The University of Manchester
Wolfson Molecular Imaging Centre

IMAGe meeting

Journal Club

Consensus nomenclature for *in vivo* imaging of reversibly binding radioligands

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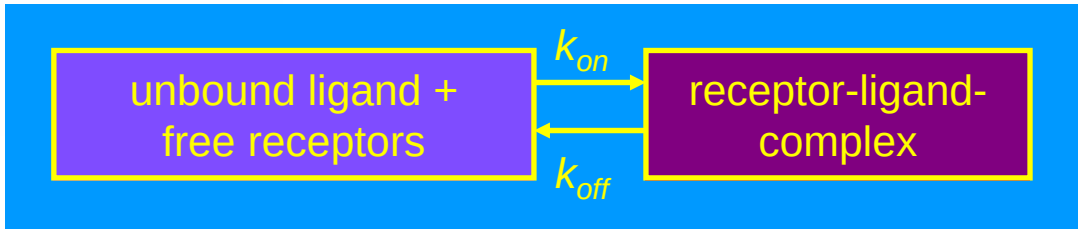
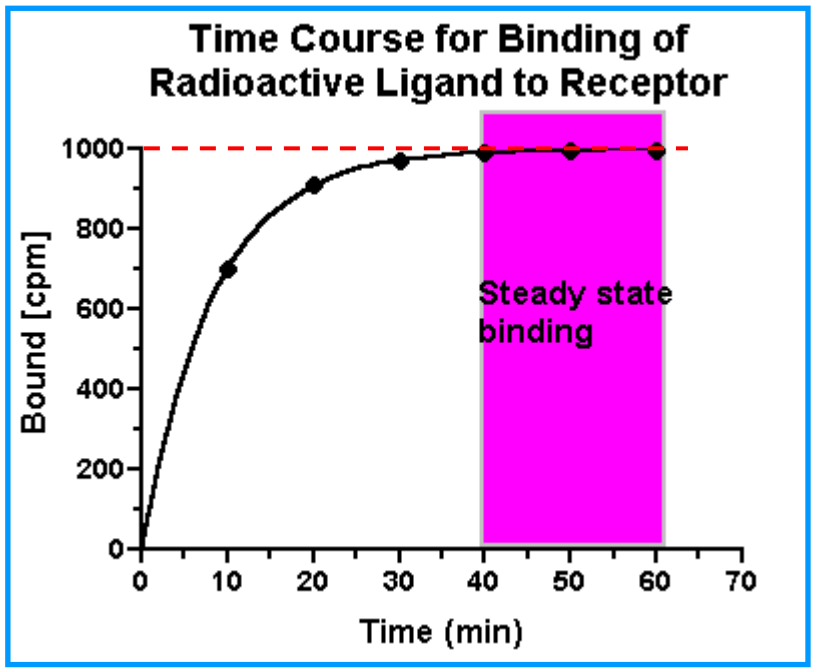
Innis, R.B.; Cunningham, V.J.; Delforge, J.; Fujita, M.; Gjedde, A.; Gunn, R.N.; Holden, J.; Houle, S.; Huang, S.-C.; Ichise, M.; Iida, H.; Ito, H.; Kimura, Y.; Koeppe, R.A.; Knudsen, G.M.; Knuuti, J.; Lammertsma, A.A.; Laruelle, M.; Logan, J.; Maguire, R.P.; Mintun, M.A.; Morris, E.D.; Parsey, R.; Price, J.C.; Slifstein, M.; Sossi, V.; Suhara, T.; Votaw, J.R.; Wong, D.F.; Carson, R.E. Consensus nomenclature for *in vivo* imaging of reversibly binding radioligands. *J. Cereb. Blood Flow Metab.* 27 (2007), 1533 – 1539.

1. Introduction: receptor autoradiography

Reversible binding of a ligand to a receptor (in vitro binding assay):



$$[L] + [R] \underset{k_{off}}{\overset{k_{on}}{\rightleftharpoons}} [RL]$$



law of mass action:

$$\frac{d\,[RL]}{d\,t} = k_{on} \cdot [L] \cdot [R] - k_{off} \cdot [RL]$$

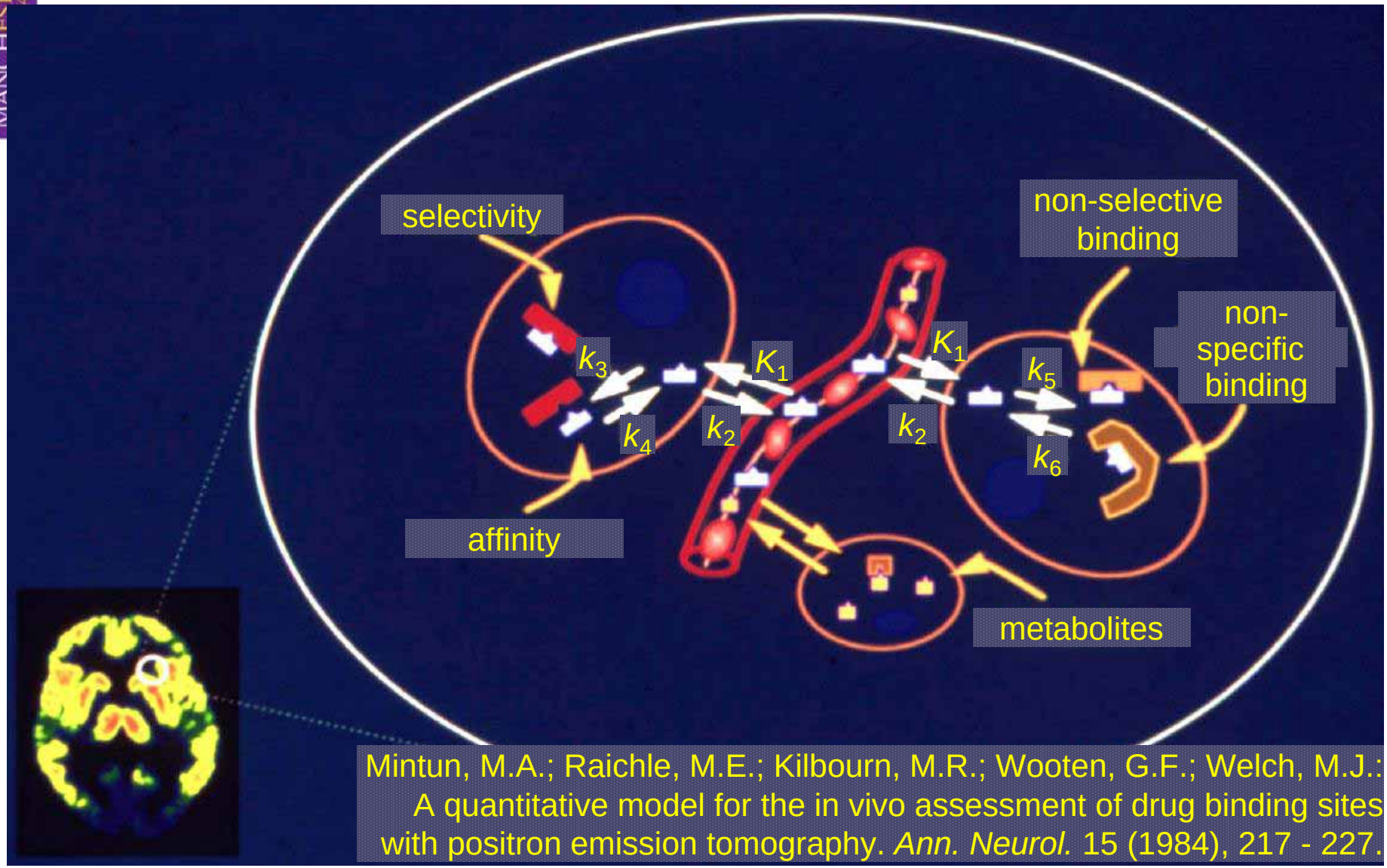
dissociation constant: $K_D = \frac{k_{off}}{k_{on}}$

maximum binding capacity (total number of receptors): $B_{max} = [R] + [RL]$

$$\frac{d\,[RL]}{d\,t} = k_{on} \cdot [L] \cdot (B_{max} - [RL]) - k_{off} \cdot [RL]$$

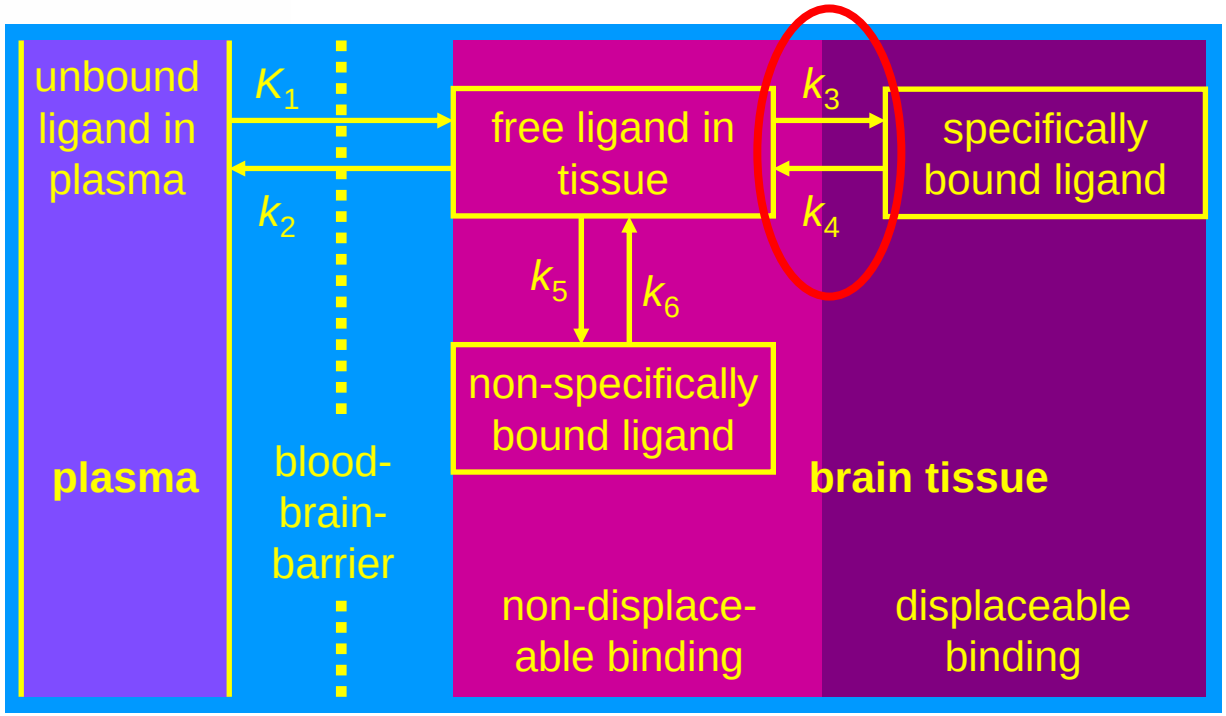
in PET: k_3 in PET: k_4

2. The standard model for receptor studies with PET



Mintun, M.A.; Raichle, M.E.; Kilbourn, M.R.; Wooten, G.F.; Welch, M.J.: A quantitative model for the in vivo assessment of drug binding sites with positron emission tomography. *Ann. Neurol.* 15 (1984), 217 - 227.

2. The standard model for receptor studies with PET



free fraction in plasma: f_P

free fraction in brain tissue: $f_{ND} = \frac{1}{1 + \frac{k_5}{k_6}}$

at thermodynamic equilibrium: $\frac{f_P}{f_{ND}} = \frac{K_1}{k_2}$

influx rate constant: $K_1 = F \cdot E$

blood flow F

extraction $E = 1 - e^{-\frac{PS}{F}}$

product of permeability and capillary surface area PS

rate constants: $k_2 \ldots k_6$

binding potential:

$$BP_F = \frac{B_{max} - [RL]}{K_D} = \frac{k_3}{k_4}$$

volume of distribution:

$$V_{FT} = \frac{K_1}{k_2}$$

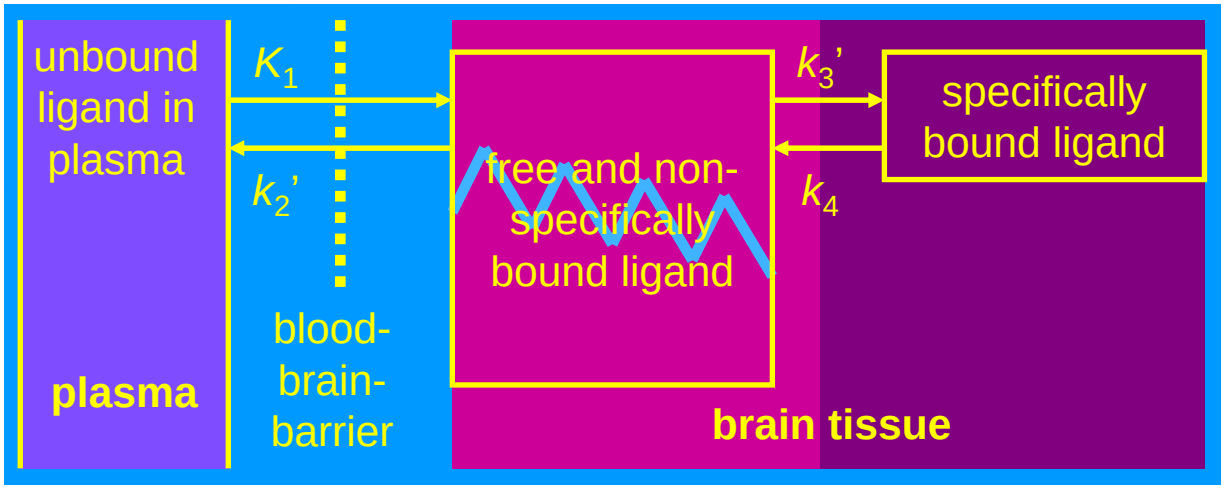
$$V_{ND} = \frac{K_1}{k_2} \cdot \left(1 + \frac{k_5}{k_6} \right)$$

$$V_T = \frac{K_1}{k_2} \cdot \left(1 + \frac{k_3}{k_4} + \frac{k_5}{k_6} \right)$$

$$V_T = V_{ND} \cdot (1 + f_{ND} \cdot BP_F)$$

$$BP_{ND} = \frac{V_T}{V_{ND}} - 1$$

3. Simplified models for receptor studies with PET

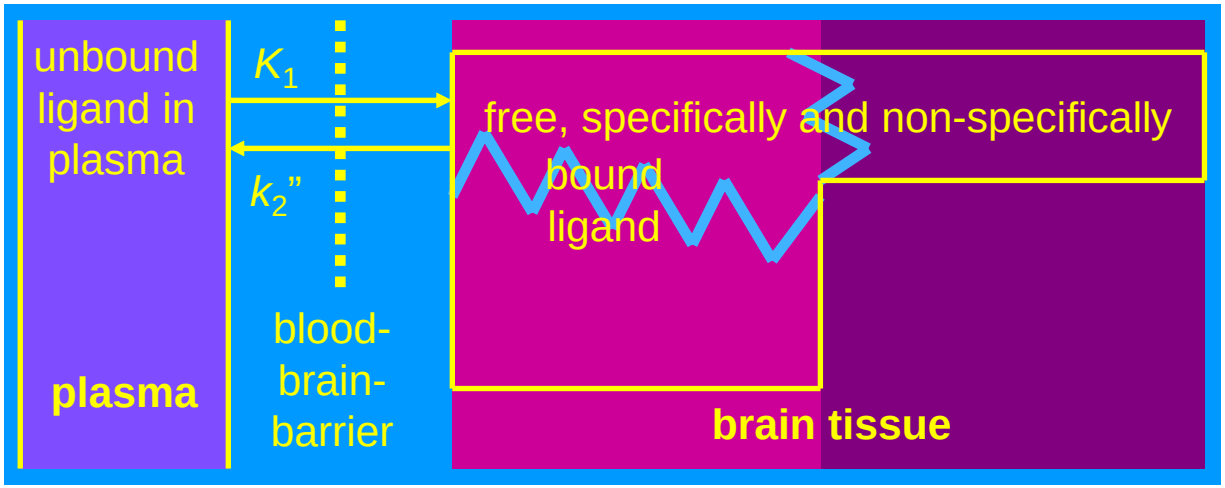


Two-tissue compartment model:

$$k_2' = k_2 \cdot f_{ND} \qquad k_3' = k_3 \cdot f_{ND}$$

$$V_{ND} = \frac{K_1}{k_2'}$$

$$V_T = \frac{K_1}{k_2'} \cdot \left(1 + \frac{k_3'}{k_4}\right)$$



One-tissue compartment model:

$$k_2'' = \frac{k_2'}{1 + \frac{k_3'}{k_4}}$$

$$V_T = \frac{K_1}{k_2''}$$

Koeppe, R.A.; Holthoff, V.A.; Frey, K.A.; Kilbourn, M.R.; Kuhl, D.E.: Compartmental analysis of [^{11}C]flumazenil kinetics for the estimation of ligand transport rate and receptor distribution using positron emission tomography. *J. Cereb. Blood Flow Metab.* 11 (1991), 735 - 744.