The effect of long term antidepressant treatment on spiroperidol-labeled 5-HT receptor binding was investigated. Male Sprague-Dawley rats (150-175 g) received daily i.p. injections of drugs for 21 days, all except pargyline (25 mg/kg) being given at 10 mg/kg. The frontal cerebral cortex was used for most binding studies. Amitriptyline, imipramine, desipramine, nortriptyline, iprindole and fluoxetine competed at several neurotransmitter receptor binding sites, but their relative potencies did not correlate with their clinical potencies. In general, the greatest potencies occurred at histamine H₁ receptors, labeled by ³H mepyramine, but they were also potent at muscarinic cholinergic receptors labeled by ³H quinuclidinylbenzilate. Their relative potencies at α-adrenergic receptors labeled by ³H dioxane (WB-4101) were similar to effects at muscarinic receptors and correlated with sedation and relief of psychomotor agitation. 2 Distinct populations of 5-HT receptors were labeled, with ³H 5-HT (5-HT-1) and ³H spiroperidol (5-HT-2) respectively, ³H LSD labeling both sites to the same extent. The antidepressants were much more potent at the 5-HT-2 receptors than at the 5-HT-1 receptors, effects on ³H LSD binding being intermediate. The drugs were less potent at dopamine (DA) receptors labeled by ³H spiroperidol in the corpus striatum, and at β-adrenergic receptors labeled by ³H dihydroalprenolol (DHA) than at any other receptor binding sites. Haloperidol and chlorpromazine had considerable affinities for several receptors, resembling the more active antidepressants at α-adrenergic and 5-HT-2 sites, and the most potent drugs at DA receptors. Amitriptyline, imipramine, desipramine, iprindole and pargyline reduced ³H DHA binding to β-adrenergic, and ³H spiroperidol binding to 5-HT-2 receptors, by 20 and 40%, respectively. Desipramine reduced ³H DHA binding by 29% and binding to 5-HT-2 receptors by 21%. Binding to β-adrenergic and 5-HT receptors was unaffected by methysergide, chlorpromazine, haloperidol and fluoxetine. ³H 5-HT binding to 5-HT-1 receptors decreased with imipramine and pargyline. ³H LSD binding was affected in a manner intermediate to effects on ³H spiroperidol and ³H 5-HT binding. Long-term drug treatment had no effect on muscarinic cholinergic or α-adrenergic receptors. Neuroleptics, but not antidepressants, increased binding to ³H spiroperidol DA receptors in the corpus striatum. 2 Tab. 21 Ref.