FGL Peptide and BCL

Two Neural Cell Adhesion Molecule (NCAM)-derived Peptides as Novel Neuroprotective Peptides and FGF Receptor Ligands

The synthetic NCAM-derived peptide, FGL, modulates the transcriptional response to traumatic brain injury

Cerebral responses to traumatic brain injury (TBI) include up- and downregulation of a vast number of proteins involved in endogenous inflammatory responses and defense mechanisms developing postinjury. The present study analyzed the global gene expression profile in response to cryo-induced TBI by means of microarray analysis. Adolescent rats were subjected to TBI and treated with either placebo or a neural cell adhesion molecule (NCAM)-derived fibroblast growth factor receptor (FGFR) agonist, FGL peptide, which has been demonstrated to have neuroprotective effects. mRNA levels were measured at various time-points postlesion (6h, 1 day and 4 days). The effects of injury, treatment, and injury-treatment interaction were observed. TBI alone rendered a large number of genes affected. Analysis of lesion and treatment interactions resulted in a clear effect of the interaction between injury and FGL-treatment compared to injury and placebo-treatment. Genes affected by TBI alone included inflammation markers, protein kinases, ion channel members and growth factors. Genes encoding regulators of apoptosis, signal transduction and metabolism were altered by the interaction between FGL-treatment and TBI. FGL-treatment in non-injured animals rendered genes regulating signaling, transport and cytoskeleton maintenance significantly increased. Thus, the hypothesis of a putative neuroprotective role of FGL was supported by our findings.

Pedersen MV, et al. Neurosci Lett. 2008 May 30;437(2):148-153

Phoenix offers:

FGL peptide

pGlu - Val - Tyr - Val - Val - Ala - Glu - Asn - Gln - Gln - Gly- Lys - Ser - Lys - Ala

FGFR ligand

FGL ala peptide

pGlu - Val - Tyr - Val - Val - Ala - Glu - Asn - Ala - Ala - Gly- Lys - Ser - Lys - Ala

Gly [9,10] replaced with Ala
No biological activity
Can be used as a negative control

BCL

Asn - Leu - Ile - Lys - Gln - Asp - Asp - Gly - Gly - Ser - Pro - Ile - Arg - His - Tyr

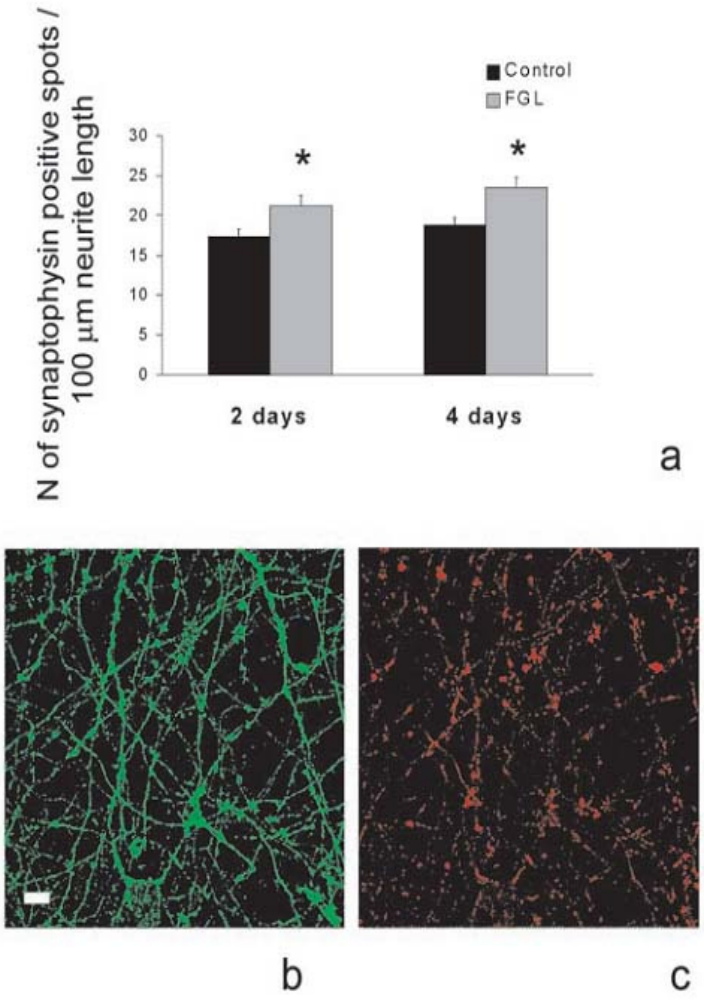
PHOENIX PHARMACEUTICALS, INC.
330 BEACH ROAD, BURLINGAME CA, 94010, USA
PHONE: (650) 558-8898 EMAIL: info@phoenixpeptide.com
WWW.PHOENIXPEPTIDE.COM

PHOENIX EUROPE GMBH
VIKTORIASTRASSE 3-5, D-76133 KARLSRUHE, GERMANY
PHONE: +49-721-1611950 EMAIL: germany@phoenixpeptide.com
WWW.PHOENIXPEPTIDE.COM

A Peptide Motif from the Second Fibronectin Module of the Neural Cell Adhesion Molecule, NCAM, NLIKQDDGGSPIRHY, is a Binding Site for the FGF Receptor

The mechanism of fibroblast growth factor receptor (FGFR) activation by the neural cell adhesion molecule (NCAM) is not well understood. A motif in the second NCAM fibronectin type III (FN3) module, termed FGL, has by means of nuclear magnetic resonance (NMR) and surface plasmon resonance (SPR) analyses been demonstrated to be involved in NCAM-FGFR interactions. An FGFR activation motif (FRM) in the first NCAM FN3 module also has been suggested to take part in NCAM interactions with FGFR. Here, we show for the first time that a peptide motif in the second NCAM FN3 module, different from the previously described FGL motif (NLIKQDDGGSPIRHY; termed BCL) binds and activates FGFR and induces FGFR-dependent neurite outgrowth in cultures of cerebellar granule neurons. Our results provide evidence that the BCL motif is one of the multiple FGFR binding sites in NCAM.

Jacobsen J, et al. Neurochem Res. 2008 Mar 27. [Epub ahead of print]



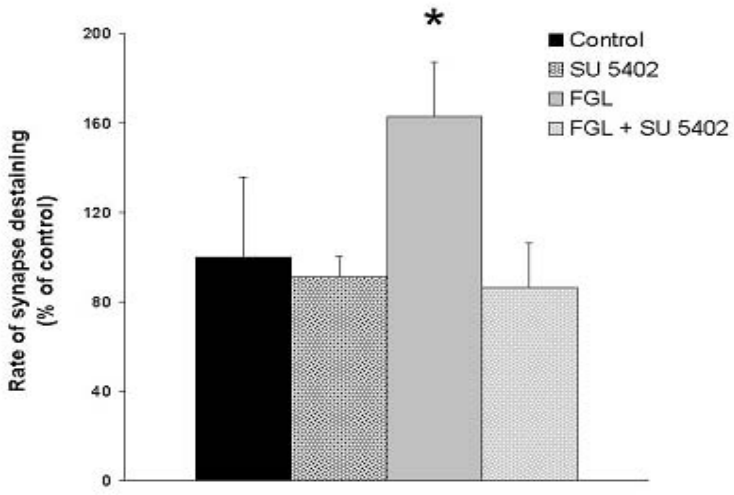


Figure 4. The FGL-enhanced presynaptic function is abrogated by the FGFR inhibitor SU5402. Hippocampal cultures were treated with 20 μg/ml FGL for 48 hr in the presence or absence of 10 μg/ml SU5402. Results from five to eight independent experiments are expressed as a percentage $\pm$ SEM, with untreated controls set at 100%. *$p < 0.05$ when FGL plus SU5402-treated cells were compared with FGL-treated cells.

A novel anti-inflammatory role of NCAM-derived mimetic peptide, FGL.

Age-related cognitive deficits in hippocampus are correlated with neuroinflammatory changes, typified by increased pro-inflammatory cytokine production and microglial activation. We provide evidence that the neural cell adhesion molecule (NCAM)-derived mimetic peptide, FG loop (FGL), acts as a novel anti-inflammatory agent. Administration of FGL to aged rats attenuated the increased expression of markers of activated microglia, the increase in pro-inflammatory interleukin-1beta (IL-1beta) and the impairment in long-term potentiation (LTP). We report that the age-related increase in microglial activation was accompanied by decreased expression of neuronal CD200, and suggest that the proclivity of FGL to suppress microglial activation is due to its stimulatory effect on neuronal CD200. We demonstrate that FGL enhanced interleukin-4 (IL-4) release from glial cells and IL-4 in turn enhanced neuronal CD200 in vitro. We provide evidence that the increase in CD200 is reliant on IL-4-induced extracellular signal-regulated kinase (ERK) signal transduction. These findings provide the first evidence of a role for FGL as an anti-inflammatory agent and identify a mechanism by which FGL controls microglial activation.

Downer EJ, et al. Neurobiol Aging. 2008 May 9. [Epub ahead of print]

Dendritic Spine and Synapse Morphological Alterations Induced by a Neural Cell Adhesion Molecule (NCAM) Mimetic.

The neural cell adhesion molecule (NCAM) is a glycoprotein expressed on the surface of neurons and glial cells. It plays a key role in morphogenesis of the nervous system, regeneration of damaged neural tissue and synaptic plasticity. The extracellular domain of NCAM engages in homophilic interactions (NCAM binding to NCAM) and in heterophilic interactions between NCAM and other proteins such as the fibroblast growth factor (FGF) receptor. It promotes synaptogenesis and activity-dependent remodelling of synapses but less is know of its influence on synaptic and dendritic morphology. Recently, quantitative electron microscopy and 3-dimensional reconstruction (3-D) of ultrathin serial sections has been used to examine the morphology of synapses and dendritic spines in the hippocampus of rats treated with a neural cell adhesion molecule-derived fibroblast growth factor receptor agonist, FGL-peptide (an NCAM mimetic). These data show clearly that the FGL peptide has marked influences on both spine and synaptic form.

Stewart M, et al. Neurochem Res. 2008 Mar 13

An NCAM-derived FGF-receptor agonist, the FGL-peptide, induces neurite outgrowth and neuronal survival in primary rat neurons.

The Neural Cell Adhesion Molecule (NCAM) plays a crucial role in development of the central nervous system regulating cell migration, differentiation and synaptogenesis. NCAM mediates cell-cell adhesion through homophilic NCAM binding, subsequently resulting in activation of the fibroblast growth factor receptor (FGFR). NCAM-mediated adhesion leads to activation of various intracellular signal transduction pathways, including the Ras-mitogen activated protein kinase (MAPK) and the phosphatidylinositol-3-kinase (PI3K)-Akt pathways. A synthetic peptide derived from the second fibronectin type III module of NCAM, the FGL peptide, binds to and induces phosphorylation of FGFR without prior homophilic NCAM binding. We here present evidence that this peptide is able to mimic NCAM heterophilic binding to the FGFR by inducing neuronal differentiation as reflected by neurite outgrowth through a direct interaction with FGFR in primary cultures of three different neuronal cell types all expressing FGFR subtype 1: dopaminergic, hippocampal and cerebellar granule neurons. Moreover, we show that the FGL peptide promotes neuronal survival upon induction of cell death in the same three cell types. The effects of the FGL peptide are shown to depend on activation of FGFR and the MAPK and PI3K intracellular signalling pathways, all three kinases being necessary for the effects of FGL on neurite outgrowth and neuronal survival.

Neiiendam JL et al, J Neurochem. 2004 Nov;91(4):920-35.

A cell adhesion molecule mimetic, FGL peptide, induces alterations in synapse and dendritic spine structure in the dentate gyrus of aged rats: a three-dimensional ultrastructural study.

The FGL peptide is a neural cell adhesion molecule (NCAM) mimetic comprising a 15-amino-acid-long sequence of the FG loop region of the second fibronectin type III module of NCAM. It corresponds to the binding site of NCAM for the fibroblast growth factor receptor 1. FGL improves cognitive function through enhancement of synaptic function. We examined the effect of FGL on synaptic and dendritic structure in the brains of aged (22-month-old) rats that were injected subcutaneously (8 mg/kg) at 2-day intervals until 19 days after the start of the experiment. Animals were perfused with fixative, brains removed and coronal sections cut at 50 microm. The hippocampal volume was measured, tissue embedded and ultrathin sections viewed in a JEOL 1010 electron microscope. Analyses were made of synaptic and dendritic parameters following three-dimensional reconstruction via images from a series of approximately 100 serial ultrathin sections. FGL affected neither hippocampal volume nor spine or synaptic density in the middle molecular layer of the dentate gyrus. However, it increased the ratio of mushroom to thin spines, number of multivesicular bodies and also increased the frequency of appearance of coated pits. Three-dimensional analysis showed a significant decrease in both post-synaptic density and apposition zone curvature of mushroom spines following FGL treatment, whereas for thin spines the convexity of the apposition zone increased. These data indicate that FGL induces large changes in the fine structure of synapses and dendritic spines in hippocampus of aged rats, complementing data showing its effect on cognitive processes.

Popov VI, et al. Eur J Neurosci. 2008 Jan;27(2):301-14

Chronic stress in adulthood followed by intermittent stress impairs spatial memory and the survival of newborn hippocampal cells in aging animals: prevention by FGL, a peptide mimetic of neural cell adhesion molecule.

In this study, we examined whether chronic stress in adulthood can exert long-term effects on spatial-cognitive abilities and on the survival of newborn hippocampal cells in aging animals. Male Wistar rats were subjected to chronic unpredictable stress at midlife (12 months old) and then reexposed each week to a stress stimulus. When evaluated in the water maze at the early stages of aging (18 months old), chronic unpredictable stress accelerated spatial-cognitive decline, an effect that was accompanied by a reduction in the survival of newborn cells and in the number of adult granular cells in the hippocampus. Interestingly, spatial-memory performance in the Morris water maze was positively correlated with the number of newborn cells that survived in the dentate gyrus: better spatial memory in the water maze was associated with more 5-bromo-2-deoxyuridine (BrdU)-labeled cells. Administration of FGL, a peptide mimetic of neural cell adhesion molecule, during the 4 weeks of continuous stress not only prevented the deleterious effects of chronic stress on spatial memory, but also reduced the survival of the newly generated hippocampal cells in aging animals. FGL treatment did not, however, prevent the decrease in the total number of granular neurons that resulted from prolonged exposure to stress. These findings suggest that the development of new drugs that mimic neural cell adhesion molecule activity might be of therapeutic relevance to treat stress-induced cognitive impairment.

Borcel E, et al. Behav Pharmacol. 2008 Feb;19(1):41-9.

CATALOG #	PRODUCT NAME	STANDARD SIZE
033-35	MGF (Human)	100 µg
073-32	FGF-21 (Mouse), recombinant	100 ug
073-32A	FGF-21 (Mouse), recombinant	1 mg
073-32B	FGF-21 (Mouse), recombinant	10 µg
073-33	FGF-21 (Human), recombinant	10 µg
073-33C	FGF-21 (Human), recombinant	1mg
073-36	FGL Peptide	100 ug
073-37	FGLala	100 ug
073-38	BCL	100 ug
B-073-36	FGL Ppeptide - Biotin Labeled	20 µg
B-073-38	BCL - Biotin Labeled	20 µg
B-G-033-35	MGF (Human) - Purified IgG Biotin Labeled	100 µl
FC3-033-35	MGF (Human) - Cy3 Labeled	1 nmol
FC3-073-36	FGL Ppeptide - Cy3 Labeled	1 nmol
FC3-073-38	BCL - Cy3 Labeled	1 nmol
FC3-G-033-35	MGF (Human) - Cy3 Labeled purified IgG	100µl
FC5-033-35	MGF (Human) - Cy5 Labeled	1 nmol
FC5-073-36	FGL Ppeptide - Cy5 Labeled	1 nmol
FC5-073-38	BCL - Cy5 Labeled	1 nmol
FC5-G-033-35	MGF (Human) - Cy5 Labeled Purified IgG	100 ul
FG-033-35A	MGF (Human) - FAM Labeled	1 nmol
FG-073-36A	FGL Ppeptide - FAM Labeled	1 nmol
FG-073-36B	FGL Ppeptide - FITC Labeled	1 nmol
FG-073-38A	BCL - FAM Labeled	1 nmol
FG-073-38B	BCL - FITC Labeled	1 nmol
FG-G-033-35A	MGF (Human) - FAM Labeled Purified IgG	100 ul
FG-G-033-35B	MGF (Human) - FITC Labeled Purified Goat IgG	100 ul
FR-033-35	MGF (Human) - Rhodamine Labeled	1 nmol
FR-073-36	FGL Ppeptide - Rhodamine Labeled	1 nmol
FR-073-38	BCL - Rhodamine Labeled	1 nmol
FR-G-033-35	MGF (Human) - Rhodamine Labeled Purified IgG	100 µl
G-033-35	MGF (Human) - Purified IgG Antibody	200 µg
H-033-35	MGF (Human) - Antibody for Immunohistochemistry	100 µl
MRK-073-33	FGF-21 (Human) - Magnetic Bead RIA kit	1 kit
RK-073-32	FGF-21 (Mouse) - RIA Kit	1 kit
RK-073-33	FGF-21 (Human) - RIA Kit	1 kit
T-033-35	MGF (Human) - Iodine 125 Labeled Tracer	10 µCi
T-073-32	FGF-21 (Mouse), recombinant	10 uCi
T-073-33	FGF-21 (Human) - I-125 Labeled	10 µCi
T-073-36	FGL Ppeptide - Iodine 125 Labeled Tracer	10 uCi
T-073-38	BCL - Iodine 125 Labeled Tracer	10 µCi
T-G-033-35	MGF (Human) - Iodine 125 Labeled Purified IgG Tracer	10 µCi
WBK-073-33	FGF-21 (Human) - Western Blot Kit	1 kit