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(57) Abrégé/Abstract:
The present invention relates to new peptide compounds capable of binding to fibroblast growth factor receptor (FGFR), said compounds comprising two individual amino acid sequences, wherein at least one of the two amino acid sequences is capable of binding to FGFR. The invention discloses the amino acid sequences of the compounds and features pharmaceutical compositions comprising thereof. Invention also relates to uses of the compounds and pharmaceutical compositions comprising thereof for the treatment or prevention of different pathological conditions, wherein FGFR plays a role in pathology and/or recovery from the disease. New peptide compounds of the invention are obtainable by the ligand presenting assembly (LPA) method.

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(54) Title: COMPOUNDS COMPRISING LPA

(57) Abstract: The present invention relates to new peptide compounds capable of binding to fibroblast growth factor receptor (FGFR), said compounds comprising two individual amino acid sequences, wherein at least one of the two amino acid sequences is capable of binding to FGFR. The invention discloses the amino acid sequences of the compounds and features pharmaceutical compositions comprising thereof. Invention also relates to uses of the compounds and pharmaceutical compositions comprising thereof for the treatment or prevention of different pathological conditions, wherein FGFR plays a role in pathology and/or recovery from the disease. New peptide compounds of the invention are obtainable by the ligand presenting assembly (LPA) method.

tions can affect intracellular signalling. Their ability to influence developmental events, including cell migration, proliferation, and differentiation may therefore result from both their adhesive and signalling properties.

The neural cell adhesion molecule, NCAM, was the first discovered neural CAM. Since the discovery NCAM has been intensively studied and now it is well characterised (Ronn et al. (2000) Int J Dev Neurosci 18:193-9) NCAM belongs to the immunoglobulin (Ig) superfamily. Its extracellular part consists of five Ig-like and two fibronectin type III (F3) modules. NCAM assists both the cell-cell and cell-substratum interactions. NCAM binds to various extracellular matrix components such as heparin/heparan sulfate, chondroitin sulfate proteoglycans, and different types of collagen. Cell-cell interactions are mostly assisted by the NCAM homophilic interaction. The different modules of NCAM have been shown to perform distinct functions. Thus, NCAM homophilic binding is now believed to depend on the first three Ig modules. The heparin binding sequence is localised to the Ig2 module. NCAM also binds to the neural cell adhesion molecule L1. This interaction is believed to take place between the fourth Ig module of NCAM and an oligomannosidic moiety expressed on L1. The two membrane-proximal F3 modules of NCAM have been shown involved in fibroblast growth factor receptor (FGFR) binding.

A number of research groups has now accumulated a large body of evidence indicating that intracellular signalling cascades underlying the NCAM-mediated axonal outgrowth are similar to signal transduction cascades which are activated due to stimulation of FGFR (Povlsen et al. (2003) Neurochem Res 1:127-41).

Fibroblast growth factor receptors (FGFRs) are a family of four closely related receptor protein tyrosine kinases consisting extracellularly of three Ig-like modules and intracellularly of a split tyrosine-kinase module (Powers et al. (2000) Endocr Relat Cancer 7:165-97). The receptors are known as key regulators of morphogenesis, development, angiogenesis, and wound healing. FGFR activation and signalling are dependent on dimerization of the receptor which is induced by high affinity binding of FGFR natural ligand, fibroblast growth factor (FGF), and it also requires participation of cell surface heparin or heparan sulphate proteoglycans. Fibroblast growth factors (FGFs) and their receptors constitute an elaborate signaling system that participates in many developmental and repair processes of virtually all mammalian tissues, in particular, they play a prominent role in functioning of the peripheral and

central neural system. Thus, among 23 members of the FGF family, ten have been identified in the brain (Jungnickel et al, (2004) Mol Cell Neurosci. 25:21-9; Reuss and von Bohlen und Halbach (2003) Cell Tissue Res. 313:139-57).

NCAM has recently been regarded as a member of a new class of putative alternative ligands of FGFR, the low affinity binding ligands. There has been obtained evidence for a direct interaction between NCAM and the receptor (Kiselyov et al. (2003) Structure (Camb) 11:691-701).

The identified NCAM fragment having the sequence EVYVVAENQQGKSKA (FGL peptide) involved in the direct interaction between NCAM and FGFR has recently been suggested as a new candidate drug for the treatment of a variety of pathologic disorders where the regulation of activity of FGFR may play the key role (WO 03/016351). WO 03/016351 describes some biological effects of the FGL peptide due to binding and activating FGFR. According to WO 03/016351, presentation of a single copy (monomer) of the peptide to neuronal cells in vitro is enough to promote cell survival and differentiation. However, rather a high concentration of the peptide is needed to achieve the effects.

Multiple presentation of peptide sequences, e.g. antigenic peptides, has been shown to be a valuable mean to amplify biological responses of peptide sequences in vitro (Berezin and Bock (2004) J Mol Neurosci.22:33-39; Ronn et al (1999) Nat Biotechnol 17:1000-5), and it has also been effectively used in animal models in vivo (Cambon et al. (2004) J Neurosci. 17:4197-204).

Synthetic dendritic polymers of biologically active peptide sequences are now used in research and some clinical applications. A dendritic polymer consists of a number of copies of a monomeric peptide sequence, which is attached to a core molecule at multiple sites forming thereby a branching polymer. Lysine is most commonly used amino acid in the core matrix because it has two reactive amino groups available for branching reactions. The multimerization of peptide sequences on the lysine core is known as the *multiple antigen peptide* (MAP) presentation. A method for the synthesis of MAP(s) (dendrimeric peptides) was described in PCT/US90/02039.

In general, two routs can be used for the synthesis of a dendrimeric peptide, namely the direct and indirect route. In both cases, the C-terminal core is first assembled on a solid support using bi-protected Boc-Lys(Boc) in case of Boc chemistry, or Fmoc-

Lys(Fmoc) in the case of Fmoc chemistry in order to obtain the desired degree of branching.

In the direct route synthesis is done by stepwise assembling of the particular peptide on the lysinyl core by the well-known Merrifield method. This stepwise method produces peptides with a C to N orientation. The peptide chains may be synthesised in tandem, or, alternatively, each peptide can be synthesised on the different lysine arms of the core using orthogonal deprotection methods.

Although this approach for dendrimeric peptide synthesis is convenient, the quality of the final product may be questionable and problems of obtaining a well-defined product have been widely discussed in the literature. Problems arise during chain assembly. The MAP type dendrimers are macromolecules, where each single peptide chains may uncontrolled interact with each other and prevent thereby high efficiency coupling to the core leading to production of non-homogenous compound, which require effort to purification. Characterisation of these products by, e.g. electrospray mass spectroscopy (ES-MS) is difficult and as a result, dendritic peptide products are often used without full characterisation.

In the indirect route the synthesis is done by coupling of purified unprotected peptide fragments to the core matrix. Two general methods for this type of ligation may be used, which, respectively, are based on thiol and carbonyl chemistries.

The thiol chemistry may be carried out by incorporation of chloroacetyl group(s) on the lysine matrix and subsequent coupling to a purified, synthetic N-terminal cysteinyl peptide to yield a dendrimer with unambiguous structure. The reverse placement may be achieved with thiol on the core matrix by using an S-acetyl group on the lysinyl core and the haloacetyl group on the peptide. In the carbonyl chemistry the condensation takes place between a carbonyl group and a weak base. There are two types of weak bases, which may be used for this reaction. The first includes hydroxylamines and hydrazines, and the second includes 1,2-di-substituted moieties such as 1,2-aminoethanthiol and 1,2-aminoethanol. The last two groups are found in N-terminal Cys and Thr or Ser respectively, and the condensation products are thiazolidine and oxazolidine. The carbonyl group on the core matrix may be obtained by periodate oxidation of N-terminal Ser, Thr or Cys. Both methods are well known in

the art (see e. g. Lu et al., (1991) Mol Immunol 28:623-630; Defoort et al., (1992) Int J Pept Prot Res 40:214-221; Drijfhout et al. (1991) Int J Pept Prot Res 37:27-32).

Another problem associated with the MAP type compounds is orientation of peptide chains. In the direct route with stepwise assembling of the desired peptide on the lysinyl core only a compound having peptide chains with C to N orientation can only be obtained. The indirect route allows the both orientations, C to N and N to C, but the process has other major disadvantages, e. g. undesirable side reactions due to oxidation of disulphides, leading to impure products, interference with cystein residues present in the native peptide chains, and the procedure demands optimisation for every synthesis.

Finding the optimal number of multiplication of a peptide sequence is another problem to be solved. Most studies of dendritic peptide polymers synthesised by the MAP method have been carried out using tetra- or octameric polymers. However, application of the compounds comprising 4-8 sequences of 15 or more amino acids in vivo is challenged by a problem of the capability of a compound to penetrate the blood-brain barrier, which is crucial if the compound is for the treatment of the brain. Dimers of the peptide sequences may be a solution to this problem, in case the dimers possess biological activity of the dendritic tetramer analogues. Production and use of biologically active peptide dimers comprising different linkers is also well known in the art (see e.g. WO00/18791, WO00/24770).

Summary of invention

Although, a dendrimeric version of the FGL peptide consisting of four sequences of FGL has been shown to be effective in vivo in rat (Cambon et al. (2004) J Neurosci. 17:4197-204), the athours of the present invention found that it is preliminary to consider using of the dendrimer as a drug candidate for the treatment of human patients. Final purification of the dendritic tetramer of the FGL peptide revealed that the product of the MAP synthesis is highly heterogenous and its characterisation is difficult. To solve this problem the authors of the present invention attempted to synthesise different dimers of FGF, using known synthetic procedures. Surprisingly, the only FGL dimer that had biological activity similar to the FGL dendrimer was a dimer produced by the ligand presenting assembly method (LPA), as disclosed in

WO00/18791. Other dimers of FGL, such as a dimer wherein the FGL sequences were linked by a Cys residue, as disclosed in Goodwin et al. (1998) Bioorg Med Chem Lett 8:2231-2234, or by a Lys residue, as disclosed in Rajagopalan et al. (1995) Int J Pept Protein Res 45:173-179, did not have same activity.

Accordingly, in the first aspect the present invention relates to a compound comprising two individual peptide sequences, wherein at least one of the two individual sequences comprises an amino acid sequence of the formula

L1-A-L2-B-L3-C-L4-D-L5

wherein

one of A, B, C, D is selected from a hydrophobic amino acid residue,

one of A, B, C, D is selected from a basic amino acid residue, Asn or Gln,

one of A, B, C, D is selected from an acidic amino acid residue, Asn or Gln,

one of A, B, C, D is Gly or Ala, and

L1, L2, L3, L4 and L5 is selected from a chemical bond or an amino acid sequence having n amino acid residues, wherein n is an integer of from 0 to 5,

said two peptide sequences being connected to each other through a linker of the general formula

X[(A)nCOOH][(B)mCOOH]

n and m independently are an integer of from 1 to 20,

X is HN, $H_2N(CR_2)pCR$, $RHN(CR_2)pCR$, $HO(CR_2)pCR$, $HS(CR_2)pCR$, halogen-$(CR_2)pCR$, $HOOC(CR_2)pCR$, $ROOC(CR_2)pCR$, $HCO(CR_2)pCR$, $RCO(CR_2)pCR$, $[HOOC(A)n][HOOC(B)m]CR(CR_2)pCR$, $H_2N(CR_2)p$, $RHN(CR_2)p$, $HO(CR_2)p$, $HS(CR_2)p$, halogen-$(CR_2)p$, $HOOC(CR_2)p$, $ROOC(CR_2)p$, $HCO(CR_2)p$, $RCO(CR_2)p$, or $[HOOC(A)n][HOOC(B)m](CR_2)p$, wherein p is 0 or integer of from 1 to 20,

A and B independently are a substituted or unsubstituted C_{1-10} alkyl, a substituted or unsubstituted C_{2-10} alkenyl, a substituted or unsubstituted cyclic moiety, a substituted or unsubstituted heterocyclic moiety, a substituted or unsubstituted aromatic moiety, or A and B together form a substituted or unsubstituted cyclic moiety, substituted or unsubstituted heterocyclic moiety, substituted or unsubstituted aromatic moiety.

The above compound is according to the invention is obtainable by the LPA method.

In another aspect, the invention relates to a pharmaceutical composition comprising a compound as defined above.

In still another aspect, the invention concerns using the above compound for the manufacture of a medicament for

a) treatment of conditions of the central and peripheral nervous system associated with postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression;

b) treatment of diseases or conditions of the muscles including conditions with impaired function of neuro-muscular connections, such as after organ transplantation, or such as genetic or traumatic atrophic muscle disorders; or for treatment of diseases or conditions of various organs, such as degenerative conditions of the gonads, of the pancreas such as diabetes mellitus type I and II, of the kidney such as nephrosis and of the heart, liver and bowel;

c) promotion of wound-healing;

d) prevention of death of heart muscle cells, such as after acute myocardial infarction, or after angiogenesis;

e) promotion of revascularsation;

f) stimulation of the ability to learn and/or the short and/or long-term memory;

g) prevention of cell death due to ischemia;

h) prevention of body damages due to alcohol consumption;

i) treatment of prion diseases;

j) treatment of cancer.

Description of Drawings

Figure 1 shows the flow chart of the synthesis of the LPA-type FGL dimer (FGL_L)

Figure 2 presents the HPLC purification profile of FGL_L

Figure 3 presents the HPLC purification profile of FGL_D

Figure 4 demonstrates the effect of the FGL peptide on survival of primary neurons treated with various neurotoxic agents.

Dopaminergic neurons (DN) (**a** and **b**) from day 15 rat embryos grown at a density of 150,000 cells/cm^2 for six days without or with various concentrations of peptide on 24-well cell culture plates coated with poly-D-lysine were exposed to 100 µM 6-OHDA for two hours. Medium was changed and various concentrations of FGL_d were added. The neurons were grown for another 24 hours before the cultures they were fixed and immunostained for tyrosine hydroxylase.

Hippocampal neurons (HN) (**c** and **d**) from day 19 rat embryos were seeded at a density of 40,000 cells/cm^2 on poly-L-lysine coated 8-well permanox chamber slides and grown for 24 hours in medium containing 20 µM Amyloid-β 25-35 peptide (Aβ 25-35) at the presence of various concentrations of FGL_d, before they were fixed and stained with Hoechst 33258.

Cerebella granular meurons (CGN) (**e** and **f**) from postnatal day 7 rats were grown at a density of 100,000 cells/cm^2 for 7 days on poly-L-lysine coated microtiter plates in the medium containing 40 mM KCl, then the medium was substituted to a 5 mM KCl containing medium suplemented with various concentrations of FGL_d. After two days of incubation, the cultures were fixed and stained with Hoechst 33258.

(a) - Effect of 10 ng/ml GDNF on survival of dopaminergic neurons treated with 6-OHDA.

(b) Effect of various concentrations of FGL_d on survival of dopaminergic neurons treated with 6-OHDA.

(c) Effect of 50 ng/ml BDNF on hippocampal cultures treated with Aβ 25-35.

(d) Effect of various concentrations of FGL_d on survival of hippocampal neurons treated with Aβ 25-35.

(e) Effect of 50 ng/ml IGF-1 on CGN cultures induced to undergo apoptosis by depriving the neurons of high potassium.

(f) Effect of various concentrations of FGLd on CGN cultures induced to undergo apoptosis.

Results from at least four independent experiments for each type of culture are expressed as percentage ± SEM of live neurons as compared to the total number of neurons. Control cultures induced to undergo cell death without FGL-treatment were set at 100 %. + $p<0.05$, ++ $p<0.01$ when compared to the untreated controls. * $p<0.05$, ** $p<0.01$ and *** $p<0.001$ when compared to the cultures induced to undergo cell death.

Figure 5 demonstrates the effect of the FGL peptide on DNA-fragmentation in CGN cultures induced to undergo apoptosis by changing the medium after the neurons were grown for six days in high KCl medium (40 mM) to a low KCl medium (5 mM KCl). The number of neurons with fragmented DNA was measured using the Apo-Alert apoptosis detection kit and the fraction of TUNEL-positive neurons was estimated by counting. Results from at least four independent experiments are shown as percentage of cells showing DNA-fragmentation relative to the total number of cells ± SEM with control cultures in low KCl set at 100 %.

(a) Effect of depriving CGN cultures of high KCl on number of cells undergoing apoptosis.

(b) Effect of FGLd in apoptosis-induced CGN cultures.

* $p<0.05$, ** $p<0.01$ and *** $p<0.001$ when compared to low KCl-treated CGN cultures.

Figure 6 shows the effect of FGL on phosphorylation of Erk1/2. CGN were grown for three days at a density of 290,000 cells/cm^2 on poly-L-lysine coated microtiter plates, were subsequently treated with FGL_d for 10 - 90 min, fixed and stained with antibodies against phospho-p42/44. The total number of neurons was estimated using crystal violet staining. Results from at least three independent experiments are expressed as percentage ± SEM with untreated cultures set at 100 %. * $p<0.05$ and ** $p<0.01$ when compared to the controls.

Figure 7 shows the effect of FGL on phosphorylation of Akt. CGN were grown for three days at a density of 290,000 cells/cm^2 on poly-L-lysine coated microtiter plates, were subsequently treated with FGL_L at various concentrations for 10 or 30 minutes respectively and subsequently fixed and stained with antibodies against Akt phosphorylated on Ser473. The total number of neurons was estimated using crystal violet staining. Results from at least three independent experiments are expressed as percentage ± SEM with untreated cultures set at 100 %. * $p<0.05$ when compared to the controls.

Figure 8 shows the effect of inhibitors of FGFR, MEK and PI3K on FGL-induced survival of CGN induced to undergo apoptosis. CGN were grown at a density of 100,000 cells/cm^2 for seven days on poly-L-lysine coated 8-well permanox slides in medium containing 40 mM KCl, before the medium was changed to a 5 mM KCl containing medium together with FGL_d. Thereafter the MEK inhibitor PD98059 (●), PI3K inhibitor LY294002 (▲) and FGFR inhibitor SU5402 (■) were added at various concentrations. The addition of the inhibitors followed in all cases by the addition of 10 µg/ml FGL_d. After two days of incubation with the peptide and inhibitors, the cultures were fixed and stained with Hoechst 33258. Results from at least four individual experiments are shown as percentage of the number of live neurons relative to the total number of neurons ± SEM, with control cultures treated with FGL_d set at 100 %.

Figure 9 shows the effect of the FGL peptide on neurite outgrowth from dopaminergic (●), hippocampal (▲) and cerebellar granule neurons (■). Dopaminergic neurons were grown at a density of 100,000 cells/cm^2 on poly-D-lysine coated 24-well cell culture plates for 72 hours with various concentrations of FGL_d. The cultures were subsequently immunostained for tyrosine hydroxylase. Hippocampal neurons and CGN were plated at a density of 10,000 cells/cm^2 on 8-well permanox chamber slides and incubated for 24 hours in the presence of various concentrations of FGL_d. Subsequently the neurons were immunostained for GAP-43. Results from at least five independent experiments for each neuronal culture are shown as percentage ± SEM with the untreated controls set at 100 %. * $p<0.05$, ** $p<0.01$, *** $p<0.001$ when compared to the controls.

Figure 10 shows the effect of three dimeric versions of the FGL peptide on neurite outgrowth of hippocampal neurons from newborn rats. Primary cultures of hippocampal neurons were grown for 24 hours at a density of 10,000 cells/cm^2 with various concentrations of FGL_L (■), FGL_{lys} (▲) or FGL_{cys} (●) and then were immunostained for GAP-43. Results from at least four independent experiments are shown as percentage ± SEM with untreated controls set at 100 %. ** $p<0.01$ when compared to the controls.

Figure 11 shows the effect of inhibitors of FGFR, MEK and PI3K on FGL-induced neurite outgrowth in CGN cultures. CGN cultures were grown for 24 hours at a density of 10,000 cells/cm^2 on 8-well permanox slides in the presence of the FGL peptide and an inhibitor. PD98059 (●) was added at concentrations of 12.5, 25 and 50 µM simultaneously with 10 µg/ml FGL_d; LY294002 (▲) was added at concentrations of 3.5, 7 and 10 µM simultaneously with 27 µg/ml FGL_d. SU5402 (■) was added in concentrations of 20, 40 and 80 µM simultaneously with 27 µg/ml FGL_d. After the treatment cells were fixed and immunostained for GAP-43. Results from at least four independent experiments are shown as percentage ± SEM, with FGLd-treated control cultures set at 100 %. The dashed line indicates the average neurite length in cultures without FGL_d-treatment. * $p<0.05$, ** $p<0.01$ when compared to the FGL_d-treated controls.

Figure 12 shows the effect of FGL_d, $FGL_{control}$ and vehicle on the rate of FM 1-43 destaining of primary cultures of hippocampal neurons from E19 rats. Each value represents the mean of 4-8 experiments and error bars indicate S.E.M. Neither treatment with 5 µg/ml FGL_d for any time period, nor the treatment with 20 µg/ml for 24 hours had any effect on the rate of FM 1-43 unloading. In contrast, synapses in cultures treated with 20 µg/ml FGL_d for 1 hour and 48 hours showed a significantly increased rate of FM 1-43 unloading when compared to control cultures, indicating an enhanced presynaptic response in these cultures. The values were compared using an unpaired t-test. *p= 0.04 (1h) and **p = 0.0032 (48h). $FGL_{control}$ is a control peptide consisting the sequence EVYVVAENAAGKSKA (SEQ ID NO: 147). Mutation of Gln residues of the FGL sequence to Ala has been shown to abrogate the FGL activity (Kiselyov et al. 2003 see above. cit).

Figure 13 demonstrates the effect of early sub-occipital administration of FGL_L, FGL_D and $FGL_{control}$ on memory (Social Recognition test) of rats in which cognitive impairment was induced by intracerebroventricular (i.c.v.) -injection of the (25-35) β-amyloid fragment. The results are from the experiment in which the suboccipital administration of 5.0 μg FGL per administration per rat was done at days 7, 10, and 13 after A-β-induced neurotoxicity. The Social Recognition test was performed 21 days after i.c.v. administration of the (25-35) β-amyloid fragment and estimated as the ratio between the times the adult rat spent exploring a juvenile rat during a first (T_1) and a second (T_2) meeting. The number of animals in the groups varied from 4 to 22. The results were analysed using one-way ANOVA ($F(2,27)=15.4$, $P<0.0001$) and significance of results was contingent on achieving a p-value of less than 0.05 (**$p<0.01$), when compared to the A-β/V group (Newman-Keuls post-test). A statistically significant effect was also observed between the control and the V/V-treated group compared to the A-β/V group ($p<0.001$). 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively. 'V/V' stands for the rats received vehicle as replacement of A-β and FGL. $FGL_{control}$ as above.

Figure 14 shows the effect of early suboccipital administration of FGL_L and FGL_d on formation of amyloid burden in the cingulate cortex of rats in which cognitive impairment was induced by i.c.v. -injection of the (25-35) β-amyloid fragment (5.0 μg FGL per administration per rat) on days 7, 10 and 13 after (25-35) β-amyloid (A-β) fragment-induced neurotoxicity. The number of animals in the groups varied from 3 to 13. Results were analysed using one-way ANOVA ($F(2,18)=5.2$, $p=0.016$), and significance of results was contingent on achieving a p-value of less than 0.05 (*$p<0.05$ and **$p<0.01$), when compared with the A-β/V group (Newman-Keuls post-test). A statistically significant difference was observed between the V/V treated group and the A-β/V treated group ($p<0.05$). 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively.

Figure 15 shows the effect of early sub-occipital administration of FGL_L and FGL_d on formation of the amyloid burden in the CA3 area of hippocampus of rats in which cognitive impairment was induced by i.c.v. -injection of the (25-35) β-amyloid fragment (5.0 μg FGL per administration per rat) on days 7, 10 and 13 after (25-35) β-amyloid (A-β) fragment-induced neurotoxicity. The number of animals in the groups

varied from 2 to 12. Results were analysed using one-way ANOVA ($F(2,15)=9.54$, $p=0.002$), and significance of results was contingent on achieving a p-value of less than 0.05 (***$p<0.001$), when compared with the A-β/V group (Newman-Keuls post-test). A statistically significant difference was observed between the V/V treated group and the A-β/V treated group ($p<0.01$). 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively.

Figure 16 shows the effect of early sub-occipital administration of FGL_L and FGL_d on neuronal death in the hippocampus of rats in which cognitive impairment was induced by i.c.v. -injection of the (25-35) β-amyloid fragment. The effect of 5.0 μg FGL per administration per rat, administered sub-occipitally on days 7, 10 and 13 after (25-35) β-amyloid (A-β) fragment-induced toxicity, on neuronal cell death in the CA3 zone of the rat hippocampus. The number of animals in the groups varied from 4 to 8. The results were analysed using one-way ANOVA ($F(3,17)=13.76$, $p<0.001$) and significance of results was contingent on achieving a p-value of less than 0.05 (***$p<0.001$), when compared with the A-β/V group (Newman-Keuls post-test). A statistically significant difference was observed between the Control group and the A-β/V treated group ($p<0.001$). 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively.

Figure 17 demonstrates the effects of 5.0 μg FGL_L (per administration per rat) administered sub-occipitally on days 30, 33, and 36 after (25-35) β-amyloid fragment (A-β)-induced neurotoxicity in the Social Recognition test. The Social Recognition test was performed 44 days after i.c.v. administration of the A-β fragment and estimated as the ratio between the times the adult rat spent exploring a juvenile rat during a first (T_1) and a second (T_2) meeting. The number of animals per group varied from 4 to 5. The results were analysed using unpaired t-test and significance of results was contingent on achieving a p-value of less than 0.05 (*$p<0.05$), when compared to the A-β/V group. A significant impairment of short-term memory was induced by treatment with A-β ($p<0.05$, unpaired t-test between Control and A-β/V). 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively.

Figure 18 shows the effects of 5.0 μg FGL_L (per administration per rat) administered sub-occipitally on days 30, 33 and 36 after A-β fragment-induced neurotoxicity on the amyloid burden in the cingulate cortex of rats. The number of animals per group varied from 3 to 13. The results were analysed using one-way ANOVA ($F(2,12)=18.6$, $P=0.002$) and significance of results was contingent on achieving a p-value of less than 0.05 (***$p<0.001$) when compared with the A-β/V group (Bonferroni's multiple comparison test). A statistically significant difference was observed between the V/V-treated group and the A-β/V-treated group ($p<0.001$). 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively.

Figure 19 shows the effects of 5.0 μg FGL_L (per administration per rat) administered sub-occipitally on days 30, 33 and 36 after (25-35) β-amyloid (A-β) fragment-induced neurotoxicity on the amyloid burden in the CA3 area of hippocampus of rats. The number of animals per group varied from 3 to 5. The results were analysed using one-way ANOVA ($F(2,9)=10.6$, $P=0.004$) and significance of results was contingent on achieving a p-value of less than 0.05 (***$p<0.001$) when compared with the A-β/V group (Newman-Keuls post-test). A statistically significant difference was observed between the Control-treated group and the A-β/V-treated group ($p<0.01$). 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively.

Figure 20 shows the effect of 5.0 μg FGL_L (per administration per rat) administered sub-occipitally on days 7, 10 and 13 after (25-35) β-amyloid (A-β) fragment-induced toxicity on neuronal cell death in the cingulate cortex. The number of animals in the groups varied from 4 to 8. The results were analysed using one-way ANOVA ($F(2,9)=26.9$; $p<0.001$, Newmann-Keuls post-test: A-β/V compared with the control group (***$p<0.001$) and compared with the A-β/FGL_L treated group (**$p<0.01$). Significance of results was contingent on achieving a p-value of less than 0.05, when compared with the A-β/V group (Newman-Keuls post-test). A statistically significant difference was observed between the Control-treated group and the A-β/V-treated group ($p<0.001$). 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively.

Figure 21 shows the effect of three intranasal administrations of vehicle, 200 μg FGL_L, and 400 μg FGL_L per rat, at days 7, 10 and 13 after i.c.v. administration of the (25-35) β-amyloid (A-β) fragment in the Social Recognition test. The social recognition test was performed 21 days after i.c.v. administration of the (25-35) β-amyloid (β-A) fragment and estimated as the ratio between the times the adult rat spent on exploration of a juvenile rat during a first (T_1) and a second (T_2) meeting. Number of animals in the groups varied from 3 to 8. Results are shown as means ± SEM and analysed by unpaired t-test ($p<0.001$ of control vs A-β/V) and one-way ANOVA ($F(2,19)=5.6$; $p=0.01$; Newmann-Keuls post-test, $p<0.05$ of A-β/V vs A-β/$FGL_{L,400}$; and $p>0.05$ of A-β/V vs A-β/$FGL_{L,200}$; whereas $p<0.05$ of A-β/$FGL_{L,400}$ vs A-β/$FGL_{L,200}$). Significance of results was contingent on achieving a p-value of less than 0.05 (*$p<0.05$) when compared to the A-β/V treated group. 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively.

Figure 22 shows the effect of three intranasal administrations of vehicle, 200 μg FGL_L, and 400 μg FGL_L per rat, at days 7, 10 and 13 after i.c.v. administration of the (25-35) β-amyloid (β-A) on neuronal cell death in the cingulate cortex. The number of animals in the groups varied from 4 to 8. The results were analysed using unpaired t-test (of the control group versus the A-β/V-treated group ($p<0.001$) and one-way ANOVA ($F(2,16)=8.6$; $p=0.003$), with Newman-Keuls post-test **$p<0.01$ of A-β/V vs A-β/$FGL_{L,400}$ and $p>0.05$ of A-β/V vs. A-β/$FGL_{L,200}$). Significance of results was contingent on achieving a p-value of less than 0.05 (**$p<0.01$), when compared with the A-β/V treated group. 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively.

Figure 23 shows the effect of 5.9 μg FGL_d administration on rats tested for the Rearing Activity in the Open Field test. The peptide was applied sub-occipitally at days 7, 10, and 13 after the (25-35) β-amyloid fragment induced neurotoxicity. The numbers '1', '2', and '3' indicate the periods of measurement: '1' denotes 1-3 min., '2' denotes 8-10 min., and '3' denotes 18-20 min. 'V/V' indicates that the rats received vehicle as replacement for the (25-35) β-amyloid fragment and FGL_d, The number of animals per group varied from 9 to 11. 'A-β' and 'V' are the abbreviations of the (25-35) β-amyloid fragment and vehicle, respectively. The results were analysed using unpaired t-test and significance of results was contingent on achieving a

p-value of less than 0.05 (*p<0.05, **p<0.01), when compared with the first measurement period (1-3 min.).

Figure 24 shows the results of performance of the Surface Righting Reflex test by rat pups at PND4 after intranasal administration of 2.6 μg FGL_L, FGL_d, or $FGL_{control}$ per pup at PND 1, 2, and 3. The number of litters of each treatment group was six. The results were analysed using one-way ANOVA (F=4.05; P=0.039), and the Newman-Keuls test showed a statistically significant effect of FGL_L (P<0.05) and FGL_d (P<0.05) when compared to the control- and $FGL_{control}$ groups. $FGL_{control}$ as above.

Figure 25 shows the results of performance the Negative Geotaxis Reflex test by rat pups at PND 6 and PND 9 after intranasal administration of 2.6 μg FGL_L, FGL_d, or $FGL_{control}$ per pup at PND 1, 2, and 3. The number of litters of each treatment group was six. The results were analysed using one-way ANOVA (F_{PND6}=5.14; P_{PND6}=0.008). At PND 6, statistically significant effects were observed for the FGL_L (*p<0.05) and FGL_d (**p<0.01) groups, when compared to the control- and FGL_c ($FGL_{control}$) groups. At PND 9, no significant effect of FGL was observed (One-way ANOVA: F_{PND9}=0.94; P_{PND9}=0.44). $FGL_{control}$ as above.

Figure 26 shows the schematic presentation of the time course of in vivo studies.

Figure 27 shows the survival effect of the peptide of SEQ ID NO: 2 (EFloop) in cultures of rat cerebellar granule neurons at low KCl concentration. Control cells were treated with insulin growth factor 1(IGF-1) at the same culture conditions.

Figure 28 shows neuritogenic effect of the EFL peptide (SEQ ID NO: 2) on rat hippocampal neurons in vitro. The length of neurites in the EFL treated cultures is compared to the length of neurites in cultures treated with vehicle (phosphate buffred saline).

Detailed description of the invention

1. Compound

Compounds capable of modulating the function of fibroblast growth factor receptor (FGFR) are of greatest importance in view of development of effective drugs for therapeutic treatment of a variety of diseases and pathologic conditions. Thus, it is an objection of the present invention to provide novel compounds capable of binding to FGFR and modulating the FGFR activity. According to the invention the compounds comprise at least two peptide sequences, wherein at least one of the two sequences comprises a structural motif common for the amino acid sequences capable of low affinity binding to FGFR.

1. Peptide sequences

Thus, in one aspect the invention relates to two individual peptide sequences, wherein at least one of said two individual peptide sequences comprises an amino acid sequence of the formula

L1-A-L2-B-L3-C-L4-D-L5

wherein

one of A, B, C, D is selected from a hydrophobic amino acid residue,

one of A, B, C, D is selected from a basic amino acid residue, Asn or Gln,

one of A, B, C, D is selected from an acidic amino acid residue, Asn or Gln,

one of A, B, C, D is Gly or Ala, and

L1, L2, L3, L4 and L5 is selected from a chemical bond or an amino acid sequence having n amino acid residues, wherein n is an integer of from 0 to 5.

In the present context the standard one-letter code for amino acid residues as well as the standard three-letter code are applied. Abbreviations for amino acids are in accordance with the recommendations in the IUPAC-IUB Joint Commission on Biochemical Nomenclature Eur. J. Biochem, 1984, vol. 184, pp 9-37. Throughout the description and claims either the three letter code or the one letter code for natural amino acids are used. Where the L or D form has not been specified it is to be understood that the amino acid in question has the natural L form, cf. Pure & Appl. Chem. Vol. (56(5) pp 595-624 (1984) or the D form, so that the peptides formed may be constituted of amino acids of L form, D form, or a sequence of mixed L forms and D forms.

Where nothing is specified it is to be understood that the C-terminal amino acid of a peptide of the invention exists as the free carboxylic acid, this may also be specified as "-OH". However, the C-terminal amino acid of a compound of the invention may be the amidated derivative, which is indicated as "-NH_2". Where nothing else is stated the N-terminal amino acid of a polypeptide comprise a free amino-group, this may also be specified as "H-".

Where nothing else is specified amino acid can be selected from any amino acid, whether naturally occurring or not, such as alfa amino acids, beta amino acids, and/or gamma amino acids. Accordingly, the group comprises but are not limited to: Ala, Val, Leu, Ile, Pro, Phe, Trp, Met, Gly, Ser, Thr, Cys, Tyr, Asn, Gln, Asp, Glu, Lys, Arg, His Aib, Nal, Sar, Orn, Lysine analogues, DAP, DAPA and 4Hyp.

Also, according to the invention modifications of the compounds/peptides may be performed, such as for example glycosylation and/or acetylation of the amino acids.

Basic amino acid residues are according to invention represented by the residues of amino acids Arg, Lys, and His, acidic amino acid residues – by the residues of amino acids Glu and Asp, and hydrophobic amino acid residues by the residues of amino acids Leu, Ile, Val, Phe, Trp, and Tyr. In a preferred embodiment a basic amino acid residue is represented by Arg or Lys.

1.1 Length of the peptide sequences

A compound of the invention may comprise two individual peptide fragments comprising together between 6 -160 amino acid residues, such as 6-150 amino acid residues, for example 6-140 amino acid residues, such as 6-130 amino acid residues, for example 6-120 amino acid residues, such as 6-110 amino acid residues, for example 6-100 amino acid residues, such as 6-90 amino acid residues, for example 6-80 amino acid residues, such as 6-70 amino acid residues, for example 6-60 amino acid residues, such as 6-50 amino acid residues, for example 6-40 amino acid residues, such as 6-30 amino acid residues, for example 6-20 amino acid residues, such as 6-10 amino acid residues. Thus, in one embodiment the length of the amino acid sequence of any of the two individual peptide fragments

of a compound may vary. In another embodiment the length of the amino acid sequence of each peptide fragment of a compound may be identical.

The wording "individual peptide fragments/sequences" in the present context means that the peptide fragments/sequences (two or more) are not contiguously connected by a peptide bond in one amino acid sequence, but they may be connected to each other through a linker, such as for example a linker discussed below.

Accordingly, either of the individual peptide sequences of a compound may independently consist of 3-80 amino acid residues, such as 3-70, for example 3-60, such as 3-50 amino acid residues, for example 3-30 amino acid residues, such as 3-20 amino acid residues, for example 3-15 amino acid residues, such as 3-10 amino acid residues

In another embodiment either of the sequences of the compound may independently have the length of between 4-80 amino acid residues, such as 4-70, for example 4-60, such as 4-50 amino acid residues, for example 4-40 amino acid residues, such as 4-30 amino acid residues, for example 4-20 amino acid residues, such as 4-15 amino acid residues.

In further embodiment the sequences may independently have the length of between 5-80 amino acid residues, such as 5-70, for example 5-60, such as 5-50 amino acid residues, for example 5-40 amino acid residues, such as 5-30 amino acid residues, for example 5-20 amino acid residues, such as 5-15 amino acid residues, for example 5-10 amino acid residues.

In yet further embodiment the sequences may independently have the length of between 6-80 amino acid residues, such as 6-70, for example 6-60, such as 6-50 amino acid residues, for example 6-40 amino acid residues, such as 6-30 amino acid residues, for example 6-20 amino acid residues, such as 6-15 amino acid residues, for example 6-10 amino acid residues.

The invention also relates to a compound comprising two individual amino acid sequences, which may independently have the length of between 7-80 amino acid residues, such as 7-70, for example 7-60, such as 7-50 amino acid residues, for

example 7-40 amino acid residues, such as 7-30 amino acid residues, for example 7-20 amino acid residues, such as 7-15 amino acid residues, for example 8, 9, 10, 11, 12, 13, or 14 amino acid residues.

The length of the individual sequences may also be of 8-80 amino acid residues, such as 8-70, for example 8-60, such as 8-50 amino acid residues, for example 8-40 amino acid residues, such as 8-30 amino acid residues, for example 8-20 amino acid residues. Or it may be of 9-80 amino acid residues, such as 9-70 amino acid residues, for example 9-60 amino acid residues, such as 9-50 amino acid residues, for example 9-40 amino acid residues, such as 9-30 amino acid residues, for example 9-20 amino acid residues.

A compound which comprises two individual amino acid sequences, either of which is having the length of between 10-80 amino acid residues, such as 10-70 amino acid residues, for example 10-60 amino acid residues, such as 10-50 amino acid residues, for example 10-40 amino acid residues, such as 10-30 amino acid residues, for example 10-20 amino acid residues is also within the scope of the invention.

In one preferred embodiment a compound comprises two individual amino acid sequences, wherein either of the sequences may independently have the length of between 15-80 amino acid residues, such as 15-70 amino acid residues, for example 15-60 amino acid residues, such as 15-50 amino acid residues, for example 15-40 amino acid residues, such as 15-30 amino acid residues, for example 15-20.

In another preferred embodiment of the invention the minimal length of any of the two of amino acid sequences of the compound may independently be of 16, 17, 18, 19, 20, 21, 22, 23, 24 or 25 amino acid residues, and the maximal is 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 amino acid residues. It is also a preferred compound, wherein the length of any of the two individual sequences is of between 25 and 36 amino acid residues.

In still another preferred embodiment the length of a peptide fragment of the compound may independently be of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acid

residues. The length of an individual peptide fragment in the range of 9 to 20 amino acid residues is most preferred.

In yet another preferred embodiment of the invention at least one of the two peptide sequences of the compound derives from the sequence of a polypeptide selected from the group comprising cell adhesion molecules, cell-surface receptors, heparan sulphate proteoglycans, and metalloproteases, extracellular matrix molecules or growth factors.

2.2 Origin of the peptide sequences

Thus, it is preferred that at least one of the two peptide sequences of the compound is derived from the sequence of a polypeptide selected from the group comprising cell adhesion molecules, cell-surface receptors, heparan sulphate proteoglycans, and metalloproteases, extracellular matrix molecules and growth factors.

The authors of the present invention have recently identified a new class of FGFR ligands, which differ from the FGFR natural high affinity ligands, FGFs, 1) on their capacity of binding to FGFR and 2) on the structure of their binding site for the receptor. New FGFR ligands are capable of low affinity binding to the receptor at a binding site on FGFR, which is also different from the known FGF binding site of the receptor. According to the application, the FGFR binding site of the new low affinity FGFR ligands comprises a sequence comprising the above discussed motif. The new class of FGFR ligands includes according to the application the proteins, which may have a biological function independent on the activity of FGFR. Furthermore, a new low affinity FGFR ligand may have 1) a function that is executed due to its binding and activating FGFR, and 2) a function that is executed through another mechanism. The function (1) and function (2) may have different biological significance. Due to a relatively low affinity of binding to the receptor the new ligands according to invention are not capable to modulate the receptor activation, which has already been initiated by FGF. According to the invention the new group of low affinity FGFR ligands comprises molecules known in the art as cell adhesion molecules, cell-surface receptors, heparan sulphate proteoglycans, and metalloproteases, extracellular matrix molecules or growth factors.

According to the invention the cell adhesion molecule may be selected from the group comprising

- Neural Cell Adhesion Molecule (NCAM) (Swiss-Prot Ass. Nos: P13591, P13595-01, P13595),
- Neural cell adhesion molecule L1 (Swiss-Prot Ass. Nos: Q9QYQ7, Q9QY38, P11627, Q05695, P32004),
- Neural Cell Adhesion Molecule-2 (NCAM-2) (Swiss-Prot Ass. No: P36335)
- Neuron-glia Cell Adhesion Molecule (Ng-CAM) (Swiss-Prot Ass. No: Q03696; Q90933),
- Neural cell adhesion molecule CALL (Swiss-Prot Ass. No: O00533),
- Neuroglian (Swiss-Prot Ass. No: P91767, P20241),
- Nr-CAM (HBRAVO, NRCAM, NR-CAM 12) (Swiss-Prot Ass. Nos: Q92823, O15179, Q9QVN3
- Axonin-1/TAG-1 (Swiss-Prot Ass. Nos: Q02246, P22063, P28685),
- Axonal-associated Cell Adhesion Molecule (AxCAM) (NCBI Ass. No: NP_031544.1; Swiss-Prot Ass. No: Q8TC35),
- Myelin-Associated Glycoprotein (MAG) (Swiss-Prot Ass. No: P20917),
- Neural cell adhesion molecule BIG-1 (Swiss-Prot Ass. No: Q62682),
- Neural cell adhesion molecule BIG-2 (Swiss-Prot Ass. No: Q62845),
- Fasciclin (FAS-2) (Swiss-Prot Ass. No: P22648),
- Neural cell adhesion molecule HNB-3/NB-3 (Swiss-Prot Ass. Nos: Q9UQ52, P97528, Q9JMB8)
- Neural cell adhesion molecule HNB-2/NB-2 (Swiss-Prot Ass. Nos: O94779, P07409, P97527),
- Cadherin (Swiss-Prot Ass. No: Q9VW71),
- Junctional Adhesion Molecule-1 (JAM-1) (Swiss-Prot Ass. Nos: Q9JKD5, O88792),
- Neural cell adhesion F3/F11(Contactin) (Swiss-Prot Ass. Nos: Q63198, P1260, Q12860, Q28106, P14781, O93250),
- Neurofascin (Swiss-Prot Ass. Nos: Q90924, Q91Z60; O42414),
- B-lymphocyte cell adhesion molecule CD22 (Swiss-Prot Ass. Nos: Q9R094, P20273),
- Neogenin (NEO1) (Swiss-Prot Ass. Nos: Q92859, P97603, Q90610, P97798),
- Intercellular Cell Adhesion Molecule-5 (ICAM-5/telencephalin) (Swiss-Prot Ass. Nos: Q8TAM9, Q60625) or

- Galactose binding lectin-12 (galectin-12) (Swiss-Prot Ass. Nos: Q91VD1, Q9JKX2, Q9NZ03),
- Galactose binding lectin-4 (galectin-4) (Swiss-Prot Ass. No: Q8K419; P38552),

or fragments, or variants thereof.

The functional cell-surface receptor may selected from the group comprising

- Fibroblast Growth Factor Receptor 1 (FGFR1) (Swiss-Prot Ass. Nos: Q9QZM7, Q99AVV7, Q9UD50, Q63827),
- Fibroblast Growth Factor Receptor 2 (FGFR2) (Swiss-Prot Ass. Nos: Q96KM2, P21802, Q63241),
- Fibroblast Growth Factor Receptor 3 (FGFR3) (Swiss-Prot Ass. Nos: Q95M13, AF487554, Q99052),
- Fibroblast Growth Factor Receptor 4 (FGFR4) (Swiss-Prot Ass. No: Q91742),
- Neurotrophin Tyrosin Kinase Type-2 (NTRKT-2) (Swiss-Prot Ass. No: Q8WXJ5),
- Leukocyte Antigen Related Protein-Tyrosine Phosphatase (LAR-PTPRF) (Swiss-Prot Ass. Nos: Q9EQ17, Q64605, Q64604, Q9QW67, Q9VIS8 P10586),
- Nephrin (Swiss-Prot Ass. Nos: Q925S5, Q9JIX2, Q9ET59, Q9R044, Q9QZS7, Q06500),
- Protein-Tyrosine Phosphatase Receptor type S (PTPRS) (Swiss-Prot Ass. Nos: Q64699, Q13332, O75870),
- Protein-Tyrosine Phosphatase Receptor type kappa (R-PTP-kappa) (Swiss-Prot Ass. No: Q15262),
- Protein-Tyrosine Phosphatase Receptor type D (PTPRD) (Swiss-Prot Ass. Nos: Q8WX65, Q9IAJ1, P23468, Q64487),
- Ephrin type-A receptor 8 (EPHA8/Tyrosine-Protein Kinase Receptor EEK) (Swiss-Prot Ass. Nos: O09127, P29322),
- Ephrin type-A receptor 3 (EPHA8/Tyrosine-Protein Kinase Receptor ETK-1/CEK4) (Swiss-Prot Ass. No: P29318),
- Ephrin type-A receptor 2 (Swiss-Prot Ass. No: Q8N3Z2)
- Insulin Receptor (IR) (Swiss-Prot Ass. No: Q9PWN6)
- Insulin-like Growth Factor-1 Receptor (IGF-1) (Swiss-Prot Ass. Nos: Q9QVW4, P08069, P24062, Q60751, P15127, P15208)
- Insulin-related Receptor (IRR) (Swiss-Prot Ass. No: P14616),

-Tyrosine-Protein Kinase Receptor Tie-1 (Swiss-Prot Ass. Nos: 06805, P35590, Q06806),

- Roundabout receptor-1 (robo-1) (Swiss-Prot Ass. Nos: O44924, AF041082, Q9Y6N7),
- Neuronal nicotinic acetylcholine receptor alpha 3 subunit (CHRNA3) (Swiss-Prot Ass. Nos: Q8VHH6, P04757, Q8R4G9, P32297)
- Neuronal acetylcholine receptor alpha 6 subunit (Swiss-Prot Ass. Nos: Q15825, Q9R0W9)
- Platelet-Derived Growth Factor Receptor Beta (PDGFRB) (Swiss-Prot Ass. Nos: Q8R406, Q05030),
- Interleukin-6 Receptor (IL-6R) (Swiss-Prot Ass. No: Q00560),
- Interleukin-23 Receptor (IL-23R) (Swiss-Prot Ass. No: AF461422),
- Beta-common cytokine receptor of IL-3, IL5 and GmCsf (Swiss-Prot Ass. No: P32927)
- Cytokine Receptor-Like molecule 3 (CRLF1) (Swiss-Prot Ass. No: Q9JM58),
- Class I Cytokine Receptor (ZCYTOR5) (Swiss-Prot Ass. No: Q9UHH5)
- Netrin-1 receptor DCC (Swiss-Prot Ass. No: P43146),
- Leukocyte Fc Receptor-like Protein (IFGP2) (Swiss-Prot Ass. Nos: Q96PJ6, Q96KM2),
- Macrophage Scavenger Receptor 2 (MSR2) (Swiss-Prot Ass. No: Q91YK7), or
- Granulocyte Colony Stimulating Factor Receptor (G-CSF-R) (Swiss-Prot Ass. No: Q99062),

or fragments, or variants thereof.

The heparan sulphate proteoglycan according to the invention is perlecan (Swiss-Prot Ass. No: P98160), or a fragment, or a variant thereof.

The metalloprotease may be selected from the group comprising

- ADAM-8 (Swiss-Prot Ass. No: Q05910),
- ADAM-19 (Swiss-Prot Ass. Nos: Q9H013, O35674),
- ADAM-8 (Swiss-Prot Ass. No: P78325),
- ADAM-12 (Swiss-Prot Ass. Nos: O43184, Q61824),
- ADAM-28 (Swiss-Prot Ass. Nos: Q9JLN6, Q61824, Q9XSL6, Q9UKQ2),
- ADAM-33 precursor (Swiss-Prot Ass. Nos: Q8R533, Q923W9),
- ADAM-9 (Swiss-Prot Ass. Nos: Q13433, Q61072),

- ADAM-7 (Swiss-Prot Ass. NoS: Q9H2U9, O35227, Q63180),
- ADAM-1A Fertilin alpha (Swiss-Prot Ass. No: Q8R533),
- ADAM-15 (Swiss-Prot Ass. Nos: Q9QYV0, O88839, Q13444),
- Metalloproteinase-desintegrin domain containing protein (TECAM) (Swiss-Prot Ass. No: AF163291),
- Metalloproteinase 1 (Swiss-Prot Ass. Nos: O95204, Q9BSI6),

or fragments, or variants thereof.

The extracellular matrix molecule may selected from the group comprising

- Collagen type VII (Swiss-Prot Ass. No: Q63870),
- Fibronectin (Swiss-Prot Ass. Nos: Q95KV4, Q95KV5, P07589, Q28377, U42594, O95609, P11276), or
- Tenascin-R (Swiss-Prot Ass. Nos: Q15568, O00531, Q90995, P10039),

or fragments, or variants thereof.

The growth factor according to the invention is Cytokine-like factor-1 (CLF-1) (Swiss-Prot Ass. No:O75462), or a fragment, or a variant thereof.

The term " fragment " in the present context is meant a polypeptide having the amino acid sequence, which is about 25 - 99 % of the length of the predetermined protein/polypeptide amino acid sequence, said polypeptide being a fuctional homologue of the predetermined polypeptide selected from the above groups.

The term "variant" in the present content means a polypeptide having the amino acid sequence, which i) is 50-100 % homologous to the sequence of the predetermined polypeptide, and/or ii) comprises other chemical moieties, such various post-translational modifications of amino acid residues, for example phosphorylation, acylation, glycosilation of the amino acids residues, and/or iii) is physically associated with or chemically bound, such as covalently bound, to another biological molecule(s), for example a polypeptide(s), lipid(s) or carbohydrate(s), said polypeptide being a fuctional homologue of the predetermined polypeptide selected from the above groups. The term "physically associated " means that the molecules are associated via hydrophobic or electrostatic interactions.

By the term "functional homologue" of a predetermined polypeptide is in the present context meant a molecule which is capable of one or more biological functions of the predetermined polypeptide, in a preferred embodiment the biological function(s), which is executed through the mechanism of binding and activating FGFR .

As it has been discussed above, a preferred functional cell-surface receptor of the invention is a receptor selected from the family of fibroblast growth factor receptors (FGFRs). The above molecules according to the invention comprise an alternative low affinity binding site for FGFR, which is different from the known FGFR high affinity binding site of FGFs.

A low affinity FGFR binding site of the above molecules is characterised in that it comprises an amino acid sequence which has at least 60 %, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably 95% homology to the sequence EVYVVAENQQGKSKA (SEQ ID NO 1), The sequence EVYVVAENQQGKSKA is derived from the neural cell adhesion molecule (NCAM) and known in the prior art as the FGL peptide of NCAM. The homology of one amino acid sequence with another amino acid sequence is defined as a percentage of identical amino acids in the two collated sequences. The homology between amino acid sequences may be calculated using well known algorithms such as BLOSUM 30, BLOSUM 40, BLOSUM 45, BLOSUM 50, BLOSUM 55, BLOSUM 60, BLOSUM 62, BLOSUM 65, BLOSUM 70, BLOSUM 75, BLOSUM 80, BLOSUM 85, or BLOSUM 90.

In another embodiment, the FGFR binding site of the above molecules comprises an amino acid sequence that has an amino acid sequence having at least 60 %, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably 95% positive amino acid matches compared to to the sequence EVYVVAENQQGKSKA (SEQ ID NO 1). Such sequence is defined by the application as a variant of a predetermined sequence, for example SEQ ID NO: 1. A positive amino acid match is defined as an identity or similarity defined by physical and/or chemical properties of the amino acids having the same position in two compared sequences. Preferred positive amino acid matches of the present invention are K to R, E to D, L to M, Q to E, I to V, I to L, A to S, Y to W, K to Q, S to T, N to S and Q to R.

In still another embodiment an FGFR binding site of a new low affinity binding ligand of FGFR may comprise a fragment or a homologue of the sequence, which

i) has at least 60 %, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably 95% homology to the sequence EVYVVAENQQGKSKA (SEQ ID NO 1), or

ii) has at least 60 %, more preferably at least 70%, more preferably at least 80%, more preferably at least 90%, more preferably 95% positive amino acid matches compared to to the sequence EVYVVAENQQGKSKA (SEQ ID NO 1

In still yet another embodiment the FGFR binding site of a new low affinity FGFR ligand of the invention may be characterised by the specific 3D feature, namely, it may essentially consists of one or more "strand-loop-strand" structural motifs. It is a preferred feature of the sequences discussed above. According to the invention the strand-loop-strand structure is a preferred 3D structure of an amino acid sequence of the formula

L1-A-L2-B-L3-C-L4-D-L5

wherein

one of A, B, C, D is selected from a hydrophobic amino acid residue,

one of A, B, C, D is selected from a basic amino acid residue, Asn or Gln,

one of A, B, C, D is selected from an acidic amino acid residue, Asn or Gln,

one of A, B, C, D is Gly or Ala, and

L1, L2, L3, L4 and L5 is selected from a chemical bond or an amino acid sequence having n amino acid residues, wherein n is an integer of from 0 to 5.

According to the invention at least one of the two individual amino acid sequences preferably comprises at least one of the above identified structural motifs and is preferably derived from any of the above molecules. Such sequence according to the invention may be selected from any of the sequences identified as SEQ ID NOs: 1-146. In some embodiments one of the two individual sequences may be selected from one group of sequences of the groups 1 to 12 as identified below, and another of the two individual sequences may be selected from another group of sequences. In other embodiments the sequences may be selected from the same group of sequences.

Thus, in one embodiment one amino acid sequence of the compound or either of the sequences may be independently selected from the sequences of the group 1:

EVYVVAENQQGKSKA (SEQ ID NO 1),

NIEVWVEAENALGKKV (SEQ ID NO: 2),

ATNRQGKVKAFAHL (SEQ ID NO: 3),

RYVELYVVADSQEFQK (SEQ ID NO: 4)

VAENSRGKNVAKG (SEQ ID NO: 5),

GEYWCVAENQYGQR (SEQ ID NO: 6),

RLAALNGKGLGEIS (SEQ ID NO: 7),

KYIAENMKAQNVAKEI (SEQ ID NO: 8),

TIMGLKPETRYAVR (SEQ ID NO: 9).

In another embodiment at least one of the at least two peptide sequences may be selected from the group 2 consisting of the sequences

NMGIWVQAENALG (SEQ ID NO: 11),

IWVQAENMLG (SEQ ID NO: 12),

EIWVEATNRLG (SEQ ID NO: 13),

VWVQAANALG (SEQ ID NO: 14),

EVWIEKDPAKGRI (SEQ ID NO: 15),

ATNKGGEVKKNGHL (SEQ ID NO: 16).

In still another embodiment at least one of the at least two peptide sequences may be selected from the group 3 consisting of the sequences

KYVELYLVADYLEFQK (SEQ ID NO: 17),

RYVELYVVVDNAEFQ (SEQ ID NO: 18),

KYVELVIVADNREFQR (SEQ ID NO: 19),

KYIEYYLVLDNGEFKR (SEQ ID NO: 20),

RYLELYIVADHTLF (SEQ ID NO: 21),

KYVELFIVADDTVYRR (SEQ ID NO: 24),

KFIELFVVADEYVYRR (SEQ ID NO: 25),

KIVEKVIVADNSEVRK (SEQ ID NO: 26),

VELVIVADHSEAQK (SEQ ID NO: 27)

SEQUENCE LISTING

<110> ENKAM Pharmaceutical A/S

<120> Compounds comprising LPA

<130> P 770 PC00

<160> 146

<170> PatentIn version 3.1

<210> 1

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> NCAM Fn III, 2 [Swiss-Prot: P13591]: FGFR binding motif

<400> 1

Glu Val Tyr Val Val Ala Glu Asn Gln Gln Gly Lys Ser Lys Ala
1 5 10 15

<210> 2

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Interleukin-6 receptor beta chain [Swiss-Prot: Q00560]: FGFR bind
ing motif

<400> 2

Asn Ile Glu Val Trp Val Glu Ala Glu Asn Ala Leu Gly Lys Lys Val
1 5 10 15

<210> 3

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Heparan sulfate proteoglycan perlecan [Swiss-Prot: P98160]: FGFR binding motif

<400> 3

Ala Thr Asn Arg Gln Gly Lys Val Lys Ala Phe Ala His Leu
1 5 10

<210> 4

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Disintegrin and metalloprotease domain 8 (ADAM-8) [Swiss-Prot: Q05910]: FGFR binding motif

<400> 4

Arg Tyr Val Glu Leu Tyr Val Val Ala Asp Ser Gln Glu Phe Gln Lys
1 5 10 15

<210> 5

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Axonal-associated cell adhesion molecule [NCBI: NP_446331]: FGFR binding motif

<400> 5

Val Ala Glu Asn Ser Arg Gly Lys Asn Val Ala Lys Gly
1 5 10

<210> 6

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Myelin-associated glycoprotein (MAG) [Swiss-Prot: P20917]: FGFR binding motif

<400> 6

Gly Glu Tyr Trp Cys Val Ala Glu Asn Gln Tyr Gly Gln Arg
1 5 10

<210> 7

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Neuronal nicotinic acetylcholine receptor alpha 3 subunit (CHRNA 3) [Swiss-Prot: Q8VHH6/P04757:/Q8R4G9/P32297]: FGFR binding motif

<400> 7

Lys Tyr Ile Ala Glu Asn Met Lys Ala Gln Asn Val Ala Lys Glu Ile
1 5 10 15

<210> 8

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> FIII,1 domain of NCAM (Swiss-Prot: P13591): FGFR binding motif

<400> 8

Thr Ile Met Gly Leu Lys Pro Glu Thr Arg Tyr Ala Val Arg
1 5 10

<210> 9

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Granulocyte colony stimulating factor receptor precursor (G-CSF-R; CD114 antigen)[Swiss-Prot: Q99062]: FGFR binding motif

<400> 9

Lys Gly Leu Gly Glu Ile Ser Ala Ala Thr Glu Phe Lys Thr
1 5 10

<210> 10

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> NCAM Fn III, 1 [Swiss-Prot: P13591]: FGFR binding motif

<400> 10

Asn Met Gly Ile Trp Val Gln Ala Glu Asn Ala Leu Gly
1 5 10

<210> 11

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> FIII,1 domain of NCAM [Swiss-Prot: P13591]: FGFR binding motif

<400> 11

Arg Leu Ala Ala Leu Asn Gly Lys Gly Leu Gly Glu Ile Ser
1 5 10

<210> 12

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> Granulocyte colony stimulating factor receptor precursor (G-CSF-R; CD114 antigen) [Swiss-Prot: P40223]: FGFR binding motif

<400> 12

Ile Trp Val Gln Ala Glu Asn Met Leu Gly
1 5 10

<210> 13

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Cytokine-like factor-1 precursor (CLF-1) [Swiss-Prot: O75462]: FGFR binding motif

<400> 13

Glu Ile Trp Val Glu Ala Thr Asn Arg Leu Gly
1 5 10

<210> 14

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> Interleukin-23 receptor (IL-23R) [Q8NFQ9]: FGFR binding motif

<400> 14

Val Trp Val Gln Ala Ala Asn Ala Leu Gly
1 5 10

<210> 15

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Complement factor 1 q , alpha polypeptide (C1QA) [Swiss-Prot: Q9DCM6]: FGFR binding motif

<400> 15

Glu Val Trp Ile Glu Lys Asp Pro Ala Lys Gly Arg Ile
1 5 10

<210> 16

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Fasciclin II precursor (FAS2) [Swiss-Prot: P22648]: FGFR binding motif

<400> 16

Ala Thr Asn Lys Gly Gly Glu Val Lys Lys Asn Gly His Leu
1 5 10

<210> 17

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-19 precursor (EC 3.4.24.-) [Swiss-Prot: Q9H013/O35674]: FGFR binding motif

<400> 17

Lys Tyr Val Glu Leu Tyr Leu Val Ala Asp Tyr Leu Glu Phe Gln Lys
1 5 10 15

<210> 18

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-8 precursor (EC 3.4.24.-) [Swiss-Prot: P78325]: FGFR binding motif

<400> 18

Arg Tyr Val Glu Leu Tyr Val Val Val Asp Asn Ala Glu Phe Gln
1 5 10 15

<210> 19

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-12 precursor (EC 3.4.24.-)[Swiss-Prot: O43184; Q61824]: FGFR binding motif

<400> 19

Lys Tyr Val Glu Leu Val Ile Val Ala Asp Asn Arg Glu Phe Gln Arg
1 5 10 15

<210> 20

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Metalloproteinase-disintegrin domain containing protein TECADAM [AF163291] : FGFR binding motif

<400> 20

Lys Tyr Ile Glu Tyr Tyr Val Val Leu Asp Asn Gly Glu Phe Lys Lys
1 5 10 15

<210> 21

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-33 precursor (EC 3.4.24.-)[Swiss-Prot: Q9BZ11/Q923W9]: FGFR binding motif

<400> 21

Arg Tyr Leu Glu Leu Tyr Ile Val Ala Asp His Thr Leu Phe
1 5 10

<210> 22

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-1A Fertilin alpha [Swiss-Prot: Q8R533]: FGFR binding motif

<400> 22

Lys Tyr Val Glu Met Phe Val Val Val Asn His Gln Arg Phe Gln
1 5 10 15

<210> 23

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-9 [Swiss-Prot: Q13433; Q61072]: FGFR binding motif

<400> 23

Arg Tyr Val Glu Leu Phe Ile Val Val Asp Lys Glu Arg Tyr
1 5 10

<210> 24

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-7 precursor [Swiss-Prot: Q9H2U9]: FGFR binding motif

<400> 24

Lys Tyr Val Glu Leu Phe Ile Val Ala Asp Asp Thr Val Tyr Arg Arg
1 5 10 15

<210> 25

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-7 precursor [Swiss-Prot: O35227; Q63180]: FGFR binding motif

<400> 25

Lys Phe Ile Glu Leu Phe Val Val Ala Asp Glu Tyr Val Tyr Arg Arg
1 5 10 15

<210> 26

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-15 precursor [Swiss-Prot: Q9QYV0; O88839]: FGFR binding motif

<400> 26

Lys Ile Val Glu Lys Val Ile Val Ala Asp Asn Ser Glu Val Arg Lys
1 5 10 15

<210> 27

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> ADAM-15 precursor [Swiss-Prot: Q13444]: FGFR binding motif

<400> 27

Val Glu Leu Val Ile Val Ala Asp His Ser Glu Ala Gln Lys
1 5 10

<210> 28

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Neural cell adhesion protein BIG-2 precursor [Swiss-Prot: Q62845]
: FGFR binding motif

<400> 28

Val Ala Glu Asn Ser Arg Gly Lys Asn Ile Ala Lys Gly
1 5 10

<210> 29

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Neuronal glycoprotein CNTN3 [Swiss-Prot: Q07409]: FGFR binding mo
tif

<400> 29

Ile Ala Glu Asn Ser Arg Gly Lys Asn Val Ala Arg Gly
1 5 10

<210> 30

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> NB-2(HNB-2/NB-2), a neural cell recognition molecule of the conta
ctin/F3 subgroup [Swiss-Prot: O94779/P97527]: FGFR binding motif

<400> 30

Ala Glu Asn Ser Arg Gly Lys Asn Ser Phe Arg Gly
1 5 10

<210> 31

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> HNB-3/NB-3 [Swiss-Prot: Q9UQ52/P97528/Q9JMB8]: FGFR binding motif

<400> 31

Ile Ala Ser Asn Leu Arg Gly Arg Asn Leu Ala Lys Gly
1 5 10

<210> 32

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Putative fat-like cadherin precursor (Drosiphila) [Swiss-Prot: Q9VW71]: FGFR binding motif

<400> 32

Ile Pro Glu Asn Ser Leu Gly Lys Thr Tyr Ala Lys Gly
1 5 10

<210> 33

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Neuronal nicotinic acetylcholine receptor alpha 3 subunit (CHRNA3) [Swiss-Prot: Q8VHH6/P04757/Q8R4G9/P32297]: FGFR binding motif

<400> 33

Ile Ala Glu Asn Met Lys Ala Gln Asn Glu Ala Lys
1 5 10

<210> 34

<211> 16

<212> PRT

<213> Artificial sequence

<220>

<223> Neuronal acetylcholine receptor protein, alpha-6 chain precursor (CHRNA6) [Swiss-prot:Q15825]: FGFR binding motif

<400> 34

Gln Phe Ile Ala Glu Asn Met Lys Ser His Asn Glu Thr Lys Glu Val
1 5 10 15

<210> 35

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> ROBO-1 [O44924]: FGFR binding motif

<400> 35

Gly Glu Tyr Trp Cys Val Ala Lys Asn Arg Val Gly Gln
1 5 10

<210> 36

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> ROBO-1[AF041082; Q9Y6N7]: FGFR binding motif

<400> 36

Gly Ser Tyr Thr Cys Val Ala Glu Asn Met Val Gly Lys
1 5 10

<210> 37

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> ROBO-1[AF041082; Q9Y6N7]: FGFR binding motif

<400> 37

Gly Lys Tyr Val Cys Val Gly Thr Asn Met Val Gly Glu Arg
1 5 10

<210> 38

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> FGFR2 [Q96KM2; P21802]: FGFR binding motif

<400> 38

Asn Tyr Thr Cys Val Val Glu Asn Glu Tyr Gly
1 5 10

<210> 39

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> FGFR2[Q63241]: FGFR binding site

<400> 39

Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly

1 5 10

<210> 40

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Fc receptor-like protein 1[Q96KM2] / fragment of IFGP 1 [Q96PJ6]: FGFR binding motif

<400> 40

Gln Tyr Tyr Cys Val Ala Glu Asn Gly Tyr Gly
1 5 10

<210> 41

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Junctional adhesion molecule (JAM-1) [Q9JKD5/O88792]: FGFR binding motif

<400> 41

Gly Glu Tyr Tyr Gln Glu Ala Glu Gln Asn Gly Tyr Gly
1 5 10

<210> 42

<211> 12

<212> PRT

<213> Artificial sequence

<400> 42

Gly Asn Tyr Thr Cys Leu Val Glu Asn Glu Tyr Gly
1 5 10

<210> 43

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Contactin precursor (Neural adhesion molecule F3) [Q63198;/P1260; Q12860]: FGFR binding motif

<400> 43

Gly Met Tyr Gln Cys Leu Ala Glu Asn Ala Tyr Gly
1 5 10

<210> 44

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Contactin precursor (Neural adhesion molecule F3/F11) [Q28106]: FGFR binding motif

<400> 44

Gly Met Tyr Gln Cys Ala Glu Asn Thr His Gly
1 5 10

<210> 45

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Contactin precursor (Neural adhesion molecule F3/F11) [Q28106]: FGFR binding motif

<400> 45

Gly Ile Tyr Tyr Cys Leu Ala Ser Asn Asn Tyr Gly
1 5 10

<210> 46

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> IFGP2[Q96PJ5]: FGFR binding motif

<400> 46

Gly Gly Tyr Tyr Cys Thr Ala Asp Asn Ser Tyr Gly
1 5 10

<210> 47

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Neurofascin precursor [Q90924]: FGFR binding motif

<400> 47

Gly Glu Tyr Gln Cys Phe Ala Arg Asn Asp Tyr Gly
1 5 10

<210> 48

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Neurofascin [Q90924]: FGFR binding motif

<400> 48

Gly Glu Tyr Phe Cys Leu Ala Ser Asn Lys Met Gly
1 5 10

<210> 49

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Neurofascin 155 Da isoform [Q91Z60]: FGFR binding motif

<400> 49

Gly Glu Tyr Gln Cys Phe Ala Arg Asn Lys Phe Gly
1 5 10

<210> 50

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Neurofascin 155 Da isoform [Q91Z60]: FGFR binding motif

<400> 50

Gly Glu Tyr Phe Cys Leu Ala Ser Asn Lys Met Gly
1 5 10

<210> 51

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Macrophage scavenger receptor 2 (MSR2) [Q91YK7]:FGFR binding motif

<400> 51

Gly Gly Tyr Tyr Cys Thr Ala Asp Asn Asn Tyr Gly
1 5 10

<210> 52

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Macrophage scavenger receptor 2 (MSR2) [Q91YK7]: FGFR binding motif

<400> 52

Gly Asn Tyr Ser Cys Glu Ala Glu Asn Ala Trp Gly Thr Lys
1 5 10

<210> 53

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Neural cell adhesion molecule L1[Q9QYQ7; Q9QY38; P11627; Q05695; P32004]: FGFR binding motif

<400> 53

Gly Glu Tyr Thr Cys Leu Ala Glu Asn Ser Leu Gly
1 5 10

<210> 54

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Neural-glial cell adhesion molecule Ng-CAM [Q03696]: FGFR binding motif

<400> 54

Gly Glu Tyr Glu Cys Val Ala Glu Asn Gly Arg Leu Gly
1 5 10

<210> 55

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> FGFR3 [Q95M13; AF487554; Q99052]: FGFR binding motif

<400> 55

Gly Asn Tyr Thr Cys Val Val Glu Asn Lys Phe Gly Arg
1 5 10

<210> 56

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> FGFR3 [Q95M13; Q99052]: FGFR binding motif

<400> 56

Gly Glu Tyr Thr Cys Leu Ala Gly Asn Ser Ile Gly
1 5 10

<210> 57

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Neural cell adhesion molecule 2 (NCAM2) [P36335]: FGFR binding mo
tif

<400> 57

Gly Glu Tyr Phe Cys Val Ala Ser Asn Pro Ile Gly
1 5 10

<210> 58

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Neural cell adhesion molecule 2 (NCAM2)[P36335]: FGFR binding mot
if

<400> 58

Glu Tyr Thr Cys Ile Ala Asn Asn Gln Ala Gly Glu
1 5 10

<210> 59

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Axonin-1 (TAG-1) [Q02246;P22063; P28685]: FGFR binding motif

<400> 59

Gly Met Tyr Gln Cys Val Ala Glu Asn Lys His Leu Gly
1 5 10

<210> 60

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Neural cell adhesion molecule NCAM-140 AND ncam-140 [P13595]: FGF R binding motif

<400> 60

Gly Glu Tyr Met Cys Thr Ala Ser Asn Thr Ile Gly Gln
1 5 10

<210> 61

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Neural cell adhesion molecule NCAM-140 AND ncam-140 [P13595]: FGF R binding motif

<400> 61

Glu Tyr Val Cys Ile Ala Glu Asn Lys Ala Gly Glu Gln
1 5 10

<210> 62

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Neurotrophin receptor tyrosin kinase type 2 (NTRKT) [Q8WXJ5]:FGFR binding motif

<400> 62

Gly Asp Tyr Thr Leu Ile Ala Lys Asn Glu Tyr Gly Lys
1 5 10

<210> 63

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Colorectal cancer suppressor DCC [P43146]: FGFR binding motif

<400> 63

Gly Phe Tyr Gln Cys Val Ala Glu Asn Glu Ala Gly
1 5 10

<210> 64

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Tyrosine phosphatase LAR (ptprf) [Q9EQ17; Q64604; P23468]: FGFR b
inding motif

<400> 64

Gly Lys Tyr Glu Cys Val Ala Thr Asn Ser Ala Gly Thr Arg
1 5 10

<210> 65

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Platelet-derived growth factor receptor beta (PDGFRB) [Q8R406; Q0
5030]: FGFR binding motif

<400> 65

Gly Glu Tyr Phe Cys Val Tyr Asn Asn Ser Leu Gly
1 5 10

<210> 66

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Intercellular adhesion molecule-5 (ICAM-5, telencephalin) [Q8TAM9 ; Q60625]: FGFR binding motif

<400> 66

Gly Glu Tyr Glu Cys Ala Ala Thr Asn Ala His Gly Arg
1 5 10

<210> 67

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> B-cell receptor CD22 precursor (Leu-14; B-lymphocyte cell adhesio n molecule) [P20273]: FGFR binding motif

<400> 67

Gly Ala Tyr Trp Cys Gln Gly Thr Asn Ser Val Gly Lys
1 5 10

<210> 68

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> B-cell receptor CD22 precursor (Leu-14; B-lymphocyte cell adhesio
n molecule) [P20273]: FGFR binding motif

<400> 68

Gly Thr Tyr Ser Cys Val Ala Glu Asn Ile Leu Gly
1 5 10

<210> 69

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> NCAM-2 [Swiss-Prot: O15394; O35136]: FGFR binding motif

<400> 69

Arg Val Ala Ala Val Asn Gly Lys Gly Gln Gly Asp Tyr Ser
1 5 10

<210> 70

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> HCF-2 (Host cell factor 2) [Swiss-Prot: Q9Y5Z7]: FGFR binding mot
if: FGFR binding motif

<400> 70

Arg Val Ala Ala Ile Asn Gly Cys Gly Ile Gly Pro Phe Ser
1 5 10

<210> 71

<211> 9

<212> PRT

<213> Artificial sequence

<220>

<223> ICLN (Chloride channel regulator, inducer) [Swiss-Prot: P97506; Q 9NRD2; Q61189; P54105]: FGFR binding motif

<400> 71

Ala Val Leu Asn Gly Lys Gly Leu Gly
1 5

<210> 72

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Galectin-12 [Swiss-Prot: Q91VD1; Q9JKX2; Q9NZ03]: FGFR binding mo tif

<400> 72

Ala Leu Asn Gly Gln Gly Leu Gly Ala Thr Ser
1 5 10

<210> 73

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Human receptor-like protein tyrosine phosphatase leukocyte common antigen-related molecule (PTPRF) [Swiss-Prot: P10586]: FGFR bind ing motif

<400> 73

Arg Leu Ala Ala Lys Asn Arg Ala Gly Leu Gly Glu
1 5 10

<210> 74

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Natural resistance-associated macrophage protein 1(NRAMP-1, SLC11 A1) [Swiss-Prot: O77741]: FGFR binding motif

<400> 74

Arg Leu Gly Val Val Thr Gly Lys Asp Leu Gly Glu Ile
1 5 10

<210> 75

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> NCAM2 (180 kDa isoform precursor) [Swiss-Prot: P36335]: FGFR bin ding motif

<400> 75

Thr Val Thr Gly Leu Lys Pro Glu Thr Ser Tyr Met Val Lys
1 5 10

<210> 76

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Nephrin [Swiss-Prot: Q925S5; Q9JIX2; Q9ET59; Q9R044; Q9QZS7]: FGF R binding motif

<400> 76

Thr Leu Thr Gly Leu Lys Pro Ser Thr Arg Tyr Arg Ile
1 5 10

<210> 77

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Nephrin [Swiss-Prot: O60500]: FGFR binding motif

<400> 77

Thr Leu Thr Gly Leu Gln Pro Ser Thr Arg Tyr Arg Val
1 5 10

<210> 78

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Tyrosine phosphatase LAR (PTPRF) [Swiss-Prot : Q9EQ17]: FGFR binding motif

<400> 78

Thr Leu Leu Gly Leu Lys Pro Asp Thr Thr Tyr Asp Ile Lys
1 5 10

<210> 79

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Leukocyte common antigen-related phosphatase ptp2 precursor (LAR-PTP2) [Swiss-Prot: Q64605]: FGFR binding motif

<400> 79

Thr Leu Gln Gly Leu Arg Pro Glu Thr Ala Tyr Glu Leu Arg

1 5 10

<210> 80

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Protein-tyrosine phosphatase, receptor-type, S precursor (EC 3.1.3.48) (Protein-tyrosine phosphatase sigma) (RPTP-sigma) [Swiss-Prot: Q64699]: FGFR binding motif

<400> 80

Thr Leu Arg Gly Leu Arg Pro Glu Thr Ala Tyr Glu Leu Arg
1 5 10

<210> 81

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Tyrosine-protein kinase receptor Tie-1 precursor (TIE1.) (EC 2.7.1.112) [Swiss-Prot: Q06805; P35590]: FGFR binding motif

<400> 81

Thr Leu Met Asn Leu Arg Pro Lys Thr Gly Tyr Ser Val Arg
1 5 10

<210> 82

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Ephrin type-A receptor 8 precursor to (EPHA8..) (EC 2.7.1.112)(Ty

rosine-protein kinase receptor EEK) (EPH-and ELK-related kinase)]: [Swiss-Prot: O09127; O09127; P29322];FGFR binding motif

<400> 82

Thr Val Ser Gly Leu Lys Pro Gly Thr Arg Tyr
1 5 10

<210> 83

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Ephrin type-A receptor 3 precursor (EC 2.7.1.112) (Tyrosine-protein kinase receptor ETK1) (CEK4) (EPHA3..) [tn: P29318]: FGFR binding motif

<400> 83

Thr Ile Ser Gly Leu Lys Pro Asp Thr Thr Tyr
1 5 10

<210> 84

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Protein-tyrosine phosphatase receptor-type S precursor (EC 3.1.3.48) (Protein-tyrosine phosphatase sigma, PTPRS) [Swiss-Prot: Q13332]: FGFR binding motif

<400> 84

Thr Leu Gln Gly Leu Lys Pro Asp Thr Ala Tyr
1 5 10

<210> 85

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Insulin receptor [Swiss-Prot: Q9PWN6]: FGFR binding motif

<400> 85

Leu Arg Gly Leu Lys Pro Trp Thr Gln Tyr Ala Val
1 5 10

<210> 86

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Type VII collagen [Swiss-Prot: Q63870]: FGFR binding motif

<400> 86

Ile Asp Gly Leu Glu Pro Asp Thr Glu Tyr Ile Val Arg
1 5 10

<210> 87

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Insulin-like growth factor-1 receptor precursor [Swiss-Prot: O737
98]: FGFR binding motif

<400> 87

Leu Gln Gly Leu Lys Pro Trp Thr Gln Tyr Ala Ile
1 5 10

<210> 88

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Fibronectin [Swiss-Prot: Q95KV4; Q95KV5; P07589; Q28377; U42594; O95609]: FGFR binding motif

<400> 88

Thr Ile Thr Gly Leu Glu Pro Gly Thr Glu Tyr Thr Ile Gln
1 5 10

<210> 89

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> Insulin-like growth factor I receptor (IGF I receptor beta-subun it, IGF I receptor alpha-subunit) [Swiss-Prot: Q9QVW4; P08069; P2 4062; Q60751; P15127; P15208]: FGFR binding motif

<400> 89

Gly Leu Lys Pro Trp Thr Gln Tyr Ala Val
1 5 10

<210> 90

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Insulin receptor-related protein precursor (EC 2.7.1.112) (IRR) (IR-related receptor) [Swiss-Prot: P14616]: FGFR binding motif

<400> 90

Thr Leu Ala Ser Leu Lys Pro Trp Thr Gln Tyr Ala Val
1 5 10

<210> 91

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Tenascin-R (restrictin) [Swiss-Prot: Q15568; O00531]: FGFR bindin
g motif

<400> 91

Leu Met Gly Leu Gln Pro Ala Thr Glu Tyr Ile Val
1 5 10

<210> 92

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Neogenin precursor (NEO1..) [Swiss-Prot: Q92859; P97603; Q90610;
P97798]: FGFR binding motif

<400> 92

Lys Gly Met Gly Pro Met Ser Glu Ala Val Gln Phe Arg Thr
1 5 10

<210> 93

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Protein tyrosine phosphatase receptor type D (PTPRD, BA175E13.1)
[Swiss-Prot: Q8WX65; Q9IAJ1; P23468; Q64487]: FGFR binding motif

<400> 93

Thr Leu Thr Gly Leu Lys Pro Asp Thr Thr Tyr Asp Val Lys
1 5 10

<210> 94

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Protein tyrosine phosphatase receptor type D (PTPRD, BA175E13.1)
[Swiss-Prot: Q8WX65; Q9IAJ1; P23468; Q64487]: FGFR binding motif

<400> 94

Ile Ser Gly Leu Gln Pro Glu Thr Ser Tyr Ser Leu
1 5 10

<210> 95

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Protein-tyrosine phosphatase receptor-type F precursor (EC 3.1.3
.48) (LAR protein) (Leukocyte antigen related) [Swiss-Prot: Q6460
4; Q9QW67; P10586]: FGFR binding motif

<400> 95

Thr Leu Leu Gly Leu Lys Pro Asp Thr Thr Tyr Asp Ile Lys
1 5 10

<210> 96

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Protein-tyrosine phosphatase receptor-type F precursor (EC 3.1.3.48) (Leukocyte antigen related) [Swiss-Prot: Q64604; Q9QW67; P10586]: FGFR binding motif

<400> 96

Thr Ile Ser Gly Leu Thr Pro Glu Thr Thr Tyr Ser Ile
1 5 10

<210> 97

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> CD22 [Q9R094]: FGFR binding motif

<400> 97

Gly Asn Tyr Ser Cys Leu Ala Glu Asn Arg Leu Gly Arg
1 5 10

<210> 98

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> FGFR-4 [Q91742]: FGFR binding motif

<400> 98

Gly Asn Tyr Thr Cys Val Val Glu Asn Arg Val Gly
1 5 10

<210> 99

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> ICAM-5 [Q8TAM9]: FGFR binding motif

<400> 99

Gly Thr Tyr His Cys Val Ala Thr Asn Ala His Gly
1 5 10

<210> 100

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> FIII,4 domain of L1: FGFR binding motif [Swiss-Prot: Q9QY38]

<400> 100

Leu Ser His Asn Gly Val Leu Thr Gly Tyr Leu Leu Ser Tyr
1 5 10

<210> 101

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Neuron-glia cell adhesion molecule (Ng-CaM) precursor .[Gallus ga
llus]; [Swiss-Prot: Q90933]: FGFR binding motif

<400> 101

Asn Gly Val Leu Thr Gly Tyr Val Leu Arg Tyr
1 5 10

<210> 102

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Neurofascin precursor .[Gallus gallus]; [Swiss-Prot: O42414]: FGF R binding motif

<400> 102

Asn Gly Val Leu Thr Gly Tyr Asn Leu Arg Tyr
1 5 10

<210> 103

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> (CALL) Neural cell adhesion molecule. [Homo sapiens] .[Swiss-Prot: O00533]: FGFR binding motif

<400> 103

Asn Gly Asn Leu Thr Gly Tyr Leu Leu Gln Tyr
1 5 10

<210> 104

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> f Neuroglian.[Manduca sexta] .[Swiss-Prot: P91767]: FGFR bindin g motif

<400> 104

Val Asp Glu Asn Gly Val Leu Thr Gly Tyr Lys Ile Tyr Tyr
1 5 10

<210> 105

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Protein-tyrosine phosphotase sigma [Swiss-Prot: O75870]; and [Swiss-Prot: Q13332] [Homo sapiens] :FGFR binding motif

<400> 105

Thr His Asn Gly Ala Leu Val Gly Tyr Ser Val Arg Tyr
1 5 10

<210> 106

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> NR-CaM 12 [Rattus sp] , [Swiss-Prot: Q9QVN3]: FGFR binding motif

<400> 106

Asn Gly Ile Leu Thr Glu Tyr Ile Leu Lys Tyr
1 5 10

<210> 107

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Neurofascin 155 kDa isoform.[Rattus norvegicus],[Swiss-Prot: Q91Z60]: FGFR binding motif

<400> 107

Asn Gly Ile Leu Ile Gly Tyr Thr Leu Arg Tyr

1 5 10

<210> 108

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Neogenin (Fragment).[Gallus gallus], [Swiss-Prot: Q90610]: FGFR b
inding motif

<400> 108

Thr His Ser Gly Gln Ile Thr Gly Tyr Lys Ile Arg Tyr
1 5 10

<210> 109

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Neogenin (Fragment).[Gallus gallus], [Swiss-Prot: Q90610]:FGFR bi
nding motif

<400> 109

Asn Gly Lys Ile Thr Gly Tyr Ile Ile Tyr Tyr
1 5 10

<210> 110

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> Metalloprotease 1 (pitrilysin family).[Homo sapiens] [Swiss-Pro
t: Q9BSI6]:FGFR binding motif

<400> 110

Leu Ser His Asn Gly Ile Phe Thr Leu Tyr
1 5 10

<210> 111

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> HBRAVO/Nr-CaM.[Homo sapiens].[Swiss-Prot: Q92823; O15179]: FGFR b
inding motif

<400> 111

Asn Gly Ile Leu Thr Glu Tyr Thr Leu Lys Tyr
1 5 10

<210> 112

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Protein-tyrosine phosphatase kappa precursor (EC 3.1.3.48) (R-PTP
-kappa).[Homo sapiens].[Swiss-Prot: Q15262]: FGFR binding motif

<400> 112

Leu Asp Pro Asn Gly Ile Ile Thr Gln Tyr Glu Ile Ser Tyr
1 5 10

<210> 113

<211> 11

<212> PRT

<213> Artificial sequence

<220>

<223> Neogenin precursor (NEO1..).[Homo sapiens and Mus musculus][Swiss-Prot: Q92859; P97798]: FGFR binding motif

<400> 113

Asn Gly Lys Ile Thr Gly Tyr Ile Ile Tyr Tyr
1 5 10

<210> 114

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> Neural cell adhesion L1(SPLICE ISOFORM 2)[Homo sapiens [Swiss-Prot: P32004]; [Mus musculus Swiss-Prot: Q9QY38]: FGFR binding motif

<400> 114

His Leu Glu Val Gln Ala Phe Asn Gly Arg Gly Ser Gly Pro Ala
1 5 10 15

<210> 115

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> NB-2.[Rattus norvegicus] [Swiss-Prot: P97527]:FGFR binding motif

<400> 115

His Leu Thr Val Arg Ala Tyr Asn Gly Ala Gly Tyr Gly Pro
1 5 10

<210> 116

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> Neural cell adhesion protein BIG-2 precursor.[Rattus norvegicus][Swiss-Prot: Q62845]: FGFR binding motif

<400> 116

His Leu Ser Val Lys Ala Tyr Asn Ser Ala Gly Thr Gly Pro Ser
1 5 10 15

<210> 117

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> Axonal-associated cell adhesion molecule.[Homo sapiens]. [Swiss-Prot: Q8TC35]:FGFR binding motif

<400> 117

His Leu Ala Val Lys Ala Tyr Asn Ser Ala Gly Thr Gly Pro Ser
1 5 10 15

<210> 118

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Contactin A/F3/F11.[Xenopus laevis] [Swiss-Prot: O93250]: FGFR binding motif

<400> 118

Asn Leu Glu Val Arg Ala Phe Asn Ser Ala Gly Asp Gly Pro
1 5 10

<210> 119

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Neural cell adhesion molecule CALL. [Homo sapiens] [Swiss-Prot: O0
0533]:FGFR binding motif

<400> 119

His Leu Thr Val Leu Ala Tyr Asn Ser Lys Gly Ala Gly Pro
1 5 10

<210> 120

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Neuron-glia cell adhesion molecule (Ng-CaM) precursor. [Gallus gal
lus] [Swiss-Prot: Q909339]: FGFR binding motif

<400> 120

Leu Arg Val Leu Val Phe Asn Gly Arg Gly Asp Gly Pro
1 5 10

<210> 121

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Contactin precursor (Neural cell recognition molecule F11). [Gallu
s gallus] [Swiss-Prot: P14781]: FGFR binding motif

<400> 121

His Ile Asp Val Ser Ala Phe Asn Ser Ala Gly Tyr Gly Pro
1 5 10

<210> 122

<211> 10

<212> PRT

<213> Artificial sequence

<220>

<223> SLIT [Drosophila melanogaster] [Swiss-Prot: Q9XYV4]: FGFR binding motif

<400> 122

His Leu Ala Val Glu Leu Phe Asn Gly Arg
1 5 10

<210> 123

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Galectin-4. [Mus musculus] [Swiss-Prot: Q8K419, P38552]: FGFR binding motif

<400> 123

Leu Glu Leu Gln Ser Ile Asn Phe Leu Gly Gly Gln Pro Ala
1 5 10

<210> 124

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> HNB-2. [Homo sapiens] Swiss-Prot: O94779: FGFR binding motif

<400> 124

His Phe Thr Val Arg Ala Tyr Asn Gly Ala Gly Tyr Gly Pro
1 5 10

<210> 125

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> The EFL peptide (from the FIII,3 domain of L1) [Swiss-Prot: P3200
4]: FGFR binding motif

<400> 125

His Leu Glu Val Gln Ala Phe Asn Gly Arg Gly Ser Gln Pro Ala
1 5 10 15

<210> 126

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Fragment of Neuroglian (Drosophila)[Swiss-prot: P202419]: FGFR b
inding motif

<400> 126

Val Ile Ala Asp Gln Pro Thr Phe Val Lys Tyr Leu Ile Lys
1 5 10

<210> 127

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Fragment of Fibronectin (bovine) [Swiss-prot: P07589]: FGFR bindi
ng motif

<400> 127

Thr Ile Lys Gly Leu Arg Pro Gly Val Val Tyr Glu Gly Gln
1 5 10

<210> 128

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Tenascin (chick) [Swiss-prot: P10039]: FGFR binding motif

<400> 128

Thr Leu Thr Glu Leu Ser Pro Ser Thr Gln Tyr Thr Val Lys
1 5 10

<210> 129

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Ephrin type A receptor2 [Swiss-prot: Q8N3Z2]: FGFR binding motif

<400> 129

Thr Leu Asp Asp Leu Ala Pro Asp Thr Thr Tyr Leu Val Gln
1 5 10

<210> 130

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> LAR [Swiss-prot Q9VIS8]: FGFR binding motif

<400> 130

Thr Val Ser Asp Val Thr Pro His Ala Ile Tyr Thr Val Arg
1 5 10

<210> 131

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> RTK (Tie-1,hu) [Swiss-prot P35590]: FGFR binding motif

<400> 131

Ile Ile Arg Gly Leu Asn Ala Ser Thr Arg Tyr Leu Phe Arg
1 5 10

<210> 132

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> RTK (Tie-1,hu) [Swiss-prot P35590]: FGFR binding motif

<400> 132

Thr Leu Met Asn Leu Arg Pro Lys Thr Gly Tyr Ser Val Arg
1 5 10

<210> 133

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Consensus sequence (conserved domain database):FGFR binding motif

<400> 133

Thr Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Glu Val Arg
1 5 10

<210> 134

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> The beta-common cytokine receptor of IL-3. Il-5 and GmCsf [Swiss-prot P32927]: FGFR binding motif

<400> 134

Gly Pro Glu His Leu Met Pro Ser Ser Thr Tyr Val Ala Arg
1 5 10

<210> 135

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Unc-22 (C. Elegance) [Swiss-prot: Q23550]: FGFR binding motif

<400> 135

Arg Val Thr Gly Leu Thr Pro Lys Lys Thr Tyr Glu Phe Arg
1 5 10

<210> 136

<211> 14

<212> PRT

<213> Artificial sequence

<220>

<223> Consensus sequence (conserved domain database): FGFR binding motif

<400> 136

Thr Leu Thr Gly Leu Lys Pro Gly Thr Glu Tyr Glu Phe Arg
1 5 10

<210> 137

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> Consensus sequence (conserved domain database):FGFR binding motif

<400> 137

Glu Val Arg Val Gln Ala Val Asn Gly Gly Gly Asn Gly Pro Pro
1 5 10 15

<210> 138

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Drosophila Neuroglian [Swiss-prot: P20241]: FGFR binding motif

<400> 138

Leu Ile Lys Val Val Ala Ile Asn Asp Arg Gly Glu
1 5 10

<210> 139

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Fibronectin (mouse) [Swiss-prot: P11276]: FGFR binding motif

<400> 139

Val Val Ser Ile Ile Ala Val Asn Gly Arg Glu Glu
1 5 10

<210> 140

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Fibronectin (bovine) [Swiss-prot: P07589]:FGFR binding motif

<400> 140

Val Val Ser Val Tyr Ala Gln Asn Gln Asn Gly Glu
1 5 10

<210> 141

<211> 12

<212> PRT

<213> Artificial sequence

<220>

<223> Tenascine (chick) [Swiss-prot: Q90995]: FGFR binding motif

<400> 141

Thr Ile Ser Leu Val Ala Glu Lys Gly Arg His Lys
1 5 10

<210> 142

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> L1 (human, F3,EFL) [Swiss-prot: P32004]: FGFR binding motif

<400> 142

His Leu Glu Val Gln Ala Phe Asn Gly Arg Gly Ser Gly Pro Ala
1 5 10 15

<210> 143

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> L1 (mouse, F3,EFL) [Swiss-prot: P11627]: FGFR binding motif

<400> 143

His Val Glu Val Gln Ala Phe Asn Gly Arg Gly Leu Gly Pro Ala
1 5 10 15

<210> 144

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> L1 (rat, F3,EFL) [Swiss-prot: Q05695]: FGFR binding motif

<400> 144

His Val Glu Val Gln Ala Phe Asn Gly Arg Gly Leu Gly Pro Ala
1 5 10 15

<210> 145

<211> 13

<212> PRT

<213> Artificial sequence

<220>

<223> Consensus sequence (conserved domain database): FGFR binding motif

<400> 145

Glu Phe Arg Val Arg Ala Val Asn Gly Ala Gly Glu Gly
1 5 10

<210> 146

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> The beta-common cytokine receptor of IL-3. Il-5 and GmCsf [Swiss-prot: P32927]: FGFR binding motif

<400> 146

Val Ala Arg Val Arg Thr Arg Leu Ala Pro Gly Ser Arg Leu Ser
1 5 10 15

<210> 147

<211> 15

<212> PRT

<213> Artificial sequence

<220>

<223> Control peptide (Mutated FGL peptide)

<400> 1

Glu Val Tyr Val Val Ala Glu Asn Ala Ala Gly Lys Ser Lys Ala
1 5 10 15

Claims

1. A compound comprising two individual peptide sequences, wherein at least one of the two sequences comprises a sequence of the formula

L1-A-L2-B-L3-C-L4-D-L5

wherein

one of A, B, C, D is selected from a hydrophobic amino acid residue,

one of A, B, C, D is selected from a basic amino acid residue, Asn or Gln,

one of A, B, C, D is selected from an acidic amino acid residue, Asn or Gln,

one of A, B, C, D is Gly or Ala, and

L1, L2, L3, L4 and L5 is selected from a chemical bond or an amino acid sequence having n amino acid residues, wherein n is an integer of from 0 to 5,

wherein

said peptide sequences are connected to each other through a linker of the formula

X[(A)nCOOH][(B)mCOOH]

n and m independently are an integer of from 1 to 20,

X is HN, $H_2N(CR_2)pCR$, $RHN(CR_2)pCR$, $HO(CR_2)pCR$, $HS(CR_2)pCR$, halogen-$(CR_2)pCR$, $HOOC(CR_2)pCR$, $ROOC(CR_2)pCR$, $HCO(CR_2)pCR$, $RCO(CR_2)pCR$, $[HOOC(A)n][HOOC(B)m]CR(CR_2)pCR$, $H_2N(CR_2)p$, $RHN(CR_2)p$, $HO(CR_2)p$, $HS(CR_2)p$, halogen-$(CR_2)p$, $HOOC(CR_2)p$, $ROOC(CR_2)p$, $HCO(CR_2)p$, $RCO(CR_2)p$, or $[HOOC(A)n][HOOC(B)m](CR_2)p$, wherein p is 0 or integer of from 1 to 20,

A and B independently are a substituted or unsubstituted C_{1-10} alkyl, a substituted or unsubstituted C_{2-10} alkenyl, a substituted or unsubstituted cyclic moiety, a substituted or unsubstituted heterocyclic moiety, a substituted or unsubstituted aromatic moiety, or A and B together form a substituted or unsubstituted cyclic moiety, substituted or unsubstituted heterocyclic moiety, or substituted or unsubstituted aromatic moiety.

2. The compound according to claim 1, wherein the at least one of the two peptide sequences is capable of binding to a functional cell surface receptor.

3. The compound according to claim 2, wherein the functional cell surface receptor is a receptor selected from the family of fibroblast growth factor receptors (FGFRs) comprising FGFR1, FGFR2, FGFR3 and FGFR4, or functional homologues thereof.

4. The compound according to claim 2, wherein the at least one of the two peptide sequences is derived from the sequence of a polypeptide selected from the group comprising cell adhesion molecules, cell-surface receptors, heparan sulphate proteoglycans, and metalloproteases, extracellular matrix molecules or growth factors.

5. The compound according to the claim 4, wherein the cell adhesion molecule is selected from the group comprising
- Neural Cell Adhesion Molecule (NCAM) (Swiss-Prot Ass. Nos: P13591, P13595-01, P13595),
- Neural cell adhesion molecule L1 (Swiss-Prot Ass. Nos: Q9QYQ7, Q9QY38, P11627, Q05695, P32004),
- Neural Cell Adhesion Molecule-2 (NCAM-2) (Swiss-Prot Ass. No: P36335)
- Neuron-glia Cell Adhesion Molecule (Ng-CAM) (Swiss-Prot Ass. No: Q03696; Q90933),
- Neural cell adhesion molecule CALL (Swiss-Prot Ass. No: O00533),
- Neuroglian (Swiss-Prot Ass. No: P91767, P20241),
- Nr-CAM (HBRAVO, NRCAM, NR-CAM 12) (Swiss-Prot Ass. Nos: Q92823, O15179, Q9QVN3
- Axonin-1/TAG-1 (Swiss-Prot Ass. Nos: Q02246, P22063, P28685),
- Axonal-associated Cell Adhesion Molecule (AxCAM) (NCBI Ass. No: NP_031544.1; Swiss-Prot Ass. No: Q8TC35),
- Myelin-Associated Glycoprotein (MAG) (Swiss-Prot Ass. No: P20917),
- Neural cell adhesion molecule BIG-1 (Swiss-Prot Ass. No: Q62682),
- Neural cell adhesion molecule BIG-2 (Swiss-Prot Ass. No: Q62845),
- Fasciclin (FAS-2) (Swiss-Prot Ass. No: P22648),
- Neural cell adhesion molecule HNB-3/NB-3 (Swiss-Prot Ass. Nos: Q9UQ52, P97528, Q9JMB8)
- Neural cell adhesion molecule HNB-2/NB-2 (Swiss-Prot Ass. Nos: O94779,

P07409, P97527),
- Cadherin (Swiss-Prot Ass. No: Q9VW71),
- Junctional Adhesion Molecule-1 (JAM-1) (Swiss-Prot Ass. Nos: Q9JKD5, O88792),
- Neural cell adhesion F3/F11(Contactin) (Swiss-Prot Ass. Nos: Q63198, P1260, Q12860, Q28106, P14781, O93250),
- Neurofascin (Swiss-Prot Ass. Nos: Q90924, Q91Z60; O42414),
- B-lymphocyte cell adhesion molecule CD22 (Swiss-Prot Ass. Nos: Q9R094, P20273),
- Neogenin (NEO1) (Swiss-Prot Ass. Nos: Q92859, P97603, Q90610, P97798),
- Intercellular Cell Adhesion Molecule-5 (ICAM-5/telencephalin) (Swiss-Prot Ass. Nos: Q8TAM9, Q60625) or
- Galactose binding lectin-12 (galectin-12) (Swiss-Prot Ass. Nos: Q91VD1, Q9JKX2, Q9NZ03),
- Galactose binding lectin-4 (galectin-4) (Swiss-Prot Ass. No: Q8K419; P38552),

or fragments, or variants thereof.

6. The compound according to the claim 4, wherein the cell-surface receptor is selected from the group comprising
- Fibroblast Growth Factor Receptor 1 (FGFR1) (Swiss-Prot Ass. Nos: Q9QZM7, Q99AVV7, Q9UD50, Q63827),
- Fibroblast Growth Factor Receptor 2 (FGFR2) (Swiss-Prot Ass. Nos: Q96KM2, P21802, Q63241),
- Fibroblast Growth Factor Receptor 3 (FGFR3) (Swiss-Prot Ass. Nos: Q95M13, AF487554, Q99052),
- Fibroblast Growth Factor Receptor 4 (FGFR4) (Swiss-Prot Ass. No: Q91742),
- Neurotrophin Tyrosin Kinase Type-2 (NTRKT-2) (Swiss-Prot Ass. No: Q8WXJ5),
- Leukocyte Antigen Related Protein-Tyrosine Phosphatase (LAR-PTPRF) (Swiss-Prot Ass. Nos: Q9EQ17, Q64605, Q64604, Q9QW67, Q9VIS8 P10586),
- Nephrin (Swiss-Prot Ass. Nos: Q925S5, Q9JIX2, Q9ET59, Q9R044, Q9QZS7, Q06500),
- Protein-Tyrosine Phosphatase Receptor type S (PTPRS) (Swiss-Prot Ass. Nos: Q64699, Q13332, O75870),

- Protein-Tyrosine Phosphatase Receptor type kappa (R-PTP-kappa) (Swiss-Prot Ass. No: Q15262),
- Protein-Tyrosine Phosphatase Receptor type D (PTPRD) (Swiss-Prot Ass. Nos: Q8WX65, Q9IAJ1, P23468, Q64487),
- Ephrin type-A receptor 8 (EPHA8/Tyrosine-Protein Kinase Receptor EEK) (Swiss-Prot Ass. Nos: O09127, P29322),
- Ephrin type-A receptor 3 (EPHA8/Tyrosine-Protein Kinase Receptor ETK-1/CEK4) (Swiss-Prot Ass. No: P29318),
- Ephrin type-A receptor 2 (Swiss-Prot Ass. No: Q8N3Z2)
- Insulin Receptor (IR) (Swiss-Prot Ass. No: Q9PWN6)
- Insulin-like Growth Factor-1 Receptor (IGF-1) (Swiss-Prot Ass. Nos: Q9QVW4, P08069, P24062, Q60751, P15127, P15208)
- Insulin-related Receptor (IRR) (Swiss-Prot Ass. No: P14616),
-Tyrosine-Protein Kinase Receptor Tie-1 (Swiss-Prot Ass. Nos: 06805, P35590, Q06806),
- Roundabout receptor-1 (robo-1) (Swiss-Prot Ass. Nos: O44924, AF041082, Q9Y6N7),
- Neuronal nicotinic acetylcholine receptor alpha 3 subunit (CHRNA3) (Swiss-Prot Ass. Nos: Q8VHH6, P04757, Q8R4G9, P32297)
- Neuronal acetylcholine receptor alpha 6 subunit (Swiss-Prot Ass. Nos: Q15825, Q9R0W9)
- Platelet-Derived Growth Factor Receptor Beta (PDGFRB) (Swiss-Prot Ass. Nos: Q8R406, Q05030),
- Interleukin-6 Receptor (IL-6R) (Swiss-Prot Ass. No: Q00560),
- Interleukin-23 Receptor (IL-23R) (Swiss-Prot Ass. No: AF461422),
- Beta-common cytokine receptor of IL-3, IL5 and GmCsf (Swiss-Prot Ass. No: P32927)
- Cytokine Receptor-Like molecule 3 (CRLF1) (Swiss-Prot Ass. No: Q9JM58),
- Class I Cytokine Receptor (ZCYTOR5) (Swiss-Prot Ass. No: Q9UHH5)
- Netrin-1 receptor DCC (Swiss-Prot Ass. No: P43146),
- Leukocyte Fc Receptor-like Protein (IFGP2) (Swiss-Prot Ass. Nos: Q96PJ6, Q96KM2),
- Macrophage Scavenger Receptor 2 (MSR2) (Swiss-Prot Ass. No: Q91YK7), or
- Granulocyte Colony Stimulating Factor Receptor (G-CSF-R) (Swiss-Prot Ass. No: Q99062),.

or fragments, or variants thereof.

7. The compound according to the claim 4, wherein the heparan sulphate proteoglycan is perlecan (Swiss-Prot Ass. No: P98160), or a fragment, or a variant thereof.

8. The compound according to the claim 4, wherein the metalloprotease is selected from the group comprising
- ADAM-8 (Swiss-Prot Ass. No: Q05910),
- ADAM-19 (Swiss-Prot Ass. Nos: Q9H013, O35674),
- ADAM-8 (Swiss-Prot Ass. No: P78325),
- ADAM-12 (Swiss-Prot Ass. Nos: O43184, Q61824),
- ADAM-28 (Swiss-Prot Ass. Nos: Q9JLN6, Q61824, Q9XSL6, Q9UKQ2),
- ADAM-33 precursor (Swiss-Prot Ass. Nos: Q8R533, Q923W9),
- ADAM-9 (Swiss-Prot Ass. Nos: Q13433, Q61072),
- ADAM-7 (Swiss-Prot Ass. NoS: Q9H2U9, O35227, Q63180),
- ADAM-1A Fertilin alpha (Swiss-Prot Ass. No: Q8R533),
- ADAM-15 (Swiss-Prot Ass. Nos: Q9QYV0, O88839, Q13444),
- Metalloproteinase-desintegrin domain containing protein (TECAM) (Swiss-Prot Ass. No: AF163291),
- Metalloproteinase 1 (Swiss-Prot Ass. Nos: O95204, Q9BSI6),
or fragments, or variants thereof.

9. The compound according to the claim 4, wherein the extracellular matrix molecule is selected from the group comprising
- Collagen type VII (Swiss-Prot Ass. No: Q63870),
- Fibronectin (Swiss-Prot Ass. Nos: Q95KV4, Q95KV5, P07589, Q28377, U42594, O95609, P11276), or
- Tenascin-R (Swiss-Prot Ass. Nos: Q15568, O00531, Q90995, P10039),
or fragments, or variants thereof.

10. The compound according to the claim 4, wherein the growth factor is Cytokine-like factor-1 (CLF-1) (Swiss-Prot Ass. No:O75462), or a fragment, or a variant thereof.

11. The compound according to any of the claims 1 to 10, wherein the at least one of the two peptide sequences is a peptide fragment having the amino acid sequence selected from

EVYVVAENQQGKSKA (SEQ ID NO 1),
NIEVWVEAENALGKKV (SEQ ID NO: 2),
ATNRQGKVKAFAHL (SEQ ID NO: 3),
RYVELYVVADSQEFQK (SEQ ID NO: 4)
VAENSRGKNVAKG (SEQ ID NO: 5),
GEYWCVAENQYGQR (SEQ ID NO: 6),
RLAALNGKGLGEIS (SEQ ID NO: 7),
KYIAENMKAQNVAKEI (SEQ ID NO: 8),
TIMGLKPETRYAVR (SEQ ID NO: 9),
KGLGEISAATEFKT (SEQ ID NO: 10),
NMGIWVQAENALG (SEQ ID NO: 11),
IWVQAENMLG (SEQ ID NO: 12),
EIWVEATNRLG (SEQ ID NO: 13),
VWVQAANALG (SEQ ID NO: 14),
EVWIEKDPAKGRI (SEQ ID NO: 15),
ATNKGGEVKKNGHL (SEQ ID NO: 16),
KYVELYLVADYLEFQK (SEQ ID NO: 17),
RYVELYVVVDNAEFQ (SEQ ID NO: 18),
KYVELVIVADNREFQR (SEQ ID NO: 19),
KYIEYYLVLDNGEFKR (SEQ ID NO: 20),
RYLELYIVADHTLF (SEQ ID NO: 21),
KYVEMFVVVNHQRFQ (SEQ ID NO: 22) ,
RYVELFIVVDKERY (SEQ ID NO: 23),
KYVELFIVADDTVYRR (SEQ ID NO: 24),
KFIELFVVADEYVYRR (SEQ ID NO: 25),
KIVEKVIVADNSEVRK (SEQ ID NO: 26),
VELVIVADHSEAQK (SEQ ID NO: 27),
VAENSRGKNIAKG (SEQ ID NO: 28),
IAENSRGKNVARG (SEQ ID NO: 29),
AENSRGKNSFRG (SEQ ID NO: 30),
IASNLRGRNLAKG (SEQ ID NO: 31),
IPENSLGKTYAKG (SEQ ID NO: 32),

IAENMKAQNEAK (SEQ ID NO: 33),
QFIAENMKSHNETKEV (SEQ ID NO: 34),
GEYWCVAKNRVGQ (SEQ ID NO: 35),
GSYTCVAENMVGK (SEQ ID NO: 36),
GKYVCVGTNMVGER (SEQ ID NO: 37),
GNYTCVVENEYG (SEQ ID NO: 38),
GEYTCLAGNSIG (SEQ ID NO: 39),
QYYCVAENGYG (SEQ ID NO: 40),
GEYYQEAEQNGYG (SEQ ID NO: 41),
GNYTCLVENEYG (SEQ ID NO: 42),
GMYQCLAENAYG (SEQ ID NO: 43),
GMYQCAENTHG (SEQ ID NO: 44),
GIYYCLASNNYG (SEQ ID NO: 45),
GGYYCTADNSYG (SEQ ID NO: 46),
GEYQCFARNDYG (SEQ ID NO: 47),
GEYFCLASNKMG (SEQ ID NO: 48),
GEYQCFARNKFG (SEQ ID NO: 49),
GEYFCLASNKMG (SEQ ID NO: 50),
GGYYCTADNNYG (SEQ ID NO: 51),
GNYSCEAENAWGTK (SEQ ID NO: 52),
GEYTCLAENSLG (SEQ ID NO: 53),
GEYECVAENGRLG (SEQ ID NO: 54),
GNYTCVVENKFGR (SEQ ID NO: 55),
GEYTCLAGNSIG (SEQ ID NO: 56),
GEYFCVASNPIG (SEQ ID NO: 57),
EYTCIANNQAGE (SEQ ID NO: 58),
GMYQCVAENKHLG (SEQ ID NO: 59),
GEYMCTASNTIGQ (SEQ ID NO: 60),
EYVCIAENKAGEQ (SEQ ID NO: 61),
GDYTLIAKNEYGK (SEQ ID NO: 62),
GFYQCVAENEAG (SEQ ID NO: 63),
GKYECVATNSAGTR (SEQ ID NO: 64),
GEYFCVYNNSLG (SEQ ID NO: 65),
GEYECAATNAHGR (SEQ ID NO: 66),
GAYWCQGTNSVGK (SEQ ID NO: 67),

GTYSCVAENILG (SEQ ID NO: 68),
RVAAVNGKGQGDYS (SEQ ID NO: 69),
RVAAINGCGIGPFS (SEQ ID NO: 70),
AVLNGKGLG (SEQ ID NO: 71),
ALNGQGLGATS (SEQ ID NO: 72),
RLAAKNRAGLGE (SEQ ID NO: 73),
RLGVVTGKDLGEI (SEQ ID NO: 74),
TVTGLKPETSYMVK (SEQ ID NO: 75),
TLTGLKPSTRYRI (SEQ ID NO: 76),
TLTGLQPSTRYRV (SEQ ID NO: 77),
TLLGLKPDTTYDIK (SEQ ID NO: 78),
TLQGLRPETAYELR (SEQ ID NO: 79),
TLRGLRPETAYELR (SEQ ID NO: 80),
TLMNLRPKTGYSVR (SEQ ID NO: 81),
TVSGLKPGTRY (SEQ ID NO: 82),
TISGLKPDTTY (SEQ ID NO: 83),
TLQGLKPDTAY (SEQ ID NO: 84),
LRGLKPWTQYAV (SEQ ID NO: 85),
IDGLEPDTEYIVR (SEQ ID NO: 86),
LQGLKPWTQYAI (SEQ ID NO: 87),
TITGLEPGTEYTIQ (SEQ ID NO: 88),
GLKPWTQYAV (SEQ ID NO: 89),
TLASLKPWTQYAV (SEQ ID NO: 90),
LMGLQPATEYIV (SEQ ID NO: 91),
KGMGPMSEAVQFRT (SEQ ID NO: 92),
TLTGLKPDTTYDVK (SEQ ID NO: 93),
ISGLQPETSYSL (SEQ ID NO: 94),
TLLGLKPDTTYDIK (SEQ ID NO: 95),
TISGLTPETTYSI (SEQ ID NO: 96),
GNYSCLAENRLGR (SEQ ID NO: 97),
GNYTCVVENRVG (SEQ ID NO: 98),
GTYHCVATNAHG (SEQ ID NO: 99),
LSHNGVLTGYLLSY (SEQ ID NO: 100),
NGVLTGYVLRY (SEQ ID NO: 101),
NGVLTGYNLRY (SEQ ID NO: 102),

110

NGNLTGYLLQY (SEQ ID NO: 103),
VDENGVLTGYKIYY (SEQ ID NO: 104),
THNGALVGYSVRY (SEQ ID NO: 105),
NGILTEYILKY (SEQ ID NO: 106),
NGILIGYTLRY (SEQ ID NO: 107),
THSGQITGYKIRY (SEQ ID NO: 108),
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HFTVRAYNGAGYGP (SEQ ID NO: 124),
HLEVQAFNGRGSQPA (SEQ ID NO: 125),
VIADQPTFVKYLIK (SEQ ID NO: 126),
TIKGLRPGVVYEGQ (SEQ ID NO: 127),
TLTELSPSTQYTVK (SEQ ID NO: 128),
TLDDLAPDTTYLVQ (SEQ ID NO: 129),
TVSDVTPHAIYTVR (SEQ ID NO: 130),
IIRGLNASTRYLFR (SEQ ID NO:131),
TLMNLRPKTGYSVR (SEQ ID NO:132),
TLTGLKPGTEYEVR (SEQ ID NO: 133),
GPEHLMPSSTYVAR (SEQ ID NO: 134),
RVTGLTPKKTYEFR (SEQ ID NO: 135),
LTGLKPGTEYEFR (SEQ ID NO: 136),
EVRVQAVNGGGNGPP (SEQ ID NO: 137),

LIKVVAINDRGE (SEQ ID NO: 138),
VVSIIAVNGREE (SEQ ID NO: 139),
VVSVYAQNQNGE (SEQ ID NO: 140),
TISLVAEKGRHK (SEQ ID NO: 141),
HLEVQAFNGRGSGPA (SEQ ID NO: 142),
HVEVQAFNGRGLGPA (SEQ ID NO: 143),
HVEVQAFNGRGLGPA (SEQ ID NO: 144),
EFRVRAVNGAGEG (SEQ ID NO: 145), or
VARVRTRLAPGSRLS (SEQ ID NO: 146), or
or a fragment, or a variant, or homologue thereof.

12. The compound according to claims 1 to 10, wherein the at least one of the two peptide sequences is SEQ ID NO: 1 (EVYVVAENQQGKSKA), or a fragment, variant, or homologue of said sequence.

13. The compound of claim 12, wherein the variant or homologue of SEQ ID NO: 1 is selected from SEQ ID NOs: 2-9, 100 or 125,

14. The compound according to claims 1 to 10, wherein the at least one of the two peptide sequences is SEQ ID NO: 2 (NIEVWVEAENALGKKV), or a fragment, variant or homologue of said sequence.

15. The compound according to any of the preceding claims, wherein the compound comprises two individual peptide fragments comprising different amino acid sequences, said different amino acid sequences being selected from any of the peptide fragments of claim 11.

16. The compound according to any of the preceding claims, wherein the compound comprises two peptide fragments comprising the identical amino acid sequence, said amino acid sequence being selected from any of the peptide fragments of claim 11.

17. The compound according to claim 16, wherein the peptide fragments are independently having the sequence EVYVVAENQQGKSKA (SEQ ID NO: 1).

18. The compound according to claim 16, wherein the peptide fragments are independently having the sequence NIEVWVEAENALGKKV (SEQ ID NO: 2).

19. The compound according to claim 15, wherein one of the two peptide fragments is having the sequence EVYVVAENQQGKSKA (SEQ ID NO: 1), and the other is having the sequence NIEVWVEAENALGKKV (SEQ ID NO: 2).

20. The compound according to any of the preceding claims, said compound being obtained by a method for preparing an LPA enabling presentation of sequence(s) as defined in claim 11 comprising the steps of

(a) providing by solid phase synthesis or fragment coupling ligands comprising desired sequence(s), the ligands being attached to a solid phase,

(b) if nessesary, deprotecting any N-terminal amino acid groups while th eligands/s) are still attached to the solid phase,

(c) reacting the ligand(s) having unprotected N-terminal groups with an achiral di- tri- or tetracarboxylic acid so as to provide a construct having a ring structure, and

(d) cleaving the construct from the solid phase so as to provide an LPA comprising ligands having free C-terminal groups.

21. A pharmaceutical composition comprising a compound as defined in claims 1-20.

22. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for treatment of conditions of the central and peripheral nervous system associated with postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic damage, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression; for treatment of diseases or conditions of the muscles including conditions with impaired function of neuro-muscular connections, such as after organ transplantation, or such as genetic or traumatic atrophic muscle disorders; or for treatment of diseases or conditions of various organs, such as degenerative conditions of

the gonads, of the pancreas such as diabetes mellitus type I and II, of the kidney such as nephrosis and of the heart, liver and bowel.

23. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the treatment of postoperative nerve damage, traumatic nerve damage, impaired myelination of nerve fibers, postischaemic, e.g. resulting from a stroke, Parkinson's disease, Alzheimer's disease, Huntington's disease, dementias such as multiinfarct dementia, sclerosis, nerve degeneration associated with diabetes mellitus, disorders affecting the circadian clock or neuro-muscular transmission, and schizophrenia, mood disorders, such as manic depression.

24. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the promotion of wound-healing.

25. Use a compound as defined in claims 1-20 for the manufacture of a medicament for the treatment of cancer

26. The use according to claim 25, wherein the cancer is any type of solid tumors requiring neoangiogenesis

27. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the prevention of death of heart muscle cells, such as after acute myocardial infarction, or after angiogenesis

28. Use a compound as defined in any of claims 1-20 for the manufacture of a medicament for revascularsation.

29. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the stimulation of the ability to learn and/or the short and/or long-term memory

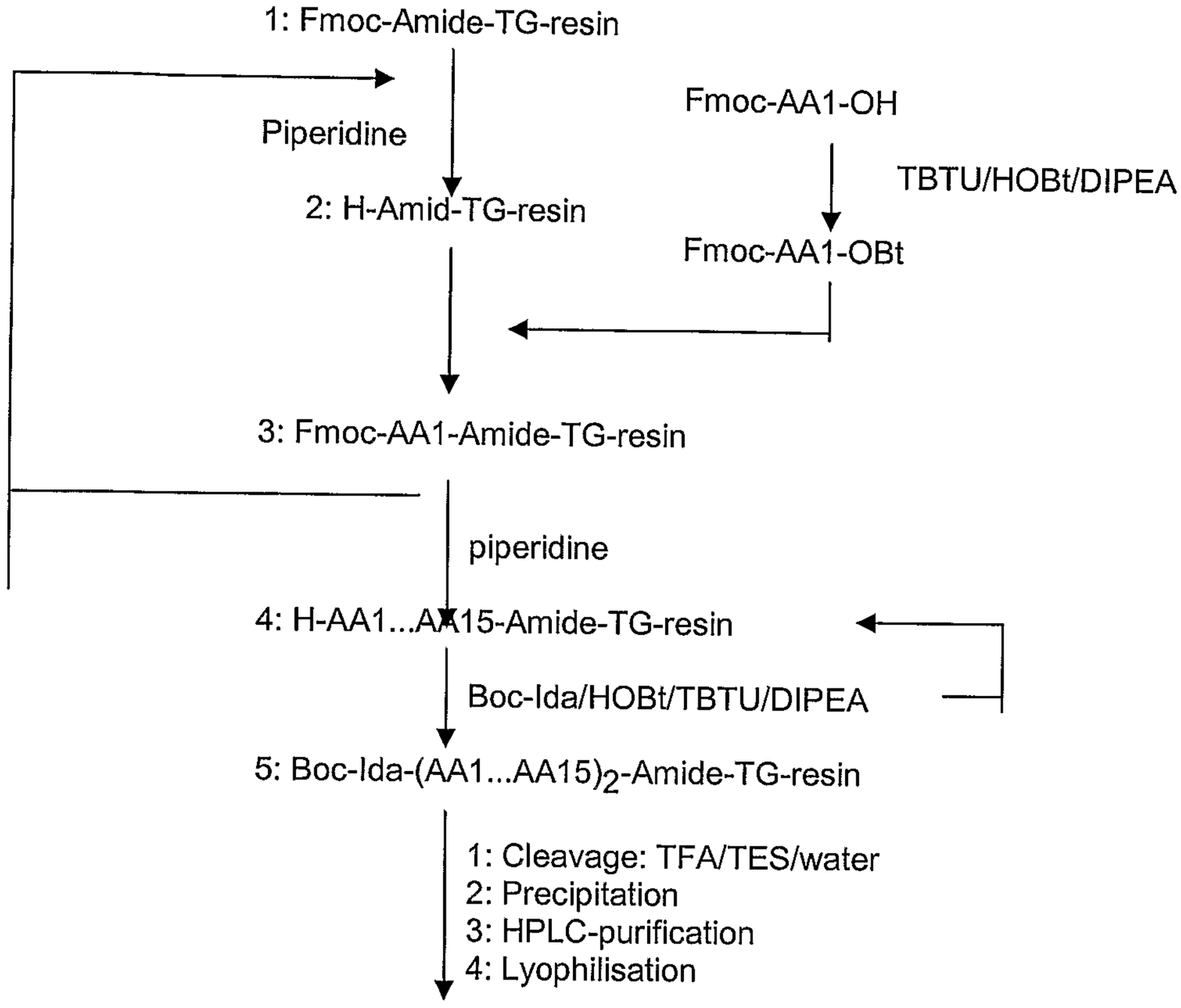
30. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the prevention of cell death due to ischemia.

31. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the prevention of body damages due to alcohol consumption.

32. Use a compound as defined in any of the claims 1-20 for the manufacture of a medicament for the treatment of prion diseases.

33. Use of a medicament of any of the claims 22-31 or pharmaceutical composition according to claim 21 for the treatment of a disease or condition as defined in claims 22-31.

34. A method of treatment of an individual in need comprising a step of administering to said individual a compound as defined in any of the claims 1 to 20, and/or a pharmaceutical composition as defined in claim 21, and/or medicament as defined in claims 22-31.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Piperidine
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Fmoc-AA1-OH
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3: Fmoc-AA1-Amide-TG-resin
piperidine
4: H-AA1...AA15-Amide-TG-resin
Boc-Ida/HOBt/TBTU/DIPEA
5: Boc-Ida-(AA1...AA15)2-Amide-TG-resin
1: Cleavage: TFA/TES/water
2: Precipitation
3: HPLC-purification
4: Lyophilisation
6: FGLL

Figure 1

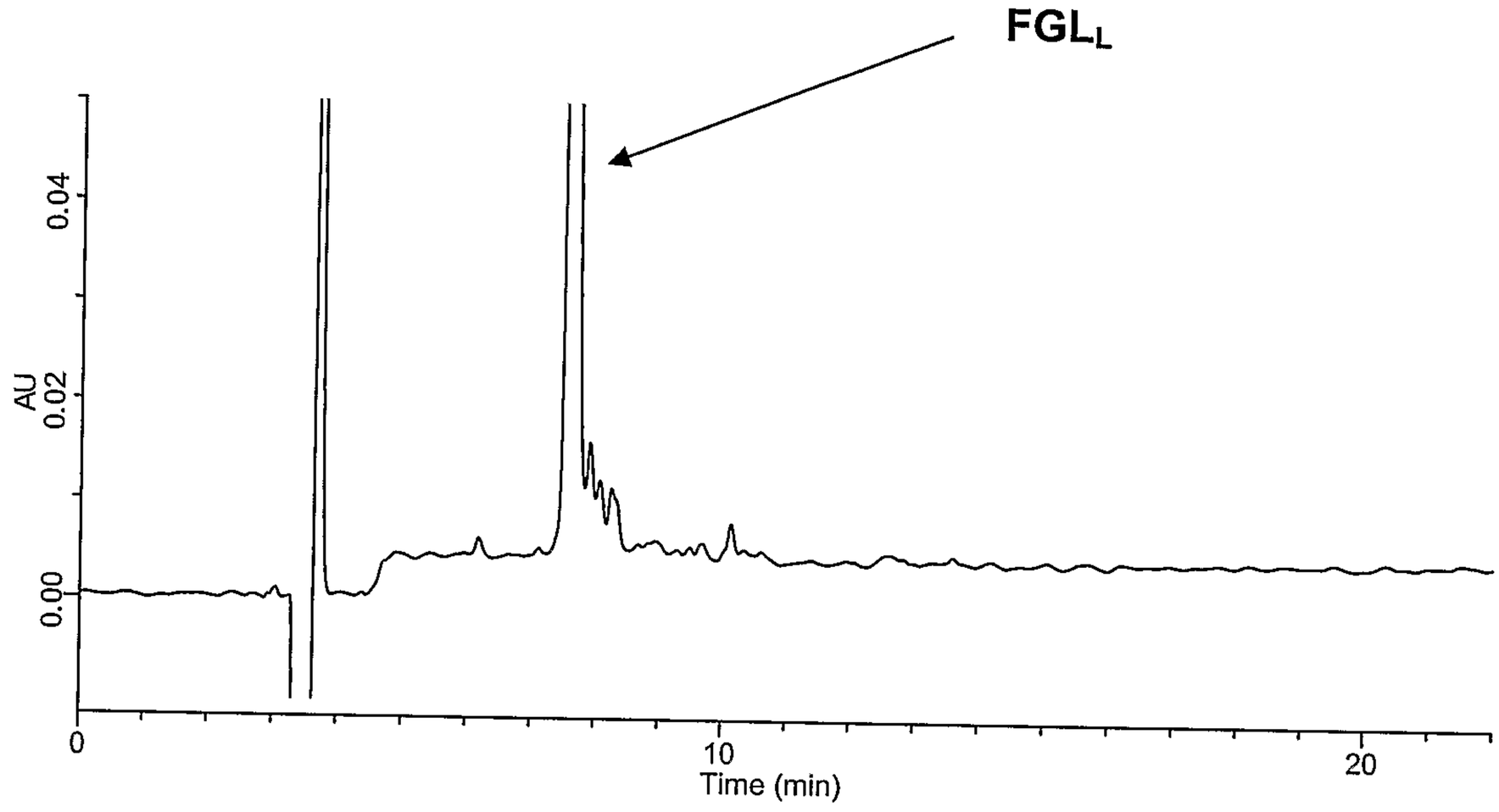


Figure 2

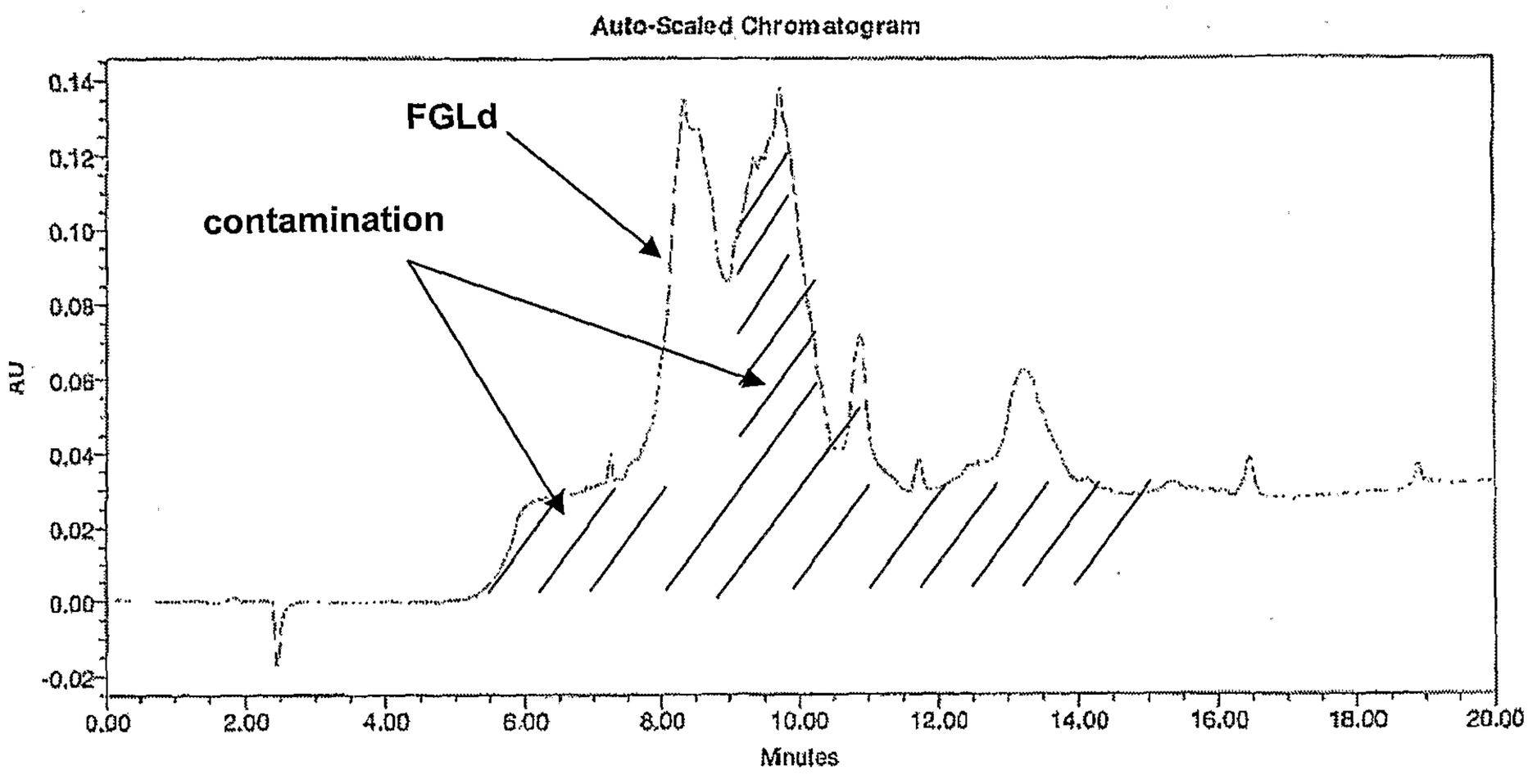

Auto-Scaled Chromatogram
FGLd
contamination
AU
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
-0.02
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
20.00
Minutes

Figure 3

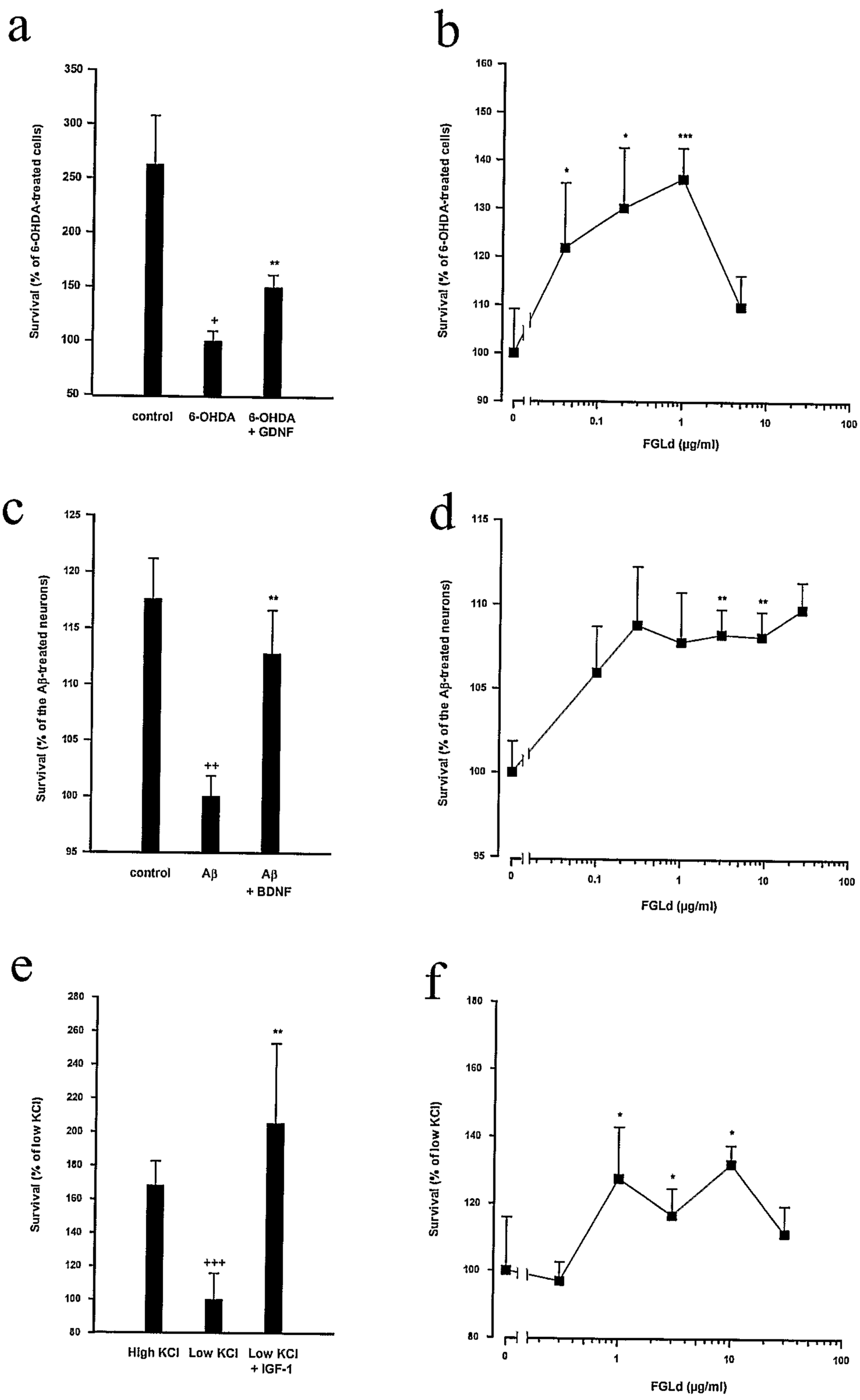
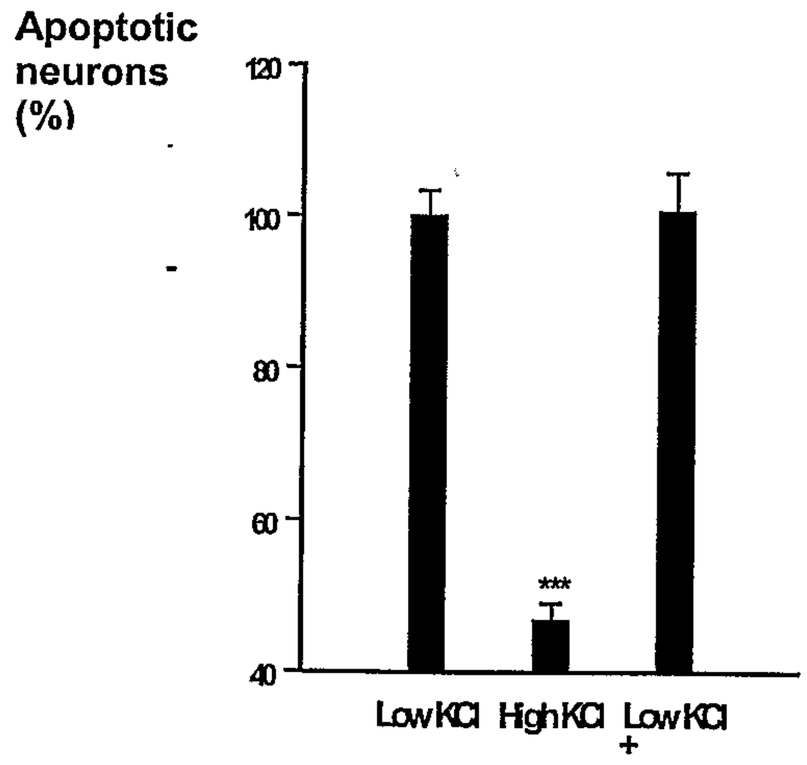

a
Survival (% of 6-OHDA-treated cells)
350
300
250
200
150
100
50
+
**
control
6-OHDA
6-OHDA + GDNF
b
Survival (% of 6-OHDA-treated cells)
160
150
140
130
120
110
100
90
*
*
***
0
0.1
1
10
100
FGLd (µg/ml)
c
Survival (% of the Aβ-treated neurons)
125
120
115
110
105
100
95
++
**
control
Aβ
Aβ + BDNF
d
Survival (% of the Aβ-treated neurons)
115
110
105
100
95
**
**
0
0.1
1
10
100
FGLd (µg/ml)
e
Survival (% of low KCl)
280
260
240
220
200
180
160
140
120
100
80
+++
**
High KCl
Low KCl
Low KCl + IGF-1
f
Survival (% of low KCl)
160
140
120
100
80
*
*
*
0
1
10
100
FGLd (µg/ml)

Figure 4

a


Apoptotic neurons (%)
120
100
80
60
40
***
LowKCl
HighKCl
LowKCl + FGL control

b

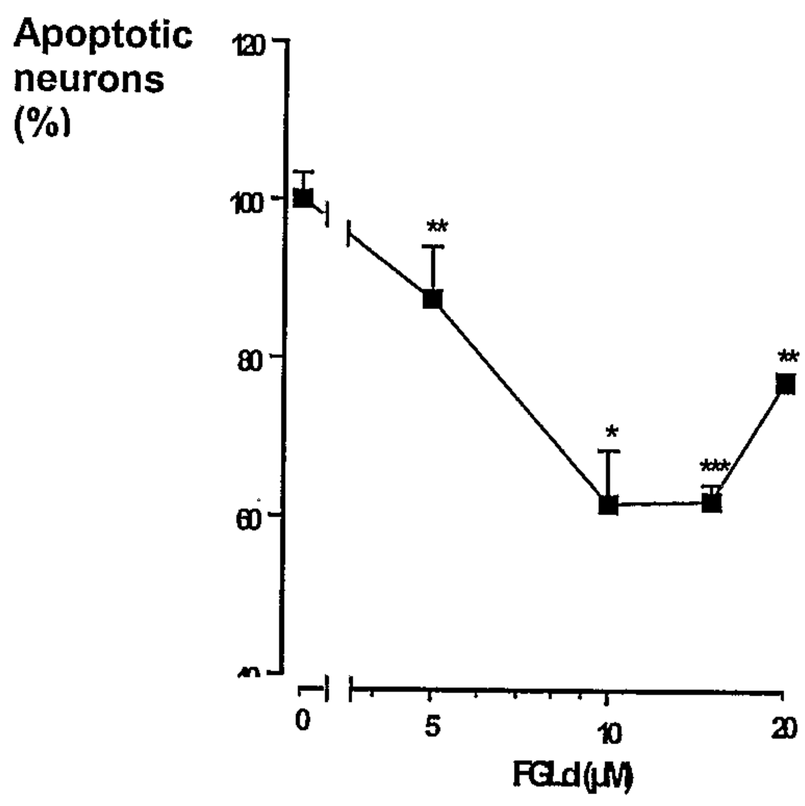

Apoptotic neurons (%)
120
100
80
60
**
*
***
**
0
5
10
20
FGL d (µM)

Figure 5

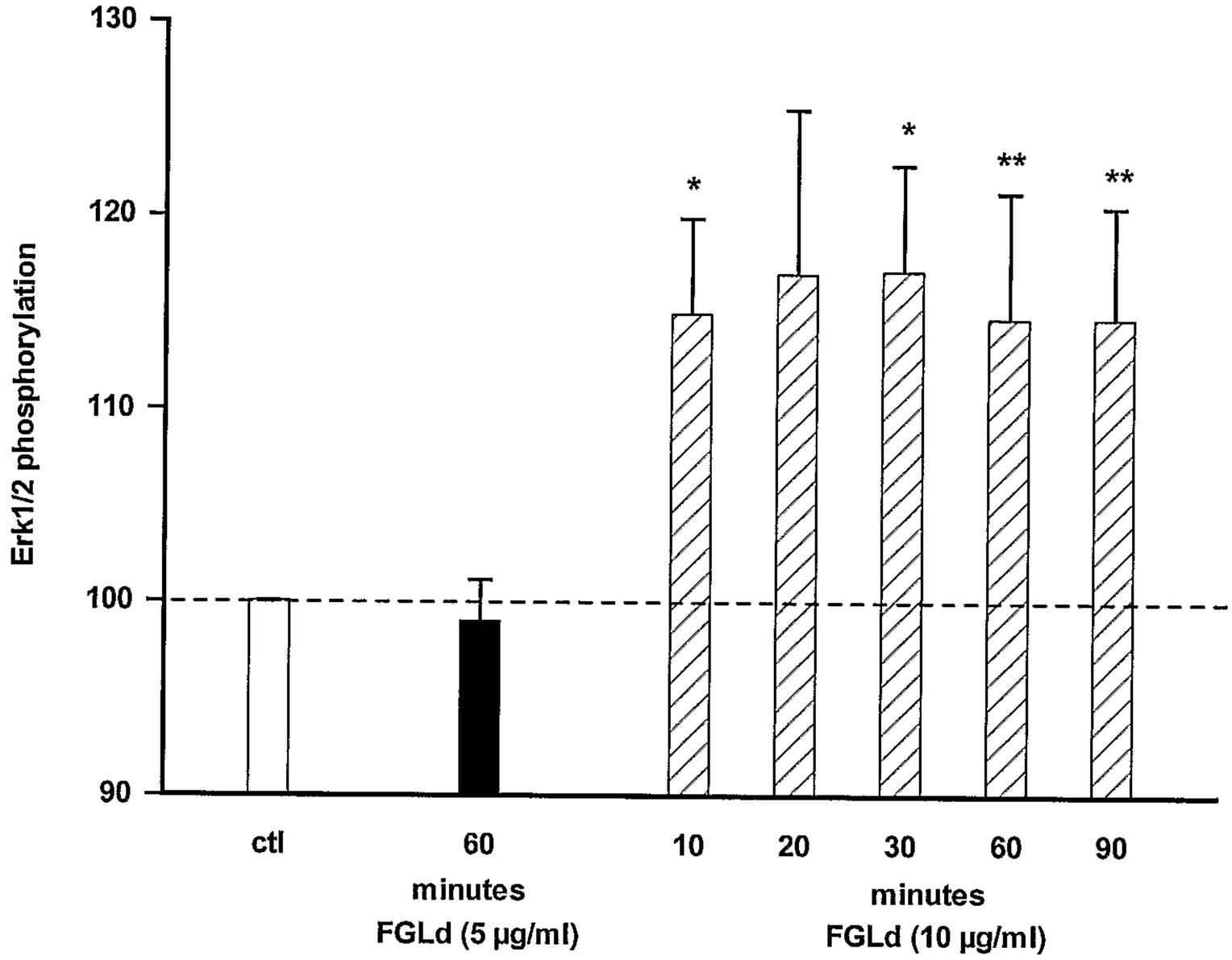

130
120
110
100
90
Erk1/2 phosphorylation
*
*
**
**
ctl
60
10
20
30
60
90
minutes
minutes
FGLd (5 µg/ml)
FGLd (10 µg/ml)

Figure 6

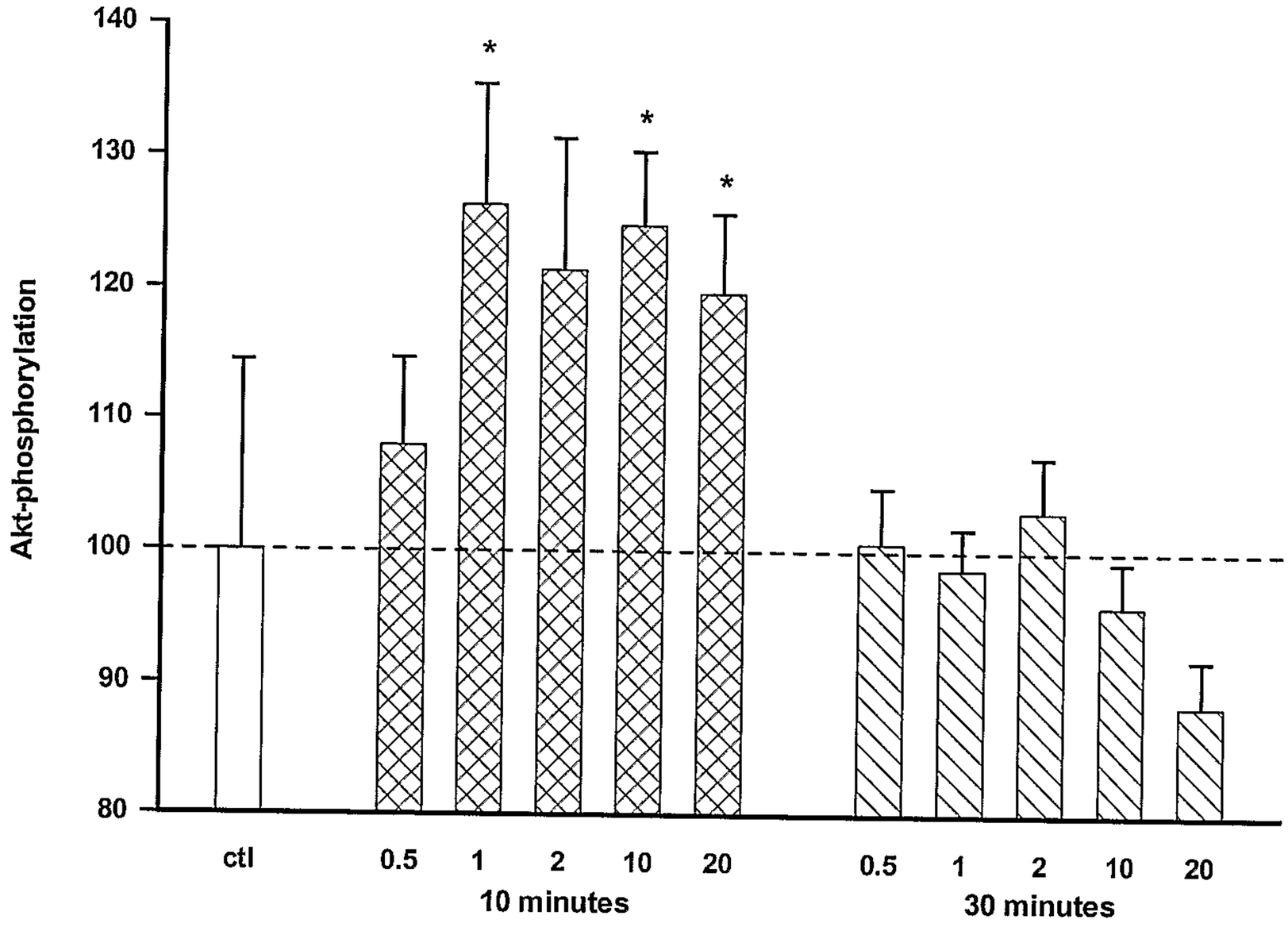

Akt-phosphorylation
140
130
120
110
100
90
80
*
*
ctl
0.5
1
2
10
20
0.5
1
2
10
20
10 minutes
30 minutes
FGLIpa (µg/ml)

Figure 7

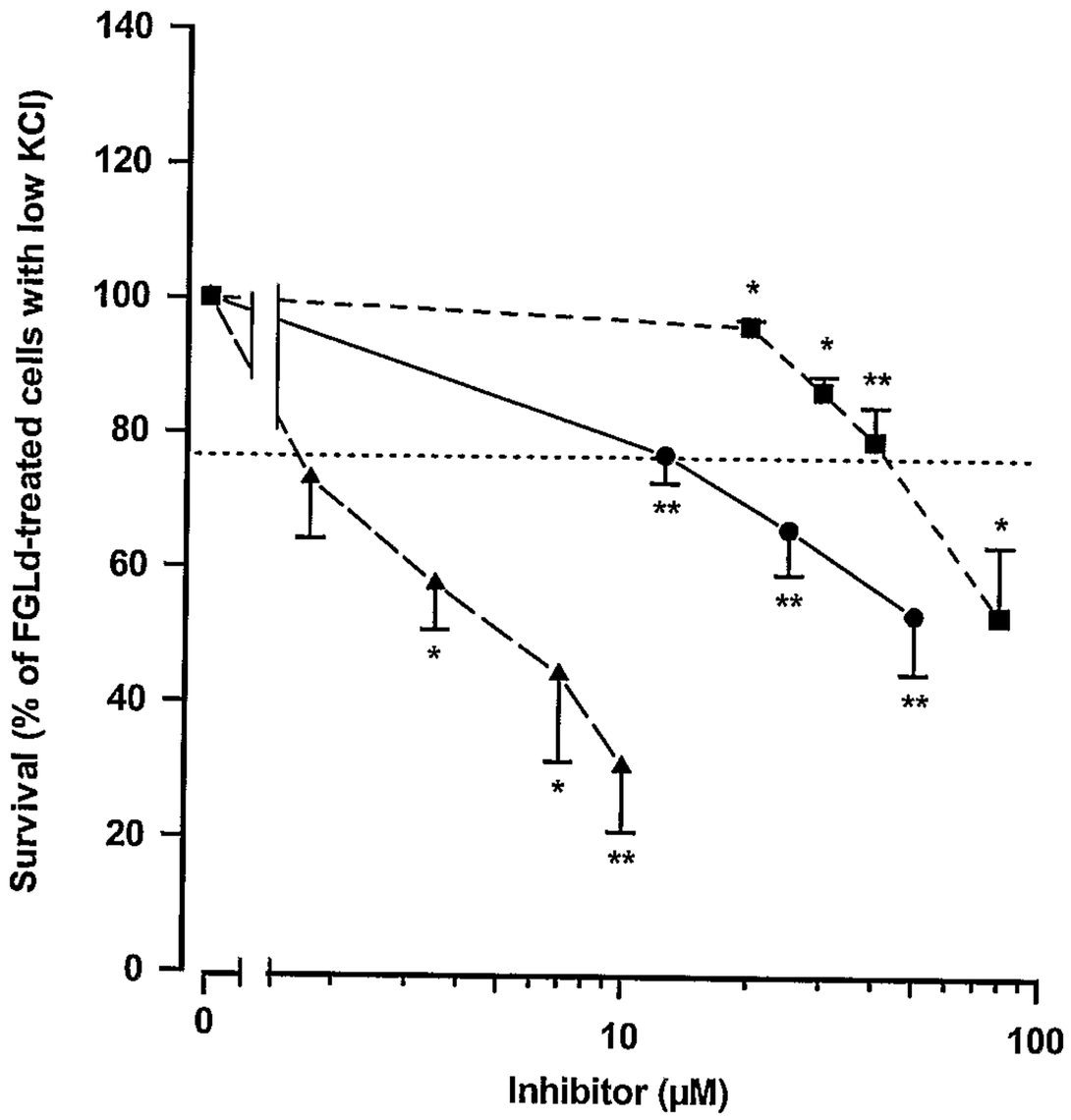

Survival (% of FGLd-treated cells with low KCl)
140
120
100
80
60
40
20
0
0
10
100
Inhibitor (μM)
*
**

Figure 8

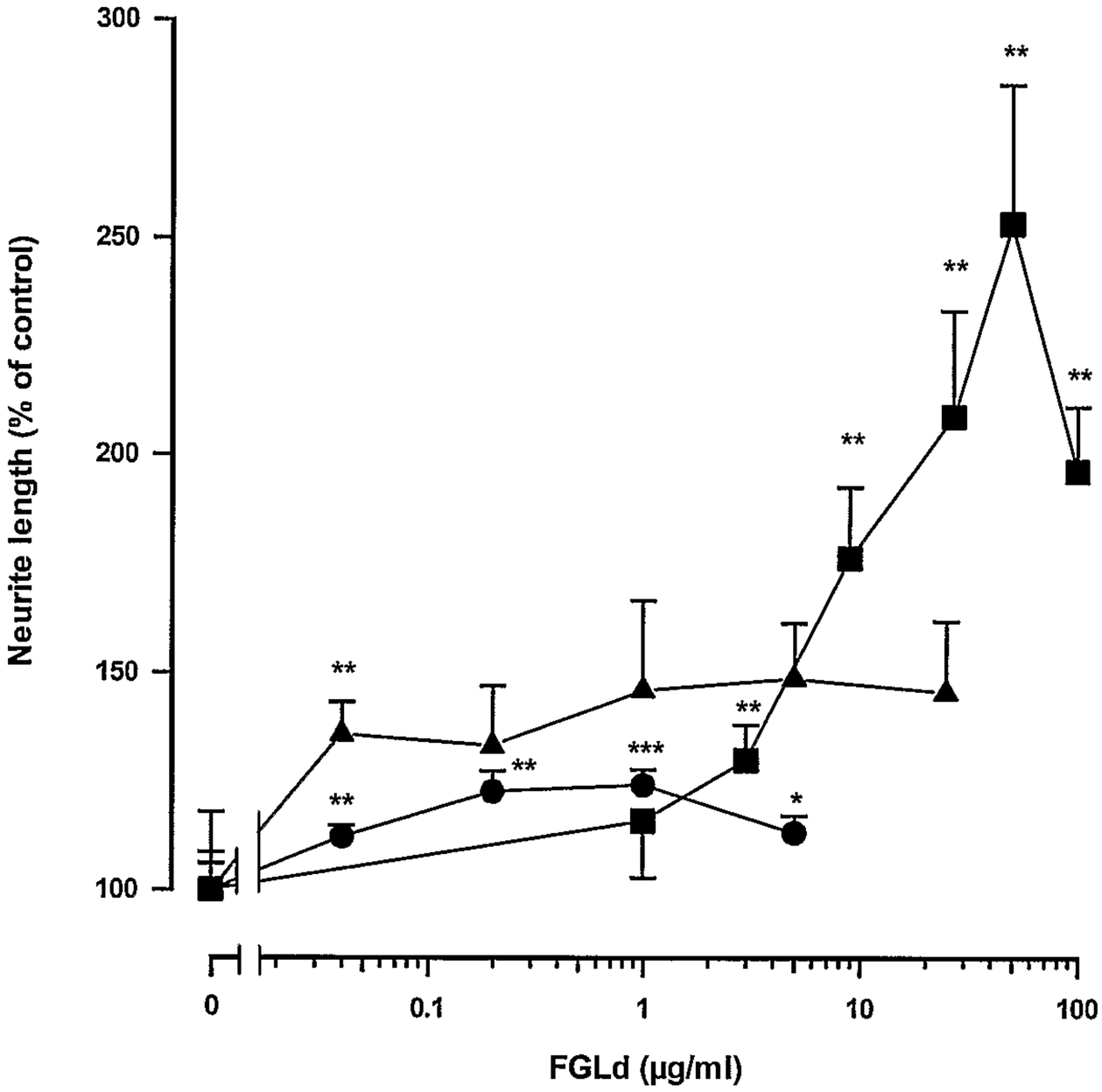

Neurite length (% of control)
300
250
200
150
100
0
0.1
1
10
100
FGLd (µg/ml)
**
**
**
**
**
**
***
**
*

Figure 9

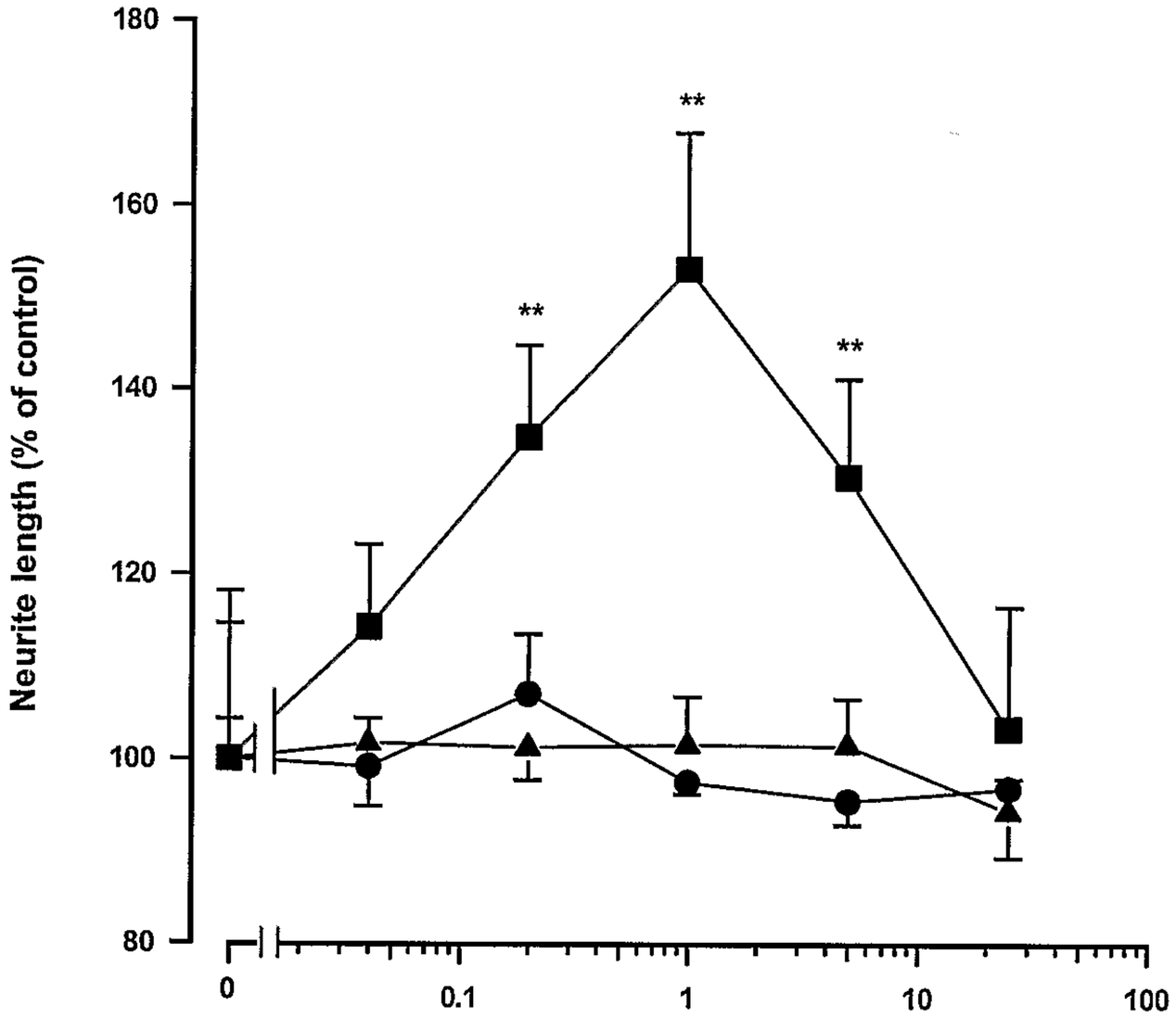

Neurite length (% of control)
180
160
140
120
100
80
0
0.1
1
10
100
**
**
**
Peptide concentration (µg/ml)

Figure 10

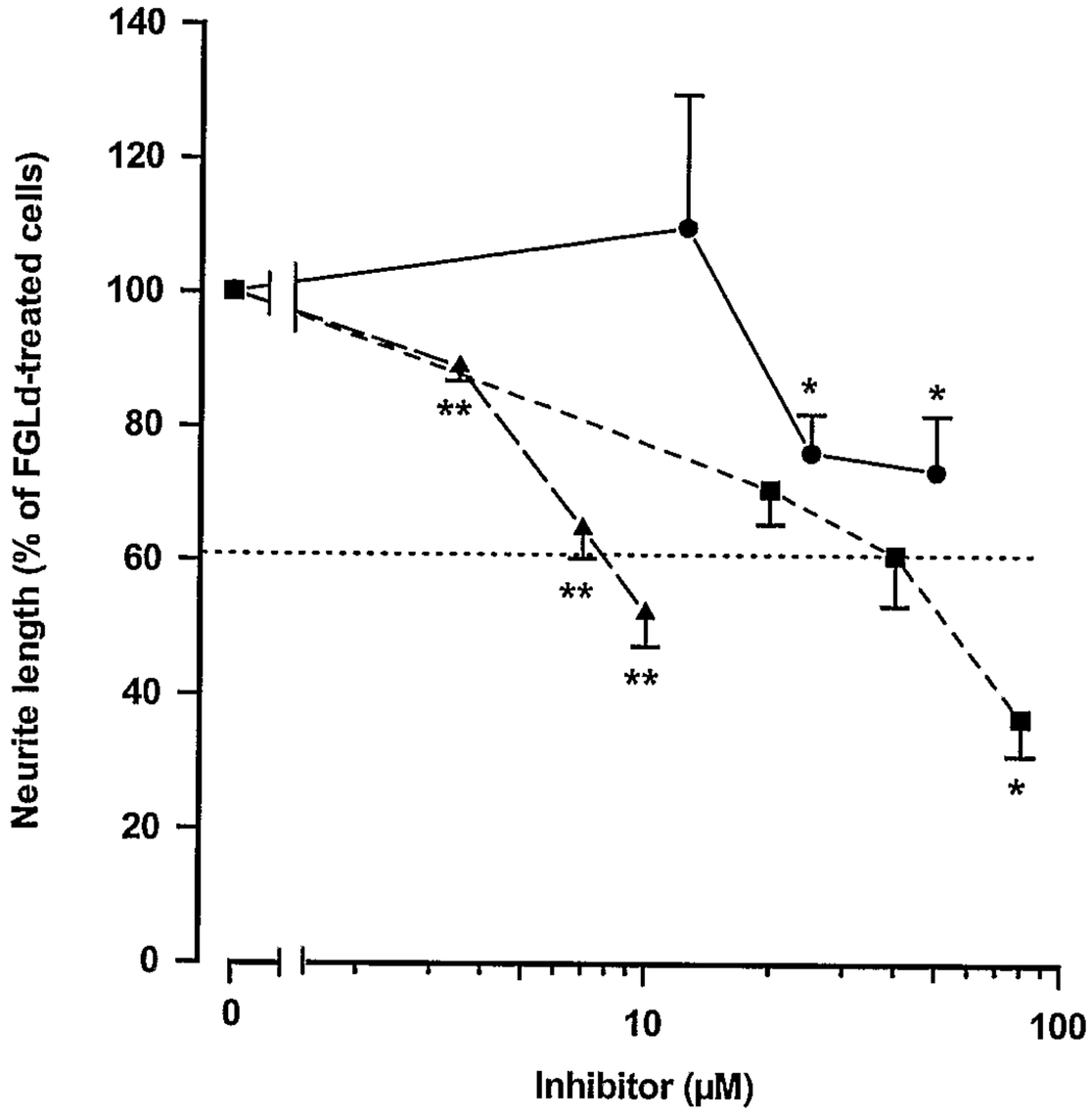

Neurite length (% of FGLd-treated cells)
140
120
100
80
60
40
20
0
0
10
100
Inhibitor (μM)
**
**
**
*
*
*

Figure 11

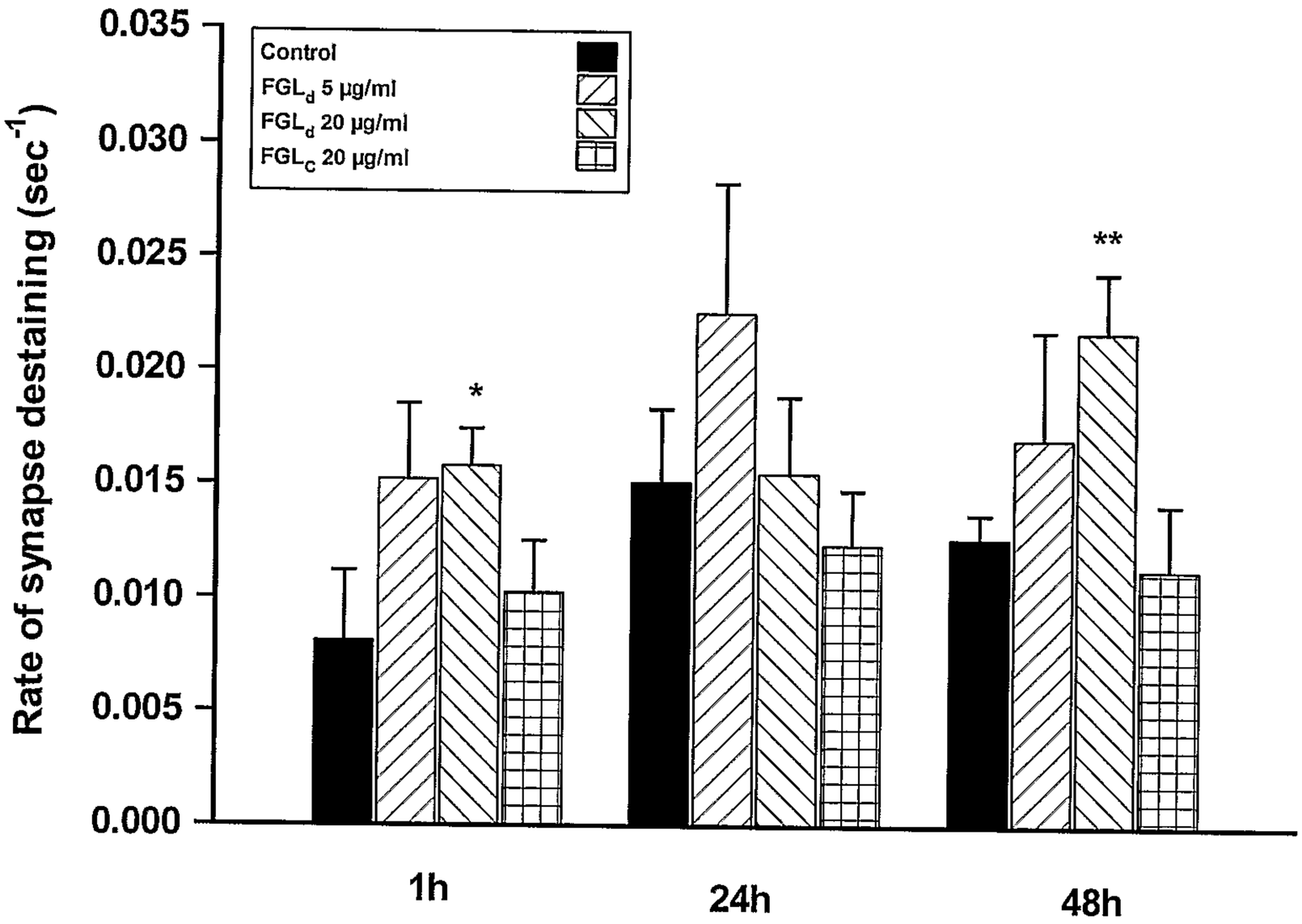

Control
FGL$_d$ 5 µg/ml
FGL$_d$ 20 µg/ml
FGL$_c$ 20 µg/ml
Rate of synapse destaining (sec^{-1})
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0.000
*
**
1h
24h
48h

Figure 12

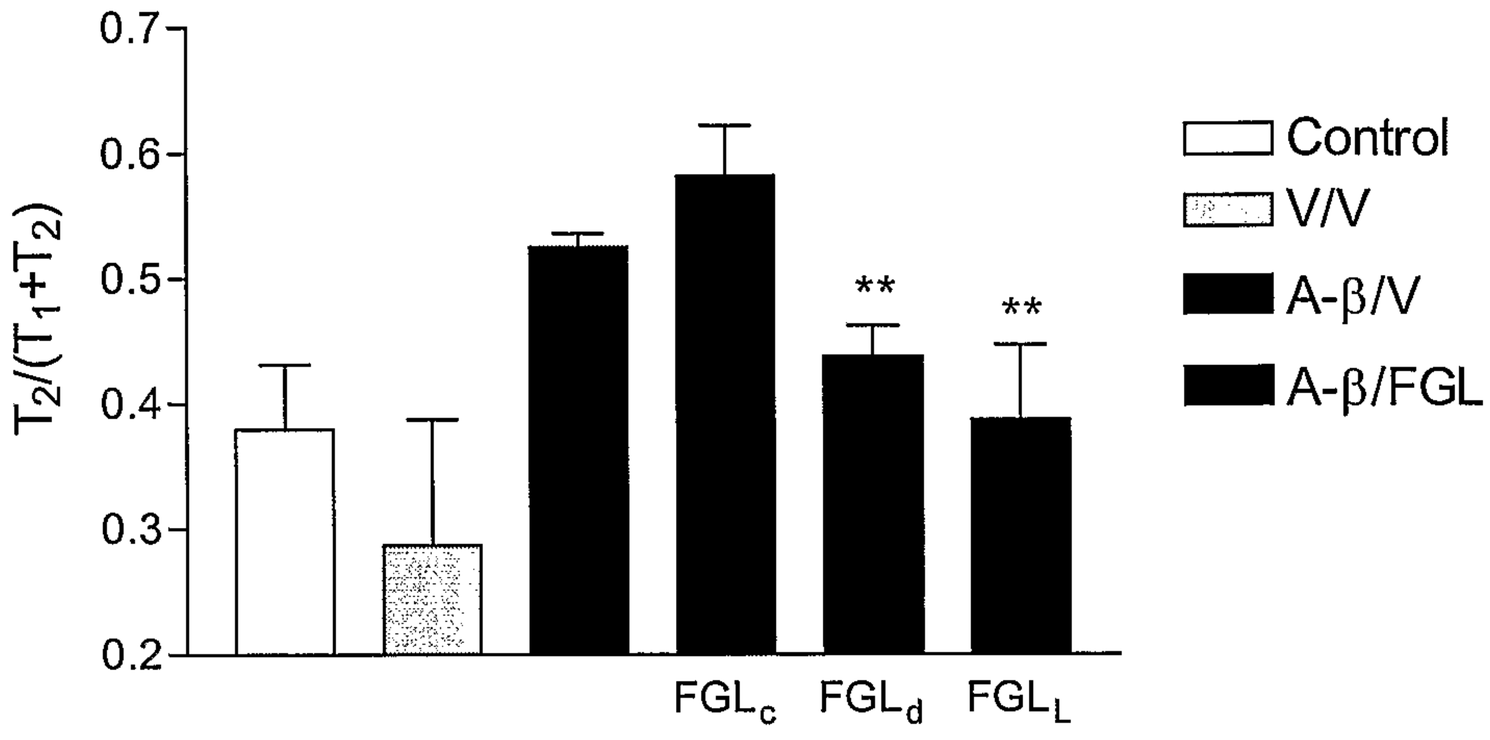


Figure 13

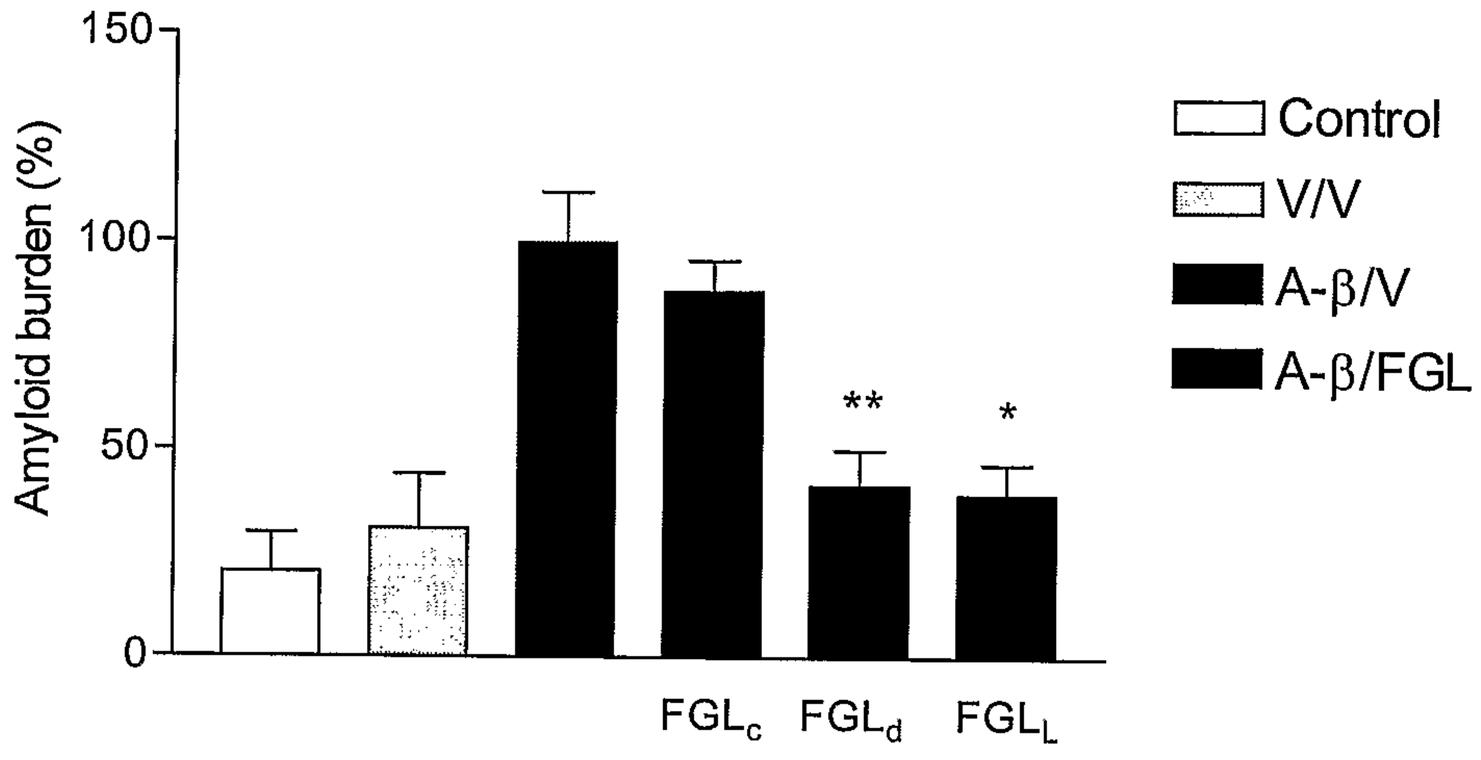

Amyloid burden (%)
150
100
50
0
**
*
FGL$_c$
FGL$_d$
FGL$_L$
Control
V/V
A-β/V
A-β/FGL

Figure 14

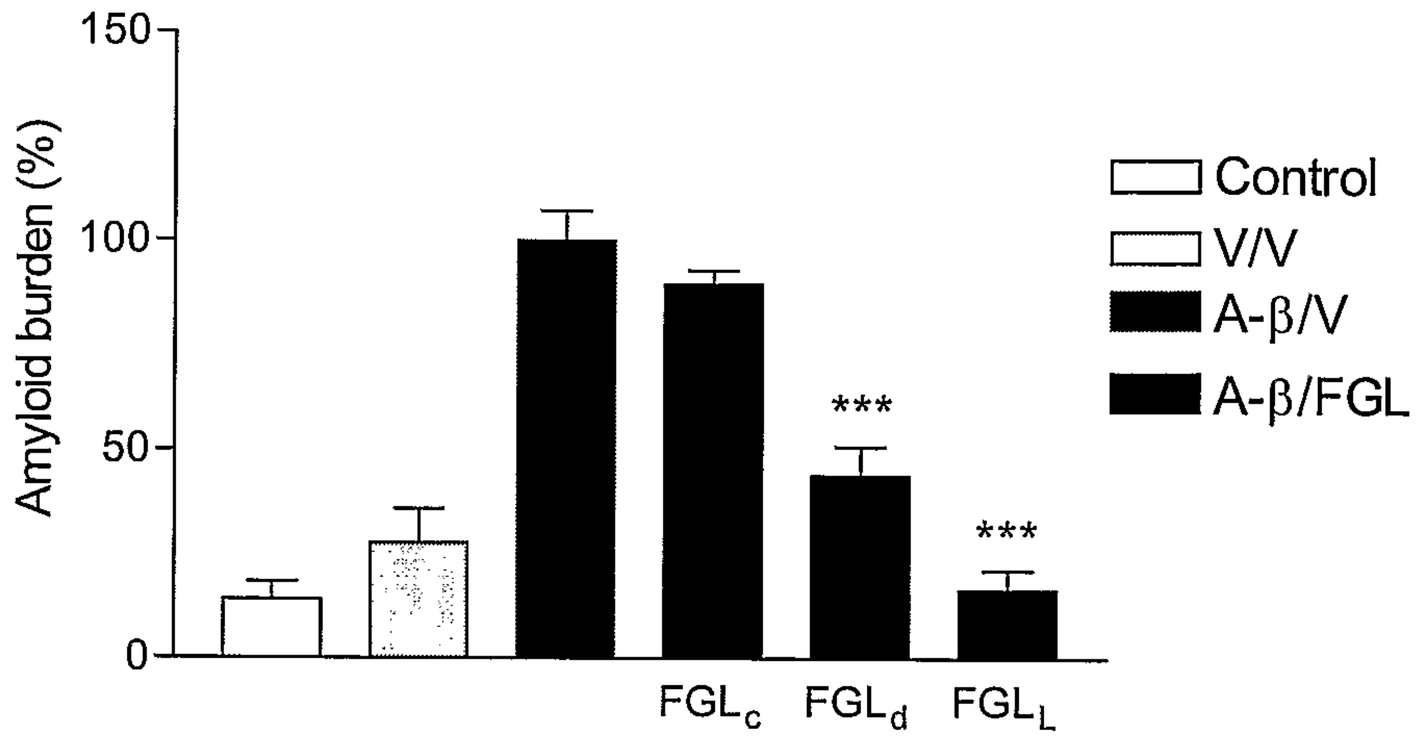

Amyloid burden (%)
150
100
50
0
***
***
FGL$_c$
FGL$_d$
FGL$_L$
Control
V/V
A-β/V
A-β/FGL

Figure 15

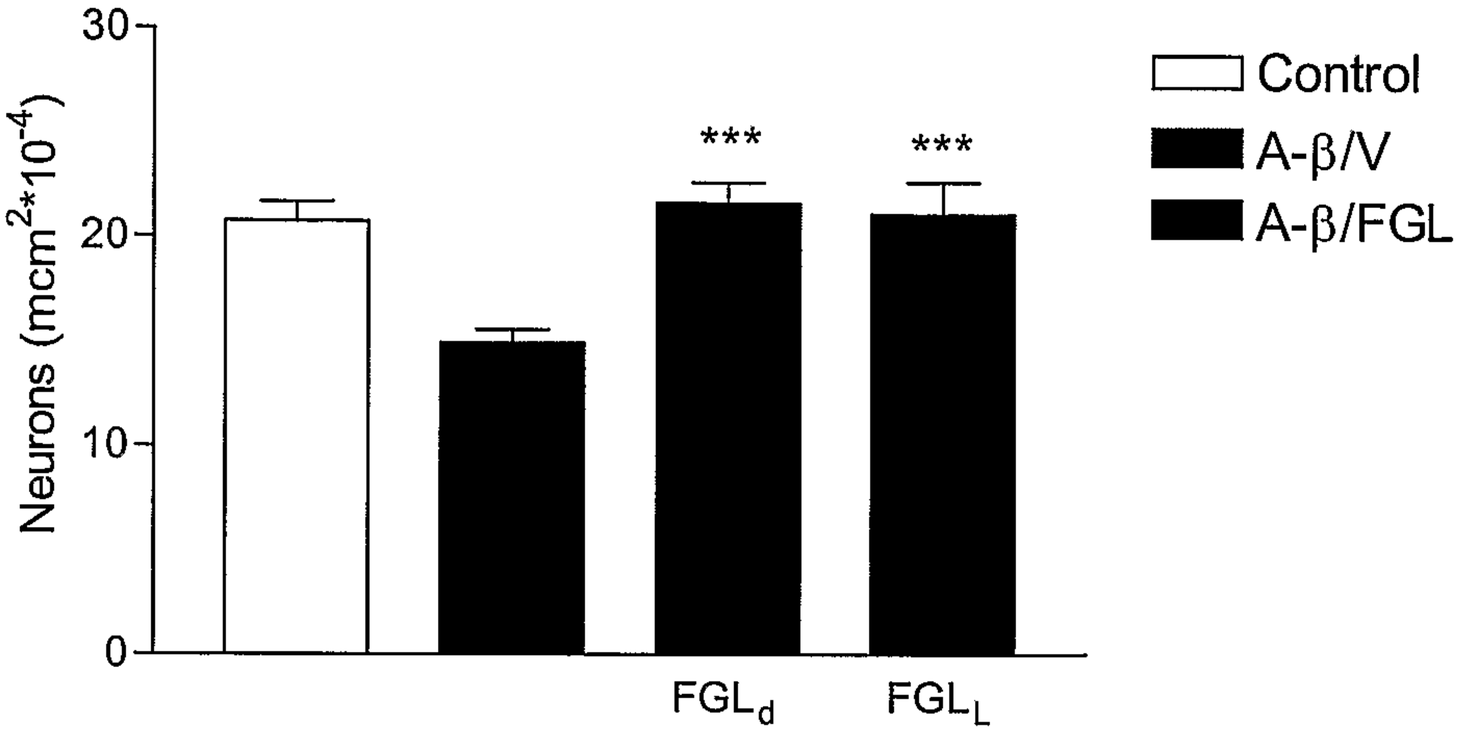


Figure 16

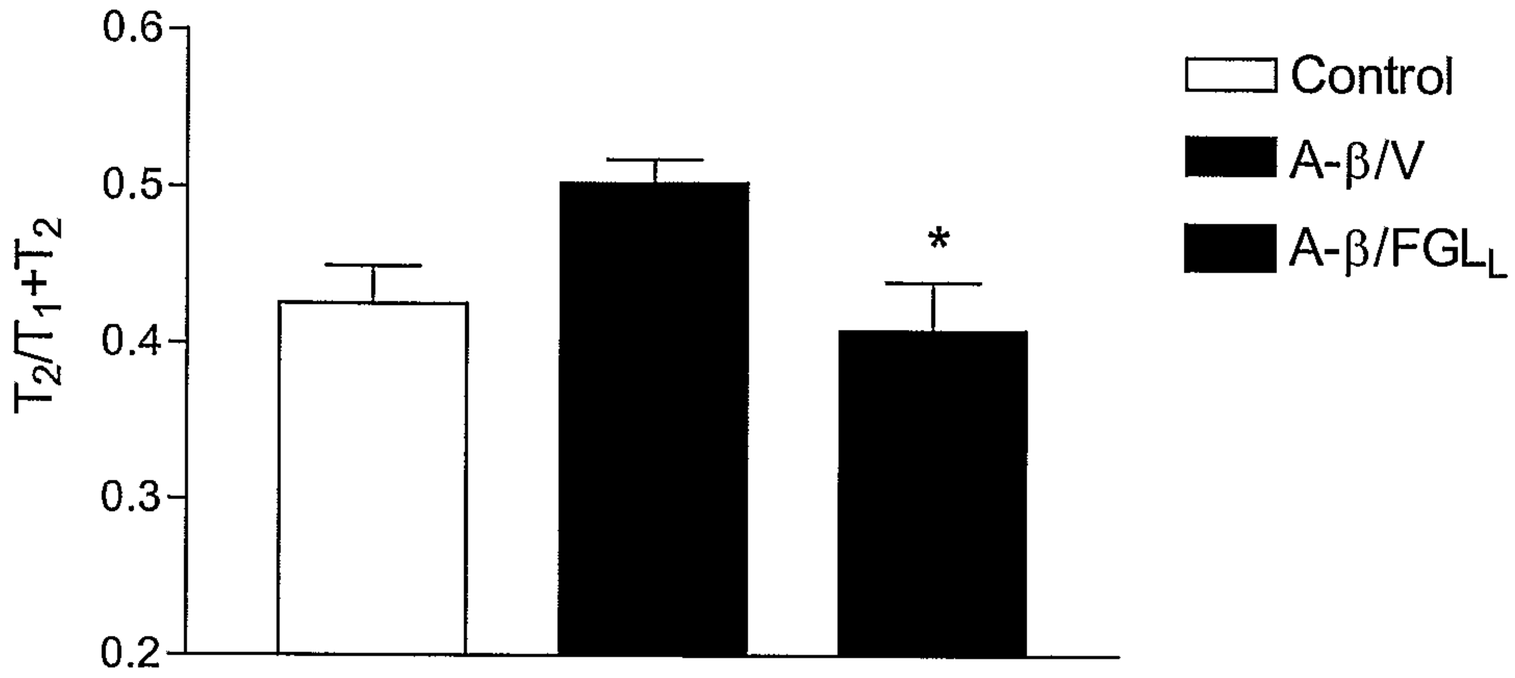


Figure 17

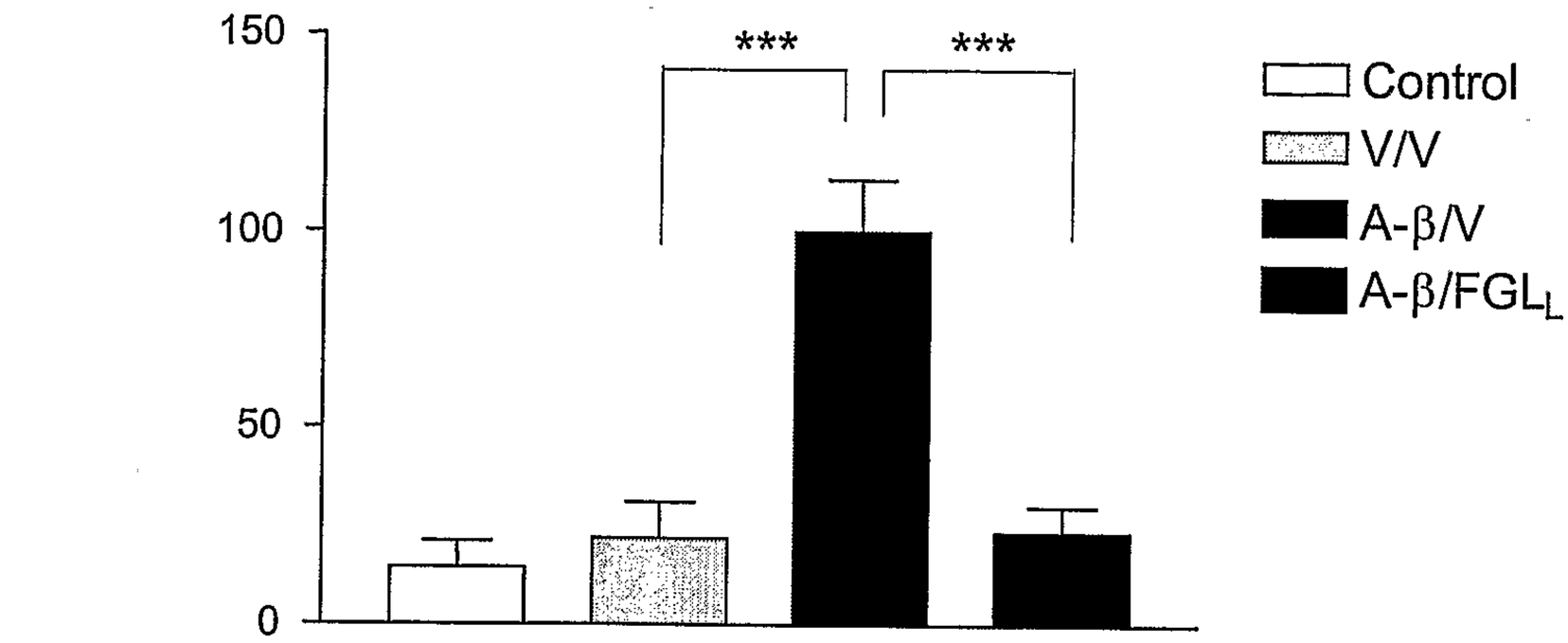


Figure 18

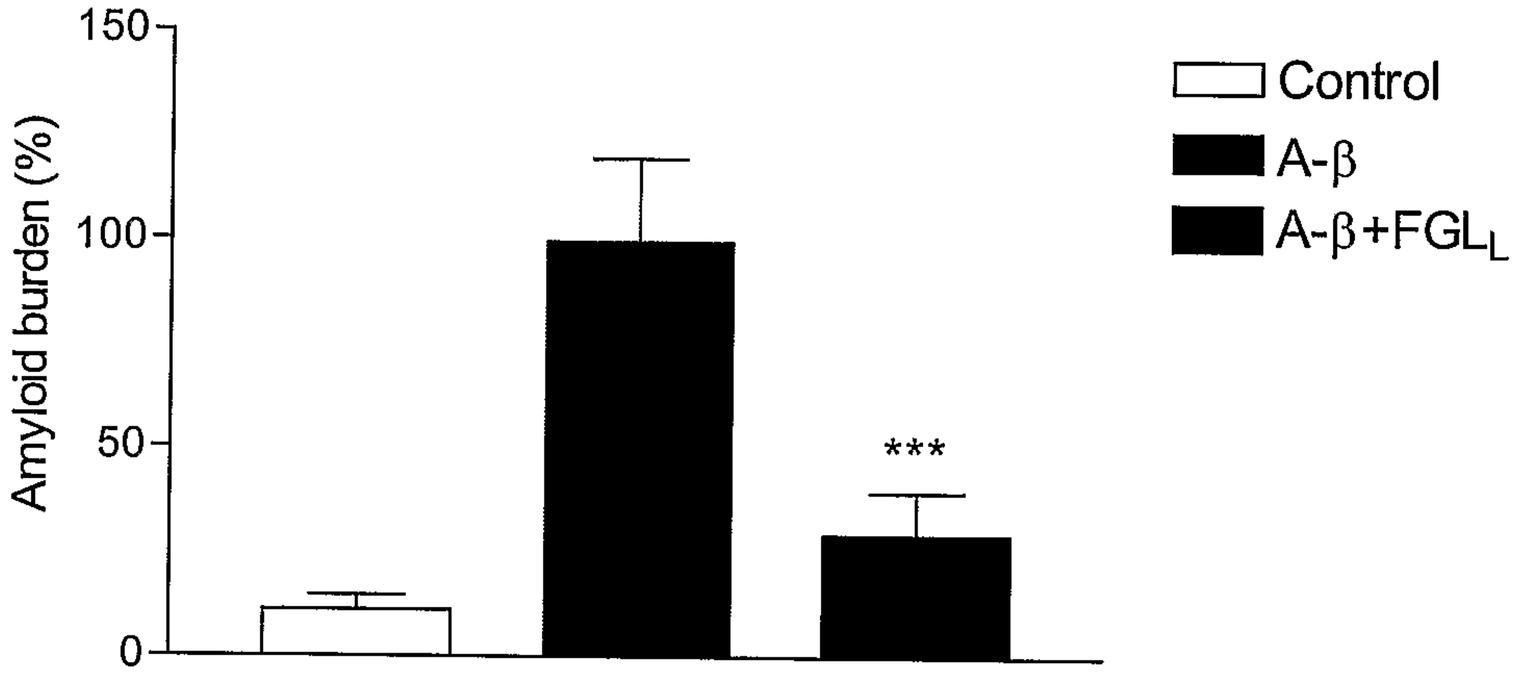


Figure 19

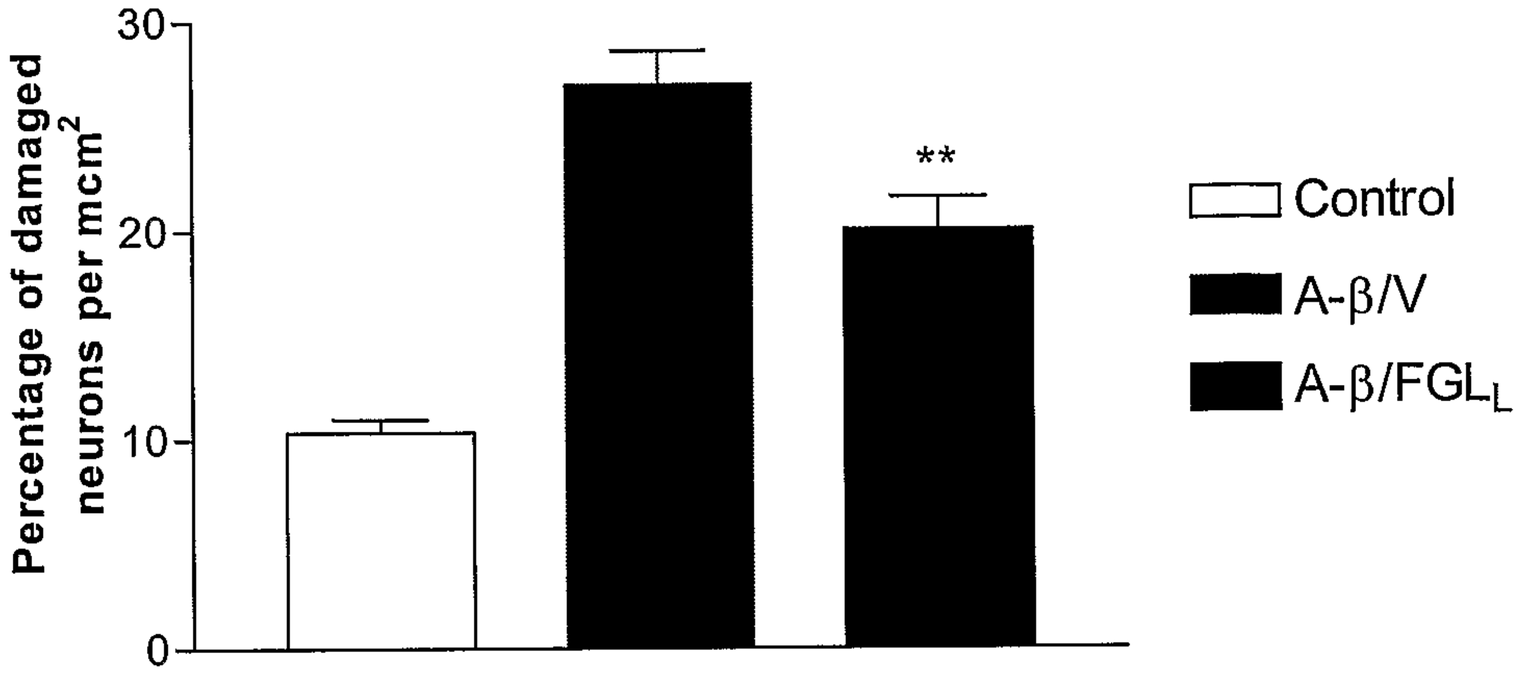

Percentage of damaged neurons per mcm2
30
20
10
0
**
Control
A-β/V
A-β/FGL_L

Figure 20

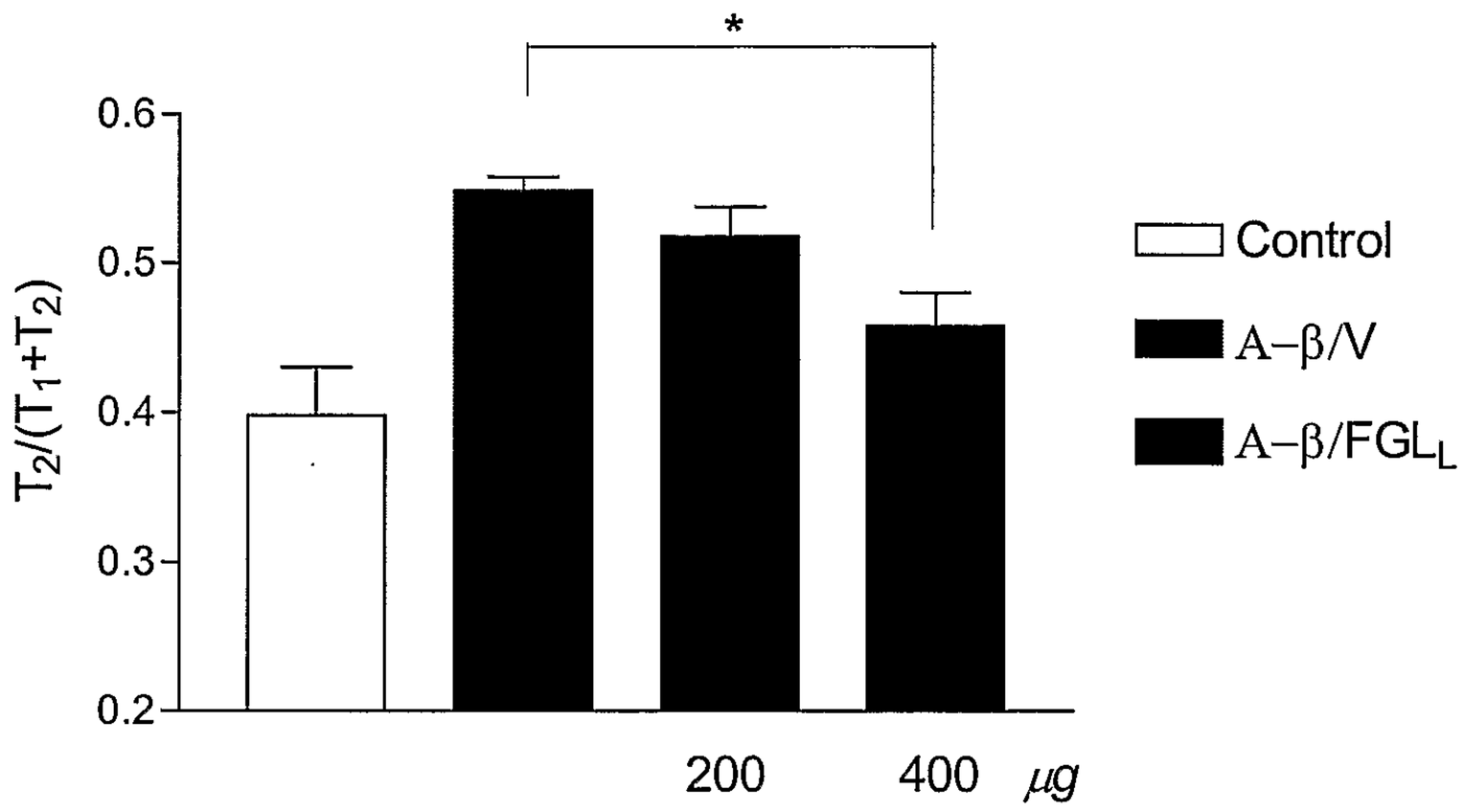


Figure 21

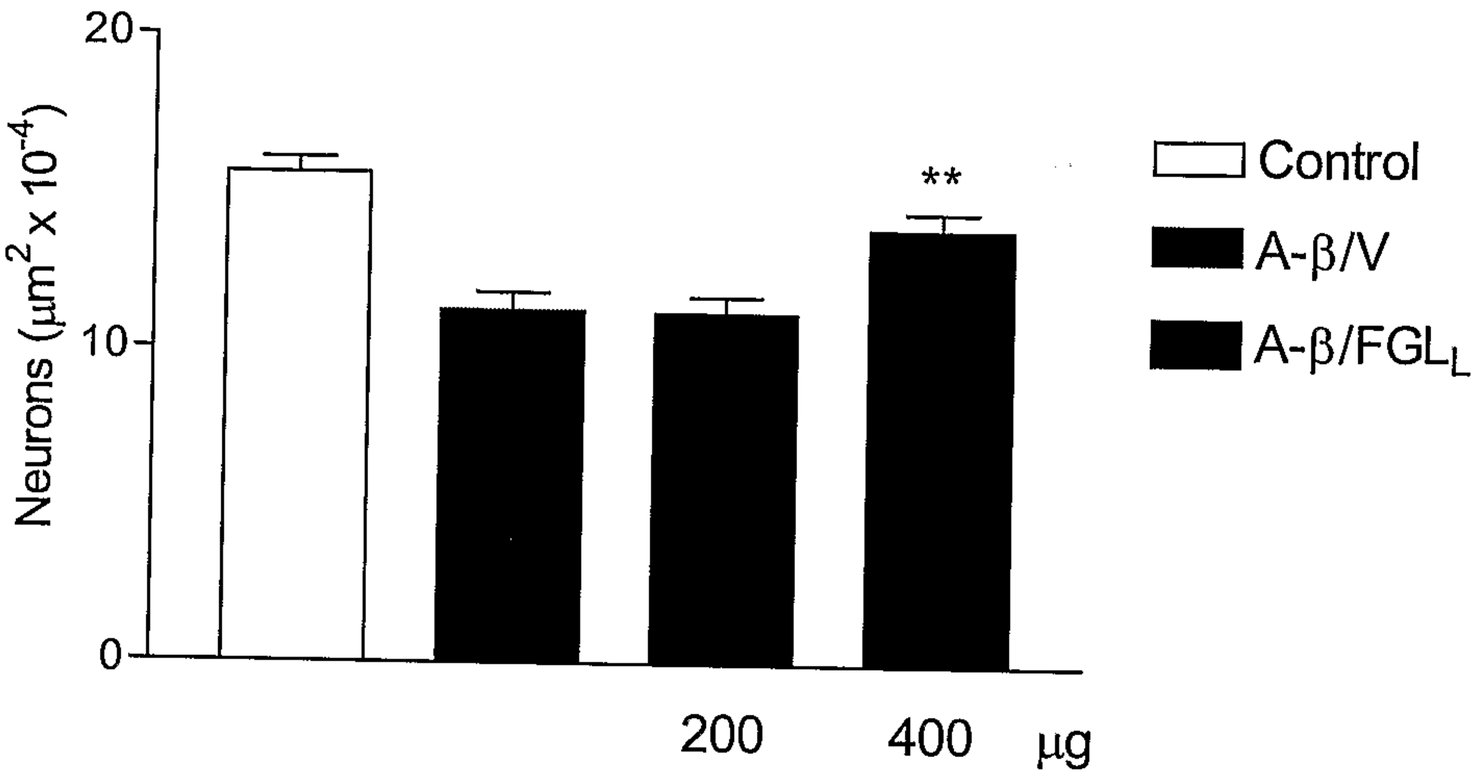


Figure 22

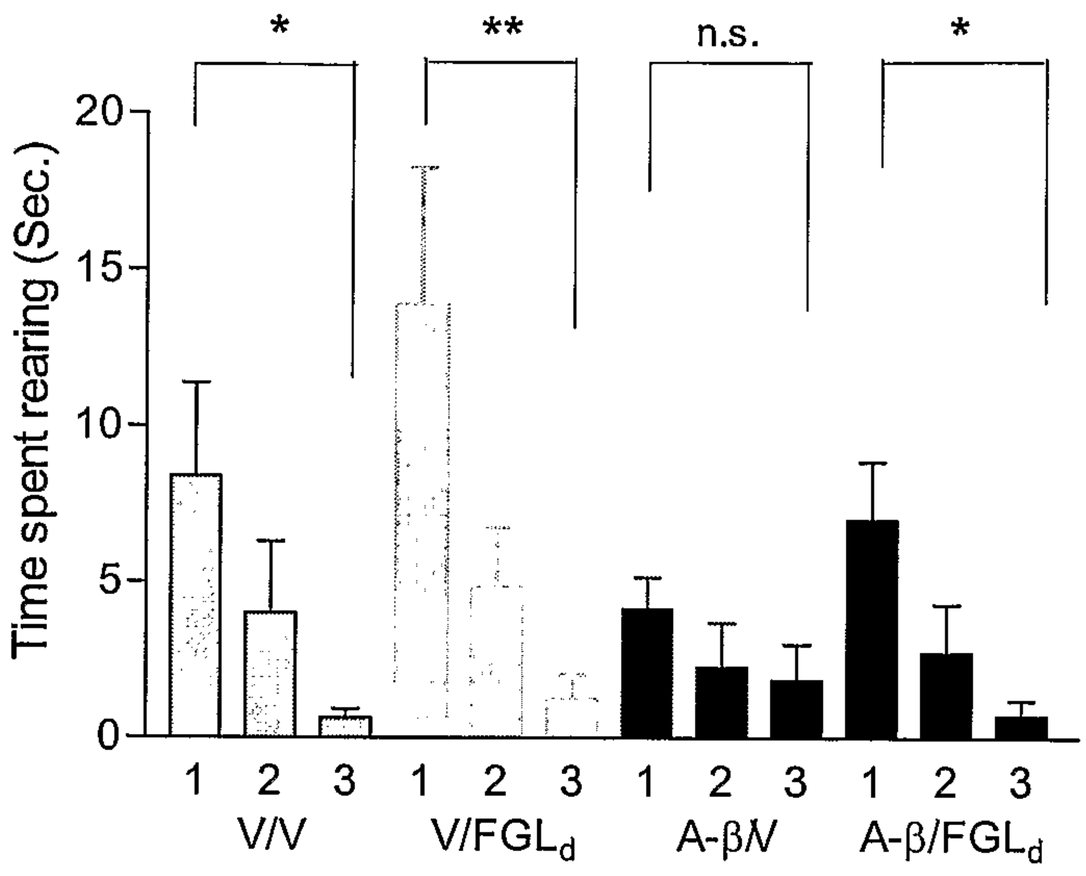

*
**
n.s.
*
Time spent rearing (Sec.)
20
15
10
5
0
1 2 3 1 2 3 1 2 3 1 2 3
V/V
V/FGL$_d$
A-β/V
A-β/FGL$_d$

Figure 23

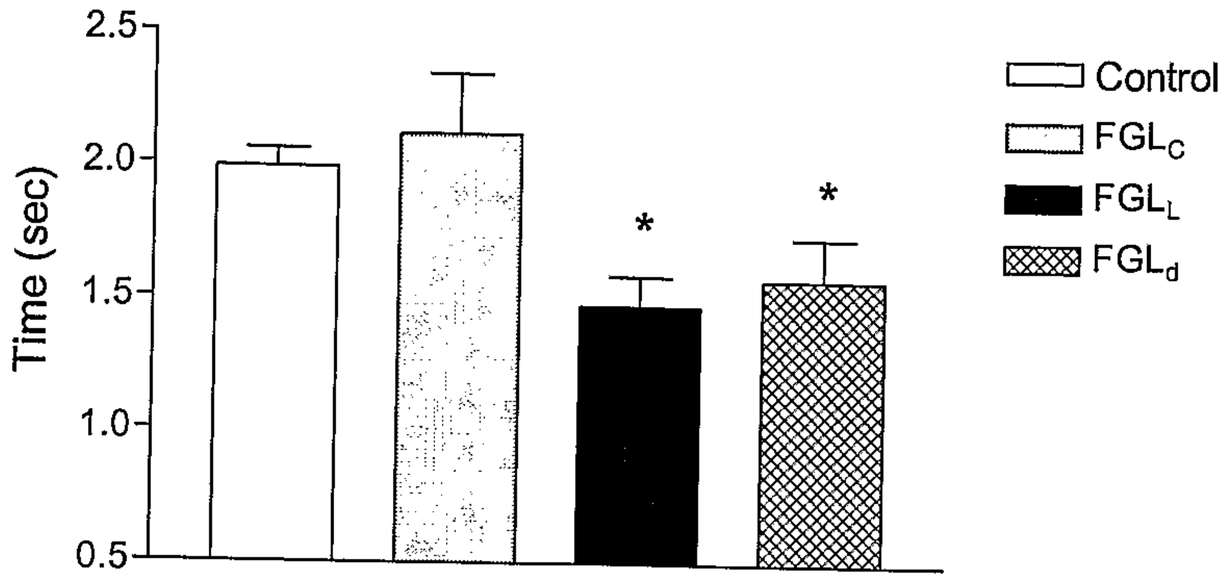


Figure 24

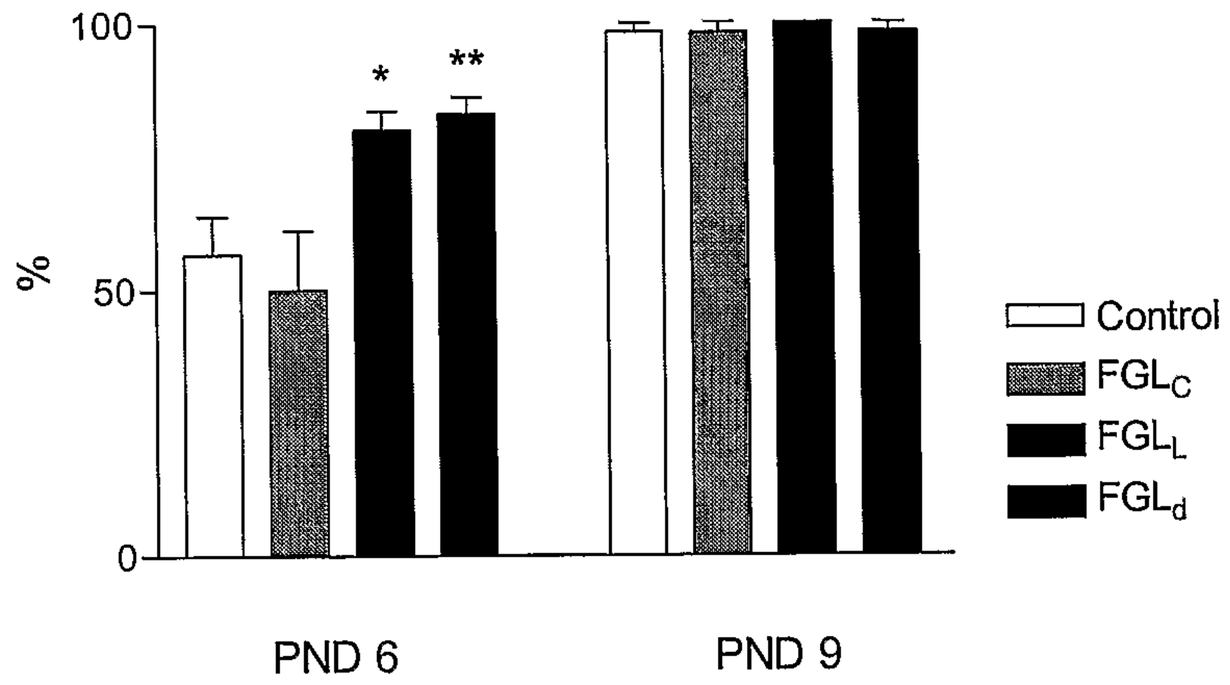


Figure 25

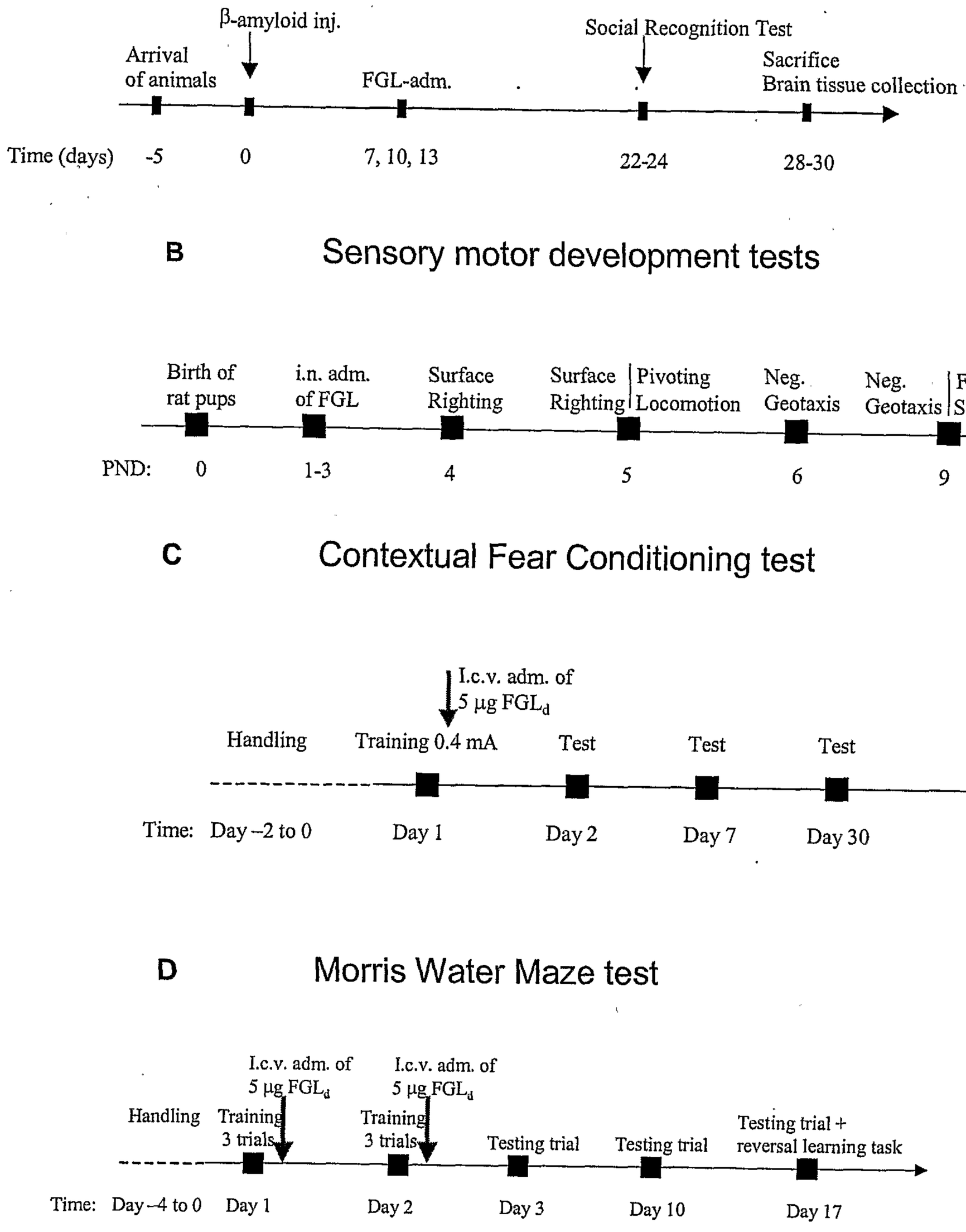

A
Social-recognition test
β-amyloid inj.
Social Recognition Test
Arrival of animals
FGL-adm.
Sacrifice Brain tissue collection
Time (days)
-5
0
7, 10, 13
22-24
28-30
B
Sensory motor development tests
Birth of rat pups
i.n. adm. of FGL
Surface Righting
Surface Righting
Pivoting Locomotion
Neg. Geotaxis
Neg. Geotaxis
Forepaw Suspension
PND:
0
1-3
4
5
6
9
C
Contextual Fear Conditioning test
I.c.v. adm. of 5 µg FGLd
Handling
Training 0.4 mA
Test
Test
Test
Time:
Day –2 to 0
Day 1
Day 2
Day 7
Day 30
D
Morris Water Maze test
I.c.v. adm. of 5 µg FGLd
I.c.v. adm. of 5 µg FGLd
Handling
Training 3 trials
Training 3 trials
Testing trial
Testing trial
Testing trial + reversal learning task
Time:
Day –4 to 0
Day 1
Day 2
Day 3
Day 10
Day 17

Figure 26

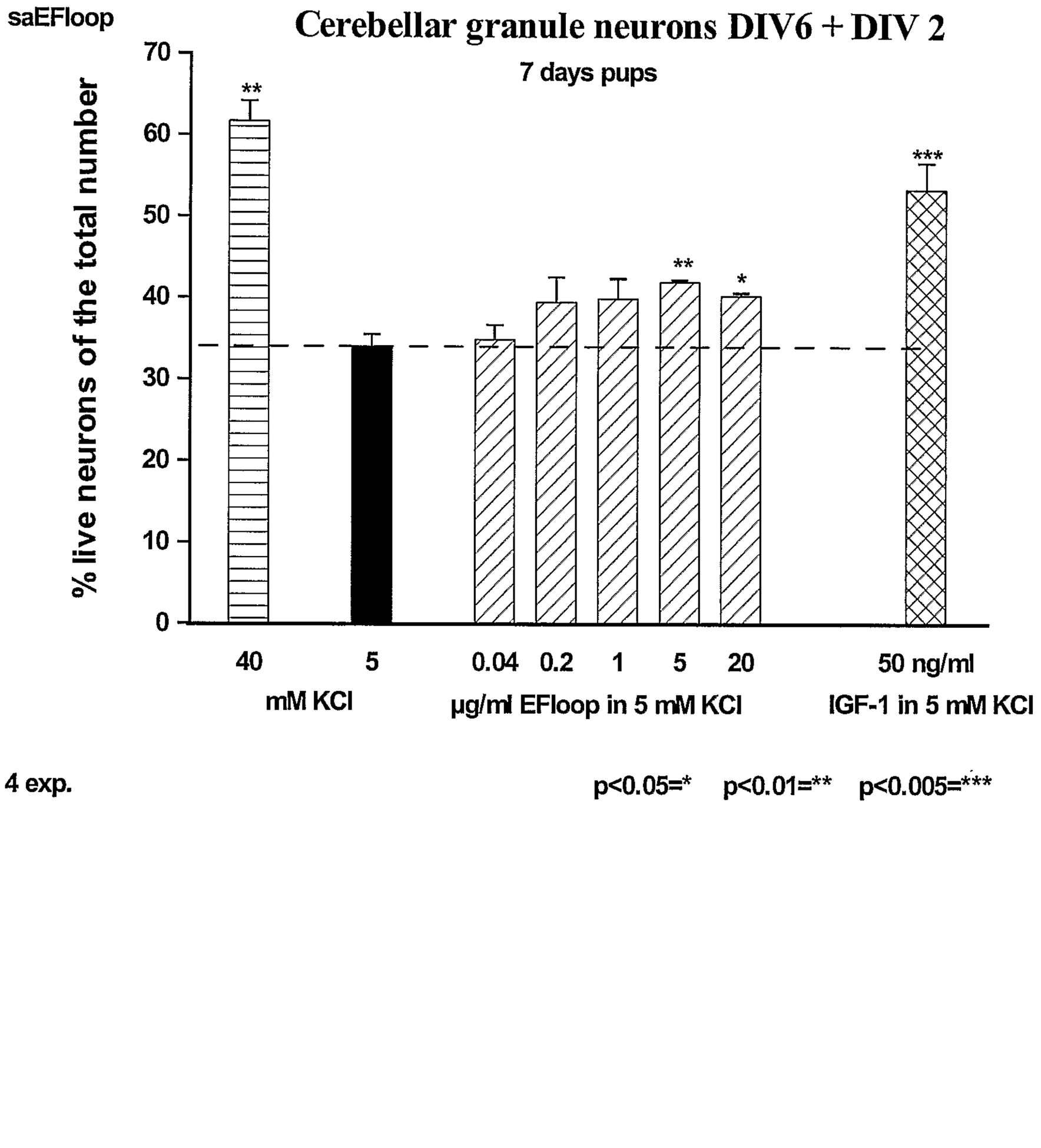

saEFloop
Cerebellar granule neurons DIV6 + DIV 2
7 days pups
% live neurons of the total number
70
60
50
40
30
20
10
0
**
**
*
***
40
5
0.04
0.2
1
5
20
50 ng/ml
mM KCl
µg/ml EFloop in 5 mM KCl
IGF-1 in 5 mM KCl
4 exp.
p<0.05=*
p<0.01=**
p<0.005=***

Figure 27

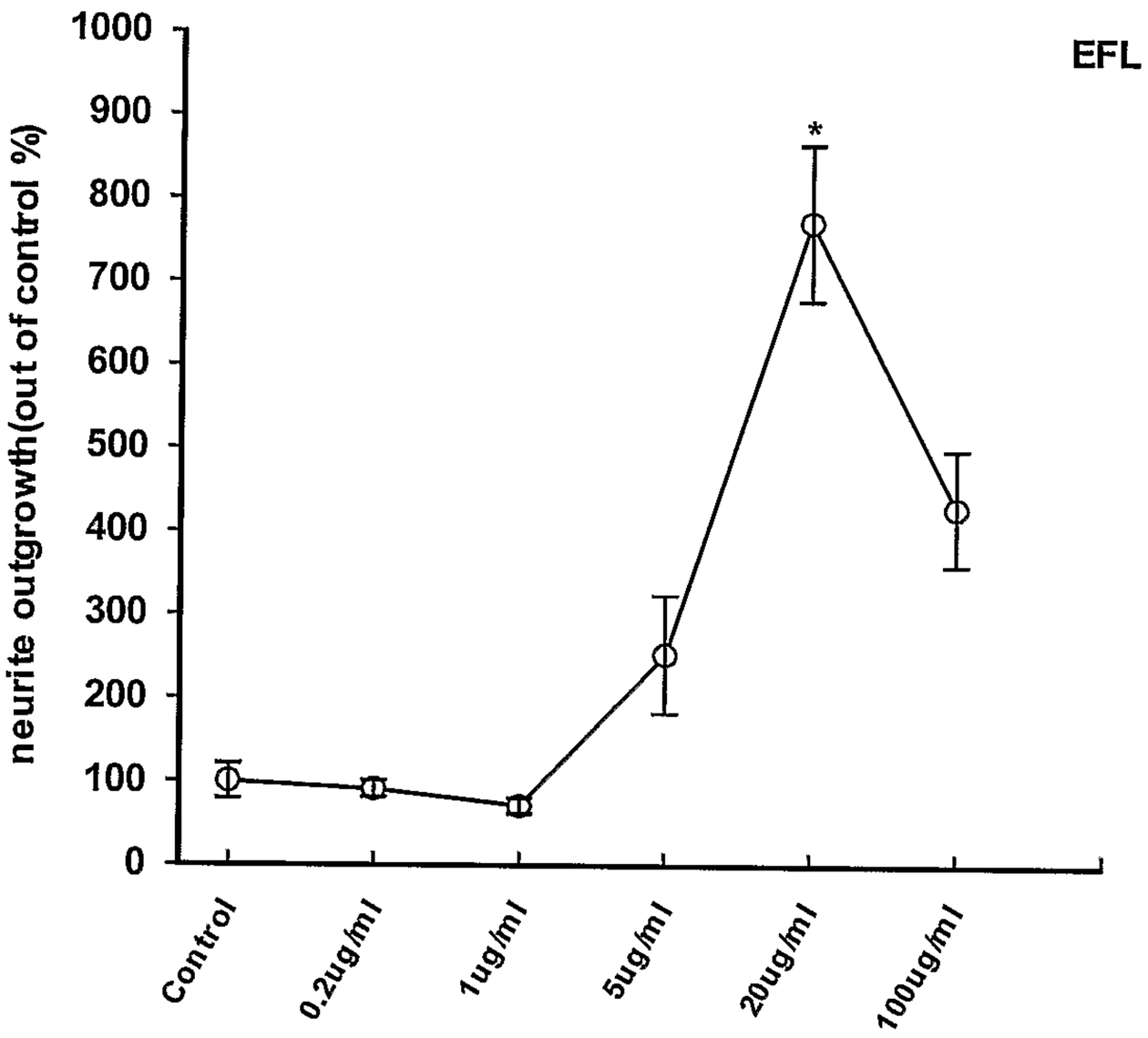

EFL
neurite outgrowth(out of control %)
1000
900
800
700
600
500
400
300
200
100
0
*
Control
0.2ug/ml
1ug/ml
5ug/ml
20ug/ml
100ug/ml

Figure 28