PL1. DESIGNER DRUGS FOR THE NEW MILLENIUM: $GABA_A$ RECEPTOR SUBTYPE SELECTIVE AGENTS

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ABSTRACT

Converging lines of evidence indicate that $GABA_A$ receptors are part of the brain's "biowarning system". For example, dramatic changes in $GABA_A$ receptor function precede measurable alterations in the HPA axis following presentation of environmental stimuli. Thus, its is perhaps not surprising that $GABA_A$ receptors mediate the actions of the most widely prescribed class of anxiolytic (anti-anxiety) agents, the benzodiazepines (e.g., diazepam). Currently available 1,4-benzodiazepines (as well as other anxiolytics acting through $GABA_A$ receptors, such as barbiturates and ethanol) produce other pharmacological actions that may be considered undesirable. Because $GABA_A$ receptors are a heterogeneous family of ligand-gated ion channels, the design of subtype selective agents has been proposed as one strategy to produce agents with a more limited range of action (e.g. an anxiolytic lacking sedative properties). Studies in both recombinant and native $GABA_A$ receptors clearly demonstrate that the α subunit (that is, $\alpha_{1\rightarrow6}$) is the principal determinant of ligand affinity for a structurally diverse group of compounds acting at allosteric modulatory sites that have traditionally been termed "benzodiazepine receptors". While representatives from several chemical classes (e.g., the imidazopyridine, zolpidem) exhibit selectivity for $GABA_A$ receptors containing an α_1 subunit, the pharmacological profiles of these compounds are not dramatically different from "classical" 1,4-benzodiazepines. This may not be viewed as unanticipated, since receptors containing the α_1 subunit probably constitute > 50% of the total $GABA_A$ receptors pool, and are widely distributed throughout the central nervous system. It can be hypothesized that compounds exhibiting selectivity for $GABA_A$ receptor isoforms present in relatively low abundance would possess a more selective range of actions. Based on the reported 10-15 fold selectivity of Ro 15-4513 for recombinant $GABA_A$ receptors containing an α_5 subunit (compared to receptors expressing other α subunits), we synthesized a series of novel 8-substituted imidazobenzodiazepines. These compounds possess a marked selectivity (up to 75-fold) for α_5 subunit-containing recombinant and native $GABA_A$ receptors. *In vivo* studies suggest the pharmacological actions of these compounds are mediated through occupation of α_5 containing $GABA_A$ receptors. A radiolabelled form of an α_5 selective imidazobenzodiazepine ([^{3}H]RY 80) has been used to characterize native and recombinant type $GABA_A$ receptors containing α_5 subunits. As had been previously demonstrated for other α subunits, it is likely that amino acid residues proximal to the first transmembrane domain are responsible for the high degree of selectivity of such compounds for $GABA_A$ receptors containing an α_5 subunits. Molecular modeling studies, together with the use of both mutational analysis and transgenic models should result in α_5 selective agents, prototypic designer drugs for the new millenium.