

## Reaction Volume Concept

**TO THE EDITOR:** We wish to respond to several issues raised by Wong and Gjedde in their recent editorial (1) that accompanied our article on the concept of the reaction volume ( $V_R$ ) in the vivo ligand receptor model (2). We agree with their discussion about compartmental model analysis and with the equilibrium definitions [in our article, equilibrium refers to the "transient" equilibrium concept reaction described in Wong and Gjedde's editorial (1)]. However, we disagree with their analysis about the  $V_R$  concept.

The  $V_R$  is precisely defined in our article [see Eq. 6 (2)] by the ratio between the mean concentration of the free ligand in 1 ml of tissue [denoted by  $M_F(t)$ ] and the local free ligand concentration in the receptor site vicinity [denoted by  $C_{F,rec}(t)$ ]. This definition clearly indicates that the  $V_R$  is not related to the ligand concentration in the plasma or to the exchanges between blood circulation and tissue.

Therefore, it is surprising that Wong and Gjedde conclude that "the concept of  $V_R$  is in reality none other than the mathematical description of the different free fractions in plasma and brain tissue". It is true that the relationships between  $V_R$  and the various distribution volume concepts or other combined parameters can be derived under particular conditions. For example, our Equation 8 gives a relationship between  $V_R$  and  $V_{DF}$  (the distribution volume of the free ligand), assuming that the equilibrium state is quickly reached, and shows that, under this hypothesis, the ratio of  $V_R$  over  $V_{DF}$  is a constant independent of time. However, such relationships (which can include the plasma ligand concentration) cannot be considered as a definition for  $V_R$ .

Wong and Gjedde suggest the use of physical distribution volume denoted by  $V_d$ . This volume  $V_d$  is defined by  $\lambda_F V_{DF}$  with our notations (1). From Equation 8 in our article, we immediately deduce that  $V_d = V_R$ , if the free ligand concentration in the capillary wall vicinity (denoted by  $C_{F,cap}$ ) is equal to the concentration in the receptor site vicinity ( $C_{F,rec}$ ). This condition is implicitly assumed in the usual compartmental model. The main interest of the  $V_R$  concept is to precisely take into account a possible heterogeneity of the concentration in the free ligand compartment (i.e.,  $C_{F,cap} \neq C_{F,rec}$ ).

Another important consequence of our definition is that the  $V_R$  is not a function of the complexity of the compartmental model. Let us assume that a complex model relying on many free ligand subcompartments is needed to adequately describe the kinetics of the free ligand between the capillary wall and the receptor sites. First, the  $V_R$  is only a function of the free ligand concentration in the subcompartment, which represents the vicinity of the receptor sites [ $C_{F,rec}(t)$ ], and second, it is a sum in a unit volume of the ligand quantities present in all free ligand subcompartments (which corresponds to the mean free ligand concentration  $M_F(t)$  in the global free ligand compartment). The first concentration is the concentration that we have to take into account in the binding reaction; the second one is the concentration which is used in the usual mathematical model of the ligand-receptor interactions. In our Figure 2, the double line between the two subcompartments  $C_{F,cap}$  and  $C_{F,rec}$  indicated that the complexity of the kinetics between these two compartments are unknown and are not taken into account in the  $V_R$  definition.

Therefore, it is never said in our article (2) that there are only two compartments and that "the entire gradient is at the interface between these

two compartments" as reported by Wong and Gjedde (1). Moreover, the heterogeneity may not only be the results of concentration gradients resulting from a nonequilibrium state. For example, biological membranes or different local tissue properties (such as local lipophilicity) can lead to local heterogeneities even in steady-state conditions.

Obviously, the  $V_R$  concept can be discussed. As noted by Wong and Gjedde (1), there is no experimental evidence that the  $V_R$  is of a constant magnitude with time. In our article,  $V_R$  is assumed to be constant since the equilibrium state inside the free ligand compartment is assumed to be quickly reached. The same difficulty is present, and thus the same hypothesis is needed in the distribution volume concept.

It is also true that a common glossary of terms is needed, as suggested by Wong and Gjedde (1). However, the multiplicity of the terms mainly shows the multiplicity of the possible biological interpretations of the parameters introduced in the model. One of the interests of the  $V_R$  concept is that it can help in summarizing the global effect of free ligand concentration heterogeneity on the binding reaction, whatever the complexity of this heterogeneity, without imposing particular biological explanations that are always difficult to support. Several examples given in our article (2) show the interest of the  $V_R$  concept and tend to illustrate it.

Jacques Delforge

André Syrota

Bernard Bendriem

C.E.A., Atomic Energy Commission

Service Hospitalier Frédéric Joliot

Orsay, France

## REFERENCES

1. Wong D, Gjedde A. Compartments and reaction volume of brain fluid spaces: shaken, not stirred. *J Nucl Med* 1996;37:126-127.
2. Delforge J, Syrota A, Bendriem B. Concept of reaction volume in the in vivo ligand-receptor model. *J Nucl Med* 1996;37:118-125.

**REPLY:** We thank Dr. Delforge for clarifying the definition of the  $V_R$  that he uniquely defines as the ratio between the quantity of ligand available for binding and the concentration of ligand so available in the pool immediately adjacent to the binding sites. Even at steady-state, he claims, this concentration need not be equal to the concentration of the ligand in the tissue water adjacent to the vascular wall, or to the average tissue water concentration at any time. The concept divides the tissue pool of unbound ligand into two or more compartments, as illustrated by the double line in Dr. Delforge's Figure 2. We did not limit the number of possible compartments generated by this concept to two.

In computed tomography, so-called tissue "free fractions" are defined as the reciprocals of volumes. These fractions are necessary because tissue concentrations cannot be measured tomographically in vivo. The commonly used average tissue free ligand "fraction"  $f_2$  is assumed to be the ratio between the concentration of the ligand in tissue water ( $C_{e_{aq}}$ ) and the total mass of unbound, i.e., exchangeable, ligand in the tissue ( $M_e$ ),

$$f_2 = C_{e_{aq}}/M_e \quad \text{Eq. 1}$$

The free fraction in blood plasma is assumed to be the ratio between the concentration of the ligand in plasma water ( $C_{p_{aq}}$ ) and the concentration of the ligand actually measured in arterial whole-blood or plasma ( $C_a$ ), which is a true fraction,

$$f_1 = C_{p,q}/C_a.$$

Eq. 2

plasma, or plasma water concentrations of the ligand, in practice the definition does not preclude a possible physiological influence of these concentrations.

Similarly, the free "fraction" of ligand in the  $V_R$  could be,

$$f_R = C_{F,rec}/M_e,$$

Eq. 3

which illustrates our point that *the concept of the  $V_R$  is based on the mathematical description of the various and possibly varying free fractions in plasma and tissue*. In case of tissue, the reciprocal "fractions" define volumes that differ if the solvent concentrations differ.

Although the definition of the  $V_R$  has no reference to the whole-blood,

**Albert Gjedde**

*Aarhus University Hospitals*

*Aarhus, Denmark*

**Dean F. Wong**

*Johns Hopkins Medical Institutions*

*Baltimore, Maryland*