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Studies on the Pharmacological Properties of Dopamine Receptors in Various Areas of the Central Nervous System

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The hypothesis of a unique physiological role of dopamine as a neurotransmitter in the mammalian brain was first put forth by Carlsson and associates in 1958 (6). The involvement of dopamine-specific receptors in the behavioral mode of action of different drugs was proposed in 1965 (13,33).

van Rossum (33), on one hand, suggested that several neuroleptic drugs may act as antagonists at central dopamine receptors. On the other hand, Ernst (13) suggested that apomorphine may bring about its behavioral effects by an agonistic interaction at the central dopamine receptors. However, the direct demonstration and the molecular pharmacological characterization of the central dopamine receptors were hampered by the approach used by these authors. Their studies in fact were based on behavioral phenomena induced by drugs injected peripherally.

Over the last years new findings have offered more direct approaches to study dopamine receptor pharmacology. An adenylate cyclase, preferentially stimulated by dopamine, has been described in homogenates of bovine superior cervical ganglia (24), calf and rat retinas (1), rat caudate nucleus (25), and nucleus accumbens and tuberculum olfactorium in the mesolimbic system (20). These findings have led to the suggestion that in these areas the dopamine-stimulated adenylate cyclase and the dopamine receptor may be related, and that the physiological effects of dopamine could be mediated by cyclic adenosine monophosphate (cyclic AMP). On the other hand, with the recently developed technique of radioreceptor binding it has been possible to label apparent postsynaptic dopamine receptor sites with [^{3}H]dopamine or with [^{3}H]haloperidol (2,3,9,36) and with [^{3}H]spiroperidol (14). This technique, in addition to providing evidence for a specific binding in those brain regions rich in dopaminergic synapses, offered a new approach to investigating the affinity of drugs for the dopamine receptor (10,35,36).

The aim of this chapter is to present some data on the presence and characterization of dopamine-stimulated adenylate cyclase in various brain areas, and on the effects of various classes of recently characterized dopaminergic drugs on the activity of this enzyme and on the radioreceptor binding model. The implications of our data are that not all of the cerebral dopamine receptors are associated with an adenylate cyclase system.

LOCALIZATION OF DOPAMINE-STIMULATED ADENYLATE CYCLASE IN DOPAMINERGIC AREAS

As we stated above, pioneering studies have demonstrated the presence of an adenylate cyclase preferentially stimulated by dopamine in mammalian nucleus caudatus, nucleus accumbens, tuberculum olfactorium, and retina. In our laboratories we have extended these studies to other brain areas with dopaminergic innervation. The results of our experiments have shown the presence of a dopamine-stimulated adenylate cyclase, which is selectively inhibited by phenothiazines and butyrophenones, in the rat entorhinal cortex (41), substantia nigra (37,40), and median eminence (Table 1). This last result has also been reported recently by Clement-Cormier and Robison (7). However, we have not been able to identify a dopamine-stimulated adenylate cyclase in the pituitary gland (Table 2), in either the anterior or the posterior part. This negative finding is apparently in contrast with the data reported by MacLeod and co-workers (29), showing the presence of dopamine receptor in the anterior part of the pituitary, a finding fully confirmed in our laboratories (see Table 2). Moreover, the functional demonstration of dopamine receptor in the pituitary has also been given by MacLeod et al. (29)

TABLE 1. *Dopamine-stimulated adenylate cyclase activity in various areas of the CNS*

Brain area	Adenylate cyclase activity (pmoles cAMP/min/mg protein)		
	Basal	DA (50 μM)	DA (50 μM) +haloperidol
Striatum	204 ± 14	398 ± 19[a]	212 ± 12
Substantia nigra	198 ± 13	410 ± 22[a]	221 ± 16
Tuberculum olfactorium	141 ± 9	275 ± 15[a]	150 ± 11
Nucleus accumbens	186 ± 10	359 ± 18[a]	194 ± 12
Entorhinal cortex	65 ± 2	106 ± 6[a]	71 ± 3
Pituitary	78 ± 6	81 ± 5	74 ± 4
Median eminence	88 ± 2	116 ± 3[a]	85 ± 2
Retina	15 ± 1	31 ± 2[a]	16 ± 1

Values are the mean ± SEM of at least 10 separate determinations run in triplicate. Haloperidol was added at a concentration of 5μM. Dopamine-stimulated adenylate cyclase was determined in all the experiments following the method described by Carenzi et al. (5).

[a] $p < 0.001$ in comparison with basal values.

TABLE 2. *Stereospecific binding of ^{3}H-haloperidol and ^{3}H-dopamine and dopamine-stimulated adenylate cyclase activity in rat striatum and pituitary*

Brain area	^{3}H-haloperidol (fmoles bound/mg protein)	^{3}H-dopamine (fmoles bound/mg protein)	Dopamine-stimulated adenylate cyclase activity (pmoles cAMP/min/mg protein)
Striatum	184 ± 19	53 ± 4	196 ± 13[a]
Pituitary	81 ± 11	46 ± 2	Not detectable

^{3}H-haloperidol and ^{3}H-dopamine were added at a concentration of 2 nM and 4 nM, respectively, and the binding determined following the method of Burt et al. (2). Values represent the mean ± SEM of at least 10 separate determinations run in triplicate.

[a] pmoles of cAMP formed above basal activity (dopamine 5×10^{-5} M) (basal activity: 184 ± 11 pmoles cAMP/min/mg protein.

and Gräf et al. (19) since dopamine agonists and dopamine itself are able to control prolactin release either in the gland incubated *in vitro* (29) or in the gland severed *in vivo* from basal hypothalamus (19).

On the other hand, of particular relevance is the finding of a dopamine-stimulated adenylate cyclase in the substantia nigra (26,31,32,37,40). This cyclase appears to be stimulated by dopamine released from dendrites of dopaminergic cell bodies (16) and to be located on terminals of neurons which have their cell bodies in the corpus striatum (40), as suggested by experiments using brain lesions. This view has been recently confirmed using the kainic acid approach. Kainic acid injected into the striatum destroys selectively the cell bodies of neurons present in the nucleus, leaving intact nerve terminals (34). In these experimental conditions the stimulation induced by dopamine on striatal and nigral adenylate cyclase activity is virtually totally abolished (Table 3). These data strongly support the hypothesis of

TABLE 3. *Effect of striatal injection of kainic acid on striatal and nigral dopamine-stimulated adenylate cyclase*

		Adenylate cyclase activity (pmoles cAMP/min/mg protein)		
		Control side	Lesioned side	(%)
Striatum	Basal	186 ± 13	110 ± 8	−42
	DA 5×10^{-5} M	371 ± 18	125 ± 9	−66
	DA stimulated	192 ± 14	12 ± 1	−94
Substantia nigra	Basal	198 ± 13	93 ± 6	−53
	DA 5×10^{-5} M	426 ± 22	112 ± 9	−74
	DA stimulated	221 ± 14	18 ± 2	−80

Rats were injected with 3 μg of kainic acid in the right and with saline in the left striatum and were sacrificed 9 days later. The striatum of each side was homogenized and assayed individually for adenylate cyclase activity. Values are the mean ± SEM of 6 determinations in triplicate.

a localization of dopamine-stimulated adenylate cyclase at postsynaptic level in the striatum and at presynaptic level in the substantia nigra.

EFFECTS OF DOPAMINERGIC ERGOT DERIVATIVES ON DOPAMINE RECEPTORS

In addition to the anatomical localization of dopamine-stimulated adenylate cyclase in various brain areas, we have investigated the pharmacological properties of dopamine receptors in order to test the hypothesis of different classes of dopamine receptors. This hypothesis is first suggested by the finding that in the pituitary gland it is possible to demonstrate the presence of dopamine receptor probably not coupled to a specific dopamine-stimulated adenylate cyclase (Table 2). In particular, we shall report the data obtained with newly pharmacologically characterized dopamine agonists (ergot derivatives) and dopamine antagonists (benzamides, of which sulpiride is the prototype).

The effect of a number of ergot derivatives on adenylate cyclase activity in striatum and pituitary gland preparations is reported in Table 4. Bromocryptine, lisuride, and lergotrile, which have been reported in behavioral and pharmacological models to exert a strong stimulation of different dopamine functions (4,11,15,21–23,28,30,37), and metergoline do not stimulate the

TABLE 4. *Comparison of the effects of various dopamine agonists on adenylate cyclase activity in rat striatum and pituitary gland homogenates*

Drug	Adenylate cyclase activity (pmoles/min/mg protein)	
	Striatum	Pituitary
Basal	196 ± 11	78 ± 6
Dopamine	392 ± 20[a]	81 ± 5
Apomorphine	311 ± 16[a]	82 ± 5
Lergotrile	194 ± 11	84 ± 7
LSD	265 ± 14[b]	79 ± 4
Ergometrine	241 ± 14[b]	79 ± 5
Bromocryptine	189 ± 10	77 ± 6
Lisuride	182 ± 9	71 ± 4
Metergoline	189 ± 10	80 ± 4
DH-Ergotamine	191 ± 9	74 ± 5
DH-Ergotoxine	184 ± 10	81 ± 5

Drugs were added at a concentration of 50 μM. Norepinephrine, epinephrine, isoproterenol, serotonin, histamine, and epinine do not stimulate the adenylate cyclase activity of pituitary gland when added at a concentration of 100 μM. Values are the mean ± SEM of at least 4 separate determinations run in triplicate.

[a] $p < 0.001$ in comparison with basal value.

[b] $p < 0.01$ in comparison with basal value.

TABLE 5. *Inhibition of dopamine-stimulated adenylate cyclase in rat striatum by various ergot derivatives*

Drug	IC_{50} (M)
LSD	7×10^{-7}
Ergometrine	9×10^{-7}
Bromocriptine	3×10^{-7}
Lisuride	1×10^{-7}
Metergoline	2×10^{-7}
Lergotrile	3×10^{-7}
Ergotamine	7×10^{-7}
DH-Ergotamine	5×10^{-7}
DH-Ergotoxine	3.3×10^{-6}
DH-Ergocornine	4.5×10^{-6}
DH-Ergocryptine	3×10^{-6}
DH-Ergocristine	3×10^{-6}

The values listed are the mean concentrations of each drug required to inhibit the stimulation induced by dopamine (10 M) by 50%. Each IC_{50} value was determined from a log-probit using 3 or more concentrations of drug. Numbers are mean of at least 4 separate determinations run in triplicate. The SEM for each IC_{50} is less than 10% of the IC_{50}.

activity of striatal or pituitary adenylate cyclase. Only LSD and ergometrine, among the several ergot derivatives tested, appear to behave as weak dopamine agonists, and only in striatal preparations. On the contrary, at micromolar concentrations, all these compounds inhibited striatal dopamine-stimulated adenylate cyclase activity. The inhibitory concentration 50 (IC_{50}) on the enzyme activity obtained with concentration-response studies for the various ergot derivatives is shown in Table 5. These surprising results which appear to be in apparent contradiction with all previously reported behavioral, pharmacological, and clinical data are in agreement with some of our previous data (18,38,39,43) and raise a number of questions on the mode of action of dopaminergic ergot derivatives and on the hypothesis of the coupling between the dopamine receptor recognition sites and the dopamine-stimulated adenylate cyclase. It may be pertinent in this regard to recall that data obtained with the radioreceptor binding technique seem to indicate for some ergot derivatives, such as bromocryptine, a prevailing antagonistic action at central dopamine receptors rather than an agonistic effect (2,17).

EFFECTS OF BENZAMIDES (SULPIRIDE) ON DOPAMINE RECEPTORS

In another set of experiments we have extended our studies on the pharmacological characterization of cerebral dopamine receptors, testing the effect

TABLE 6. *Effect of sulpiride on dopamine-sensitive adenylate cyclase activity in rat striatal homogenates*

	With preincubation (pmoles cAMP/min/mg protein)	%	Without preincubation (pmoles cAMP/min/mg protein)	%
Control	252 ± 7	—	268 ± 15	—
DA	587 ± 26[a]	133	669 ± 22[a]	149
Sulpiride	262 ± 17	—	308 ± 14	—
Sulpiride + DA	542 ± 25[a]	115	643 ± 17[a]	140

Some samples were preincubated at 30°C for 10 min in absence of ATP and dopamine. Dopamine and sulpiride were added at a concentration of 50 μM. Values are the mean ± SEM of 4 separate determinations run in triplicate.

[a] $p < 0.001$ when compared to control.

of sulpiride on dopamine-stimulated adenylate cyclase and on the radioreceptor model. Sulpiride belongs to the class of benzamides, and has been classified as a putative dopamine antagonist with a weak cataleptogenic activity in animals, antipsychotic activity, and strong prolactin-stimulatory effects (42). As we already reported in 1975 (42) sulpiride, contrary to other cataleptogenic and noncataleptogenic neuroleptics, does not inhibit the cyclic AMP accumulation induced by dopamine in striatal and limbic area homogenates. After several periods of preincubation, sulpiride does not show any inhibitory effect. These data are summarized in Table 6. Furthermore, sulpiride, unlike haloperidol, does not block the accumulation of cyclic AMP induced *in vivo* by apomorphine (42), a result which fully substantiates the finding obtained *in vitro*.

However, the hypothesis of a specific interaction of sulpiride with cerebral dopamine receptors is supported by some findings reported below. Sulpiride,

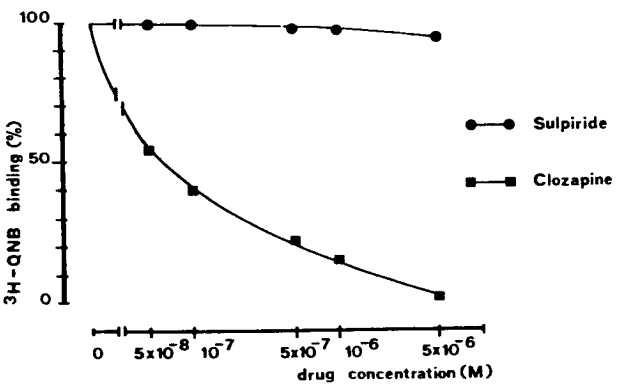

FIG. 1. Competition by sulpiride and clozapine for specific [^{3}H]QNB binding in membranes of rat striatum. [^{3}H]QNB binding was measured following the method of Yamamura and Snyder (44). For each curve specific binding of multiple experiments was averaged on a percentage basis, taking binding in the presence of 10^{-6} M unlabeled QNB as a blank. The ordinate refers to specific binding values.

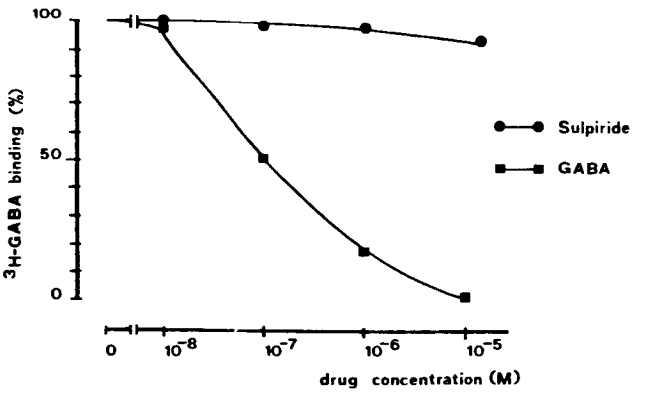

FIG. 2. Competition by sulpiride and GABA for specific [^{3}H]GABA binding in membranes of rat striatum. [^{3}H]GABA binding was measured following the method of Enna et al. (12). For each curve specific binding of multiple experiments was averaged on a percentage basis, taking binding in the presence of 10^{-3} M unlabeled GABA as a blank. The ordinate refers to specific binding values.

for instance, is completely devoid of antimuscarinic central activity, as is shown by the lack of interaction with [^{3}H]-3-quinuclidinylbenzilate (^{3}H-QNB)-binding in membranes of rat striatum (Fig. 1). This finding differentiates sulpiride from clozapine, another neuroleptic whose weak cataleptogenic activity has been ascribed to the strong interaction with muscarinic central receptors. On the other hand, sulpiride has no direct activity on GABA central receptors, as demonstrated by the lack of displacement of [^{3}H]GABA from rat striatal membrane preparations (Fig. 2).

These data, taken together, have led us to investigate whether or not sulpiride interacts with a population of cerberal dopamine receptors not associated

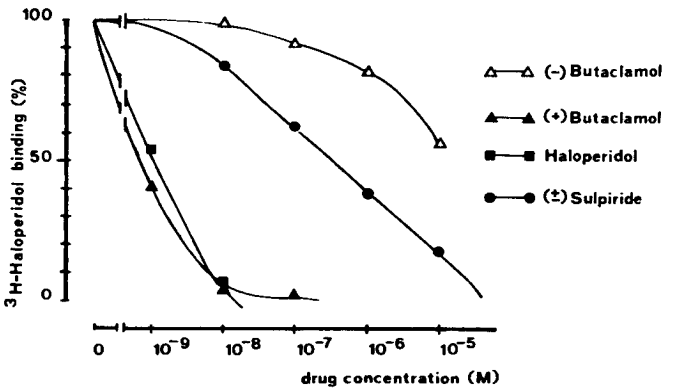

FIG. 3. Competition by sulpiride, haloperidol, (+)-butaclamol, and (−)-butaclamol for specific [^{3}H]haloperidol binding in membranes of rat striatum. [^{3}H]haloperidol binding was measured following the method of Burt et al. (2). For each curve specific binding of multiple experiments was averaged on a percentage basis, taking binding in the presence of 10^{-4} M dopamine as a blank. The ordinate refers to specific binding values.

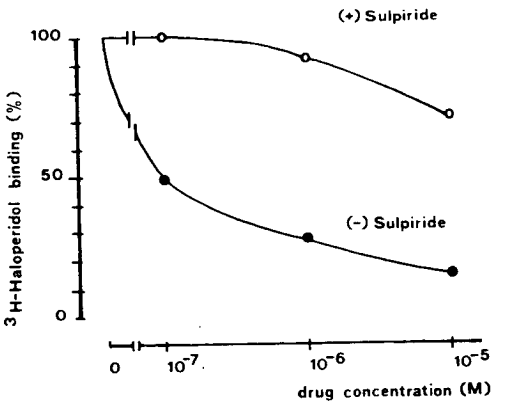

FIG. 4. Competition by (+)-sulpiride and (−)-sulpiride for specific [^{3}H]haloperidol binding in membranes of rat striatum. [^{3}H]haloperidol binding was measured as indicated in Fig. 3. For each curve specific binding of multiple experiments was averaged on a percentage basis, taking binding in the presence of 10^{-4} M dopamine as a blank. The ordinate refers to specific binding values.

with an adenylate cyclase system. Therefore, we have studied the effect of the drug on the stereospecific binding of [^{3}H]haloperidol to rat cerebral membrane preparations. Figure 3 shows that sulpiride can displace [^{3}H]haloperidol from putative dopamine binding sites in membranes prepared from rat striatum. The potency of sulpiride is lower than that of (+)-butaclamol and haloperidol, which correlates with clinical observations, but significantly more pronounced than that of (−)-butaclamol. The specificity of the action of sulpiride at the level of dopamine central receptors has been confirmed in our laboratories by the observation that only the (−)-enantiomer of the drug shows the property of displacing [^{3}H]haloperidol from its stereospecific binding sites in rat striatal membranes (Fig. 4). The calculated IC_{50} of this effect is about 100 nM for (−)-sulpiride and more than 10,000 nM for (+)-sulpiride.

CONCLUDING REMARKS

One of the main conclusions that can be drawn from our observations and from the data obtained in other laboratories is that dopamine-stimulated adenylate cyclase is a unique tool to map dopamine receptors in the mammalian brain.

On the other hand, available evidence accumulated over the past few years suggests that whereas the traditional methods of measuring dopamine receptor activity involve behavioral tests which are often imprecise, the evaluation of dopamine-stimulated adenylate cyclase activity provides a reliable approach to establish whether a drug either blocks or activates dopamine receptors. However, this does not appear to be the case with the

drug studied in our laboratories. Sulpiride, which shows a rather specific interaction with dopamine receptors in radioreceptor binding studies, does not block dopamine-stimulated adenylate cyclase either *in vitro* or *in vivo*. On the other hand, ergot derivatives, which are supposed to have potent stimulatory effects on dopamine receptors, do not stimulate cyclic AMP accumulation in striatal homogenates but show blocking properties on the enzyme activity stimulated by dopamine.

It has been stressed that we still do not know whether the effects of any particular neurotransmitter are coupled directly with the activation of adenylate cyclase. Available evidence indicates that different receptor populations of the same transmitter are either associated or not with a cyclic AMP system. Beta-adrenergic receptors, for instance, appear to be associated with an adenylate cyclase, although alpha-adrenergic receptors are not. The same applies to histamine-2 and histamine-1 receptors, respectively. It might well be also that dopamine receptors are two different populations of which only one is directly coupled to the activation of adenylate cyclase. Although more experiments are necessary before definite conclusions can be drawn, our results support this contention.

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