eral to be higher than those of the other amino acids (26). The largest single arteriovenous difference was for valine and equaled 19.3 μmol/liter of blood. The total for all the amino acids was 125 μmol/liter. When this value is compared with an average arteriovenous difference for glucose of approximately 560 μmol/liter (144,147) and allowance is made for the fact that much if not most of the amino acid uptake is for synthesis of proteins, neurotransmitters, etc., rather than oxidation, it is clear that exogenously supplied amino acids contribute relatively little to the gross energy metabolism of the brain. Even in the starved patients studied by Owen et al. (102), in whom cerebral glucose consumption was reduced to half, the total arteriovenous difference for α-amino nitrogenous compounds was statistically insignificant and at most could account for less than 10% of the total oxygen consumption.

MEASUREMENT OF LOCAL CEREBRAL BLOOD FLOW

The rates of blood flow and metabolism presented in Tables 1-1 and 1-2 and discussed above represent the average values in the brain as a whole. The brain is a heterogeneous organ, however, and is composed of almost innumerable structures and tissues that often function independently or even inversely with respect to one another and consist of widely divergent structural elements. Correspondingly, their local rates of blood flow and energy metabolism vary widely but under physiological conditions are closely correlated with one another (150).

The measurement of local rates of cerebral metabolism will be discussed below. Most of the methods for the measurement of local rates of cerebral blood flow have been based on the principles of inert gas exchange between blood and tissues developed by Kety (65). All these methods utilize a freely diffusible, chemically inert radioactive tracer that exchanges freely between blood and cerebral tissues. They are generally referred to as tissue indicator equilibration techniques and are essentially the same, differing only with respect to the species of radioactive tracer utilized, whether the procedure is carried out during saturation of the tissues with the tracer or clearance of the tracer from the tissues, and the nature of the computational routine employed.

Theory of Tissue Indicator Equilibration Technique

Kety's (65) principles of inert gas exchange were first applied to the measurement of local cerebral blood flow by Kety and his associates (29,67,73). The method is ultimately based on the Fick Principle, which states that the rate of change of the amount of a chemically inert tracer substance in the tissue under study is equal to the difference between the amounts brought to the tissue in the arterial blood and removed from it in the venous blood. This relationship can be expressed as follows:

$$dQ_i/dt = F(Ca - Cv) \qquad (1\text{-}1)$$

where Q_i is the quantity of tracer in tissue, i, F is the rate of blood flow through the tissue, and Ca and Cv are the tracer concentrations in the arterial blood and representative venous blood draining the tissue, respectively.

Dividing by tissue mass W: $\frac{vol}{time}\,\frac{1}{mass}, \frac{mass}{vol}$

$$dCi/dt = F/W(Ca - Cv) \qquad (1\text{-}2)$$

where Ci equals the tissue concentration of tracer.

For tissues that are homogeneous with respect to tissue perfusion rate and solubility of tracer, Kety (65) derived the following relationship between the tissue arteriovenous and arterial-tissue concentration differences:

$$(Ca - Cv) = m(Ca - Ci/\lambda) \qquad (1\text{-}3)$$

where λ equals the tissue/blood partition coefficient (Chapter 7) for the tracer and m is a constant between 0 and 1 that represents the net effect of diffusion limitations, capillary impermeability, arteriovenous shunts, and all other factors that might tend to limit the equilibration of the tissue with the blood perfusing it. In the absence of diffusion limitations, $m = 1$, and Eq. 1-3 simplifies to

$$Cv = (Ci/\lambda) \tag{1-4}$$

Substituting Eq. 1-3 into Eq. 1-2:

$$dCi/dt = \frac{mF}{\lambda W}(\lambda Ca - Ci) \tag{1-5}$$

Let $K = mF/\lambda W$, the so-called clearance constant.

Integrating Eq. 1-5 between time 0 and time T:

$$Ci(T) = Ci(0)e^{-KT} + \lambda K e^{-KT}\int_0^T Ca(t)e^{Kt}\,dt \tag{1-6}$$

Equation 1-6 is the general equation for all conditions for time courses of the arterial curve. In studies carried out during desaturation following a period of saturation, Eq. 1-6 can be used with the second term on the right side of the equation correcting for recirculation. Zero time is then the time of the onset of desaturation. This is the form generally used in ^{133}Xe clearance studies of regional cerebral blood flow in humans (77). If Ca drops to zero at ~~zero~~ some time after a period of saturation, as is approximately so after an intracarotid injection of radioactive inert gas, then Eq. 1-6 reduces to

$$Ci(T) = Ci(0)e^{-KT} \tag{1-7}$$

The method has generally been applied during saturation when used with autoradiography in animals. In that case $Ci(0)$ equals zero, and Eq. 1-6 reduces to

$$Ci(T) = \lambda K e^{-KT}\int_0^T Ca(t)e^{Kt}\,dt \tag{1-8}$$

or, alternatively,

$$Ci(T) = \lambda K\int_0^T Ca(t)e^{-K(T-t)}\,dt \tag{1-9}$$

Equations 1-8 and 1-9 are the basis of the autoradiographic technique for measuring local cerebral blood flow. They state that if the time course of the arterial concentration of the tracer between time 0 and time T is measured, the tissue/blood partition coefficient is known, and the local tissue concentration of tracer at time T is measured, then the local clearance constant K can be computed. If there are no arteriovenous shunts and no diffusion limitations (i.e., $m = 1$), then the local blood flow can be calculated from the clearance constant by the relationship

$$K = mF/\lambda W$$

If the complete time course of the local tissue tracer concentration can also be measured, as it can with emission tomography, then the integrated form of Eq. 1-8 can be used. Thus

$$\int_0^T Ci(t)\,dt = \lambda\left[\int_0^T Ca(t)dt - e^{-KT}\int_0^T Ca(t)e^{Kt}\,dt\right] \tag{1-10}$$

[^{131}I]Trifluoroiodomethane Technique

Procedure

The first method for the measurement of local cerebral blood flow by the tissue indicator equilibration technique was the [^{131}I]trifluoroiodomethane ([^{131}I]CF_3I) technique (29,73). The tracer was the radioactive, relatively chemically stable gas, which could diffuse freely through the blood-brain barrier. The species was the cat. The tracer was administered by continuous intravenous infusion of a solution of the tracer in blood or physiological saline for 1 min during which timed arterial samples were