

P004 Salicylidene salicylhydrazide, a selective inhibitor of $\beta 1$ containing GABA_A receptors

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A high throughput screening assay measuring fluorescence emission identified salicylidene salicylhydrazide (SCS) as being a potent inhibitor of GABA_A receptors. The aim of this study was to characterise the properties of SCS at human GABA_A receptors using electrophysiological techniques. SCS inhibited $\beta 1$ containing receptors while having no effect on $\beta 2$ or $\beta 3$ containing receptors. Variation in the type of α subunit, γ subunit and the presence of θ did not affect the functional selectivity of SCS. Chimeras of $\beta 1$ and $\beta 2$ and subsequent point mutations showed that threonine 255, located within transmembrane domain (TM) 1 and isoleucine 308, located extracellularly just prior to TM3, were required for inhibition by SCS.

Additional studies showed that SCS did not compete with flumazenil, picrotoxin, bicuculline, pregnenolone sulphate or dehydroepiandrosterone sulphate. In addition it did not interact with the GABA binding site nor show any use or voltage dependence. In summary, SCS is a potent selective allosteric inhibitor of $\beta 1$ containing GABA_A receptors possibly acting via a previously unidentified site. The unique $\beta 1$ subtype selectivity was a result of threonine 230 within TM1 and isoleucine 283 within TM3 of the $\beta 1$ subunit