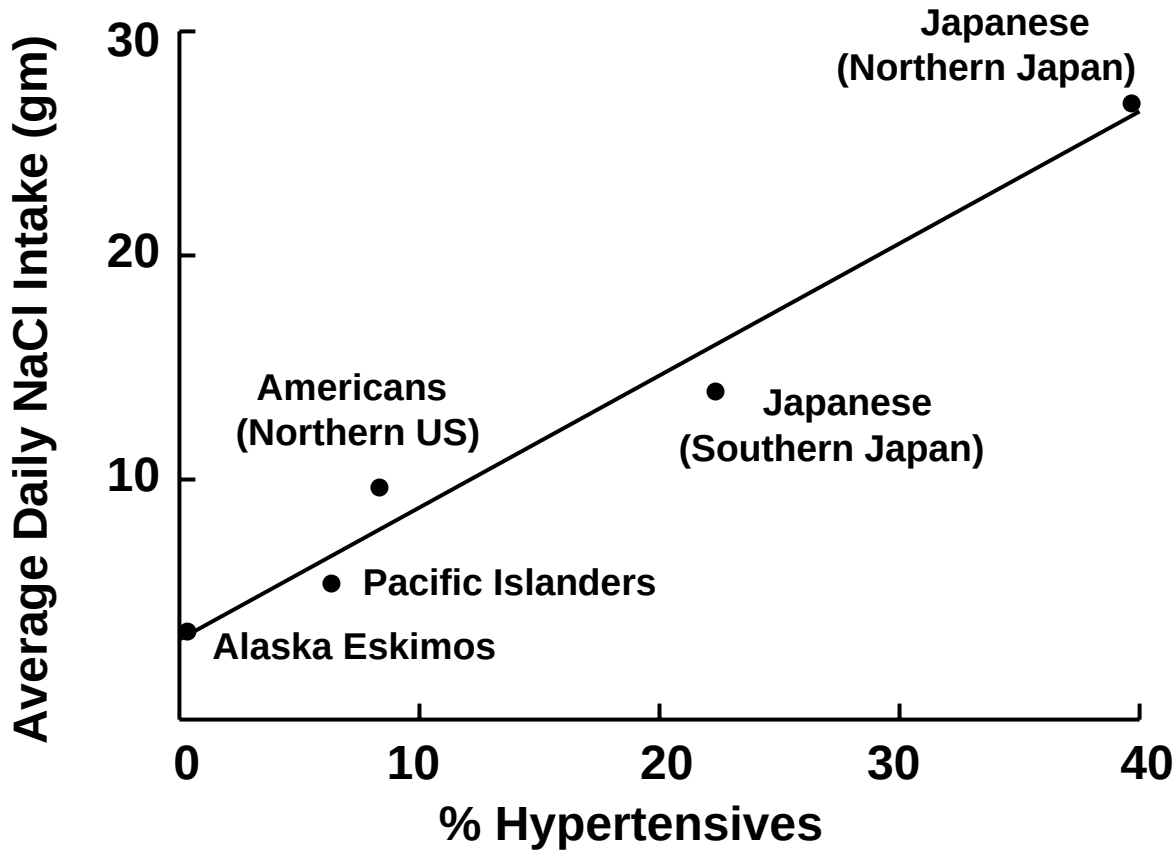
Genes, Diets, & Hypertension

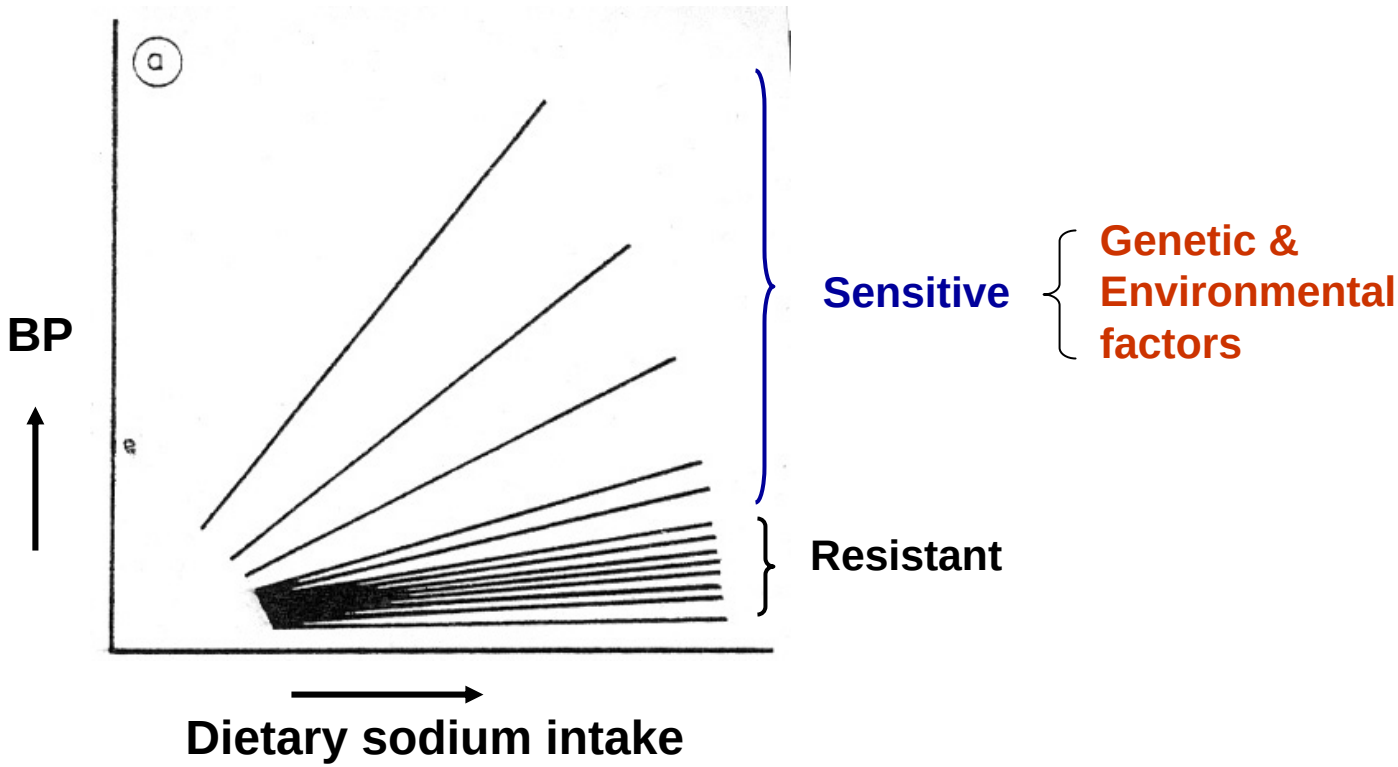
Chou-Long Huang, MD PhD

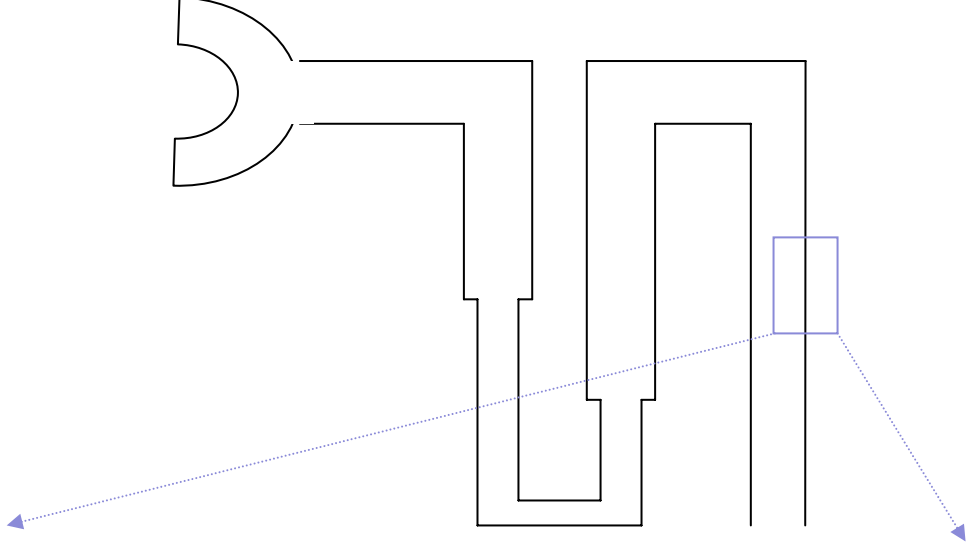
Relationship between salt intake and hypertension



Dahl, 1960

Sensitivity to Salt-Induced Hypertension





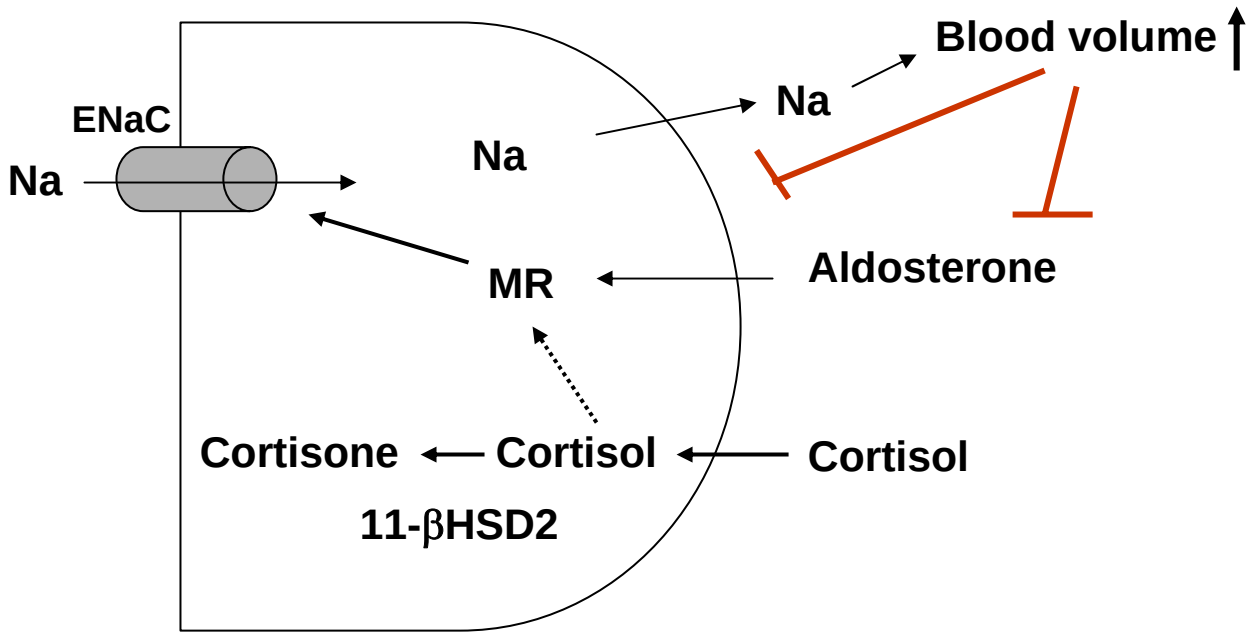
Epithelial Na Channel (ENaC)

Steroid Hormones:

1. **Sex hormones**
2. **Mineralocorticoids**
3. **Glucocorticoids**

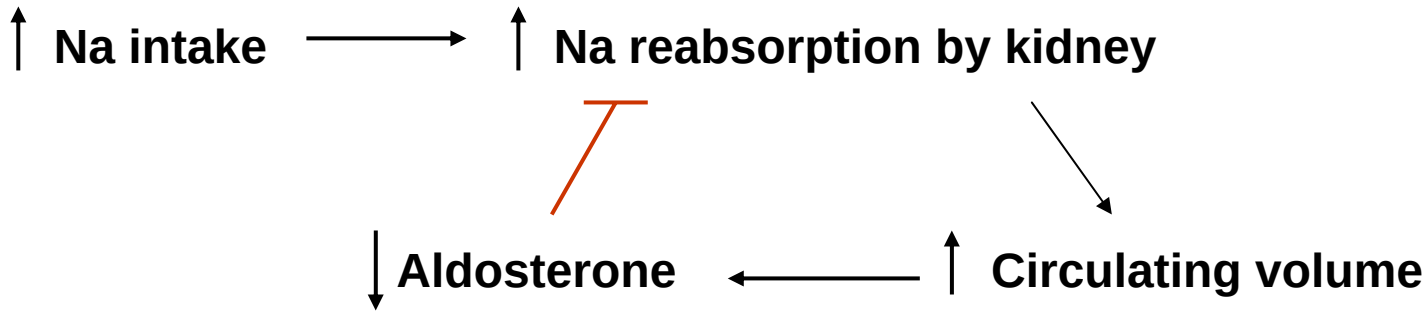
Mineralcorticoid receptor (MR)

11-βHydroxysteriod dehydrogenase

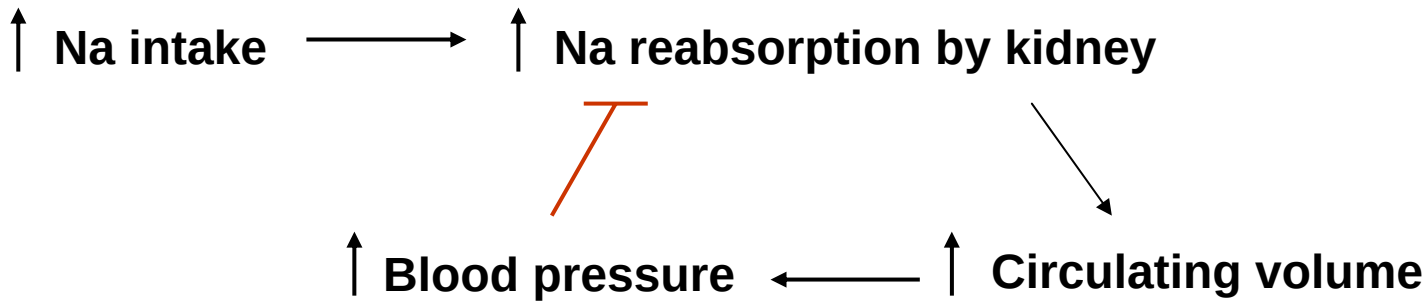


Defense Mechanisms Against Salt-Induced Hypertension

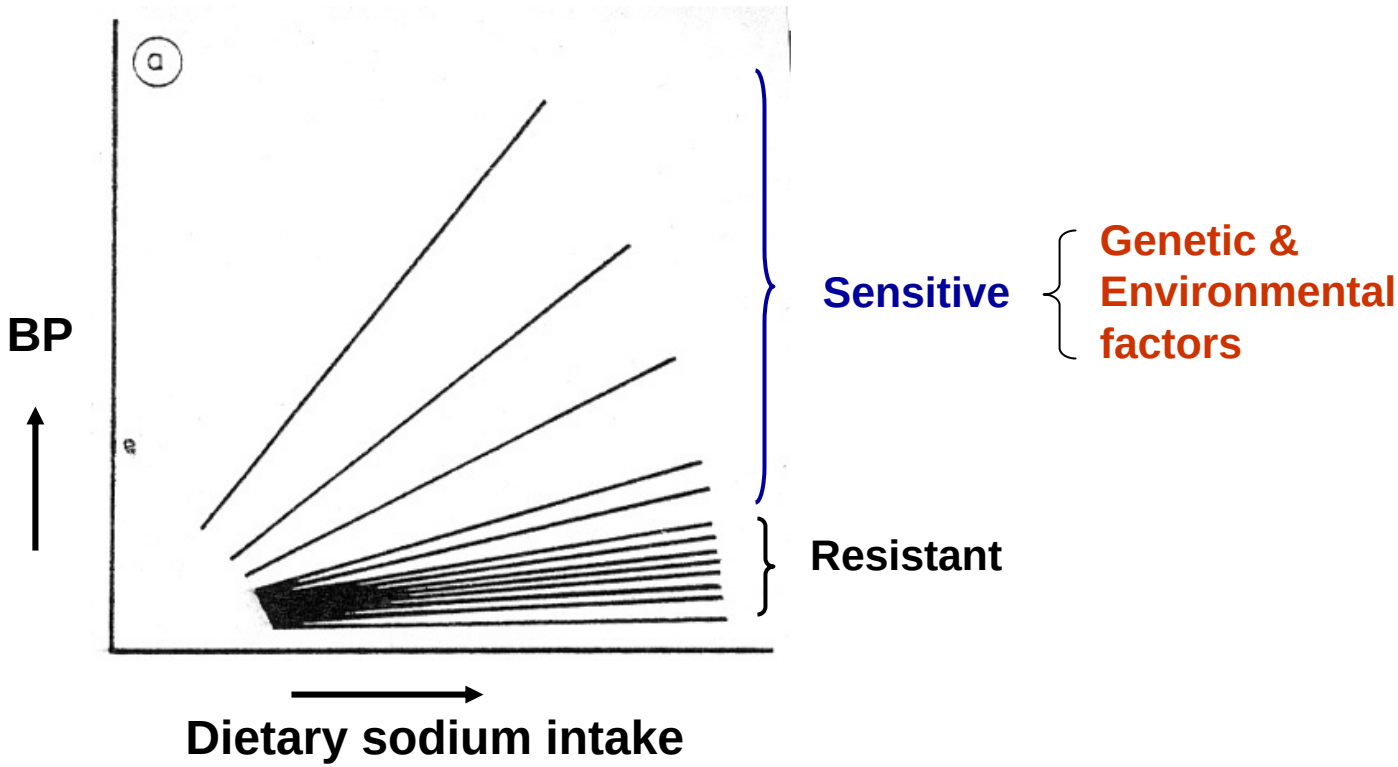
1. Aldosterone



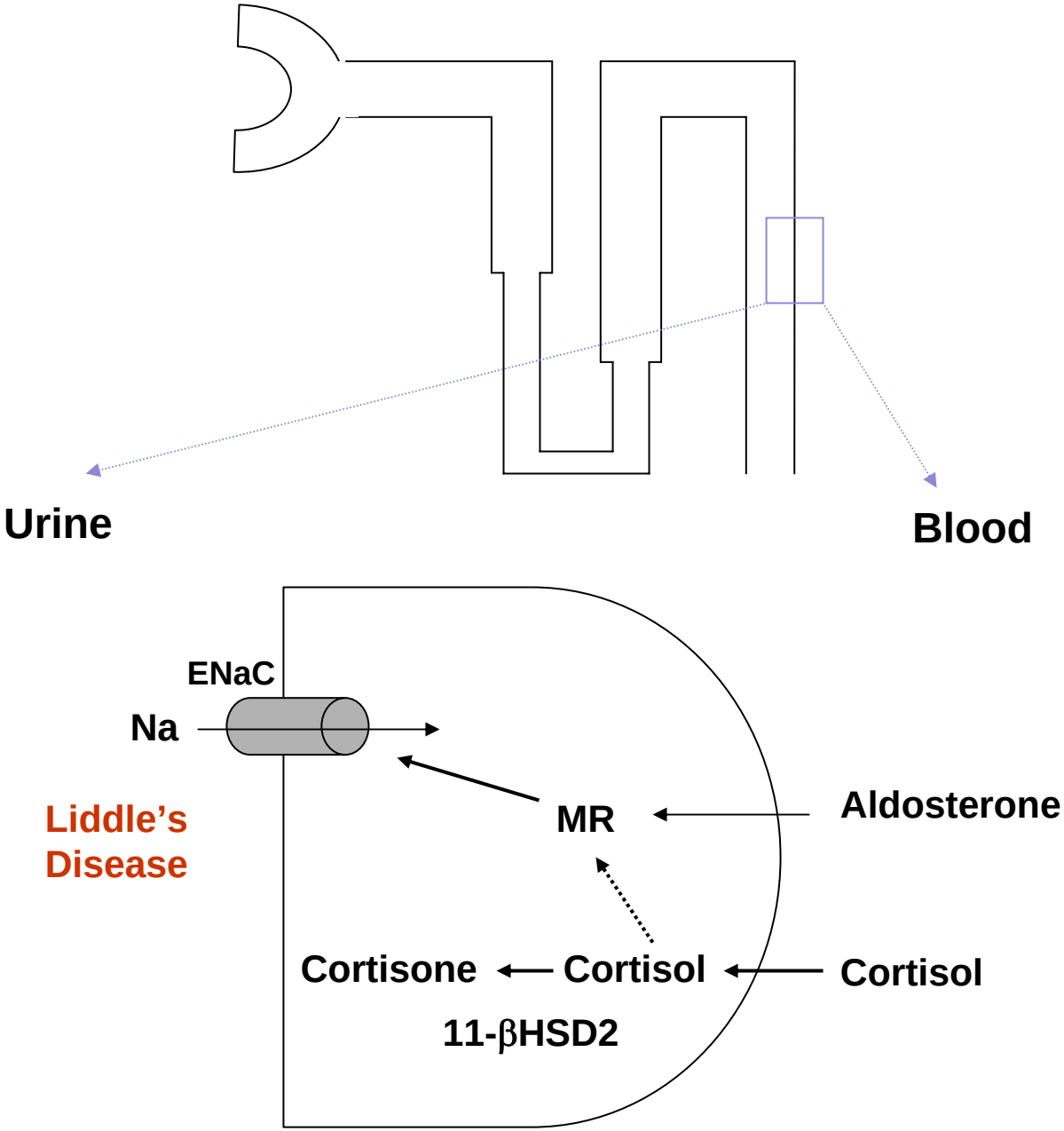
2. Pressure-Natriuresis



Sensitivity to Salt-Induced Hypertension



Genetic Factors (Diseases) That Increase Na Reabsorption

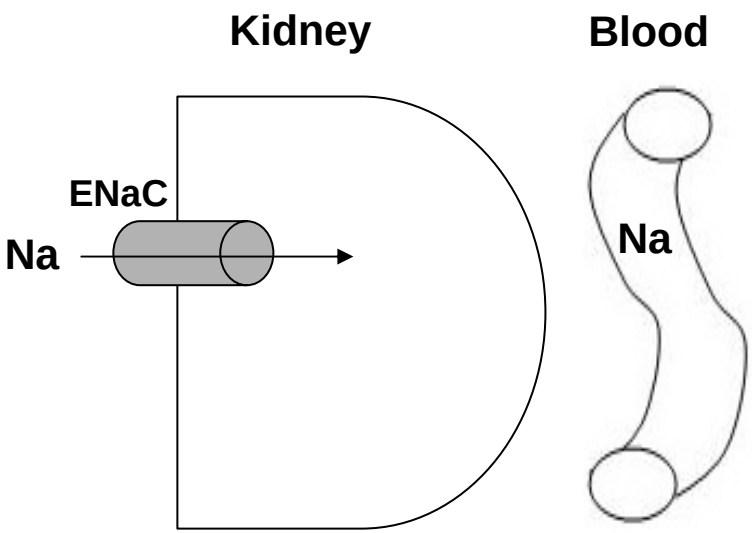


Liddle's Disease

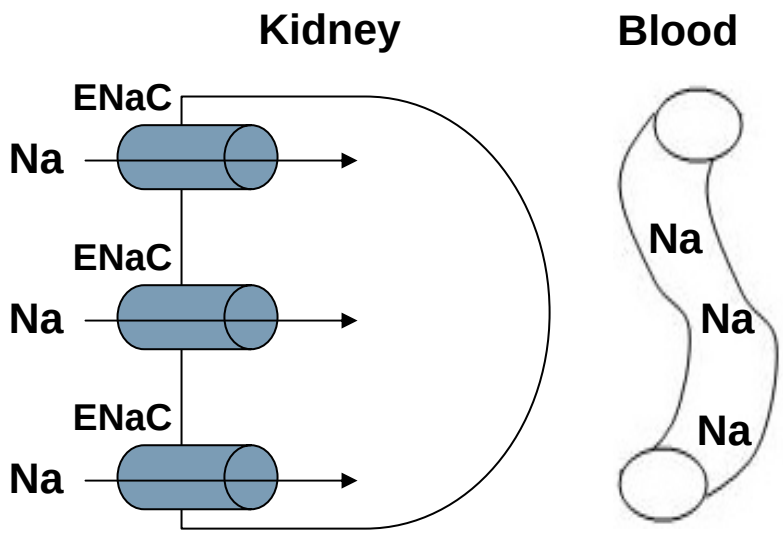
1. Autosomal-dominant disease featured by hypertension and hypokalemia (low blood potassium).

2. Occurs a result of gain-of-function mutations of ENaC, leading to increased number of ENaC channels at the cell surface

Normal

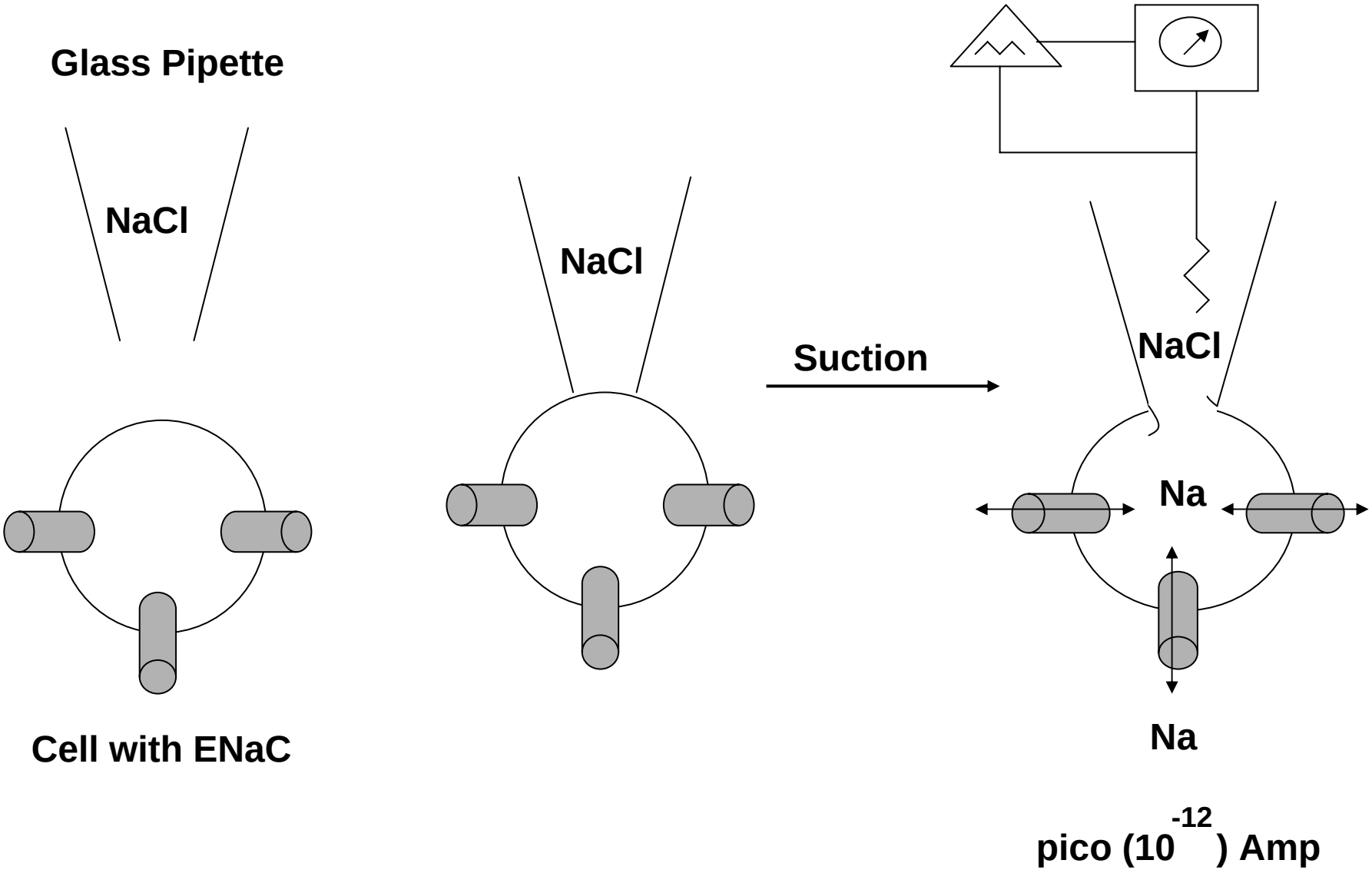


Liddle's Disease



Hypertension

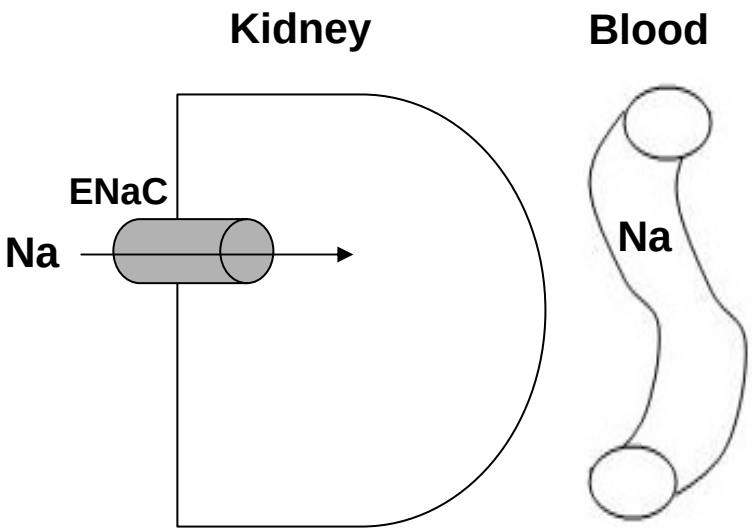
Patch-Clamp Recording of Ion Channels



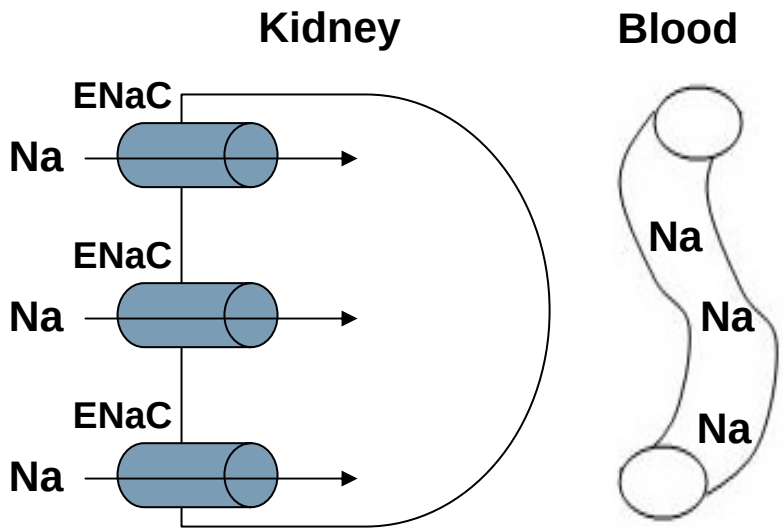
pico (10^{-12}) Amp

Liddle's Disease

Normal

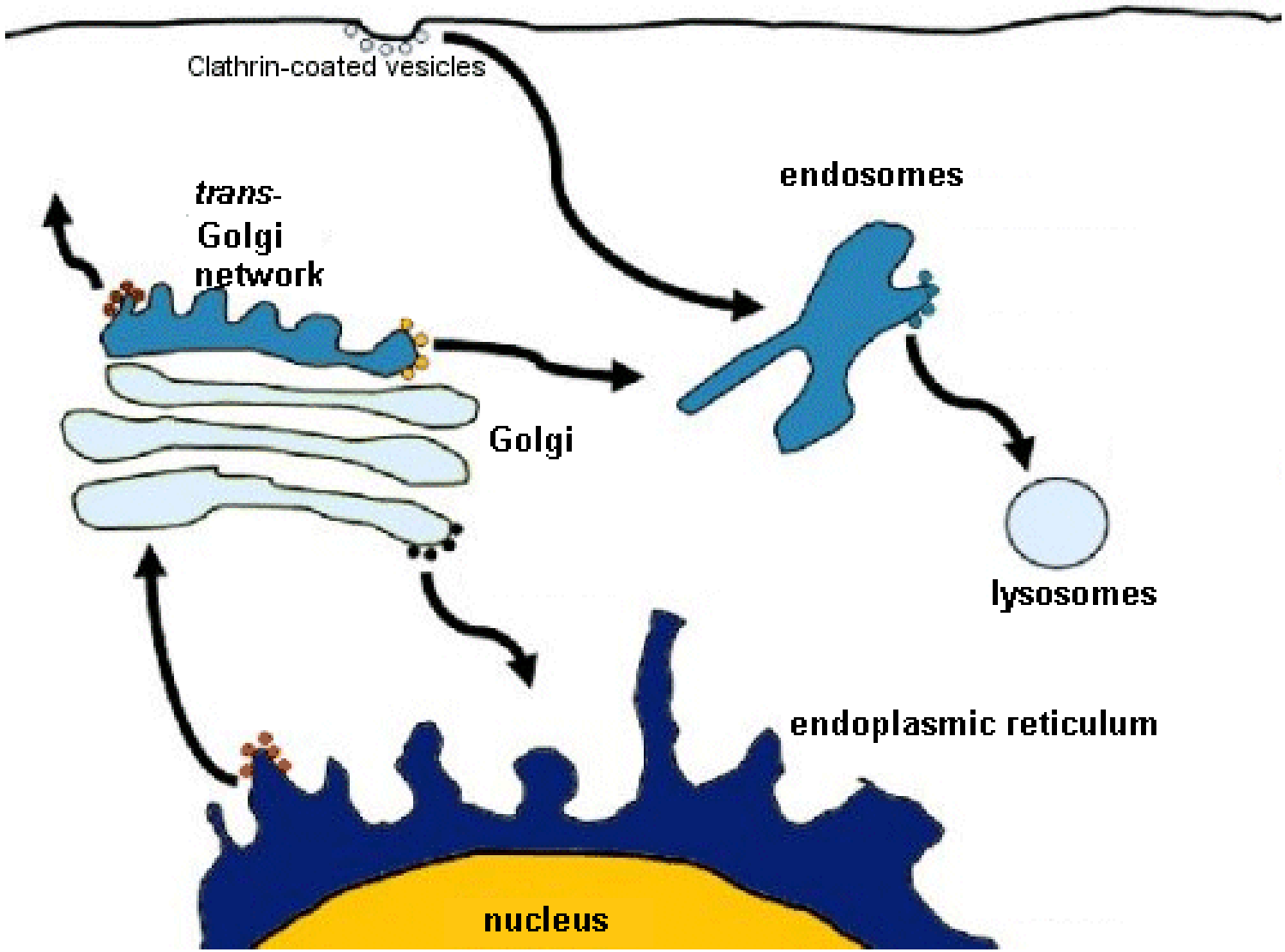


Liddle's Disease

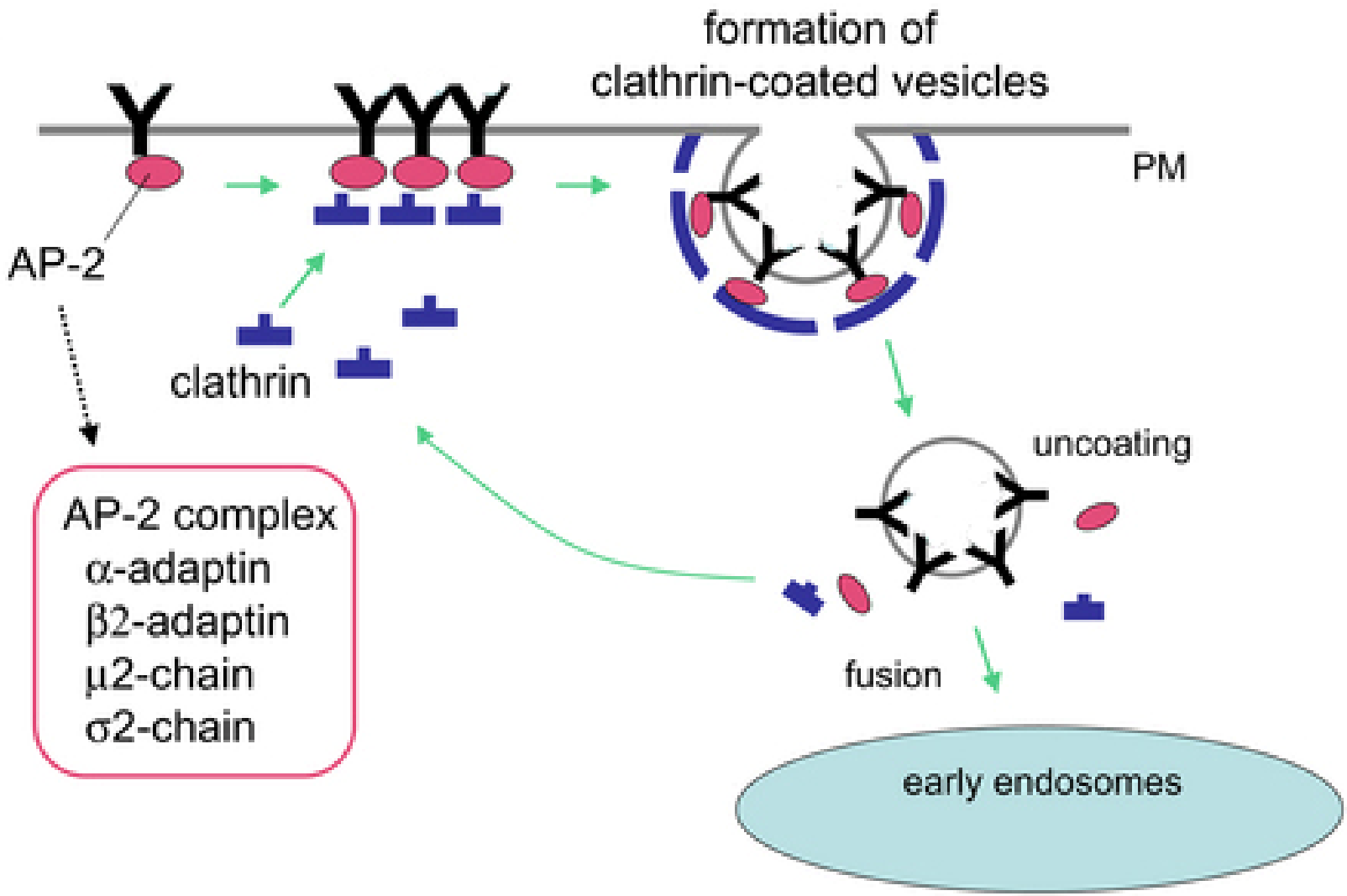


Hypertension

Cell Membrane Proteins are Endocytosed and Degraded

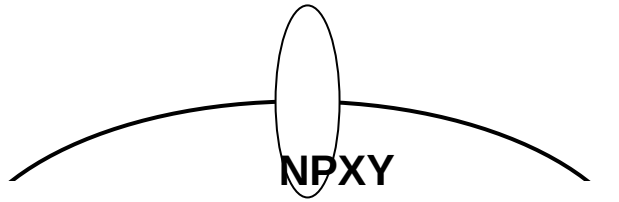


Clathrin-dependent endocytosis

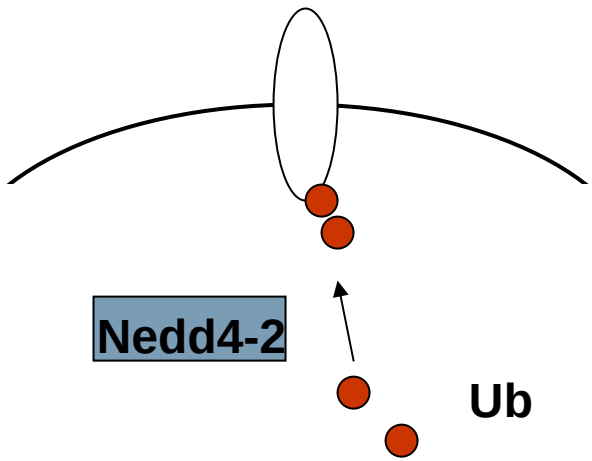


Recognition of Proteins for Clathrin-Mediated Endocytosis

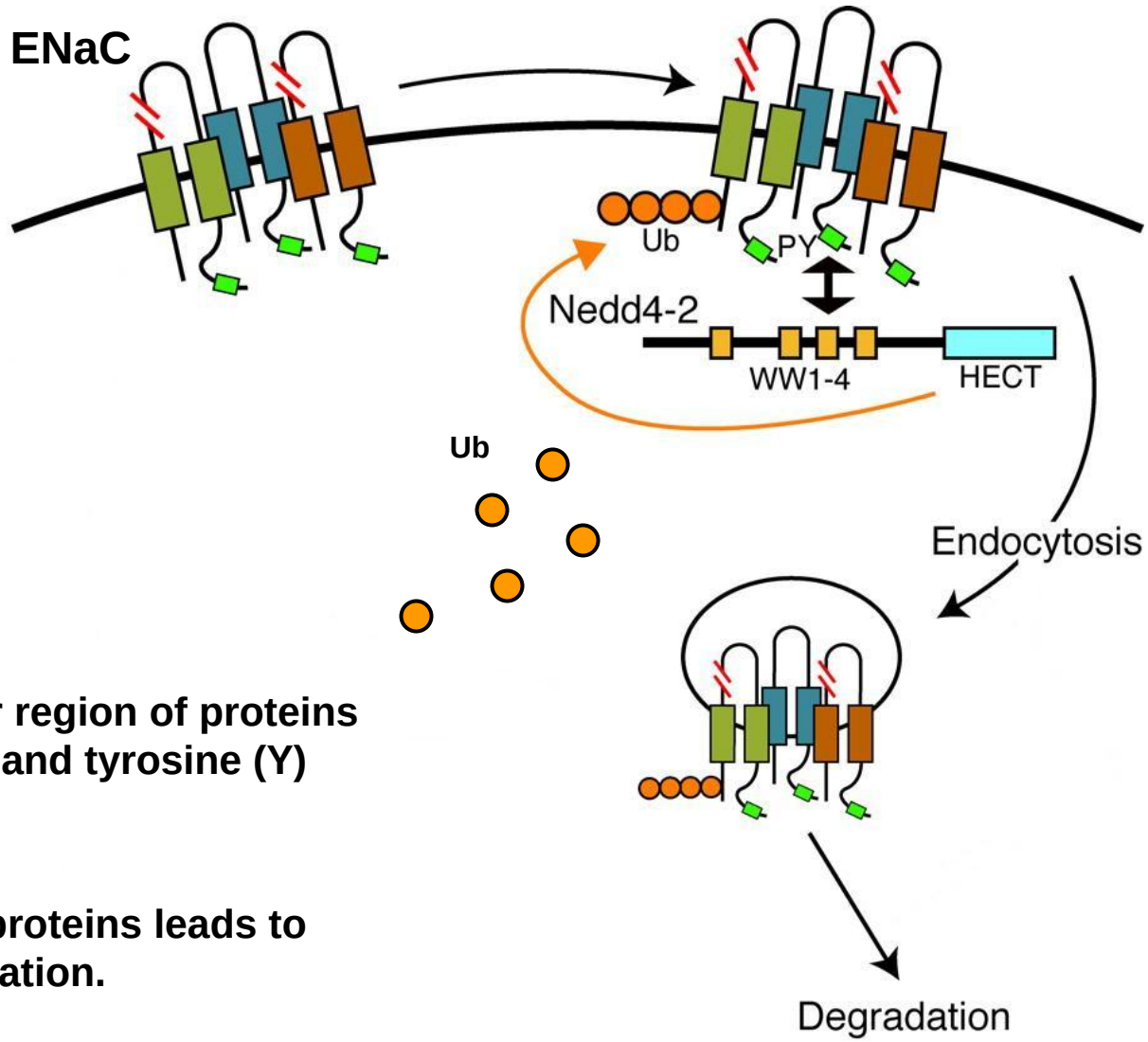
1. Intracellular region contains specific amino acid sequence for recognition by AP2 or clathrin



2. Tagging mechanism:
   Ubiquitin (Ub) is a 76 amino acid peptide that can be used to tag proteins destined for endocytosis



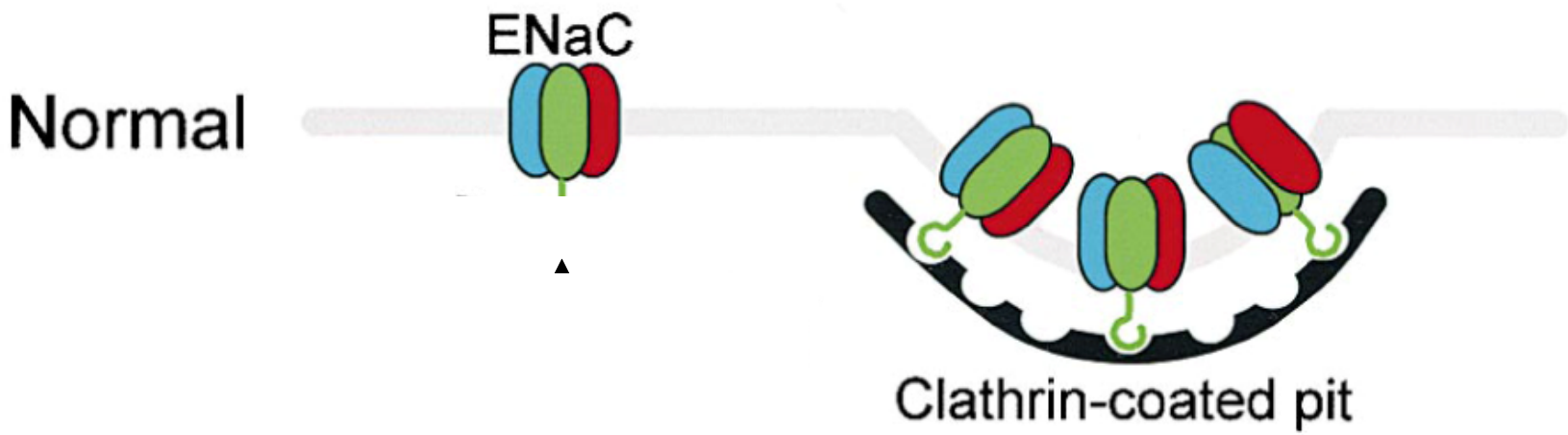
Nedd4-2 is a ubiquitin ligase. Nedd4-2 attachs ubiquitin (Ub) molecules to membrane proteins.



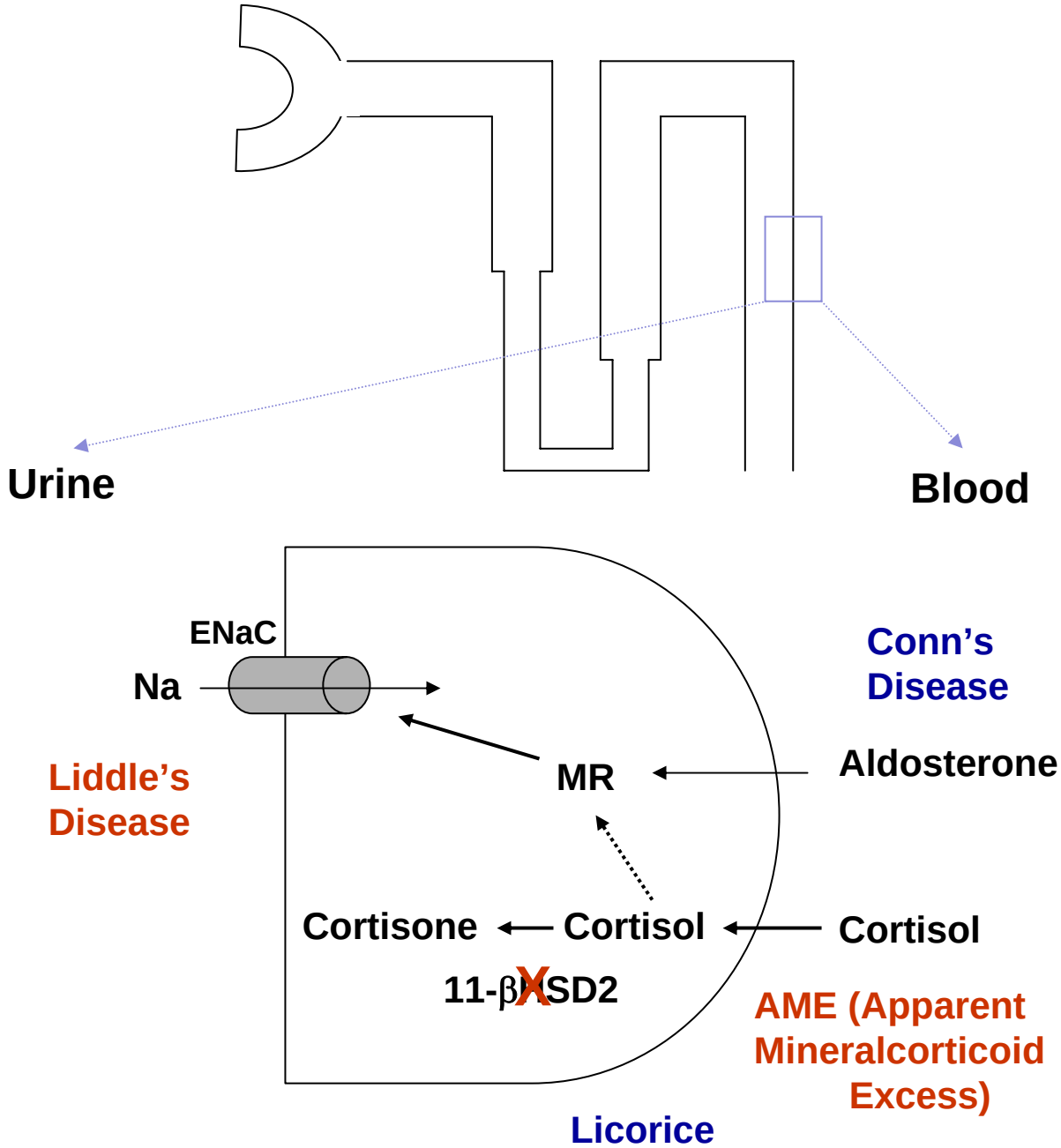
Nedd4-2 binds to intracellular region of proteins rich in amino acid proline (P) and tyrosine (Y)

Ubiquitination of membrane proteins leads to their endocytosis and degradation.

Mutations of ENaC in Liddle's Disease Prevent Ubiquitination



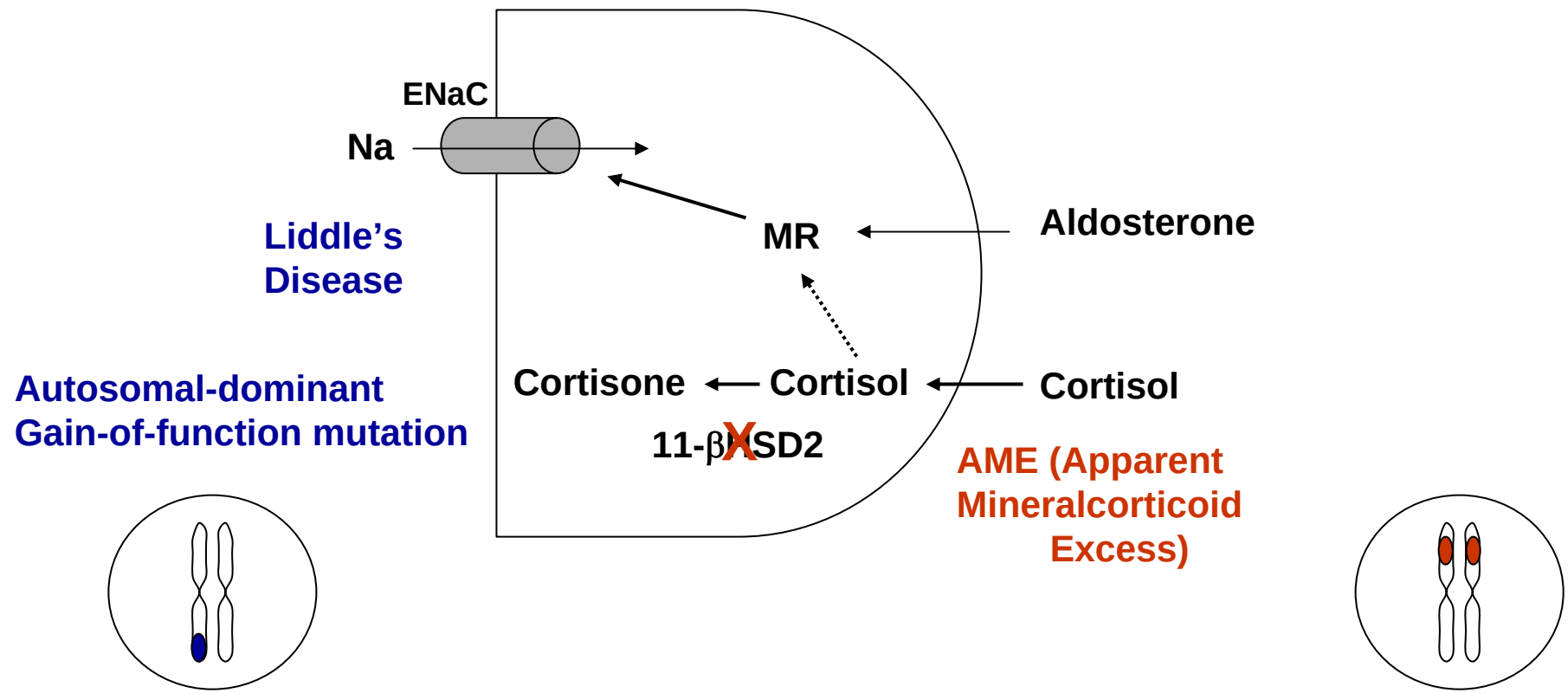
Genetic Factors (Diseases) That Increase Na Reabsorption



Apparent Mineralcorticoid Excess (AME)

1. Autosomal-recessive disease

2. Occurs as result of loss-of-function mutations of 11-βHSD2

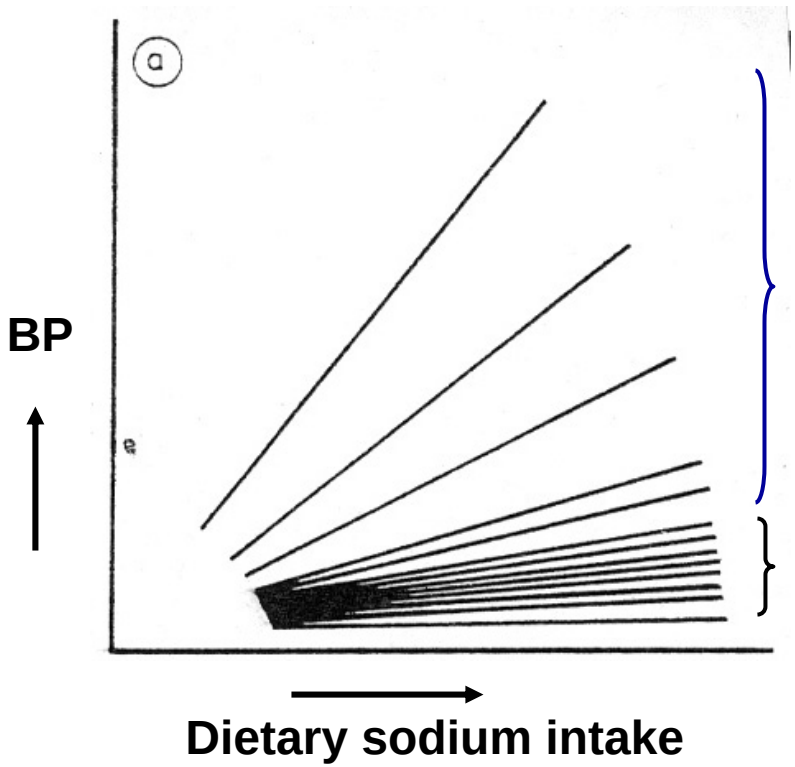


In general, loss-of-function mutations are inherited as recessive

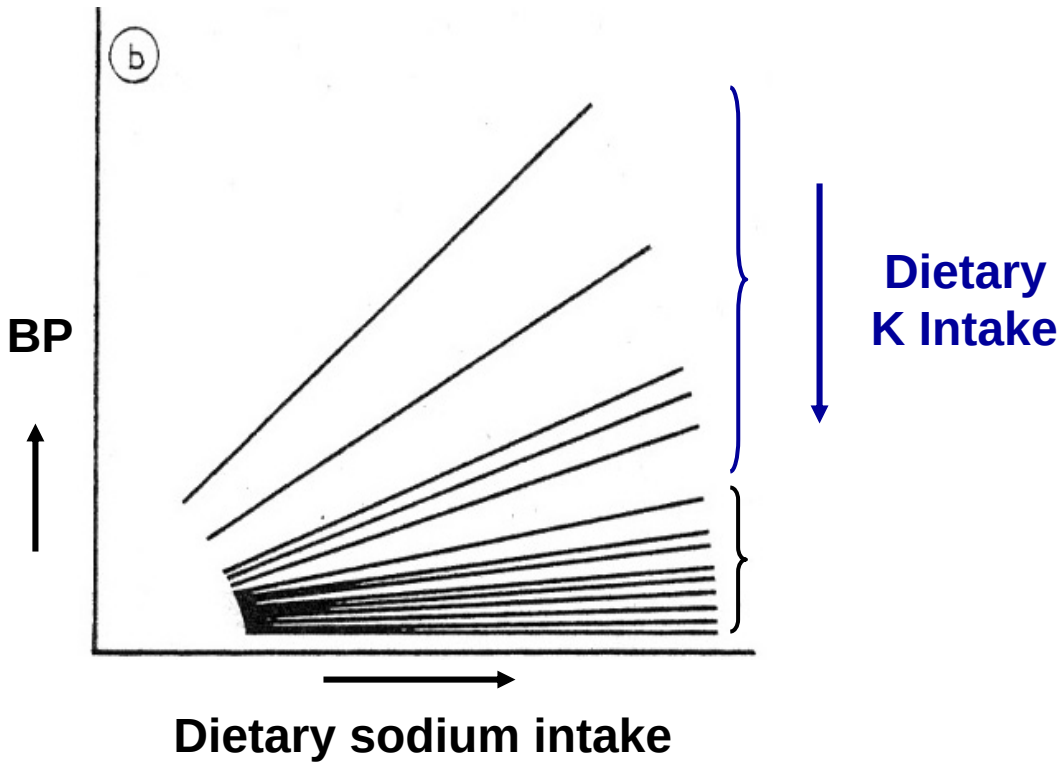
Exceptions:

1. **Haplo-insufficiency (50% of protein function is insufficient)**
2. **Second-hit phenomena (somatic mutation on top of inherited recessive mutation**
3. **Dominant-negative effect (mutant protein antagonizes non-mutant protein function)**

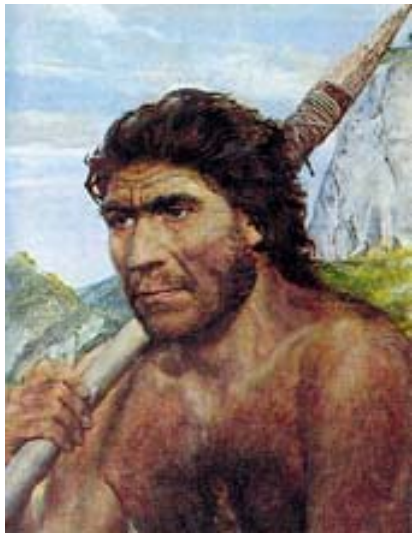
Sensitivity to Salt-Induced Hypertension



Role of Dietary Potassium in Salt-Sensitive Hypertension

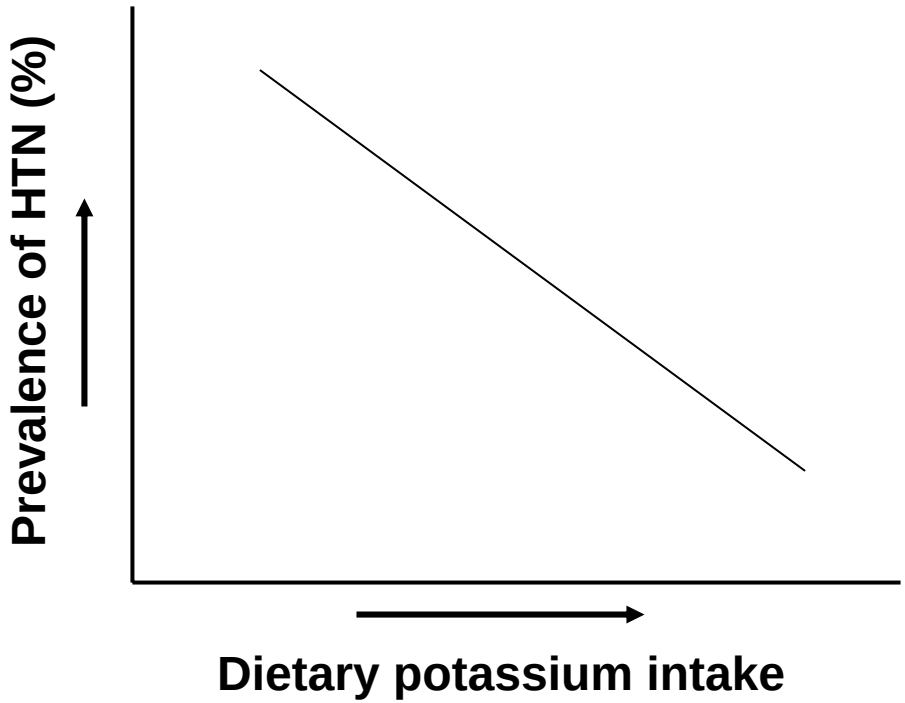


Dietary Sodium and Potassium Intake in Paleolithic vs Current Nutrition

	Late paleolithic	Current
		
Sodium (meq)	~20	~150
Potassium (meq)	~320	~50
Ratio	1:16	3:1

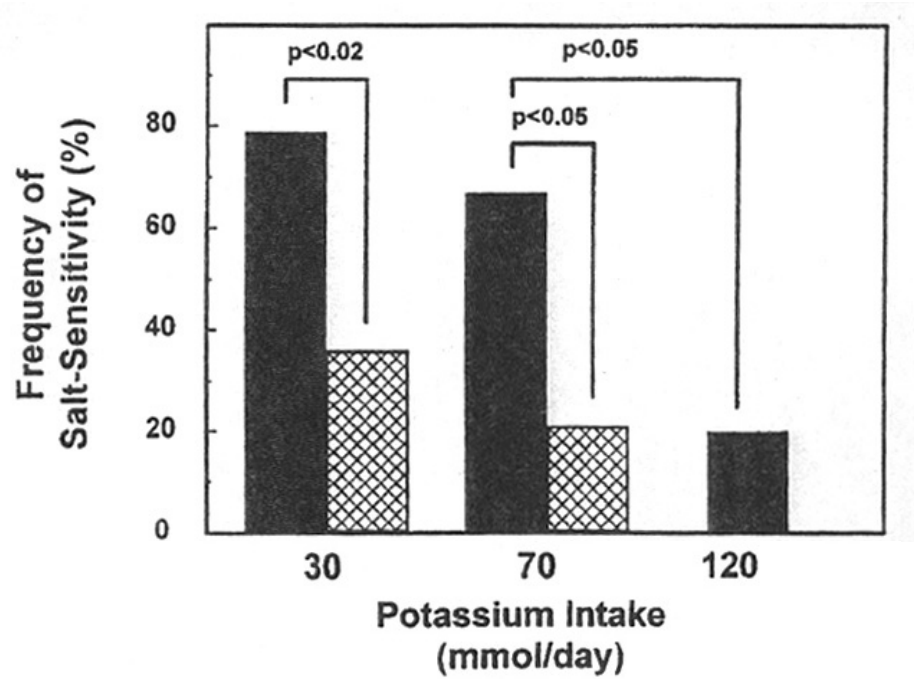
Eaton and Konner, “Paleolithic Nutrition”, NEJM, 1985

Prevalence of Hypertension Inversely Related to Potassium Intake



Herbert Langford, in **“**Dietary potassium and hypertension: Epidemiologic data”. Annals. Int. Med, 1983.A low potassium intake can be considered an unindicted coconspirator in hypertension.

High Dietary Potassium Intake Suppress Salt-Induced Hypertension



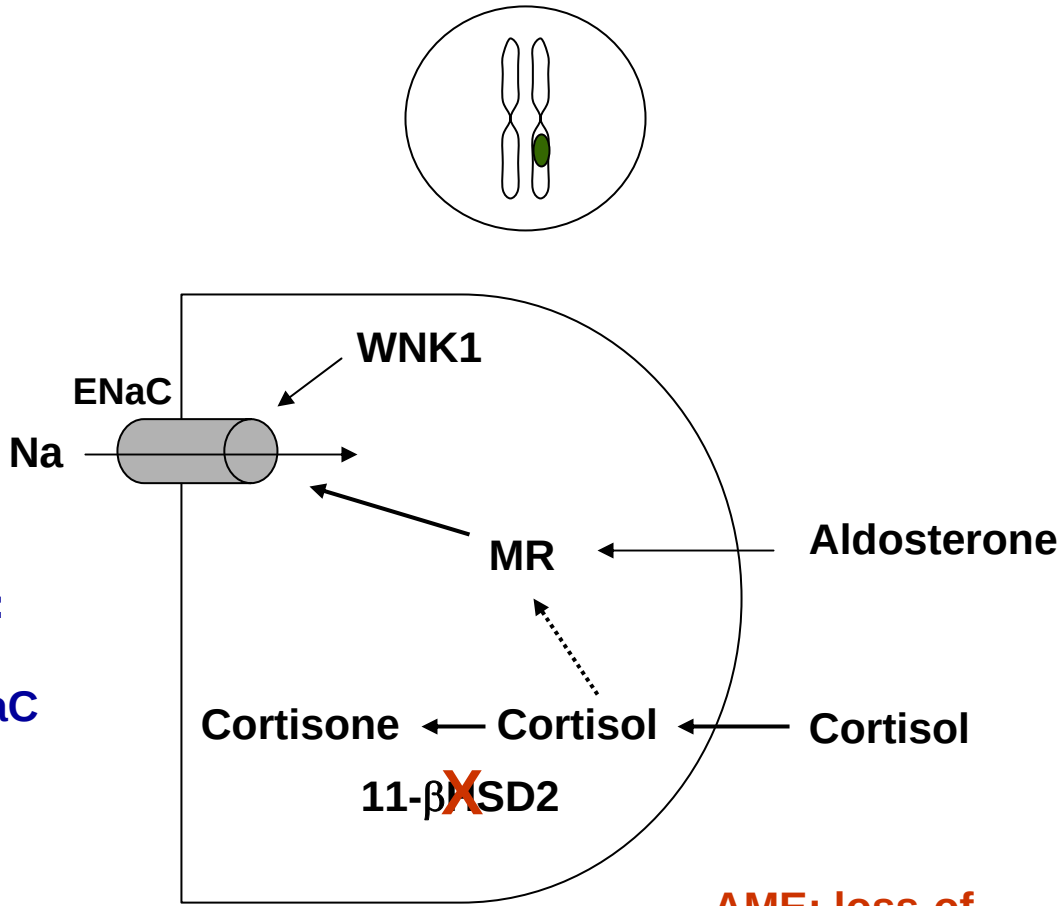
24 B, 14 W healthy normotensive subjects

Na	**15 meq**				**250 meq**		
K	**30 meq**				**70 meq or 120 meq**		
Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**

Morris et a., Hypertension, 1999

Genetic Diseases That Increase Na Reabsorption

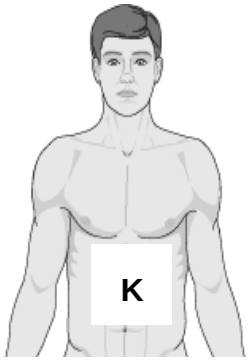
Gordon's syndrome: gain-of-function mutation of WNK1 kinase



Liddle's Disease: gain-of-function mutations of ENaC

AME: loss-of-function mutations of 11-βHSD2

Low potassium intake



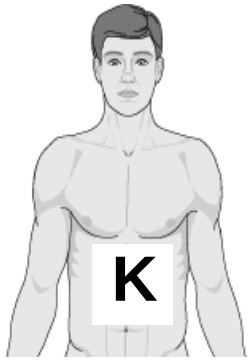
Blood pressure

ENaC

Na

WNK1

High potassium intake



Blood pressure

ENaC

Na

WNK1

Mechanism of Salt-Induced Hypertension