SL651498, a GABA$_A$ Receptor Agonist with Subtype-Selective Efficacy, as a Potential Treatment for Generalized Anxiety Disorder and Muscle Spasms

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Key Words: Anxiety — Anxiolytic — Benzodiazepine — Diazepam — GABA$_A$ receptor— Muscle spasm—SL651498.

ABSTRACT

SL651498 (6-fluoro-9-methyl-2-phenyl-4-(pyrrolidin-1-yl-carbonyl)-2, 9-dihydro-1H-pyrido[3,4-b]indol-1-one) was identified as a drug development candidate from a research program designed to discover subtype-selective GABA$_A$ receptor agonists for the treatment of generalized anxiety disorder and muscle spasms. The drug displays high affinity for rat native GABA$_A$ receptors containing $\alpha_1$ ($K_i = 6.8$ nM) and $\alpha_2$ ($K_i = 12.3$ nM) subunits, and weaker affinity for $\alpha_5$-containing GABA$_A$ receptors ($K_i = 117$ nM). Studies on recombinant rat GABA$_A$ receptors confirm these findings and indicate intermediate affinity for the $\alpha_3\beta_2\gamma_2$ subtype. SL651498 behaves as a full agonist at recombinant rat GABA$_A$ receptors containing $\alpha_2$ and $\alpha_3$ subunits, and as a partial agonist at recombinant GABA$_A$ receptors expressing $\alpha_1$ and $\alpha_5$ subunits. SL651498 produced anxiolytic-like and skeletal muscle relaxant effects qualitatively similar to those of benzodiazepines (BZs) [minimal effective dose (MED): 1 to 10 mg/kg, i.p. and 3 to 10 mg/kg, p.o.]. However, unlike these latter drugs, SL651498 induced muscle weakness, ataxia or sedation at doses much higher than those having anxiolytic-like activity (MED: 30 to 100 mg/kg, i.p. or p.o.). Moreover, in contrast to BZs, SL651498 did not produce tolerance to its anticonvulsant activity or physical dependence. It was much less active than BZs in potentiating the depressant effects of ethanol or impairing cognitive processes in rodents. The differential profile of SL651498 as compared to BZs may be related to its selective efficacy at the $\alpha_2$- and $\alpha_3$-containing GABA$_A$ receptors. This suggests that selectively targeting GABA$_A$ receptor subtypes can lead to drugs with increased clinical specificity. SL651498 represents a promising alternative to agents currently used for the treatment of anxiety disorders and muscle spasms without the major side effects seen with classical BZs.