Pharmacology of the Blood–Brain Barrier

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1. INTRODUCTION

All so-called permeability studies of the blood–brain barrier (BBB) actually measure one of several transfer constants (e.g., the extraction fraction) and not a true permeability coefficient. The permeability coefficient or, more simply, the permeability is classically defined as the flux (i.e., the rate of unidirectional solute flow) per unit membrane area divided by the driving forces for the flux, which are the concentration, pressure, and electrical gradients, in most cases. Experimental measurements of permeability involve an assessment of the flux across the membrane of predetermined surface area that separates two solutions of nearly identical composition. For the BBB, which is generally believed to be formed by the capillary endothelium, the classic definition of the permeability coefficient should be retained because it can be used to understand BBB function more clearly.

By contrast, the standard methods of measuring the permeability coefficient cannot be employed for the cerebral capillaries, since neither the capillary surface area nor the composition of the blood within the capillaries and the interstitial fluid surrounding them can be tightly controlled or precisely known.

These experimental complications for assessing BBB permeability arise for several somewhat obscure reasons. First, the number of perfused capillaries and thus the effective capillary surface area $S$ is uncertain for the system. Accordingly, the measured flux is for some unknown surface area of capillary membrane. Second, although the composition of arterial blood can be altered and measured, the actual composition of the fluid within the capillary varies as it passes along the capillary because of exchange across the BBB: the extent of this change in intracapillary fluid composition depends on the BBB permeability and effective distribution volume of each solute within the intracapillary fluid as well as the linear velocity of blood flow along the capillary. This means that the driving force for the flux across the BBB can only be estimated. For these and other reasons, the capillary
permeability coefficient within the brain cannot be directly measured, and the constant obtained is referred to as a transfer constant.

Although strict adherence to the principle that brain capillary permeability cannot be directly measured could be viewed as the "hangup" of an ideologue or purist, it has definite advantages, since it forces the investigator to consider other factors such as variations in capillary surface area and blood flow as causes of changes or differences in blood–brain exchange and to design experiments to evaluate the appropriate variables of the system. With this purpose in mind, a brief treatment of methods of measuring transfer constants and converting them into expressions of capillary permeability is presented first. Following this, mechanisms of transfer across the BBB, regional and local differences in these transfer processes, and finally drug distribution between blood and brain are discussed.

2. METHODS OF MEASURING DRUG TRANSFER

The parameters that can be measured when investigating blood–brain transport are the amounts of the test material in plasma and brain samples and the sampling times. One of three transfer constants—the extraction fraction \((E)\), the influx constant \((K_i)\), or the efflux constant \(k_o\)—is then calculated from these data. None of these constants is a membrane permeability coefficient per se; however a functional expression of capillary permeability that combines the two unknown variables that set the flux rate across the BBB, the permeability coefficient \(P\) and the effective capillary surface area \(S\), can be derived from them.26,27 This expression is known as the permeability–surface area or \(PS\) product.

The extraction fraction is determined by injecting a bolus containing both a test substance plus a reference material into one carotid artery and measuring brain uptake during the next several seconds. It is defined as

\[
E = \frac{B}{A}
\]

(1)

where \(B\) is the amount of test substance taken up by brain tissue and \(A\) is the total amount of extractable test material that has flowed into brain capillaries during the experimental period, as indicated by the reference material. The indicator diffusion,18,19 the brain-uptake index (BUI),53,54 and the external registration70 techniques are used to measure \(E\). Useful values of \(E\) are obtained by these three techniques when the capillary is moderately to highly permeable to the test material, the experimental duration is very short (usually less than 5 sec), and the backflux of test material from brain to blood is minute compared with the influx.26,27 The extraction fraction is the transfer constant which should be measured in most instances when dealing with a rapidly transformed drug or substrate.

The influx constant is measured in experiments in which the test solute is intravenously administered by either bolus injection32,33,51 or continuous infusion,3,9 and samples of plasma and central nervous system (CNS) tissue are obtained at various times thereafter. This constant is calculated from these data by the relationship

\[
K_i = \frac{B}{\int_0^T C_a(t)dt}
\]

(2)