Supplementary Material

Supplementary Methods

Brain concentrations of p75^{NTR} ligands

Brain concentration of LM11A-31 was previously described [1]. Using the same protocols, CNS bioavailability of LM11A-24 was assessed in 3-month old male CD-1 mice. Food was withheld from the mice for a minimum of 12 h prior to dosing until 4 h post-dose when food was returned. Water was supplied *ad libitum*. LM11A-24 was administered at 50 mg/kg by oral gavage and mice were sacrificed at 15, 30, 60, 120, or 240 min after dosing (n=3 mice per time-point). Brain concentration of LM11A-24 was determined by liquid chromatography/mass spectroscopy at Absorption Systems. Test accuracy was verified by generating a standard curve in which known amounts of LM11A-24 were added to blank brain extract.

p38 western blotting

Hippocampal neurons at *in vitro* day (DIV) 21-22 were incubated for 4 h in fresh neurobasal/B27 culture media (CM) alone or containing 5 μM oligomeric $A\beta_{42}$ in the presence or absence of NGF (100 ng/ml, ~4 nM) or LM11A-31 (100 nM). Following incubation, cells were harvested in RIPA buffer (20 mM Tris, pH 8.0, 137 mM NaCl, 1% NP-40, 10% glycerol, 1 mM PMSF, 500 μM orthovanadate, 10 μg/ml aprotinin, and 1 μg/ml leupeptin), and whole-cell extracts were then prepared. Lysates were resolved by electrophoresis, transferred to a PVDF membrane, and probed with rabbit anti-phospho-p38 (1:1000; Cell Signaling). Immunoblots were processed using the ECL Chemiluminescence System (Amersham) and bands were

quantitated by densitometry. Data was analyzed using a one-way ANOVA with Dunnett Multiple Comparisons test. Significance was set at $p<0.05$. For the figure, **p or $^{++}$p is <0.01.

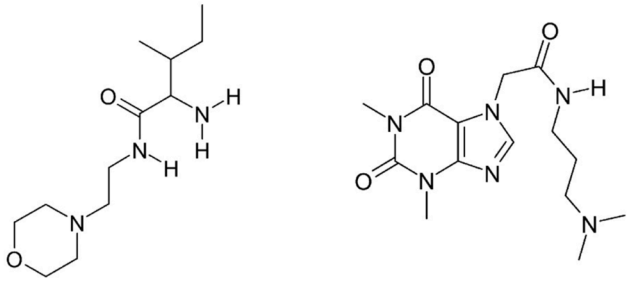
Supplementary References

[1] Massa SM, Xie Y, Yang T, Harrington AW, Kim ML, Yoon SO, Kraemer R, Moore LA, Hempstead BL, Longo FM (2006) Small, nonpeptide p75NTR ligands induce survival signaling and inhibit proNGF-induced death. *J Neurosci* **26**, 5288-5300.

[2] Knowles JK, Simmons DA, Nguyen TV, Vander Griend L, Xie Y, Zhang H, Yang T, Pollak J, Chang T, Arancio O, Buckwalter MS, Wyss-Coray T, Massa SM, Longo FM (2013) A small molecule p75 ligand prevents cognitive deficits and neurite degeneration in an Alzheimer's mouse model. *Neurobiol Aging* **34**, 2052-2063.

[3] Yang T, Knowles JK, Lu Q, Zhang H, Arancio O, Moore LA, Chang T, Wang Q, Andreasson K, Rajadas J, Fuller GG, Xie Y, Massa SM, Longo FM (2008) Small molecule, non-peptide p75 ligands inhibit Abeta-induced neurodegeneration and synaptic impairment. *PLoS One* **3**, e3604.

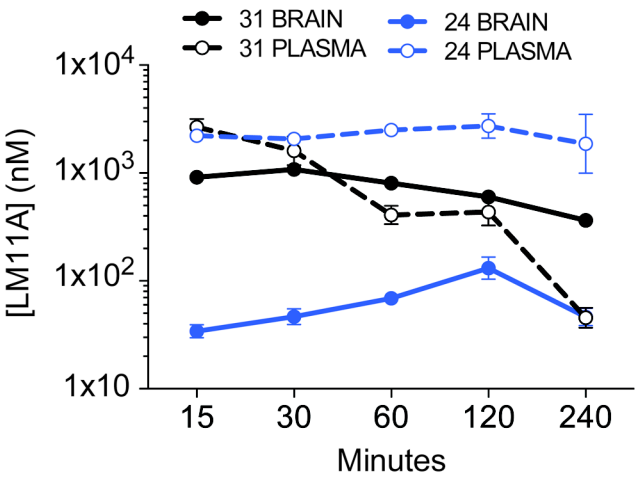
A



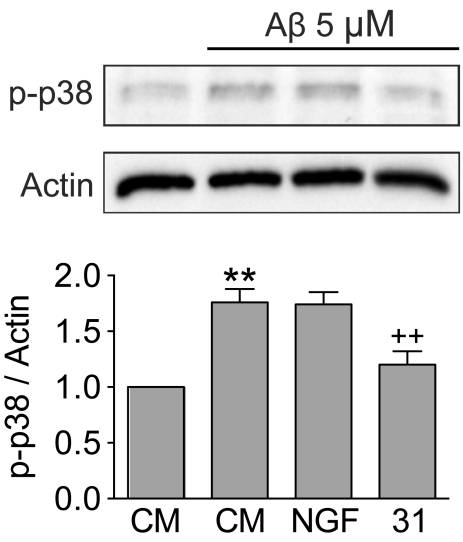
LM11A-31 LM11A-24

LM11A compound structures from Massa et al. 2006 J Neurosci

B



LM11A-31 data from Knowles et al. 2013 Neurobiol Aging


Aβ 5 μM
p-p38
Actin
p-p38 / Actin
2.0
1.5
1.0
0.5
0.0
**
++
CM
CM
NGF
31

Cerep compound ID	% Inhibition of control specific binding	
	LM11A-31 (10 μM)	**LM11A-24 (10 μM)**
A1 (h)	-10	2
A2A (h)	-9	11
A3 (h)	-6	14
α1 (non-selective)	4	-12
α2 (non-selective)	-4	4
β1 (h)	-1	3
β2 (h)	-3	-2
AT1 (h)	-7	14
BZD (central)	-2	-10
B2 (h)	-5	9
CB1 (h)	11	13
CCKA (h) (CCK1)	-17	---
D1 (h)	-2	15
D2S (h)	8	-6
ETA (h)	4	-5
GABA (non-selective)	-2	17
GAL2 (h)	3	-43
CXCR2 (h) (IL-8B)	-2	-4
CCR1 (h)	0	-8
Ghrelin (h) (GHS)	-8	---
H1 (h)	-2	-2
H2 (h)	7	-5
MC4 (h)	-7	-7
MT1 (h)	1	18
M1 (h)	-2	4
M2 (h)	-3	-3
M3 (h)	0	-5
NK2 (h)	-6	-2
NK3 (h)	-2	5
Y1 (h)	-13	-11
Y2 (h)	-3	0
NT1 (h) (NTS1)	-3	7
δ2 (h) (DOP)	-1	21
κ (KOP)	0	-4
μ (h) (MOP) (agonist site)	10	0
ORL1 (h) (NOP)	-8	-9
TXA2/PGH2 (h) (TP)	1	-1
5-HT1A (h)	-2	2
5-HT1B	-3	0
5-HT2A (h)	1	-14
5-HT2B (h)	---	-3
5-HT3 (h)	0	-7
5-HT5A (h)	-2	-13
5-HT6 (h)	-2	-3
5-HT7 (h)	-3	-6
sst (non-selective)	-5	-13
VIP1 (h) (VPAC1)	1	-6
V1a (h)	2	-2
Ca2+ channel (L, verapamil site) (phenylalkylamines)	5	-10
K+ V channel	-7	0
SK+ Ca channel	-3	4
Na+ channel (site 2)	5	-32
Cl channel	-6	-17
NE transporter (h)	-9	4
DA transporter (h)	1	3
5-HT transporter (h)	1	8

LM11A-31 data were previously published (Yang et al. 2008 PLoS ONE)