Pharmacokinetics of binding of single ligand to multiple receptors

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The distinctions between enzymes, transporters, and receptors fade, as novel findings show that specific proteins share properties of all three functions, albeit in different proportions. The subtle differences among some proteins have huge consequences for the function of the proteins. The substantial effects on function necessitate the consideration of multiple proteins with subtly varying properties at the same time. Hence the discipline of multireceptor pharmacology shares with neuroenergetics the position as one of the fastest developing topics of current neuroscience.

As the rich pharmacology of dirty drugs, multireceptor pharmacology has two focal points: The potentially beneficial effect(s) of less selective drugs on brain function, and the classification of brain tissues and states in terms of their multiplicity of receptors. In analogy to Brodmann's map, increasingly detailed receptor distributions provide increasingly distinct tissue and state classifications. Because the state classifications have great functional relevance, they supplement the more conventional histopathology. Multireceptor profiles represent a uniquely dynamic classification of brain regions and brain states and in addition provide a template for potential pharmacological intervention.

The pharmacokinetics of multireceptors is similar to that of single receptors, except that there is much more of it. The key measurement is that of the binding potential, which is defined as the ratio of the numbers of bound and exchangeable ligand molecules (p_B). The equations to the right indicate that the total binding to a multiplicity of receptors is the product of the concentration of the common ligand, the sum of binding potentials of each receptor in the absence of the ligand, and the weighted fraction of free receptors. Assuming the effect of a pharmacological intervention to be proportional to the total binding of the drug at all receptors, the equations relate the effect to the concentration of the drug, the binding potentials in the absence of the drug, and the current multireceptor "profile", σ_w.

$$p_B = \frac{B}{C} = \frac{\sum_{i=1}^{n} B_i}{C}$$

$$p_B = \sum_{i=1}^{n} \left(\frac{B_{max_i}}{C + K_{d_i} \left(1 + \sum_{j=1}^{m} \frac{C_{j,i}}{K_{j,i}}\right)} \right)$$

$$p_B = \sum_{i=1}^{n} \left(\frac{\frac{B_{max_i}}{K_{d_i}}}{1 + \frac{C}{K_{d_i}} + \sum_{j=1}^{m} \frac{C_{j,i}}{K_{j,i}}} \right)$$

$$p_B = \sum_{i=1}^{n} \left(\frac{p_{B_{o_i}}}{1 + \chi + \sum_{j=1}^{m} \chi_{j,i}} \right)$$

$$p_B = \sum_{i=1}^{n} \left(p_{B_{o_i}} \left[\frac{1 - \sigma_i}{1 + \sum_{j=1}^{m} \chi_{j,i}} \right] \right)$$

$$p_B = p_{B_I} - \sum_{i=1}^{n} \left(p_{B_{I_i}} \sigma_i \right)$$

$$p_B = p_{B_I} \left(1 - \sum_{i=1}^{n} (f_i \ \sigma_i) \right)$$

$$p_B = p_{B_I} \ (1 - \sigma_w)$$

$$B = p_{B_I} \ (1 - \sigma_w) \ C$$

$$\sigma_w = \sum_{i=1}^{n} (f_i \ \sigma_i) = \sum_{i=1}^{n} \left(\frac{f_i \ C}{C + K_{I_i}} \right)$$

$$\sigma_w^* \approx C^* \ \sum_{i=1}^{n} \left(\frac{f_i}{K_{I_i}} \right)$$

$$B^* \approx p_{B_I} \ (1 - \sigma_w^*) \ C^*$$

The profile of the binding to the multiplicity of receptors is also the weighted receptor occupancy. The profile can be rewritten in a form in which K_I is the IC50 of the ligand at each receptor, dictated by competitors of the receptors. By definition, a tracer is a ligand with no pharmacologically active mass. Tracers further simplify the multireceptor kinetics and show that the radioligand profile depends on competitors, while the pharmacokinetic profile depends on the ligand concentration as well as the competitor concentrations. Hence, multi-receptor profiles are dynamic and unstable.

Multireceptor profiling is important to the pharmacological treatment of brain disorders because the profile dictates the relations to the receptors in the profile. Profiles can range from the subtypes of a single receptor to a large selection of major receptor groups. Examples of the former include the radioligands raclopride and N-methylspiperone (NMSP), which bind to the respective $D_{2\text{-}3}$ and $D_{2\text{-}4}$ subtypes of the D_2-like dopamine receptors, while examples of the latter include the radioligand mirtazepine, which binds to a multitude of receptors with different half-inhibition constants, as shown in Panel 5.

A simple confirmation of the multireceptor equations is obtained with tracer raclopride and a selective antagonist of the D_3 dopamine receptor subtype. As raclopride binds to the D_2 and D_3 subtypes, while the antagonist binds only to the D_3 subtype, n=2 in the summation, and σ_1 (for i=1) is zero for the D_2 subtype. The regression of the p_B/p_{BI} ratio to the concentration of the D_3 antagonist yielded estimates of f_2 of 0.05 and of K_{I2} of 3.1 pmol g^{-1} in striatum, as shown in Panel 4.

A number of drugs fall into the category of ligands of a multitude of major receptor groups. An example is mirtazapine, which enjoys the affinities shown in Panel 5. Assuming for argument's sake that the major receptor groups of mirtazapine have approximately similar numbers of binding sites in the brain as a whole, the binding profile can be calculated from these affinities for a spectrum of concentrations varying from the lowest K_I value to the highest K_I value shown above in Panel 5. It is clear from this graph that the distribution of the bound radioligand varies greatly at different concentrations of the drug.