The epilepsy associated $GABA_A$ receptor γ_2R43Q mutation increases sensitivity to Zn^{2+} inhibition

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$GABA_A$ receptors mediate rapid inhibitory signalling in the central nervous system, and mutations in various subunits of these pentameric receptors are associated with epilepsy. Receptors composed of α and β subunits are highly sensitive to inhibition by extracellular Zn^{2+} ions; however incorporation of a γ subunit disrupts two of three known Zn^{2+} binding sites and greatly reduces Zn^{2+} sensitivity. Here we demonstrate that the epilepsy associated γ_2(R43Q) mutation greatly increases the susceptibility of heterologously expressed receptors to Zn^{2+} inhibition while preserving functional characteristics underpinned by presence of the γ_2 subunit. $\alpha_1\beta_2\gamma_2$ receptors are believed to contain a single N-terminal Zn^{2+} binding site. Mutation of residues contributed to this site by the α subunit ameliorated the effect of γ_2(R43Q) on Zn^{2+} sensitivity, indicating that γ_2(R43Q) allosterically affects Zn^{2+} binding or affects signal transduction, rather than directly interacting with Zn^{2+}. This assertion was bolstered by the increased Zn^{2+} sensitivity of mutations predicted, by molecular modelling, to interact with γ_2(R43Q). We also examined other epilepsy-associated γ_2 mutations, γ_2(K289M) and γ_2(R139G), and found that they did not substantially increase sensitivity to Zn^{2+} inhibition. Increased Zn^{2+} sensitivity may be physiologically important in hippocampal neurones, where synaptic Zn^{2+} reaches high enough levels to modulate GABAergic signalling, and may represent a novel mechanism underlying the increased occurrence of febrile seizures reported in patients harbouring the γ_2(R43Q) mutation.