PORCINE ALPHA2DELTA-1 CALCIUM CHANNEL SUBUNIT CDNA AND SOLUBLE SECRETED ALPHA2DELTA-1 SUBUNIT POLYPEPTIDES

Inventors: Jason Peter Brown, Cambridge (GB); Nicolas Steven Gee, Dundee (GB)

Correspondence Address:
WARNER-LAMBERT COMPANY
2800 PLYMOUTH RD
ANN ARBOR, MI 48105 (US)

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ABSTRACT
Soluble α2δ-1 subtype polypeptides.
Methods for cloning, expression and purification of freely soluble α2δ-1 subtype polypeptides.
PORCINE ALPHA2DELTA-1 CALCIUM CHANNEL SUBUNIT CDNA AND SOLUBLE SECRETED ALPHA2DELTA-1 SUBUNIT POLYPEPTIDES

BACKGROUND OF THE INVENTION

[0001] Voltage-dependent Ca$^{2+}$ channels (VDCCs) are heteromultimeric complexes present in both neuronal and non-neuronal tissues, including heart and skeletal muscle. VDCCs are minimally composed of three subunits: a pore-forming transmembrane $\alpha_1$ subunit, a hydrophilic intracellular $\beta$ subunit, and a membrane-associated $\alpha_2\delta-1$ subunit; a transmembrane $\gamma$ subunit is also found in skeletal muscle tissue. Multiple subtypes and/or splice variants of the $\alpha_1$, $\beta$, and $\alpha_2\delta-1$ subunits have been found. In heterologous expression studies, the $\alpha_2\delta-1$ subunit has been shown to increase $\alpha_1$ currents both by facilitating the assembly of a $\alpha_1$ subunit at the cell surface and by stimulating the peak $\alpha_1$ current. The modulatory effects of $\alpha_2\delta-1$ are more pronounced if the $\alpha_1$ and $\alpha_2\delta-1$ subunits are co-expressed with the $\beta$ subunit. However, the functions of the $\alpha_2\delta-1$, $\beta$, and $\gamma$ subunits in vivo are not yet completely understood.

[0002] Gabapentin (1-aminomethyl)cyclohexane acetic acid or Neurontin) is a structural analogue of GABA, which is mainly used as an adjunctive therapy for epilepsy. Recent research suggests that gabapentin may also have clinical utility for various indications including anxiety and pain. Although designed as a lipophilic GABA-mimetic, gabapentin does not have a high affinity for either GABA$_A$ or GABA$_B$ receptors, GABA uptake sites, or the GABA-degrading enzyme GABA-transaminase (EC 2.6.1.19).

[0003] A novel high affinity binding site for $[^3]H$gabapentin in rat, mouse, and pig brains has been characterized. Recently, the $[^3]H$gabapentin-binding protein was isolated from pig brain and identified as the $\alpha_2\delta-1$ subunit of VDCCs. None of the prototypic anticonvulsant drugs displaces $[^3]H$gabapentin binding from the $\alpha_2\delta-1$ subunit. $[^3]H$Gaba-pentin-binding is stereospecifically inhibited by two enantiomers of 3-isobutyl GABA. The rank order of potency of gabapentin, and S- and R-isobutyl GABA, at the $[^3]H$ gabapentin binding site mirrors their anticonvulsant activity in mice. However, electrophysiological studies have yielded conflicting data on the action of gabapentin at VDCCs.

[0004] The $\alpha_2\delta-1$ subunit is derived from a single gene, the product of which is extensively post-translationally modified particularly through the cleavage of the signal sequence. The polypeptide is cleaved to form disulfide-bridged $\alpha_2$ and $\delta$ peptides, both of which are heavily glycosylated. Although the $\alpha_2$ and $\delta$ peptides are membrane-associated peptides, it is unclear whether these peptides comprise one or several transmembrane domains. Furthermore, the location, size and structural configuration of these potential transmembrane domains remains to be determined.

[0005] In any event, the fact that $\alpha_2\delta-1$ is a membrane-associated protein, regardless of its precise structural configuration, renders its large scale expression in recombinant systems difficult. Indeed, since the $\alpha_2\delta-1$ protein is targeted to the membrane, it requires detergent solubilisation to purify it. Thus this important drawback imposes considerable restrictions for any potential applications requiring large amounts of recombinant protein.

SUMMARY OF THE INVENTION

[0006] In the context of the present invention, the inventors have cloned, isolated and sequenced the porcine cerebral voltage-dependent calcium channel $\alpha_2\delta-1$ subunit cDNA. (hereinafter the porcine $\alpha_2\delta-1$ subunit cDNA).

[0007] The invention therefore concerns a purified or isolated nucleic acid encoding a porcine $\alpha_2\delta-1$ subunit cDNA or a sequence complementary thereto. Oligonucleotide probes or primers specifically hybridizing to a nucleic acid encoding a porcine $\alpha_2\delta-1$ subunit, to fragments thereof or to a sequence complementary thereto are also part of the invention as well as DNA amplification and detection methods using said primers and probes.

[0008] The inventors have also found that it was possible to delete a portion of the nucleotide sequence encoding a eukaryotic, preferably a mammalian $\alpha_2\delta-1$ subunit to yield a soluble secreted protein which retains its affinity for $[^3]H$gabapentin and/or other derivatives or compounds such as pregabalin and gabapentoids.

[0009] Hence, the invention also concerns nucleotide sequence fragments of an $\alpha_2\delta-1$ subunit cDNA encoding a soluble secreted $\alpha_2\delta-1$ subunit polypeptide. Preferably, these nucleotide sequences encode a soluble secreted $\alpha_2\delta-1$ subunit polypeptide bearing a gabapentin or a $[^3]H$gabapentin binding site. More preferably, the soluble secreted $\alpha_2\delta-1$ subunit nucleic acid is derived from the porcine or human $\alpha_2\delta-1$ subunits.

[0010] A further object of the present invention concerns recombinant vectors comprising any of the nucleic acid sequence described herein, and in particular recombinant vectors comprising a nucleic acid sequence encoding a recombinant porcine $\alpha_2\delta-1$ subunit of the invention. The invention also includes recombinant vectors comprising a nucleic acid sequence encoding a soluble secreted $\alpha_2\delta-1$ subunit polypeptide.

[0011] The invention also encompasses host cells and transgenic non-human mammals comprising said nucleic acid sequences or recombinant vectors.

[0012] The invention concerns an isolated recombinant porcine $\alpha_2\delta-1$ subunit. The invention also concerns a porcine $\alpha_2\delta-1$ subunit polypeptide or a peptide fragment thereof as well as antibodies specifically directed against such porcine $\alpha_2\delta-1$ subunit polypeptide or peptide fragment.

[0013] Furthermore, the invention concerns a secreted soluble $\alpha_2\delta-1$ subunit polypeptide which is characterized in that it is a soluble secreted polypeptide having affinity for $[^3]H$gabapentin. Preferably, the soluble secreted polypeptide is derived from the porcine or human $\alpha_2\delta-1$ subunits.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The invention concerns an isolated nucleotide sequence of the porcine $\alpha_2\delta-1$ subunit cDNA. The invention also concerns truncated $\alpha_2\delta-1$ subunit cDNA sequences. These truncated sequences encode a soluble secreted polypeptide which retains affinity for $[^3]H$gabapentin. More details on the various embodiments of the invention are provided below.

[0015] A) Porcine $\alpha_2\delta-1$ Subunit cDNA

[0016] A first object of the present invention is of a purified or isolated nucleic acid encoding a porcine $\alpha_2\delta-1$ subunit, or a sequence complementary thereto.
This cDNA was isolated in several steps. First, a porcine cerebral cortical cDNA library was screened using a fragment of the rabbit skeletal muscle αβδ-1 clone as the probe. This allowed the isolation of a αβδ-1 coding region which was homologous to the 3' region of the human neuronal αβδ-1 sequence but lacked a substantial portion of the 5' coding sequence. The missing sequence was then obtained by 5'-RACE using total RNA prepared from porcine cerebral cortex.

Another object of the invention is a purified or isolated nucleic acid having at least 90%, preferably 95%, more preferably 98% and most preferably 99% nucleotide identity with the nucleotide sequence of SEQ ID No1, or a sequence complementary thereto.

A further object of the present invention is a purified or isolated nucleic acid encoding a polypeptide having at least 80%, preferably 90%, more preferably 95%, and most preferably 98 or 99% amino-acid identity with the porcine polypeptide of the amino-acid sequence of SEQ ID No5 or with a peptide fragment thereof, or a sequence complementary thereto.

Polypeptides having amino-acid identity with the αβδ-1 subunit of the invention encompass polypeptides:

that have primary structures which are related to the αβδ-1 subunit of any one of the amino-acid sequences of SEQ ID No5, due to the high sequence identity between the amino-acid sequences; or

that are biologically related to the polypeptides of any one of the amino-acid sequences of SEQ ID No5, either because these homologous polypeptides are recognized by antibodies specifically directed against the amino-acid sequence of SEQ ID No5 and/or because these homologous polypeptides have the same biological activity as the polypeptides of the amino-acid sequence of SEQ ID No5, such as for example the capacity of binding [3H]gabapentin with suitable affinity.

It is important to note that the first 24 amino acids of the amino acid sequence of SEQ ID No5 is a signal peptide. This signal peptide can in some embodiments be deleted or replaced by a signal peptide from another species. For example, if one wishes to express this protein in insect cells, the native porcine αβδ-1 signal peptide can be replaced by a signal peptide of insect origin.

The term “isolated”, when used herein, requires that the material be removed from its original environment (e.g. the natural environment if it is naturally occurring). For example, a naturally occurring polynucleotide or a peptide present in a living animal is not isolated, but the same polynucleotide or peptide, separated from some or all of the coexisting materials in the natural system, is isolated. Such polynucleotide can be part of a vector and/or such polynucleotide or peptide can be part of a composition, and still be isolated. This is so because the vector or composition is not part of the original environment of the polynucleotide sequence it contains.

The term “purified” does not require absolute purity; rather, it is intended as a relative definition. Purification of starting materials or natural materials to at least one order of magnitude, preferably two or three orders, and more preferably four or five orders of magnitude is expressly contemplated.

Throughout the present specification, the expression “nucleotide sequence” is used to designate indifferently a polynucleotide or a nucleic acid. More precisely, the expression “nucleotide sequence” encompasses the nucleic material and the sequence information and is not restricted to the sequence information (i.e., the succession of letters chosen among the four base letters) that biochemically characterizes a specific DNA or RNA molecule.

As used interchangeably herein, the terms “oligonucleotides”, “nucleic acids” and polynucleotides include RNA, DNA, or RNA/DNA hybrid sequences of more than one nucleotide in either single chain or duplex form.

Further to its general meaning understood by the one skilled in the art, the term “nucleotide” is also used herein to encompass modified nucleotides which comprise at least one of the following modifications (a) an alternative linking group, (b) an analogous form of purines, (c) an analogous form of pyrimidines, or (d) an analogous sugar. For examples of analogous linking groups, purines, pyrimidines and sugars, see for example PCT publication WO 85/04064.

The polynucleotide sequences of the invention may be prepared by any known method, including synthetic, recombinant, or a combination thereof as well as through any purification methods known in the art.

B) Secreted αβδ-1 Subunit Polypeptides

The invention also encompasses polynucleotide fragments of a nucleic acid encoding a eukaryotic, preferably a mammal αβδ-1 subunit. These fragments particularly include but are not restricted to 1) those fragments encoding a soluble secreted polypeptide of this αβδ-1 subunit which preferably retains its binding affinity for [3H]gabapentin and/or other derivatives or compounds such as pregabalin and gabapentinoids and 2) nucleotide fragments useful as nucleic acid primers or probes for amplification or detection purposes. The expression “soluble secreted αβδ-1 subunit” is intended to designate polypeptide sequences which, when produced by a recombinant host cell, are secreted at least partially into the culture medium rather than remaining associated with the host cell membrane.

1) cDNA Fragments Encoding Soluble Secreted αβδ-1 Subunit Polypeptides

One of the important embodiments of the present invention concerns truncated nucleotide sequences of αβδ-1 subunit cDNAs which encode soluble secreted αβδ-1 subunit polypeptides. The inventors have found that it was possible to generate deletion mutants of αβδ-1 subunit cDNAs which, when expressed, produce a significant amount of soluble secreted proteins, preferably soluble secreted proteins, which retain their [3H]gabapentin binding affinity. These truncated nucleotide sequences of the invention are of significant value to the skilled person as they now allow fast and reliable access to significant concentrations of selected soluble secreted αβδ-1 subunit polypeptides. To that end, the inventors have determined the minimal and optimal fragment lengths required to express a polypeptide which: 1)
binds [3H] gabapentin with sufficient affinity and; 2) is obtained in a soluble secreted form. [0034] The discussion provided below provides detailed comments on possible truncations, giving as an example the porcine α₂δ-1 subunit. However, given the very substantial cross-species homology for α₂δ-1 subunit sequences, the comments below can also be applied to other eukaryotic species, and more particularly other mammalian species such as rat, mouse, rabbit or human. Their α₂δ-1 subunit sequences, which are available in public databases, share a very substantial homology with the porcine α₂δ-1 subunit sequences.

[0035] In a first series of experiments, the inventors determined to what extent the coding sequence of the α₂δ-1 subunit could be truncated and still encode a polypeptide which binds [3H] gabapentin. [0036] The inventors found that full-length α₂δ clones expressed in COS cells or in other cells of a similar nature such as HEK cells were partially cleaved by proteolytic enzymes. However, this proteolytic cleavage does not appear to completely separate the α₂ and δ polypeptides encoded by the native gene. In fact, the inventors found that the deletion of the last 7 residues of the δ subunit appears to inhibit proteolytic cleavage of α₂δ-1. However, mutants on which a portion of the δ subunit coding sequence has been deleted encode proteins which are still binding [3H] gabapentin even though no proteolytic cleavage seems to occur. Thus, it appears that:

[0037] the α₂δ-1 polypeptide is not proteolytically cleaved into separate α₂ and δ peptides and;
[0038] at least some of the δ polypeptide must be co-expressed with α₂ to form the [3H] gabapentin binding pocket.

[0039] In order to determine the minimum fragment of the δ subunit required for [3H] gabapentin binding, the inventors constructed mutants with C-terminal deletions of the δ component. C-terminally truncated mutants extending to residues 966 and 983 of SEQ ID No5 both do not bind [3H] gabapentin. However, mutants extending to residues 1018, 1036, 1063 and 1084 of SEQ ID No5 exhibit gabapentin binding activity. Thus, the inventors have identified a 35-residue stretch between residues 984 to 1018 of SEQ ID No5 which, when deleted with the C-terminal residues which follow, results in the loss of specific [3H] gabapentin binding.

[0040] Without wishing to be bound by any particular theory, the inventors believe that this region is either directly involved in the formation of the δ [3H] gabapentin binding pocket or is required for the structural integrity of the subunit. The two pairs of cysteine residues at positions 984/987 and 1012/1014 may contribute to the tertiary structure of the protein by disulfide bridging. Further deletion experiments on residues 984-1018 of the α₂δ-1 subunit can be easily carried out by the skilled person to determine which mutants comprising a nucleotide sequence encoding within that region bind [3H] gabapentin.

[0041] In a second series of experiments, the inventors found that nucleotide sequences encoding soluble secreted porcine α₂δ-1 subunit and which retain their binding affinity for [3H] gabapentin could be generated by deleting a portion of the α₂δ-1 subunit cDNA. In order to determine the optimal deletions on the α₂δ-1 subunit cDNA that yield a soluble secreted protein devoid of membrane anchorage structures, the inventors tested the expression of several porcine α₂δ-1 subunit cDNA deletion mutants. The inventors found that by deleting from the porcine α₂δ-1 subunit cDNA a nucleotide sequence encoding as much as amino-acids 967 to 1091 of the native protein, soluble secreted polypeptides could be obtained. On the other hand, the minimal deletion required to achieve solubility appears to be located around nucleotides encoding amino-acids 1064 to 1091 of the sequence of SEQ ID No5. In this regard, the mutant polypeptide expressed using a cDNA deletion mutant from which a sequence encoding amino-acids 1064 to 1091 is removed is found in both soluble and membrane-associated forms, with [3H] gabapentin binding properties similar to that of the wild type protein. Furthermore, a mutant protein expressed using a cDNA deletion mutant from which a nucleotide sequence encoding amino-acids 1085 to 1091 is removed recovers its membrane anchorage properties. Also, mutant proteins expressed using cDNA deletion mutants from which nucleotide sequences encoding either amino-acids 1037 to 1091 or amino-acids 1019 to 1091 of SEQ ID No5 are removed are found in soluble form.

[0042] The inventors believe that the soluble secreted α₂δ-1 subunit polypeptides which are as close as possible to the native sequence and which are therefore more likely to retain their native folding and hence their [3H] gabapentin binding properties are those corresponding to the native protein in which amino-acid stretch 985-1091 to 1079-1091 of the amino-acid sequence of SEQ ID No5 has been deleted. The skilled scientist can quite easily determine within this 90 amino-acid stretch the optimal α₂δ-1 subunit polypeptides.

[0043] The invention therefore particularly concerns a nucleotide sequence encoding a polypeptide having at least 80% identity with the polypeptide comprising from amino-acid 1 to between amino-acids 985 and 1054, preferably between amino-acids 985 and 1059, and most preferably between amino-acids 1019 and 1064 of SEQ ID No5 or SEQ ID no14. Preferred nucleotide sequences include those of SEQ ID No2, SEQ ID No3, SEQ ID No4, SEQ ID no19, SEQ ID no20 and SEQ ID no21.

[0044] 2) Fragments of the Porcine α₂δ-1 Subunit cDNA Useful as Primers and Probes

[0045] The present invention also concerns a purified or isolated polynucleotide comprising at least 10 consecutive nucleotides of a nucleic acid encoding the porcine α₂δ-1 subunit described herein, preferably at least 10 consecutive nucleotides of the nucleotide sequence of SEQ ID No1, or a sequence complementary thereto. These nucleic acids consist of a contiguous span which ranges in length from 10, 12, 15, 18 or 20 to 25, 35, 40, 50, 70, 80, 100, 250, 500 or 1000 nucleotides, or be specified as being 10, 12, 15, 18, 20, 25, 35, 40, 50, 100, 200, 250, 500 or 1000 nucleotides in length. These nucleic acids are useful as probes in order to detect the presence of at least a copy of a nucleotide sequence encoding the porcine α₂δ-1 subunit, more particularly the presence of at least a copy of a nucleotide sequence of SEQ ID No1 or a sequence complementary thereto or a fragment or a variant thereof in a sample. The sequence of such nucleic acids could be slightly modified (for example
by substituting one nucleotide for another) without substantially affecting the ability of such modified sequence to hybridize with the targeted sequence of interest.

[0046] The nucleic acid probes of the invention may also be used for the analysis of the expression levels and patterns of the porcine \( \alpha_2 \beta-1 \) subunit, such as described in the PCT Application NoWO 97/05 277, the entire contents of which is herein incorporated by reference.

[0047] The invention also concerns purified or isolated nucleic acid sequences that hybridize, under stringent hybridization conditions, with a nucleic acid encoding a porcine \( \alpha_2 \beta-1 \) subunit or a sequence complementary thereto.

[0048] As an illustrative embodiment, stringent hybridization conditions can be defined as follows:

[0049] The hybridization step is conducted at 65° C. in the presence of 6xSSC buffer, 5x Denhardt’s solution, 0.5% SDS and 100 \( \mu \)g/ml of salmon sperm DNA.

[0050] The hybridization step is followed by four washing steps:

[0051] two washings during 5 minutes, preferably at 65° C. in a 2xSSC and 0.1% SDS buffer;

[0052] one washing during 30 minutes, preferably at 65° C. in a 2xSSC and 0.1% SDS buffer;

[0053] one washing during 10 minutes, preferably at 35° C. in a 0.1xSSC and 0.1% SDS buffer.

[0054] It being understood that the hybridization conditions defined above are suitable for nucleic acids of approximately twenty nucleotides in length and that these conditions may be also adapted for shorter or longer nucleic acids, according to techniques well known in the art, for example those described by Sambrook et al. (1989).

[0055] The appropriate length for probes under a particular set of assay conditions may be empirically determined by the one skilled in the art. The probes can be prepared by any suitable method, including, for example, cloning and restriction of appropriate sequences and direct chemical synthesis by a method such as the phosphodiester method of Narang et al. (1979), the phosphodiester method of Brown et al. (1979), the diethylphosphoramidite method of Beaucage et al. (1981) and the solid support method described in the application NoEP-0 707 792. The disclosures of all these documents are incorporated herein by reference.

[0056] Any of the nucleic acids of the present invention can be labelled, if desired, by incorporating a label detectable by spectroscopic, photochemical, biochemical, immunochemical, or chemical means.

[0057] For example, useful labels include radio-active substances (\(^{32}P\), \(^{35}S\), \(^{3}H\), \(^{125}I\)), fluorescent dyes (5-bromo-4-chloro-3-indolyl phosphate, fluorescein, acetylated-fluorescein, digoxigenin) or biotin. Examples of non-radioactive labelling of nucleic acid fragments are described in French Patent NoFR-78 10975 or by Udrea et al. (1988) or Sanchez-Pescador et al. (1988). Advantageously, the probes according to the present invention may have structures and characteristics such that they allow signal amplification, such structural characteristics being, for example, those of branched DNA probes as described by Udrea et al. (1991).

[0058] Any of the nucleic acid probes of the invention can be conveniently immobilized on a solid support. Solid supports are known those skilled in the art and include the walls of wells of a reaction tray, test tubes, polystyrene beads, magnetic beads, nitro-cellulose strips, membranes, micro-particles such as latex particles, sheep red blood cells, duracryes and others.

[0059] The nucleic acid probes of the invention as particularly the nucleic acid probes described above can thus be attached to or immobilized on a solid support individually or in groups of at least 2, 5, 8, 10, 12, 15, 20 or 25 distinct nucleic acids of the invention to a single solid support.

[0060] In a specific embodiment of a support on which nucleic acid probes of the invention are immobilized, such a support may also contain other immobilized probes, preferably probes that hybridize specifically with a nucleic acid encoding the porcine \( \alpha_2 \beta-1 \) subunit, or a variant thereof, or a sequence complementary thereto.

[0061] C Amplification of the Porcine \( \alpha_2 \beta-1 \) Subunit cDNA or of Soluble Secreted \( \alpha_2 \beta-1 \) Subunit Nucleotide Sequences

[0062] Another object of the invention consists of a method for the amplification of a nucleic acid encoding a porcine \( \alpha_2 \beta-1 \) subunit or a soluble secreted \( \alpha_2 \beta-1 \) subunit polypeptide, preferably a polypeptide bearing a \(^{3}H\)gabapentin binding site, said method comprising the steps of:

[0063] (a) contacting a test sample suspected of containing the target \( \alpha_2 \beta-1 \) subunit nucleic acid, a fragment or a variant thereof, or a sequence complementary thereto, with an amplification reaction reagent comprising a pair of amplification primers which can hybridize under stringent conditions, the \( \alpha_2 \beta-1 \) subunit nucleic acid region to be amplified, and

[0064] (b) optionally, detecting the amplification products.

[0065] In a first preferred embodiment of the above method, the nucleic acid encodes a porcine \( \alpha_2 \beta-1 \) subunit of SEQ ID No5, or a secreted soluble \( \alpha_2 \beta-1 \) subunit polypeptide of SEQ ID no6, SEQ ID no7, SEQ ID no8, SEQ ID no15, SEQ ID no16 and SEQ ID no17.

[0066] In a second preferred embodiment of the above method, the first primer is the nucleotide sequence of SEQ ID No9 and a second primer is complementary to a portion of the 5 un-translated region of SEQ ID No5, such as the primer having the sequence of SEQ ID No22.

[0067] In a third preferred embodiment of the above amplification method, the amplification product is detected by hybridization with a labelled probe having a sequence which is complementary to the amplified region.

[0068] The invention also concerns a kit for the amplification of a nucleic acid encoding a porcine \( \alpha_2 \beta-1 \) subunit, a fragment or a variant thereof, or a complementary sequence thereto in a test sample, wherein said kit comprises:

[0069] (a) a pair of oligonucleotide primers which can hybridize, under stringent conditions to \( \alpha_2 \beta-1 \) subunit nucleic acid to be amplified;

[0070] (b) optionally, the reagents necessary for performing the amplification reaction.
[0071] In a first preferred embodiment of the kit described above, the nucleic acid encodes the porcine α2-β-1 subunit of SEQ ID No5. In a second preferred embodiment of the above amplification kit, the amplification product is detected by hybridization with a labelled probe having a sequence which is complementary to the amplified region. In a third embodiment of the above amplification kit, the amplification primers are respectively the nucleotide sequences of SEQ ID No9 and SEQ ID No10.

[0072] D) Recombinant Vectors and Host Cells for the Expression of a Porcine α2-β-1 Subunit or of a Secreted Soluble α2-β-1 Subunit Polypeptide

[0073] 1) Recombinant Vectors

[0074] The present invention also encompasses a family of recombinant vectors comprising any one of the nucleic acids described herein. Firstly, the invention deals with a recombinant vector comprising a nucleic acid selected from the group consisting of:

[0075] (a) a purified or isolated nucleic acid encoding a porcine α2-β-1 subunit, and more preferably a polypeptide having at least 80% amino acid identity with the polypeptide of SEQ ID No5, or a sequence complementary thereto;

[0076] (b) a purified or isolated nucleic acid having at least 90% nucleotide identity with a polynucleotide selected from the group consisting of the nucleotide sequences of SEQ ID No2, SEQ ID No3, SEQ ID No4, SEQ ID no19, SEQ ID no20 and SEQ ID no21 or a sequence complementary thereto;

[0077] (c) a purified or isolated polynucleotide comprising at least 10 consecutive nucleotides of a nucleic acid described in (a) or a sequence complementary thereto.

[0078] In a first preferred embodiment a recombinant vector of the invention is used to amplify the inserted polynucleotide derived from the nucleic acid encoding a porcine α2-β-1 subunit of the invention in a suitable host cell, this polynucleotide being amplified every time the recombinant vector replicates.

[0079] Recombinant expression vectors comprising a nucleic acid encoding α2-β-1 subunit polypeptides that are described in the present specification are also part of the invention. These include, but are not restricted to, nucleic acids encoding from amino-acid 1 to between amino-acids 985 to 1054, preferably between amino-acids 984 and 1059, more preferably between amino-acids 1019 to 1064, SEQ ID No5 and SEQ ID No14.

[0080] Another preferred embodiment of the recombinant vectors according to the invention consists of expression vectors comprising a nucleic acid encoding an α2-β-1 subunit polypeptide of the invention, and more preferably a nucleic acid encoding a polypeptide selected from the group consisting of the amino acid sequences of SEQ ID No5, SEQ ID No6, SEQ ID No7, SEQ ID No8, SEQ ID no15, SEQ ID no16 and SEQ ID no17.

[0081] Within certain embodiments, expression vectors can be employed to express the porcine α2-β-1 subunit of the invention or secreted soluble α2-β-1 subunit polypeptides which can then be purified and for example, be used as a immunogen in order to raise specific antibodies directed against said porcine α2-β-1 subunit protein or secreted soluble α2-β-1 subunit polypeptides.

[0082] Preferred eukaryotic vectors of the invention are listed hereafter as illustrative but not limiting examples: pcDNA3, pFLAG, pCMV-Script, pIND, pMCINEO, pHII, pGAPZA, pMT/V5-His-TOPo, pMT/V5-His, pAc5.1/V5-HisA, pDS47/V5-His, pcDNA4, pcDNA6, pEF1, pEF4, pEF6, pUB6, pZeoSV2, pRcCMV2, pcDM8, pCR3.1, pDisplay, pSecTag2, pVP22, pEMZ, pCMV/Neo, pSinRepS, pCEP, pREP, pHook-1

[0083] Preferred bacteriophage recombinant vectors of the invention are Pl bacteriophage vectors such as described by Sternberg N. L. (1992,1994).

[0084] A suitable vector for the expression of a porcine α2-β-1 subunit polypeptide of the invention or a soluble secreted α2-β-1 subunit polypeptide is a baculovirus vector that can be propagated in insect cells and in insect cell-lines. Specific suitable host vectors includes, but are not restricted to pFastBac-1, pIZ/V5-His, pBacMan-1, pBlueBac4.5, pBlueBacHis2, pMelBacA, pVL1.392, pVL1.393

[0085] The recombinant expression vectors from the invention may also be derived from an adenovirus such as those described by Feldman and Steig. (1996) or Ohno et al. (1994).

[0086] Another preferred recombinant adenovirus according to this specific embodiment of the present invention is the human adenovirus type two or five (Ad 2 or Ad 5) or an adenovirus of animal origin (French Patent Application noFR 93 05 954).

[0087] a) Regulatory Expression Sequences

[0088] Expression requires that appropriate signals are provided in the vectors, said signals including various regulatory elements such as enhancers/promoters from both viral and mammalian sources that drive expression of the genes of interest in host cells. The regulatory sequences of the expression vectors of the invention are operably linked to the nucleic acid encoding the porcine α2-β-1 subunit protein of interest or a soluble secreted α2-β-1 subunit polypeptide.

[0089] As used herein, the term “operably linked” refers to a linkage of polynucleotide elements in a functional relationship. For instance, a promoter or an enhancer is operably linked to a coding sequence if it affects the transcription of the coding sequence.

[0090] More precisely, two DNA molecules (such as a polynucleotide containing a promoter region and a polynucleotide encoding a desired polypeptide or polynucleotide) are said to be “operably linked” if the nature of the linkage between the two polynucleotides does not: (1) result in the introduction of a frame-shift mutation or (2) interfere with the ability of the polynucleotide containing the promoter to direct the transcription of the coding polynucleotide.

[0091] Generally, recombinant expression vectors include origins of replication, selectable markers permitting transformation of the host cell, and a promoter derived from a highly expressed gene to direct transcription of a downstream structural sequence. The heterologous structural sequence is assembled in an appropriate frame with the
translation, initiation and termination sequences, and preferably a leader sequence capable of directing sequences of the translated protein into the periplasmic space or the extra-cellular medium. In a specific embodiment wherein the vector is adapted for transfecting and expressing desired sequences in eukaryotic host cells, preferred vectors comprise an origin of replication from the desired host, a suitable promoter and enhancer, and also any necessary ribosome binding sites, polyadenylation site, transcriptional termination sequences, and optionally 5'-flanking non-transcribed sequences. DNA sequences derived from the SV 40 viral genome, for example SV 40 origin early promoter, enhancer, and polyadenylation sites may be used to provide the required non-transcribed genetic elements.

[0092] b) Promoter Sequences

[0093] Suitable promoter regions used in the expression vectors according to the invention are chosen taking into account the host cell in which the heterologous nucleic acids have to be expressed.

[0094] A suitable promoter may be heterologous with respect to the nucleic acid for which it controls the expression, or alternatively can be endogenous to the native polynucleotide containing the coding sequence to be expressed.

[0095] Additionally, the promoter is generally heterologous with respect to the recombinant vector sequences within which the construct promoter/coding sequence has been inserted. Preferred eukaryotic promoters are the (to be completed by inventors)

[0096] c) Recombinant Host Cells

[0097] Host cells that have been transfected or transfected with one of the nucleic acids described herein, or with one of the recombinant vector, particularly recombinant expression vector, described herein are also part of the present invention.

[0098] Are included host cells that are transfected (prokaryotic cells) or are transfected (eukaryotic cells) with a recombinant vector such as one of those described above. Preferred host cells used as recipients for the expression vectors of the invention are the following:

[0099] (a) prokaryotic host cells: Escherichia coli, strains (i.e. DH10 Bac strain) Bacillus subtilis, Salmonella typhimurium and strains from species such as Pseudomonas, Streptomyces and Staphylococcus;

[0100] (b) eukaryotic host cells: HeLa cells (ATCC NoCCL2; NoCCL2; 1; NoCCL2; 2), CV-1 cells (ATCC NoCCL70), COS cells (ATCC NoCRL 1650; NoCRL 1651), SF-9 cells (ATCC NCRL 1711), CI27 cells (ATCC NoCRL 1804), 3T3 cells (ATCC NoCRL 6361), CHO cells (ATCC NoCRL 61), human kidney 293 cells (ATCC No45504; NoCRL 1573), BHK (ECACC No84100 501; No84111301), 9f, 9, 21 and hi-5 cells.

[0101] E) Production of Recombinant αβ-1 Subunit Polypeptides

[0102] The present invention also concerns a method for producing one of the amino acid sequences described herein and especially a polypeptide selected from the group consisting of the amino acid sequences of SEQ ID No5, SEQ ID No6, SEQ ID No7, SEQ ID No8, SEQ ID no15, SEQ ID no16 or SEQ ID no17 wherein said method comprises the steps of:

[0103] (a) inserting the nucleic acid encoding the desired amino acid sequence in an appropriate vector;

[0104] (b) culturing, in an appropriate culture medium, a host cell previously transformed or transfected with the recombinant vector of step (a);

[0105] (c) harvesting the culture medium thus obtained or lyse the host cell, for example by sonication or osmotic shock;

[0106] (d) separating or purifying, from said culture medium, or from the pellet of the resultant host cell lysate, the thus produced recombinant polypeptide of interest.

[0107] In some instances, it may be required to tag the αβ-1 subunit polypeptide prior to purification. The tag is then in most instances encoded into the nucleotide sequence that is needed to express the polypeptide. Examples of such tags include, but are not limited to sequences encoding C-myc, FLAG, a sequence of histidine residues, hemaglutin A, V5, Xpress or GST. Most of these tags can be incorporated directly into the sequence, for instance through PCR amplification by incorporating the appropriate coding sequence in one of the PCR amplification primers. However, the tag can also be introduced by other means such as covalent binding of the appropriate nucleic acid sequence encoding the tag moiety with the 3' or 5' end of the nucleic acid sequence encoding the polypeptide sequence. This is the case for GST.

[0108] Purification of the recombinant αβ-1 subunit polypeptides according to the present invention is then carried out by passage onto a nickel or copper affinity chromatography column, such as a Ni NTA column.

[0109] In another embodiment of the above method, the polypeptide thus produced is further characterized, for example by binding onto an immuno-affinity chromatography column on which polyclonal or monoclonal antibodies directed to the αβ-1 subunit polypeptide, of interest have been previously immobilised.

[0110] F) Purified Recombinant αβ-1 Polypeptides

[0111] Another object of the present invention consists of a purified or isolated recombinant polypeptide comprising the amino acid sequence of the porcine αβ-1 subunit or the amino acid sequence of a secreted soluble αβ-1 subunit polypeptide.

[0112] Preferred isolated polypeptides of the invention include those having at least 80%, preferably 90%, more preferably 95%, and most preferably 98% or 99%, amino acid identity with polypeptides comprising from amino acid 1 to between amino-acids 985 and 1054, preferably between amino-acids 985 and 1059, and more preferably between amino-acids 1019 and 1064 of SEQ ID No5 or SEQ ID no14.

[0113] In a further preferred embodiment, the polypeptide comprises an amino acid sequence having at least 80%, preferably 90%, more preferably 95%, and most preferably 98% or 99% amino acid identity with the amino acid
sequence of SEQ ID No5, SEQ ID no6, SEQ ID No7, SEQ ID No8, SEQ ID No15, SEQ ID No16 and SEQ ID No17.

[0114] G Modified ω-3-1 Subunit Polypeptides

[0115] The invention also relates to a porcine ω-3-1 subunit, or a secreted soluble ω-3-1 subunit polypeptide comprising amino acid changes ranging from 1, 2, 3, 4, 5, 10, 20, 25, 30, 35, 40 substitutions, additions or deletions of one amino acid as regards to polypeptides of anyone of the amino acid sequences of the present invention. Preferred sequences are those of SEQ ID No5, SEQ ID No6, SEQ ID No7, SEQ ID No8, SEQ ID No15, SEQ ID No16 and SEQ ID no17.

[0116] In the case of an amino acid substitution in the amino acid sequence of a polypeptide according to the invention, one or several consecutive or non-consecutive amino acids are replaced by “equivalent” amino acids. The expression “equivalent” amino acid is used herein to designate any amino acid that may be substituted for one of the amino-acids belonging to the native protein structure without decreasing the binding properties of the corresponding peptides to the antibodies raised against the polypeptides of the invention. In other words, the “equivalent” amino-acids are those which allow the generation or the synthesis of a polypeptide with a modified sequence when compared to the amino acid sequence of the ω-3-1 subunit polypeptides of interest, said modified polypeptide being able to bind to the antibodies raised against the ω-3-1 subunit polypeptide of interest and/or to induce antibodies recognizing the parent polypeptide.

[0117] Alternatively, amino acid changes encompassed are those which will not abolish the biological activity of the resulting modified polypeptide. These equivalent amino-acids may be determined either by their structural homology with the initial amino-acids to be replaced, by the similarity of their net charge or of their hydrophobicity, and optionally by the results of the cross-immunogenicity between the parent peptides and their modified counterparts.

[0118] The peptides containing one or several “equivalent” amino-acids must retain their specificity and affinity properties to the biological targets of the parent protein, as it can be assessed by a ligand binding assay or an ELISA assay.

[0119] Examples of amino-acids belonging to specific classes include Acidic (Asp, Glu), Basic (Lys, Arg, His), Non-polar (Ala, Val, Leu, Ile, Pro, Met, Phe, Trp) or uncharged Polar (Gly, Ser, Thr, Lys, Tyr, Asn, Gln) amino-acids.

[0120] Preferably, a substitution of an amino acid in a porcine ω-3-1 subunit polypeptide of the invention, or in a peptide fragment thereof, consists in the replacement of an amino acid of a particular class for another amino acid belonging to the same class.

[0121] By an equivalent amino acid according to the present invention is also contemplated the replacement of a residue in the L-form by a residue in the D form or the replacement of a Glutamic acid (E) residue by a Pyroglutamic acid compound. The synthesis of peptides containing at least one residue in the D-form is, for example, described by Koch (1977).

[0122] A specific embodiment of a modified peptide of interest according to the present invention, includes, but is not limited to, a peptide molecule, which is resistant to proteolysis. This is a peptide in which the —CONH— peptide bond is modified and replaced by a (CH3NH) reduced bond, a (NHCO) retro inversed bond, a (CH3—O) methylene-oxo bond, a (CH3S) thiomethylene bond, a (CH2CH2) carba bond, a (CO—CH3) cetomethylene bond, a (CHOH—CH2) hydroxymethylene bond, a (N—N) bond, a E-alene bond or also a —CH=CH— bond.

[0123] The invention also encompasses a porcine ω-3-1 subunit polypeptide or a secreted soluble ω-3-1 subunit polypeptide in which at least one peptide bond has been modified as described above.

[0124] The polypeptides according to the invention may also be prepared by the conventional methods of chemical synthesis, either in a homogenous solution or in solid phase. As an illustrative embodiment of such chemical polypeptide synthesis techniques, it may be cited the homogenous solution technique described by Houtenweyl (1974).

[0125] The porcine ω-3-1 subunit polypeptide of interest, or a fragment thereof may thus be prepared by chemical synthesis in liquid or solid phase by successive couplings of the different amino acid residues to be incorporated (from the N-terminal end to the C-terminal end in liquid phase, or from the C-terminal end to the N-terminal end in solid phase) wherein the N-terminal and the reactive side chains are previously blocked by conventional groups.

[0126] For solid phase synthesis, the technique described by Merrifield (1965a; 1965b) may be used in particular.

[0127] H) Antibody Production

[0128] The porcine ω-3-1 subunit polypeptides of the invention and their peptide fragments of interest can be used for the preparation of antibodies.

[0129] Polyclonal antibodies may be prepared by immunization of a mammal, especially a mouse, a rabbit or a sheep, with a polypeptide according to the invention that is combined with an adjuvant of immunity, and then by purifying the specific antibodies contained in the serum of the immunized animal on an affinity chromatography column on which has previously been immobilized the polypeptide that has been used as the antigen.

[0130] Monoclonal antibodies may be prepared from hybridomas according to the technique described by Kohler and Milstein (1975).

[0131] The present invention also deals with antibodies produced by the trioma technique and by the human B-cell hybridoma technique, such as described by Koizumi et al. (1985).

[0132] Antibodies of the invention also include chimeric single chain Fv antibody fragments (U.S. Pat. No. 4,946, 778; Martineau et al., 1998), antibody fragments obtained through phage display libraries Ridler et al. (1995) and humanized antibodies (Leger et al., 1997).
EXAMPLES

Example 1

[0133] Cloning of the Porcine Cerebral Cortical α3-β1 cDNA

[0134] An oligo tPu-primed λgt10 porcine cerebral cortical cDNA library was screened by ECL (Amersham) using a 2,381-bp HindIII fragment (coding sequence 268-2649) of the rabbit skeletal muscle α3-1 clone (pcDNA3-Rab-α3-1-4; supplied by Dr. Offord, Parke-Davis Pharmaceutical Research, Ann Arbor, Mich.) as the probe.

[0135] A positive insert was identified and subcloned into pBluescript-SK(-) to generate pB-PC-α3-1. The clone was sequenced on both strands, except for a 711-bp stretch at one end of the clone, which had a high degree of homology to mitochondrial COX oxidase.

[0136] The α3-1 coding region was homologous to the 3' region of the human neuronal α3-1 sequence but lacked 926 bp of 5' coding sequence. The missing sequence was obtained by 5'-RACE using total RNA prepared from porcine cerebral cortex. RACE was performed across a BglII site unique in known α3-1 sequences (rabbit (accession no. M21948), rat (accession number M86621), human (accession no. M76559).

[0137] Primers were designed to amplify the missing 5' portion of the α3-1 cDNA by 5' Rapid Amplification of cDNA Ends (5' RACE). Antibodies were synthesized based on the α3-1 cDNA antisense sequence derived from the α3-1 coding region obtained above, all are downstream (3') of a unique BglI restriction site. Total RNA was prepared from porcine cortical membranes and single strand cDNA synthesized using SuperScript II reverse transcriptase and the primer furthest from the BglI site (JB039; 5'-TTCTCTAAT TCGAATCAAGG-3', SEQ ID No.24). The cDNA was then purified and tailed with dCTP's using terminal deoxynucleotidyl transferase. Aliquots of this tailing reaction were then PCR amplified through 35 cycles using Taq DNA polymerase and the primer pair JB041 (5'-TTTGGATG- TAATAAAAACATAG-3', SEQ ID No25) and the universal amplification primer (5'-GCUACUACUACUGGC- CACGCGTCTAGTAC-3', SEQ ID No26). Several PCR products were generated and Qiaex gel-purified. All products were positive by Southern blot hybridization using a 1,264 bp probe (5'α3-1 coding sequence) derived from a Hind III/BglI restriction digest of pcDNA3-Rab-α3-1). Each PCR product was sub-cloned into pBluescript. The 1' and 3' ends of each insert were sequenced confirming that all clones contain α3-1 sequence as predicted from the Southern blot experiment. The longest of the inserts contained sequence that extended 24 bp into the non-coding sequence of the α3-1 cDNA.

[0138] The sequence derived from the 5' RACE product was used to design a primer (JB042; 5'-GGGGATT GAATC- TCGAATCG-3', SEQ ID No9) specific for the 5' untranslated end of the cDNA. PCR was then performed with DNA polymerase using JB042 and a primer downstream of the BglI site (5'-GCAGATTT GTTTTCAAGG-3', SEQ ID 22) The PCR product was ligated to EcoRI linkers (5'-GGAATTC-3') and then digested with EcoRI and BglII. The 1,564-bp fragment (5' portion of the α3-1 cDNA) was gel-purified.

[0139] Similarly, a 2,303-bp fragment (3' portion of the α3-1 cDNA) was isolated after digestion of pB-PC-α3-1.1 with BglII and EcoRI. The two fragments of α3-1 cDNA were then ligated to EcoRI-digested pcDNA3 in a three-way ligation. A clone was picked with the full-length α3-1 sequence in the positive orientation with respect to the cytomegalovirus promoter (pcDNA3-PC-α3-1-4)). The PCR derived 5'α3-1 sequence in this plasmid was sequenced on both strands.

Example 2

[0140] Generation and Purification of Anti-α3 and Anti-δ Polyclonal Antibodies

[0141] The α3-1 subunit was purified from porcine brains as described by Gee et al. up to, and including, the Sephacryl S400 step. The sample of partially purified α3-1 subunits was then further purified on a 1-ml CuSO4 charged immuno-diacetic acid-Sepharose column. Prior to each use, the column was recharged with CuSO4 following a modified version of the protocol described by Brown et al.

[0142] Briefly, the column was stripped of metal ions with 0.5 M EDTA/NaOH, pH 8.0 (at 21°C), washed with 20 ml of H2O, and then charged with 20 ml of 0.3 M CuSO4, before a second wash with 20 ml of H2O and equilibration in buffer A (750 mM NaCl, 0.08% Tween 20, 10 mM HEPES/KOH, pH 7.4 (at 21°C)).

[0143] The partially purified α3-1 subunits obtained from the S400 chromatography was applied to this column at 0.5 m/min. Breakthrough material was concentrated to ~100 microliter by ultrafiltration (10,000 Mf, cut-off membrane) before separation by SDS-polyacrylamide gel electrophoresis on an 8% preparative gel. The 145-kDa band was excised, and the peptide recovered from the gel by electroelution. Rabbits were immunized by Serotec (Oxford, UK).

[0144] Anti-δ antibodies were raised by immunizing rabbits with a keyhole limpet hemocyanin-conjugated peptide, VEMEDDFTASLKSQC (SEQ ID No11), corresponding to the start sequence of the δ polypeptide (residues 922-938, relative to the first residue of the mature α3 polypeptide). Peptide synthesis and immunization protocols were performed by Genomix Biotechnologies Inc. (The Woodlands, Tex.).

[0145] Purified pig brain α3-1 (125 microgramm) was electrophoresed under reducing conditions on a single wide track 4-20% gradient SDS-polyacrylamide gel. After transfer onto nitrocellulose membrane, two thin horizontal strips corresponding to the α3 and δ polypeptides were excised with a razor blade. The strips were incubated with blocking buffer (2% milk powder, 150 mM NaCl, 0.1% Tween 20, 50 mM Tris-Cl, pH 7.5) for 30 min. Immune serum (1 ml) was diluted 5-fold in blocking buffer and incubated with the appropriate strip for 2 h at 4°C. Strips were then washed three times (15 min each) with blocking buffer and eluted with 2 ml of 50 mM glycine/HCl, pH 2.3. The solution was neutralized with 0.4 ml of 1 M HEPES, pH 8.0. Aliquots of the affinity-purified antibodies were stored frozen at ~70°C.

Example 3

[0146] Construction of C-Terminally Deleted Mutant

[0147] For mutants C (A275-1091 (i.e. residues 275 to 1091 deleted)), D (A470-1091), E (A621-1091), F (A804-
1091), G (1A946-1091), H (1A967-1091), I (1A848-1091), J (1A1019-1091, SEQ ID No6), K (1A1037-1091, SEQ ID No7), L (1A604-1091, SEQ ID No8), M (1A1085-1091), and PCR-WT (3’-untranslated region deleted) regions were performed with an anchored 5’ primer (JB055, 5’-TG-GCTATCGAATTAATACG-3’, SEQ ID No12), which anneals at position 849-869 in pcdNA3-PC-αδδ(+).

[0148] For mutants A (1A135-1091) and B (1A253-1091), the anchored 5’ primer was 5’-AACTCCGGGAGATGATCATTTCG-3’ (JB115, SEQ ID No13), which anneals at position 971-991. The 3’ primer was designed to anneal internally to the αδδ coding sequence to generate the specified C-terminally truncated αδδ mutant.

[0149] All 3’ primers had the following tail structure: a double stop codon followed by an EcoRI site (5’-CAGAATTCCTCATTACGTC3’), where N is the in-frame site-specific sequence complementary to the αδδ cDNA. Pfu DNA polymerase was used in the PCR reactions a preferred sequence of which is SEQ ID No23 (5’-CAGAATTCCTCATTACGTC3’) for cloning mutant L, and the products amplified with JB055 were blunt-end cloned into pBluescript-SK(+). The insert was then subcloned into the EcoRI site of pcdNA3. Products generated with JB115 were cloned directly into the EcoRV site of pcdNA3.

[0150] Clones were sequenced to confirm primer regions and a positive orientation with respect to the cytomegalovirus promoter.

**Example 4**

[0151] Construction of a δ-Only Mutant

[0152] The αδ sequence (residues 1-921) was deleted utilizing the two-round PCR method employing Pfu DNA polymerase. The product was blunt-end cloned into pBluescriptSK(+) and then directionally subcloned into pcdNA3 as described above.

**Example 5**

[0153] Transient Expression in COS-7 Cell, Extraction of COS-7 Membranes and Recovery of the Soluble Fractions

[0154] All media contained 50 units/ml penicillin and 50 microgram per ml streptomycin. COS-7 cells were maintained in Dulbecco’s modified Eagle’s medium+glutamax, 10% fetal bovine serum (gamma irradiated) in a 37°C 5% CO2 incubator and passaged by trypsinization. For transient expression experiments, 150-mm culture dishes were seeded with 3.9×10⁸ cells and incubated for 16 h. Cells were washed twice with 30 ml of OptiMEM-1 and transfected (60 h) with 30 microgram of plasmid DNA by lipofection-mediated transfection in 21 ml of OptiMEM-1. At t=6 h, a further 21 ml of OptiMEM-1 was added. At t=24 h, the medium was replaced with 42 ml of OptiMEM-1. At t=48 h, the cells were washed twice with 30 ml of phosphate-buffered saline and then harvested in 3 ml of buffer A (1 mM EDTA, 1 mM EGTA, 20% glycerol, 10 mm HEPES, pH 7.4, at 4°C) plus 0.1 mM phenylmethylsulfonyl fluoride using a cell scraper.

[0155] All subsequent operations were performed at 4°C. The cells were rotated on a Spira mix (Dentley Instruments) for 30 min, centrifuged at 20,000 ω g for 5 min, resuspended in 1 ml of buffer A, centrifuged at 20,000 ω g for 5 min, and finally resuspended in 400 microliter of buffer A. Membrane preparations were stored at −70°C until required.

[0156] Spent tissue culture medium recovered at t=24 and 48 h was ultracentrifuged at 100,000 g for 1 h and then concentrated by ultrafiltration (10,000 Mw, cut-off) to approximately 1 ml. The concentrated sample was then extensively dialyzed against buffer A and stored at −70°C until required.

[0157] Samples of membranes (3 micrograms in 48 microliter) were agitated for 2 h on a Spira mix at 4°C in a total volume of 60 microliters with a final concentration of either 1 M NaCl or 10% ethylene glycol. Samples were ultracentrifuged at 100,000 g for 2 h, and 20 microliter of supernatant was removed for SDS-polyacrylamide gel electrophoresis. The pellet was washed again for 10 min at 4°C in 1 ml of the same buffer before ultracentrifugation at 100,000 g for 30 min. The supernatant was discarded, and the pellet was resuspended in 120 micrograms of SDS-polyacrylamide gel electrophoresis loading buffer and boiled for 20 min; 40 micrograms was loaded onto the gel.

**Example 6**

[0158] Miscellaneous Methods

[0159] Protein concentrations were determined by the method of Bradford using bovine serum albumin as a standard (17)Glibapentin binding assays were performed as described previously. For saturation analysis, incubations were performed in duplicate. All other incubations were performed in triplicate. SDS-polyacrylamide gel electrophoresis and Western blotting were performed using the Novex gel and buffer system (Novex Europa, Frankfurt, Germany). Molecular weights were determined by reference to Callicoscope markers (Bio-Rad). Detection was performed using the ECL system (Amersham).

**REFERENCES**


[0186] Dooley, D. J., Bartoszyk, G. D., Hartenstein, J., Reimann, W., Rock, D. M., and


SEQ ID NO: 25

LENGTH: 3842

TYPE: DNA

ORGANISM: Mus musculus

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<212> TYPE: DNA
<213> ORGANISM: Sus scrofa

<400> SEQUENCE: 4

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<211> LENGTH: 1091
<212> TYPE: PRT
<213> ORGANISM: Sus scrofa

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Leu | Leu | Ile | Gly | Pro | Ser | Ser | Gln | Pro | Phe | Pro | Ser | Ala | Val | Thr |
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Ile | Lys | Ser | Trp | Val | Asp | Met | Gln | Glu | Asp | Leu | Val | Thr | Leu | Ala |
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Lys | Thr | Ala | Ser | Gly | Val | Asn | Gln | Leu | Val | Asp | Ile | Tyr | Glu | Lys |
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Gln | Asp | Leu | Tyr | Thr | Val | Glu | Pro | Asn | Asn | Ala | Arg | Gln | Leu | Val |
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Leu | Val | Arg | Leu | Ala | Leu | Glu | Ala | Glu | Val | Gln | Ala | Ala | His | Gln |
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| Leu | Val | Asp | Val | Ser | Gly | Ser | Val | Ser | Gly | Leu | Thr | Leu | Lys | Leu | Ile |
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Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn
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Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn
  645  650  655

Asp Leu Lys Ile Ser Asp Asn Asn Thr Glu Phe Leu Leu Asn Phe Asn
  660  665  670

Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Thr Asp
  675  680  685

Leu Ile Asn Arg Val Leu Leu Asp Ala Gly Phe Thr Aan Gin Leu Val
  690  695  700

Gln Asn Tyr Trp Ser Lys Gin Lys Asn Ile Lys Gly Val Lys Ala Arg
  705  710  715  720

Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala
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Gly Glu Asn Trp Gin Glu Asn Pro Glu Thr Tyr Glu Asp Ser Phe Tyr
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Lys Arg Ser Leu Asp Asn Asp Tyr Val Phe Thr Ala Pro Tyr Phe
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Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys
  770  775  780

Asn Val Glu Ile Tyr Ile Gin Lys Leu Leu Lys Pro Ala Val Val
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Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn
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Ser Asp Val Met Asp Cys Val Ile Leu Asp Gly Gly Phe Leu Leu
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Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr
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Ser Cys Ile Thr Glu Gin Thr Gin Tyr Phe Phe Asp Asn Ser Lys
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Lys Thr Ala Ser Gly Val Asn Glu Leu Val Asp Ile Tyr Glu Lys Tyr
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Gln Asp Leu Tyr Thr Val Glu Pro Asn Asn Ala Arg Glu Leu Val Glu
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Leu Val Arg Leu Ala Leu Glu Ala Glu Lys Val Gln Ala His Gln
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Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
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Tyr Glu His Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
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Thr Ile Val Leu Asn Glu Leu Asn Trp Thr Ser Ala Leu Asp Glu Val
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Phe Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Leu Thr Trp Glu Phe
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Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
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Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
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Arg Pro Trp Tyr Ile Glu Gly Ala Ala Ser Pro Lys Asp Met Leu Ile
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Val Asn Val Ala Ser Phe Asn Ser Asn Ala Gln Asp Val Ser Cys Phe
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Asn Cys Asn Lys Ile Ile Met Leu Phe Thr Asp Gly Gly Glu Glu Arg 355 360 365
Ala Gin Glu Ile Phe Ala Lys Tyr Asn Lys Asp Lys Val Arg Val 370 375 380
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Pro Met Val Leu Ala Gly Asp Lys Ala Lys Gin Val Gin Trp Thr Asn 435 440 445
Val Tyr Leu Asp Ala Leu Glu Leu Leu Val Ile Thr Gly Thr Leu 450 455 460
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35  40  45
Lys Thr Ala Ser Gly Val Asn Gin Leu Val Asp Ile Tyr Glu Lys Tyr
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Ala Val Glu Met Glu Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln 945 950 955 960
Ser Cys Ile Thr Glu Gln Thr Gln Tyr Phe Phe Asp Asn Asp Ser Lys 965 970 975
Ser Phe Ser Gly Val Leu Asp Cys Gly Aaa Gln Ser Arg Ile Phe His 980 985 990
Gly Glu Lys Leu Met Aaa Thr Aaa Leu Ile Phe Ile Met Val Glu Ser 995 1000 1005
Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu Leu Ile Glu Ala Glu Gln 1010 1015 1020
Thr Ser Asp Gly Pro Asn Pro Cys Met Val Lys Gln Pro Arg Tyr 1025 1030 1035 1040
Arg Lys Gly Pro Asp Val Cys Phe Asp Asn Asn Val Leu Glu Asp Tyr 1045 1050 1055 1060
Thr Asp Cys Gly Gly Val Ser Gly Leu Aaa Pro Ser Leu Trp Tyr Ile 1065 1070
Ile Gly Ile Gln Phe Leu Leu Leu Trp Leu Val Ser Gly Ser Thr His 1075 1080 1085 1090
Arg Leu Leu 1090

<210> SEQ ID NO 15
<211> LENGTH: 1018
<212> TYPE: PRT
<213> ORGANISM: Homo sapiens

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Ile Lys Ser Trp Val Asp Lys Met Gin Asp Leu Val Thr Leu Ala 35 40 45
Lys Thr Ala Ser Gly Val Asn Gin Leu Val Asp Ile Tyr Gin Lys Tyr 50 55 60
Gln Asp Leu Tyr Thr Val Gin Gin Leu Gin Leu Gin Leu Val Glu 65 70 75 80
Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala 85 90 95
Leu Val Ser Leu Ala Leu Glu Gin Val Gin Ala Ala Ala His Gin 100 105 110
Trp Arg Glu Asp Phe Ala Ser Asn Gin Val Val Tyr Tyr Asn Ala Lys 115 120 125
Asp Asp Leu Asp Pro Gin Asn Gin Ser Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin Gin 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Asp Glu Arg Tyr Ile Asp Gly Asn Arg Thr Tyr Thr Thr Thr Pro 580 585 590
Val Asn Gly Thr Asp Tyr Ser Leu Ala Leu Val Leu Pro Thr Tyr Ser 595 600 605
Phe Tyr Tyr Ile Lys Ala Lys Leu Glu Thr Ile Thr Gln Ala Arg 610 615 620
Ser Lys Lys Gly Lys Met Lys Asp Ser Glu Thr Leu Lys Pro Asp Asn 625 630 635 640
Phe Glu Glu Ser Gly Tyr Thr Phe Ile Ala Pro Arg Asp Tyr Cys Asn 645 650 655
Asp Leu Lys Ile Ser Asp Asn Thr Glu Phe Leu Leu Asn Phe Asn 660 665 670
Glu Phe Ile Asp Arg Lys Thr Pro Asn Asn Pro Ser Cys Asn Ala Asp 675 680 685
Leu Ile Asn Arg Val Leu Leu Asp Gly Phe Thr Asn Glu Leu Val 690 695 700
Gln Asn Tyr Trp Ser Lys Glu Asn Ile Lys Gly Val Lys Ala Arg 705 710 715 720
Phe Val Val Thr Asp Gly Gly Ile Thr Arg Val Tyr Pro Lys Glu Ala 725 730 735
Gly Glu Asn Trp Glu Asn Pro Glu Thyr Asp Ser Phe Tyr 740 745 750
Lys Arg Ser Leu Asp Asn Asp Asn Tyr Val Phe Thr Ala Asp Tyr Phe 755 760 765
Asn Lys Ser Gly Pro Gly Ala Tyr Glu Ser Gly Ile Met Val Ser Lys 770 775 780
Ala Val Glu Ile Tyr Ile Glu Gly Leu Leu Lys Pro Ala Val Val 785 790 795 800
Gly Ile Lys Ile Asp Val Asn Ser Trp Ile Glu Asn Phe Thr Lys Thr 805 810 815
Ser Ile Arg Asp Pro Cys Ala Gly Pro Val Cys Asp Cys Lys Arg Asn 820 825 830
Ser Asp Val Met Asp Cys Val Ile Leu Asp Asp Gly Gly Phe Leu Leu 835 840 845
Met Ala Asn His Asp Asp Tyr Thr Asn Gln Ile Gly Arg Phe Phe Gly 850 855 860
Glu Ile Asp Pro Ser Leu Met Arg His Leu Val Asn Ile Ser Val Tyr 865 870 875 880
Ala Phe Asn Lys Ser Tyr Asp Tyr Gln Ser Val Cys Glu Pro Gly Ala 885 890 895
Ala Pro Lys Gln Gly Ala Gly His Arg Ser Ala Tyr Val Pro Ser Val 900 905 910
Ala Asp Ile Leu Gln Ile Gly Trp Thr Ala Thr Ala Ala Ala Trp Ser 915 920 925
Ile Leu Gln Gln Phe Leu Leu Ser Leu Thr Phe Pro Arg Leu Leu Glu 930 935 940
Ala Val Glu Met Glu Asp Asp Phe Thr Ala Ser Leu Ser Lys Gln 945 950 955 960
Ser Cys Ile Thr Glu Gln Thr Glu Tyr Phe Phe Asp Asn Asp Ser Lys 965 970 975
Ser Phe Ser Gly Val Leu Asp Cys Gly Asn Cys Ser Arg Ile Phe His
960 985 990
Gly Glu Lys Leu Met Asn Thr Asn Leu Ile Phe Ile Met Val Glu Ser
995 1000 1005
Lys Gly Thr Cys Pro Cys Asp Thr Arg Leu
1010 1015

<210> SEQ ID NO: 16
<211> LENGTH: 1036
<212> TYPE: FRN
<213> ORGANISM: Homo sapiens

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Ile Lys Ser Trp Val Asp Lys Met Gin Glu Asp Leu Val Thr Leu Ala
35 40 45
Lys Thr Ala Ser Gly Val Asn Gin Leu Val Asp Ile Tyr Glu Lys Tyr
50 55 60
Gln Asp Leu Tyr Thr Val Glu Pro Asn Ala Arg Gin Leu Val Glu
65 70 75 80
Ile Ala Asp Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85 90 95
Leu Val Ser Leu Ala Leu Glu Ala Glu Val Gin Ala Ala His Gin
100 105 110
Trp Arg Glu Asp Phe Ala Ser Asn Glu Val Val Tyr Tyr Asn Ala Lys
115 120 125
Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Gin Arg
130 135 140
Ile Lys Pro Val Phe Ile Glu Asp Ala Asn Phe Gly Gin Gin Ile Ser
145 150 155 160
Tyr Gin His Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
165 170 175
Thr Ile Val Leu Asn Glu Leu Leu Thr Ser Thr Ala Leu Asp Glu Val
180 185 190
Phe Lys Lys Asn Arg Glu Glu Asp Pro Ser Leu Leu Leu Trp Gin Val Phe
195 200 205
Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
210 215 220
Asp Asn Ser Arg Thr Pro Asn Lys Ile Asp Leu Tyr Asp Val Arg Arg
225 230 235 240
Arg Pro Trp Tyr Ile Gin Glu Ala Ala Ser Pro Lys Gin Met Leu Ile
245 250 255
Leu Val Asp Val Ser Gly Ser Val Ser Gly Leu Thr Leu Lys Leu Leu
260 265 270
Arg Thr Ser Val Ser Glu Met Leu Glu Thr Ser Asp Asp Asp Phe
275 280 285
Val Asp Val Ala Ser Phe Asn Ser Asn Ala Gin Asp Val Ser Cys Phe
290 295 300
Gln His Leu Val Gin Ala Asn Val Arg Asn Lys Lys Val Leu Lys Asp
305 310 315 320
Lys Thr Ala Ser Gly Val Asn Gln Leu Val Asp Ile Tyr Glu Lys Tyr
50
55
60
Gln Asp Leu Tyr Thr Val Glu Pro Asn Ala Arg Gln Leu Val Glu
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70
75
80
Ile Ala Ala Arg Asp Ile Glu Lys Leu Leu Ser Asn Arg Ser Lys Ala
85
90
95
100
105
110
Leu Val Ser Leu Ala Leu Glu Ala Glu Lys Val Gln Ala Ala His Gln
100
105
110
Trp Arg Glu Asp Phe Ala Ser Ann Glu Val Val Tyr Tyr Asn Ala Lys
115
120
125
Asp Asp Leu Asp Pro Glu Lys Asn Asp Ser Glu Pro Gly Ser Glu Arg
130
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Tyr Gin His Ala Val His Ile Pro Thr Asp Ile Tyr Glu Gly Ser
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Gly Ser Ala Thr Gly Leu Ala Arg Tyr Tyr Pro Ala Ser Pro Trp Val
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Asp Ann Ser Arg Thr Pro Ann Lys Ile Asp Leu Tyr Asp Val Arg Arg
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Gln His Leu Val Gln Ala Ann Val Arg Ann Lys Val Leu Lys Asp
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1. A purified or isolated nucleic acid encoding a eukaryotic secreted soluble cerebral cortical voltage-dependent calcium channel α₆δ-1 subunit polypeptide.

2. A purified or isolated nucleic acid according to claim 1, comprising a polynucleotide having at least 90% identity with the sequence encoding from amino-acid 1 to between amino-acids 1009 to 1083 of SEQ ID NO:5 or SEQ ID NO:14.

3. A purified or isolated nucleic acid according to claim 1, having at least 90% identity with the sequence encoding from amino-acid 1 to between amino-acids 1043 and 1088 of SEQ ID NO:5 or SEQ ID NO:14.

4. A purified or isolated nucleotide sequence according to claim 1 wherein said sequence is the sequence of SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:19, SEQ ID NO:20, or SEQ ID NO:21.

5. A purified or isolated nucleic acid, having at least 90% identity with the nucleotide sequence of SEQ ID NO:1.

6. A purified or isolated polynucleotide comprising at least 10 consecutive nucleotides of the nucleotide sequence of SEQ ID NO:1.

7. A polynucleotide probe or primer hybridizing, under stringent conditions, with the nucleic acid according to claim 5.

8. A method for the amplification of a nucleic acid encoding a eukaryotic secreted soluble cerebral cortical voltage-dependent calcium channel α₆δ-1 subunit polypeptide, said method comprising the steps of:

(a) contacting a test sample suspected of containing the target secreted soluble α₆δ-1 subunit nucleic acid, or a sequence complementary thereto, with an amplification reaction reagent comprising a pair of amplification primers located on either side of the α₆δ-1 subunit nucleic acid region to be amplified, and

(b) optionally, detecting the amplification products.

9. A kit for the amplification of a nucleic acid encoding a secreted soluble α₆δ-1 subunit polypeptide, or a complementary sequence thereto in a test sample, wherein said kit comprises:

(a) a pair of oligonucleotide primers which can hybridize, under stringent conditions, to the secreted soluble α₆δ-1 subunit nucleic acid region to be amplified; and

(b) optionally, the reagents necessary for performing the amplification reaction.

10. A recombinant vector comprising a nucleic acid according to claim 1.

11. A recombinant host cell comprising a nucleic acid according to claim 1.

12. A method for producing a secreted soluble α₆δ-1 subunit wherein said method comprises the steps of:

(a) inserting the nucleic acid encoding the desired α₆δ-1 subunit polypeptide in an appropriate vector;

(b) cultivating, in an appropriate culture medium, a host cell previously transformed or transfected with the recombinant vector of step (a);

(c) harvesting the culture medium thus obtained or lyse the host cell, for example by sonication or osmotic shock;

(d) separating or purifying, from said culture medium, or from the pellet of the resultant host cell lysate, the thus produced α₆δ-1 subunit polypeptide of interest.