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Kainic acid lesions of striatum and decortication reduce specific [^{3}H]sulpiride binding in rats, so D-2 receptors exist post-synaptically on cortico-striate afferents and striatal neurons

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Unilateral kainic acid lesions of rat striatum reduced specific striatal [^{3}H]spiperone and [^{3}H]sulpiride binding sites (Bmax) by 52 and 67% respectively compared with the intact side. The dissociation constant (K_D) for [^{3}H]spiperone binding was unchanged but that for [^{3}H]sulpiride binding was reduced. Specific striatal [^{3}H]spiperone and [^{3}H]sulpiride binding was reduced by 22 and 37% respectively in unilateral decorticate animals, but there was no change in K_D. Unilateral 6-hydroxydopamine lesions of the medial forebrain bundle caused no change in striatal [^{3}H]spiperone binding sites or K_D value, but produced a 27% increase in [^{3}H]sulpiride binding sites with no change in K_D. These data support the hypothesis of D-2 receptors located on cortico-striate glutamate fibres, but also indicate the presence of both D-1 and D-2 receptors on the cell bodies of striatal neurons.

Within the nigro-striatal neuronal complex a number of different types of dopamine receptors are recognized by their anatomical location. Thus, dopamine receptors are present on the presynaptic terminals and cell bodies of dopamine neurons, on the presynaptic terminals of strionigral and cortico-striate fibres, and on the cell bodies of striatal neurons (Kehr et al 1972; Reisine et al 1979; Spano et al 1977; Schwarcz et al 1978; Govoni et al 1978). A further distinction between dopamine receptors is made biochemically; it is believed that there are two distinct classes of cerebral dopamine receptors, one of which (D-1) is a receptor linked to the enzyme adenylate cyclase while the other (D-2) is independent of this enzyme (Kebabian & Calne 1979). This concept is supported by receptor binding data demonstrating multiple sites for dopamine agonist and antagonist binding (Burt et al 1976; Titeler et al 1978), and by behavioural (Costall & Naylor 1975; Cools et al 1976) and electrophysiological experiments (Cools & van Rossum 1976; Skirboll & Bunney 1979) which also demonstrate the existence of functionally different dopamine receptor populations within the same brain region.

It has been suggested that the D-1 and D-2 receptor populations have different anatomical locations. Thus kainic acid lesions of striatum to destroy those dopamine receptors located on cell bodies, result in a loss of both specific striatal [^{3}H]spiperone binding and adenylate cyclase (suggesting the presence of D-1 receptors on striatal neurons), whereas decortication to remove the cortico-striate glutamate pathway results only in loss of [^{3}H]-spiperone binding but not adenylate cyclase (suggesting the presence of D-2 receptors on cortical afferent terminals) (Schwarcz et al 1978). However, the use of [^{3}H]spiperone to label both dopamine receptor populations is open to criticism. Thus, while spiperone can inhibit dopamine stimulation of striatal adenylate cyclase (Hyttel 1978), the concentration required is more than 1000 times greater than that needed to totally inhibit specific [^{3}H]butyrophenone binding. At conventional ligand concentration it is unlikely that [^{3}H]spiperone binds to D-1 receptors to any significant degree. Loss of [^{3}H]-spiperone binding sites following lesioning procedures, therefore, is more likely to reflect loss of D-2 sites whether or not it is accompanied by changes in adenylate cyclase activity.

D-1 and D-2 dopamine receptors can be distinguished by their antagonist specificity. Compounds of the substituted benzamide series, such as sulpiride, are believed to be *specific* antagonists at the adenylate cyclase independent D-2 receptor (Kebabian & Calne 1979; Jenner et al 1978) since it causes no inhibition of dopamine stimulated adenylate cyclase activity. We have therefore compared the binding of [^{3}H]-sulpiride (identifying only D-2 receptors) to striatal

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preparations with that of [^{3}H]spiperone also following selective destruction of dopamine receptor populations by intrastriatal administration of kainic acid, by 6-hydroxydopamine lesions of the nigro-striatal pathway and by removal of the cortico-striatal pathway by decortication to clarify the location of D-1 and D-2 receptors in striatum. We find evidence for both D-1 and D-2 receptors on striatal cell bodies, and for D-2 receptors on cortico-striate terminals.

MATERIALS AND METHODS

Lesioning experiments

Female Wistar rats (150 ± 10 g; Charles Rivers Ltd.) were anaesthetized using chloral hydrate (300 mg kg^{-1} i.p.) and placed in a Kopf stereotaxic frame. Unilateral kainic acid lesions of striatum (A 7·9, L 2·6, V + 1·1) (De Groot 1959) were made using 2 μg in 1 μl 0·9% NaCl (saline) (buffered to pH 6·5; Sigma Chemical Co. Ltd.). Unilateral lesions of the medial forebrain bundle (A 4·5, L 1·9, V −3·0) (De Groot 1959) were made using 6-hydroxydopamine hydrobromide (8 μg in 3 μl saline containing 2 μg ascorbic acid; Sigma Chemical Co. Ltd.). In each case injections were made by slow infusion using 5 μl Hamilton syringe with Luer needle (o.d. 0·33 mm; i.d. 0·18 mm) at a rate of 1 μl min^{-1}. The effectiveness of the 6-hydroxydopamine lesion was checked 1 week before the biochemical testing by the occurrence of marked contraversive rotation following the administration of apomorphine hydrochloride (0·5 mg kg^{-1} s.c. 15 min previously). Unilateral cortical ablations were carried out by removal of the overlying calvarium and subsequent removal of the parietal and frontal cortex by shallow knife cuts to the level of the corpus callosum. Following lesioning bleeding was controlled by implantation of absorbable gelatin sponge (Sterispon No. 2; Allen & Hanbury, Ltd.) and animals received an intraperitoneal injection of ampicillin (Penbritin injectable suspension 0·1 ml containing 15 mg ampicillin trihydrate; Beecham Ltd.). Following surgery, animals with striatal or medial forebrain bundle lesions were left for some 21 days to allow for neuronal degeneration, while those animals receiving cortical ablation were allowed to recover for 5 days before biochemical examination. These timings were chosen to match those employed by Schwarcz et al (1978) in their studies on [^{3}H]spiperone.

Unilateral 6-hydroxydopamine lesions of the medial forebrain bundle were accompanied by a 97% fall in ipsilateral striatal dopamine content (0·47 ± 0·12 μg g^{-1} compared with 14·1 ± 1·2 μg g^{-1} in the intact forebrain; $P < 0.05$). In addition, these animals showed pronounced contraversive rotation to apomorphine hydrochloride (0·5 mg kg^{-1} s.c. 15 min previously), and ipsiversive rotation to (+)-amphetamine sulphate (3 mg kg^{-1} i.p. 30 min previously). Unilateral kainic acid lesions of the striatum produced animals showing ipsiversive rotation to the same dose of both apomorphine and amphetamine. Histological examination of the lesioned forebrain three weeks or more after injection of kainic acid showed a severe loss of neuronal cell bodies throughout the striatum and pronounced gliosis. Fibre bundles passing through this region appeared intact. Macroscopic examination of the brains of animals undergoing decortication showed gross loss of parietal and frontal cortex to the level of the corpus callosum.

Specific [^{3}H]spiperone and [^{3}H]sulpiride binding to striatal homogenates

Rats were killed by cervical dislocation and decapitation. The brains were rapidly removed and placed on ice. The corpus striata from the lesioned and intact sides of the brain were dissected out and placed separately in ice cold 50 mM tris buffer (pH 7·7). The preparation of striatal tissue and the determination of specific [^{3}H]spiperone binding was carried out according to Leysen et al (1978) on pooled striatal tissue preparations from the lesioned and intact forebrains of 14 animals. [^{3}H]Spiperone (20 Ci mmol^{-1}; Radiochemical Centre) was incorporated into the incubates at concentrations between 0·125–4·0 nM. Specific binding of [^{3}H]-spiperone was defined by the incorporation of (+)-butaclamol (5×10^{-6} M; Ayerst Laboratories Ltd.).

The binding of (±)-[^{3}H]sulpiride (26·2 Ci mmol^{-1}; custom synthesized by the Radiochemical Centre) was determined on the same striatal tissue pool according to the method of Theodorou et al (1979) in concentrations between 5 and 40 nM using (−)-sulpiride 5×10^{-6} M to define specific binding. The only deviation from the previously published method was that the time of incubation was reduced to 10 min.

Comparison of [^{3}H]spiperone and [^{3}H]sulpiride specific binding to striatal preparations from the lesioned and intact brain sides was carried out in parallel. Each ligand concentration was examined in triplicate. The data obtained were subjected to Scatchard analysis to determine the number of binding sites (Bmax), expressed as pmoles g^{-1} wet weight of tissue, and the dissociation constant (K_D). Statistical analysis was carried out using linear

regression analysis and comparison of data from lesioned and intact brain hemispheres was carried out using a two-tailed Student's *t*-test. In striatal tissue preparations from control animals [^{3}H]-spiperone (0·5 nM) total binding was 2941 ± 42 counts min^{-1}, non-displaceable binding in the presence of 5 × 10^{-6} M (+)-butaclamol was 162 ± 9 counts min^{-1} (so that 94·5% was specific binding), providing a gate for specific binding of 2779 ± 42 counts min^{-1}. At [^{3}H]sulpiride concentration of 15 nM total binding was 3929 counts min^{-1}, non-displaceable binding in the presence of 5 × 10^{-6} M (−)-sulpiride was 1987 ± 96 counts min^{-1} (so that 49·4% was specific binding), providing a gate for specific binding of 1942 ± 39 counts min^{-1}.

RESULTS

Kainic acid (2 μg in 1 μl) lesions of one striatum produced a 52% decrease in specific [^{3}H]spiperone (0·125 – 4·0 nM) binding sites (Bmax), and 67% decrease in specific [^{3}H]sulpiride (5–40 nM) binding sites, in the lesioned striatum compared with the intact side 21 days following surgery (Table 1; Fig. 1). While K_D for [^{3}H]spiperone binding was unchanged, that for [^{3}H]sulpiride was decreased by 50%.

Unilateral lesions of the medial forebrain bundle with 6-hydroxydopamine (8 μg in 3 μl) caused no change in K_D or Bmax for specific [^{3}H]spiperone binding when comparing preparations from the lesioned and intact forebrains 21 days after surgery (Table 1). Specific [^{3}H]sulpiride binding sites increased by 27%, but K_D did not alter.

Unilateral removal of frontal and parietal cortex 5 days previously reduced Bmax values for striatal preparations from the lesioned side by 22 and 37% for [^{3}H]spiperone and [^{3}H]sulpiride respectively, when compared with the striatal preparations from the intact forebrain (Table 1). No changes in K_D values occurred.

Table 1. Alterations in specific striatal (A) [^{3}H]-spiperone (0·125–4·0 nM) and (B) [^{3}H]sulpiride (5–40 nM) binding following unilateral 6-hydroxydopamine (8 μg in 3 μl) lesions of the medial forebrain bundle, kainic acid (2 μg in 1 μl) lesions of the striatum or unilateral decortication.

Lesion	K_D (nM) Lesioned	K_D (nM) Intact	B max (pmol^{-1} g wet weight of tissue) Lesioned	B max (pmol^{-1} g wet weight of tissue) Intact
(A) [^{3}H]Spiperone				
Kainic acid	0·18 ± 0·01 (90%)	0·20 ± 0·04	17·8 ± 0·5* (48%)	37·0 ± 3·1
6-Hydroxy-dopamine	0·37 ± 0·06 (185%)	0·24 ± 0·07	28·9 ± 2·5 (103%)	28·1 ± 3·4
Decortication	0·64 ± 0·09 (108%)	0·59 ± 0·04	19·9 ± 1·6* (78%)	25·4 ± 1·0
(B) [^{3}H]Sulpiride				
Kainic acid	14·7 ± 1·8* (50%)	29·4 ± 4·6	8·4 ± 0·5* (33%)	25·3 ± 2·6
6-Hydroxydop-amine	18·4 ± 3·1 (96%)	19·1 ± 3·5	32·0 ± 3·0* (127%)	25·1 ± 2·5
Decortication	28·8 ± 6·2 (114%)	25·3 ± 3·6	11·5 ± 1·5* (63%)	18·3 ± 1·6

Results are expressed as the mean (± 1 s.e.m.) of the regression line from all determinations carried out at each ligand concentration and subjected to Scatchard analysis. Each determination was the mean of triplicate estimates on pooled striatal tissue from 14 animals per experiment, each experiment being carried out three times on independent tissue pools, except for occasional points on the regression line where only two experiments were available. The values in brackets represent the data for lesioned hemisphere expressed in percent of values obtained for the intact forebrain. Sham operation or vehicle injections alone had no effect on kinetic constants for specific [^{3}H]spiperone or [^{3}H]sulpiride binding (unpublished data). Values for K_D for [^{3}H]spiperone and [^{3}H]sulpiride binding in striatal tissue from intact forebrains varied by up to 3-fold in the different experiments. This represents the normal day-to-day variation observed using tissue from control animals of this rat strain, employing the present technique. Bmax values in control forebrains varied much less. To overcome this difficulty tissue from lesioned and intact forebrains from the same animals was always compared on the same occasion and in strict parallel.

* $P < 0.05$ compared with striatal preparations from the intact forebrain using a two-tailed Student's *t*-test.

DISCUSSION

Although spiperone has a high affinity for neuroleptic receptors it is, like other butyrophenones, relatively weak in inhibiting dopamine stimulation of striatal adenylate cyclase preparations (Miller et al 1974). Indeed, spiperone is more than 1000 times less active in displacing [^{3}H]flupenthixol from its binding site to D-1 receptors, and in inhibiting the dopamine stimulation of striatal adenylate cyclase, than in displacing [^{3}H]haloperidol (Hyttel 1978). This would suggest [^{3}H]spiperone, at the concentrations used in the present experiments, binds to D-2 receptors. On the other hand, [^{3}H]sulpiride *only* labels D-2 receptors. It has a lower affinity for neuroleptic receptors labelled by more typical neuroleptics, and does not inhibit dopamine stimulation of striatal adenylate cyclase preparations (Jenner et al 1978), except at concentrations approximately 500 times greater than concentrations of spiperone inhibiting the activity of this enzyme (Hyttel 1978).

Although [^{3}H]spiperone and [^{3}H]sulpiride both appear to label D-2 receptors, there are some differences in the specific binding of these ligands. Most notable is the finding that specific [^{3}H]sulpiride binding to striatal homogenates is totally dependent on the presence of sodium ions, while that of [^{3}H]spiperone is only partially sodium dependent

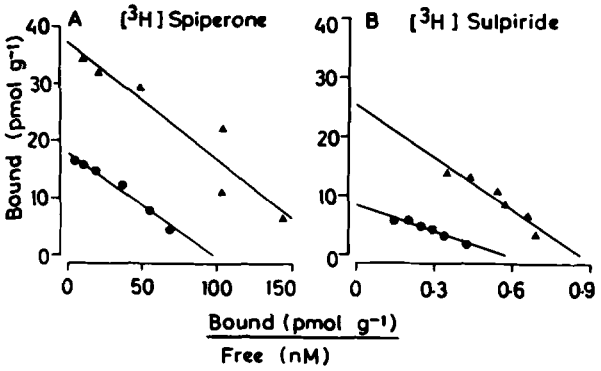

FIG. 1. Scatchard analysis of specific binding of (A) [^{3}H]spiperone (0·125–4·0 nM) and (B) [^{3}H]sulpiride (5–40 nM) to striatal preparations from intact (—▲—) and lesioned (—●—) forebrains of rats with unilateral kainic acid (2 μg in 1 μl) lesions of striatum. Each point represents the mean of all determinations carried out at each ligand concentration and subjected to Scatchard analysis. Each determination was the mean of triplicate estimates on pooled striatal tissue from 14 animals per experiment, each experiment being carried out three times on independent tissue pools, except for occasional points on the regression line where only two experiments were available. The lines of best fit were determined by linear regression analysis.

(Theodorou et al 1980). In addition, the capacity of sulpiride to displace [^{3}H]spiperone binding to rat striatal preparations also is dependent upon the presence of sodium, while that of other neuroleptics is sodium-independent (Stefanini et al 1980). This may indicate a fundamental difference in the nature of the components of D-2 receptors to which [^{3}H]-sulpiride and [^{3}H]spiperone bind, but the details of any such distinction are not yet apparent. However, such a difference may account for discrepancies between the effects of the various lesions on the binding of [^{3}H]spiperone and [^{3}H]sulpiride in the present experiments. For example, the K_D for [^{3}H]sulpiride binding changes after decortication while that of [^{3}H]spiperone was unaltered by this procedure, and 6-hydroxydopamine did not alter the Bmax for [^{3}H]spiperone binding but increased that for [^{3}H]sulpiride. These and other details of the results obtained with different lesions will now be discussed.

Our findings of reduced receptor numbers, but no change in K_D, for striatal [^{3}H]spiperone binding following kainic acid lesions of striatum or decortication are in good agreement with previous reports (Schwarcz et al 1978; Govoni et al 1978).

Since decortication is not associated with a loss of striatal dopamine stimulated adenylate cyclase (Schwarcz et al 1978), we can confirm the presence of D-2 receptors on the presynaptic terminals of cortico-striate fibres which, on other evidence, are believed to be glutaminergic (McGeer et al 1977). Destruction of the presynaptic terminals of dopamine neurons in striatum using 6-hydroxydopamine lesions of the medial forebrain bundle produced no apparent change in Bmax or K_D for [^{3}H]spiperone binding. These animals showed marked contraversive circling in response to apomorphine when tested 1 week before the biochemical examination, indicating the development of behavioural supersensitivity of the lesioned striatum due to successful destruction of the nigrostriatal dopaminergic pathways. However, Bmax might not change because destruction of binding sites on the dopamine neuronal terminals may be compensated for by an increased number of post-synaptic receptors. Other authors have reported increased numbers of [^{3}H]spiperone binding sites following 6-hydroxydopamine lesions of the medial forebrain bundle (Creese et al 1977; Nagy et al 1978; Reisine et al 1979; Waddington et al 1979). However, Leysen (1979) also was unable to demonstrate any change in [^{3}H]spiperone binding following 6-hydroxydopamine lesions, using her binding technique (Leysen et al 1978), that we employed in the present study.

In rat striatal preparations, [^{3}H]sulpiride binds to two receptor populations, a high affinity site labelled by concentrations of ligand up to 40 nM (K_D 14 nM; Bmax 32 pmol g^{-1} wet weight of tissue), and a lower affinity site labelled by ligand concentrations between 40–240 nM (K_D 56 nM; Bmax 55 pmol g^{-1} wet weight of tissue) (unpublished data). These findings agree with those of Memo et al (1981). In the present study we used ligand concentrations up to 40 nM, therefore only labelling the high affinity site for [^{3}H]sulpiride.

When [^{3}H]sulpiride was used as a ligand, striatal preparations from decorticate rats showed alterations similar to those seen with [^{3}H]spiperone, namely a decrease in Bmax with no change in K_D. This confirms the presence of D-2 receptors on cortico-striate glutamate fibres. 6-Hydroxydopamine lesions of the medial forebrain bundle increased the number of [^{3}H]sulpiride binding sites without changing K_D. This suggests that large numbers of [^{3}H]sulpiride binding sites are not located on nigro-striatal dopaminergic nerve terminals; the increase indicates a greater number of binding sites to post-synaptic receptors as a result of denervation. Kainic acid lesions of striatum in our studies reduced specific [^{3}H]sulpiride binding sites suggesting that D-2 receptors also are located on striatal cell bodies.

However, this contrasts with the work of Memo et al (1981) who found no reduction of [^{3}H]sulpiride binding to striatal preparations following striatal kainic acid lesions, despite a decrease in specific [^{3}H]spiperone binding. We can offer no explanation for this discrepancy. These authors did show a fall in both [^{3}H]sulpiride and [^{3}H]spiperone binding to striatal preparations following decortication.

Our finding of loss of [^{3}H]sulpiride binding sites after intrastriatal injection of kainic acid was associated with a decrease in K_D. This would indicate that the approximately 30% of striatal binding sites remaining (presumably located on the terminals of cortico-striate glutamate fibres) have a higher affinity for [^{3}H]sulpiride than those located on striatal neuronal cell bodies. Perhaps the existence of this limited high affinity dopamine receptor population might be responsible for the atypical pharmacological profile of sulpiride (Jenner & Marsden 1979). Thus, the failure of sulpiride to produce catalepsy or to inhibit apomorphine-induced stereotyped behaviour (behaviours associated with post-synaptic dopamine receptors on striatal cells) in doses causing enhanced dopamine turnover might be attributed to a preferential action on the high-affinity receptor population located on cortico-striate fibre terminals. However, since in normal animals specific [^{3}H]sulpiride (5–40 nM) binding to striatal preparations produces a Hill slope of unity, an alternative explanation for the apparent increase in receptor affinity may lie in an adaptive change of the remaining receptor population as a result of the kainic acid lesion.

These data suggest the presence of both D-1 and D-2 receptors on the cell bodies of striatal neurons. The physiological or anatomical relationship between the two binding sites, however, is not clear. Thus, it is not apparent whether they indicate different functions on the same neuron, analogous to the recognition site and ionophore site associated with post-synaptic GABA receptors (Ticku & Olsen 1978), or whether D-1 and D-2 receptors are located on the cell bodies of different neurons. For example it can be envisaged that while one receptor exists, on the cell bodies of striatal output neurons, the other may occur on striatal interneurons.

Alternatively, the relationship between loss of dopamine-stimulated adenylate cyclase and [^{3}H]-spiperone or [^{3}H]sulpiride binding sites after kainic acid lesioning of the striatum may be coincidental. Thus, although both adenylate cyclase and neuroleptic receptor binding sites may occur on neurons bearing post-synaptic dopamine receptors, they may have different functions. This suggestion may explain why relatively high concentrations of neuroleptics are required to inhibit dopamine stimulation of adenylate cyclase, compared with the lower concentrations which displace tritiated ligands from receptor binding sites (Seeman 1977). In addition the occurrence of dopamine-stimulated adenylate cyclase and neuroleptic binding sites in different subcellular fractions of rat striatum would argue that these components of neuronal function are distinct entities (Leysen & Laduron 1977). There is no proof that the adenylate cyclase system measured by present in vitro techniques is responsible for providing the changes in membrane potential that occur following activation of post-synaptic dopamine receptor recognition sites. Such electrophysiological changes take place within milliseconds of receptor activation, whereas adenylate cyclase activity alters over a longer time scale. Dopamine receptor activation in mammalian sympathetic ganglia initiates two events, a rapid hyperpolarization and a slower change in cytoplasmic cyclic nucleotide formation which may be concerned with adaptive or modulatory processes other than those responsible for changes in the action potential (see Libet 1979).

In conclusion we have demonstrated the existence of D-2 receptors on striatal cell bodies. This is perhaps not surprising since in man all the actions of drugs affecting cerebral dopamine systems in patients with Parkinson's disease are due to an action at D-2 receptors (Schachter et al 1980) and the same would appear true for dopamine mediated behaviours such as stereotypy (Leysen 1980) and circling (Waddington et al 1979).

In the clinical studies of patients with Parkinson's disease, the effects of a range of D-1 and D-2 receptor antagonists were studied on Parkinsonian disability and dopamine agonist-induced dyskinesias. Individual patients were pre-treated with a D-2 antagonist or a placebo, and subsequently were given a standard dose of levodopa plus carbidopa (Sinemet). Parkinsonian disability and dyskinesias were rated using standardized assessment schedules at regular intervals over the next 4–6 h by independent observers unaware of the nature of the drugs given. (Further details are available in Price et al 1980.) Of particular interest to the present study, was the investigation of the effects of racemic sulpiride compared with those of *cis*-flupenthixol and a placebo, given in random order, on 3 days of the week, with a day's interval between each test, to a total of 6 patients with idiopathic Parkinson's disease who showed a consistent therapeutic re-

sponse but also dyskinesias in response to levodopa 250 mg plus carbidopa 25 mg. Racemic sulpiride (400 mg 2 h before levodopa) was equipotent to *cis*-flupenthixol (3 mg 4 h before levodopa) in preventing the therapeutic response to levodopa and the dyskinesias it caused (Marsden et al, in preparation). With regard to the animal experiments, Leysen (1980) has shown that there is a close correlation between the capacity of a range of 23 neuroleptics to inhibit the binding of [^{3}H]spiperone to rat striatal homogenates, and their capacity to antagonize apomorphine-induced stereotypy in the rat. The neuroleptics chosen included flupenthixol and sulpiride. These results indicate that their behavioural effects are closely related to their capacity to displace the lower concentrations of [^{3}H]spiperone which preferentially label D-2 receptors in the brain.

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REFERENCES

Burt, D. R., Creese, I., Snyder, S. H. (1976) Mol. Pharmacol. 12: 800–812

Cools, A. R., van Rossum, J. M. (1976) Psychopharmacol. (Berlin) 45: 243–254

Cools, A. R., Struyker-Boudier, H. A. J., van Rossum, J. M. (1976) Eur. J. Pharmacol. 37: 283–293

Costall, B., Naylor, R. J. (1975) Eur. J. Pharmacol. 33: 301–312

Creese, I., Sibley, D. R. (1979) Commun. Psychopharmacol. 3: 385–395

Creese, I., Burt, D. R., Snyder, S. H. (1977) Science 197: 596–598

De Groot, J. (1959) Vehr. K. Ned. Akad. Wet. 52: 11–40

Govoni, S., Oligati, V. R., Trabucchi, M., Garau, L., Stefanini, E., Spano, P. F. (1978) Neurosci. Lett. 68: 207–210

Hyttel, J. (1978) Life Sci. 23: 551–556

Jenner, P., Marsden, C. D. (1979) Life Sci. 25: 479–486

Jenner, P., Clow, A., Reavill, C., Theodorou, A., Marsden, C. D. (1978) Life Sci. 23: 545–550

Jenner, P., Elliott, P. N. C., Clow, A., Reavill, C., Marsden, C. D. (1978) J. Pharm. Pharmacol. 30: 46–48

Kebabian, J. W., Calne, D. B. (1979) Nature (London) 277: 93–96

Kehr, W., Carlsson, A., Lindqvist, M., Magnusson, T., Atack, C. (1972) J. Pharm. Pharmacol. 24: 744–747

Leysen, J. E. (1979) Commun. Psychopharmacol. 3: 397–410

Leysen, J. E. (1980) Proceedings of the 2nd International Meeting on Clinical Pharmacology in Psychiatry, Tromso, Norway, in the press.

Leysen, J., Laduron, P. (1977) Life Sci. 20: 281–238

Leysen, J. E., Gommeron, W., Laduron, P. M. (1978) Biochem. Pharmacol. 27: 307–317

Libet, B. (1979) Life Sci. 24: 1043–1058

McGeer, P. L., McGeer, E. G., Scherer, U., Singh, K. (1977) Brain Res. 128: 369–373

Memo, M., Spano, P. F., Trabucchi, M. (1981) Br. J. Pharmacol. 72: 124P–125P

Miller, R. J., Horn, A. S., Iversen, L. L. (1974) Mol. Pharmacol. 10: 758–766

Nagy, J. I., Lee, T., Seeman, P., Fibiger, H. C. (1978) Nature (London) 274: 278–281

Price, P., Debono, A., Jenner, P., Parkes, J. D., Marsden, C. D. (1980) in: Poirier, L. J., Sourkes, T. L., Bedard, P. J. (eds) Advances in Neurology, vol. 24, Raven Press, New York, p. 423

Reisine, T. D., Nagy, J. I., Fibiger, H. C., Yamamura, H. I. (1979) Brain Res. 169: 209–214

Schachter, M., Bedard, P., de Bono, A. G., Jenner, P., Marsden, C. D., Price, P., Parkes, J. D., Keenan, J., Smith, B., Rosenthaler, J., Horowski, R., Dorrow, R. (1980) Nature (London) 286: 157–159

Schwarcz, R., Creese, I., Coyle, J. T., Snyder, S. H. (1978) Ibid. 271: 766–768

Seeman, P. (1977) Biochem. Pharmacol. 26: 1741–1748

Skirboll, L. R., Bunney, B. S. (1979) in: Usdin, E., Kopin, I. J., Barchas, J. (eds) Catecholamines: Basic and Clinical Frontiers, pp 634–636, Pergamon Press, New York

Spano, P. F., Trabucchi, M., Di Chiara, G. (1977) Science 196: 1343–1345

Stefanini, E., Marchisio, A. M., Devoto, P., Vernaleone, F., Collu, R., Spano, P. F. (1980) Brain Research 198: 229

Theodorou, A., Crockett, M., Jenner, P., Marsden, C. D. (1979) J. Pharm. Pharmacol. 31: 424–426

Theodorou, A. E., Hall, M. D., Jenner, P., Marsden, C. D. (1980) J. Pharm. Pharmacol. 32: 441–444

Ticku, M. K., Olsen, R. W. (1978) Life Sci. 22: 1643–1652

Titeler, M., Weinreich, P., Sinclair, D., Seeman, P. (1978) Proc. Natl. Acad. Sci. U.S.A. 75: 1153–1156

Waddington, J. L., Cross, A. J., Longden, A., Owen, F., Poulter, M. (1979) Neuropharmacology 18: 643–645

Waddington, J. L., Cross, A. J., Longden, A., Owen, F., Poulter, M. (1979) Eur. J. Pharmacol. 58: 341–342