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Lipid Solubility and Drug Penetration of the Blood Brain Barrier (38444)

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Entry of many drugs into the fluid environment of central nervous system (CNS) cells is significantly restricted by their failure to penetrate the blood-brain barrier (BBB). The BBB is generally believed to consist of the selectively permeable layer of CNS capillary endothelial cells (1). The ability of a drug in free solution (not bound to protein) in blood plasma to penetrate these cells is determined largely by the ability of the drug to detach itself from plasma and cytoplasmic water and enter the lipid of the endothelial cell plasma membranes.

It is generally recognized that lipid-soluble substances penetrate the BBB and lipid-insoluble substances do not. More accurately, it is probably the relative affinity for water and lipid which determines the degree of membrane penetration. The relative affinity of a drug for lipid and water can be estimated *in vitro* by determining its lipid/water partition coefficient. The present studies attempt to define quantitatively this relationship between lipid vs water affinity and BBB permeability.

Materials and Method. BBB penetration by a radiolabeled drug was estimated *in vivo* by determining how much is lost to brain tissue during one passage through brain microcirculation following carotid injection. This loss of drug is most easily determined as a percentage of the loss of a highly diffusible tracer, such as ^{3}H-water (THO), injected simultaneously (2, 3). This loss of test substance, expressed as a percentage of THO loss, has been termed the brain uptake index (BUI). This uptake has been most extensively studied in the rat and occurs during the first 1–2 sec after carotid injection.

Lipid/water partition coefficients and BUI's were measured for 19 drugs chosen to cover a wide range of lipid solubility. Approximately 3 ml of refined olive oil (Sigma Chemicals) and 3 ml of Ringer's solution (buffered to pH 7.55–7.58) with HEPES buffer (Calbiochem) were placed in an 8 ml bottle and approximately 0.5 μCi of the labeled drug was added to the Ringer's phase. After capping under 100% nitrogen, the bottle was mechanically shaken vigorously for 30 sec and then rocked at 37° for 2 hr to assure a steady-state had been achieved. The partition coefficient was (CPM/G oil)/(CPM/G Ringer's).

Results and Discussion. The results are shown in Fig. 1 and Table I. When BUI is plotted vs its partition coefficient the brain uptake rises above 2% (background level of the method) when the partition coefficient rises above about 0.02. When this coefficient is greater than about 0.03 the brain uptake for most drugs is nearly complete in a single passage. The incomplete removal of the more lipophilic drugs, such as diphenylhydantoin and phenobarbital, may be due to partial binding to plasma proteins in the brief interval between injection and capillary passage, although the injection rate is sufficiently high that the artery clears during the injection suggesting only minimal mixing occurs in the artery.

These results suggest that, in the design of drugs for CNS effects there will be little additional drug delivered to brain in the first passage after iv injection after the partition coefficient rises above about 0.1.

For drugs taken for their mind-altering effects, a short duration of action is usually desirable so that drug effects can be confined to a definite time interval. To accomplish this the drug must be sequestered in some tissue, rendered inactive or excreted. If a drug is excessively lipid-soluble it accumulates in body fat from which it continues to maintain some blood level for prolonged periods. Such a drug is Δ9-tetrahydrocannabinol (THC) which has a parti-

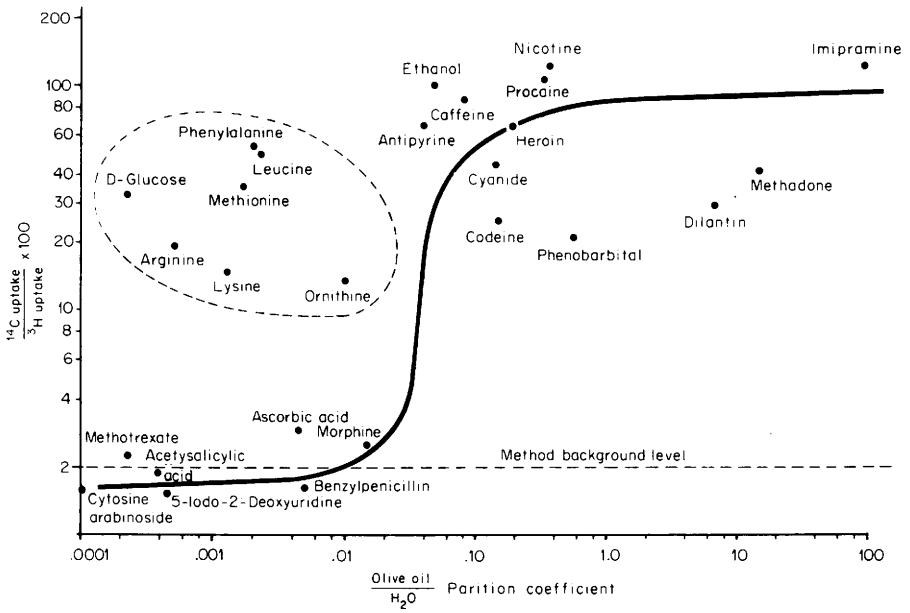

FIG. 1. A plot of % clearance of radiolabeled substances vs lipid/water partition coefficient during the course of a single brain passage following carotid arterial injection. Drugs with a partition coefficient greater than about 0.03 show nearly complete clearance. The encircled substances on the left which have minimal lipid affinity yet show appreciable clearances are brain metabolites which penetrate the blood brain barrier by virtue of specific carrier transport systems related to lipid affinity.

tion coefficient of several thousand (4) and a correspondingly long-term pharmacological effect. This usually will be considered an undesirable characteristic. Although the BUI of THC was not studied here it can be presumed to undergo complete clearance by brain in a single passage.

A drug with a more ideal partition coefficient is ethanol (0.04). This is high enough to allow complete clearance, and thus a rapid onset of action, but, since it favors water over lipid by a factor of 25, very little lipid accumulation can occur. This probably is significantly correlated with the ability of obese individuals to become intoxicated with little more ethanol intake than lean individuals. It must be an important factor in the rapid clearance of even severe ethanolic intoxication.

Diphenylhydantoin is quite lipid soluble (partition coefficient 6.83), and this results in considerable depot-fat storage. This has been shown to result in a requirement of only a single daily administration rather than the three divided doses long considered standard practice (5).

Many drugs are not useful in CNS because they are insufficiently lipid soluble to penetrate the BBB. Most antibiotics achieve very low levels in CNS for this reason. If a drug can have polar sites shielded by substituting nonpolar groups, it may become sufficiently lipid soluble to allow rapid BBB penetration. If the relatively nonpolar substituted groups can readily be hydrolyzed off in CNS, then the original compound will reappear in brain. This process of reversible lipophilic derivatization has been termed latentiation (6) and is exemplified by acetylation of morphine to heroin (7). This greatly enhances its brain uptake (8). In the brain it is de-acetylated back to morphine (9). This ploy to get drugs through the BBB has been used with several classes of compounds (10–14) but will, in the future, probably be much more extensively exploited.

The present studies indicate that the lipid/water partition coefficient of such derivatives need only be raised to above about 0.03 to gain immediate access to brain cells after intravenous injection. Drugs with lower solubility will also penetrate the BBB but at a slower rate and will have time to distribute to other tissue compartments competing with brain (15). Drugs largely cleared during a single brain passage are flow-limited in their delivery to brain and, accordingly, a large fraction of the administered dose will

TABLE I. Brain Uptake and Partition Coefficients of Drugs Following Carotid Injection.[a]

Test substances	Conc injected (m*M*/liter)	Brain uptake index (BUI) (% of ^{3}HOH)	Partition coefficients olive oil/water
^{3}HOH reference		100	
Nicotine	0.03	131 ± 7	0.39
Imipramine	0.22	128 ± 11	86
Procaine	0.48	113 ± 8	0.34
Iso-propanol	0.069	110 ± 2	—
Ethanol	0.02	104 ± 4	0.046
Caffeine	0.27	90 ± 3	0.084
Antipyrine	0.11	68 ± 3	0.040
Heroin	0.031	68 ± 6	0.2
Levo-methadone	0.054	42 ± 3	14
Cyanide	1.2	41 ± 4	0.15
5,5-Diphenylhydantoin	0.27	31 ± 3	6.83
Codeine	0.021	26 ± 2	0.16
Phentobarbital	0.4	22 ± 2	0.57
L-Ascorbic Acid	0.26	3.0 ± .2	0.0046
Morphine	0.022	2.6 ± .2	0.016
Methotrexate	0.020	2.3 ± .4	0.00024
Acetylsalicylic Acid	0.68	1.8 ± .4	0.00037
Benzylpenicillin	0.044	1.7 ± .2	0.0051
Cytosine arabinoside	0.00061	1.6 ± .4	0.00010
5-Iodo-2-deoxyuridine	0.00036	1.5 ± .21	0.00047

[a] For each mean and SD, $n = 3$ except for codeine $n = 6$. All compounds were carbon labeled, except methadone, methotrexate, cytosine arabinoside and iododeoxyuridine were tritiated. The pH of all solutions was 7.55–7.58. The P values were obtained using the Student's t test. The BUI's for all tritiated compounds were based on a ^{14}C-isopropanol diffusible reference and were corrected back to ^{3}HOH reference. Radiochemical purity averaged 98%. Substances were from Amersham/Searle, Chicago; New England Nuclear, Boston; Schwarz/Mann, Orangeburg, NY; and Dhom, Los Angeles, CA. Specific labeling sites are not included since it is assumed no biotransformation occurs prior to BBB penetration.

appear in brain. When attempting to optimize the partition coefficient when choosing drugs, extreme lipid affinity is undesirable since such drugs would tend to sequester in membranous lipid compartments in gut, liver or lung (depending on the route of administration) and not be available for brain uptake.

Summary. Lipid/water partition coefficients of 19 radiolabeled drugs were correlated with uptake by brain during a single microcirculatory passage following carotid arterial injection. Uptake was measured relative to a simultaneously injected diffusible reference. When the lipid/water partition coefficient was greater than about 0.03 a substantial fraction of the drug penetrated the blood-brain barrier and for most drugs above this range, uptake was essentially complete. These data suggest there is probably little reason to greatly exceed this degree of lipid solubility when designing drugs for blood-brain barrier penetration and central nervous system effects.

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