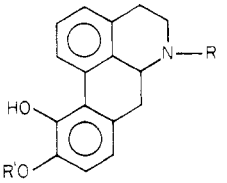
Communications to the Editor

Aporphines. 30. (-)-*N*-(2-Chloroethyl)-10,11-dihydroxynoraporphine (Chloroethylnorapomorphine), a Novel Irreversible Dopamine Receptor Antagonist

Sir:

The dopaminergic properties of various N-substituted, aromatic ring hydroxylated aporphine derivatives as represented by apomorphine (APO, **1a**) have been well doc-



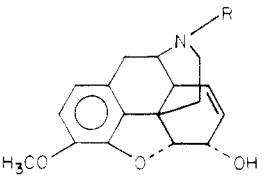
1a (APO), R′ = H; R = CH_3
b (NPA), R′ = H; R = *n*-propyl
c (NCA), R′ = H; R = CH_2CH_2Cl
d, R′ = CH_3; R = CH_2CH_2OH
e, R′ = H; R = CH_2CH_2OH

umented.[1-3] Currently, (-)-*N*-propylnorapomorphine (NPA, **1b**) is the most potent dopaminergic agonist in the aporphine series; NPA causes contralateral circling (in nigrostriatal lesioned rats) and stereotyped biting behaviors in intact rats at much lower doses than APO.[3,4] Tritiated APO and NPA are also highly selective in binding to putative dopaminergic (DA) receptors.[5] The greater potency of NPA as compared to APO in this series of dopaminergic agents indicates the importance of an alkyl side chain of optimal size and hydrophobic properties.

Our continuing investigation of the catecholamine function in the central nervous system led to the development of an analogue of APO and NPA which may selectively and possibly irreversibly alkylate the dopamine receptor. The design of such a dopamine receptor antagonist involved, as our first approach, the replacement of the *N*-methyl or *N*-propyl moieties of APO (**1a**) and NPA (**1b**), respectively, with an *N*-(chloroethyl) group. Such an agent, it was rationalized, might not only mimic the receptor affinities of APO and NPA but also bind irreversibly to the DA receptor.

In this communication, we report the synthesis of such a compound, (-)-*N*-(chloroethyl)norapomorphine (NCA, **1c**), which might be of value as a pharmacological and biochemical probe of the DA receptor and as a long-acting antidopamine or neuroleptic agent. Our preliminary in vitro evaluation of the effect of **1c** on DA-sensitive adenylate cyclase activity in rat striatal homogenates is also presented.

N-Demethylation of codeine (**2a**) was carried out by the methods of Abdel-Monem and Portoghese[6] and Rice[7] to



2a (codeine), R = CH_3
b (norcodeine), R = H
c, R = CH_2CH_2OH

give norcodeine (**2b**) in 70% yield. Subsequent N-alkylation of **2b** with bromoethanol, followed by rearrangement of *N*-(hydroxyethyl)norcodeine (**2c**) with methanesulfonic acid, gives *N*-(hydroxyethyl)norapocodeine (**1d**) by the procedure described recently by Granchelli et al.[8] Treatment of **1d** with 48% HBr at 120–125 °C under N_2 for 2 h afforded **1e** (79%) by dealkylation; **1e** was obtained as its HCl salt after neutralization of the reaction mixture, extraction, and treatment of the free base with ethereal HCl. An analytical sample of **1e** was obtained through further recrystallizations of the HCl salt from MeOH–Et_2O to give a white solid: mp 243–247 °C; NMR of free base (Me_2SO-d_6) δ 2.40–4.10 (broad signals, 14, H at C-4, C-5, C-6a, C-7, NCH_2CH_2OH, phenolic OH), 6.60–7.37 (m, 4, aromatic), 8.03–8.30 (dd, 1, aromatic H at C-1); MS *m/e* 297 (M^+), 266 (base); UV λ_{max} (EtOH) 275 nm (log ε 4.17); $[\alpha]^{28}_{546(Hg)}$ −47.0°. Anal. ($C_{18}H_{19}NO_3$·HCl·0.5H_2O) C, H, N. Treatment of **1e** with $SOCl_2$ in CH_3CN at room temperature, followed by evaporation of the reaction mixture, gave a residue which was then neutralized with NH_4OH and extracted with ether. The salt was prepared by treatment of the ether extract with ethereal HCl to give **1c**·HCl (64%): mp 173–178 °C (methanol–ether); NMR of the free base (MeOH-d_4) δ 2.33–4.40 (broad signals, 13, H at C-4, C-5, C-6a, C-7, NCH_2CH_2Cl and phenolic OH), 6.53–7.40 (m, 4, aromatic), 8.1–8.37 (dd, 1, aromatic H at C-1); MS *m/e* 315 (M^+), 266 (base); UV λ_{max} (EtOH) 275 nm (log ε 4.169); $[\alpha]^{28}_{546(Hg)}$ −35°. Anal. ($C_{18}H_{18}NO_2$·HCl·2H_2O) C, H, N.[9]

We found that preincubation of homogenates of DA-rich rat brain tissue with NCA (**1c**) inhibited subsequent stimulation of DA-sensitive adenylate cyclase to increase production of cyclic AMP (cAMP) by methods previously described for the *N*-(chloroethyl)-substituted catecholamine antagonist phenoxybenzamine (PBZ);[10] EC_{50} for NCA was 25–30 μM (Table I). Moreover, copreincubation of homogenates of rat striatum with both NCA and 50 μM DA (Table I) protected against the inhibition induced by 30 μM NCA; NE (100 μM) had no such protective effect. The inhibitory effect of preincubating with 30 μM NCA was not overcome by increasing DA to 100–200 μM in the assay, suggesting an irreversible and noncompetitive type of inhibition. Phenoxybenzamine (PBZ, 10 μM), an alkylating drug previously found to exert an irreversible blocking action of DA-sensitive adenylate cyclase,[10] exerted effects similar to those of NCA.

(1) N. Kumar and P. C. Jain, *Prog. Drug. Res.*, **21**, 409 (1977).
(2) L. L. Iversen, A. S. Horn, and R. J. Miller, *Adv. Neurol.*, **9**, 197 (1975).
(3) M. K. Menon, W. G. Clark, and J. L. Neumeyer, *Eur. J. Pharmacol.*, **52**, 1 (1979).
(4) J. L. Neumeyer, W. P. Dafeldecker, B. Costall, and R. J. Naylor, *J. Med. Chem.*, **20**, 190 (1977).
(5) M. Titeler and P. Seeman, *Eur. J. Pharmacol.*, **56**, 291 (1979).
(6) M. M. Abdel-Monem and P. S. Portoghese, *J. Med. Chem.*, **15**, 208 (1972).
(7) K. Rice, *J. Org. Chem.*, **40**, 1850 (1975).
(8) F. E. Granchelli, C. N. Filer, A. H. Soloway, and J. L. Neumeyer, *J. Org. Chem.*, in press.
(9) H: calcd, 5.34; found, 5.97.
(10) K. G. Walton, P. Liepmann, and R. J. Baldessarini, *Eur. J. Pharmacol.*, **52**, 231 (1978).

0022-2623/80/1823-0594$01.00/0

Table I. Effect of (-)-N-(Chloroethyl)norapomorphine (NCA) on Dopamine-Sensitive Adenylate Cyclase in Rat Striatal Homogenates[a]

preincubation concn, μM		% stimulation of cAMP productn, means ± SEM	% inhibn
NCA	DA		
0	0	100.0 ± 4.1	0
10	0	83.9 ± 6.3	16
30	0	43.9 ± 4.5	56
75	0	8.1 ± 1.3	92
30	50	102.8 ± 5.3	-3
0	50	98.0 ± 6.9	2

[a] NCA·HCl (1c·HCl) was preincubated for 10 min at 37 °C with homogenates of rat corpus striatum in a physiologic buffer, alone or with 50 μM DA added, and then washed free of the drugs. Washed tissue was then incubated with 0, 50, or 200 μM dopamine in the presence of excess ATP for 2.5 min at 37 °C, the level of cyclic AMP (cAMP) in the incubation mixture with vs. without DA was assayed by a protein-binding method,[10] and the increase in cAMP levels due to DA was estimated for all conditions ($n \geq 5$ replications). The typical basal level of production of cAMP without adding DA (mean ± SEM) was 1.21 ± 0.09 pmol 2.5 min^{-1} (80 μg of tissue)$^{-1}$ or (4 μg of protein)$^{-1}$.

We suggest that the process by which NCA inhibits DA-sensitive adenylate cyclase involves strong and possibly covalent bonding by receptor alkylation, analogous to the action of PBZ at the norepinephrine α receptor and other sites. Further support for the pharmacologic activity of NCA is provided by recent in vivo observations by Costall et al.[11] They found in mouse and rat that (-)-NCA when administered peripherally or intrastriatally can produce selective, potent, and long-lasting (up to 5 days) behavioral and biochemical effects indicative of DA-receptor blockade. These observations and our present results lead us to conclude that the mechanism of action of this agent is uniquely different from the dopamine receptor blockade produced by such reversible, competitive, and relatively short-acting neuroleptic agents as the phenothiazines, butyrophenones, and their congeners.

Acknowledgment. This research was supported, in part, by NIH Grants NS-15439 and NCI-NO-1-CM-53741 (Northeastern University), NIMH Grants MH-30511 and MH-31154 (McLean Hospital), and Research Career Award MH-47370 (R.J.B., Harvard Medical School). We thank Dr. Paul Vouros and Hamdy Maksoud for the mass spectral data and interpretations.

(11) B. Costall, D. H. Fortune, S. J. Law, R. J. Naylor, J. L. Neumeyer, and V. Nohria, *Nature (London)*, in press.

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Received December 31, 1979

Articles

Structure-Activity Analyzed by Pattern Recognition: The Asymmetric Case

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Received October 31, 1979

In classification studies in which pattern-recognition methods are used to distinguish active compounds from inactive ones, a type of data structure which we call "asymmetric" can be observed. This type of data structure can be quite common and its occurrence can have a profound effect on the classification analysis outcome. The origin of asymmetric data structure and a strategy for obtaining meaningful classification results when it is observed are discussed and illustrated with an example of active and inactive antimalarial quinones.

In recently reported SIMCA pattern-recognition studies of the classification of 4-nitroquinoline 1-oxides,[1] polycyclic aromatic hydrocarbons,[2] and N-nitroso compounds[3] as carcinogens or noncarcinogens, we discovered what we term "asymmetric" data structure. This resulted from the carcinogens (active compounds) forming in descriptor space well-defined cluster(s), while the inactive compounds were more or less randomly distributed in the same data space. Such asymmetric data structures can be rather common in the application of classification methodology to the problem of predicting the type of biological response of a new or untested compound. This has an effect on the data analytical strategy used and can ruin the data analysis if not recognized. We discuss here the rationale for asymmetric structure–activity data illustrated by a recently observed example of this type of data structure. We also present a strategy and method for obtaining relevant classification results when asymmetric data structures are observed.

Origin of Asymmetric Data Structure. Asymmetric data structures are primarily encountered in classification problems and will therefore be presented in a context

(1) W. J. Dunn III and S. Wold, *J. Med. Chem.*, 21, 1001 (1979).
(2) B. Norden, U. Edlund, and S. Wold, *Acta Chem. Scand., Ser. B*, 32, 1 (1979).
(3) W. J. Dunn III and S. Wold, *Bioorg. Chem.*, accepted for publication.

0022-2623/80/1823-0595$01.00/0