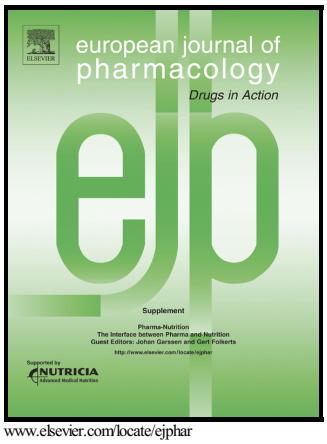

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Characterization of pulmonary sigma receptors by radioligand binding.

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Abstract

This study establishes the expression of appreciable populations of sites on mouse lung membranes that exhibit radioligand binding properties and pharmacology consistent with assignment as sigma$_1$ and sigma$_2$ receptors. Specific binding of the sigma$_1$ receptor radioligand [^{3}H](+)-pentazocine reached steady state within 6 h at 37 °C. Saturation studies revealed high affinity binding to a single class of sites (K_d 1.36 ± 0.04 nM; B_{max} 967 ± 11 fmol / mg protein). Inhibition studies showed appropriate sigma$_1$ receptor pharmacology, including higher affinity for (+)-*N*-allylnormetazocine with respect to the (-)-enantiomer, and positive allosteric modulation of dextromethorphan binding by phenytoin. Using [^{3}H]1,3-di(2-tolyl)guanidine in the presence of (+)-pentazocine to assess sigma$_2$ receptor binding, steady state was achieved within 2 min at 25 °C. Cold saturation studies revealed one high affinity, low capacity binding site (K_d 31.8 ± 8.3 nM; B_{max} 921 ± 228 fmol / mg protein) that displayed sigma$_2$ receptor pharmacology. A very low affinity, high capacity interaction also was observed that represents saturable, but not sigma receptor specific, binding. A panel of ligands showed rank order inhibition of radioligand binding appropriate for the sigma$_2$ receptor, with ifenprodil displaying the highest apparent affinity. In vivo, dextromethorphan inhibited the specific binding of a radioiodinated sigma$_1$ receptor ligand in lung with an ED_{50} of 1.2 μmol / kg, a value near the recommended dosage for the drug as a