ФАРМАЦЕВТИЧЕСКАЯ ХИМИЯ
ЛЕКЦИЯ 5

Основные понятия фармацевтической химии. Фармакокинетика. Фармакодинамика. Молекулярные мишени.

Фармакокинетика (от др.-греч. *φάρμακον* — лекарство и *κίνησις* — движение) — раздел фармакологии, изучающий кинетические закономерности химических и биологических процессов, происходящих с лекарственным средством в организме.

Иначе говоря, фармакокинетика — это судьба отдельно взятой молекулы лекарственного вещества (биохимическая трансформация молекул лекарства в организме).

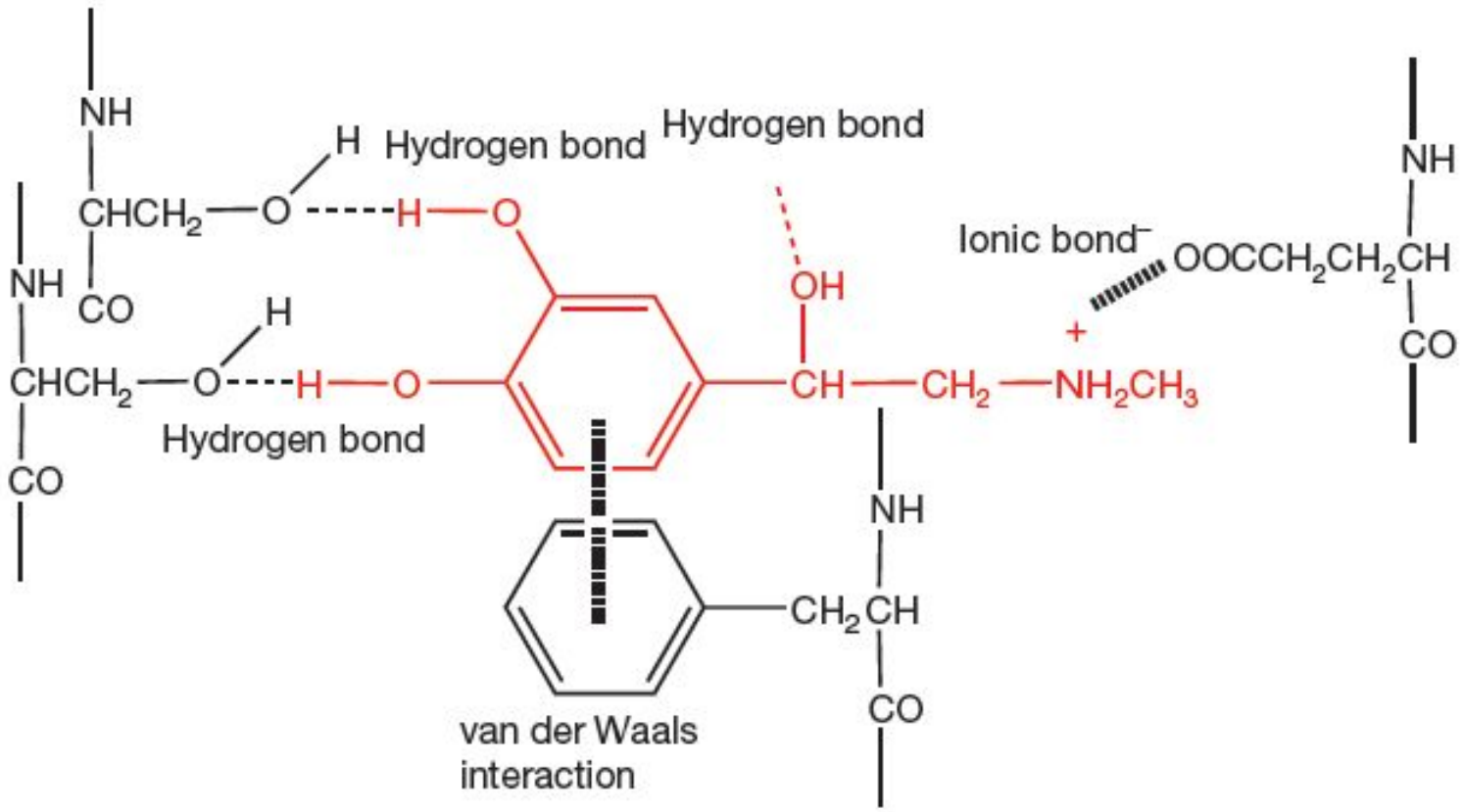
Основные фармакокинетические процессы: всасывание, экскреция (выведение), распределение и метаболизм.

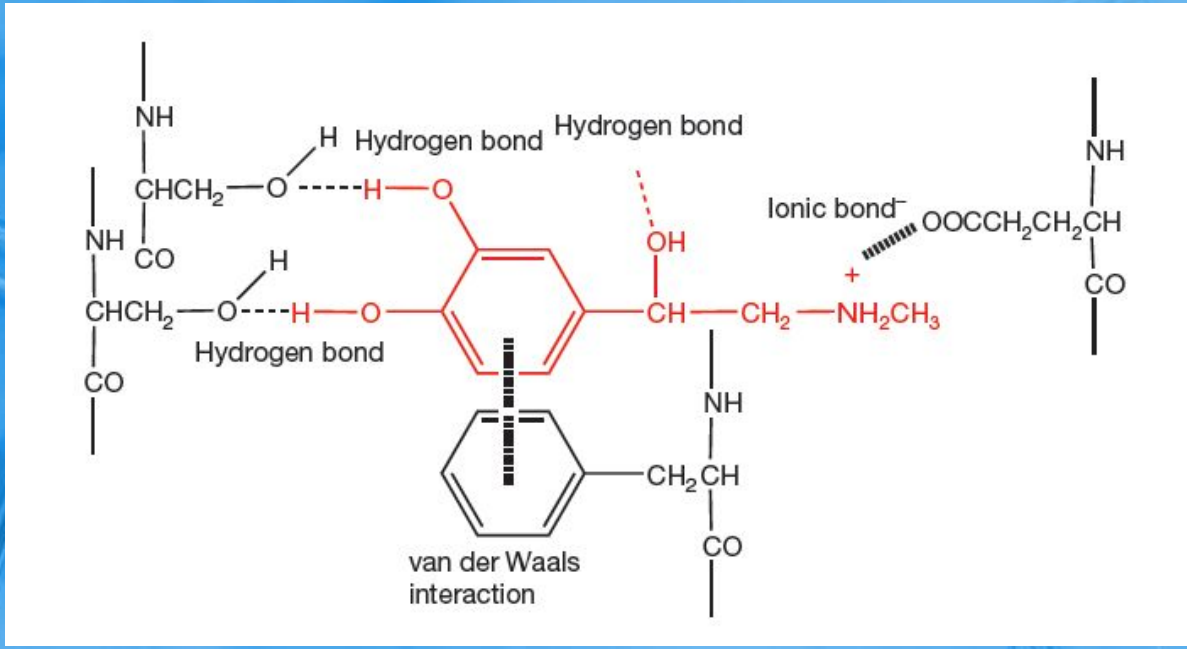
Фармакодинамика — раздел фармакологии, изучающий локализацию, механизм действия и фармакологические эффекты лекарственных средств, силу и длительность их действия. Фармакодинамика — это судьба организма после действия этого лекарственного вещества (механизм действия и эффекты)

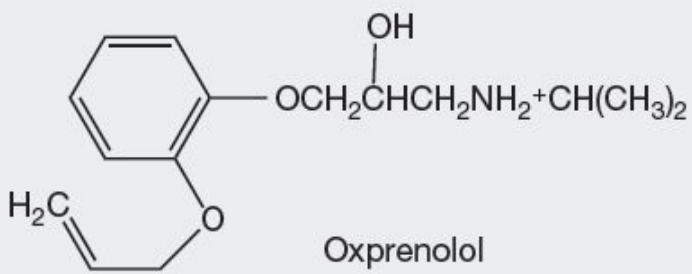
Отмечают 5 главных эффектов, оказываемых лекарственными средствами:

- подавляющее,
- стимулирующее,
- разрушающее клетки (цитотоксическое),
- раздражающее,
- замещающее недостающие вещества.

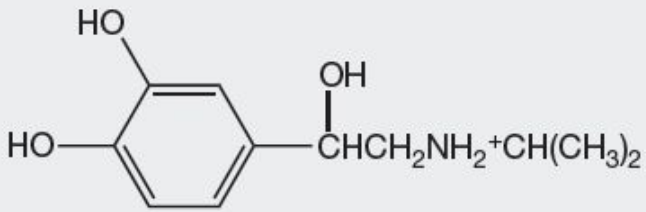
Молекулярная мишень — это молекула с центром связывания для лекарства. Эта молекула может содержать мембранные белки, распознающие гормоны или рецепторы, а также ионные каналы, нуклеиновые кислоты, молекулы-переносчики или ферменты.


NH
H
Hydrogen bond
Hydrogen bond
CHCH2
O
H
O
NH
CO
OH
Ionic bond
OOCCH2CH2CH
NH
CO
H
CHCH2
O
H
O
CH
CH2
NH2CH3
Hydrogen bond
CO
NH
CH2CH
CO
van der Waals
interaction

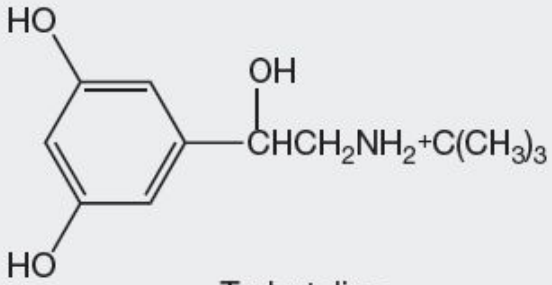




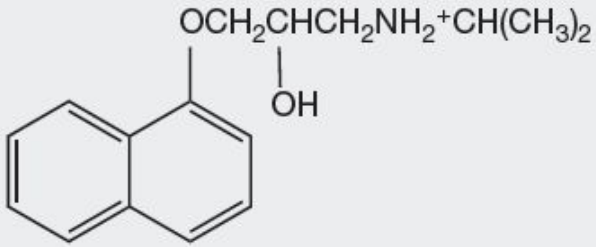
Oxprenolol



Isoprenaline

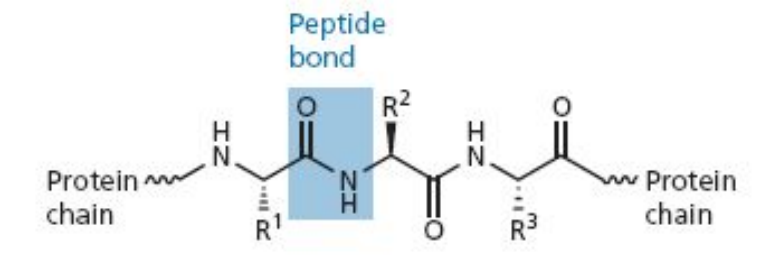


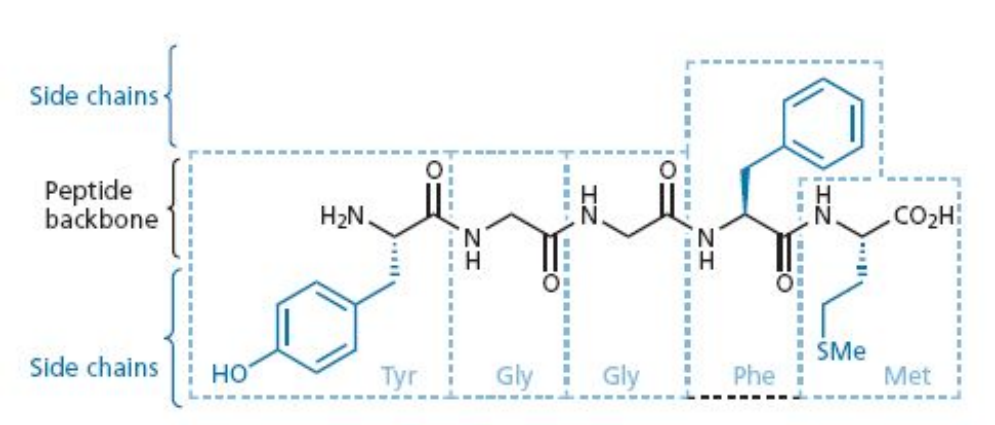
Terbutaline



Propranolol

БЕЛКИ. ПЕРВИЧНАЯ СТРУКТУРА





H-Tyr-Gly-Gly-Phe-Met-OH or YGGFM.

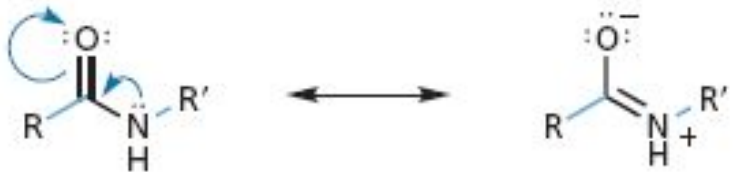
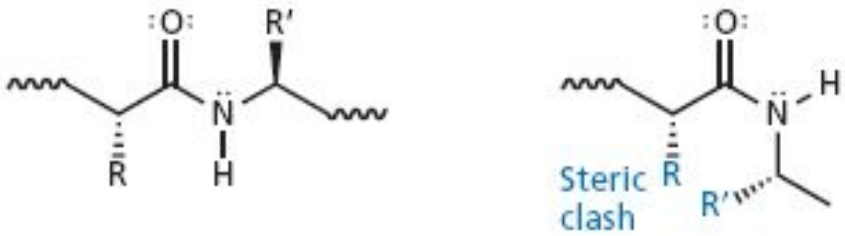


FIGURE 2.3 The planar peptide bond (bond rotation allowed for coloured bonds only).



trans conformation (favoured)

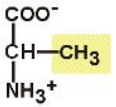
cis conformation (unfavoured)

FIGURE 2.4 *Trans* and *cis* conformations of the peptide bond.

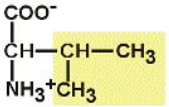
Неполярные

Алифатические

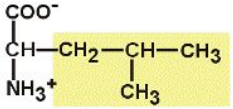
Аланин
Ала, A



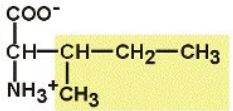
Валин
Вал, V



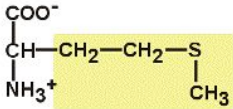
Лейцин
Лей, L



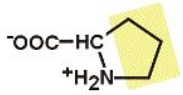
Изолейцин
Иле, J



Метионин
Мет, M



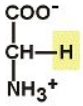
Пролин
Про, P



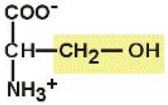
Полярные

Незаряженные

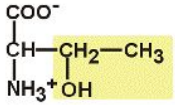
Глицин
Гли, G



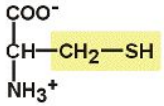
Серин
Сер, S



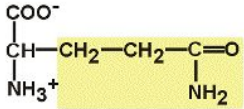
Треонин
Тре, T



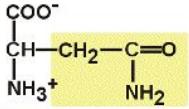
Цистеин
Цис, C



Глутамин
Глн, Q

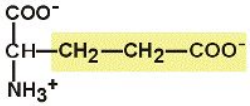


Аспарагин
Асн, N

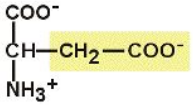


Отрицательно заряженные

Глутаминовая кислота
Глу, E

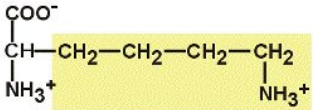


Аспарагиновая кислота
Асп, D

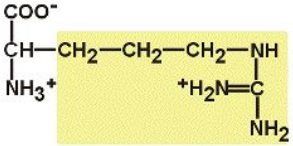


Положительно заряженные

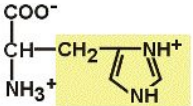
Лизин
Лиз, K



Аргинин
Арг, R

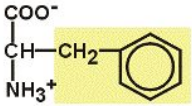


Гистидин
Гис, H

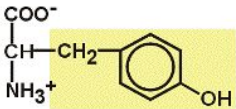


Ароматические

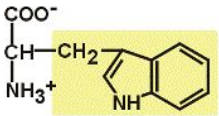
Фенилаланин
Фен, F



Тирозин
Тир, Y



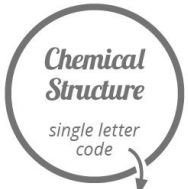
Триптофан
Три, W



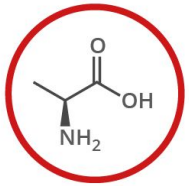
A GUIDE TO THE TWENTY COMMON AMINO ACIDS

AMINO ACIDS ARE THE BUILDING BLOCKS OF PROTEINS IN LIVING ORGANISMS. THERE ARE OVER 500 AMINO ACIDS FOUND IN NATURE - HOWEVER, THE HUMAN GENETIC CODE ONLY DIRECTLY ENCODES 20. 'ESSENTIAL' AMINO ACIDS MUST BE OBTAINED FROM THE DIET, WHILST NON-ESSENTIAL AMINO ACIDS CAN BE SYNTHESISED IN THE BODY.

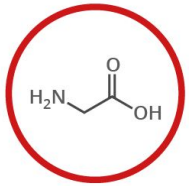
Chart Key: ALIPHATIC | AROMATIC | ACIDIC | BASIC | HYDROXYLIC | SULFUR-CONTAINING | AMIDIC | NON-ESSENTIAL | ESSENTIAL



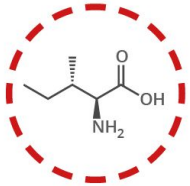
NAME A
three letter code
DNA codons



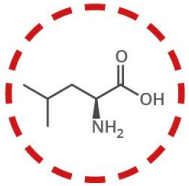
ALANINE A
Ala
GCT, GCC, GCA, GCG



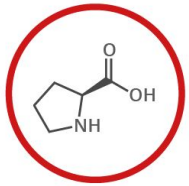
GLYCINE G
Gly
GGT, GGC, GGA, GGG



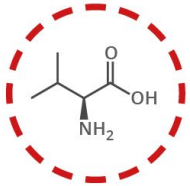
ISOLEUCINE I
Ile
ATT, ATC, ATA



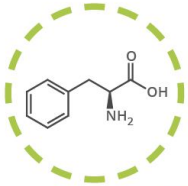
LEUCINE L
Leu
CTT, CTC, CTA, CTG, TTA, TTG



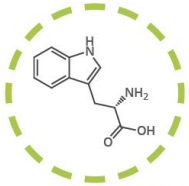
PROLINE P
Pro
CCT, CCC, CCA, CCG



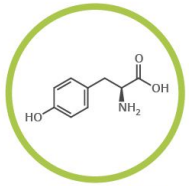
VALINE V
Val
GTT, GTC, GTA, GTG



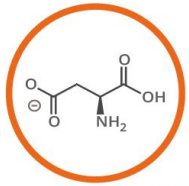
PHENYLALANINE F
Phe
TTT, TTC



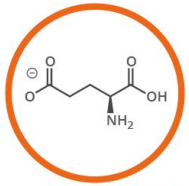
TRYPTOPHAN W
Trp
TGG



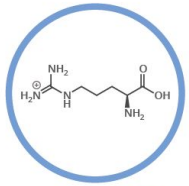
TYROSINE Y
Tyr
TAT, TAC



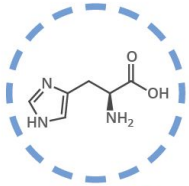
ASPARTIC ACID D
Asp
GAT, GAC



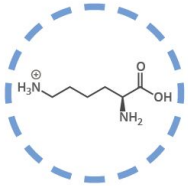
GLUTAMIC ACID E
Glu
GAA, GAG



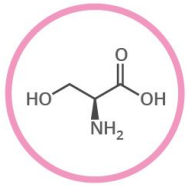
ARGININE R
Arg
CGT, CGC, CGA, CGG, AGA, AGG



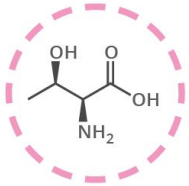
HISTIDINE H
His
CAT, CAC



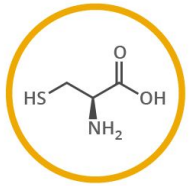
LYSINE K
Lys
AAA, AAG



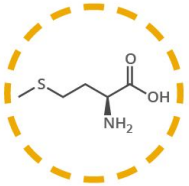
SERINE S
Ser
TCT, TCC, TCA, TCG, AGT, AGC



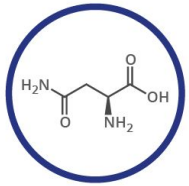
THREONINE T
Thr
ACT, ACC, ACA, ACG



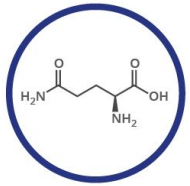
CYSTEINE C
Cys
TGT, TGC



METHIONINE M
Met
ATG



ASPARAGINE N
Asn
AAT, AAC



GLUTAMINE Q
Gln
CAA, CAG

Note: This chart only shows those amino acids for which the human genetic code directly codes for. Selenocysteine is often referred to as the 21st amino acid, but is encoded in a special manner. In some cases, distinguishing between asparagine/aspartic acid and glutamine/glutamic acid is difficult. In these cases, the codes asx (B) and glx (Z) are respectively used.

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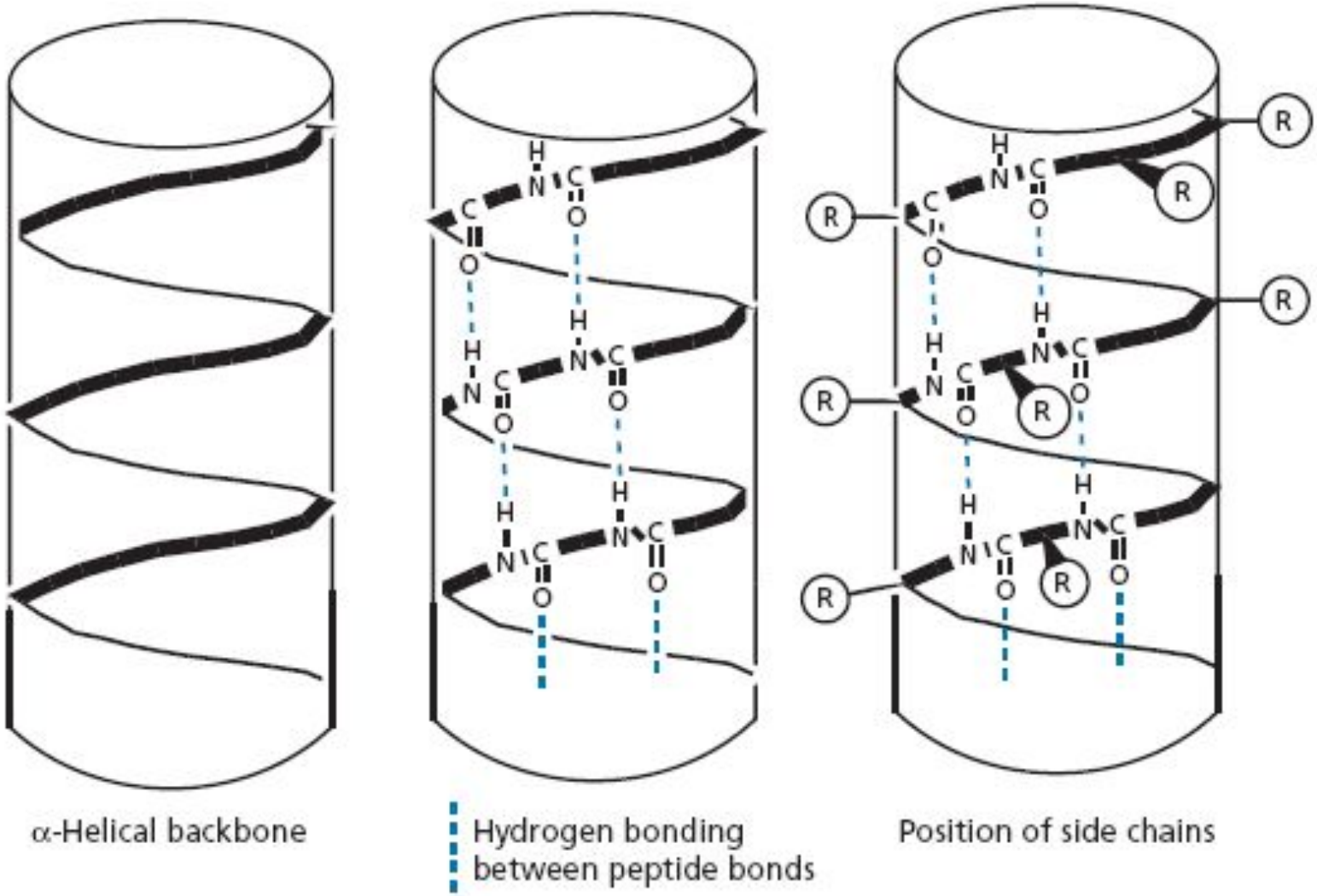
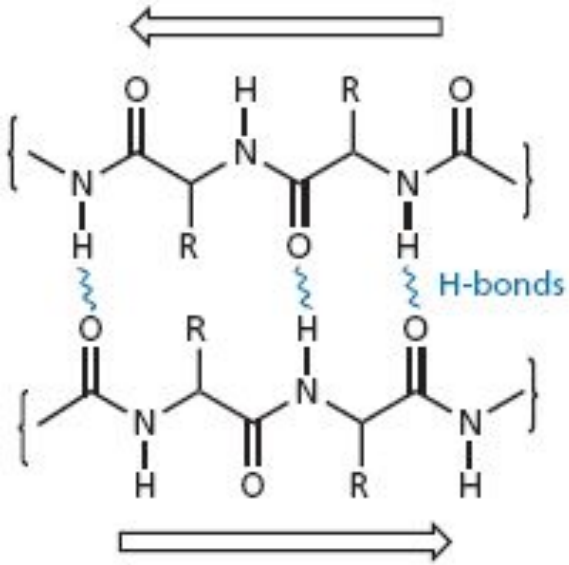
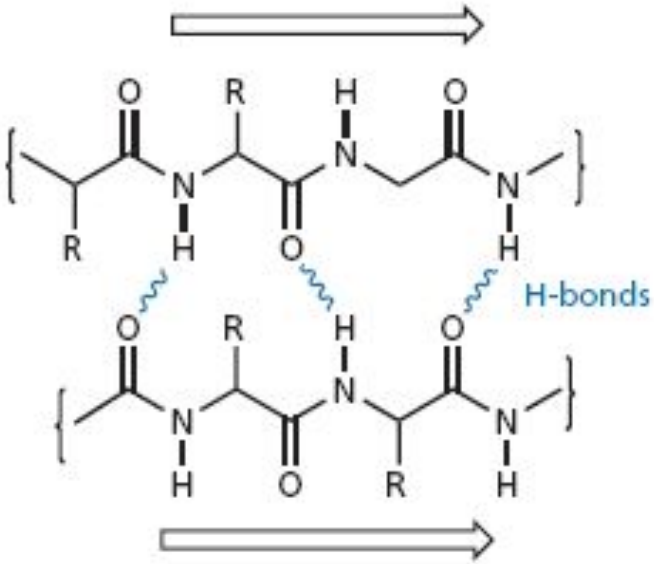
БЕЛКИ. ВТОРИЧНАЯ СТРУКТУРА

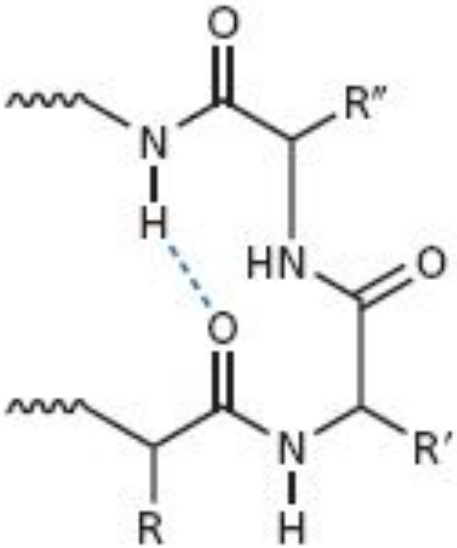


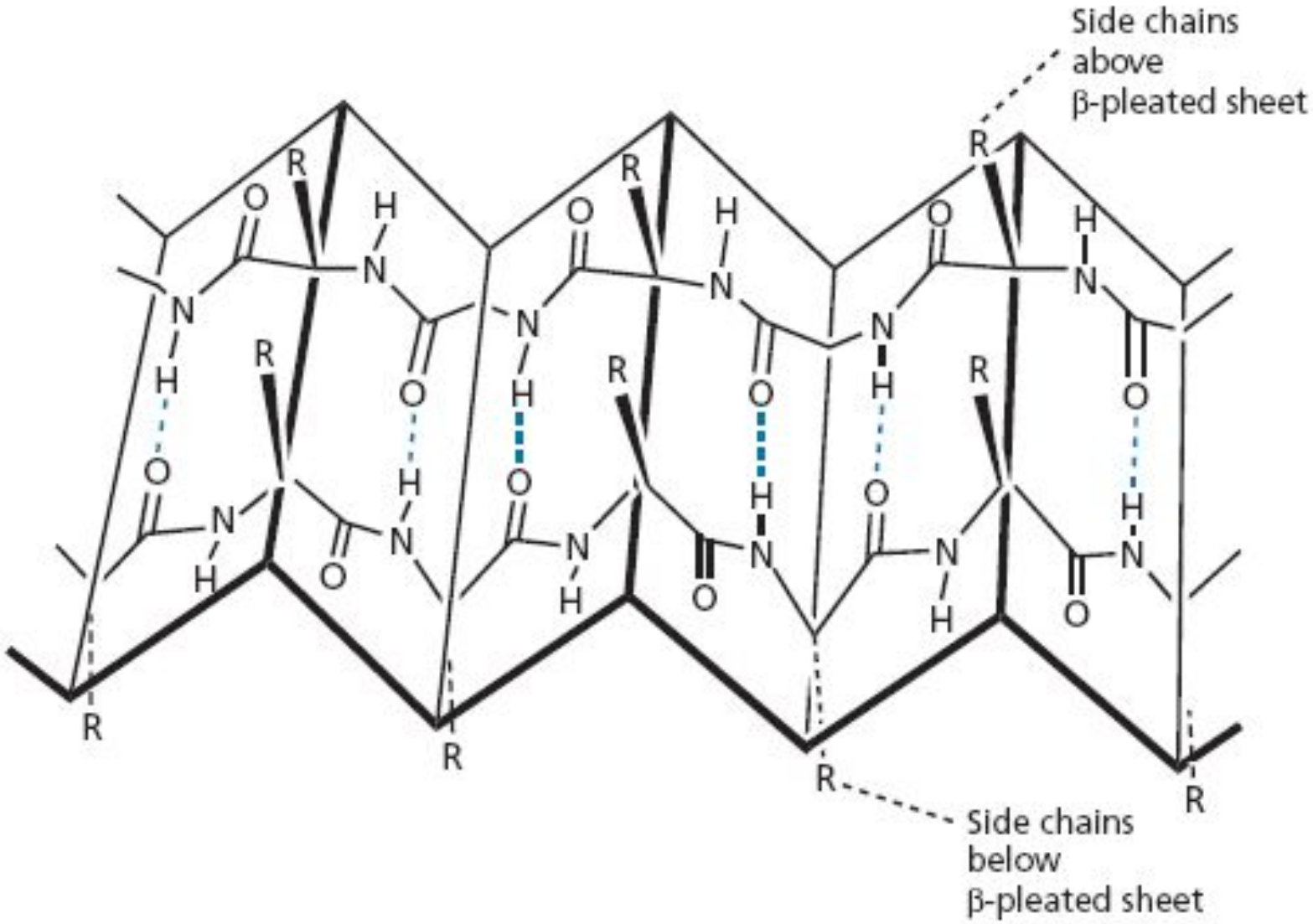


Antiparallel β-sheet

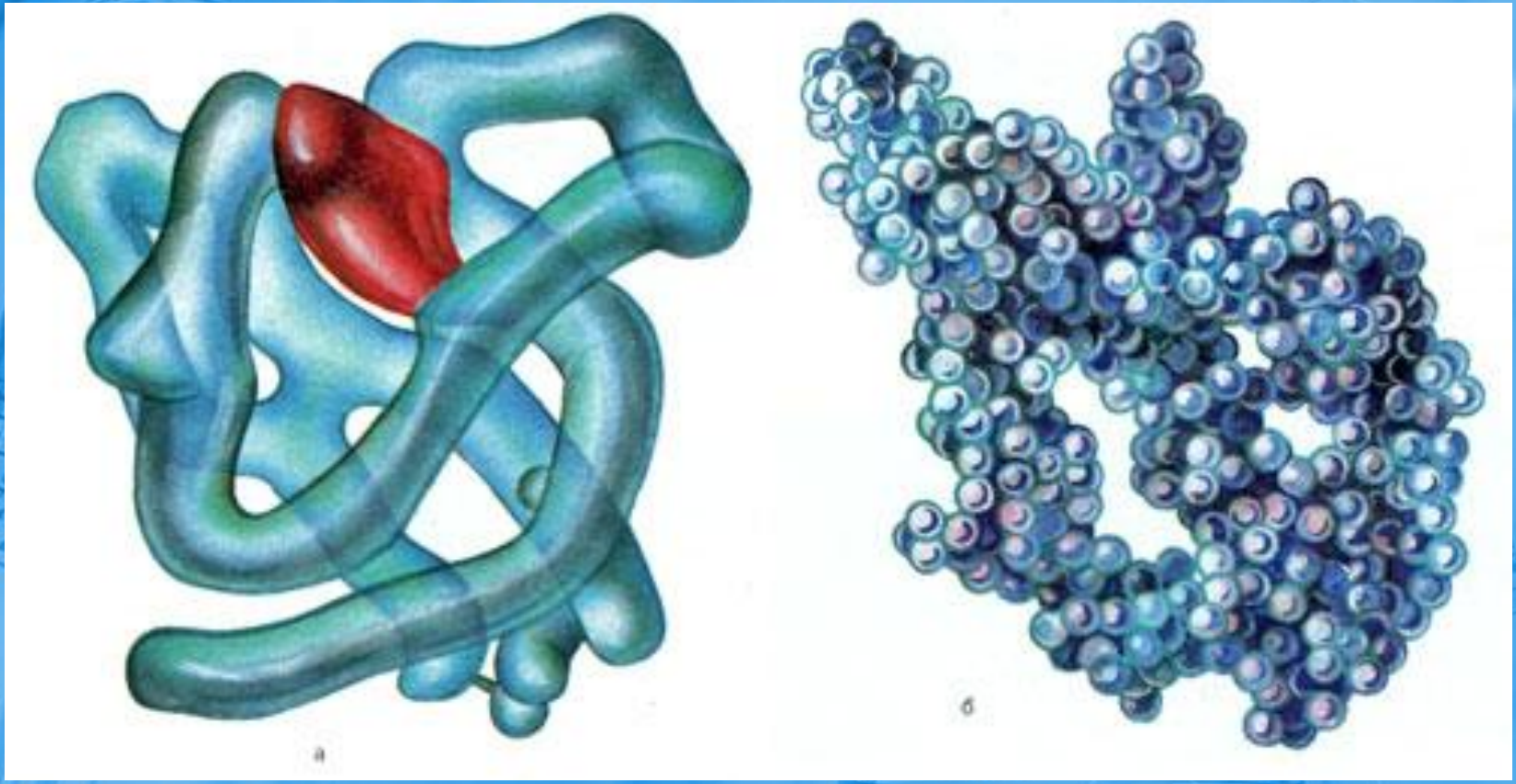


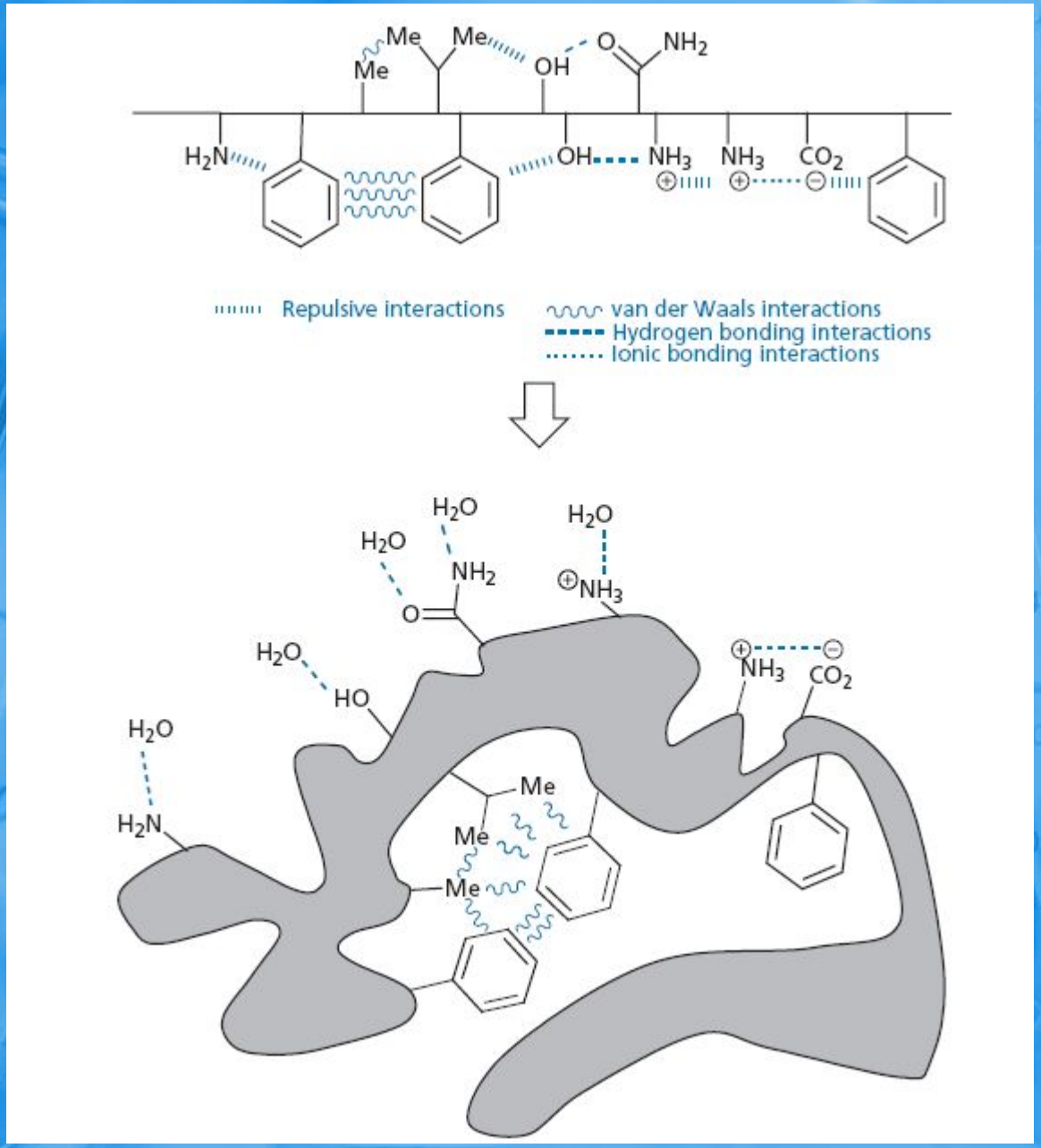
Parallel β-sheet

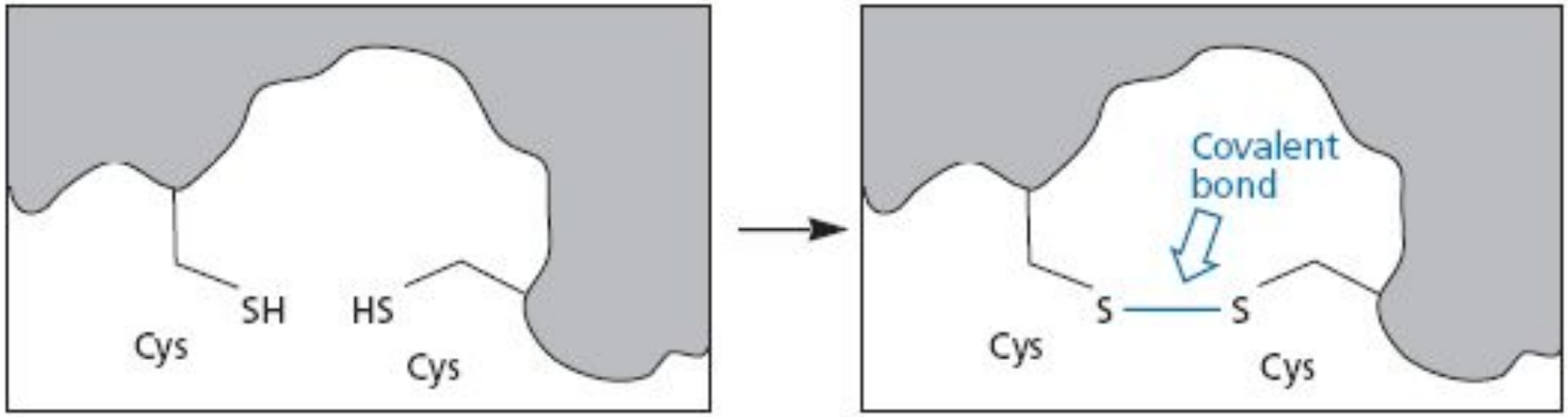


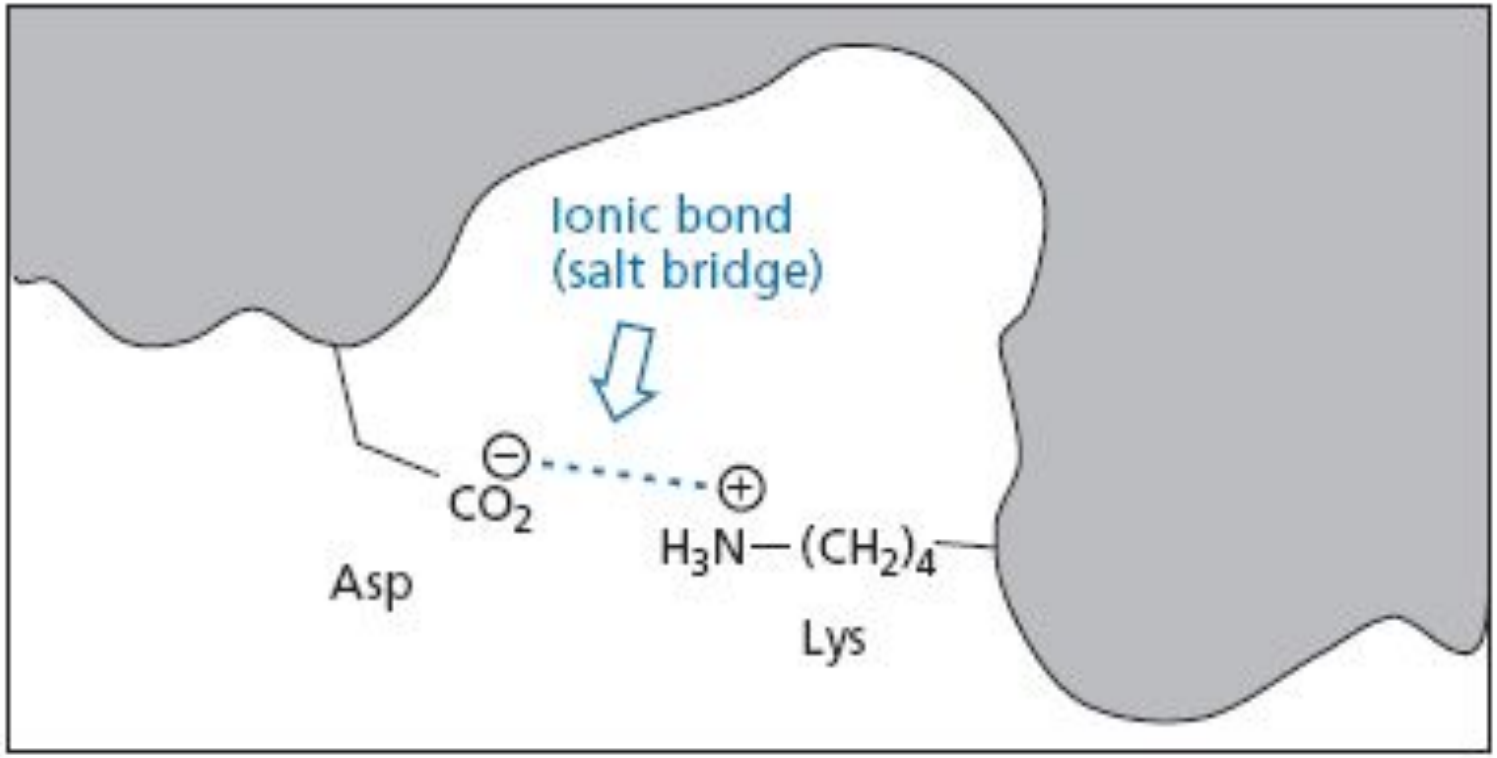

Side chains
above
β-pleated sheet
Side chains
below
β-pleated sheet

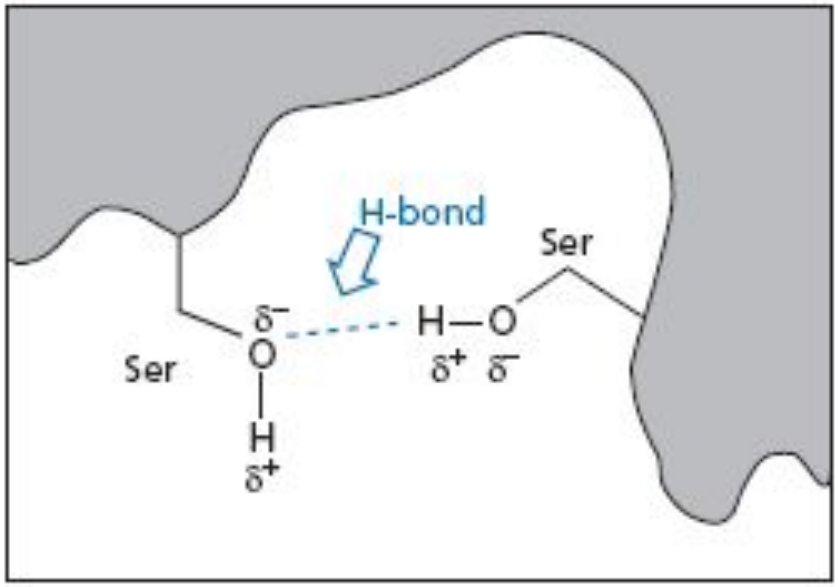
БЕЛКИ. ТРЕТИЧНАЯ СТРУКТУРА

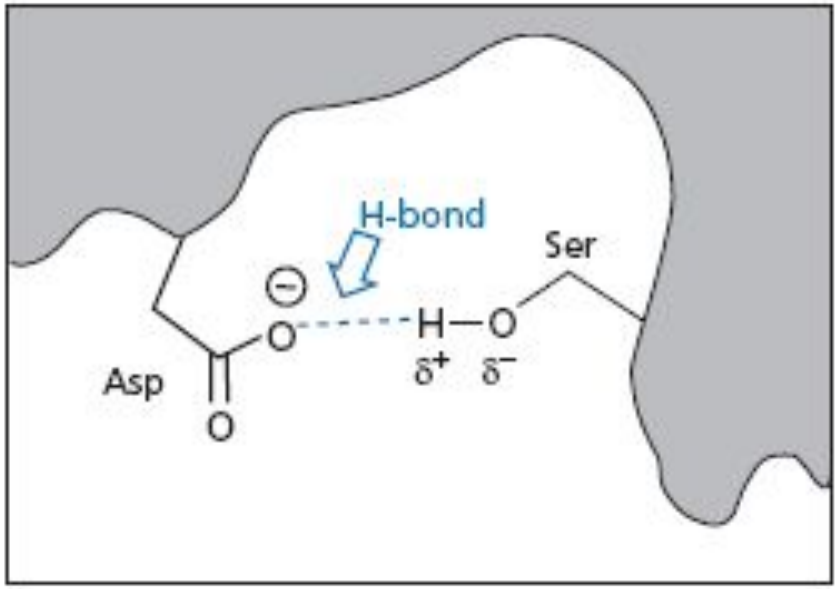


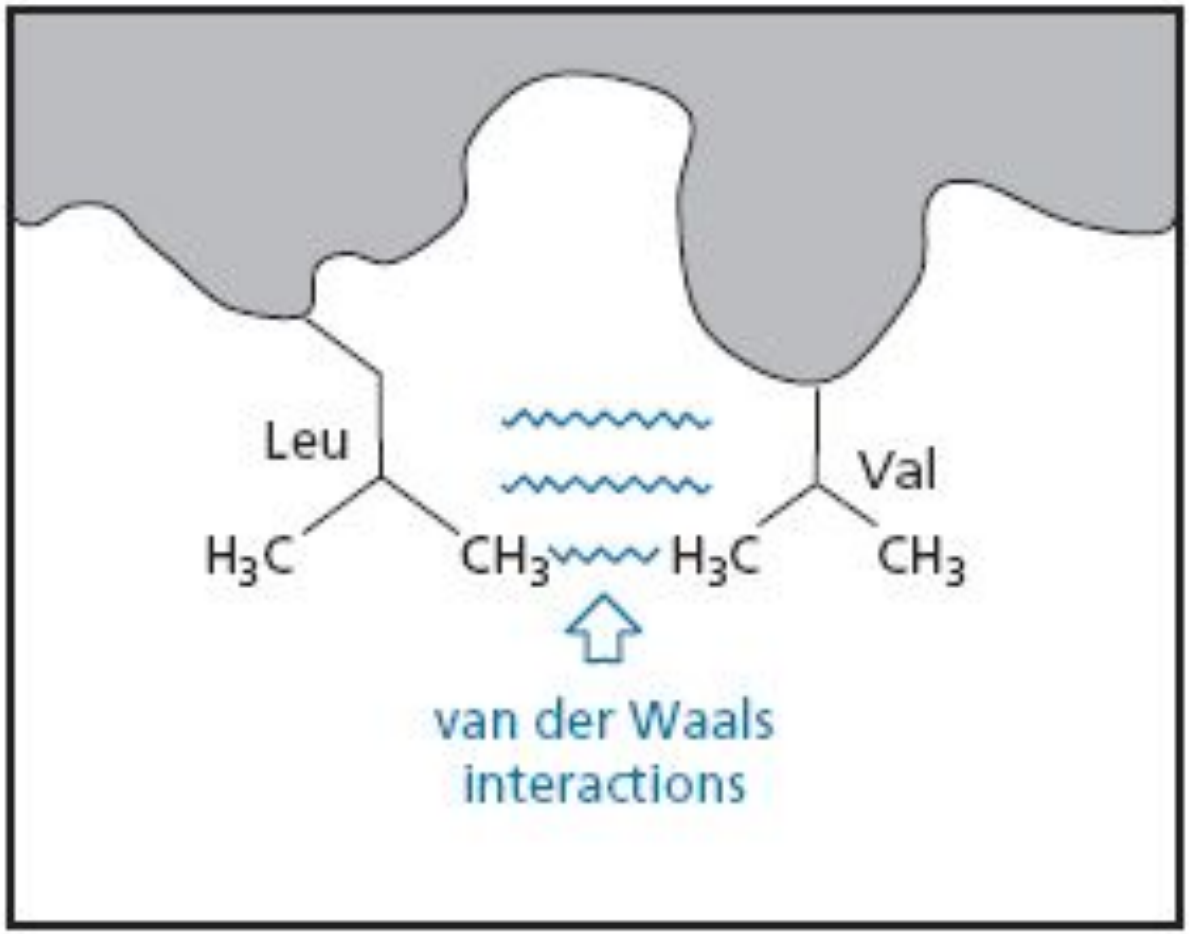

Me
Me
Me
OH
O
NH2
H2N
OH
NH3
NH3
CO2
Repulsive interactions
van der Waals interactions
Hydrogen bonding interactions
Ionic bonding interactions
H2O
H2O
H2O
NH2
NH3
O
H2O
HO
NH3
CO2
H2O
H2N
Me
Me
Me

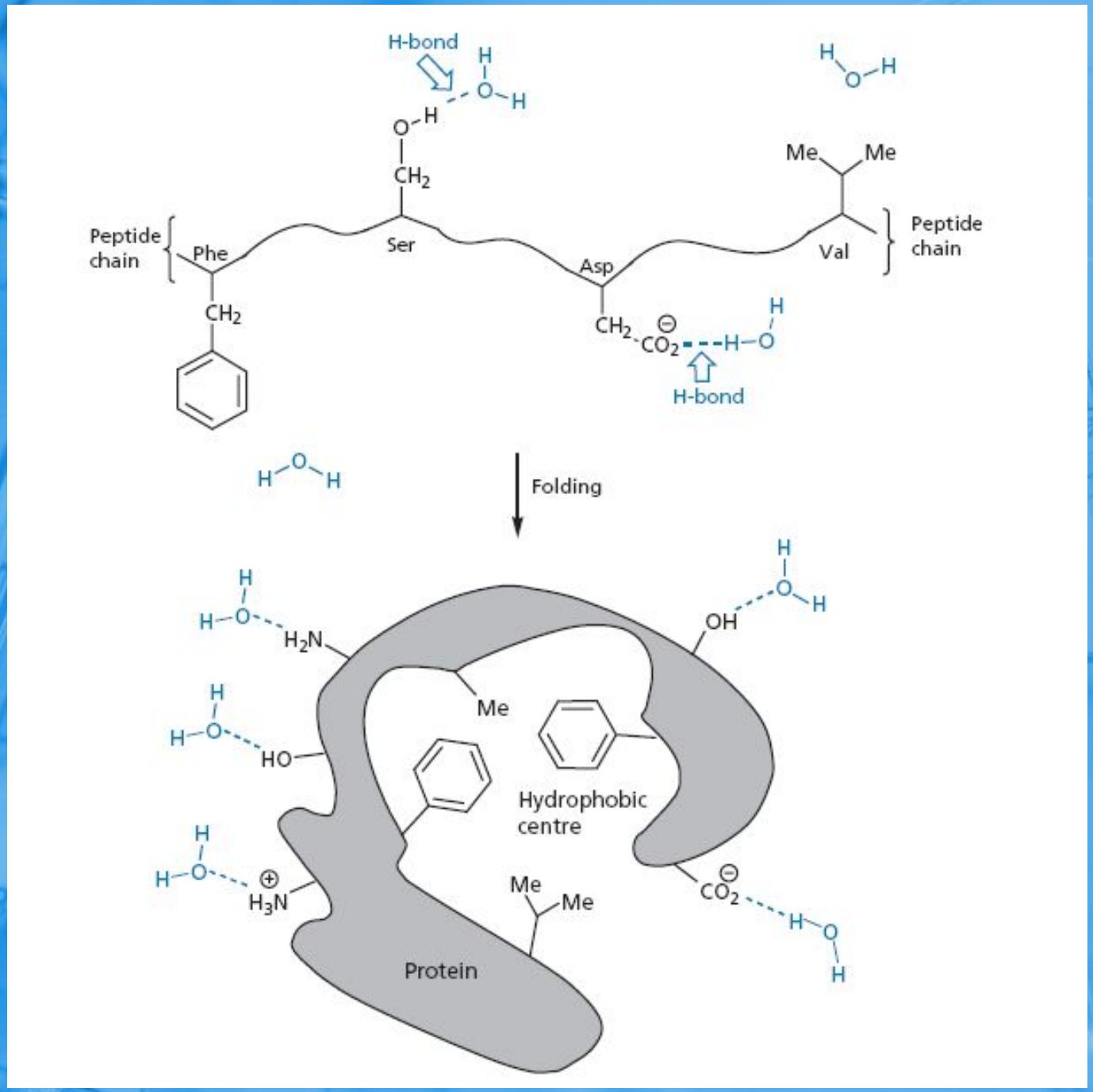

SH
HS
Cys
Cys
Covalent
bond
S
S
Cys
Cys

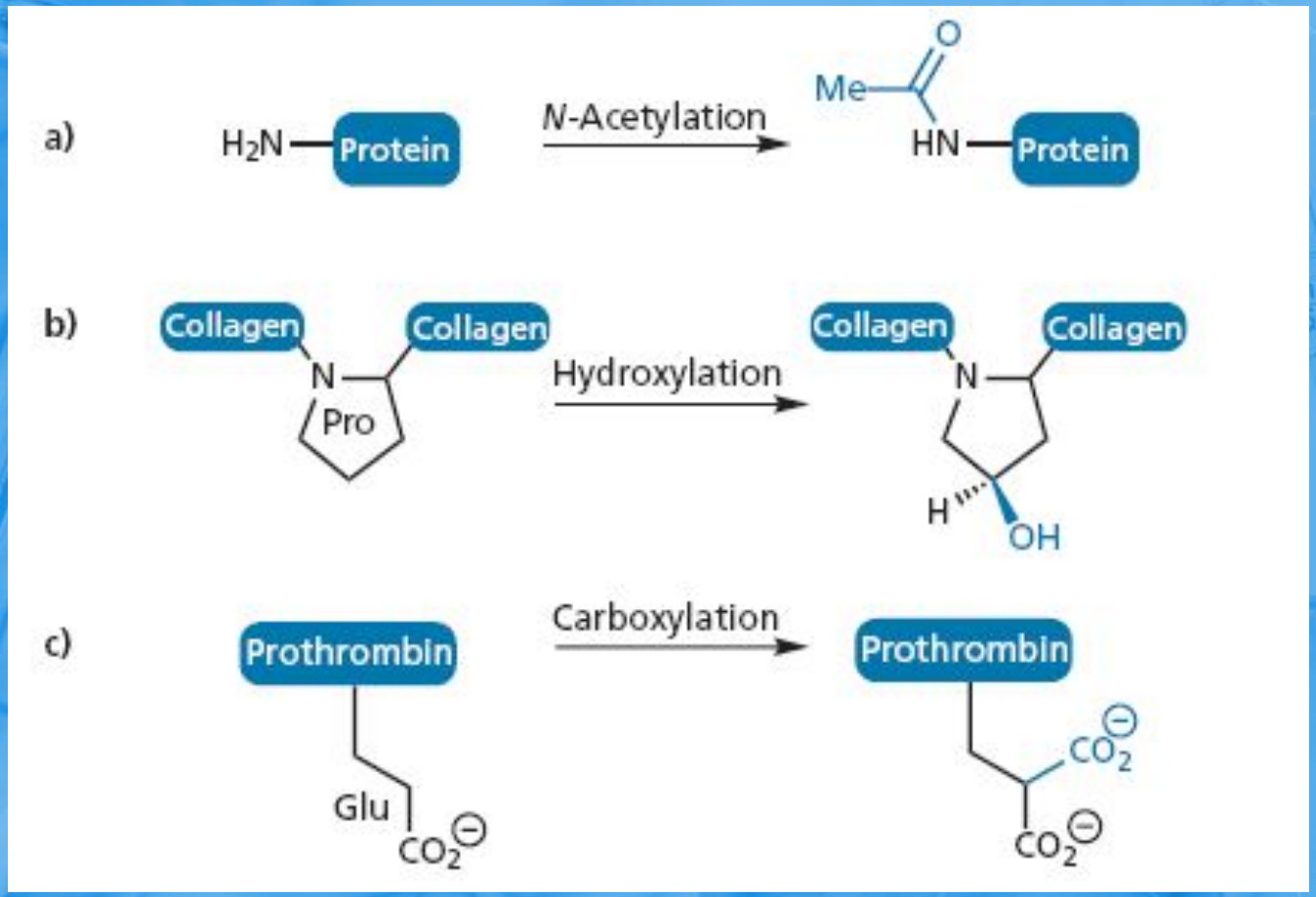

Ionic bond
(salt bridge)
CO_2
$H_3N-(CH_2)_4$
Asp
Lys

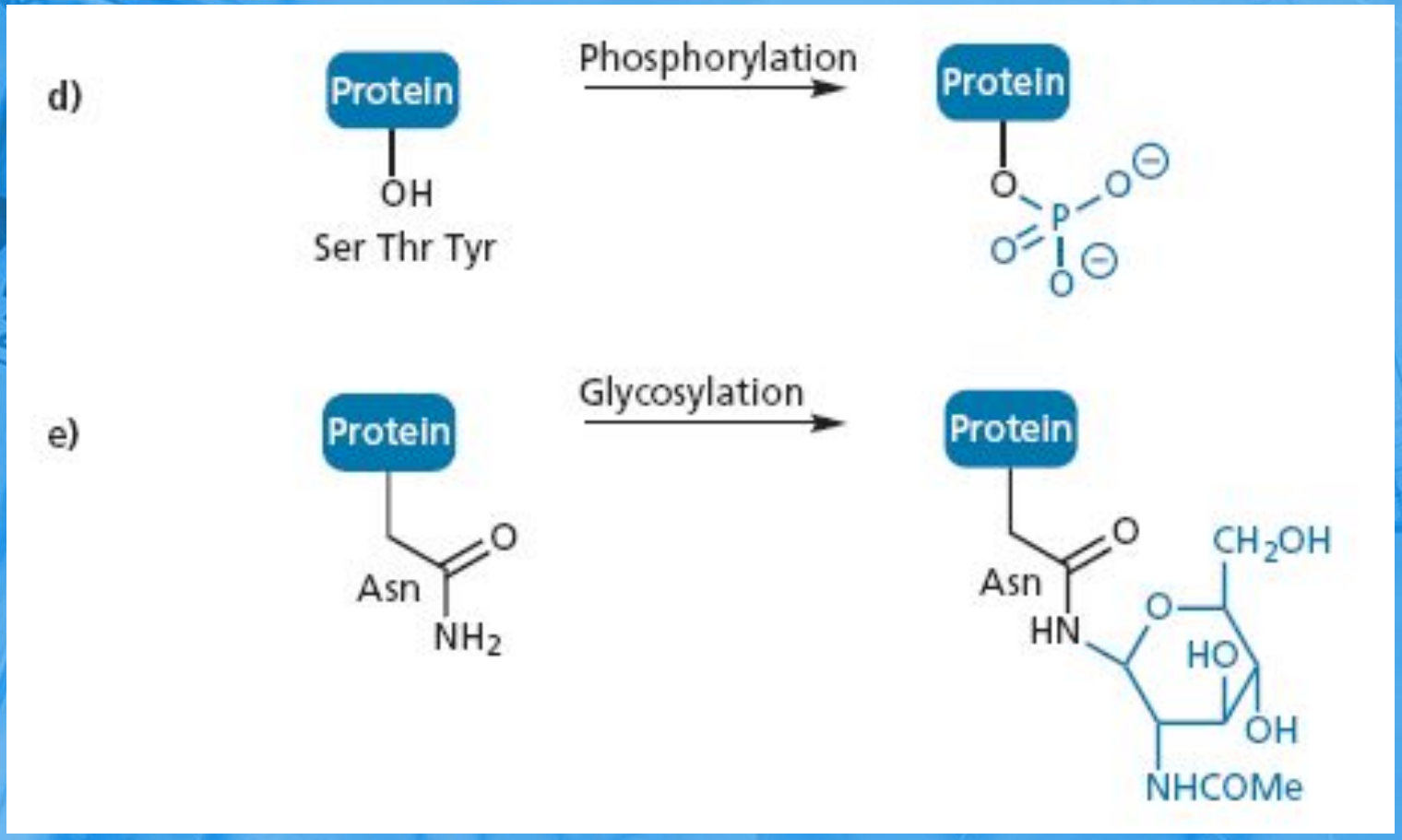

H-bond
Ser
Ser
δ−
O
H
δ+
H—O
δ+ δ−


H-bond
Ser
Asp
O
O
H—O
δ+ δ−


Leu
Val
H_3C
CH_3
H_3C
CH_3
van der Waals
interactions


H-bond
Peptide chain
Phe
Ser
Asp
Val
Me
Me
Peptide chain
H-bond
Folding
Me
Hydrophobic centre
Me
Me
Protein


a)
H2N
Protein
N-Acetylation
Me
O
HN
Protein
b)
Collagen
Collagen
N
Pro
Hydroxylation
Collagen
Collagen
N
H
OH
c)
Prothrombin
Glu
CO2
Carboxylation
Prothrombin
CO2
CO2


d)
Protein
OH
Ser Thr Tyr
Phosphorylation
Protein
O
P
O
O
O
e)
Protein
Asn
O
NH2
Glycosylation
Protein
Asn
O
HN
CH2OH
O
HO
OH
NHCOMe

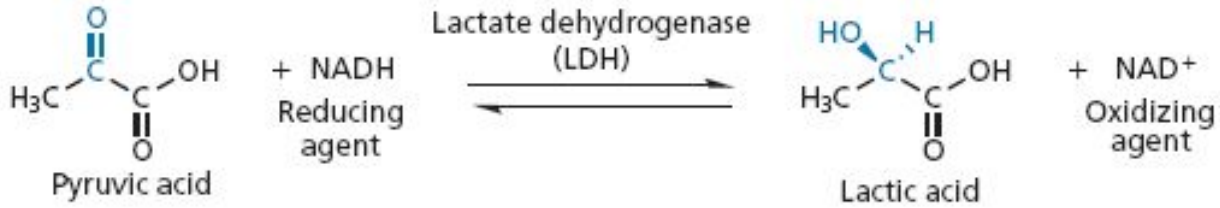
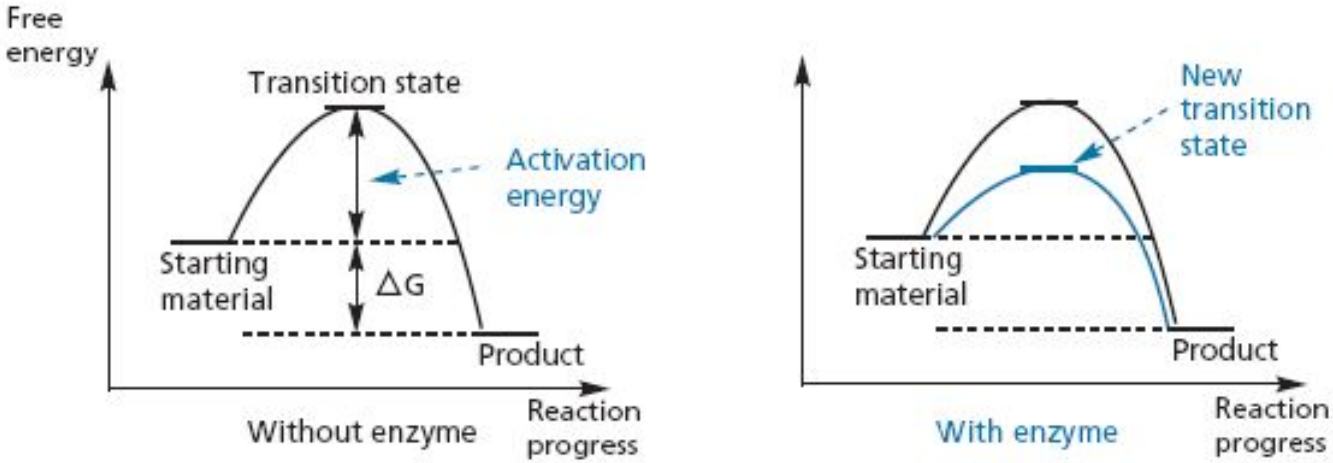
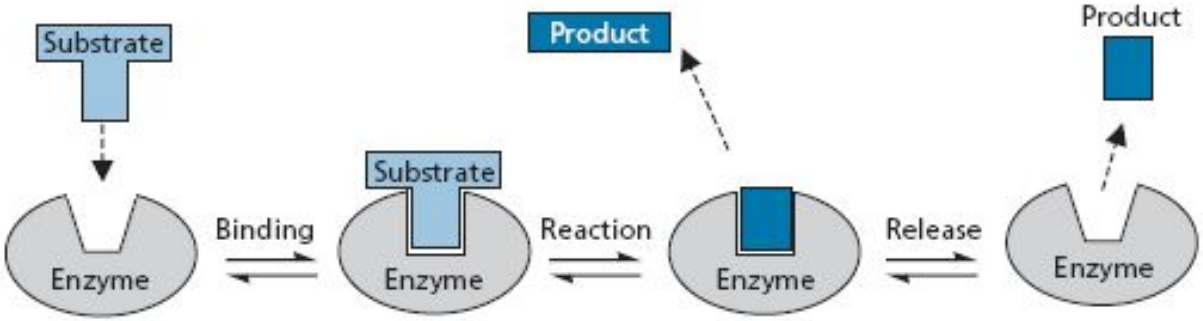
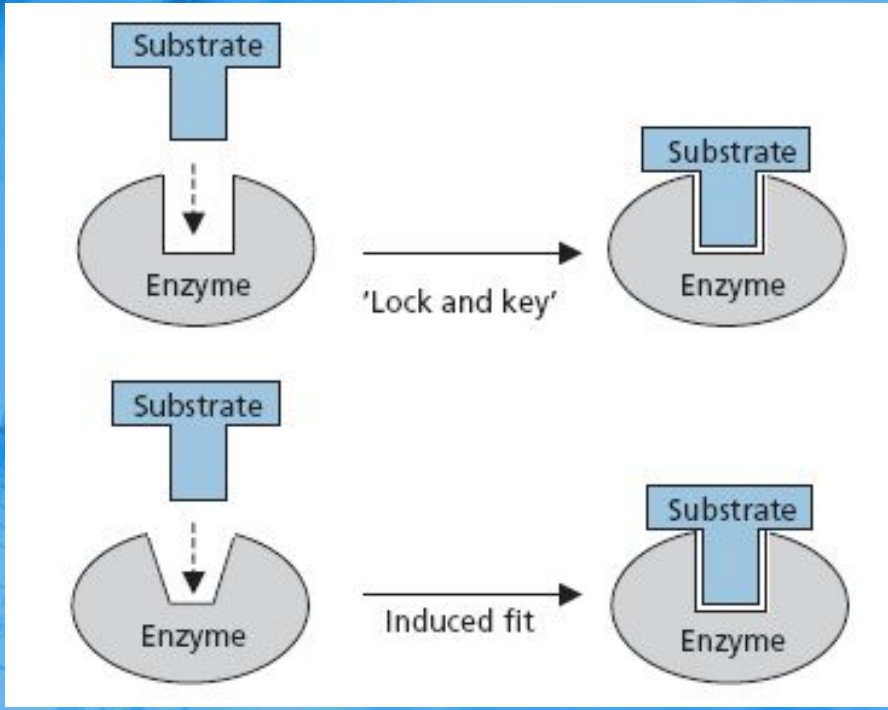
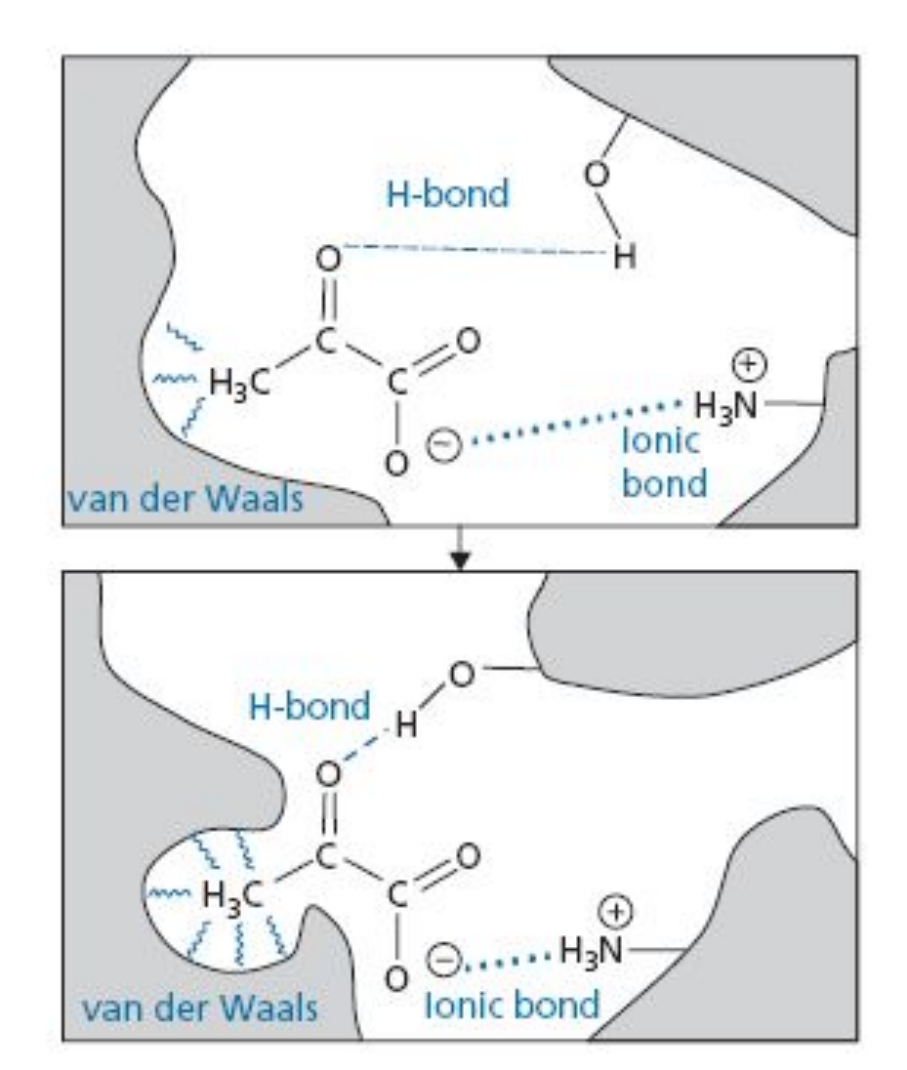


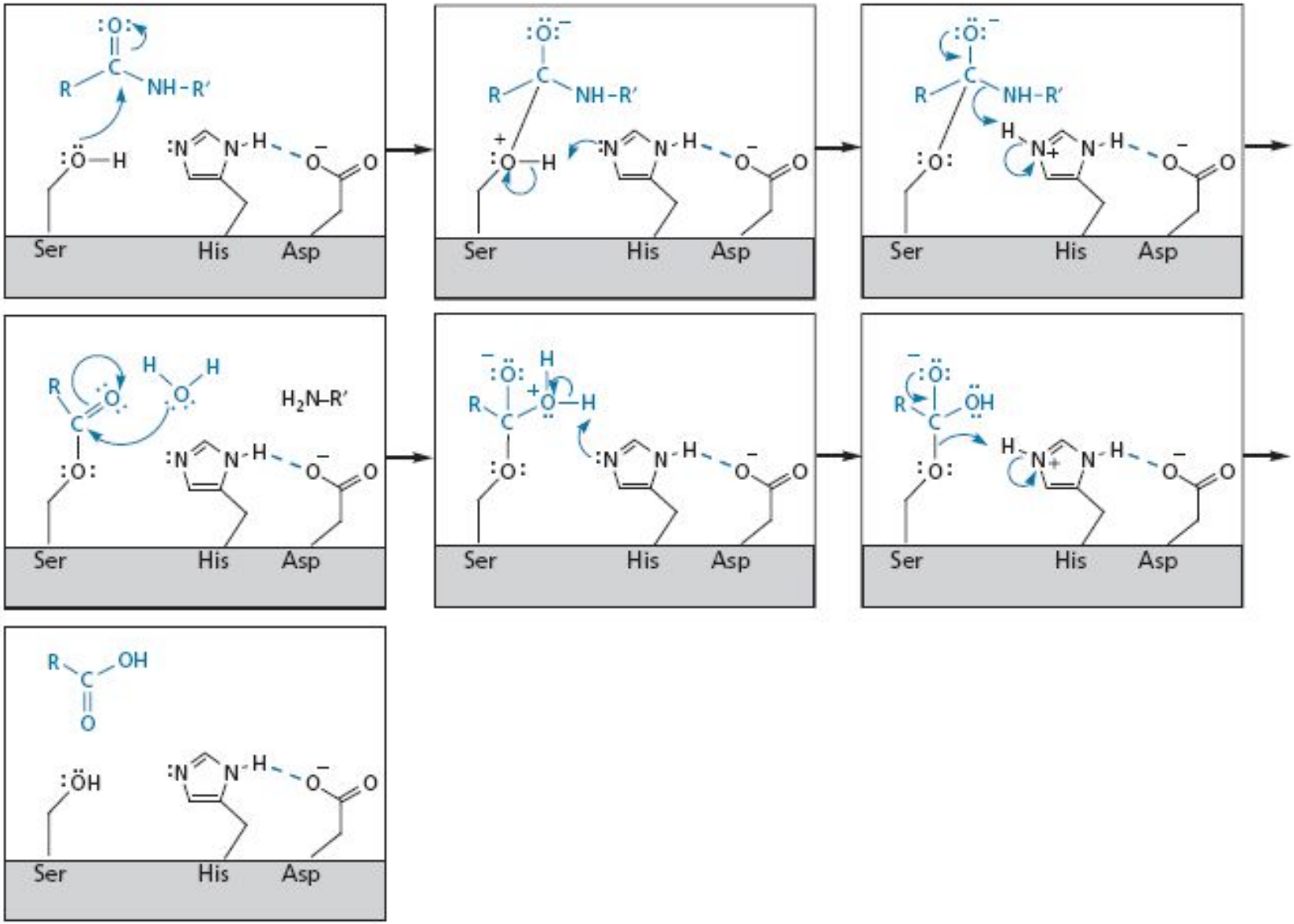
FIGURE 3.1 Reaction catalysed by lactate dehydrogenase.

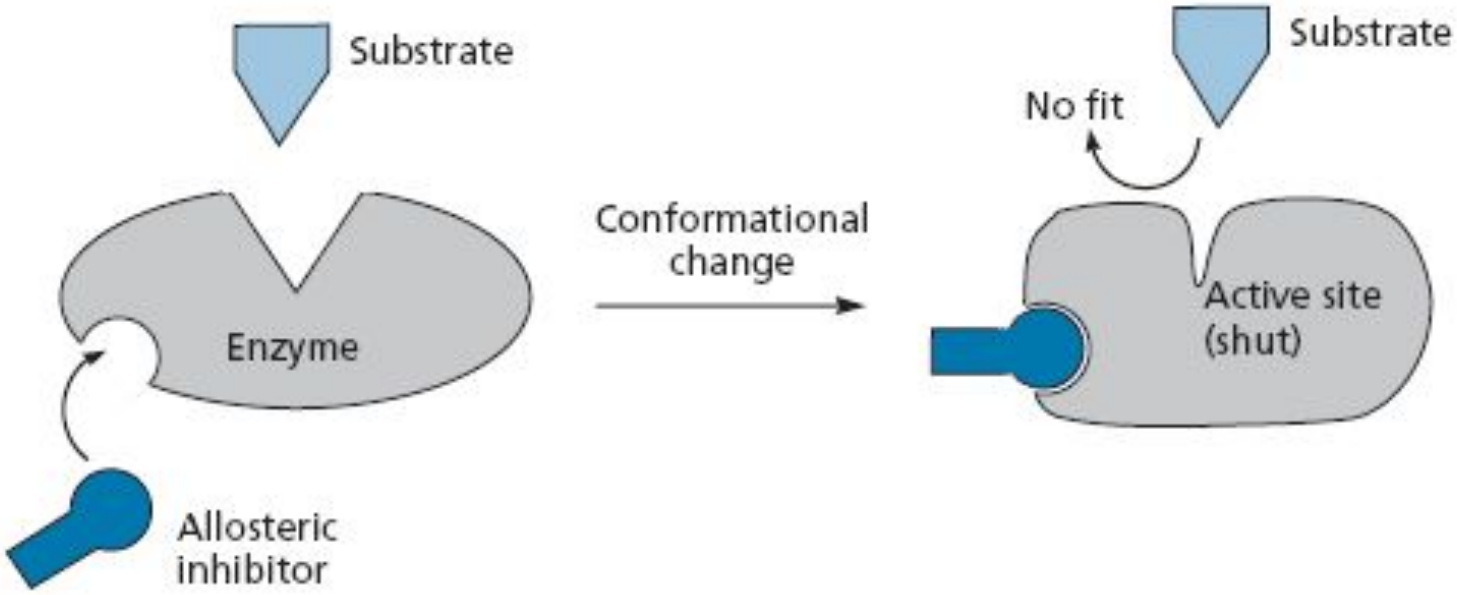





Substrate
Enzyme
'Lock and key'
Substrate
Enzyme
Substrate
Enzyme
Induced fit
Substrate
Enzyme

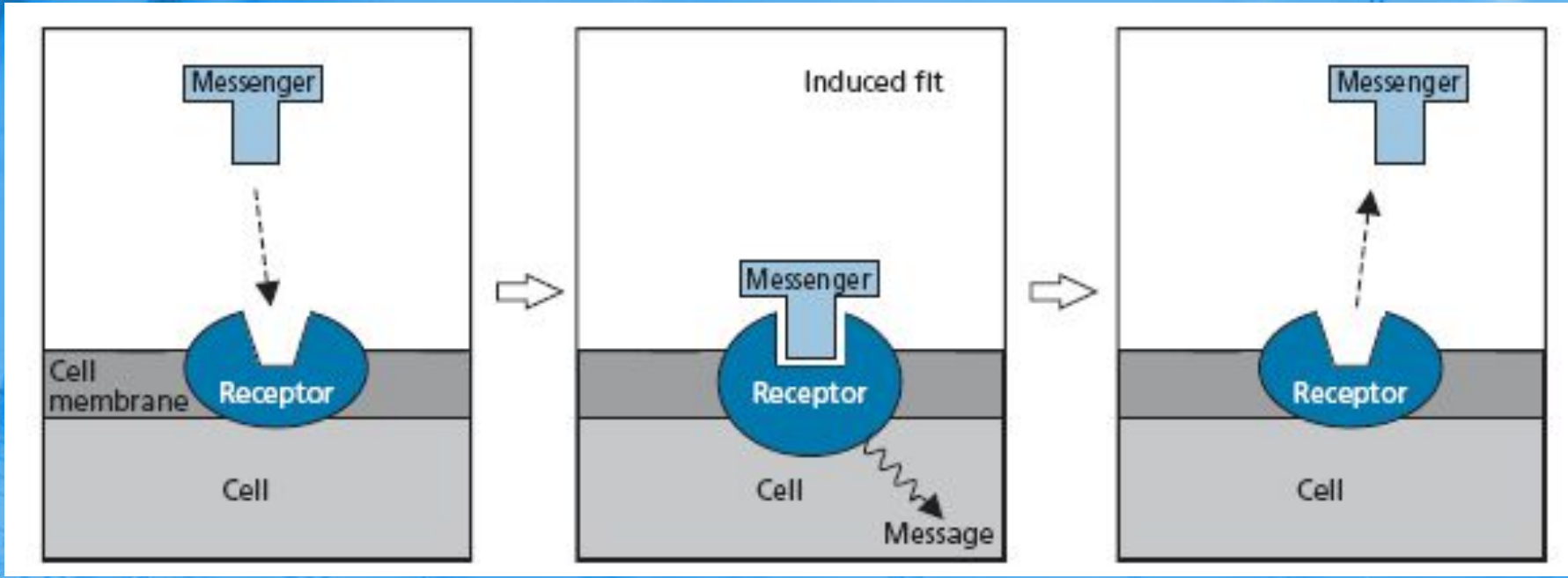

H-bond
van der Waals
Ionic bond
H-bond
van der Waals
Ionic bond

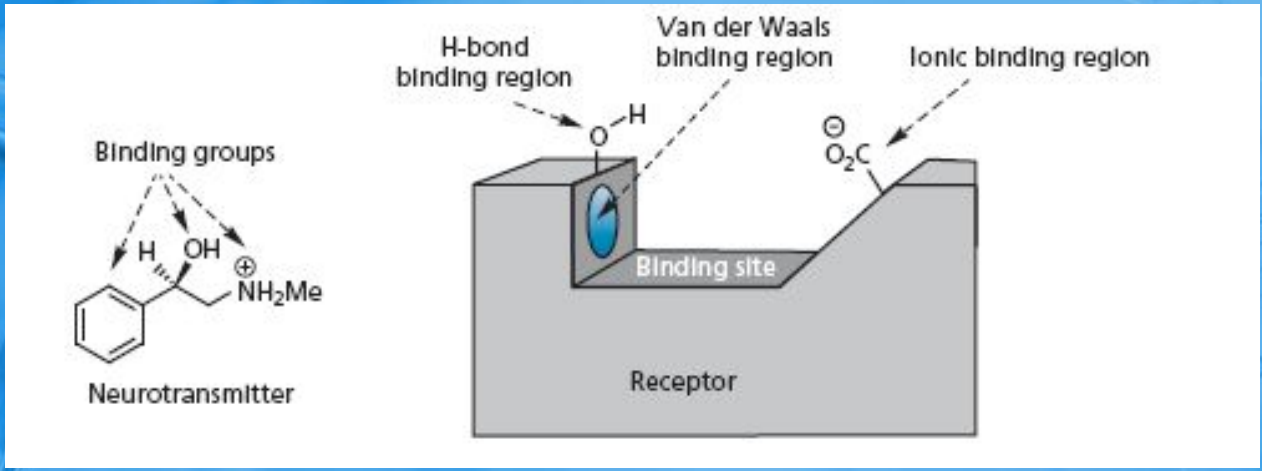

Ser
His
Asp
NH-R′
H₂N-R′

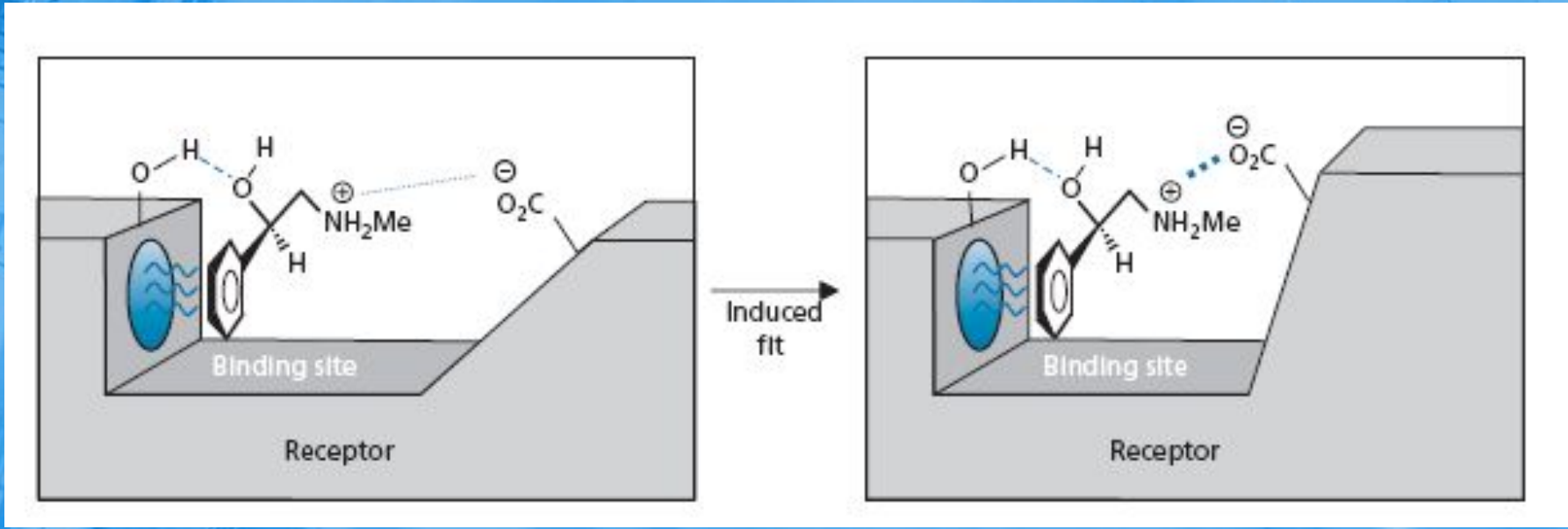

Substrate
Enzyme
Allosteric
inhibitor
Conformational
change
Substrate
No fit
Active site
(shut)

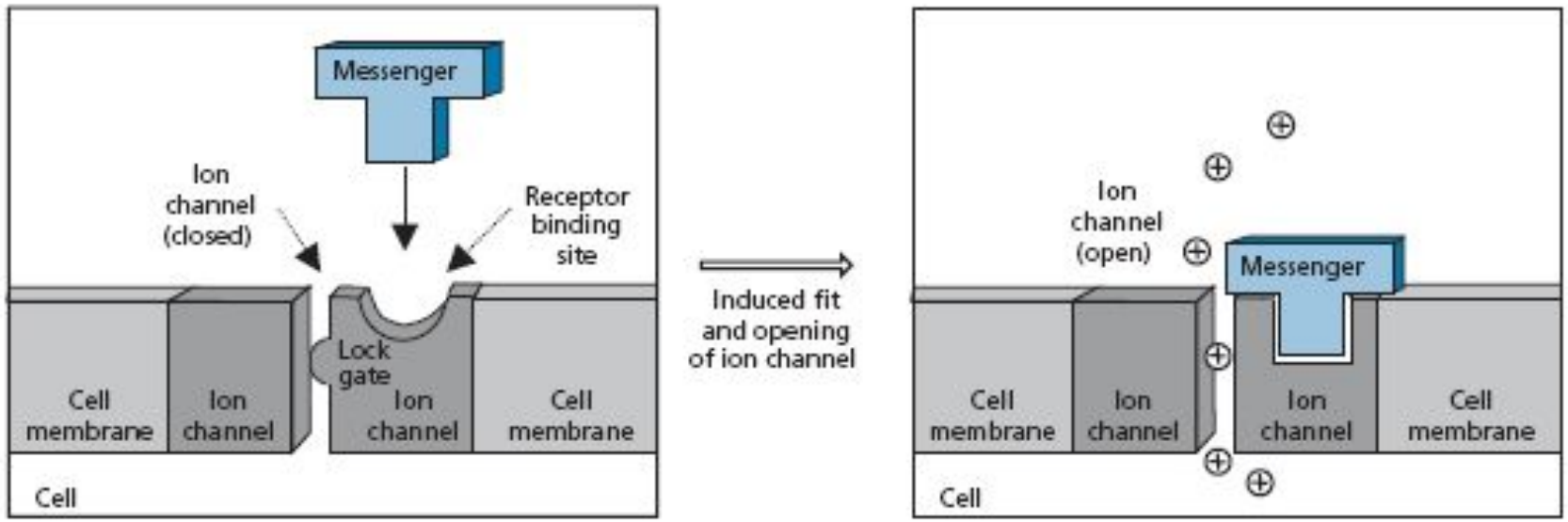
Клеточный рецептор — молекула (обычно белок или гликопротеид) на поверхности клетки, клеточных органелл или растворенная в цитоплазме. Специфично реагирует изменением своей пространственной конфигурации на присоединение к ней молекулы определённого химического вещества, передающего внешний регуляторный сигнал и, в свою очередь, передает этот сигнал внутрь клетки или клеточной органеллы, нередко при помощи так называемых вторичных посредников или трансмембранных ионных токов.

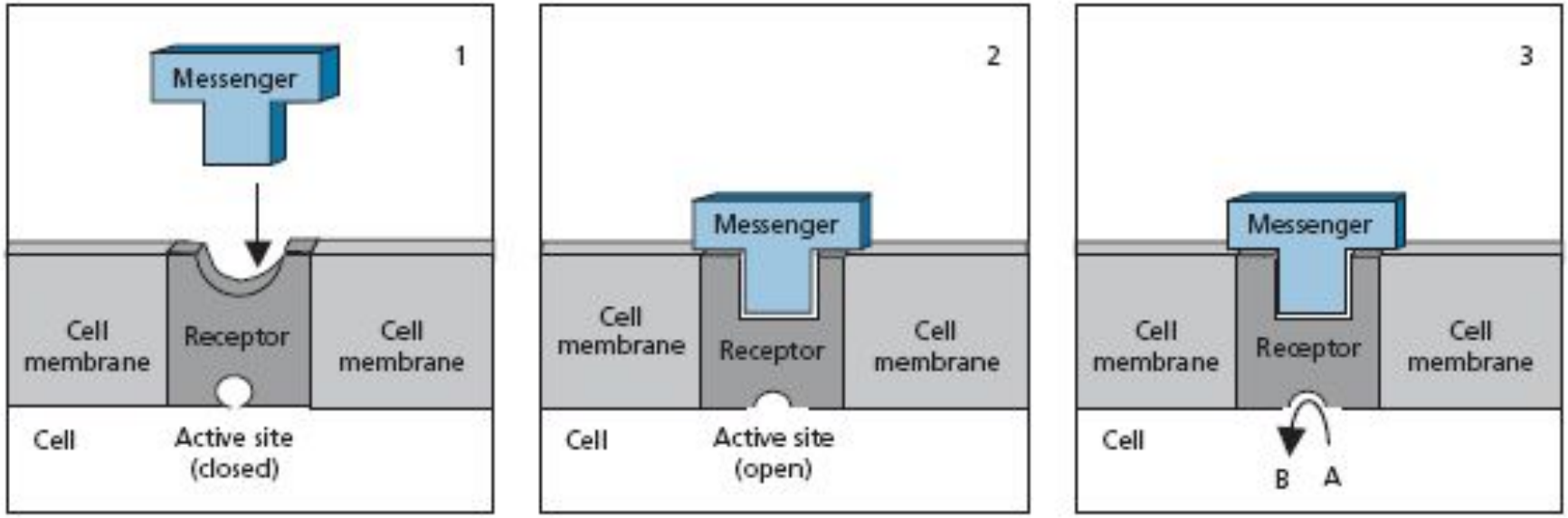
Вещество, специфически соединяющееся с рецептором, называется лигандом этого рецептора. Внутри организма это обычно гормон или нейромедиатор либо их искусственные заменители, применяемые в качестве лекарственных средств и ядов (агонисты). Некоторые лиганды, напротив, блокируют рецепторы (антагонисты).


Messenger
Cell membrane
Receptor
Cell
Induced fit
Messenger
Receptor
Cell
Message
Messenger
Receptor
Cell


Binding groups
H
OH
NH2Me
Neurotransmitter
H-bond
binding region
Van der Waals
binding region
Ionic binding region
O
H
O2C
Binding site
Receptor


O
H
H
O
NH2Me
O2C
H
Binding site
Receptor
Induced
fit
O
H
H
O
O2C
NH2Me
H
Binding site
Receptor


Messenger
Ion channel (closed)
Receptor binding site
Lock gate
Cell membrane
Ion channel
Ion channel
Cell membrane
Cell
Induced fit and opening of ion channel
Ion channel (open)
Messenger
Cell membrane
Ion channel
Ion channel
Cell membrane
Cell


1
Messenger
Cell membrane
Receptor
Cell membrane
Cell
Active site (closed)
2
Messenger
Cell membrane
Receptor
Cell membrane
Cell
Active site (open)
3
Messenger
Cell membrane
Receptor
Cell membrane
Cell
B
A