

P007 Subtype-Selective Effects On Human $\alpha 4\beta 3\delta$ And $\alpha 4\beta 3\gamma 2$ GABA_A Receptors Mediated By Steroids
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Recent evidence has implicated selective potentiation of the delta subunit of GABA_A receptors as an important mediator of *in vitro* and *in vivo* neurosteroid activity. However, data only exists for a small number of steroids. In the present study, a high throughput potentiometric assay based on fluorescence resonance energy transfer (FRET) was used to characterise the efficacy and GABA_A receptor selectivity profile for a wider set of steroids. Ltk-cells, stably transfected with human GABA_A receptor subunits to form $\alpha 4\beta 3\delta$ or $\alpha 4\beta 3\gamma 2$ receptor subtypes, were incubated with CC2-DMPE and DiSBAC₂(3) and membrane potential-dependent changes in FRET recorded using a Voltage/Ion probe Reader. The ability of steroids to modulate an EC₅₀ GABA response was then examined. Whilst some steroids were non-selective, 5 β -pregnan-3 β -ol-20-one, 5 β -pregnane-3 α , 20 β -diol, 5 β -pregnane-3 α , 17 α -diol-11, 20-dione and 5 α -pregnane-3, 11, 20-trione showed particularly high efficacy and selectivity for $\alpha 4\beta 3\delta$ over $\alpha 4\beta 3\gamma$ receptors. These results help dissect structural features of steroids which underlie receptor selectivity, as indicated by molecular modelling of this compound series using Principal Components Analysis.