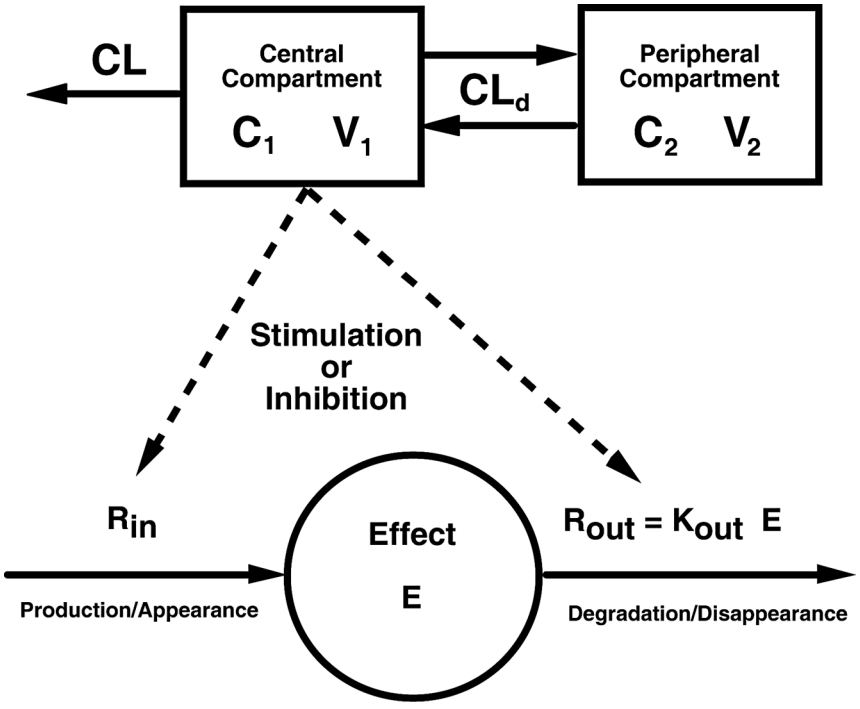

Figure 10 Pharmacodynamic indirect effect model wherein the effect is maintained by equilibrium between a zero-order appearance rate, R_{in}, and a first-order disappearance rate, R_{out}. A drug effect is caused by stimulation or inhibition of R_{in} or R_{out}. The degree of stimulation or inhibition is dependent on the plasma drug concentration. The PD parameters are R_{in}, K_{out} (the first order rate constant for effect disappearance), EC_{50} (the concentration that produces 50% of maximum inhibition or stimulation), and E_{max} (the maximum inhibition or stimulation). The pharmacokinetic model is identical as in Fig. 7. For filgrastim (see Fig. 9), R_{out} is transiently stimulated in the first hour after dosing and R_{in} is stimulated later on causing an increase in neutrophil count after chronic dosing. In addition, the elimination clearance is inhibited by the effect.

5. PROTEIN BINDING OF PROTEIN THERAPEUTICS

The binding of drugs to circulating plasma proteins can influence both the distribution and clearance of drugs, and consequently their pharmacodynamics. Since it is generally accepted for small drug molecules including small proteins that only the unbound drug molecules can pass through membranes, distribution and elimination clearances of total drug are usually smaller than those of free drug. Accordingly, the activity of the drug is more closely related to the unbound drug concentration than to the total plasma