A single subunit (GB2) is required for G-protein activation by the heterodimeric GABA(B) receptor

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Title A single subunit (GB2) is required for G-protein activation by the heterodimeric GABA(B) receptor
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Although G-protein-coupled receptors (GPCRs) have been shown to assemble into functional homo or heteromers, the role of each protomer in G-protein activation is not known. Among the GPCRs, the gamma-aminobutyric acid (GABA) type B receptor (GABA(B)R) is the only one known so far that needs two subunits, GB1 and GB2, to function. The GB1 subunit contains the GABA binding site but is unable to activate G-proteins alone. In contrast the GB2 subunit, which does not bind GABA, has an heptahelical domain able to activate G-proteins when assembled into homodimers (Galvez, T., Duthey, B., Kniazeff, J., Blahos, J., Rovelli, G., Bettler, B., Prézeau, L., and Pin, J.-P. (2001) EMBO J. 20, 2152-2159). In the present study, we have examined the role of each subunit within the GB1-GB2 heteromer, in G-protein coupling. To that end, point mutations in the highly conserved third intracellular loop known to prevent G-protein activation of the related Ca-sensing or metabotropic glutamate receptors were introduced into GB1 and GB2. One mutation, L686P introduced in GB2 prevents the formation of a functional receptor, even though the heteromer reaches the cell surface, and even though the mutated subunit still associates with GB1 and increases GABA affinity on GB1. This was observed either in HEK293 cells where the activation of the G-protein was assessed by measurement of inositol phosphate accumulation, or in cultured neurons where the inhibition of the Ca(2+) channel current was measured. In contrast, the same mutation when introduced into GB1 does not modify the G-protein coupling properties of the heteromeric GABA(B) receptor either in HEK293 cells or in neurons. Accordingly, whereas in all GPCRs the same protein is responsible for both agonist binding and G-protein activation, these two functions are assumed by two distinct subunits in the GABA(B) heteromer: one subunit, GB1, binds the agonists whereas the other, GB2, activates the G-protein. This illustrates the importance of a single subunit for G-protein activation within a dimeric receptor.

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