$GABA_B$ Receptor Subtypes Differentially Affect Synaptic Inhibition in the Dentate Gyrus

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$GABA_B$ receptors are G-protein-coupled receptors for the inhibitory neurotransmitter GABA. Two functional subtypes are expressed in the brain by combining a $GABA_{B1}$ isoform, $GABA_{B1a}$ or $GABA_{B1b}$, with a $GABA_{B2}$ subunit. The $GABA_{B(1a,2)}$ receptors exclusively exert presynaptic inhibition on glutamate synapses, but both subtypes reduce GABA release. It is, however, unclear whether the subtypes are co-expressed or differentially localised on inhibitory pathways. We assessed the hypothesis that $GABA_B$ subtypes may differentially modulate synaptic inhibition by selective expression in inhibitory pathways.

We examined the function and localisation of $GABA_B$ receptors in the dentate gyrus of $GABA_{B1}$ isoform knockout mice using multielectrode electrophysiological recordings and immunohistochemical labelling. In the rat dentate gyrus, the predominant function of $GABA_B$ receptors is the enhancement of granule cell (GC) excitability via presynaptic inhibition of GABA release. Here, in murine dentate gyrus, $GABA_B$ receptor activation by the agonist, baclofen (10 µM), did not alter the excitatory synaptic transmission measured by the field excitatory postsynaptic potential ($p > 0.05$), but increased the population spike of GCs in both the wild-type (142.7 ± 6.1% of control, $n = 7$) and knockout mice (136.1 ± 4.3% ($n = 9$) for $GABA_{B1a}^{-/-}$ mice and 161.7 ± 9.4% ($n = 6$) for $GABA_{B1b}^{-/-}$ mice). The significantly larger effect in $GABA_{B1b}^{-/-}$ mice ($p < 0.001$, repeated two-way ANOVA) indicated a more powerful effect by $GABA_{B(1a,2)}$ receptors. In addition, all baclofen-induced effects were prevented by the $GABA_B$ receptor antagonist CGP55845 (1 µM, $p < 0.001$, repeated two-way ANOVA), or $GABA_A$ receptor antagonist bicuculline (10 µM, $n = 6$ mice from each genotype), showing a mechanism via $GABA_B$ receptor-mediated reduction of GABA release. Immunohistochemical labelling of $GABA_{B1}$ and $GABA_{B2}$ subunits highlighted cell body staining in hilar neurons and neuropil labelling in the molecular and GC layers. However, in $GABA_{B1a}^{-/-}$ mice neuropil staining in the inner molecular and GC layers was reduced together with the number of immunopositive hilar neurons at the hilus-GC border zone (by 24.3%, $p < 0.05$, one-way ANOVA with Tukey's multiple comparisons). In $GABA_{B1b}^{-/-}$ mice, in contrast, reduction of neuropil staining was found in the outer molecular layers, and the number of immunolabeled hilar neurons decreased at both the border zone (by 28.7%, $p < 0.05$) and in deep layers (25.9%, $p < 0.05$). $GABA_{B(1a,2)}$ receptors may, therefore, predominantly modulate GABA release from hilar projections onto the perisomatic and proximal dendritic regions of the GCs and thereby exert more powerful disinhibition than $GABA_{B(1b,2)}$ receptors, which control the distal dendritic fields. By selective expression in interneurons and their projections, $GABA_B$ receptor subtypes may, therefore, differentially modulate synaptic inhibition.

The work was supported by the BBSRC.