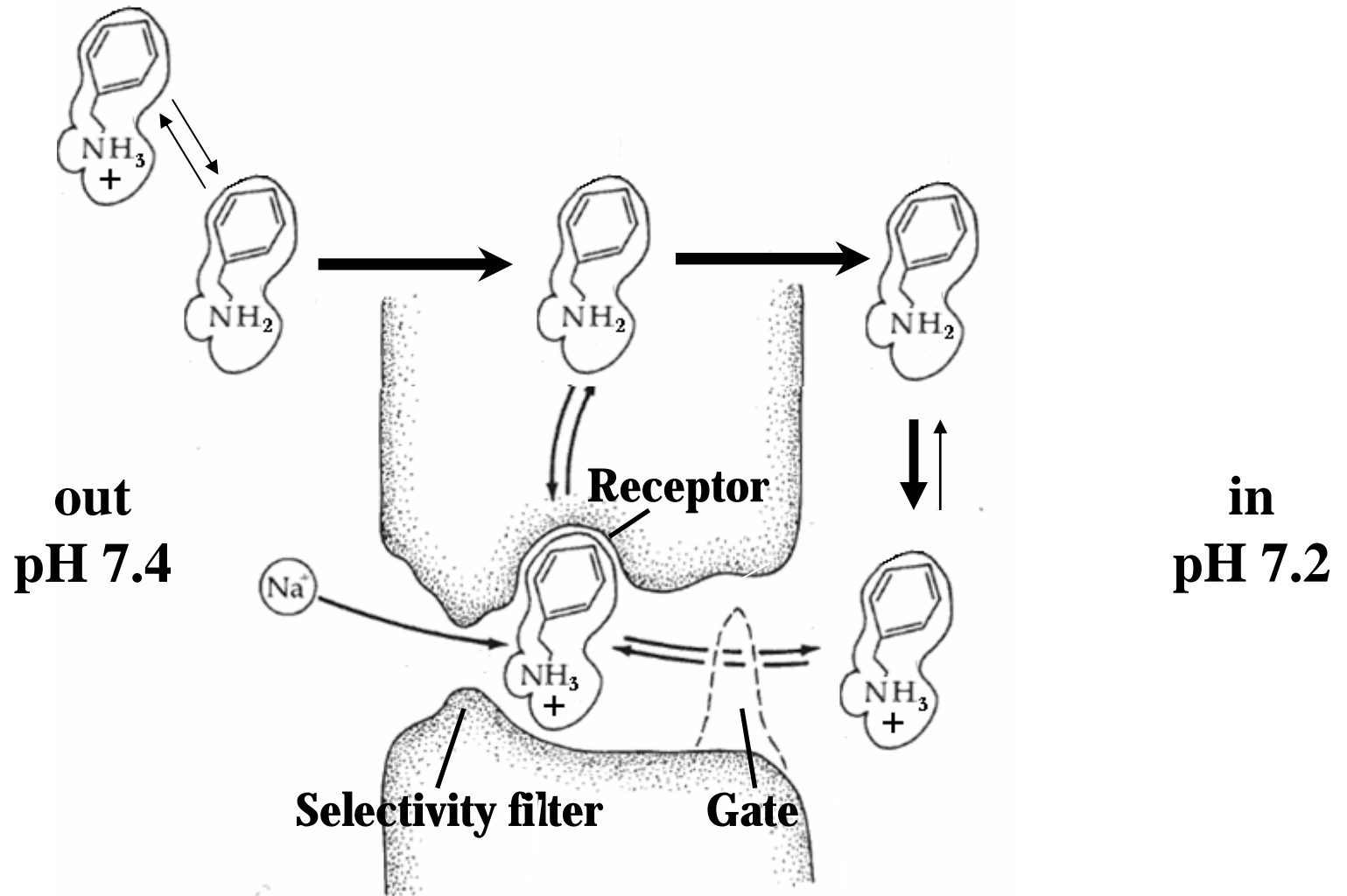
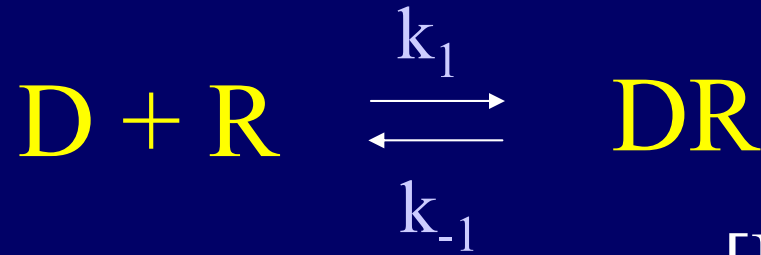


DRUG-CHANNEL INTERACTION

Drug access to its binding site



Drug-receptor interaction



$$\% \text{ block (R occupancy)} = \frac{[DR]}{[DR] + [R]}$$

$$\text{affinity } K = \frac{k_1}{k_{-1}} = \frac{[DR]}{[D][R]} \quad ; \quad [DR] = K [D] [R]$$

With a finite number of R:

$$\text{block} \propto [DR] \propto K [D]$$

affinity
constant

drug
concentration

	Charged drug	Neutral drug
For a given level of plasma [D], local [D] may depend on	<ul style="list-style-type: none"> •in/out [D] •channel state •strength of V field 	drug lipid/water partition
K may depend on	channel conformation (state)	channel conformation (state)

Term definitions

Direct

channel blockade is directly proportional to “usage” (or heart rate)

Use-dependency

drug effect (block) depends on channel “usage”

Rate-dependency:

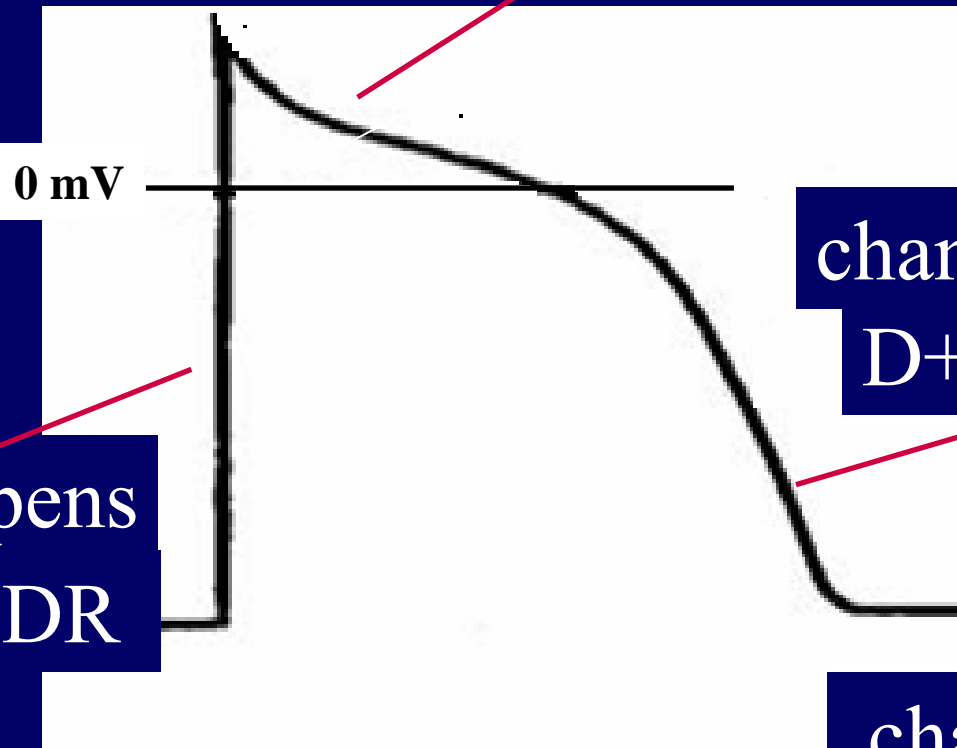
drug effect depends on heart rate

Reverse

channel blockade inversely proportional to “usage” (or heart rate)

Binding cycle of a Na-channel blocker (with direct rate-dependency)

inactivating channel



channel opens



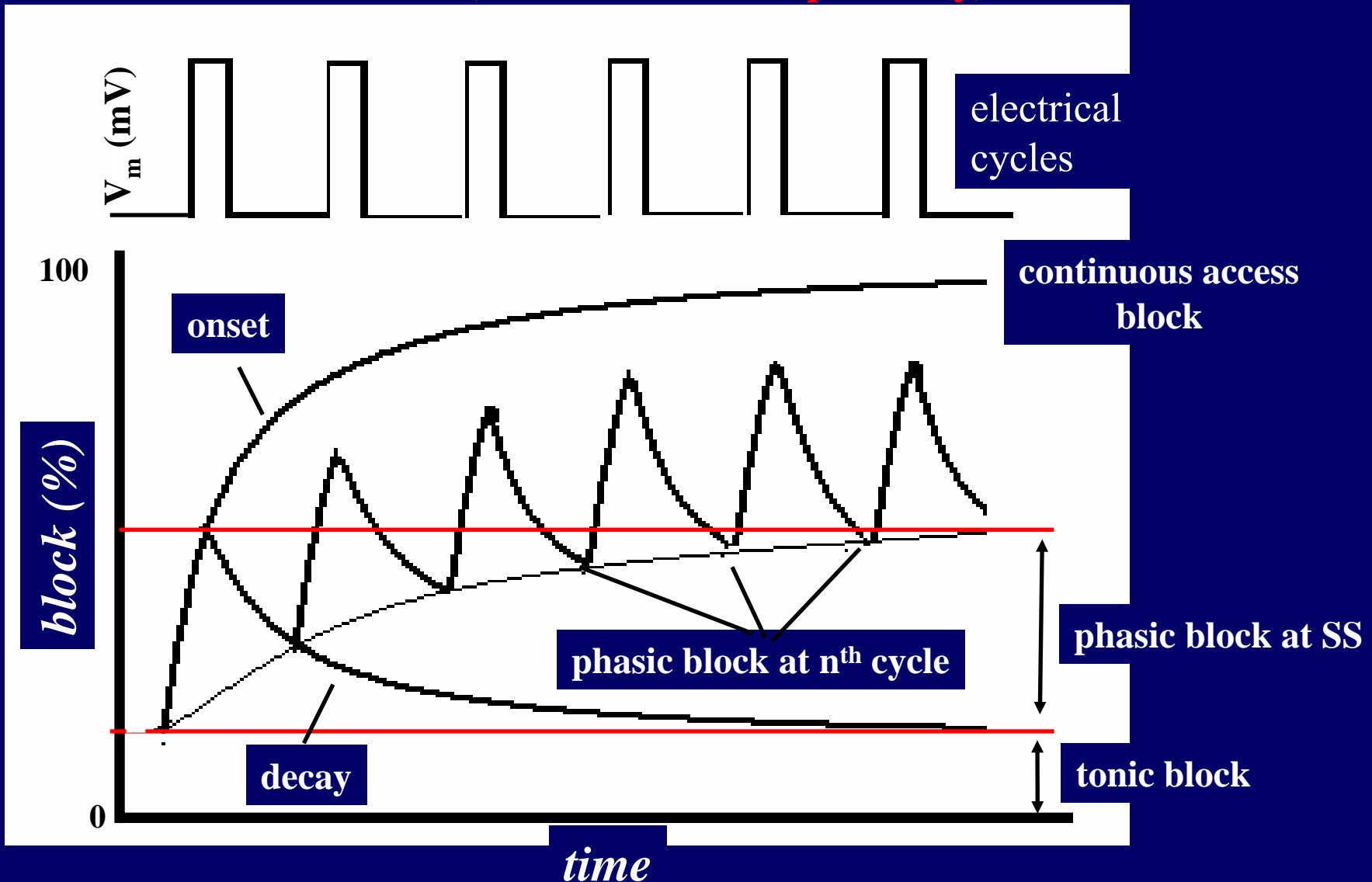
channel recovers



channel closed



Rate-dependent channel block (with direct rate-dependency)



“Reverse rate-dependency” of APD modulation

