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Letter To Editor
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DRUG – PROTEIN BINDING

(Some care must be taken to determine the value of K_B correctly in the special case of r=1)

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The binding of a drug to its target protein is the event that leads to medicinal activity. Therefore, the amount of drug - protein complex formed by a drug ultimately determines the medicinal effects displayed by that compound.

This is described by a simple equilibrium reaction.

$D + P \rightleftharpoons DP$ With dissociation constant

$K = [D][P]/[DP]$ (1)

In this equation $[D] = [D]_T - [DP]$ and $[P] = [P]_T - [DP]$

Where $[D]_T$ and $[P]_T$ are the initial total concentrations of the drug and protein, respectively.

Using the equilibrium relationship $K[DP] = [D][P]$ and

Substituting, $[P] = [P]_T - [DP]$

Gives: $K[DP] = [D]\{[P]_T - [DP]\}$

From which, bound fraction, F_{BP}, of the protein is given by: $F_{BP} = [DP] / [P]_T = [D] / K + [D]$ (2)

On the other hand,

Using the equilibrium relationship $K[DP] = [D][P]$ and

Substituting, $[D] = [D]_T - [DP]$

Gives: $K[DP] = [P]\{[D]_T - [DP]\}$ from which, bound fraction,

F_{BD}, of the drug is given by: $F_{BD} = [DP] / [D]_T = [P] / K + [P]$ (3)

Dividing Eq. (2) by (3) we thus get

$$F_{BP} / F_{BD} = [D]_T / [P]_T = [D]\{K + [P]\} / [P]\{K + [D]\}$$

Setting $[D]_T = [P]_T = [X]_T$, along with $[D] = [P] = [X]$, then above expression turns into

$[X]_T / [X]_T = [X]\{K + [X]\} / [X]\{K + [X]\}$ which is just a tautology, 1=1.

We think this makes sense intuitively: if the starting (total) concentrations of drug and protein are equal, then it is easy for the free concentrations to be equal. However, if the starting concentrations are unequal, then it is hard for the free concentrations to be equal.

If we set now

$$[D] / [P] = r$$

Then we get

$$F_{BP} / F_{BD} = r\{K + [P]\} / \{K + [D]\}$$

Or $F_{BP}\{K+[D]\} = r\,F_{BD}\{K+[P]\}$

Or $F_{BP}K + F_{BP}[D] = r\,F_{BD}K + [D]\,F_{BD}$

On rearrangement this leads to

$$K\{F_{BP} - r\,F_{BD}\} = [D]\{F_{BD} - F_{BP}\}$$

Or $$K/[D] = \{F_{BD} - F_{BP}\}/\{F_{BP} - r\,F_{BD}\} \quad (4)$$

Right after this expression, we reach the conclusion that, when r=1, it follows that K = 0. This implies a situation in which all the protein is completely bound up in drug-protein complexes. It is a limiting case in which the binding constant $K_B = 1/K$ is infinite.

From Eq. (1) K_B follows as

$$K_B = [DP]/[D][P]$$

If we set now

$$[P] = [D]/r$$

Then the above expression turns into

$$K_B = r[DP]/[D]^2$$

When r =1, it follows that

$$K_B = [DP]/[D]^2$$

However, in special case of r=1, K_B does not need to be infinite, because we just showed above that, for r=1, $K_B = [DP]/[D]^2$. Therefore, it is not a given that K_B will go infinity; indeed some care must be taken to determine the value of K_B correctly in the special case of r=1.

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