Alternative splicing generates a novel isoform of the rat metabotropic GABA(B)R1 receptor

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Here we present a novel isoform of the metabotropic G-protein-coupled receptor for gamma-aminobutyric acid (GABA). The isoform, termed GABA(B)R1c (R1c), differs from the recently identified R1a and R1b receptors by an in-frame insertion of 31 amino acids between the second extracellular loop and the fifth transmembrane region. Analysis of the rat GABA(B)R1 gene demonstrates that the insertion is the result of an alternative splicing event within a 567-bp intron between exons 16 and 17. In situ hybridization in the rat brain shows a wide distribution of R1c transcripts and an overlap with the R1a and R1b transcripts. The highest mRNA levels are found in cerebellar Purkinje cells, cerebral cortex, thalamus and hippocampal CA1 and CA3 regions. Western blots and immunodetection of recombinant epitope-tagged receptors as well as [125I]CGP71872 photoaffinity labelling of cell membranes demonstrate that R1c is correctly expressed, although at a lower level than the previously identified isoforms. When coexpressed with the newly characterized GABA(B)R2, R1c functionally couples to G-protein-activated Kir3.1/3.2 channels in Xenopus oocytes and to PLC-activating chimeric G(alpha)qo subunits in HEK-293 cells with a similar EC50 for agonists. These data suggest that the R1c isoform represents a functional GABA(B)R in the rat brain.

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