科技资料

Neurological Adverse Reactions to Anticancer Drugs

J. Hildebrand (Ed.)

Neurological Adverse Reactions to Anticancer Drugs

With 8 Figures and 15 Tables

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Foreword

The European School of Oncology came into existence to respond to a need for information, education and training in the field of the diagnosis and treatment of cancer. There are two main reasons why such an initiative was considered necessary. Firstly, the teaching of oncology requires a rigorously multidisciplinary approach which is difficult for the Universities to put into practice since their system is mainly disciplinary orientated. Secondly, the rate of technological development that impinges on the diagnosis and treatment of cancer has been so rapid that it is not an easy task for medical faculties to adapt their curricula flexibly.

With its residential courses for organ pathologies and the seminars on new techniques (laser, monoclonal antibodies, imaging techniques etc.) or on the principal therapeutic controversies (conservative or mutilating surgery, primary or adjuvant chemotherapy, radiotherapy alone or integrated), it is the ambition of the European School of Oncology to fill a cultural and scientific gap and, thereby, create a bridge between the University and Industry and between these two and daily medical practice.

One of the more recent initiatives of ESO has been the institution of permanent study groups, also called task forces, where a limited number of leading experts are invited to meet once a year with the aim of defining the state of the art and possibly reaching a consensus on future developments in specific fields of oncology.

The ESO Monograph series was designed with the specific purpose of disseminating the results of these study group meetings, and providing concise and updated reviews of the topic discussed.

It was decided to keep the layout relatively simple, in order to restrict the costs and make the monographs available in the shortest possible time, thus overcoming a common problem in medical literature: that of the material being outdated even before publication.

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Purposes and Plan

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Most antineoplastic drugs are neurotoxic, and brain damage would probably be the major limitation of cancer chemotherapy were it not the blood-brain barrier. The latter normally protects not only the central nervous system, but also large segments of the peripheral nerves from ionised and water-soluble molecules, including naturally occurring toxins and drugs. The understanding of the blood-brain barrier's function under normal conditions and of its changes under various pathological circumstances is essential for the assessment of the neurological adverse reactions to antineoplastic chemotherapy. These aspects are considered in the first chapter.

Quite naturally, the antineoplastic mechanisms of anticancer drugs have been more extensively investigated and are thus much better understood than their neurotoxicity. Yet, despite this gap, a substantial amount of pertinent information, resulting from laboratory and clinical studies, has been gathered, and is summarised in the second chapter.

Chemotherapy and radiation therapy are often used in combination, thus mutually enhancing their neurotoxic effects. The mechanisms of this interaction, still only partially elucidated, are discussed in the third chapter.

Finally, the last 2 chapters are devoted to the clinical aspects, diagnosis and differential diagnosis of various neurological conditions related to antineoplastic chemotherapy. The syndromes have been individualised according to the main locations of the neurological lesions. But, needless to say, many of these may overlap in the same patient, leading to more complex clinical pictures.

In preparing this monograph, the editor was fortunate to collaborate with an outstanding group of enthusiastic clinicians and scientists, and wishes to express his warmest appreciation.

The Blood-Brain Barrier: Morphology, Physiology and its Changes in Cancer Patients

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Introduction

It has been clear since the time of Ehrlich that the greater part of the CNS is not stained when Trypan blue is injected into the blood stream, even when other organs of the body are very heavily stained.
Goldman, Ehrlich's student, demonstrated that this phenomenon was not as Ehrlich had thought, a failure of the dye to bind to the brain, because the dye did bind to the brain when injected into the subarachnoid space, but was excluded from the brain by a blood-brain barrier (BBB) [1]. The BBB is present in vertebrate brains and absent in most invertebrate brains, and thus it parallels the phylogenetic distribution of myelin [2]. In fact, the term blood-brain barrier is a misnomer. There are in fact, as indicated below, several barriers and their role is that of permitting a great selectivity in the blood-brain exchange of solutes with the almost complete exclusion of some of them, and an enhancement of exchange for others [3-5]. There are 3 compartments within the cranial cavity (blood, cerebrospinal fluid and brain parenchyma), but only 2 barriers can be considered: 1) the blood-brain barrier between the blood and brain extracellular space, 2) the blood-CSF barrier at the level of the choroid plexus and arachnoid villi. There is no real CSF-brain barrier at the level of the ependyma and pia mater [6]. A barrier also exists within the peripheral nervous system: the blood-nerve barrier [7].
The BBB can be explored *in vivo* and *in vitro* (Table 1) in both humans and experimental animals. Some of these techniques will be detailed below.

Morphology of the Blood-Brain Barrier

Electron microscopy studies have localised the BBB at the capillary endothelium [8]. Cerebral capillaries are microvessels with a diameter of around 3 to 7 microns. A single layer of endothelial cells is surrounded with a basement membrane within which pericytes may be embedded. The basement membrane is in close association with the foot processes of astrocytes (Fig. 1).

Endothelial Cell

The brain capillary endothelial cell has 4 major properties. The first is the presence of continuous high resistance tight junctions that fuse brain capillary endothelia together into a continuous cellular layer separating blood from the interstitial fluid [6,8]. This is in contrast with non-neural endothelium where cells have discontinuous junctions. The tight junctions may be perforated by aqueous channels whose diameters are no larger than 6 to 8 ångström, allowing passage of only 3 molecules generally found in the body: water, sodium and chloride. The second property is the absence of fenestration whereas non-neural endothelial cells are fenestrated. The third property is the small number of plasmalemma vesicles [8]. In other tissues, these

Table 1. Some techniques exploring the BBB

	TECHNIQUE	DISADVANTAGES
In vivo experiments		
Humans	Radionuclide scans, CT and MRI (infusion of contrast)	Non-quantitative data Contrast enhancement also depends on the number of vessels
	Positron emission tomography (Rubidium 82, drugs)	Poor spatial resolution
	Osmotic opening of the BBB	Potentially dangerous
Animals	Injection of Evans blue	Non-quantitative data
	Extraction fraction	Requires sacrifice of the animals
	Quantitative autoradiography (AIB, drugs)	
	Identification of vascular permeability factors	
In vitro experiments		
	Optic and electron microscopy Immunohistochemistry Culture of brain microvasculature Characterisation of vascular permeability factors	

vesicles are abundant and serve to transport molecules by pinocytosis across the endothelium. When counted by electron microscopy, rat brain endothelial cells seem to have about 5% of the number of pinocytic vesicles found in non-neural tissues. Finally, the brain capillary endothelial cell contains a very high density of mitochondria, which is about 4 times that of non-neural capillary endothelial cells [2,3], reflecting a higher metabolic activity, probably related to the barrier function of these capillaries.

Brain endothelial cells also express several proteins which are usually not found in non-neural endothelia [9]. The presence of gamma-glutamyl transpeptidase is a marker for brain and retinal-derived endothelium. Intimate contact of the endothelial cells with astrocytes is necessary for this enzyme expression. Of particular interest is the finding by Cordon-Cardo et al. that multidrug resistance gene (P-glycoprotein) is expressed by normal endothelial cells at BBB-sites, raising the question that this protein, which is believed to function as an energy-dependent drug efflux pump, plays a role in the barrier function of the brain endothelial cell for molecules such as doxorubicin, actinomycin D, and vincristine [10]. P-glycoprotein is heterogeneously expressed by endothelial cells within primary brain tumours, with the most anaplastic areas containing the lowest number of capillaries staining for P-glycoprotein. Interestingly, the protein could be detected in some endothelial cells in metastatic

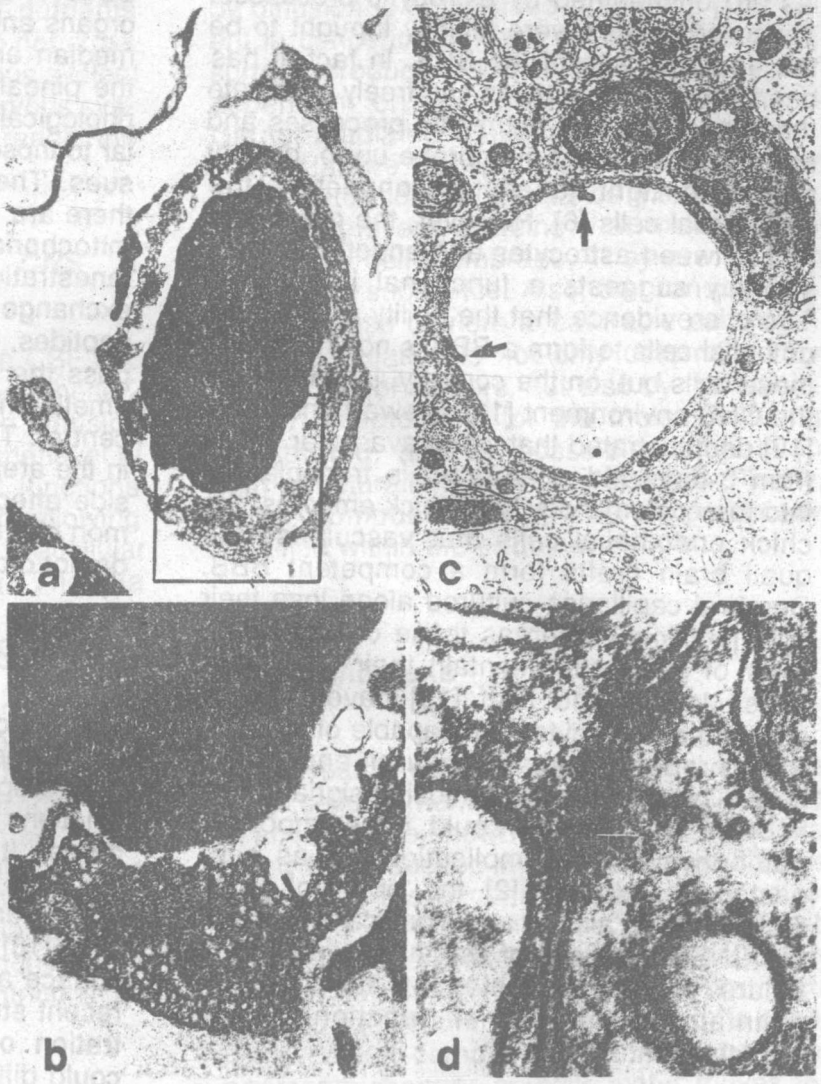

Fig. 1. Morphological differences between muscle and cerebellar capillaries.
a) Muscle capillary. Note the presence of interendothelial junctions and of numerous endothelial vesicles; x 8800. The square is enlarged in panel b
b) Muscle capillary. A junction and multiple endothelial vesicles (arrows) are seen; x 20000
c) Cerebellar capillary. Presence of interendothelial junctions (arrows), absence of endothelial vesicles; x 6600
d) Cerebellar capillary. Tight interendothelail junctions (arrow head); 17000
Reprinted from Hauw JJ and Lefauconnier JM [2] with permission

brain tumours, suggesting its presence is induced by brain structures.

Other Structures of Cerebral Capillaries

The basement membrane is a thin (3-4 nm) extracellular matrix of collagen and glycoproteins, located between the endothelial cell and the low processes of the astrocytes. Pericytes are embedded within the basement membrane. They could play a role in the synthesis of the basement membrane, in the support and regulation of endothelial cell growth, and in the control of the diameter of the capillary wall, thus participating in the regulation of the blood flow. Cerebral capillar-

ies are ensheathed by astrocytic processes. These processes were initially thought to be the anatomic site of the BBB. In fact, it has been shown that proteins can freely permeate the space between astrocytic processes and enter the basement membrane up to, but not past, the tight junctions connecting the endothelial cells [6]. However, the close contact between astrocytes and endothelial cells strongly suggests a functional interaction. There is evidence that the ability of CNS endothelial cells to form a BBB is not intrinsic to these cells but, on the contrary, is induced by the CNS environment [11]. Stewart and Wiley [12] demonstrated that when avascular tissue from 3-days old quail brain is transplanted into the coelomic cavity of chick embryos, the chick endothelial cells that vascularise the quail brain grafts form a competent BBB. Cerebral capillaries cultured alone lose their tight junctions, whereas those cultured on a layer of glial cells maintain their tight junctions. Janzer and Raff [13] have recently shown that astrocytes are capable of inducing BBB properties in non-neural endothelial cells. The nature of the inducing signal is unknown. This finding could have important pathophysiological implications if, as suggested by Oldendorf [2], the "opening" of the BBB found in almost any significant lesion of the CNS regardless of its cause, was due to failure or malfunctioning of astrocytes in maintaining the barrier function of the endothelium.

Innervation

The noradrenergic innervation of brain capillaries is derived from cell bodies in the locus coeruleus: its precise function is still obscure, but there is evidence that the state of activity in the noradrenergic brain stem neurons may participate in the local microregulation of cerebral blood flow and capillary permeability to water [14,15], possibly through modulation of NA/K-ATPase activity [16]. There is also evidence of a cholinergic innervation of brain capillaries [17].

Regions of the Brain Without Barrier and the Blood-CSF Barrier

A few small regions of the CNS are devoid of BBB. They are called the circumventricular organs and consist of the area postrema, the median eminence, the preoptic recess, and the pineal gland. In these regions, the morphological features of the capillaries are similar to those of other capillaries of systemic tissues. The tight junctions are discontinued, there are more plasmalemma vesicles, fewer mitochondria, and sometimes endothelial fenestration. These regions could be local exchange sites between blood and brain for peptides, or other polar substances unable to pass the BBB [2]. The area postrema is an emetic chemoreceptor trigger zone (vomiting centre). The absence of a blood-brain barrier in the area postrema may explain, in part, the side effect of nausea and vomiting, so common even with chemotherapeutic agents that do not cross the normal blood-brain barrier.

The Choroid Plexus

The endothelial cells of the choroid plexus are permeable. However, cells of the choroid plexus epithelium are linked together by tight junctions and are the seat of the blood-CSF barrier. It was widely accepted that the compositions of CSF and extracellular fluid of the brain were identical. However, this is debatable [18]. The BBB has a 5000-fold greater surface area than the blood-CSF barrier, and recent studies have shown that the concentration of substances in brain interstitium could differ markedly from the concentration in CSF [2]. The composition of CSF is determined by the secretory processes in the choroid plexus epithelia, while the content of brain interstitium is primarily determined by transport through the BBB, and possibly by a secretory function of neural and glial cells. According to Oldendorf [2], the BBB seems to leak a slight amount of blood plasma components into the CSF, probably due to the presence of some residual transcytosis [19] because pathologically stagnant CSF shows a steady rise in plasma proteins, whereas newly formed choroidal secretion is nearly free of protein. The blood-CSF barrier differs from the BBB in other respects as well. Certain acidic substances (e.g., penicillin, methotrexate) are transported from the CSF to the blood by the choroid plexus, particularly that of the fourth ventricle. This reflux can

be blocked by probenecid. There is also evidence that certain trace-essential nutrients (e.g., folic acid, vitamin B12) that do not cross the BBB, but are essential for nervous system function, are transported into the nervous system via the choroid plexus and reach the brain by diffusion.

Exchanges Between CSF and CNS Parenchyma

There is no real barrier between the CSF and the parenchyma. Exchanges between these 2 compartments are effected through diffusion along a concentration gradient. At the level of the ependyma, there are no tight junctions between the cells of the epithelium, allowing exchange between the CSF and extracellular space of the brain parenchyma. The pia mater is discontinued and the CSF is in direct contact with the parenchyma via a basal lamina allowing diffusion of the molecules from the CSF to the brain. The clinical implication of the lack of a CSF-brain barrier is that drugs which fail to reach the brain parenchyma after intravenous injections may achieve substantial levels in the brain (particularly those areas of the brain near the CSF) after intraventricular injections, as illustrated by the presence of substantial levels of methotrexate in the brain parenchyma of rabbits one hour after an intraventricular injection.

Physiology of the Blood-Brain Barrier

In order to reach the brain, molecules must cross the membranes and the cytoplasm of the endothelial cell. If the anatomic barriers were complete, substances vital to brain metabolism, including glucose and essential amino acids, could not enter the brain and brain function would cease. Thus, the capillary endothelium must possess transporter systems which promote entry of vital substances into the brain. The transcellular transport of molecules is performed through diffusion or carrier-mediated transport [4,5,20].

The rate at which a molecule crosses the BBB by diffusion is determined mainly by a gradient in concentration and by the permeability surface product. Permeability itself is highly dependent on lipid solubility (see below). Carrier-mediated transport (facilitated diffusion or active transport) allows the entry of some water-soluble substance into the brain. The carriers are proteins that move solute across the cell membrane. They are specific for a given substance. Also, the transport activity of these carriers is saturable and regulated. Regulation is not only determined by the amount of carriers, but also by the affinity of the receptor site for the molecule being transported, and by posssible competition with structurally related compounds. Finally, some compounds may be enzymatically modified within the endothelial cells.

Water and Ions

Water readily crosses the BBB as it does for other cellular membranes. However, Raichle et al. [21] have shown that at normal cerebral blood flow, labelled water did not equilibrate freely with the exchangeable water pool of the brain during a single capillary transit, suggesting the presence of a brain capillary permeability limitation of water. The brain is in osmotic equilibrium with the blood in its capillaries. When osmolarity in one of the compartments changes acutely, water moves toward the compartment of higher osmolarity. Hyperhydration is often used prior to chemotherapy with cis-platinum in order to reduce renal toxicity. However, hyperhydration prior to cis-platinum chemotherapy can lead to acute hypo-osmolality with the adjacent shift of water from the systemic circulation into the brain, therefore precipitating acute cerebral swelling and herniation in patients with intracranial lesions [22]. Conversely, the intravenous injection of hyperosmolar agents such as mannitol can pull water from the brain, acutely relieving many of the symptoms of cerebral oedema. The response of the brain to systemic osmolar changes is not as complete as that in other organs. Both acute and chronic changes in osmolality (especially chronic changes) pro-

duce fewer changes in brain water than would be expected were the brain a simple osmometer. This phenomenon apparently occurs as a result of active changes in osmoles of the brain, which serve to protect the brain against excessive swelling or shrinkage that might be expected from severe osmolar changes systemically [20,23,24].

Ions are restricted in their passage across the BBB. The concentration of K+ in the extracellular fluid is strictly regulated and determines the threshold potential of the neurons. Thus, despite a definite concentration gradient favouring movements of K+ from the blood (3-5 mM concentration) to the extracellular compartment of the brain (2.8 mM concentration), changes in the blood concentration of K+ do not result in changes in the interstitial fluid concentration of K+. Betz [25] demonstrated that this asymmetric distribution of K+ transport, which is transported from the abluminal side of the capillary endothelium into the capillary, was due to a polar distribution of Na, K-ATPase in the brain capillary. High extracellular potassium levels both increase the metabolic rate of brain cells and lower the seizure threshold. Breakdown of the blood-brain barrier in and around tumours, which increases the influx of potassium into the brain may be one reason that seizures are a common presenting symptom in patients with brain tumours. Conversely, corticosteroids, although not an anticonvulsant agent, may by its effect on the blood-brain barrier help ameliorate seizures related to brain tumour. For Na+ transport, in addition to the NA, K-ATPase located at the antiluminal side, the luminal membrane of the endothelial cell has 2 saturable transport systems for sodium entry. The sodium-chloride cotransport carrier (inhibited by furosemide) and the sodium channel (inhibited by amiloride) are similar to Na pores found in some epithelia. The BBB to sodium is reduced in experimental diabetes, possibly through glucose mediated inhibition of the Na+ K+-ATPase [26].

Glucose

Glucose, a polar compound, is the most important metabolic substrate of the brain. The transport of glucose across the BBB has been extensively studied. Highly specific carriers are present within endothelial cells. The density of the glucose transporter moiety in brain capillaries is 10 to 20 times higher than the density of the transporter in membranes of other mammalian tissues [27]. Glucose influx is closely coupled to regional cerebral glucose utilisation (RGCU) and regional cerebral blood flow. When metabolism is increased, glucose transport follows [28]. The mechanism by which glucose transport is modulated remains unknown. After crossing the BBB, glucose diffuses in the extracellular space and is metabolised through the glycolytic pathway. Under some circumstances, transport of glucose across the BBB may limit brain metabolism. For example, when the metabolic demand of the brain increases (hypoxia, seizure), the number of carriers may be inadequate to sustain function, even when the blood glucose level is normal. It has also been suggested that chronic hyperglycaemia induces a compensatory decrease in the number of glucose carriers (i.e., down regulation) explaining why rapid normalisation of blood glucose in severe chronic diabetes could induce neurological symptoms of hypoglycaemia [29], but this remains controversial [26].

Amino-Acid Transport

Transport across the BBB is believed to be the rate-limiting step for the penetration of amino acids into brain cells, because the maximal velocities of neuronal membrane transport systems are much greater. Several transport systems have been described: the neutral [30], the acidic and the basic amino-acid carrier systems [31,32]. It is important to realise that various amino acids share the same carriers. Thus, influx of an amino acid is not only determined by its plasmatic concentration and affinity for a carrier, but also by the concentration and affinity of other amino acids which compete with the same carrier. This provides a basis for the selective vulnerability of the brain to derangements in amino-acid availability caused by a selective hyperaminoacidaemia.

Other Transport Systems

There are specific transport systems for monocarboxylic acids, such as lactic acid (the main functions of the carrier is here to eliminate lactic acid produced by the brain), for ketone bodies which provide an alternate fuel for brain energy metabolism [31], and for nucleic acid precursors. Most neurotransmitters do not enter the brain because of their low lipid solubility and lack of specific transport carriers.
In the past, BBB was considered impermeable to circulating peptides. Recent studies have suggested a specific transport system at the BBB for circulating peptides such as insulin, insulin-like growth factor and transferrin [2].

The Blood-Nerve Barrier

The main features of the peripheral nerve vessels are the richness of anastomoses and the presence of microvascular networks of plexuses. Numerous vessels pierce the perineurial plexuses to join the endoneurial network, composed mainly of capillaries running longitudinally along the nerves. Small nerves may lack an endoneurial network and acquire nutrients directly from the perineurial vessels. Several papers have reviewed the morphological and physiological properties of the blood-nerve barrier [7,33]. The techniques used to study the blood-nerve barrier are similar to those used for blood-brain barrier study (infusions of Evans blue, radiolabelled albumin, or horseradish peroxidase). Quantitative methods have also been used but their results are often difficult to interpret, since one cannot sample selectively endoneurium and epineurial tissue. The barriers in peripheral nerves are less efficient and not as constant as those in the brain. After injection of Evans blue, the dorsal root ganglia and the epineurium are intensely stained, whereas the endoneurium is unstained, clearly indicating that these structures do not possess a blood-tissue barrier. The epineurial vessels have no barrier function and do not differ from other permeable vessels found elsewhere in the organism (absence of continuous tight junctions, fenestrae, high number of pinocytic vesicles). However, diffusion of extravasated molecules from the epineurium into the endoneurium is prevented by the barrier function of the perineurium. Although there is a certain degree of variability between species, it is generally recognised that the blood-nerve barrier is located at the endothelial cells of the endoneurium. Electron microscopy studies have shown that endothelial cells of the endoneurium were fused by tight junctions similar to those in the brain parenchyma. Olsson and Reese [34] noted the absence of fenestrations, and the rarity of pinocytosis across the endothelium of the endoneurium of large nerves. Nevertheless, a small quantity of the tracer (horseradish peroxidase) can cross the barrier, since endoneurial macrophages with uptake of the tracer can be seen as early as 5 minutes after an intravenous injection of horseradish peroxidase. Furthermore, tracers leak into the endoneurium of thin intramuscular nerve branches (probably across the perineurium, or by diffusion from the neuromuscular junctions). Therefore, the penetration of blood-borne substances differ in terminal nerve branches from that in large nerve trunks. This aspect could be important for neurotoxic drugs and for the pathophysiology of some dying back neuropathy. In addition, it is known that normal and severed axons can incorporate a number of protein tracers and deliver them to the nerve-cell body by retrograde axonal transport. As for the blood-brain barrier, the role of the blood-nerve barrier seems to prevent access of noxious agents into the nerve.

Drug Transport Across the Blood-Brain Barrier

It is of great importance to oncologists to know the major criteria that determine drug entry within the nervous system. For example, if a combination of drugs is used to treat an acute leukaemia and if none of these drugs cross the blood-brain barrier, it is well known that additional treatment of the CNS should be designed in order to prevent the occurrence of CNS metastases. Of equal impor-

Table 2. Entry of some chemotherapeutic agents across the BBB and blood-CSF barrier

Agents/Route (a)	Entry across the BBB and b-CSF barrier (b)	CNS toxicity at usual dose (c)	CNS toxicity if BBB entry (d)
Plant Alkaloids			
Vincristine IV	+ (e)	+ (f)	lethal (IT)
Vinblastine IV	?	+	NK (h)
Vindesine IV	?	+	NK
VP 16 IV	+	0	0? (IA)
VM 26 IV	+/++	0	+/++ (IA)
Antibiotics			
Doxorubicin IV	+	0	+++ (IA)
Bleomycin	+	0	NK
Antimetabolites			
Methotrexate IV	+	0	rare (if HD IV)
Methotrexate IT	bypassed	rare (g)	
5-fluorouracil IV	++	0/+	rare (if HD IV) (i)
Cytarabine IV	++	0	rare (if HD IV)
Cytarabine IT	bypassed	rare	
Hydroxyurea PO	+/++	0	NK
Alkylating Agents			
Cyclophosphamide PO/IV	+/++ (IV)	0/+	+ (if HD IV)
Melphalan PO	+	0	+++ (IA)
CCNU PO	+++	0	-
BCNU IV	+++	0	++/+++ (IA)
ACNU IV, IA	+++	0	0 (IA)
HECNU IV, IA	+++	0	+/++ (IA)
Cisplatin IV	+	+	+/++ (IA)
Carboplatine	+/++	0	+ (IA)
Others			
Procarbazine PO	++	0/+	NK

(a) usual route
(b) entry across the blood-brain and blood-CSF barrier at usual route and dose
(c) CNS toxicity at usual dose and usual route of administration
(d) CNS toxicity when drug entry is increased: intra-arterial (IA) or intrathecal (IT) administration
(e) entry: small +, moderate ++, high +++
(f) toxicity: mild +, moderate ++, severe +++
(g) when associated with radiation therapy
(h) NK: not known
(i) HD IV: high-dose intravenous

tance is the knowledge of the direct effects of cancer treatment on BBB. Thus, if prophylactic radiation therapy is administered simultaneously to polychemotherapy, particularly high-dose IV methotrexate, the risk of delayed leukoencephalopathy is much increased, presumably because radiation therapy facilitated methotrexate entry across the BBB [35]. A logical consequence is therefore to administer methotrexate prior to radiation in order to treat the CNS, while reducing the risk of neurotoxicity. We will focus on the transport of chemotherapeutic agents used in cancer treatment.

Transport of Chemotherapeutic Drugs Across the BBB (Table 2)

A few drugs penetrate the CNS with facilitated diffusion, such as the alkylating drug melphalan [36]. However, the movement of most drugs across the capillary endothelium appears to be diffusional. The amount of drug that diffuses across the BBB is determined by several factors [37-39]:

1) Plasmatic concentration of freely exchangeable drug. The amount of drug transported passively across a biological membrane is proportional to its concentration (C). Binding to plasma proteins limits entry of a molecule into the brain. However, some plasma-protein bound substances may become available for transport through the barrier because of specific interactions between plasma proteins and the endothelial surface [2]. The mechanism involves endothelial-mediated enhanced dissociation of ligand from the protein. For example, albumin has at least 6 different binding sites, and the degree to which a given ligand is transported through the BBB depends on which site the ligand is bound to. Bilirubin is normally bound to a site on albumin that does not release the ligand in the brain capillary, whereas diphenyihydantoin are normally bound to sites that do release these ligands within the cerebral microcirculation. The amount of the ionised form of the drug at blood pH is important, since permeability of the BBB to a drug is 10,000 times higher for the non-ionised form than for its ionised form.

2) The length of time (t) the drug circulates through capillaries is another important factor. C and t are expressed as the plasma concentration-time integral and represent the driving force for blood-to-tissue transport. One can construct Cxt curves for various areas of the tumour and in the surrounding brain to evaluate the potential effectiveness of any given chemotherapeutic agent. The area under the txC curve expresses the total exposure of the tissue to the chemotherapeutic agent.

3) The permeability coefficient (P) of the capillaries with respect to the drug.

Lipid solubility is one of the most important factors that determines the permeability coefficient (P). There is a direct correlation between lipid solubility of a substance and its entry into the brain (Fig. 2). Lipid solubility can be estimated by the oil/water or octanol/water partition coefficient. Molecules with high oil/water or octanol/water partition coefficient show increased entry into the brain. Molecular weight also affects the permeability coefficient (P). For diffusion across the normal BBB, an equation relates the rate at which a compound passively crosses a lipid membrane:

$$P = \S(\text{lipid solubility})/(\text{molecular weight})^{1/2},$$

where § is a proportionality constant.

4) The total amount of drug that crosses the capillaries from blood into tissue is also dependent on the total surface area of the capillaries available for exchange per unit mass of tissue.

5) In addition, if drug transfer across the capillaries is rapid (highly lipid-soluble compounds) and dependent on the amount of drug brought to the capillaries by the arterial system, then the amount of drug which enters the brain is dependent on cerebral blood flow.

6) Once a drug enters the extracellular fluid, it can distribute within the parenchyma and it can be cleared from the tissue by several mechanisms: a) by efflux back into the blood; b) by metabolism to other active or inactive products and c) by transport into other tissue regions (e.g., CSF). As stated by Blasberg [37,38], each of these clearance mechanisms are as important as influx with respect to the time-course of drug concentration in the tumour and the overall exposure of the tumour cells to the drug.

It is possible to quantitatively evaluate the amount of drug which crosses brain capillar-

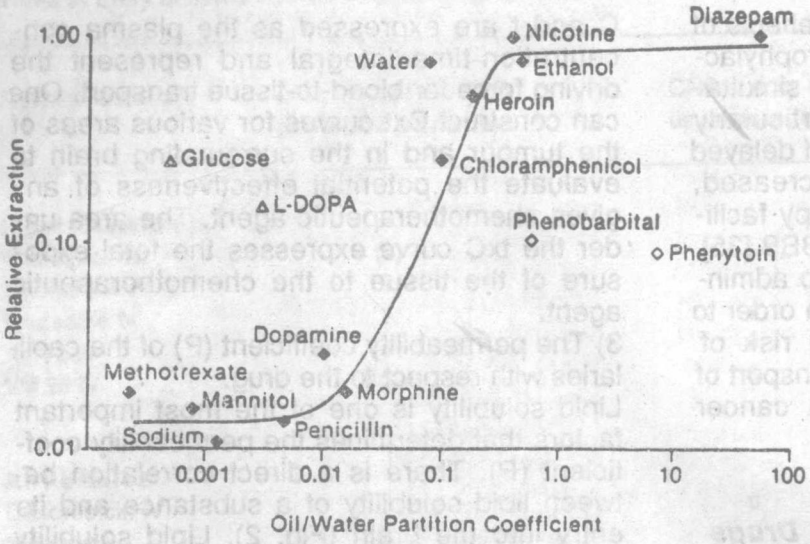

Fig. 2. Relationship between lipid solubility and brain uptake of selected compounds. In general, compounds with higher oil to water partition coefficients show increased entry into the brain. Uptake of the 2 anticonvulsants, phenobarbital and phenytoin, is lower than predicted from their lipid solubility partly because of their binding to plasma proteins. Uptake of glucose is greater than predicted from its lipid solubility because specific carriers facilitate its transport across the brain capillary. Reprinted from Goldstein GW and Betz AL [40]

ies in a unit mass of tissue over a given period of time, by using a simplified pharmacokinetic model. Ideally, one should calculate the permeability surface area product (PS, expressed in ml/g/min). However, PS cannot be measured directly by *in vivo* experiments. Nevertheless, one can measure a transfer rate constant (K) from the results of multiple passages of a substance through the capillaries which can be considered a plasma clearance constant. One can also calculate an extraction fraction (E) which represents the fraction removed from the blood in one capillary passage.

The technique of quantitative autoradiography has been used to measure the entry of chemotherapeutic agents into the normal brain and into experimentally-induced brain tumours. Studies using methotrexate, PCNU and cisplatin have been reported [41-43]. As expected, the entry of methotrexate like the entry of AIB is very low in the normal parenchyma and non-homogeneous in the tumour, being most marked where the BBB is most broken down. On the contrary, PCNU enters both tumour and normal brain in the distribution of blood flow. It is, of course, also non-homogeneous in the tumour since blood flow to a tumour, like blood-brain barrier disruption, is non-homogeneous. In humans, positron emission tomography studies have been performed with radiolabelled BCNU and cis-platinum [44]. BCNU, being a lipid-soluble agent, enters the brain in proportion to the blood flow to the area without regard to the presence or absence of a blood-brain barrier. Cis-platinum as a water-soluble agent enters in proportion to the degree of blood-brain barrier function with little relative to the blood flow.

Techniques Increasing Drug Entry into the Brain

There are several ways to overcome a low permeability through the BBB.

1) To increase the concentration gradient by using high dose, but this will also increase the systemic risk and sometimes also the neurotoxic risk. For example, it has not been demonstrated that the infusion of high-dose IV BCNU with bone marrow rescue in the treatment of primary malignant brain tumours was superior to standard treatment with IV BCNU, but some