γ hydroxybutyrate activates specific $GABA_A$ receptor subtypes

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γ-hydroxybutyrate (GHB) is a small molecule with complex pharmacology. Present in low concentrations in the mammalian brain, it acts as a neuromodulator. When taken exogenously, it is used to treat narcolepsy and to ameliorate the withdrawal effects of alcohol, and is used as a recreational drug at higher concentrations, sometimes used as a date-rape drug. However, the pharmacology of GHB is unclear, and the full extent of its interactions with membrane proteins in the brain is yet to be fully elucidated. It has been demonstrated that GHB activates the $GABA_B$ receptor at high concentrations, but the receptor that mediates other actions of GHB has yet to be identified.

Through biochemical and electrophysiological studies, we have identified that GHB activates a subset of $GABA_A$Rs. The $GABA_A$R is a ligand-gated ion channel that forms a pentameric complex surrounding a central chloride-conducting pore. It is formed by a combination of α (1-6), β (1-3), δ, γ, ε, and π subunits according to a predetermined set of rules. We expressed a variety of known subtypes (>10, n>3 each) in *Xenopus* oocytes and determined that GHB elicited a chloride current from oocytes expressing α4, β1-3 and δ subtypes. GHB activated oocytes injected with α4, β1 and δ subunits with an EC_{50} of 140 nM (n=5). GHB demonstrated selectivity for the β1-subunit with rank potency order of β1> β3> β2 when co-expressed with the δ-subunit. This activation was blocked by gabazine, a selective inhibitor of $GABA_A$Rs (n=4). Furthermore, the GHB analogue NCS-382 that competes with GHB binding in the brain, also activated activated oocytes injected with α4, β1 and δ subunits. Binding studies of brains from knockout α4 and δ-$GABA_A$R mice demonstrated reduced binding in α4 but not δ-knockout mice. Taken together, these data demonstrate GHB activates α4βδ $GABA_A$Rs with different potencies, but requiring the α4-subunit for the maximum elicitation of a chloride current.