silberberg** DH, Weiss SR.
Expression of MHC class I genes in mouse hepatitis virus (MHV-A59) infection and in multiple sclerosis. Adv Exp Med Biol. 1987;218:219-22.

7. Suzumura A, Mezitis SG, Gonatas NK, **Silberberg** DH.
MHC antigen expression on bulk isolated macrophage-microglia from newborn mouse brain: induction of Ia antigen expression by gamma-interferon. J Neuroimmunol. 1987;15(3):263-78.

8. Lavi E, **Suzumura** A, Hirayama M, Highkin MK, Dambach DM, **Silberberg** DH, Weiss SR.
Coronavirus mouse hepatitis virus (MHV)-A59 causes a persistent, productive infection in primary glial cell cultures. Microb Pathog. 1987 ;3(2):79-86

9. Lavi E, **Suzumura** A, Murasko DM, Murray EM, **Silberberg** DH, Weiss SR.
Tumor necrosis factor induces expression of MHC class I antigens on mouse astrocytes. Ann N Y Acad Sci. 1988;540:488-90

10. Suzumura A, **Silberberg** DH. MHC antigen expression on glial cells. Ann N Y Acad Sci. 1988;540:495-7.

11. Suzumura A, Lavi E, Bhat S, Murasko D, Weiss SR, **Silberberg** DH.
Induction of glial cell MHC antigen expression in neurotropic coronavirus infections. Characterization of the H-2-inducing soluble factor elaborated by infected brain cells.
J Immunol. 1988 ;140(6):2068-72

12. Lavi E, **Suzumura** A, Murasko DM, Murray EM, **Silberberg** DH, Weiss SR.
Tumor necrosis factor induces expression of MHC class I antigens on mouse astrocytes. J Neuroimmunol. 1988 Jun;18(3): 245-53.

グリア細胞とのかかわり ②

- Sawada M, Kondo N, Suzumura A, Marunouchi T.
  Production of tumor necrosis factor-alpha by microglia and astrocytes in culture. Brain Res. 1989 ;491(2):394-7.
- Sawada M, Suzumura A, Yamamoto H, Marunouchi T.
  Activation and proliferation of the isolated microglia by colony stimulating factor-1 and possible involvement of protein kinase C. Brain Res. 1990 ;509(1):119-24.
- Ohno K, Suzumura A, Sawada M, Marunouchi T.
  Production of granulocyte/macrophage colony-stimulating factor by cultured astrocytes. Biochem Biophys Res Commun. 1990 ;169(2):719-24.
- Sawada M, Suzumura A, Itoh Y, Marunouchi T.
  Production of interleukin-5 by mouse astrocytes and microglia in culture. Neurosci Lett. 1993 ;155(2):175-8.
- Suzumura A, Sawada M, Yamamoto H, Marunouchi T.
  Transforming growth factor-beta suppresses activation and proliferation of microglia in vitro. J Immunol. 1993 ;151(4):2150-8.
- Suzumura A, Sawada M, Itoh Y, Marunouchi T.
  Interleukin-4 induces proliferation and activation of microglia but suppresses their induction of class II major histocompatibility complex antigen expression. J Neuroimmunol. 1994 ;53(2):209-18.

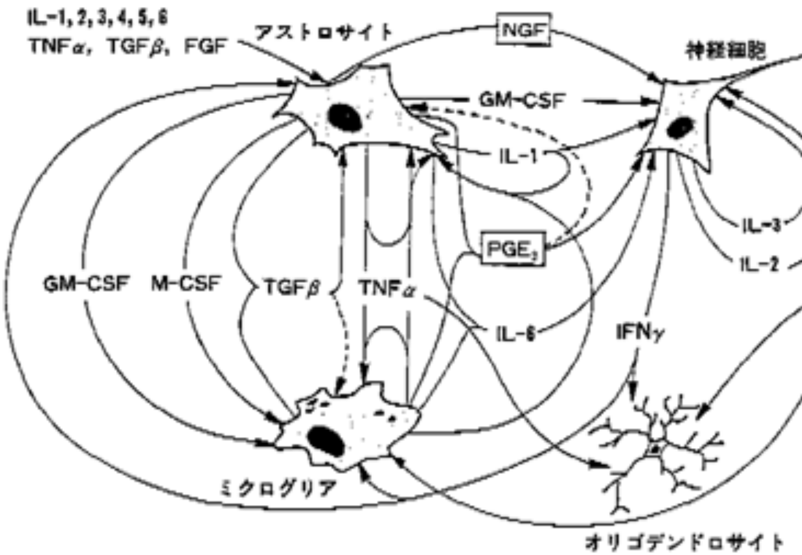


図１　**中枢神経系のサイトカインネットワーク**
実線は陽性の刺激，点線は抑制性の刺激を示す．説明は本文参照

免疫学的特権部位としての脳

- 主要組織適合性抗原の欠如
  すべての神経系細胞にClass Ⅰ
  ミクログリアにClass Ⅱ が誘導可
- 血液脳関門の存在
- リンパ組織の欠如
  活性化T細胞はBBBを潜り抜ける
- グリア細胞による免疫性サイトカインの産生

神経系は免疫学的にActiveな部位になり得る

グリア細胞とのかかわり③

- Suzumura A, Sawada M, Makino M, Takayanagi T.
  Propentofylline inhibits production of TNFalpha and infection of LP-BM5 murine leukemia virus in glial cells. J Neurovirol. 1998 Oct;4(5):553-9.
- Yoshikawa M, Suzumura A, Tamaru T, Takayanagi T, Sawada M.
  Effects of phosphodiesterase inhibitors on cytokine production by microglia. Mult Scler. 1999 ;5(2):126-33.
- Suzumura A, Nakamuro T, Tamaru T, Takayanagi T.
  Drop in relapse rate of MS by combination therapy of three different phosphodiesterase inhibitors. Mult Scler. 2000 ;6(1):56-8.
- Mizuno T, Kurotani T, Komatsu Y, Kawanokuchi J, Kato H, Mitsuma N, Suzumura A.
  Neuroprotective role of phosphodiesterase inhibitor ibudilast on neuronal cell death induced by activated microglia. Neuropharmacology. 2004 ;46(3):404-11.
- Feng J, Misu T, Fujihara K, Sakoda S, Nakatsuji Y, Fukaura H, Kikuchi S, Tashiro K, Suzumura A, Ishii N, Sugamura K, Nakashima I, Itoyama Y.
  Ibudilast, a nonselective phosphodiesterase inhibitor, regulates Th1/Th2 balance and NKT cell subset in multiple sclerosis. Mult Scler. 2004;10(5):494-8.
- Suzumura A, Ito A, Mizuno T.
  Phosphodiesterase inhibitors suppress IL-12 production with microglia and T helper 1 development. Mult Scler. 2003 ;9(6):574-8.

PDE阻害薬:多発性硬化症、Alzheimer病治療

グリア細胞とのかかわり④

- Mizuno T, Kawanokuchi J, Numata K, Suzumura A.
  Production and neuroprotective functions of fractalkine in the central nervous system.
  Brain Res. 2003 ;979(1-2):65-70.
- Takeuchi H, Mizuno T, Zhang G, Wang J, Kawanokuchi J, Kuno R, Suzumura A
  Neuritic beading induced by activated microglia is an early feature of neuronal dysfunction toward neuronal death by inhibition of mitochondrial respiration and axonal transport.
  J Biol Chem. 2005 ;280(11):10444-54.
- Takeuchi H, Jin S, Wang J, Zhang G, Kawanokuchi J, Kuno R, Sonobe Y, Mizuno T, Suzumura A.
  Tumor necrosis factor-alpha induces neurotoxicity via glutamate release from hemichannels of activated microglia in an autocrine manner. J Biol Chem. 2006 ;281(30):21362-8.
- Mizuno T, Zhang G, Takeuchi H, Kawanokuchi J, Wang J, Sonobe Y, Jin S, Takada N, Komatsu Y, Suzumura A.
  Interferon-gamma directly induces neurotoxicity through a neuron specific, calcium-permeable complex of IFN-gamma receptor and AMPA GluR1 receptor. FASEB J. 2008 ; 22(6):1797-806.

グリア細胞とのかかわり⑤

- 神経—グリア相関からの治療への展望

Granulocyte-Colony Stimulating Factor Attenuates Oligomeric Amyloid β Neurotoxicity by Activation of Neprilysin. Doi Y, Takeuchi H, Mizoguchi H, Fukumoto K, Horiuchi H, Jin S, Kawanokuchi J, Parajuli B, Sonobe Y, Mizuno T, Suzumura A. PLoS One. 2014 ;9(7):e103458.

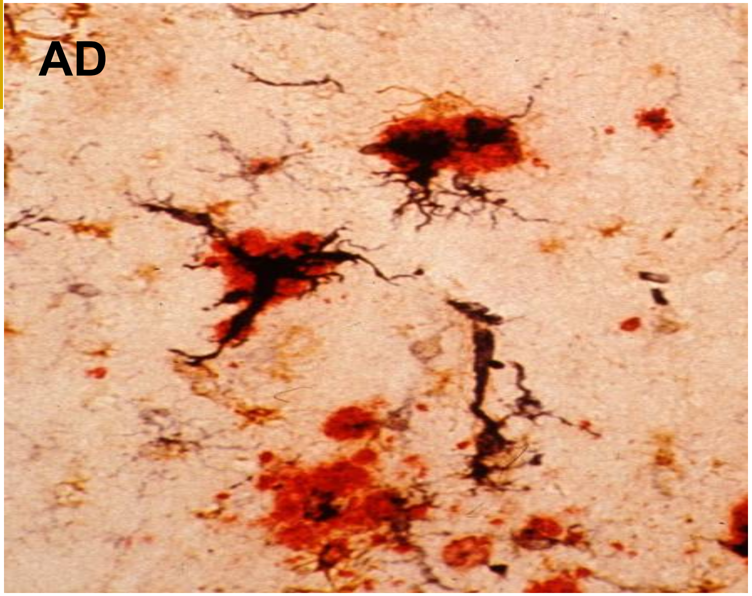
FGF-2 released from degenerating neurons exerts microglial-induced neuroprotection via FGFR3-ERK signaling pathway. Noda M, Takii K, Parajuli B, Kawanokuchi J, Sonobe Y, Takeuchi H, Mizuno T[1], Suzumura A. J Neuroinflammation. 2014;11:76.

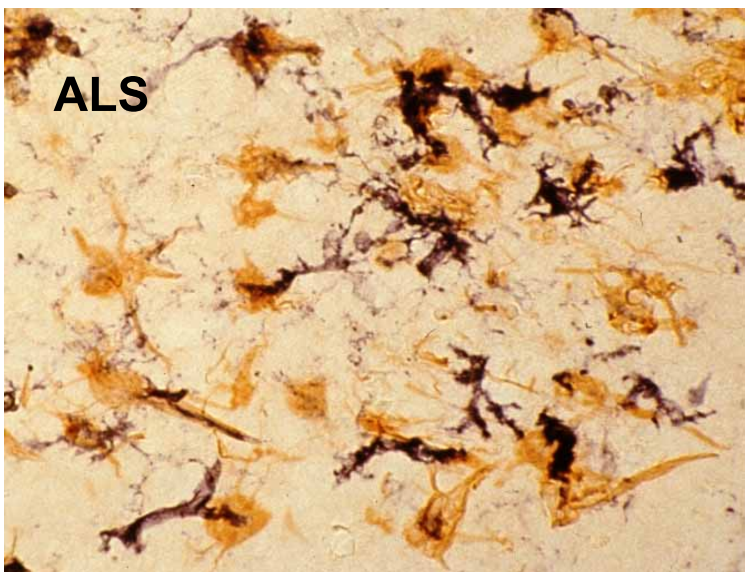
Evidence for aberrant astrocyte hemichannel activity in Juvenile Neuronal Ceroid Lipofuscinosis (JNCL). Burkovetskaya M, Karpuk N, Xiong J, Bosch M, Boska MD, Takeuchi H, Suzumura A, Kielian T. PLoS One. 2014;9(4):e95023.

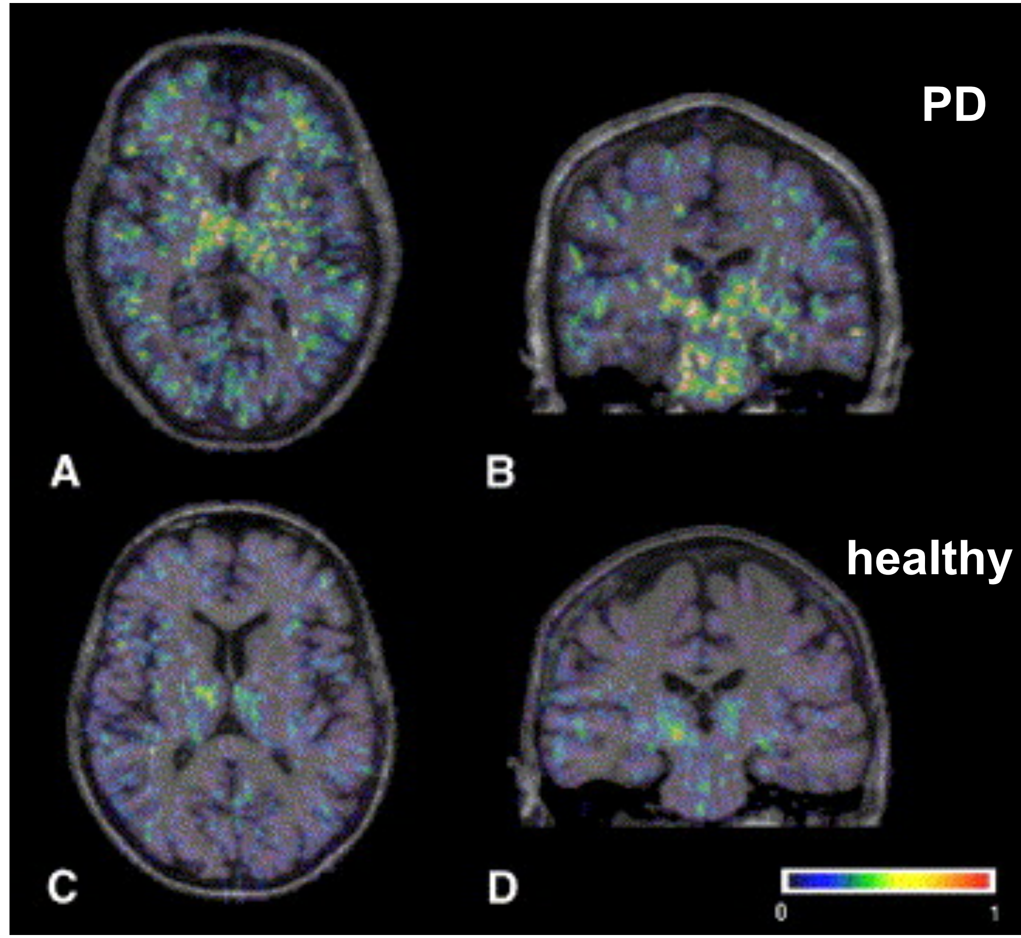
- 新たなサイトカインのCNS特有の作用

  IL19

  Eotaxin1,3



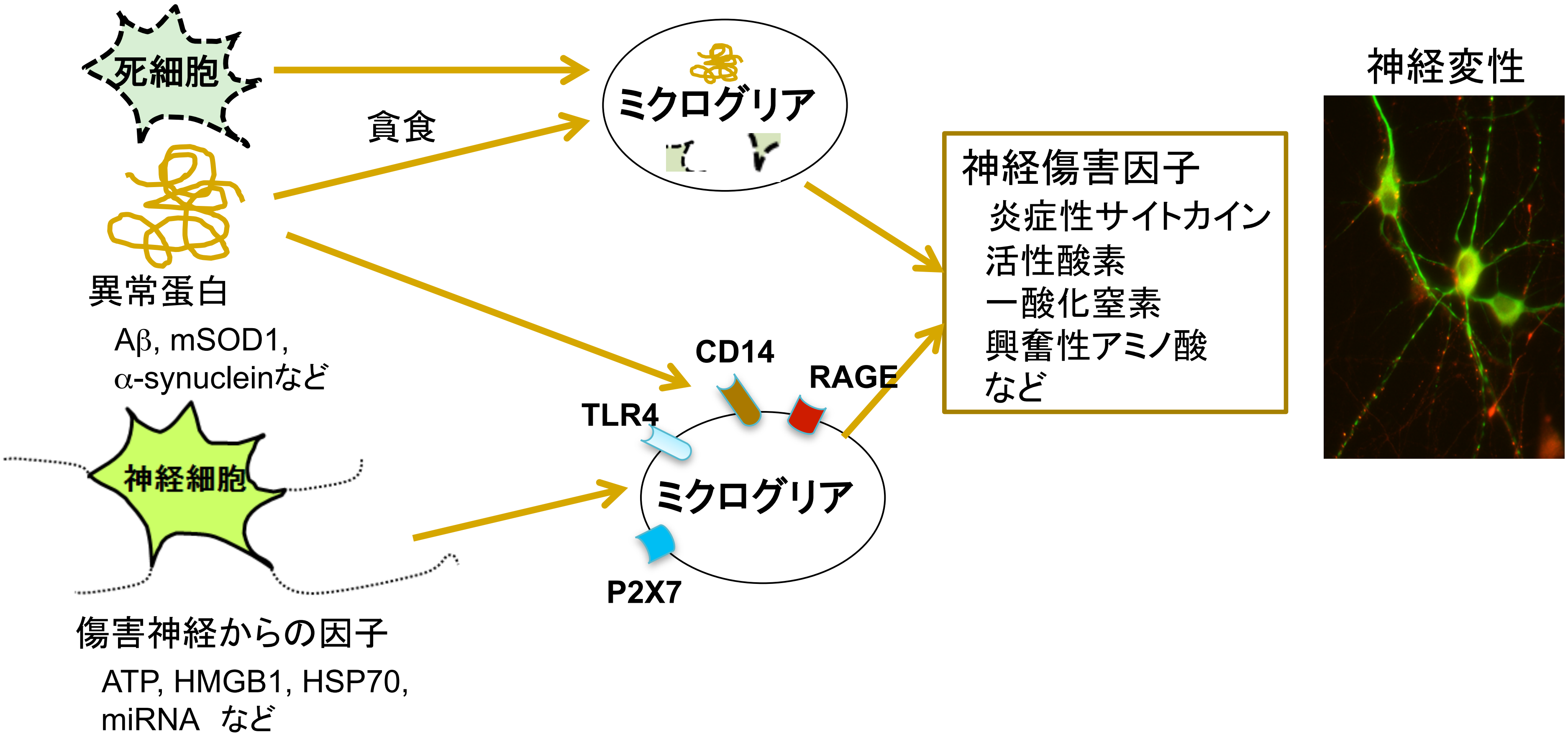




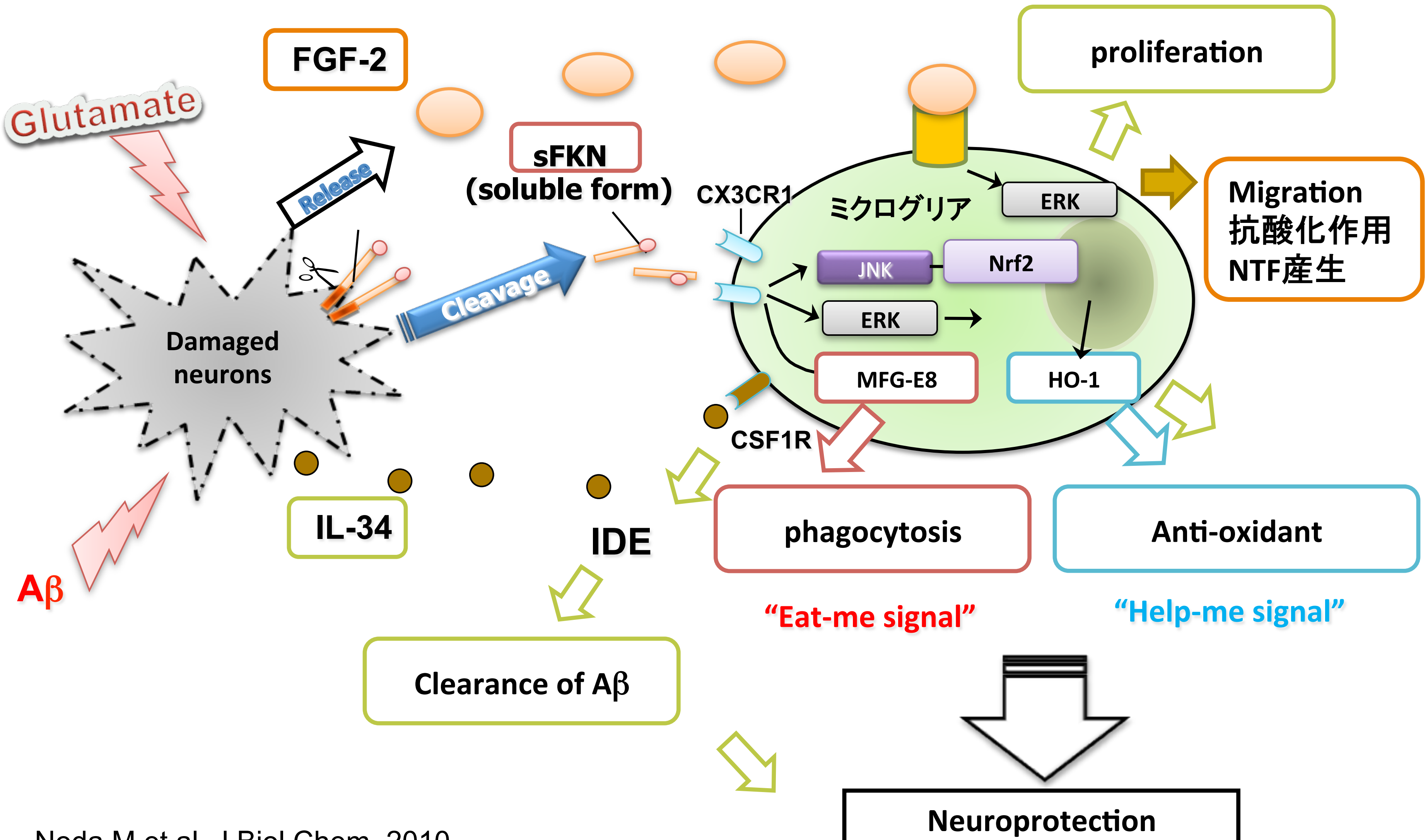
[11C](*R*)-PK11195 binding in the thalamus and pons

Neurobiol Dis. 2006 Feb;21(2):404-12.

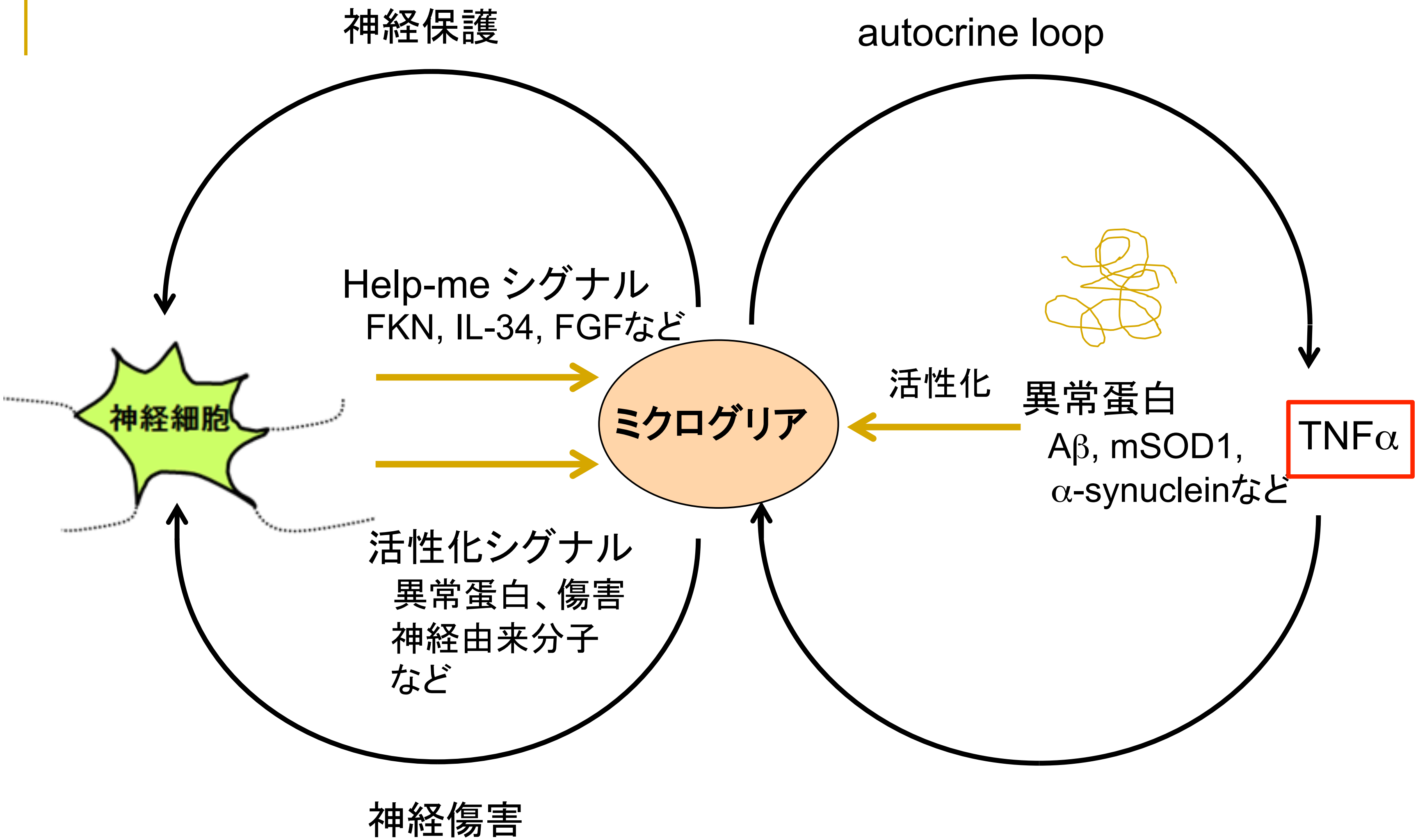
神経変性疾患におけるミクログリアの活性化機序



傷害神経細胞由来の保護因子の増強



Noda M et al. J Biol Chem. 2010
Mizno T et al. Am J Pathol. 2011
Noda M et al. J Neuroinflammation 2014



Neuron-microglia interaction 神経変性の進行、慢性化に関与

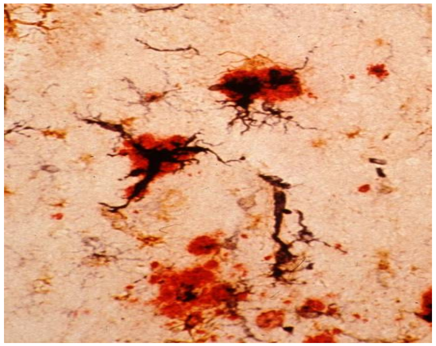
神経細胞ーミクログリア相互作用を利用した新しい神経疾患治療薬の創生

１. ミクログリア由来の炎症因子、神経傷害因子の抑制

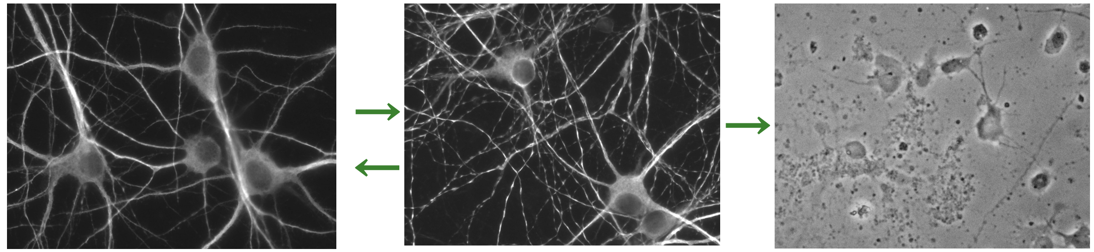
２. ミクログリア由来の神経保護因子の増強

３. 傷害神経細胞由来の保護因子の増強

ミクログリアの神経細胞傷害

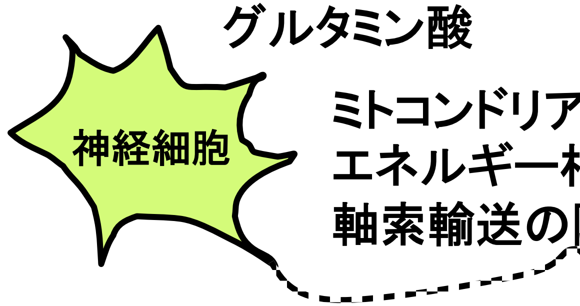


老人班におけるAβの沈着（茶）
とミクログリア（黒）



活性化ミクログリアの上清による神経細胞傷害

グルタミン酸

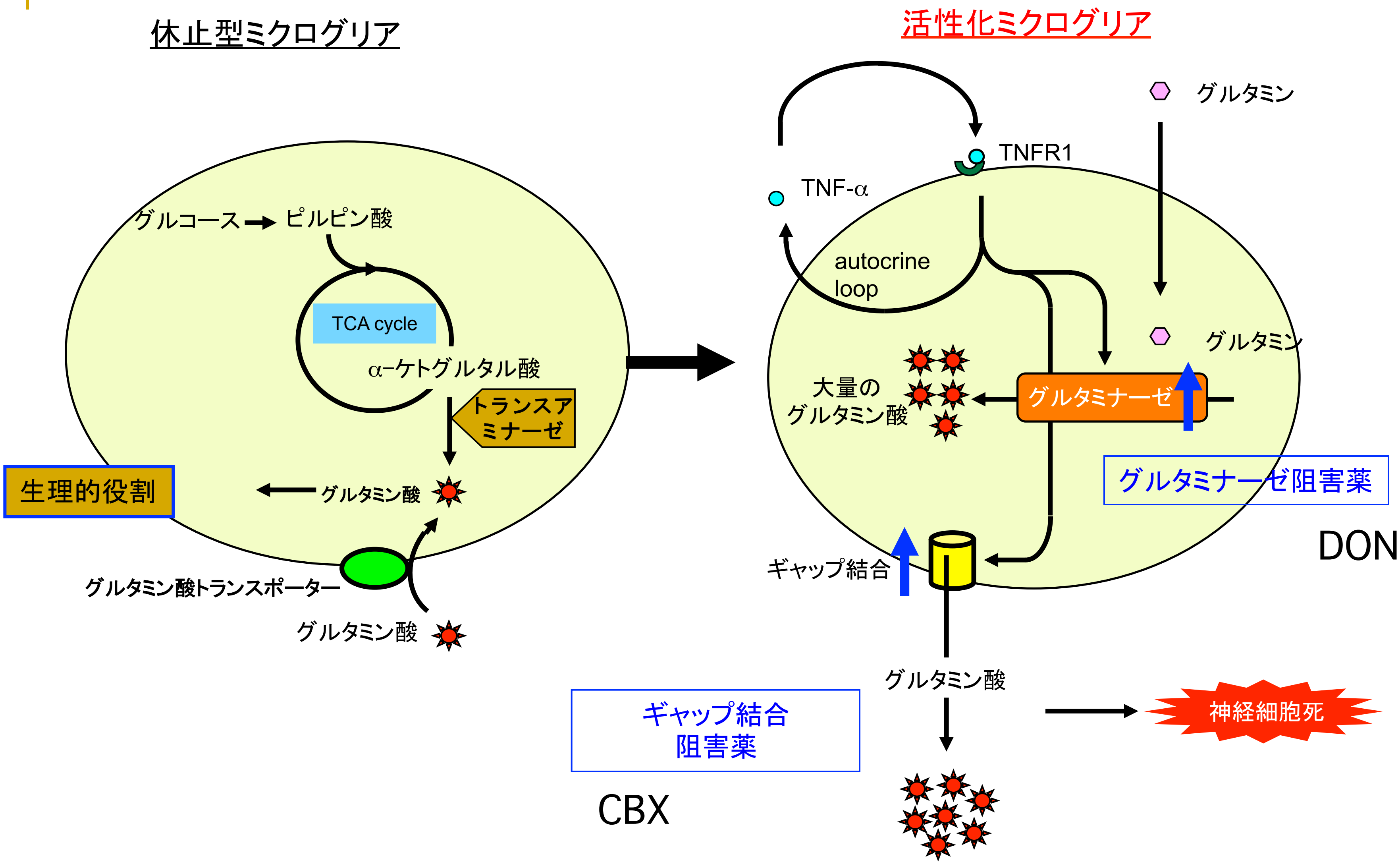


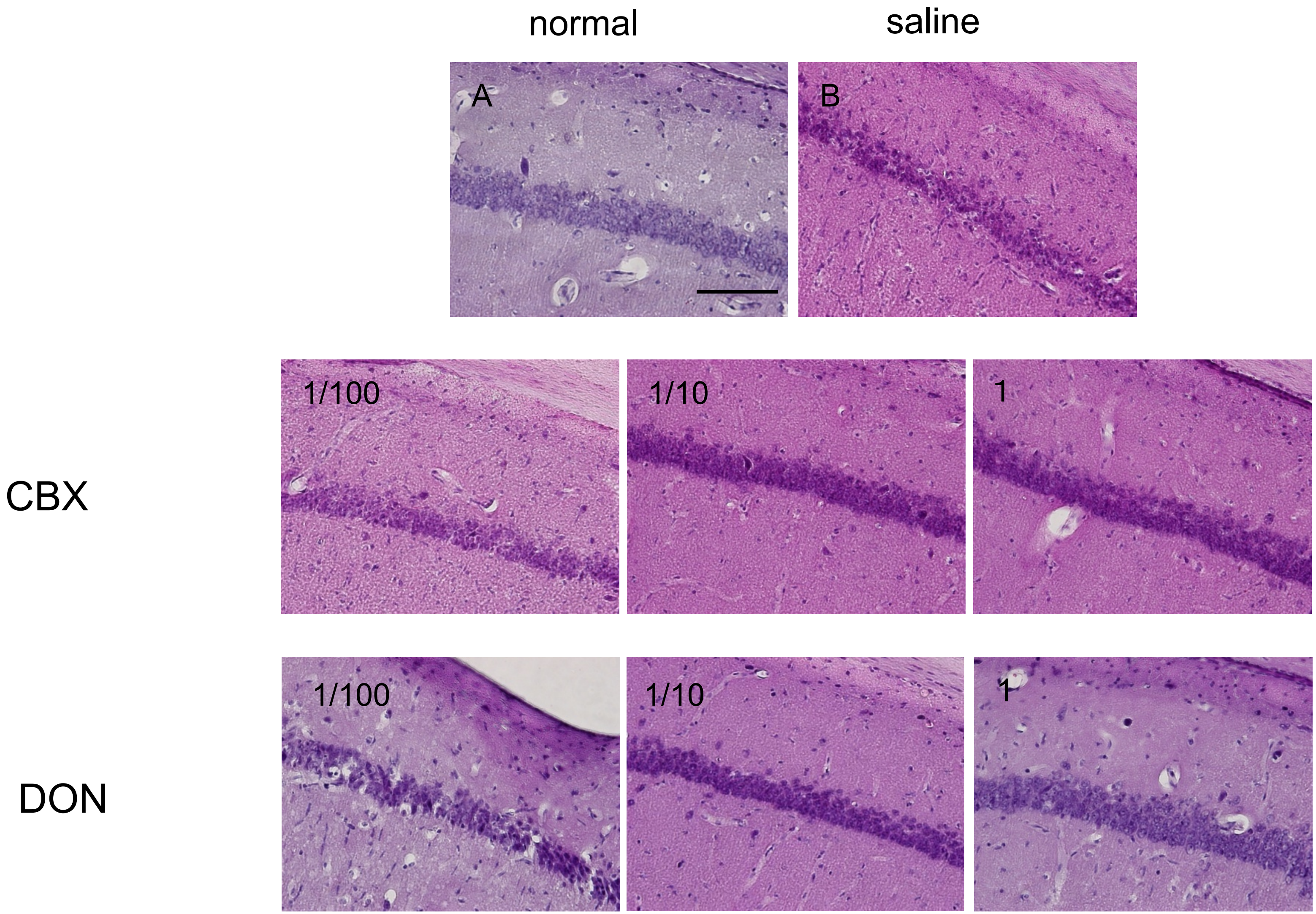
ミトコンドリアの障害
エネルギー枯渇
軸索輸送の障害

↓

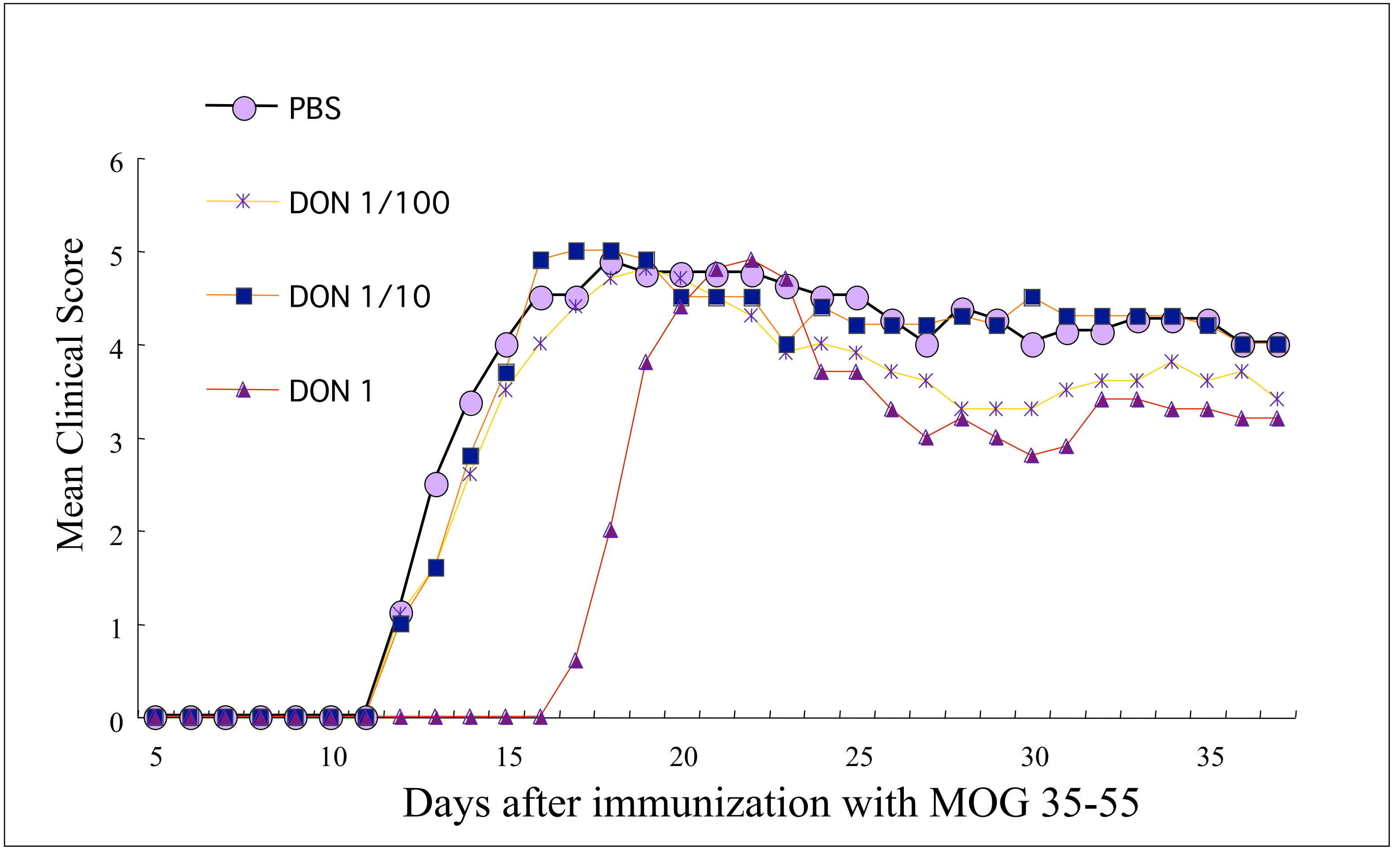
神経細胞死

Takeuchi,H., et al. J. Biol. Chem. 280: 10444-10454, 2005.

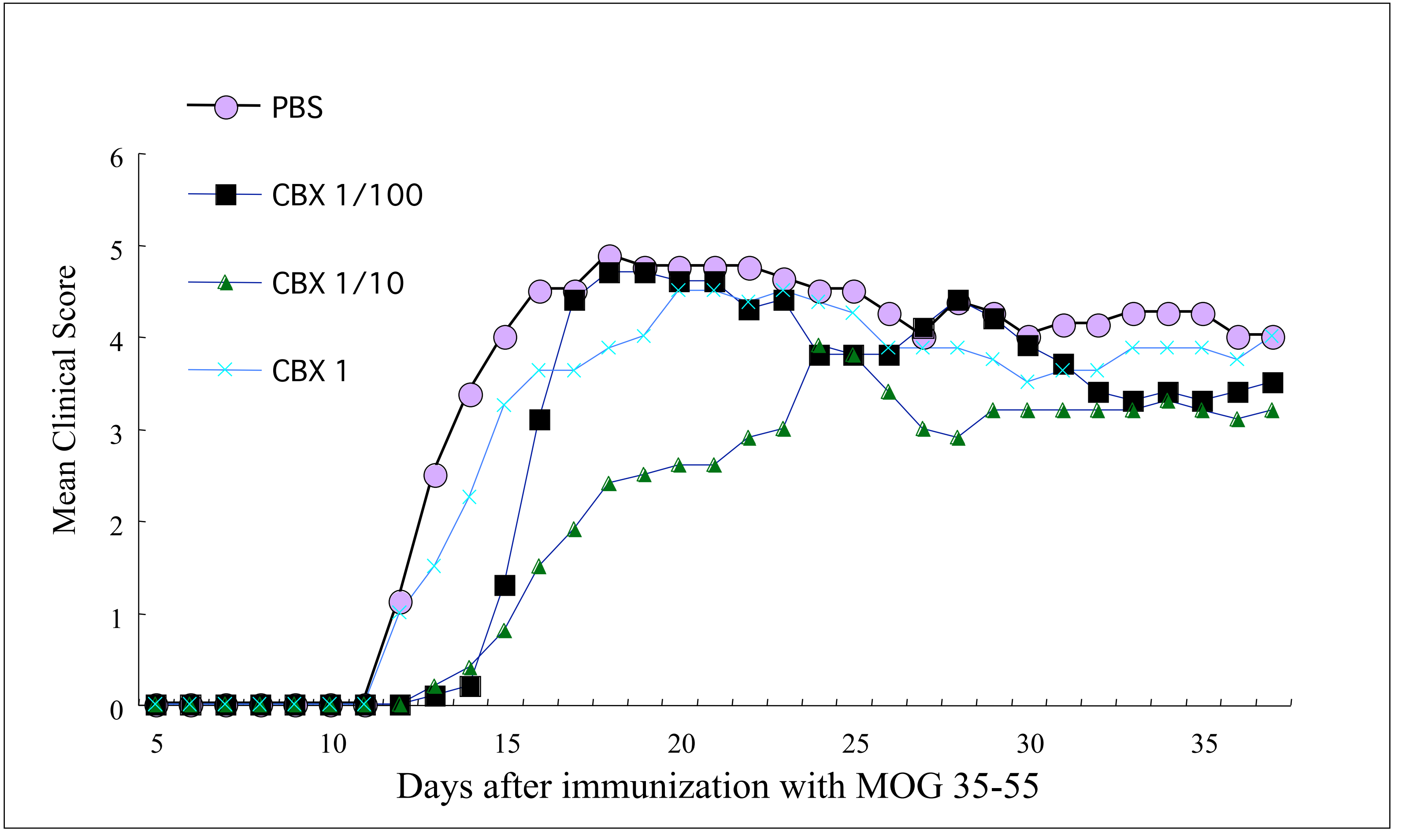

休止型ミクログリア
活性化ミクログリア
グルコース
ピルビン酸
TCA cycle
α−ケトグルタル酸
トランスアミナーゼ
グルタミン酸
生理的役割
グルタミン酸トランスポーター
グルタミン酸
TNFR1
TNF-α
autocrine loop
グルタミン
グルタミン
大量のグルタミン酸
グルタミナーゼ
グルタミナーゼ阻害薬
DON
ギャップ結合
グルタミン酸
ギャップ結合阻害薬
CBX
神経細胞死


normal
saline
A
B
CBX
1/100
1/10
1
DON
1/100
1/10
1

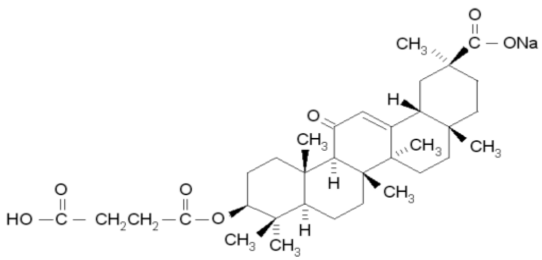
Effects on EAE（DON）



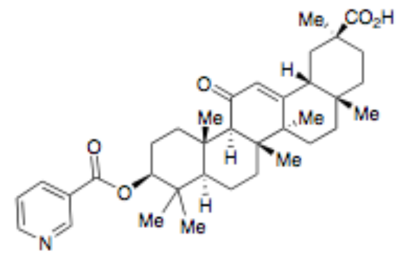
Effects on EAE（CBX）



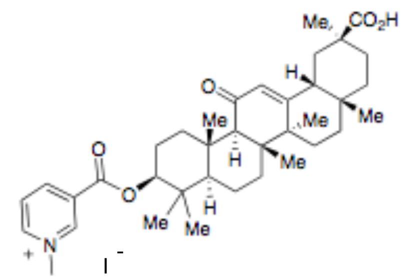
ギャップ結合阻害剤として新規化合物2種を抽出・選定



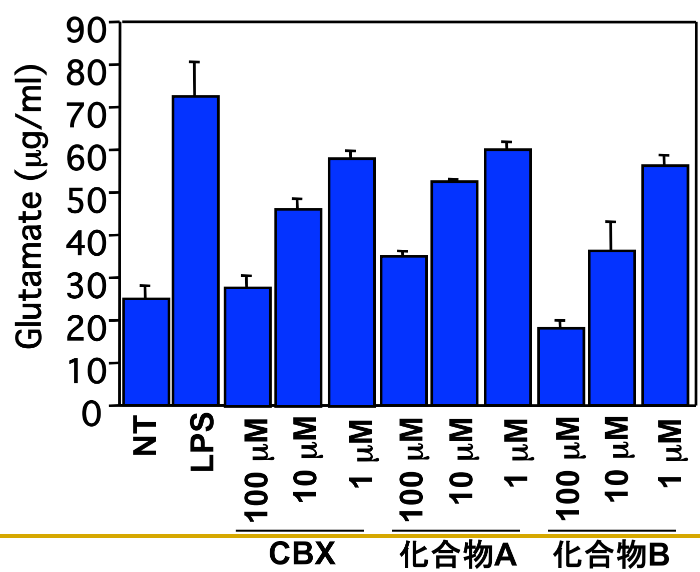
Carbenoxolone
分子式：$C_{34}H_{48}O_7Na_2$
分子量: 614.7

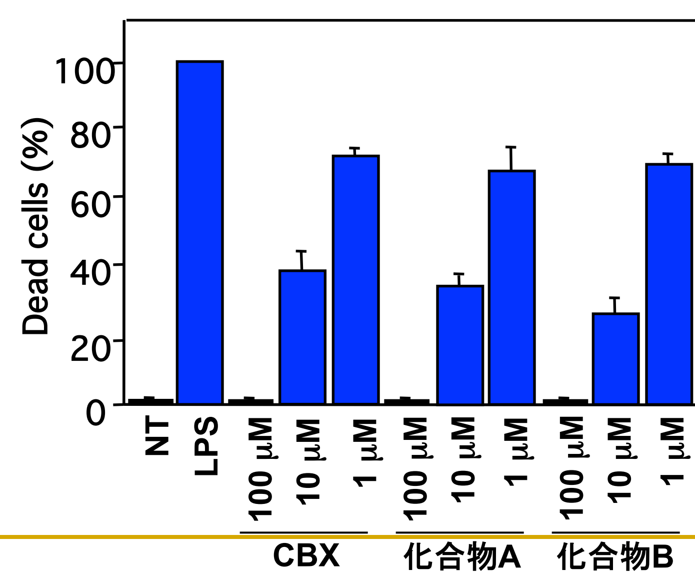


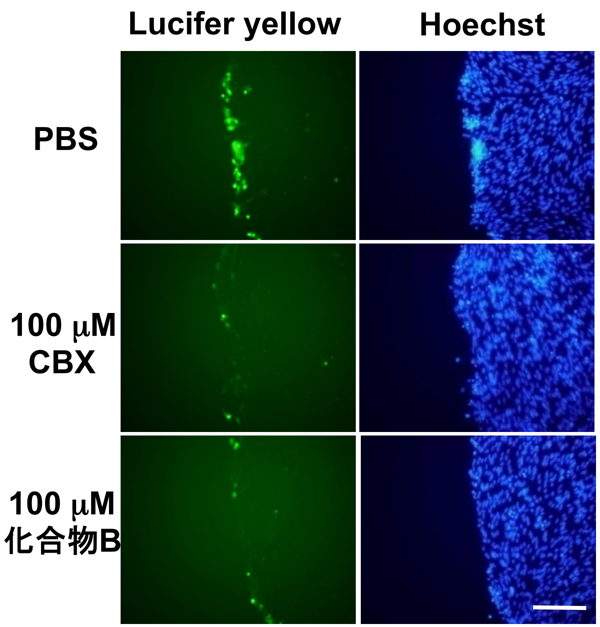
化合物A
分子式：$C_{36}H_{49}NO_5$
分子量: 575.78

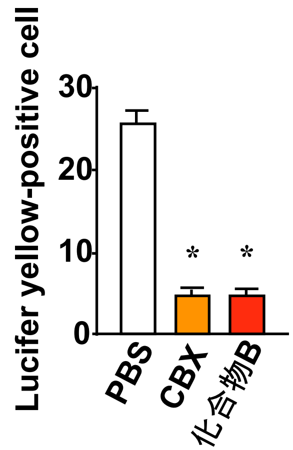


化合物B
分子式：$C_{36}H_{52}INO_5$
分子量: 717.72

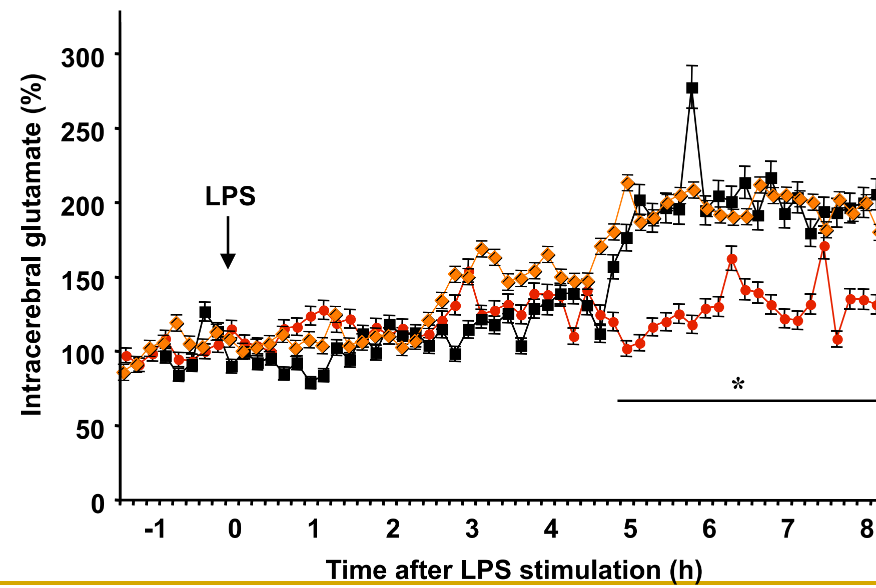








化合物BはCBXと同様のギャップ結合阻害作用を持つ

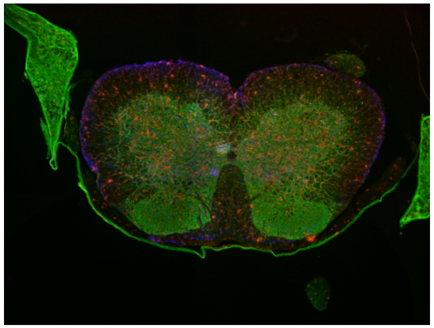


化合物Bは末梢投与でも脳内のグルタミン酸産生を抑制する
→脳内で働く

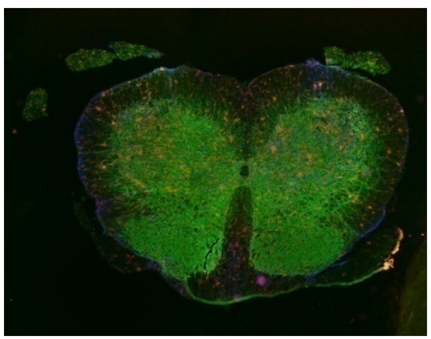
化合物B（INI0602)のALSモデルに対する効果

mutant SOD1 Tg mouse (G93A)
Rapid progression model

Lumber spinal cord (20w)



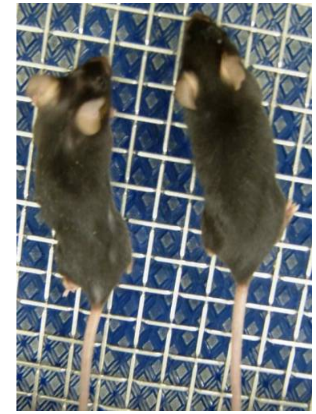
PBS

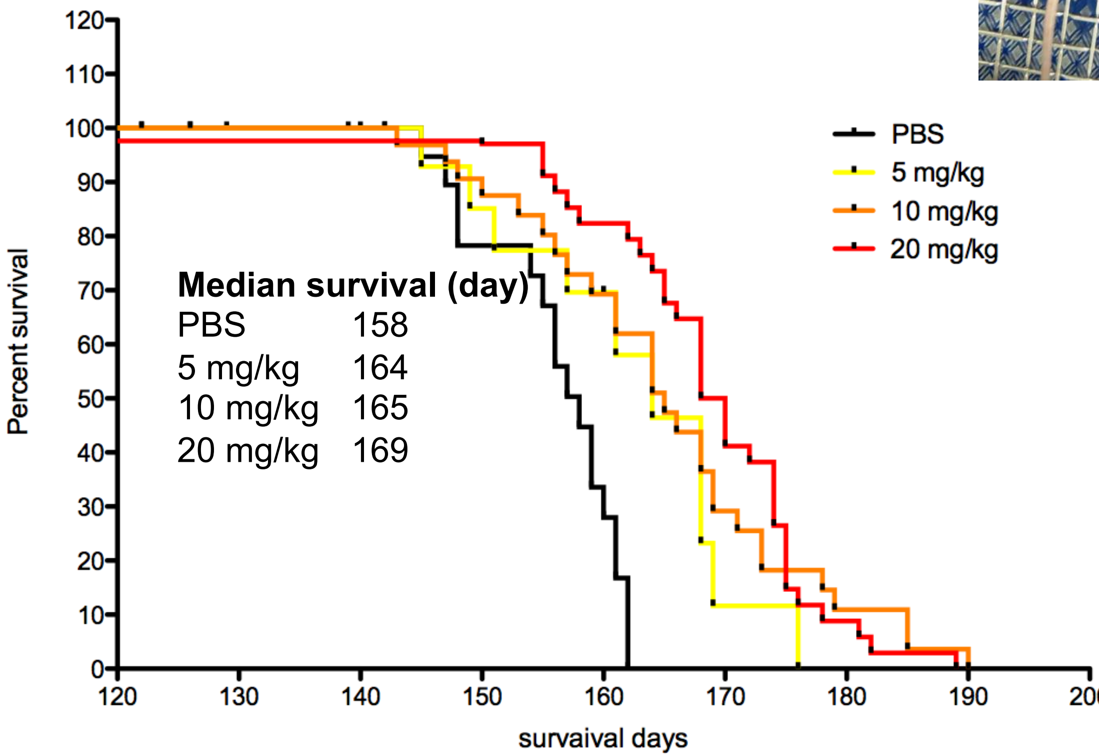


INI0602
20mg/kg

Green: MAP2
Red: CD11b
Blue: GFAP

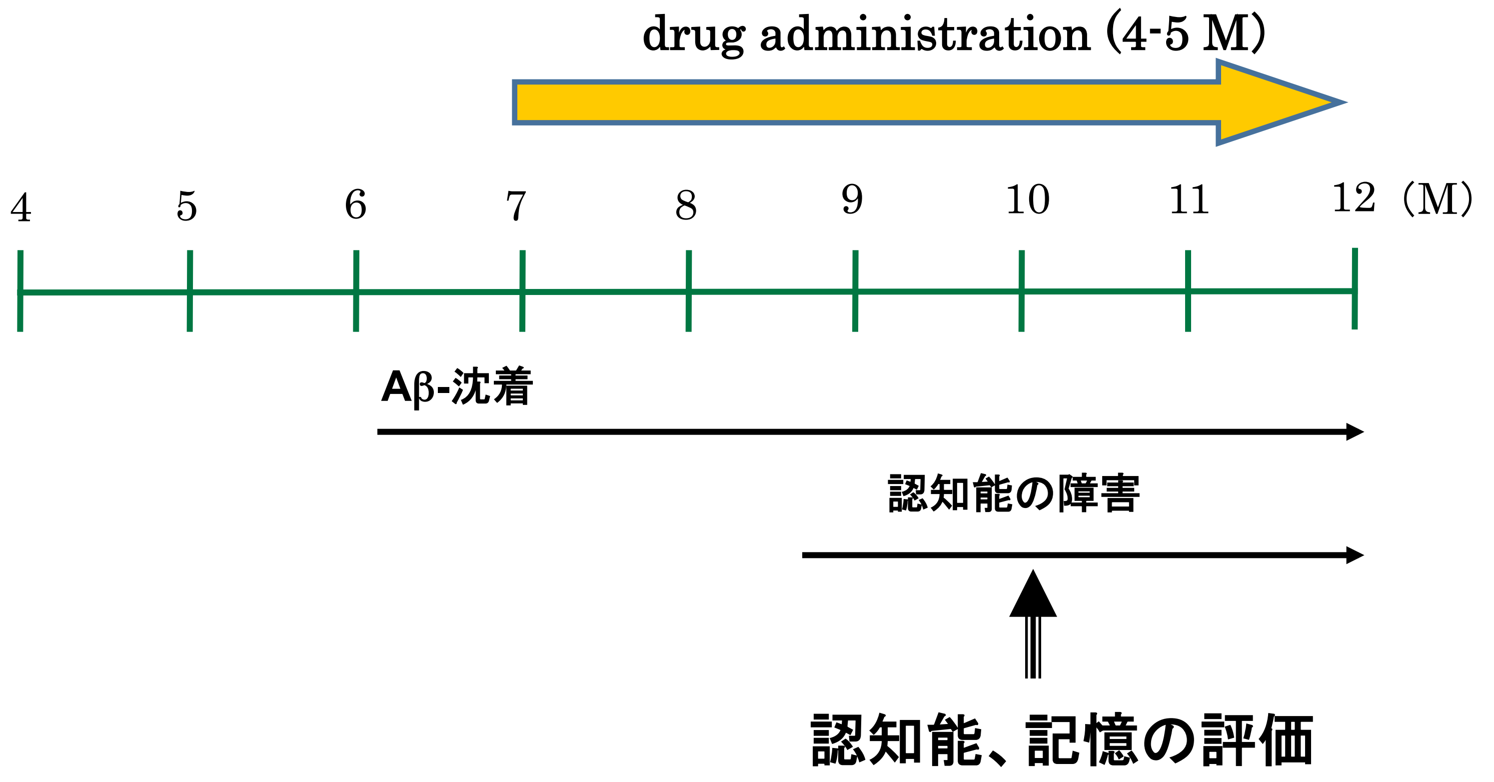
20weeks old



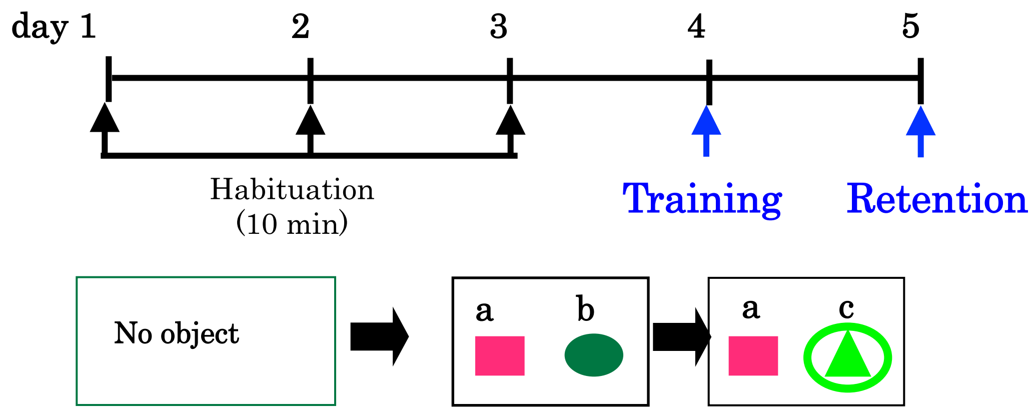


アルツハイマー病モデルでの有効性

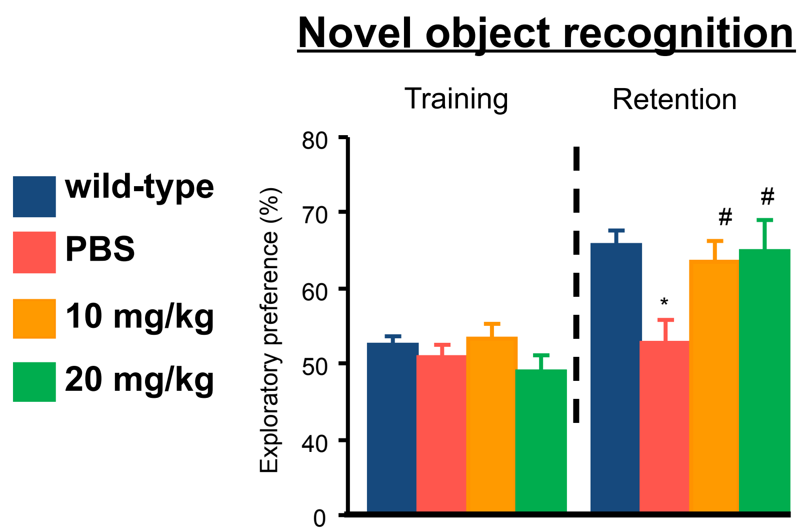
mutant APPswe/PSEN1 Tg mice



新規物質探索テスト(NOR)

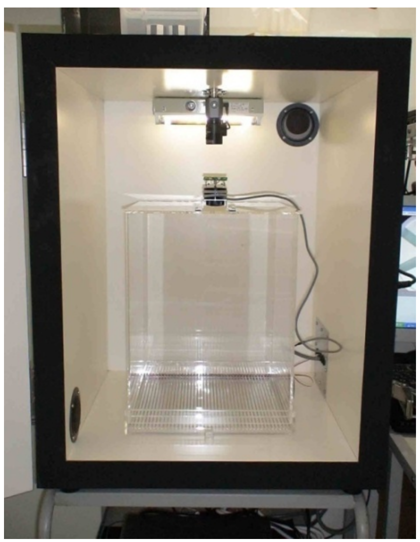


$$\text{NOR (\%)} = \frac{c}{a + c} \times 100$$



恐怖条件付け学習試験

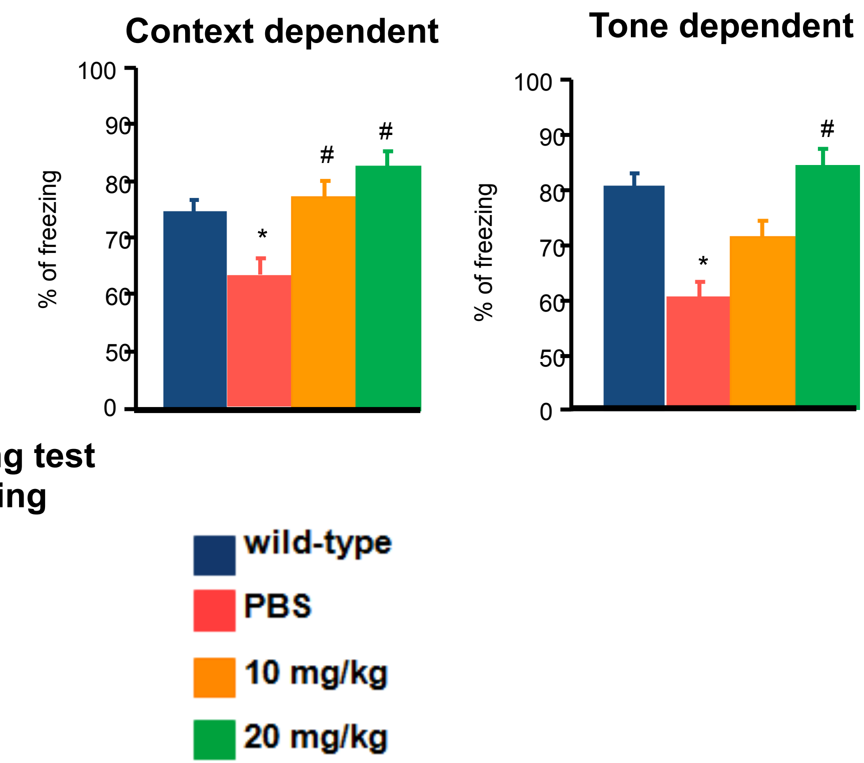
Training（fear conditioning）



contextual learning test
associative learning
(hippocampal)

cued (tone) learning test
(amygdala)

恐怖受験付け学習試験



Effects of INI0602 on Parkinson model

6-OHDA injection in mouse striatum 5 µl (10 µg)

PBS, or *INI0602 inj 5 µl*

Bar hole :
Bregma right 2mm,
depth 3.5-4 mm

Apomorphin i.p.

day 1

day 1
(after 15 min)

day 2

day 7 ~ 10

•Immunostaining

•(tyrosine hydroxylase/ Iba-1)

MRI Imaging

Sacrifice

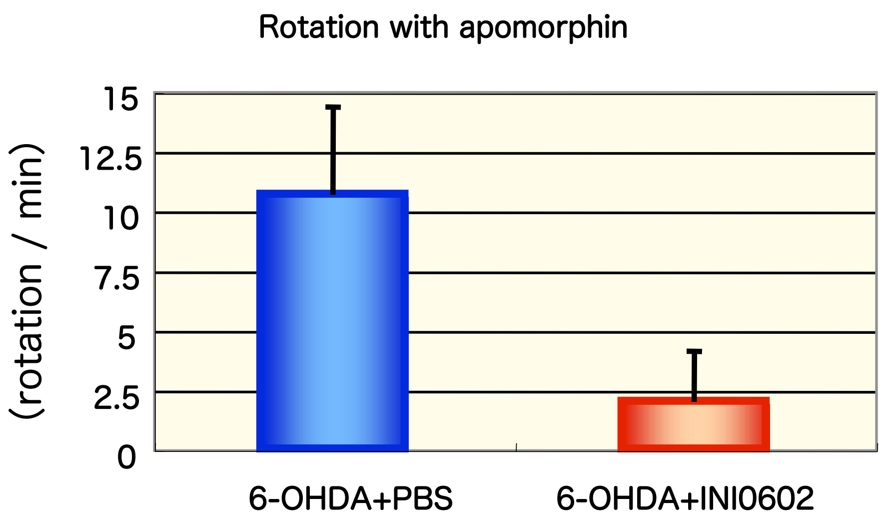
- perfused with PBS after cardiocentesis
- sagital frozen sections-10µm were mounted on slides

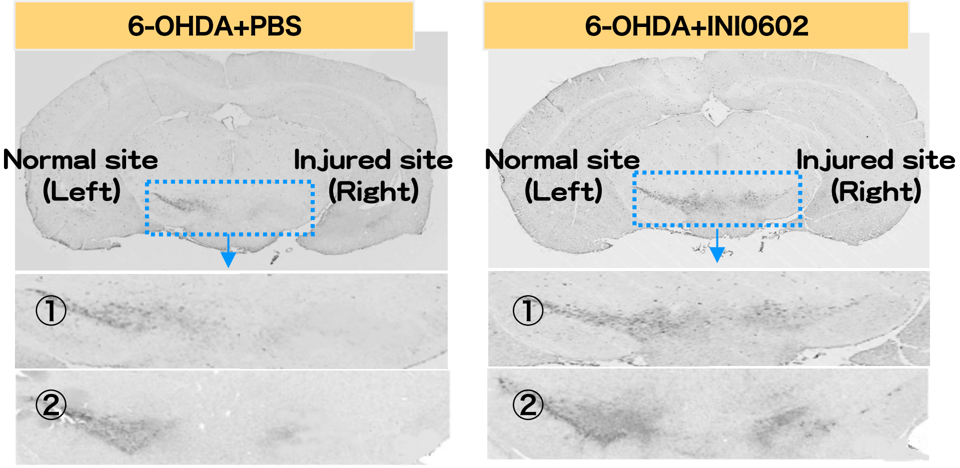
Effects of INI0602 on Parkinson disease model

6-OHDA + PBS

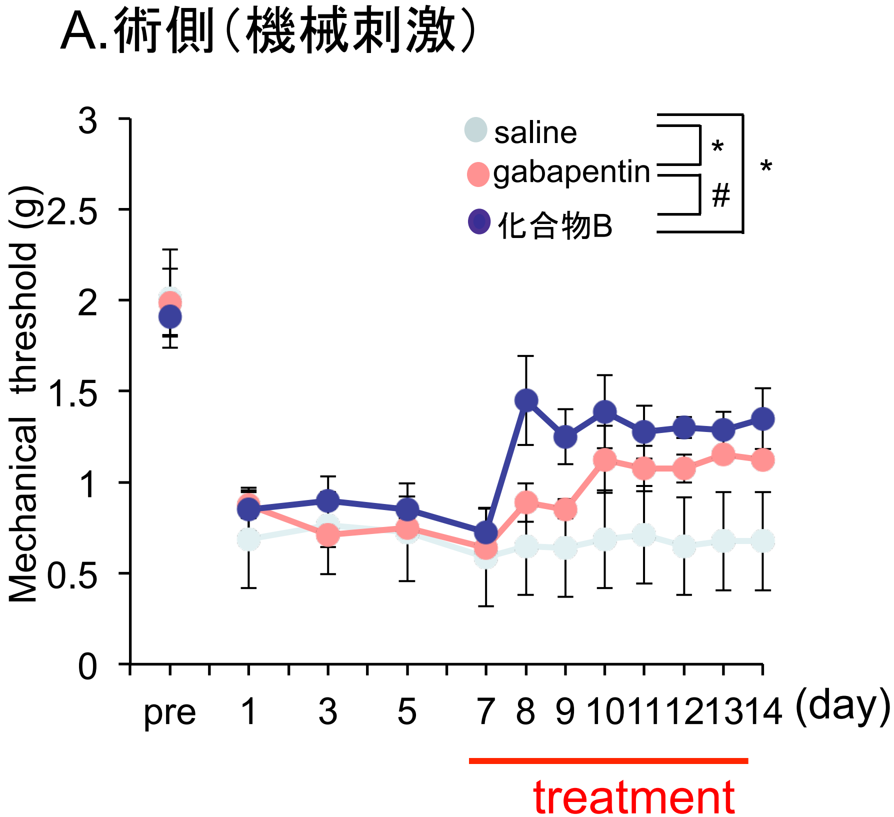
6-OHDA + INI0602

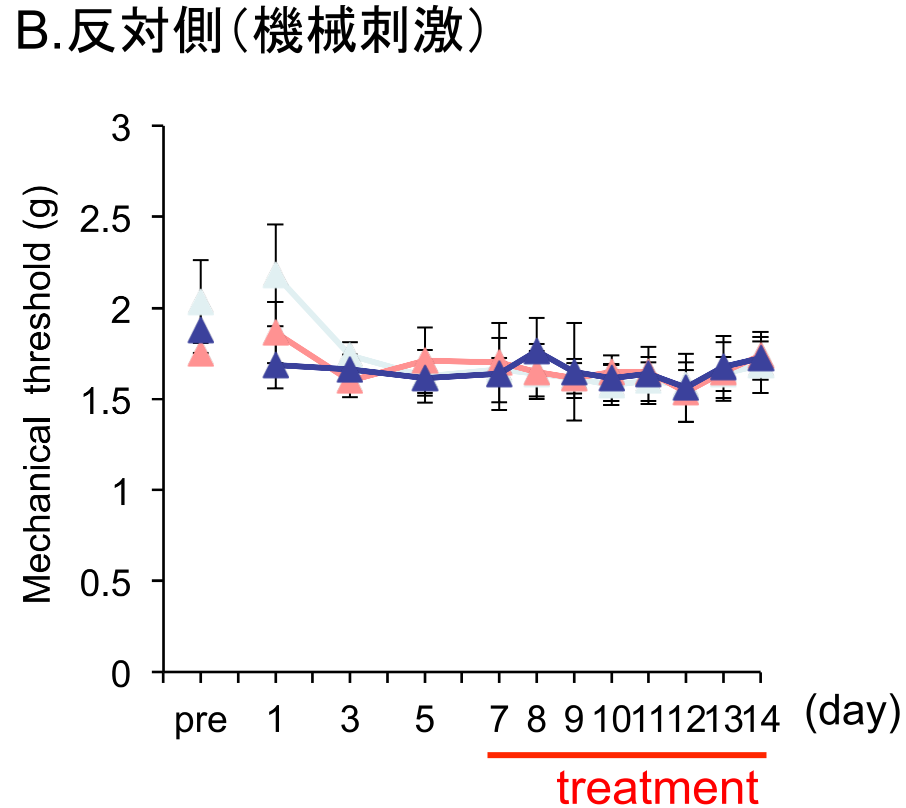
INI0602 effectively suppress clinical symptoms and neuronal loss in PD model





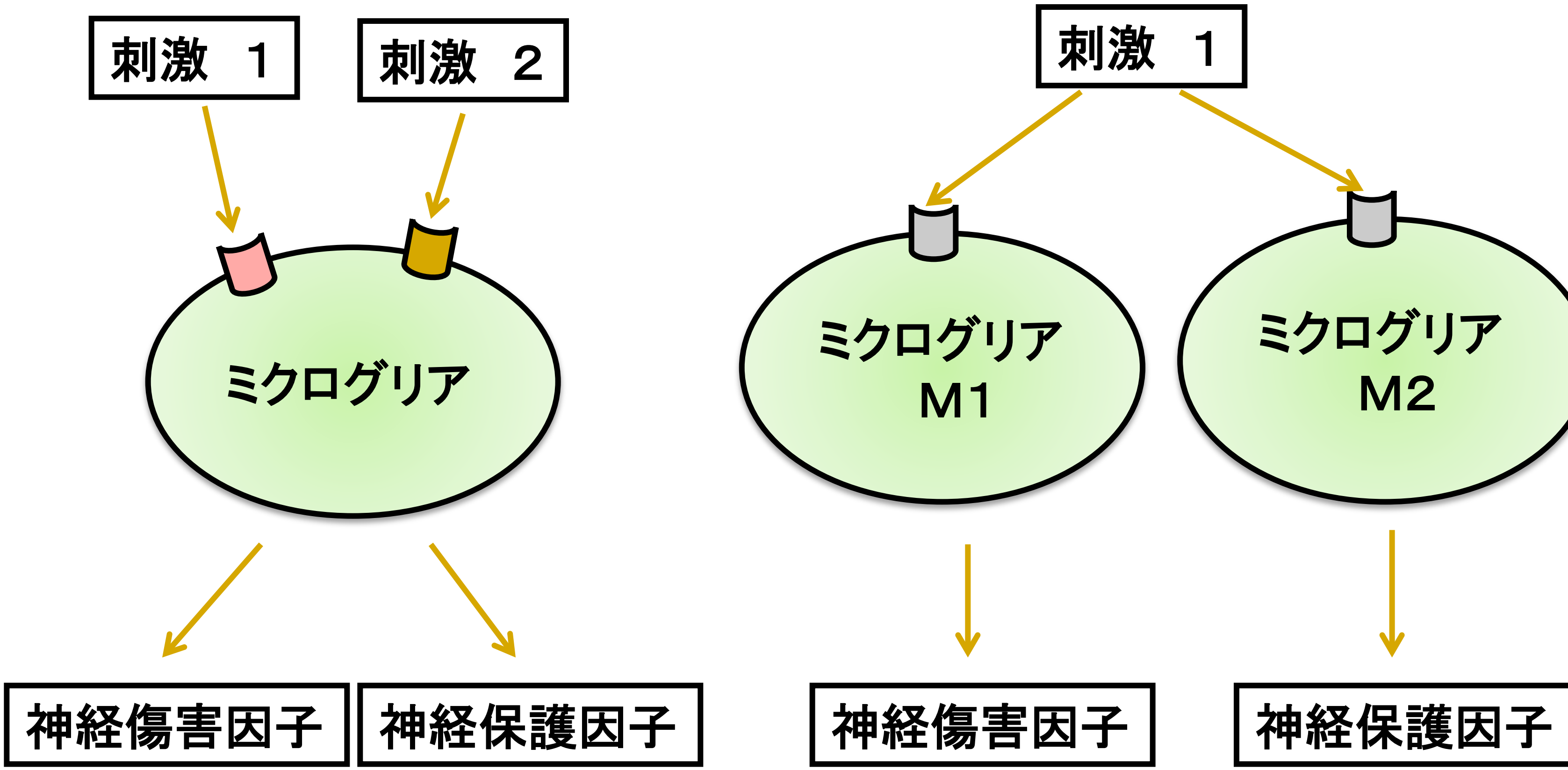
CCI 誘発慢性痛に対する薬剤の治療効果
ー機械アロディニアー





*p<0.05 vs saline
#p<0.05 vs gabapentin

2. ミクログリア由来の神経保護因子の増強



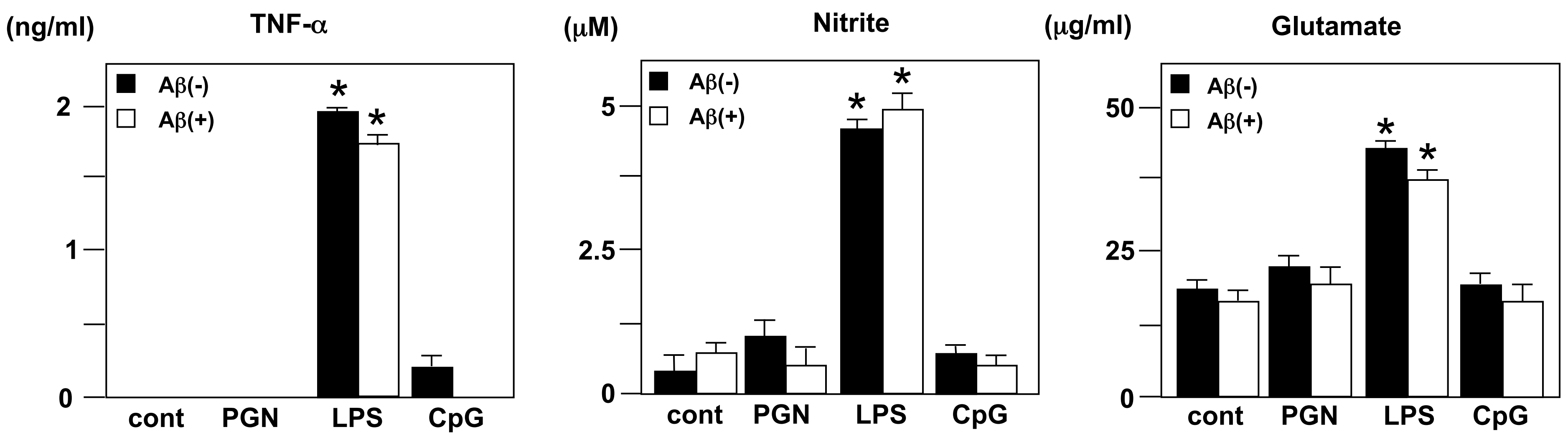
神経傷害因子

炎症性サイトカイン	IL-1β、TNF-α
一酸化窒素(NO)	
活性酸素	
peroxynitrite	
興奮性アミノ酸	

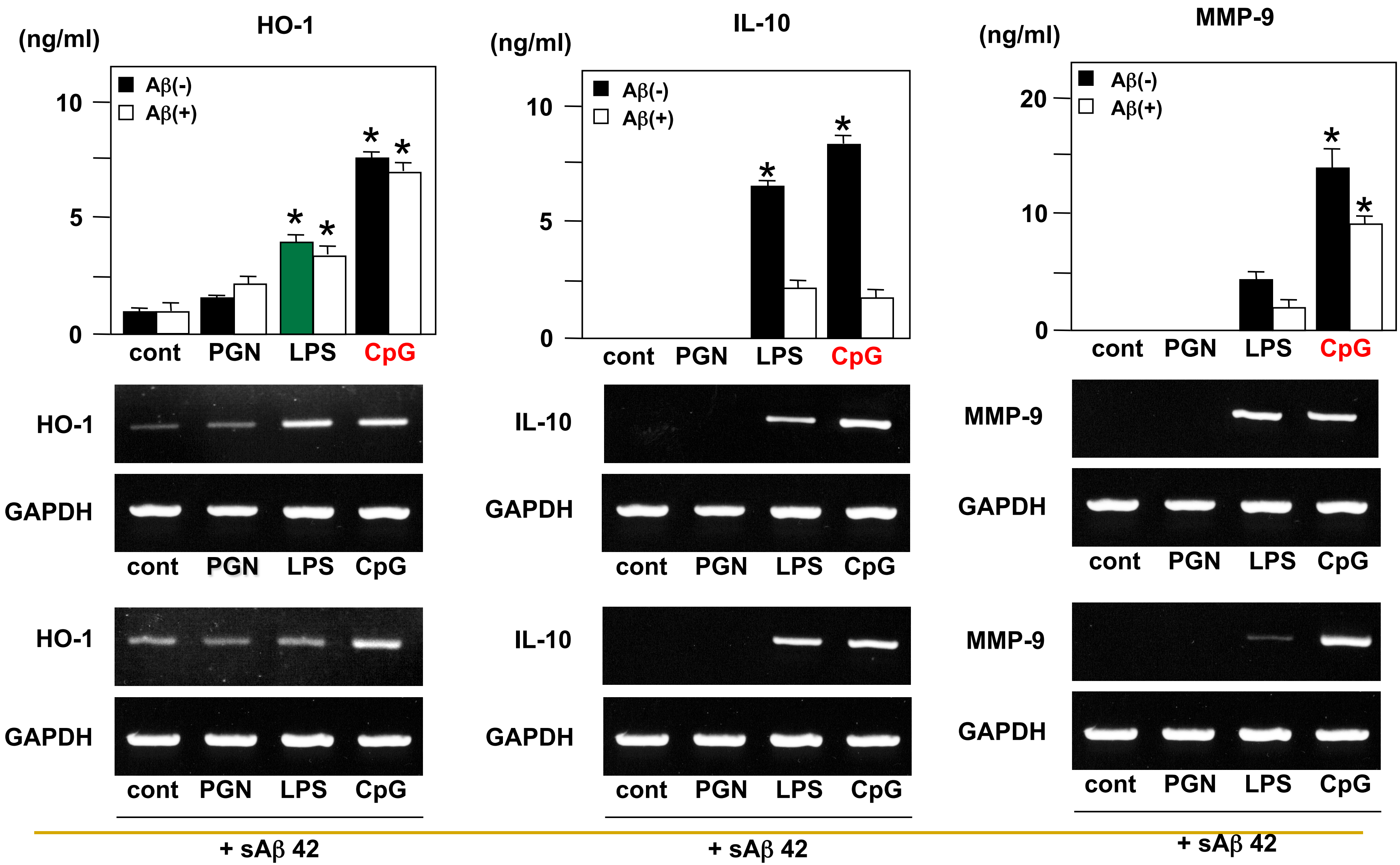
神経保護因子

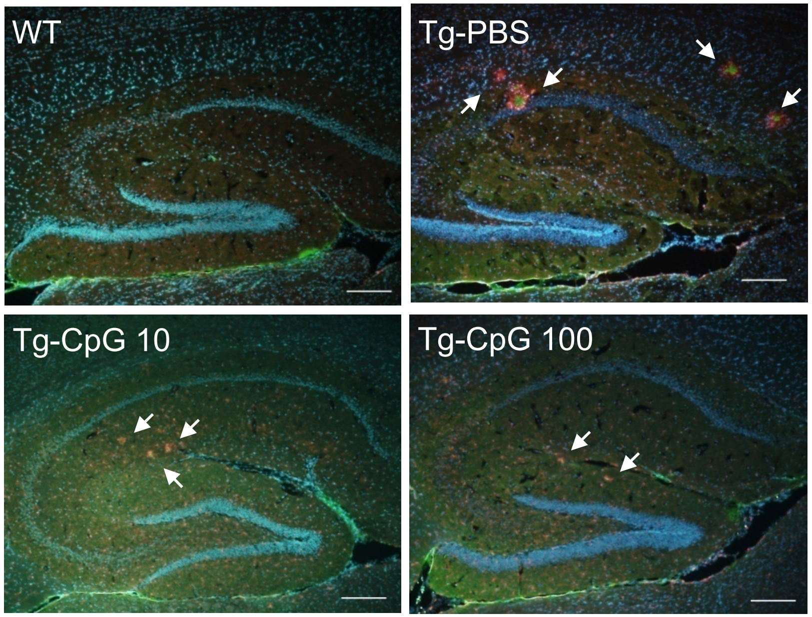
神経栄養因子	NGF、BDNF、NT-3、NT-4/5
TGFβ family	TGFβ、GDNF
IL-6 family	IL-6、LIF、CNTF
抗酸化酵素	Ho-1
Aβ分解酵素	IDE、MMP-9

CpG-DNAで刺激したミクログリアは細胞傷害因子を産生しない

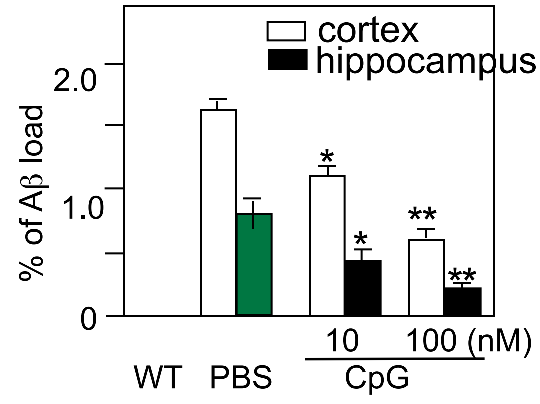


CpG-DNAで刺激したミクログリアは保護的に働く。

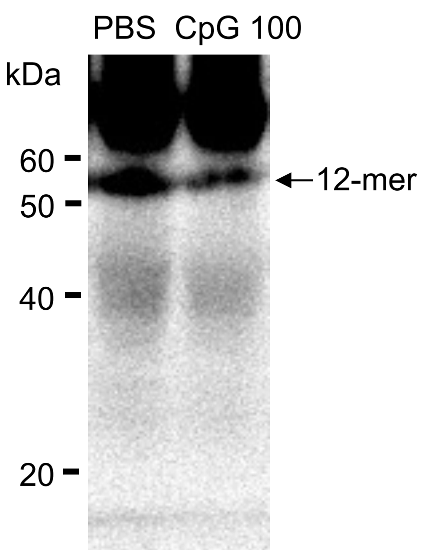




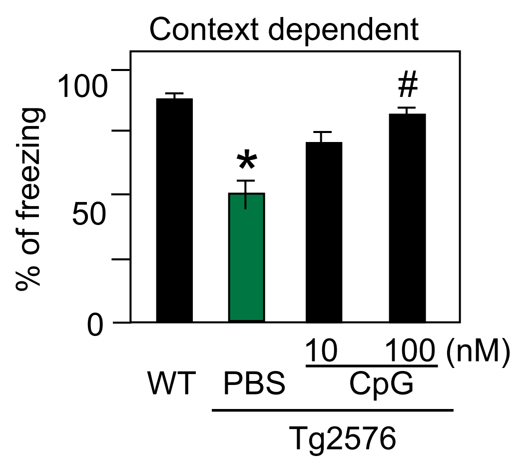
WT
Tg-PBS
Tg-CpG 10
Tg-CpG 100



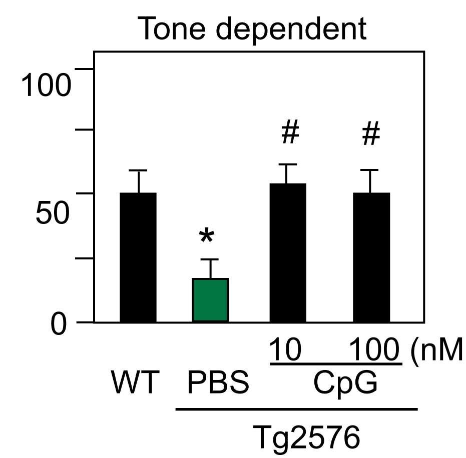
cortex
hippocampus
% of Aβ load
2.0
1.0
0
*
*
**
**
WT
PBS
10
100 (nM)
CpG



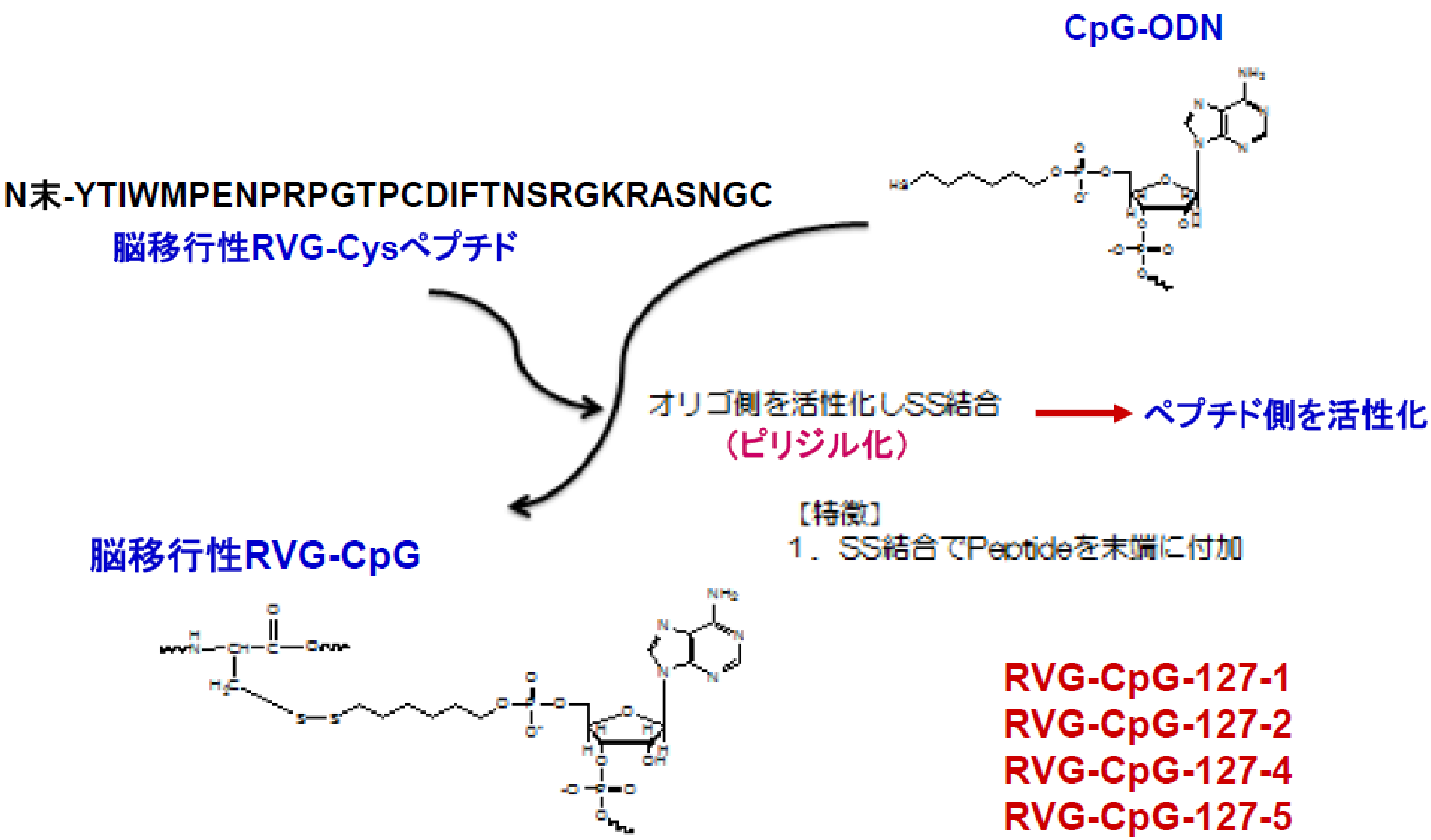
PBS
CpG 100
kDa
60
50
40
20
12-mer



Context dependent
% of freezing
100
50
0
*
#
WT
PBS
10
100 (nM)
CpG
Tg2576



Tone dependent
100
50
0
*
#
#
WT
PBS
10
100 (nM)
CpG
Tg2576

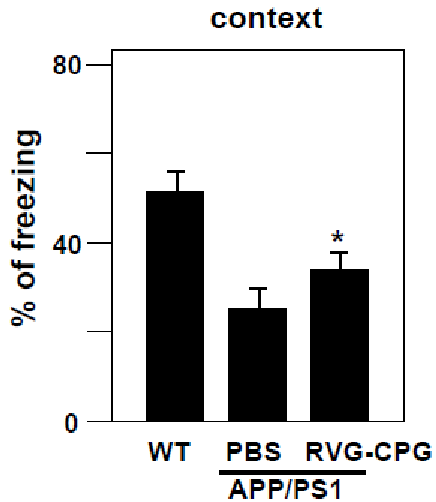


a short peptide derived from rabies virus glycoprotein(RVG) enables the transvascular delivery of siRNA to the brain (Kumar. Natrure 2007)

図6. 脳移行性CpG-ODNの作成-脳移行性ペプチドRVG付加

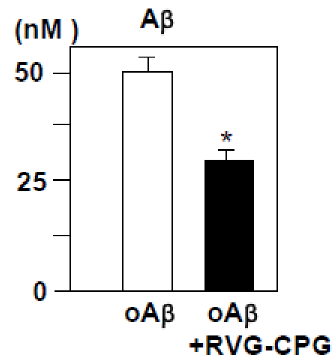
アルツハイマー病モデルマウスによる検討

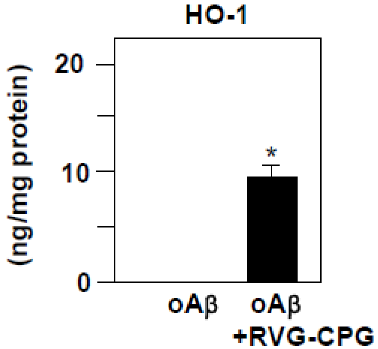
認知機能障害の改善



RVG-CpG 1 μg を隔日、3回　腹腔内投与

RVG-CpGの培養細胞における有用性





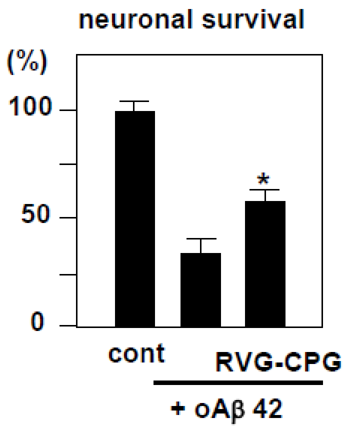
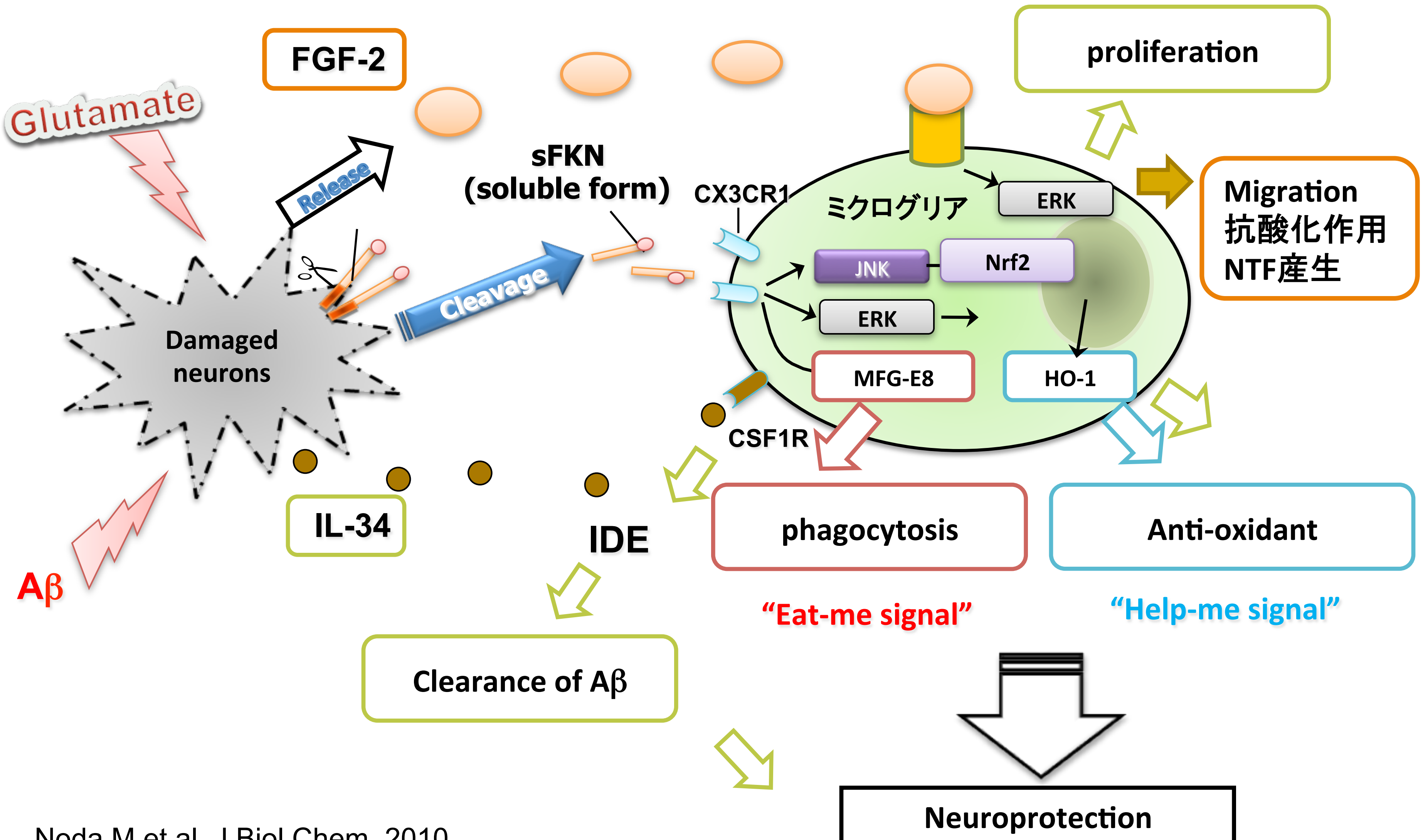


図7. 脳移行性CpG-ODN (RVG-CpG) の有効性の検証

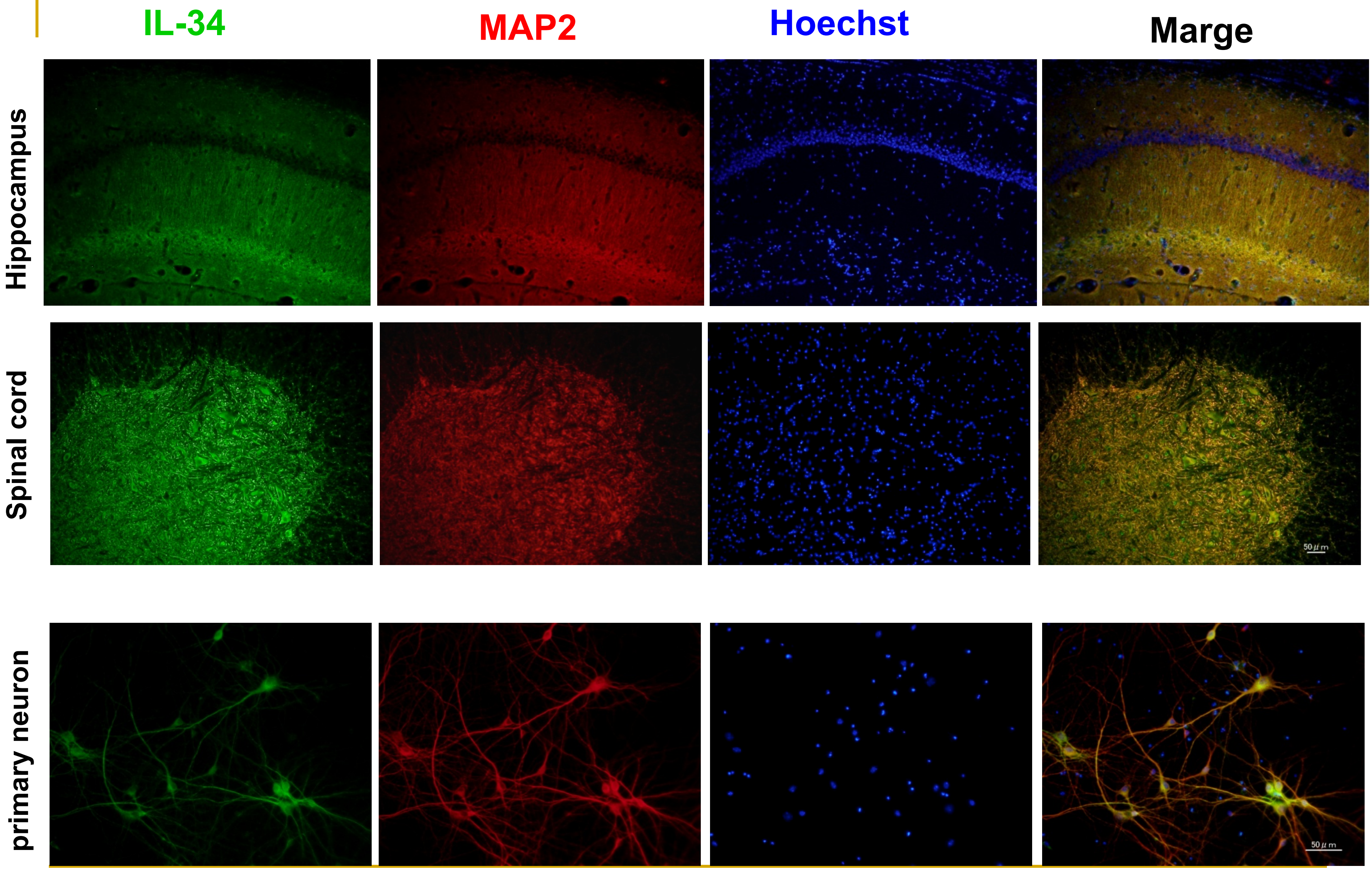
3．傷害神経細胞由来の保護因子の増強



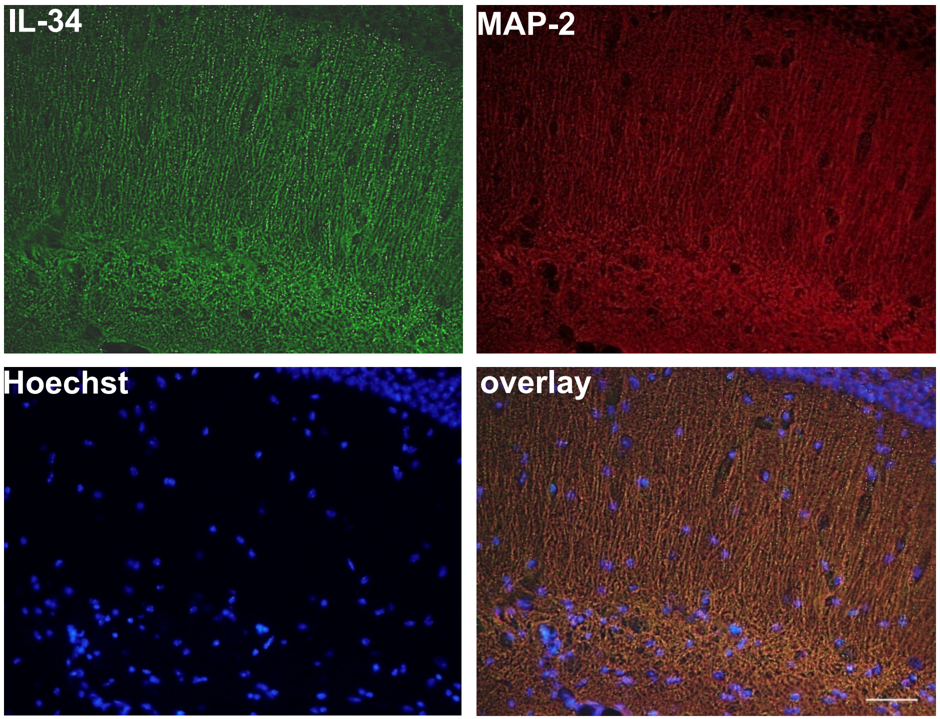
Noda M et al. J Biol Chem. 2010

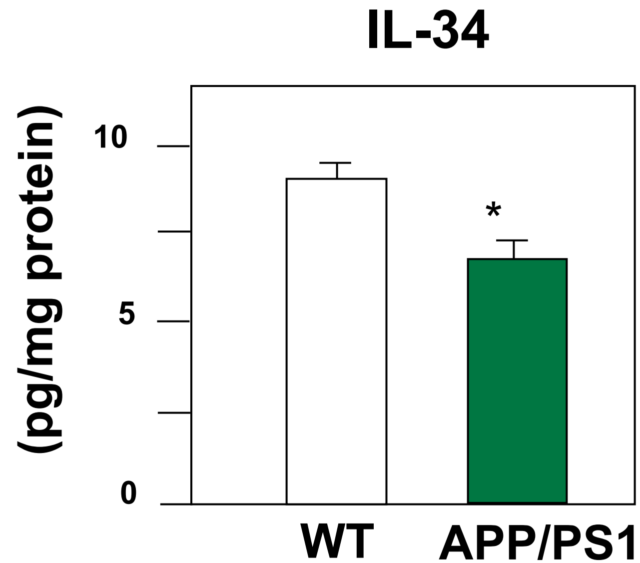
Mizno T et al. Am J Pathol. 2011

Noda M et al. J Neuroinflammation 2014

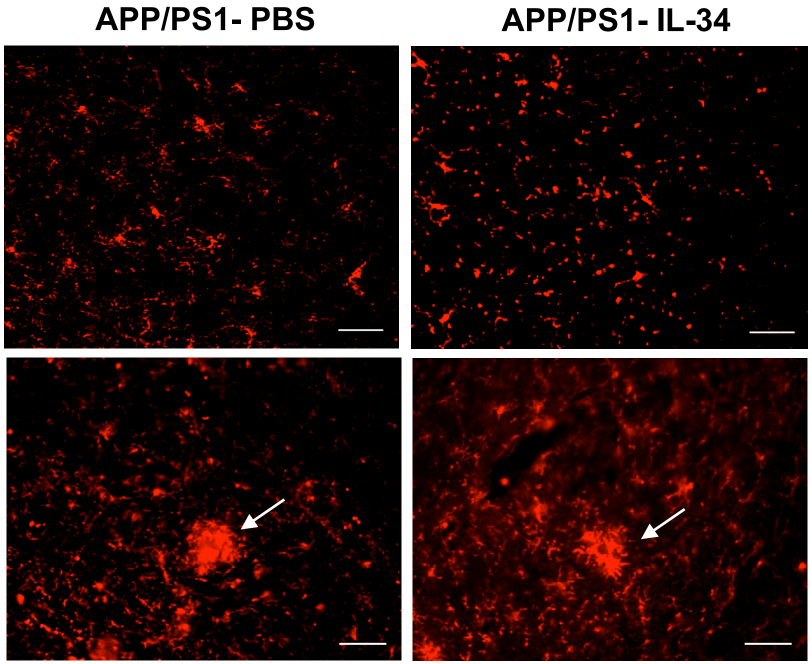

IL-34
MAP2
Hoechst
Marge
Hippocampus
Spinal cord
primary neuron
50μm
50μm

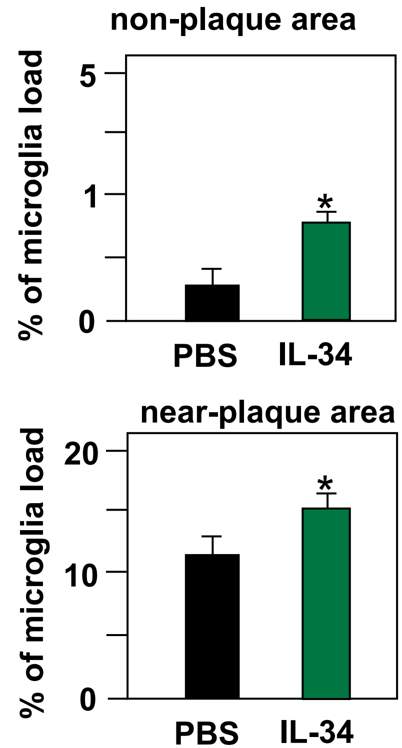
Neurons express IL-34 in vivo

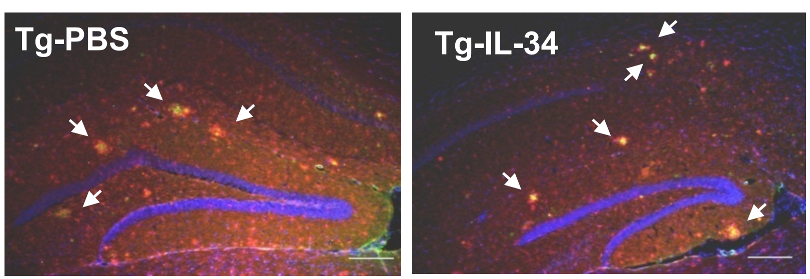


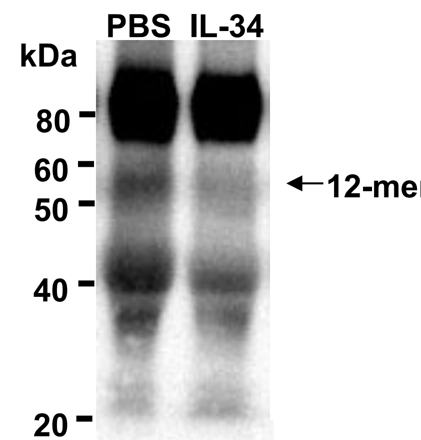


→ IL-34 は神経変性の病態で減少している
IL-34 投与は神経変性を抑制するか?

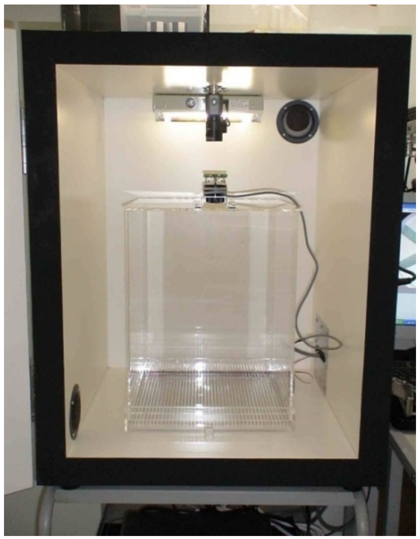

APP/PS1- PBS
APP/PS1- IL-34


non-plaque area
% of microglia load
5
1
0
*
PBS
IL-34
near-plaque area
% of microglia load
20
10
0
*
PBS
IL-34

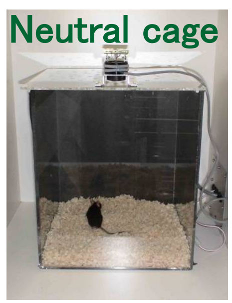

Tg-PBS
Tg-IL-34


PBS
IL-34
kDa
80
60
50
40
20
12-mer

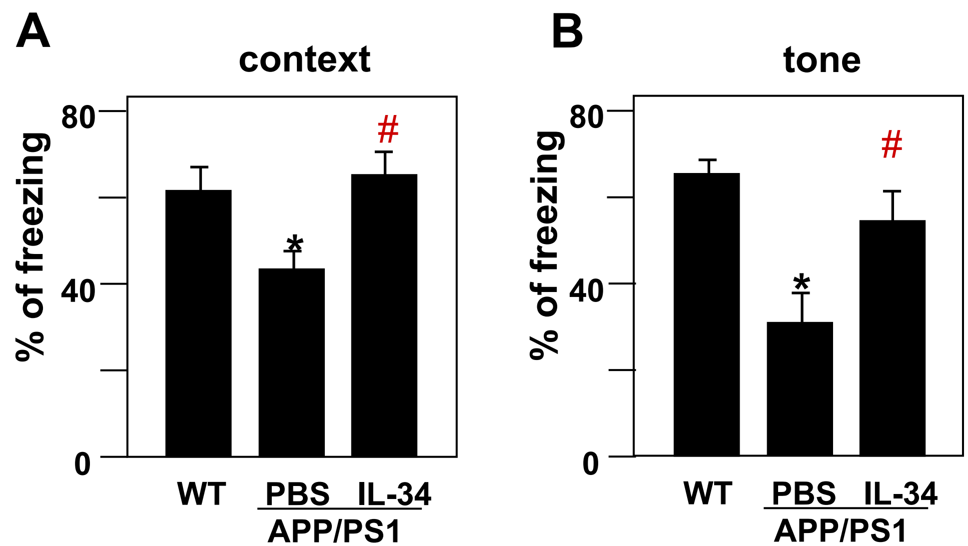
恐怖付け学習試験



contextual learning test
associative learning
(hippocampal)



cued (tone) learning test
(amygdala)



神経細胞ーミクログリア相互作用を利用した新しい神経変性疾患治療薬の創生

１. ミクログリア由来の神経傷害因子の抑制

Takeuchi H, et al. **Blockade of gap junction hemichannel suppresses disease progression in mouse models of amyotrophic lateral sclerosis and Alzheimer's disease.** PLoS One. 2011;6(6):e21108.

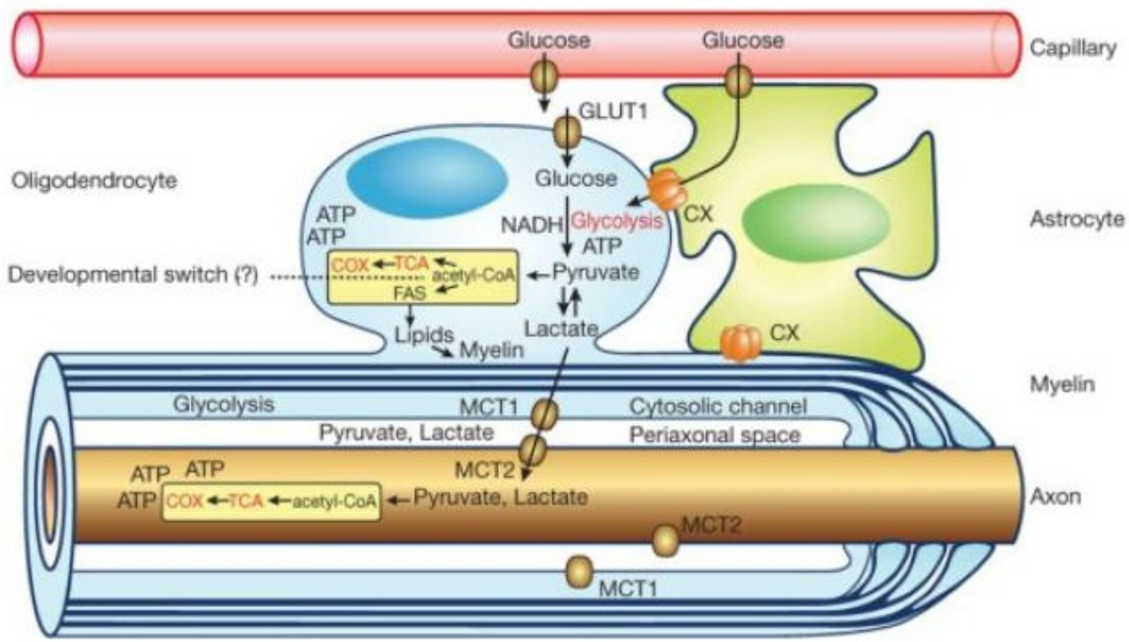
２. ミクログリア由来の神経保護因子の増強

Doi Y et al. **Microglia activated with the toll-like receptor 9 ligand CpG attenuate oligomeric amyloid {beta} neurotoxicity in in vitro and in vivo models of Alzheimer's disease.** Am J Pathol. 2009;175(5):2121-32.

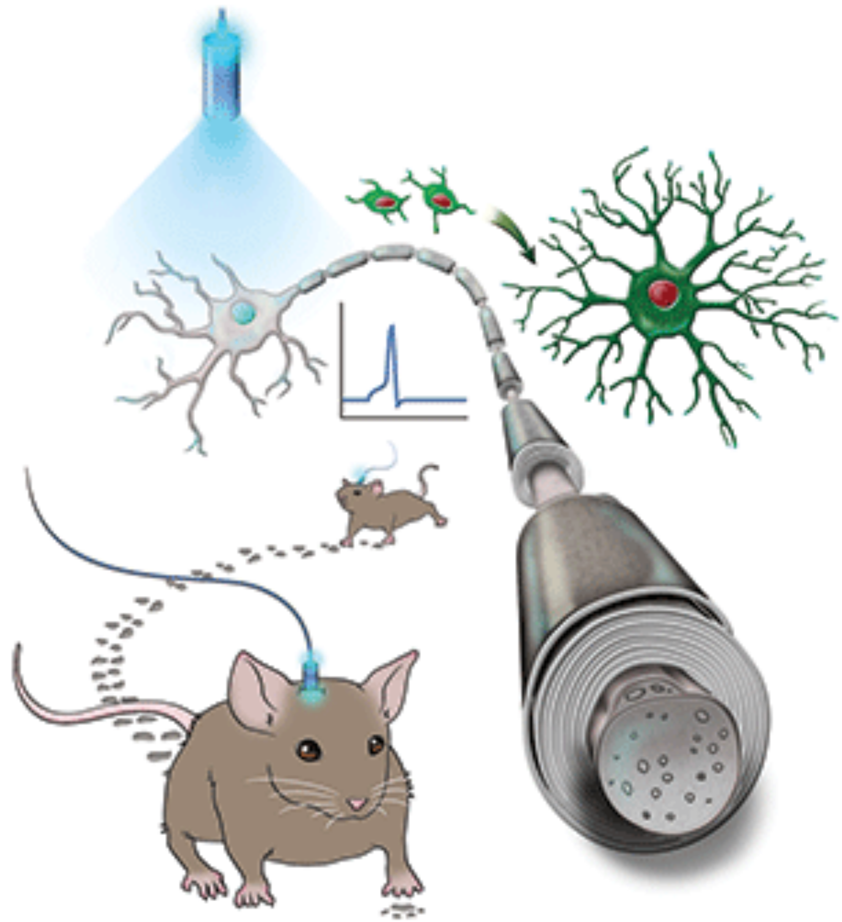
３. 傷害神経細胞由来の保護因子の増強

Mizuno T et al. **Interleukin-34 selectively enhances the neuroprotective effects of microglia to attenuate oligomeric amyloid-β neurotoxicity.** Am J Pathol. 2011;179(4):2016-27

オリゴデンドロサイト一神経相関



Glycolytic oligodendrocytes maintain myelin and long-term axonal integrity. Fünfschilling U et al. Nature. 2012;485(7399):517-21



Neuronal Activity Promotes Oligodendrogenesis and Adaptive Myelination in the Mammalian Brain

Gibson EM et al.
Science 2 May 2014:
Vol. 344 no. 6183

Thy1-channelrhodopsin 2 mice

神経細胞ーミクログリア相互作用を利用した新しい神経変性疾患治療薬の創生

１. ミクログリア由来の神経傷害因子の抑制

２. ミクログリア由来の神経保護因子の増強

３. 傷害神経細胞由来の保護因子の増強

グリア（オリゴデンドロサイト、アストロサイト）-神経相関

謝辞

名古屋第二赤十字病院神経内科　：阿部鏡太郎、柳　務　部長
名古屋大学第一内科　：祖父江逸郎　教授
Pennsylvania大学　神経内科　：Prof. Silberberg, Lisak, Zweimann, Lavi
藤田保健衛生大学神経内科　：山本纊子、丸野内 棣　教授、澤田　誠先生
奈良医大　神経内科　：高柳哲也教授
名古屋大学環研　神経免疫


RIEM
Research Institute of Enviromental Medicine
Nagoya University


水野
竹内

哀悼


高柳哲也教授定年記