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The relative dependence of calcium antagonists and neuroleptics binding to brain and heart receptors on drug lipophilicity

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Abstract—QSAR analysis of the binding of calcium antagonists to brain and heart tissue shows that relative binding to brain tissue increases with increasing octanol/water partition coefficients. A number of antischizophrenic drugs follow the same pattern.

The story of calcium channel blockers began about 25 years ago when two newly synthesized coronary vasodilators (prenylamine and verapamil) were found to have cardiodepressant side effects mimicking the cardiac effects of simple calcium withdrawal. Since then, many more calcium antagonists have been synthesized and their actions studied. Binding sites of calcium channel antagonists have been identified in the heart, ileum, skeletal muscle, arterial smooth muscle, and brain (Ehlert et al 1982). There is evidence for different tissue selectivities among various calcium antagonists (Godfraind 1987). For example, some calcium antagonists have indications for neurological disorders rather than for cardiovascular disorders because they are more effective in the brain than in the heart.

Research has shown that calcium antagonist binding sites are similar in the brain, heart, and smooth muscle, but differ in some of their effects on skeletal muscle where binding is inhibited by calcium and stimulated by chelating agents. Moreover, most dihydropyridine drugs are substantially weaker in skeletal muscle than in other tissues (Wagner et al 1988). We have been interested in the action of drugs on the CNS and the relationship of such activity to the hydrophobic character of the drugs (Hansch et al 1987). Hence the study by Quirion et al (1985) on the relative activity of calcium antagonists and neuroleptics in the brain compared to that in the heart attracted our attention. We have now found that the more hydrophobic drugs are better bound to brain tissue compared to the heart tissues.

Methods

Quirion et al (1985) studied the binding of calcium antagonists by displacement of [^{3}H]nitrendipine from cortical and heart tissue preparations. Relative activity was defined as follows:

$$\text{Ratio} = \frac{K_i \text{ of nitrendipine in brain}/K_i \text{ of test drug in brain}}{K_i \text{ of nitrendipine in heart}/K_i \text{ of test drug in heart}}$$

$K_i = IC50/1 + F/K_d$ where IC50 = concentration of drug that inhibited 50% of the specifically bound [^{3}H]nitrendipine, F = free concentration of ligand, K_d = apparent affinity of the binding site.

The octanol/water partition coefficients are for partitioning at pH 7·4. Except for compounds 7 and 8 in Table 1, all are experimental values. For compounds 7 and 8, calculated values based on the additivity of fragments (Hansch & Leo 1979) were obtained via the CLOGP program. These calculated values were corrected to pH 7·4.

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Table 1. Parameters used to derive equations 1 and 2.

Drugs	Log ratio[a] obsd	Log ratio[b] calcd	Brain K_i	Heart K_i	Log P[c]
1. Nitrendipine[d]	0·000	−0·633	0·30	0·83	0·97[e]
2. Nimodipine	−0·022	−0·274	0·41	1·08	2·86[f]
3. Nisoldipine	−0·824	0·517	0·52	0·23	1·58[f]
4. Verapamil	−0·523	−0·470	218·7	248·2	1·83[e]
5. Lidoflazine	0·301	0·151	750·0	3970	5·10[g]
6. Flunarizine	0·000	0·189	1500	4255	5·30[g]
7. Cinnarizine	0·176	0·347	906	4609	6·13[h]
8. Prenylamine	0·204	0·227	625	2837	5·50[h]
9. Fluspirilene	0·431	0·296	18·7	127·6	5·86[i]
10. Pimozide	0·362	0·364	46·2	255·3	6·22[i]
11. Clopimozide	0·477	0·531	112·5	780·1	7·10[j]
12. Penfluridol	0·699	0·626	150·0	2127	7·60[j]
13. Haloperidol	−0·301	−0·491	2250	4250	1·72[j]

[a] Potencies of nitrendipine in both preparations have been used as the unity value from which all others have been calculated (Quirion et al 1985).
[b] Calculated using eqn 2.
[c] Log P values are for pH 7·4.
[d] This point dropped in the derivation of eqn 2.
[e] From Pang & Sperelakis (1984).
[f] From Herbette et al (1986).
[g] Obtained from Dr H. Almond of the McNeill Company.
[h] Calculated from additivity principles (Hansch & Leo 1979).
[i] El Tayar et al (1988).
[j] Laduron (1976).

Results and discussion

From the data in Table 1, the following quantitative structure-activity relationships (QSAR) have been derived.

All data points

$$\log \text{ratio} = 0{\cdot}16(\pm 0{\cdot}06)\log P - 0{\cdot}62(\pm 0{\cdot}32) \quad \text{(eqn 1)}$$
$$n = 13,\ r = 0{\cdot}849,\ s = 0{\cdot}235,\ F_{1,11} = 28{\cdot}3$$

Omitting nitrendipine

$$\log \text{ratio} = 0{\cdot}19(\pm 0{\cdot}06)\log P - 0{\cdot}82(\pm 0{\cdot}28) \quad \text{(eqn 2)}$$
$$n = 12,\ r = 0{\cdot}925,\ s = 0{\cdot}176,\ F_{1,10} = 59{\cdot}5$$

In these expressions, n represents the number of data points used, r is the correlation coefficient, s is the standard deviation and the figures in parentheses are for the construction of the 95% confidence intervals. Both equations are highly significant in terms of the F statistic ($F_{1,10}$ $\alpha \cdot 001 = 21{\cdot}0$)

The positive slopes of the equations show that the more hydrophobic the drug, the more affinity it has for receptors in the brain tissues relative to heart tissue. It is well known that lipophilic drugs enter the brain in animals readily at least up to log P in the region of 2 to 3 (Hansch et al 1987). However, after this point, penetration rate falls off (Hansch et al 1965). In the present in-vitro studies, there is a wide range in log P of the drugs (0·97–7·6). An interesting implication of equations 1 and 2 is that their linear nature implies that the fall off in activity with lipophilicity must be parallel in each type of tissue. It can be seen

Table 2. Lipid composition of various tissues of male rats at 70 days of age*. The values are in % dry weight.

Rat tissues	Phospho-lipids	Cerebro-sides	Free cholesterol	Cholesterol ester	Total essential lipid
Brain	27·19	8·42	7·05	0·02	42·68
Heart	15·38	1·37	0·45	0·21	17·41
Kidney	15·19	1·30	1·00	0·94	18·43
Lung	13·75	0·91	1·43	1·02	17·11
Testes	14·97	3·96	0·82	0·66	20·41
Liver	13·90	0·13	0·29	0·66	14·98
Thymus	10·75	1·14	0·24	0·61	12·74
Spleen	10·76	0·84	1·08	0·51	13·19
Skeletal muscle	8·57	3·57	0·12	0·14	12·40

* Data adapted from William et al (1945).

from Table 1, that in each type of tissue, binding (K_i) first increases with log P and then falls off. Presumably this is because at high log P values, drugs are sequestered by lipophilic sites other than those of the receptors (Hansch & Clayton 1973). Attempts to derive parabolic equations for brain and heart K_i gave poor correlations (QSAR). However, our results do suggest that one could design drugs which are more selective for brain or heart tissue by modulating their hydrophobicity.

Since Wagner et al (1988) have shown that the receptors in brain and heart are similar, it seems likely that the more lipophilic brain tissue sequesters the more lipophilic drugs more readily, providing a higher concentration in the region of the receptor. Table 2 shows the lipid composition of various tissues of male rats at 70 days of age. The data show that almost half of the brain is lipid. The total amount of essential lipids in the brain is 2·5 times that of the heart; but cholesterol, the most hydrophobic of the essential lipids, is 15·7 times higher in the brain than in the heart. Whether or not results similar to equations 1 and 2 will be found for whole animals remains an open question, but it would seem worthy of study in our attempts to find more selective drugs.

It is of interest that the data on antischizophrenic drugs (9–13, Table 1) which are also potent inhibitors of [^{3}H]nitrendipine are well fitted by equations 1 or 2. Also this type of selectivity of brain over heart seems to hold for lipophilic β-blockers (Hansch et al 1987); however, this has not yet been supported by QSAR. It has been shown via QSAR that more selective drugs can be designed at the enzyme level (Selassie et al 1989) or the cellular level (Selassie et al 1986).

In conclusion, it is important to develop QSAR for more than simple potency with respect to one kind of biological response. With two or more QSAR, one can design drugs that are optimized to act selectively (Selassie et al 1989) with respect to a crucial type of activity. Often selectivity is lost sight of in the quest for more potent drugs, but low potency can, to some extent, be overcome by the use of larger doses; selectivity can only be achieved by design or accident.

References

Ehlert, F. J., Roeske, W. R., Itoga, E., Yamamura, H. I. (1982) The interaction of [^{3}H]nifredipine with receptors for calcium antagonists in the cerbral cortex and heart of rats. Life Sci. 30: 2191–2202

El Tayar, N., Kilpatrick, G. J., Van de Waterbeemd, H., Testa, B., Jenner, R., Marsden, C. D. (1988) Interaction of neuroleptic drugs with rat striatal D-1 and D-2 dopamine receptors: a quantitative structure-affinity relationship study. Eur. J. Med. Chem. 23; 173–182

Godfraind, T. (1987) Classification of calcium antagonists. Am. J. Cardiology 59: 11B–23B

Hansch, C., Clayton, J. M. (1973) Lipophilic character and biological activity of drugs II: the parabolic case. J. Pharm. Sci. 62: 1–21

Hansch, C., Leo, A. (1979) Substituent Constants for Correlation Analysis in Chemistry and Biology. Wiley Interscience.

Hansch, C., Steward, A. R., Iwasa, J. (1965) The correlation of localization rates of benzeneboronic acid in brain and tumor tissue with substituent constants. Mol. Pharmacol. 1: 87–92

Hansch, C., Björkroth, J. P., Leo, A. (1987) Hydrophobicity and central nervous system agents: on the principle of minimal hydrophobicity in drug design. J. Pharm. Sci. 76: 663 687

Herbette, L. G., Chester, D. W., Rhodes, D. G. (1986) Structural analysis of drug molecules in biological membranes. Biophys. J. 49: 91–94

Laduron, P. (1976) Limiting factors in the antagonism of neuroleptics on dopamine-sensitive adenylate cyclase. J. Pharm. Pharmacol. 28: 250–251

Pang, D. C., Sperelakis, N. (1984) Uptake of calcium antagonistic drugs into muscles as related to their lipid solubilities. Biochem. Pharmacol. 33: 821–826

Quirion, R., Lafaille, F., Nair, N. P. V. (1985) Comparative potencies of calcium channel antagonists and antischizophrenic drugs on central and peripheral channel binding sites. J. Pharm. Pharmacol. 37: 437–440

Selassie, C. D., Fang, Z.-X., Li, R.-L., Hansch, C., Debnath, G. I., Klein, T. E., Langbridge, R., Kaufman, B. T. (1989) On the structure selectivity problem in drug design. A comparative study of benzylpyrimidine inhibition of vertebrate and bacterial dihydrofolate reductase via molecular graphics and quantitative structure-activity relationships. J. Med. Chem. 32: 1895–1905

Selassie, C. D., Strong, C. D., Hansch, C., Delcamp, T. J., Freisheim, J. H., Khwaja, T. A. (1986) Comparison of triazines as inhibitors of L1210 dihydrofolate reductase and of L1210 cells sensitive and resistant to methotrexate. Cancer Res. 46: 744–756

Wagner, J. A., Guggino, S. E., Reynolds, I.J., Snowman, A. M., Biswa, A., Olivera, B. M., Snyder, S. H. (1988) Calcium antagonist receptors. Ann. N.Y. Acad. Sci. 522: 116–133

William, H. H., Galbraith, H., Kaucher, M., Moyer, E. Z., Richards, A. J., Macy, I. G. (1945) The effect of growth on the lipid composition of rat tissues. J. Biol. Chem. 161: 475–484