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Letter to the Editor

Flupentixol and Dopamine Receptor Selectivity

In several publications on ^{3}H-cis(Z)-flupentixol (^{3}H-FPT) binding (Hyttel 1978a, b, 1980; Cross and Owen 1980) it is claimed that ^{3}H-FPT preferentially labels one class of dopamine receptors, D-1, associated with adenylate cyclase. This statement is based on the weak effect of butyrophenones and diphenylbutylpiperidines as displacers of ^{3}H-FPT binding and as inhibitors of dopamine-stimulated adenylate cyclase activity. The rate of disappearance of ^{3}H-FPT labelling after kainate lesions resembles the rate of disappearance of adenylate cyclase but differs from that of ^{3}H-haloperidol and ^{3}H-spiroperidol binding (Leff et al. 1981). This supports the above statement. However, from the results in the articles it appears that cis(Z)-flupentixol has equal affinities for D-1 and D-2 receptors since IC50-values of 3.0 and 3.1 n*M* for displacement of ^{3}H-FPT and ^{3}H-haloperidol (^{3}H-HAL) binding, respectively, were found. The preferential labelling of D-1 receptors and the equal affinities for D-1 and D-2 receptors were hard to reconcile and therefore my arguments in the discussions in the articles were weak on this point. Therefore, it is understandable that many people have made the erroneous interpretation that cis(Z)-flupentixol predominantly (or even exclusively) binds to D-1 receptors – in other words that cis(Z)-flupentixol is a selective D-1 receptor antagonist.

Since cis(Z)-flupentixol, as stated above, has equal affinities for D-1 and D-2 receptors, Scatchard analysis did not reveal two binding components for ^{3}H-FPT.

However, by a detailed analysis of the inhibition of ^{3}H-FPT binding by butyrophenones, Cross and Owen (1980) demonstrated the presence of two components of ^{3}H-FPT binding – a high affinity site for butyrophenones, and a low affinity site for butyrophenones. These sites are related to the D-2 and D-1 receptor components, respectively. The same property has later been shown for another thioxanthene ligand, ^{3}H-piflutixol (^{3}H-PIF) (Hyttel 1981).

That the results published so far in fact reflect labelling of D-1 receptors is explained by the abundance in corpus striatum of D-1 receptors as compared to D-2 receptors (Hyttel 1978a, b).

In order to exclude from the assay any interference by D-2 receptor sites in ^{3}H-FPT or ^{3}H-PIF experiments we now routinely add 30 n*M* of spiroperidol which occupies all D-2 sites. By this means the thioxanthene ligands, ^{3}H-FPT and ^{3}H-PIF, can only bind to D-1 receptor sites. A series of 25 neuroleptics from different chemical classes were tested with inclusion of 30 n*M* of spiroperidol in the ^{3}H-PIF assay. The results obtained correlated closely with the previously published ^{3}H-FPT and adenylate cyclase data, whereas there was no such correlation with ^{3}H-HAL data.

In conclusion therefore, no selective D-1 receptor antagonist has been found. Nevertheless, when the experimental design includes 30 n*M* of spiroperidol for excluding any D-2 receptors, flupentixol or piflutixol can be used as ligands for selective labelling of D-1 receptors, even though these two thioxanthene neuroleptics are both D-1 and D-2 receptor antagonists.

References

Cross A, Owen F (1980) Characteristics of ^{3}H-cis-flupenthixol binding to calf brain membranes. Eur J Pharmacol 65:341–347

Hyttel J (1978a) A comparison of the effect of neuroleptic drugs on the binding of ^{3}H-haloperidol and ^{3}H-cis(Z)-flupenthixol and on adenylate cyclase activity in rat striatal tissue in vitro. Prog Neuro-Psychopharmac 2:329–335

Hyttel J (1978b) Effects of neuroleptics on ^{3}H-haloperidol and ^{3}H-cis (Z)-flupenthixol binding and on adenylate cyclase activity in vitro. Life Sci 23:551–556

Hyttel J (1980) Further evidence that ^{3}H-cis(Z)-flupenthixol binds to the adenylate cyclase-associated dopamine receptor (D-1) in rat corpus striatum. Psychopharmacology 67:107–109

Hyttel J (1981) Similarities between the binding of ^{3}H-piflutixol and ^{3}H-flupentixol to rat striatal dopamine receptors in vitro. Life Sci 28:563–569

Leff S, Adams L, Hyttel J, Creese I (1981) Kainate lesion dissociates striatal dopamine receptor radioligand binding sites. Eur J Pharmacol 70:71–75

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