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P 'psychosedative' 'diphenylmethane' penfluridol /Janssen/
B pimozide 'phenothiazine' un-labeled tritium labeled trifluoperazine /SK+F/ 'chlorpromazine' 'haloperidol' 'amitriptyline' /Merck-USA/ 'imipramine' 'chlordiazepoxide' /Roche/ 'diazepam' dex'amphetamine' 'LSD' 'barbiturate' pentobarbital 'morphine' 'histamine' etc. binding to 'P-ester-hydrolase' cyclic-AMP-phosphodiesterase calcium dependent activator in-vitro /IV/ /XIV/ /XXVI/ /XXXII/ /E/

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Selective Binding of Antipsychotics and Other Psychoactive Agents to the Calcium-Dependent Activator of Cyclic Nucleotide Phosphodiesterase.

Selective binding of antipsychotics and other psychoactive agents to the calcium-dependent activators of cyclic nucleotide phosphodiesterase was studied.

The following drugs (labeled and unlabeled.) were studied: phenfluridol (Janssen); pimozide (Janssen); trifluoperazine (SK+F); chlorpromazine (SK+F); haloperidol; amitriptyline (Merck-USA); imipramine; chlordiazepoxide (Roche); diazepam (Roche); dihydro-alprenolol d-amphetamine; d-LSD; pentobarbital; morphine; histamine and dopamine. Equilibrium dialysis was performed. 500 µl Activator was dialyzed in a bath containing Tris-HCl and EGTA and/or $Ca^{2+}$, together with various concentrations of radiolabeled drug At the end of dialysis, radioactivity of a 200 µl aliquot of dialysis bag contents was determined in a liquid scintillation counter. In studying the binding of nonradioactive agents, their ability to displace radioactive ($^3$H)trifluoperazine from activator was determined.

A variety of compounds displayed high-affinity, Ca-dependent binding similar to that shown for trifluoperazine. Competition studies suggested that various classes of antipsychotics bound to the same activator site. Pimozide, chlorpromazine and haloperidol had dissociation constants of 0.8, 5 and 9 µM respectively. The number of binding sites was between 1-3/molecule, of activator. Antipsychotic drugs showed more calcium specific binding than antianxiety and antidepressant drugs. A large number of drugs affecting the CNS showed no Ca-specific binding and these included LSD, amphetamine, pentobarbital, morphine, histamine and dopamine. The magnitude of Ca-dependent drug binding to activator correlated with the ability of the drugs to inhibit phosphodiesterase activation and binding of phenothiazine derivatives paralleled clinical antipsychotic activity. Trifluoperazine, flupenthixol (Lundbeck), clozapine (Sandoz), chlorpromazine, pimozide and penfluridol all displaced $^3$H -trifluoperazine from the activator with I50 values < 20 µM. Promethazine (Wyeth), trifluoperazine sulfoxide, and chlorpromazine sulfoxide were less effective and chlordiazepoxide, amitriptyline and nortriptyline (Lilly) displayed only moderate potency. Phentolamine, theophylline, papaverine and methacholine were ineffective. (+)-Butaclamol (Ayerst) was 5x more effective than the (-)-isomer in displacing $^3$H-trifluoperazine, but both stereoisomers of flupenthixol were equally effective.

6 Fig. 2 Tab. 27 Ref. S39/MCC/IMS

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