* **Research:**Introduction, Methods, Results, Discussion

**GABAA Receptor Subunit Combinations as Candidates for GABAslow Expression**

1. GABAA-slow (GABAslow) refers to a distinct form of inhibitory neurotransmission characterized by slower kinetics compared to typical fast inhibitory currents. <https://pmc.ncbi.nlm.nih.gov/articles/PMC2666407/>

## Comparison: GABAA Fast vs Slow

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| **Feature** | **GABAA fast** | **GABAA slow** |
| Rise/Decay Kinetics | Rapid (milliseconds) | Slow (tens of milliseconds) |
| Location | Somatic, perisomatic | Dendritic |
| Interneuron Origin | Basket cells, others | Specialized interneurons |
| Functional Role | Gamma oscillations, fast inhibition | Theta oscillations, slow inhibition |
| Sensitivity to Antagonists | Subtype-specific | Subtype-specific |

1. The combinations of GABAA receptor subunits represent potential dimeric associations that could contribute to this slower synaptic inhibition profile. Based on current findings using single cell RNA sequencing (Scanpy- Python based analysis of RNA ISH data from the Allen Mouse Brain Atlas), docking methodologies i.e. Autodock GPU (rigid), Discovery Studio (CDOCKER) and AI based AlphaFold3 (in house datasets using Multimeric protein-ligand design), certain subunit combinations have emerged as more likely candidates for mediating GABAslow currents. <https://pmc.ncbi.nlm.nih.gov/articles/PMC2666407/>  https://doi.org/10.1186/s43141-021-00224-0

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| **Probable Candidates** | **LAMP5 Co-Expression (%)** | **CA1 Co-Expression (%)** |
| alpha1-beta1 | 89.96 | 98.89 |
| alpha1-beta3 | 90.14 | 96.89 |
| alpha2-alpha3 | 25.68 | 11.9 |
| alpha2-alpha4 | 60.72 | 62.82 |
| alpha2-beta1 | 76.16 | 75.2 |
| alpha2-beta3 | 76.16 | 73.2 |
| alpha3-beta2 | 38.19 | 16.63 |
| alpha5-alpha3 | 15.68 | 24.71 |
| alpha5-beta3 | 36.3 | 41.43 |
| beta1-alpha3 | 40.86 | 26.77 |
| beta1-alpha4 | 76.35 | 86.78 |
| beta2-alpha3 | 38.19 | 16.63 |
| beta2-alpha4 | 74.39 | 55.53 |
| beta2-alpha5 | 33.62 | 24.74 |
| beta3-alpha3 | 41.05 | 27.19 |

**Role of α Subunits in Determining GABA Current Kinetics**

1. The α subunit isoform plays a critical role in determining the temporal characteristics of GABAA receptor-mediated currents. Different α subunits confer distinct kinetic properties to the assembled receptors. <https://pmc.ncbi.nlm.nih.gov/articles/PMC3937617/>

**α5 Subunit as a Primary Mediator of GABAslow**

The α5 subunit has been directly implicated in slow inhibitory transmission. Research indicates that α5 subunits make a significant contribution to a large-amplitude subset of GABAA,slow synapses[[1]](#fn1). Among the combinations listed, alpha5-alpha3 and beta2-alpha5 contain this critical subunit, making them promising candidates for GABAslow expression.

**α2 and α3 Subunits and Slowed Deactivation**

The α2 subunit significantly affects receptor kinetics by increasing GABA affinity, thereby slowing current deactivation[[2]](#fn2). Compared to α1-containing receptors, those with α2 subunits consistently deactivate approximately 10-fold more slowly. Single channel analysis has revealed that this slower current decay is attributable to longer burst durations at low GABA concentrations, corresponding to a roughly 4-fold higher affinity for GABA[[2]](#fn2).

Similarly, receptors containing the α3 subunit demonstrate substantially slower kinetics than those with α1. The presence of α3 has been shown to slow activation fourfold, desensitization nearly twofold, and deactivation threefold compared to α1-containing receptors[[3]](#fn3). These alterations in transition rates involved in ligand binding underlie changes in apparent activating site affinity and macroscopic current gating[[3]](#fn3).

**Critical Role of β Subunits in Receptor Function**

While α subunits largely determine kinetic properties, β subunits are crucial for receptor assembly and function.

**Importance of the β3 Subunit**

The β3 subunit specifically plays a crucial role in inhibitory transmission. Research shows that knockout of β3 impairs inhibitory transmission, particularly affecting inputs from parvalbumin-expressing interneurons onto pyramidal cells[[4]](#fn4). Expression of β3 alone is sufficient to rescue inhibitory currents in the context of a β1-3 subunit knockout, highlighting its unique importance in GABAA receptor function[[4]](#fn4).

**Analysis of Specific Dimer Candidates**

**α5-Containing Combinations (α5-α3, β2-α5)**

1. These combinations represent the strongest candidates for GABAslow expression based on direct evidence linking α5 subunits to slow inhibitory currents[[1]](#fn1). The α5-α3 combination is particularly interesting as it incorporates two subunits associated with slower kinetics. <https://pmc.ncbi.nlm.nih.gov/articles/PMC1156777/>

**α2-Containing Combinations (α2-α3, α2-β1, α2-β3, α2-β4, α2-α4)**

1. Combinations featuring the α2 subunit show significant potential for mediating slower inhibitory currents due to α2's documented effect on deactivation kinetics[[2]](#fn2). The α2-β3 pairing may be especially relevant given both subunits' important roles in inhibitory transmission. <https://pmc.ncbi.nlm.nih.gov/articles/PMC6089239/>

**α3-Containing Combinations (β1-α3, β3-α3)**

These combinations incorporate the α3 subunit, which confers slower activation, desensitization, and deactivation properties[[5]](#fn5)[[3]](#fn3). The β3-α3 combination merits particular attention as it combines two subunits individually linked to important aspects of inhibitory transmission. https://doi.org/10.1038/s41467-022-32212-4

**α1-Containing Combinations (α1-β1, α1-β2)**

These combinations are less likely to contribute significantly to GABAslow expression. Developmental studies show that a switch from α2 to α1 expression correlates with faster IPSC decay times[[6]](#fn6), suggesting α1-containing receptors typically mediate faster inhibitory currents.

**Pentameric Structure and Functional Implications**

It's important to note that functional GABAA receptors are pentamers, typically composed of 2α, 2β, and 1γ subunits. The dimeric combinations listed likely represent building blocks of complete receptors rather than functional units themselves.

Experimental evidence indicates that receptor properties are dramatically influenced by the full subunit composition. For example, α1β1 and α1β1γ2S subunits produce distinct ion channels with different conductance and gating properties[[7]](#fn7). α1β1γ2S GABARs opened for almost three times the duration as α1β1 GABARs (6.0 vs 2.3 msec, respectively)[[7]](#fn7).

**Conclusion**

Based on the available evidence, certain subunit combinations emerge as more likely candidates for GABAslow expression. The most promising candidates include those containing α5 subunits (α5-α3, β2-α5), followed by combinations featuring α2 or α3 subunits, particularly when paired with β3 (α2-β3, β3-α3).

* The α1-containing combinations (α1-β1, α1-β2) are less likely to contribute to slow inhibitory currents. However, the actual contribution of any subunit combination to GABAslow would depend on their incorporation into functional pentameric receptors and their specific synaptic localization, which cannot be definitively determined solely from the dimeric combinations listed. [10.1113/jphysiol.1995.sp021070](https://doi.org/10.1113/jphysiol.1995.sp021070)

Further experimental investigation using techniques such as targeted genetic manipulation and electrophysiological recording would be necessary to conclusively determine which of these combinations contribute most significantly to GABAslow expression in vivo.  <https://doi.org/10.1523/JNEUROSCI.20-06-02202.2000> <https://doi.org/10.1523/JNEUROSCI.13-04-01429.1993>