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COMMENTARY

NOMENCLATURE OF CENTRAL AND PERIPHERAL DOPAMINERGIC SITES AND RECEPTORS

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The recommendation of this personal commentary is that dopaminergic sites and states be defined by the rank order of the effective *absolute molarities* (*in vitro*) for the principal dopaminergic congeners. This recommendation can serve to define the receptors in both the central nervous system and peripheral tissues and will assist in communicating the following fundamental and controversial issues in the biochemical pharmacology of dopamine receptors.

First, the central question is whether or not there is more than one type of *functional* dopamine receptor. The different biological effects of dopamine [1–6] may occur because the same dopamine receptor may be located on different types of cells, or because there may be different types of dopamine receptors. An extreme view, for example, stated by Laduron [2], is that there is only one type of dopamine receptor, postsynaptic in location and having D_2-type properties (see later), which fully accounts for the central actions of dopamine, including both the postsynaptic and autoreceptor actions of dopamine.

Second, it is now clear that the "state" of a receptor can be altered by GTP [7–9]. That is, GTP lowers the affinity of the receptor for its agonist. The question then arises: are there different dopamine receptor sites *in addition* to these different states, or can all the data fit into the idea of a single receptor with two different states?

Third, this fundamental issue of "states" and/or "sites" has, therefore, resulted in a variety of nomenclatures for classifying dopamine receptors. These variations in terminology are confusing, a point recently emphasized by others [10]. Hence, do the different names or terms refer to the same site or state? Is it possible to compare nomenclatures, despite the different conditions and ^{3}H-ligands used? Which nomenclature is useful?

Fourth, particularly difficult is the question of whether or not the central and peripheral dopamine receptors are the same. Is it possible to have a single nomenclature for both central and peripheral dopamine receptors?

Advantages of nomenclature based on in vitro *studies*

Traditionally, receptors have been classified on the basis of the rank order of different congeners, the potencies of which have been measured *in vitro*. This is true, for example, in the case of nicotinic receptors, muscarinic receptors, and alpha- and beta-adrenoceptors. It would be consistent and comprehensive, therefore, if such an *in vitro* approach were adopted for dopamine receptors.

A second advantage of using the *in vitro* drug concentrations is that sufficient time is given *in vitro* to permit equilibrium. It is desirable, if not essential, to have equilibrium between the drug and the receptor before one can ascribe a rank order for the potencies of the different congeners. It is technically difficult or impossible to determine the absolute molarity of a dopamine congener when the drug is iontophoresed or directly injected in the brain [10–14]. Moreover, such an *in vivo* approach does not permit equilibrium. Hence, a classification of dopamine receptors based on the rank order of potencies of intracerebrally injected drugs [10, 14] can be misleading. For example, as discussed elsewhere [6], it is clear from the work of Woodruff *et al.* [15] and Westerink *et al.* [16] that (±)-6,7-ADTN (or 6,7-dihydroxy-2-aminotetralin) is more potent than (±)-5,6-ADTN. However, when using different incerebral-injection conditions, an anomalous result was that (±)-5,6-ADTN was more potent [17]. It is also technically impossible to obtain a rank order of potencies using the electrophysiological approach, although this technique very usefully detects neurones which respond to dopamine with either excitation (DA_e response [11]) or inhibition [1] (DA_i response [11–13]).

Comparison of nomenclatures from in vitro *data*

Table 1B compares the different nomenclatures used by different authors for *in vitro* data. It is here recommended that the sites and/or states (in Tables 1A and 1B; see also Fig. 1) be defined according to two criteria: (a) by the order of magnitudes of the absolute molarities (μM or nM) of dopamine and spiperone that were 50% effective *in vitro*; and (b) by whether or not the site was sensitive to sulpiride. In general, furthermore, the rank order of congener potencies *in vitro* at dopaminergic sites is: bromocryptine > apomorphine = (±)-ADTN > dopamine > noradrenaline.

Rank order of potencies at the D_1 *site*

There is almost general agreement in all the nomenclatures that the D_1 site signifies dopamine-stimulated adenylate cyclase [20]. It has been generally found that the D_1 site is sensitive to micromolar

Table 1A. Recommended nomenclature for dopaminergic sites and/or states*

	D_1	DA_1	D_2	D_3	D_4
Dopamine EC_{50} or IC_{50}	μM	μM	μM	nM	nM
Spiperone IC_{50}	μM	μM	nM	μM	nM
Sulpiride-sensitive?	No	Yes (*R*)	Yes (*S*)	No	Yes (*S*)

* The EC_{50} or IC_{50} values are the concentrations which either stimulate or inhibit the site by 50%. *S* = *S*-sulpiride, *R* = *R*-sulpiride.

Table 1B. Comparison of nomenclatures for dopaminergic sites and/or states

Seeman *et al.* this commentary and [6, 18, 19]*	D_1	DA_1	D_2	D_3	D_4
Kebabian and Calne [20]	D_1		D_2		D_2
Creese *et al.* [8, 21]	D_1		D_2^{Low}	D_3	D_2^{High}
Sokoloff *et al.* [22]	D_1		D_4	D_3	D_2
Goldberg and Kohli [23]		DA_1			DA_2

* Also S. List and P. Seeman, *J. Neurochem.*, in press.

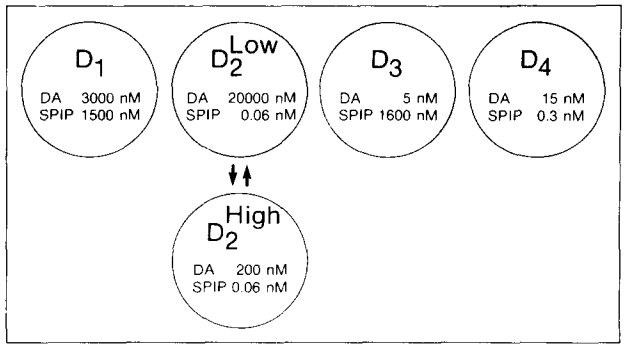

Fig. 1. Summary of dopamine receptors and sites.

Table 2. Rank order of drug potencies at D_1 sites (rat striatum)

	EC_{50} (nM) Dopamine-stimulated adenylate cyclase	IC_{50} (nM) [^{3}H]Flupenthixol [24–27]
Bromocryptine	500 [24, 28]	500
Apomorphine	~1,800 [29–32]	300
(±)-ADTN	~3,500 [15, 33–36]	600
Dopamine	~3,000 [see 6]	3,400
Noradrenaline	40,000 [30]	62,000
Spiperone	~1,500 [4]	1,300
(±)-Sulpiride	560,000 [24, 32, 37]	32,000

Table 3. Drug potencies (nM) at arterial DA_1 sites*

	[43] Rabbit cerebral	[44] Rabbit splenic	[43] Rabbit ear	[45–47] Rabbit mesenteric†	[48, 49] Rat renal	[38, 41, 50] Dog renal
Bromocryptine	110		5,600	9,000	1,300	
Apomorphine	300	100–1,000	3,500	125,000	63,000	(1,000 nmoles‡)
(±)-ADTN		200		3,000		~70,000
Dopamine	130	600	2,100	20,000	2,500	3,000–70,000
Peridol	Blocks			D: 9,000	H: 800	D: ~10,000
(±)-Sulpiride	Blocks			M: 7,000	17,000§	(29 nmoles‡§)

* Concentrations (nM) of dopaminergic agonists that caused 50% relaxation of arteries contracted by K^+ (Ref. 43) or prostaglandin $F_{2\alpha}$, except rabbit mesenteric artery. The arteries were pretreated with, or tested in the presence of, phenoxybenzamine in order to preclude responses mediated by alpha-adrenoceptors. Abbreviations: D, droperidol; H, haloperidol; and M, metoclopramide.

† Relaxed 30% by prostaglandin $F_{2\alpha}$.

‡ Refs. 51–55; these were the *in vivo* intra-arterial doses of agonists that increased renal blood flow by 50%; the antagonist doses shifted the dose-response curve by 3- to 4-fold.

§ (+)-Sulpiride was more potent than (−)-sulpiride.

concentrations of dopamine as well as to micromolar concentrations of spiperone, but that it is extremely insensitive to the substituted benzamides, such as (±)-sulpiride or metoclopramide. These properties thus define the D_1 site for any tissue response or for the binding of any ^{3}H-ligand, as summarized in Table 2. This table also shows that the rank order of dopaminergic congener potencies at the D_1 site follows the general pattern mentioned earlier.

Nomenclature for the DA_1 sites

Arteries contain dopamine receptors, termed DA_1 sites by Goldberg and Kohli [23]. These DA_1 sites are generally affected by the same drug concentrations as the central D_1 sites, with the critically important difference that DA_1 sites are sensitive to sulpiride, whereas the D_1 sites are not. This is summarized in Table 3 for six different arteries. In general, the IC_{50} values for dopamine and butyrophenone (haloperidol or droperidol) were in the micromolar range. Dopamine concentrations of between 5,000 and 90,000 nM were also required to relax the following arteries: dog coronary [38, 39], dog cerebral [40], dog mesenteric [41] and rabbit coeliac [42]. Although the rabbit cerebral artery was more sensitive to dopaminergic agonists, Oudart *et al.* [43] found no statistically significant difference between the 50%-relaxing concentrations for dopamine, apomorphine and bromocryptine, all of them being effective between 110 and 300 nM. As noted in Table 3, two arteries were more sensitive to dopamine than to apomorphine; this finding is puzzling and may suggest that other catecholamine receptors assisted in mediating the relaxation of those arteries.

Rank order of potencies at the D_2 sites

The nomenclature of the D_2 site is particularly troublesome. It has been named D_4 by Schwartz's group [22], D_o by Labrie's group [56] and is referred to by Creese and his colleagues as D_2^{low}, that is, the low-affinity state of the D_2 receptor [8].

It is important to recommend a uniform label or name for the D_2 site, since it is the only dopaminergic site in the brain which warrants being called a "receptor". This is because the IC_{50} values of agonists and antagonists at this site correlate very well with the doses which elicit the various dopaminergic behaviors (rotation, locomotion, anti-Parkinson action, psychotomimetic action, emesis and stereotypy) [6].

As shown in Table 4, the rank order of potencies at the D_2 site is the same as that for the D_1 site.

The D_3 site

The D_3 site, with its high affinity (nM) for dopamine and its low affinity (μM) for neuroleptics, has been routinely detected in our laboratory for many years [6]. This D_3 site has also been identified by Sokoloff *et al.* [22] and in Creese's laboratory [21]. Although these three laboratories agree that such a site exists, Laduron [2] has stated that the D_3 site is either an artifact or a nonspecific catechol-binding site. The properties of the D_3 site have been discussed extensively elsewhere [6].

Although there may be debate on the biological role of the D_3 site, the criteria for its nomenclature have been clear and consistent, such that there has generally been little confusion on its definition. Thus, most workers appear to have accepted the definition of the D_3 site as any site which has a nanomolar affinity for dopamine and a micromolar affinity for neuroleptics. Maeno's group [57], however, has referred to such a D_3 site as the "D_2" site.

Table 4. Rank order of drug potencies at the D_2 receptor (rat striatum)

	IC_{50} (nM) [^{3}H]Spiperone [6, 18]
Bromocryptine	38
Apomorphine	900
(±)-ADTN	1,500
Dopamine	19,000
Spiperone	0.06
(−)-Sulpiride	122
(±)-Sulpiride	250
(+)-Sulpiride	3,000

Table 5. IC_{50} (nM) values at the D_3 site (rat striatum)

	[^{3}H]Dopamine*	[19] [^{3}H]ADTN
Bromocryptine	150	317
Apomorphine	2.6	2
(±)-ADTN	1.5	5
Dopamine	6	5
Noradrenaline	22	
Spiperone	1,600	5,000
(±)-Sulpiride	43,000	9,000

* S. List and P. Seeman, *J. Neurochem.*, in press.

The rank order of potencies of the dopaminergic congeners at the D_3 site generally follows those for the D_1 and D_2 sites, with one important exception; bromocryptine is particularly weak at the D_3 site, as summarized in Table 5.

The D_4 site

As recommended in Table 1 and illustrated in Table 6, the D_4 site may be defined as a site which is sensitive to nanomolar concentrations of dopamine (i.e. 10–35 nM) and of butyrophenones (< nM spiperone). Sibley *et al.* [8], however, have described a site in the pituitary with a dissociation constant of 190 ± 17 nM for dopamine, using [^{3}H]spiperone, or 210 ± 50 nM dopamine, using [^{3}H]*N*-propylnoraporphine. Sibley *et al.* refer to this site as the D_2^{high} site (i.e. high-affinity state of the D_2 receptor).

It is important to point out that the D_4 site and the D_2^{high} state differ in their sensitivities to dopamine by a full order of magnitude. This large difference, therefore, in the opinion of this author, suggests that the D_4 site and the D_2^{high} state may be different entities. The D_4 site, on the other hand, is synonymous with the "D_2" site described by Sokoloff *et al.* [22].

It should also be noted that the D_2 and the D_4 sites may not be on the same neurones. For example, although the D_2 sites are postsynaptic to the nigral neurones (see references in Ref. 6), there must be D_4 sites which are presynaptic on the nigral neurones. This derives from the work of Kelly [58] who found that nanomolar concentrations of both apomorphine and haloperidol were effective in inhibiting and enhancing, respectively, the efflux of [^{3}H]dopamine from striatal slices (see Table 6).

Table 7. Drug potencies (nM) at peripheral nerve DA_2 sites (= central D_4 sites)*

	IC_{50} (nM)		
	[63–66] Rabbit ear	[67] Cat spleen	[44, 68–70] Other
Apomorphine	44	80	
(±)-ADTN	1.2		
Dopamine	37	50	30–200
Spiperone	0.2		
(±)-Sulpiride	<2(M)†	<1000*S*‡	*S*

* Concentrations of dopamine agonists which 50% inhibited the release of neurotransmitter from nerve terminals; usually done in the presence of cocaine (3–30 μM) to preclude re-uptake into nerve terminals.

† M = metoclopramide (not sulpiride) tested.

‡ *S* indicates that *S*-sulpiride was more potent than *R*-sulpiride. It should be noted that the rotation of light (+ or −) is different for sulpiride base and sulpiride HCl.

The D_4 sites, furthermore, have the same *in vitro* drug sensitivities as the pre-junctional DA_2 sites found on nerve terminals in the peripheral nervous system (Goldberg and Kohli [23]), as summarized in Tables 6 and 7.

Finally, it is important to note that a nomenclature based on whether or not a site is linked to adenylate cyclase can result in some confusion or a paradox. For example, the IC_{50} values for the D_4 site, as measured by ^{3}H-ligand methods (Table 6), were almost identical to the IC_{50} values which control the release of prolactin from pituicytes *in vitro* [59]; these values are also identical for the dopamine agonists which inhibit adenylate cyclase in the anterior pituitary cells [9, 56]. It appears, therefore, that the D_4 site is linked to adenylate cyclase. However, Kebabian and Calne [20] originally used the term "D_2" for a site which had nanomolar affinities for both dopa-

Table 6. Drug potencies (nM) at D_4 sites

	IC_{50} (nM)					
	[59, 60] Rat pit. cells prolactin release	[56] Bovine ant. pit. [^{3}H]APO	[9] Rat int. pit. DA-inh. cyclase	[22] Rat striatum [^{3}H]APO	[19] Rat striatum [^{3}H]ADTN	[58] Rabbit striatum [^{3}H]dopamine efflux
Bromocryptine	2.9			13	~8	
Apomorphine	3	2	9	1.3	4	9
(±)-ADTN	~2			2.1	4	
Dopamine	35	32	20	19	10	
Noradrenaline	540	500	200			
Spiperone	<0.7	0.7	<1	0.37	0.7	15(H)†
(±)-Sulpiride	S*		70	182	25	

* *S* indicates that *S*(−)-sulpiride base (Ravizza) was more potent than *R*(+)-sulpiride base; see Refs. 61 and 62.

† H = haloperidol (not spiperone) tested.

mine and butyrophenones, but which was not linked to adenylate cyclase. Kebanian's group [9], however, still refers to this anterior pituitary site as the "D_2" site, despite the fact that it *is* associated with adenylate cyclase, albeit negatively coupled. Such nomenclature difficulties may be avoided if one adheres to the recommendation in this commentary that the site or state be defined according to the absolute molar sensitivities to dopamine, spiperone and sulpiride.

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COMMENTS ON A COMMENTARY

Commentary articles are written to explore provocative new ideas and developing or controversial areas of research. To increase the exchange of information and ideas, we are publishing the following *Comments on a Commentary*, in which Dr. Ian Creese and Dr. David R. Sibley offer their observations on the article "Nomenclature of Central and Peripheral Dopaminergic Sites and Receptors" by Dr. Philip Seeman, published in this issue, and also provide some alternative thoughts on this important area of research. From time to time in the future we will solicit similar constructive comments on selected *Commentary* articles from experts in appropriate fields.

While the final decision on selection of authors for either *Commentaries* or *Comments on a Commentary* will be made at the discretion of the editors, we welcome suggestions from readers, which should be addressed to: Dr. C. N. Gillis, Department of Pharmacology, Yale University School of Medicine, 333 Cedar St., New Haven, CT 06510, U.S.A., or Professor Z. M. Bacq, Laboratoire de Pathologie et Therapeutiques, Université de Liège, 32 Boulevard de la Constitution, Liège, Belgium.

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COMMENTS ON THE COMMENTARY BY DR. SEEMAN

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Seeman's attempt to equate radioligand binding data [1] with more customary approaches to classify dopamine receptors is to be commended. Because radioligand binding measures receptor occupancy directly and the pharmacological effects of antagonists are proposed to be mediated solely through receptor occupation, a direct comparison of their molar potencies is theoretically correct. However, although the *rank order* potencies of agonists may be identical in such comparisons, their *absolute* molar potencies need not agree. A physiological response may not be linearly related to agonist binding because of spare receptors, efficacy considerations, high efficiency receptor/effector coupling mechanisms or intracellular amplification events. These caveats have not been adequately considered to warrant the proposed classification.

We disagree with the conclusion that D_2 and D_4 sites represent distinct dopamine receptors. It should be noted that antagonists have identical affinities at both sites. The distinguishing feature between D_2 and D_4 sites is that of absolute molar agonist affinities. Seeman has made a number of errors in his interpretation of these data. The first problem lies in his derivation of agonist potencies for D_2 sites. He uses IC_{50} values from agonist/^{3}H-antagonist displacement curves in membrane preparations. Such curves have low Hill coefficients (<1) and are