Serine 171, a Conserved Residue in the \( \gamma \)-Aminobutyric Acid Type A (GABA\(_A\)) Receptor \( \gamma 2 \) Subunit, Mediates Subunit Interaction and Cell Surface Localization*

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Serine 171 in the GABA\(_A\) receptor \( \gamma 2 \) subunit is highly conserved in the ligand-gated ion channel superfamily. In this paper, we report that mutating serine 171 within \( \gamma 2 \) to glycine or cysteine prevents the interaction of \( \gamma 2 \) with \( \alpha 2 \) and \( \beta 1 \) when these subunits are co-expressed in human embryonic kidney 293 cells, resulting in intracellular retention of \( \gamma 2 \). Structure analysis based on a three-dimensional homology model of \( \gamma 2 \) (Ernst, M., Brauchart, D., Boresch, S., and Sieghart, W. (2003) Neuroscience 119, 933–943) reveals that serine 171 may play a critical role in the formation and stabilization of an exposed turn structure that is part of the subunit interaction site. Mutation of serine 171 in the \( \gamma 2 \) subunit could therefore result in alteration of the structure of the subunit interaction site, preventing correct subunit assembly.

\( \gamma \)-Aminobutyric acid type A (GABA\(_A\)) receptors are members of the ligand-gated ion channel superfamily, which also includes nicotinic acetylcholine (ACh), glycine, glutamate, and 5-hydroxytryptamine type 3 (5HT3) receptors. Members of this superfamily share significant sequence similarity, implying a common evolutionary origin (2).

GABA\(_A\) receptors are the major inhibitory receptors in the brain and are the targets of clinically important drugs such as benzodiazepines, barbiturates, neurosteroids, and anesthetics (3). Several distinct classes of GABA\(_A\) receptor subunits have been identified (3–8). Heterologous expression of recombinant GABA\(_A\) receptor subunits in cultured cells demonstrates that the combination of \( \alpha \) and \( \beta \) subunits is sufficient for creating the GABA binding sites to elicit GABA-gated Cl\(^-\) currents (9). Benzodiazepines bind to a distinct site on the GABA\(_A\) receptor and positively modulate GABA-gated Cl\(^-\) current (10). Formation of the benzodiazepine binding site requires the presence of a third component, the \( \gamma \) subunit (9, 10). Typical native GABA\(_A\) receptors have been proposed to be pentameric transmembrane proteins formed by two \( \alpha \), two \( \beta \), and one \( \gamma \) subunits (9). Assembly of the hetero-pentamers occurs in the endoplasmic reticulum and requires the interaction between subunit-specific contact sites. Access to the cell surface is restricted to the correctly assembled GABA\(_A\) receptors (11–15).

We identified previously two highly conserved residues, serine 171 and tyrosine 172, in the \( \gamma 2 \) subunit. These two residues flank a novel alternative exon (16, 17). When the residues are mutated, oligomerization of \( \gamma 2 \) with \( \alpha 2 \) and \( \beta 1 \) is prevented, and cell surface access of \( \gamma 2 \) is abolished. In the present study, using single amino acid substitutions, we further demonstrate that serine 171 within \( \gamma 2 \) plays a critical role in mediating the subunit interaction and cell surface expression of \( \gamma 2 \), whereas tyrosine 172, as well as other residues surrounding Ser-171/Tyr-172, exhibit little or no effect on the function of the \( \gamma 2 \) subunit. Mapping of the \( \gamma 2 \) protein sequence onto the three-dimensional homology model of the extracellular component of the GABA\(_A\) receptor generated from the ACh-binding protein (AChBP) structure (1, 18) suggests that Ser-171 links a \( \beta \)-strand (\( \beta 7 \)) to a loop structure (loop 8) of \( \gamma 2 \). Serine 171 presumably stabilizes the loop turn by forming a hydrogen bond via its side-chain hydroxyl group. Furthermore, side-chain packing constraints may sterically exclude other amino acids at this position. This loop turn is located on the surface of a \( \beta \)-rich structure in the extracellular domain of \( \gamma 2 \) and is likely involved in oligomerization with other receptor subunits.

EXPERIMENTAL PROCEDURES

**Plasmid Constructs**—Preparation of the cDNA constructs expressing the human \( \alpha 2 \), \( \beta 1 \), and \( \gamma 2 \) subunits, with or without epitope tags, have been described previously (16). Briefly, the \( \alpha 2 \) and \( \beta 2 \) cDNAs were subcloned into the pCEP4 expression vector (Invitrogen) and used for ligand binding and immunostaining assays. To make v5-tagged constructs for co-precipitation assays, the \( \alpha 2 \) and \( \beta 1 \) cDNAs were subcloned into the pCDNA3.1 vector (Invitrogen) with a v5 tag inserted before the stop codon. The \( \gamma 2 \) cDNA was subcloned into the pCDNA3.1 vector and used for ligand binding assays. The Myc-tagged \( \gamma 2 \) (\( \gamma 2^{3xM} \)), which contains a myc-His tag at the 3’-terminus and a second myc tag inserted between the ninth and tenth residues of the mature protein, was also subcloned into the pCDNA3.1 vector and used for immunostaining and co-precipitation assays.

**Mutagenesis**—Two \( \gamma 2 \) and \( \gamma 2^{3xM} \) cDNAs in the pCDNA3.1 vector were used for mutagenesis experiments. QuickChange II site-directed mutagenesis kit (Stratagene) was used for creating the single amino acid substitution. The following amino acid substitutions were made in the mature \( \gamma 2 \) subunit: E168I, F169I, S170G, S171C, S171G, Y172C, Y172G, G173A, and P177T. Identical sets of mutations were made in the \( \gamma 2 \) and \( \gamma 2^{3xM} \) constructs, respectively. The \( \gamma 2 \) mutants generated were verified by double strand DNA sequencing.

**Cell Cultures and Transfection**—Human embryonic kidney 293 cells were maintained in Dulbecco’s modified Eagle’s medium with 10% fetal bovine serum (Invitrogen) and transfected using LipofectAMINE 2000 (Invitrogen). Transfection was performed with equal molar concentrations of the subunit constructs either in 10-cm dishes with 24 \( \mu \)g of plasmid DNA per dish or in 6-well plates with 5 \( \mu \)g/well plasmid DNA.

**Radioligand Binding**—Cells were harvested 48 h after co-transfection with the \( \alpha 2 \), \( \beta 1 \), and either the wild-type \( \gamma 2 \) or one of the \( \gamma 2 \) mutant constructs. To prepare the membrane fraction, cells were homogenized in ice-cold wash buffer (10 mM potassium phosphate, pH 7.2) by passing through a 27-gauge needle. Cell homogenates were washed by two
centrifugation-resuspension cycles in 1 ml of ice-cold wash buffer. Cell homogenates were centrifuged at 4 °C for 60 min at 15,000 × g. The pellets were resuspended in 600 µl of ice-cold assay buffer (10 mM potassium phosphate, pH 7, and 0.02 mM potassium chloride) and centrifuged at 500 × g for 5 min. The supernatant, which contained the enriched membrane fraction, was collected and stored at −80 °C after its protein concentration was determined. For radioligand binding, 150–200 µg of membrane protein preparation was incubated on ice for 60 min with 10 nM of either [3H]Ro15-1788 (78 Ci/mmol; PerkinElmer Life Sciences) or [3H]muscimol (28.5 Ci/mmol; PerkinElmer Life Sciences) in a total volume of 200 µl. Unbound ligands were removed at the end of incubation by rapid filtration on Whatman GF/C filters with a 1225 Sampling Manifold (Millipore). The filters were washed once with 15 ml of ice-cold assay buffer, and the filter-retained radioactivity was determined by liquid scintillation counting.

**RESULTS**

**Mutation of Ser-171 in γ2 Prevents Benzodiazepine Binding to the GABA
A Receptor—Serine-171 and tyrosine-172 in the γ2 subunit of GABA
A receptors are extremely conserved in the GABA
A receptor subunit family and have recently been found to be crucial to the subunit association and cell surface localization of γ2 (16). The present study further addresses the following two issues: (i) if one of the conserved residues is more important than the other in mediating the subunit interaction and cell surface expression of γ2; and (ii) if other amino acids that flank Ser-171/γ2 (Fig. 1A) are also required for the above function.

To answer these questions, we performed a single amino acid substitution at serine 171, tyrosine 172, and five other less conserved residues that flank Ser-171/γ2 subunit (Fig. 1A). To examine the effect of mutations on receptor binding, individual γ2 mutants were co-transfected with the α2 and β1 subunits into human embryo kidney 293 cells. Transfected cells were harvested after 48 h, and membrane fractions were prepared. Receptor binding was performed using [3H]Ro15-1788, a benzodiazepine antagonist, and [3H]muscimol, a GABA agonist. Mutation of Ser-171 in γ2 to either cysteine or glycine completely abolished receptor binding of [3H]Ro15-1788 while showing no disruptive effect on binding of [3H]muscimol (Fig. 1B). Mutation of Tyr-172 to threonine in γ2 showed a decrease in receptor binding of both [3H]Ro15-1788 (p < 0.01) and [3H]muscimol (p < 0.05; Fig. 1B), as compared with the binding from control cells co-expressing α2, β1, and the wild-type γ2 subunit. Other amino acid substitutions, including the Y172F mutation within γ2, showed no significant effect on the binding of both ligands.

**Mutation of Ser-171 in γ2 Prevents Its Cell Surface Localization—**Binding of benzodiazepines to the GABA
A receptor requires the presence of all three subunits (α, β, and γ) on the cell surface (11–15). Here, we examined the subcellular localization of the γ2 mutants using immunofluorescence staining. We focused on the localization of the Ser-171 and Tyr-172 mutants, because these mutants exhibited a disruptive effect on ligand binding (see above). To facilitate protein detection, the γ2 constructs were fused to a Myc-His tag at the 3′-terminus, and a second Myc tag was inserted between the ninth and tenth amino acid residues of the mature γ2 peptide as described previously (16). Cells co-expressing α2, β1, and the Myc-tagged, wild-type γ2 subunit γ2Myc showed robust cell surface staining, which was detected by the anti-Myc antibody (Fig. 2A). However, no immunostaining was detected on the surface of the cells co-expressing α2, β1, and either a γ2 mutant or γ2 subunit. Arrowheads indicate positions of the single amino acid substitutions. Boxed are serine 171 and tyrosine 172, which are conserved in the GABA
A receptor subunit family. The number on the left indicates the position of the first amino acid, B, receptor binding of [3H]Ro15-1788 and [3H]muscimol. Binding assays were performed using membrane preparations from 293 cells co-expressing α2, β1, and either the wild-type γ2 or one of the γ2 mutants as indicated. Control cells received no DNA. Data shown are percentages of the wild-type control (which was set at 100%). Bars are mean ± S.E. of triplicate determinations from a single representative experiment. Statistical significance from wild-type controls were calculated using unpaired Student t test. *p < 0.01; **p < 0.05; n = 3.

**Mutation of Ser-171 in γ2 Inhibits Subunit Interaction—**Heterologous interaction of GABA
A receptor subunits takes place in the endoplasmic reticulum, where access to the cell surface is restricted only to the correctly assembled GABA
A receptors (11–15). To study the interaction of the γ2 mutants with other receptor subunits, a v5 tag was fused to the α2 and β1 subunits at the C terminus (16). The v5-tagged α2 and β1, and the Myc-His-tagged, wild-type γ2 subunit γ2Myc showed robust cell surface staining, which was detected by the anti-Myc antibody (Fig. 2A). However, no immunostaining was detected on the surface of the cells co-expressing α2, β1, and either a γ2Myc or γ2Myc mutant (Fig. 2E). When the cell membrane was permeabilized, all transfected cells showed a strong perinuclear staining typical of an endoplasmic reticulum-staining pattern (Fig. 2, B, D, and F). Mutation of tyrosine 172 to phenylalanine showed no effect on the cell surface expression of γ2 (Fig. 2F), whereas mutating the same residue to threonine slightly decreased the γ2 cell surface-staining intensity (Fig. 2G).

**Mutation of Ser-171 in γ2 Mediates Subunit Assembly**—Binding of benzodiazepines to the GABA
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Serine 171 in γ2 Mediates Subunit Assembly

**Fig. 2. Localization of γ2Myc or γ2Myc mutants in 293 cells co-expressing α2 and β1.** Cells were co-transfected with α2, β1, and either γ2Myc or one of the γ2Myc mutants as indicated. Transfected cells were assayed 24 h after transfection for expression of Myc-tagged proteins on the cell surface (A, C, E, G, and I) or for intracellular presence of Myc-tagged proteins in permeabilized cells (B, D, F, H, and J).

**Fig. 3. Analysis of GABAA receptor subunit interaction.** The γ2 and γ2 mutant constructs carry a C terminus His6 tag in addition to their Myc tags. The α2 and β1 constructs carry a V5 tag. Human embryonic kidney 293 cells were co-transfected with the indicated DNA constructs. The recombinant proteins expressed were purified using Ni-NTA-agarose beads and eluted. Equal amounts of the eluted proteins were used for immunoblotting with an anti-Myc (top panel) and an anti-v5 (bottom panel) antibody. Molecular mass values in kilodaltons are indicated on the left. Asterisk (*) indicates a background band.

**Fig. 4. Serine 171 in γ2 is conserved in the ligand-gated ion channel superfamily.** The γ2 sequence was aligned with the sequences of the ligand-gated ion channel superfamily members (1, 18). Shown is a subset of the alignment. The sequence fragments shown cover Ser-171 and its immediate flanking sequence of γ2, which form the structures of β-strand 7, loop 8, and β-strand 8. Boxed is serine 171 in γ2. Blue-shaded amino acids are predicted as highly conserved in secondary structure (1). Asterisk (*) indicates identical amino acids across all listed proteins. H, human; T.ca, Torpedo californica; β, β-strand; L, loop.

**DISCUSSION**

The extracellular domains of the GABAA receptor subunits play essential roles in receptor assembly. For example, a γ2 subunit containing only the extracellular domain can form a stable complex with the α1 or β3 subunits (12). Residues 58–67 within the α subunit are required in the assembly of the αβ receptors, and Gln-67 within the α1 subunit has a major role in mediating its cell surface expression with the β3 subunit (19). Also, several N-terminal residues in the β subunits direct their assembly with γ subunits (15, 20).

The essential role of Ser-171/Tyr-172 in γ2 is found in the characterization of a naturally occurring γ2 subunit splice variant, γ2XL (16). γ2XL contains an additional alternative exon that is inserted in the extracellular domain between Ser-171 and Tyr-172 of the mature γ2 subunit. This variant neither co-precipitates with α2 and β1,
nor is it expressed on the cell surface. Such a disruptive effect is also found in a γ2 mutant in which both Ser-171 and Tyr-172 are converted to glycine and threonine, respectively. Interestingly, Ser-171 and Tyr-172 are the residues that flank the inserted alternative exon and are also extremely conserved in the GABA_A receptor subunit family members (16).

The findings described in this paper demonstrate that the mutation of γ2 at serine 171, either to cysteine or glycine, disrupts the interaction of the γ2 mutant with α2 and β1 in 293 cells. As a result, only α2 and β1 are oligomerized and expressed on the cell surface. The mutation of tyrosine 172 in γ2 to phenylalanine or threonine results in distinct consequences. The tyrosine-to-phenylalanine mutation in γ2 generates no disruptive effects, whereas the tyrosine-to-threonine mutation results in a partial decrease in both the subunit interaction and the cell surface expression of the γ2 mutant when it is co-expressed with α2 and β1 in 293 cells. Unlike the Ser-171 mutants, the Y172T mutant also decreases the receptor binding of [3H]muscimol, indicating that the tyrosine-to-threonine mutation in γ2 may reduce access of the α2β1 receptor to the cell surface. Tyrosine is most similar to phenylalanine but structurally distinct from threonine.

To map our mutagenesis data onto a three-dimensional context, we used a recent homology model of the extracellular part of the GABA_A receptor (1) to predict the structure-function role of serine 171 and tyrosine 172. This homology model of γ2 uses the solved three-dimensional structure of the acetylcholine-binding protein, a ligand-gated ion channel superfamily member, as a structural template (Protein Database identifier: 1I9b) (18). There is a 44% sequence similarity and a 25% sequence identity between AChBP and the γ2 extracellular domain from amino acids 24 to 179. Although the homology between AChBP and γ2 is relatively low, structure is known to be more conserved than sequence within protein families (1, 21). Several other groups have recently used the AChBP homology model to predict the three-dimensional structure of the GABA_A receptor subunits (22, 23).

Based on this homology model, the extracellular domain of γ2 is predicted to form a structure that is rich in β-sheets with an immunoglobulin-like topology. The conserved serine 171 in γ2 is located at the end of β-strand 7, near the surface of a subunit interaction site (Figs. 4 and 5). Loop 8, which links the two β-strands (β-strand 7 and 8), consists of two consecutive tight turn structures, each stabilized by hydrogen bonds. Residues preceding Ser-171 (glutamate 168, phenylalanine 169, and serine 170) are located in β-strand 7. Residues tyrosine 172, glycine 173, and proline 175 fall within loop 8. The side chain of Tyr-172 appears to be in direct contact with the β subunit. The location of Ser-171 and the orientation of its side chain suggest that this serine may play a critical role in stabilizing the first turn (residues 171–174) by forming hydrogen bonds between its hydroxyl side-chain group and the main-chain amide group of Tyr-174 (Fig. 5C). As the side-chain of Ser-171 is pointing inward and is tightly packed, only limited changes of the side-chain volume appear possible without changing the conformation of the turn. Hence, mutations of Ser-171 in γ2, which disrupt the hydrogen bonding or introduce a bulkier side chain that cannot be accommodated, might alter the conformation of the loop turn and lead to a direct or allosteric change in the subunit contact site(s). Serine and cysteine are stereochemically very similar, with nearly equivalent volumes. Prevention of the oligomerization of γ2 with α2 and β1 by the serine-to-cysteine mutation at position 171 emphasizes the importance of forming the turn-stabilizing hydrogen bonds. It appears that even a subtle change at position 171 may be magnified through subsequent adjustments along the loop, considerably altering the subunit-subunit binding site. Mutations of serine 171 may therefore be more detrimental than mutations of tyrosine 172, as the former may cause more global changes in the positioning of the entire loop 8, whereas mutations of the latter only result in localized changes that may be better tolerated.

Finally, because serine 171 and tyrosine 172 are both extremely conserved among the members of the GABA_A receptor subunit family (16), it would be interesting to speculate whether or not the same residues on other GABA_A receptor subunits play similar roles in the assembly of GABA_A receptor subunits. Additional studies of these conserved residues need to be performed to determine the structure-function relationships of other GABA_A receptor subunits.

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