Contribution of Gut Microbiota to Hypertension

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Joint Graduate Student Seminar
11/12/19

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01 Background of HTN

02 How gut microbiota affects BP

03 Probiotics therapy

04 Summary

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Goal

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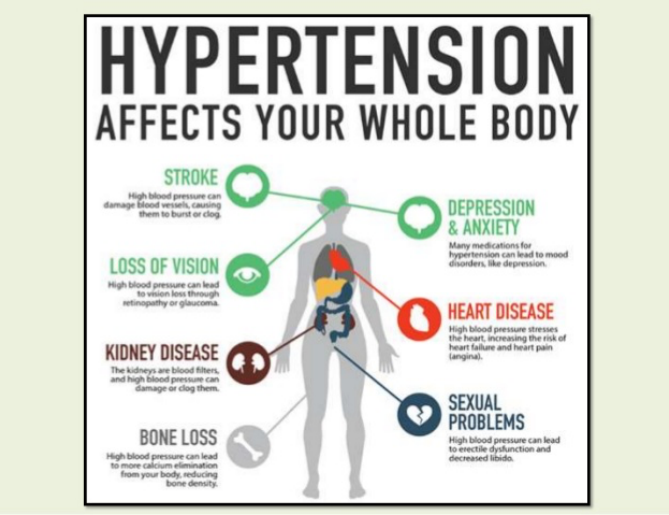
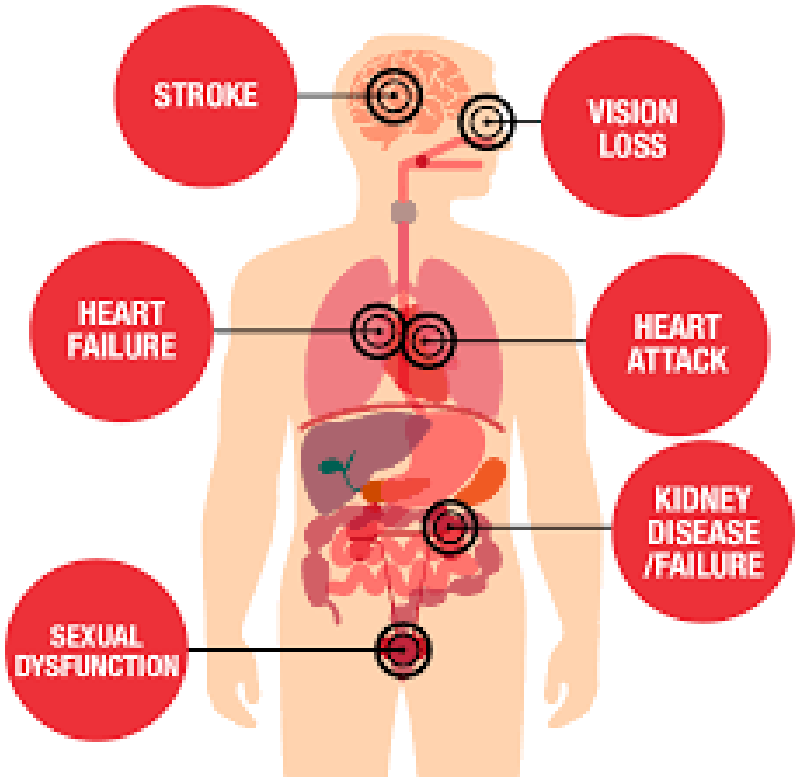


lood Pressure Category	Systolic mm Hg (upper #)		Diastolic mm Hg (lower
Normal	less than 120	and	less than 80
rehypertension	120 – 139	or	80 – 89
h Blood Pressure ertension) Stage 1	140 – 159	or	90 – 99
h Blood Pressure ertension) Stage 2	160 or higher	or	100 or highe
pertensive Crisis gency care needed)	Higher than 180	or	Higher than 1

What is Hypertension?

- Blood pressure (BP): Pressure exerted on the walls of blood vessels as the heart pumps
- Hypertension (HTN): BP too high
- Silent Killer: no warning signs or symptoms
- Severe Symptom: fatigue, nausea, vomiting, confusion, anxiety, chest pain, and muscle tremors
- Hypertension is a major cause of premature death worldwide



How common is HTN?

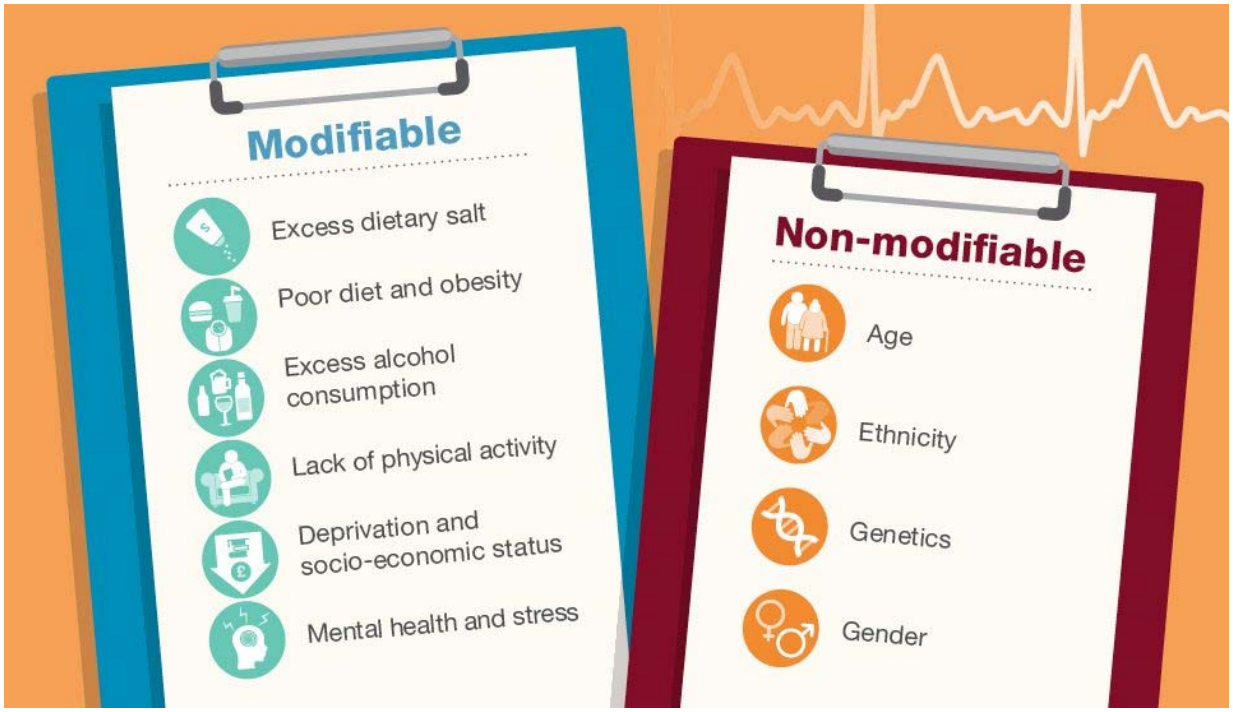
- Very common among HK adult
- Not many realize they have HTN
- In 2012, about 1 in 3 adults in Hong Kong has hypertension
- Half of them did not know about it

Background

Risk Factor → Hypertension → Cardiovascular Disease

Risk Factor for HTN

- **Modifiable Risk Factor:**
  - Unhealthy diets (excessive salt consumption, a diet high in saturated fat and trans fats, low intake of fruits and vegetables)
  - Physical inactivity
  - Consumption of tobacco and alcohol
  - Being overweight or obese
- **Non-modifiable Risk Factor:**
  - include a family history of hypertension
  - age over 65 years
  - co-existing diseases : Diabetes or kidney disease



Background

Risk Factor → Hypertension → Cardiovascular Disease

Alteration of bacteria abundance

Healthy

pHTN

HTN

China
60 HTN
60 healthy
(gender-, age-, and body weight-matched)

China
41 healthy
56 pHTN
99HTN

16S rRNA gene sequencing

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Alteration of bacteria abundance

HTN

Klebsiella

Porphyromonas

Prevotella

Actinomyces

Clostridium

Streptococcus

Parabacteroides

Eggerthella

Salmonella

Healthy

Faecalibacterium

Roseburia

Oscillibacter

Bifidobacterium

Bacteroides

Coprococcus

Butyrivibrio

Synergistetes

Office1 Standardize

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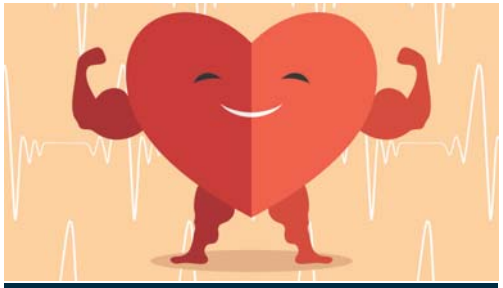
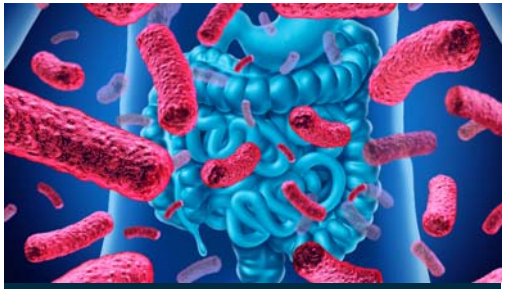
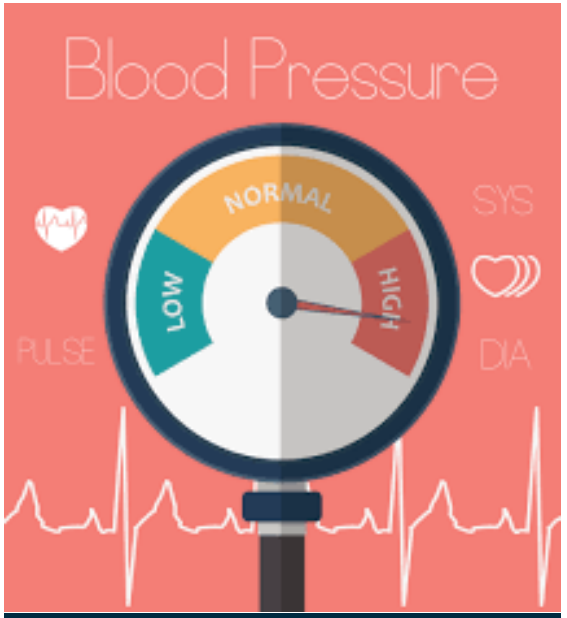
Alteration of bacteria abundance



Healthy

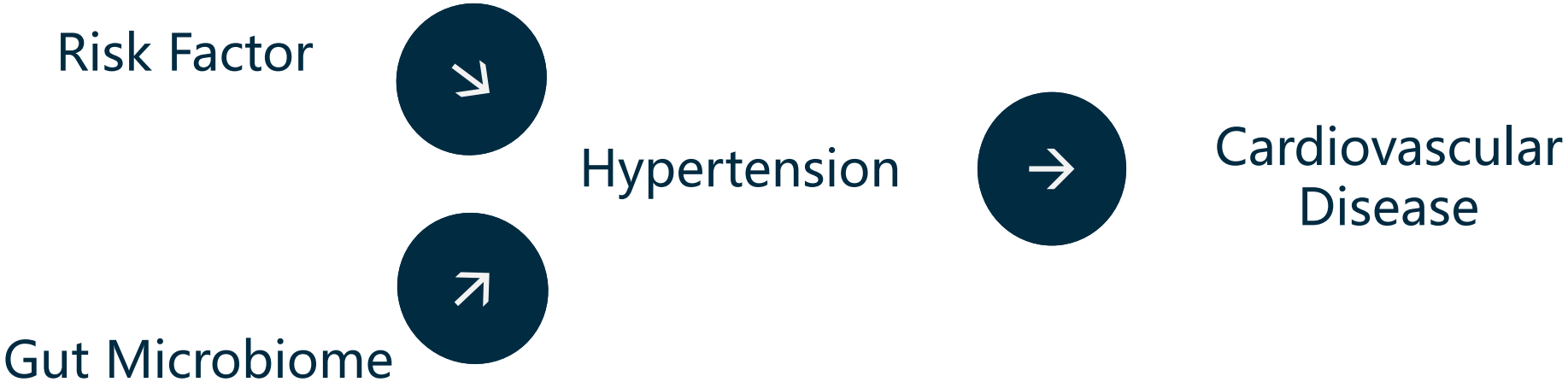


Gut Microbiome



Hypertension

Alteration of bacteria abundance



How could Gut Microbiome alter BP?

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How could Gut Microbiome alter BP?

1. Metabolite

2. Low-grade Inflammation

3. Hormones

Office3 List out three ways

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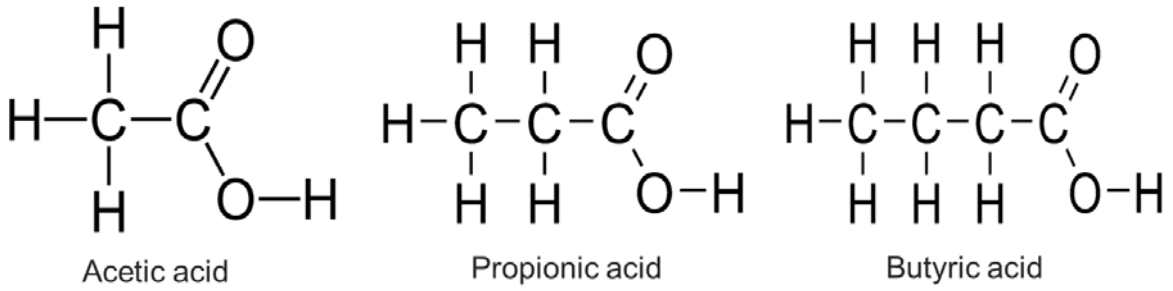
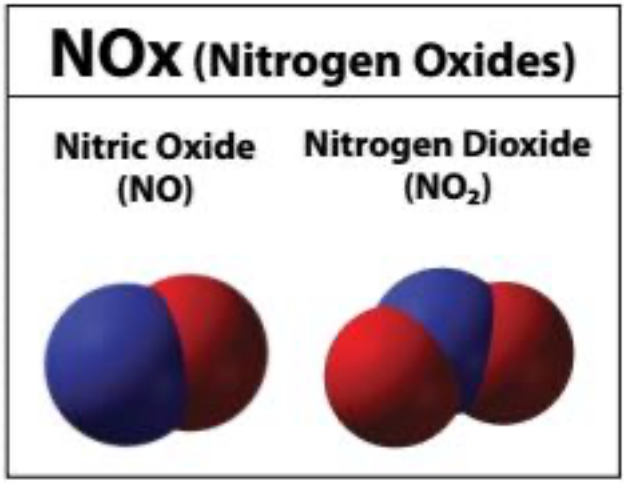
1. Metabolite from Gut Microbiota



Short Chain Fatty Acid (SCFA)



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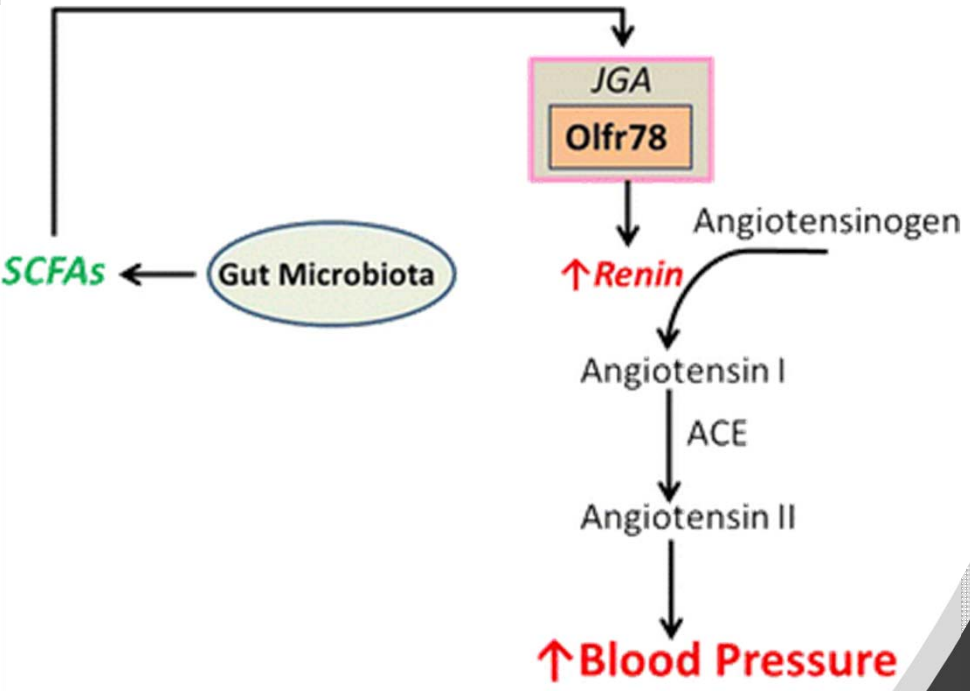

Short Chain Fatty Acid (SCFA)

- Produced by gut microbiota as fermentation products
  - Most abundant metabolites in gut
- Olfr78 is a receptor for SCFAs— acetate & propionate
  - responsible for mediating the secretion of renin
  - Rate-limiting step in the renin-angiotensin-aldosterone pathway
    - Lead to formation of angiotensin II, a potent vasoconstrictor
      → Increase body fluid volume and blood pressure

Jen Pluznick. 2015

Office4 Renin hormone

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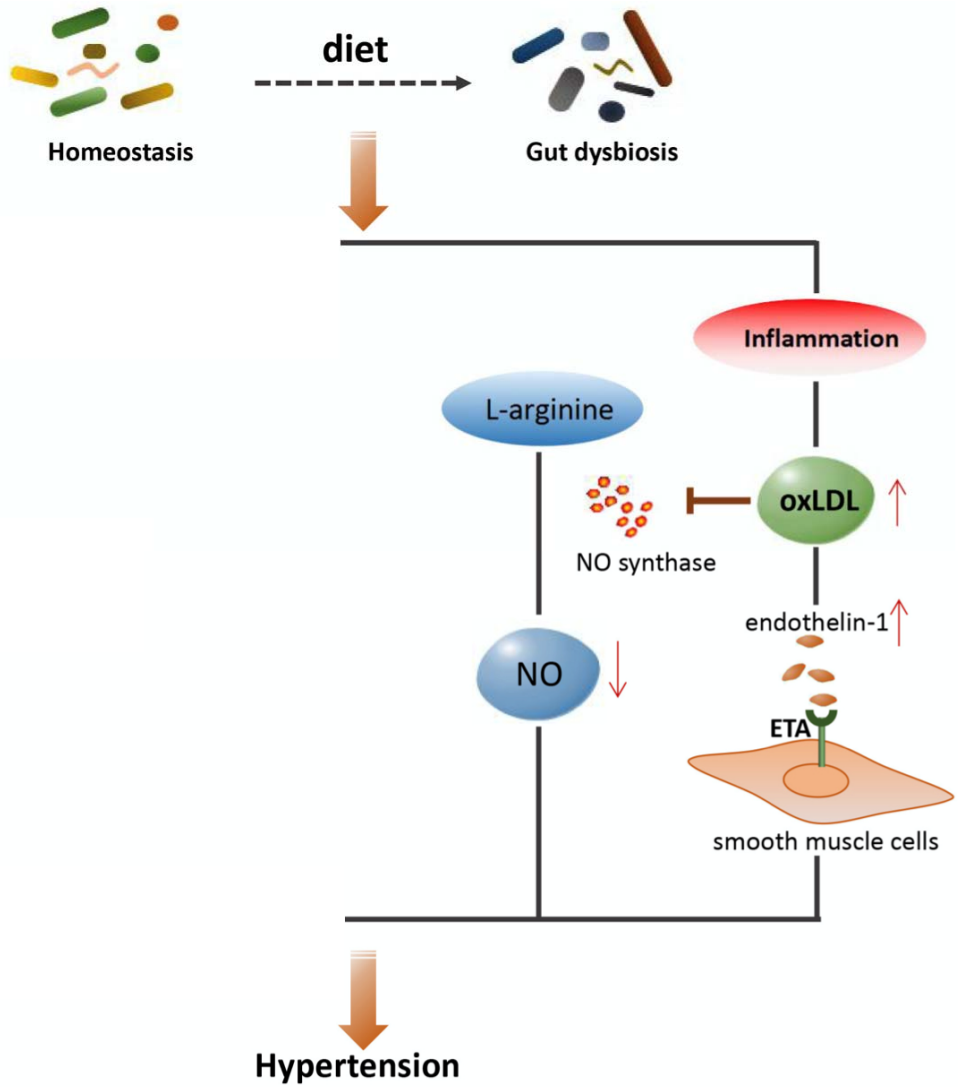
Office6

Nitric Oxide (NO)

- Nitric oxide (NO)
  - Important signaling molecule
  1. Regulation of regional blood flow
  2. smooth muscle relaxation
  3. secretory and immunological regulation in the GI tract
- Produced through oxidation of L-arginine by NO synthase
- NO is a well-established vasodilator

Junli Ma and Houkai Li. 2018



Office6 Produced naturally by human

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Office5

Nitric Oxide (NO)

- Dysbiosis can promote expression of pro-inflammatory cytokines & induce oxidative stress

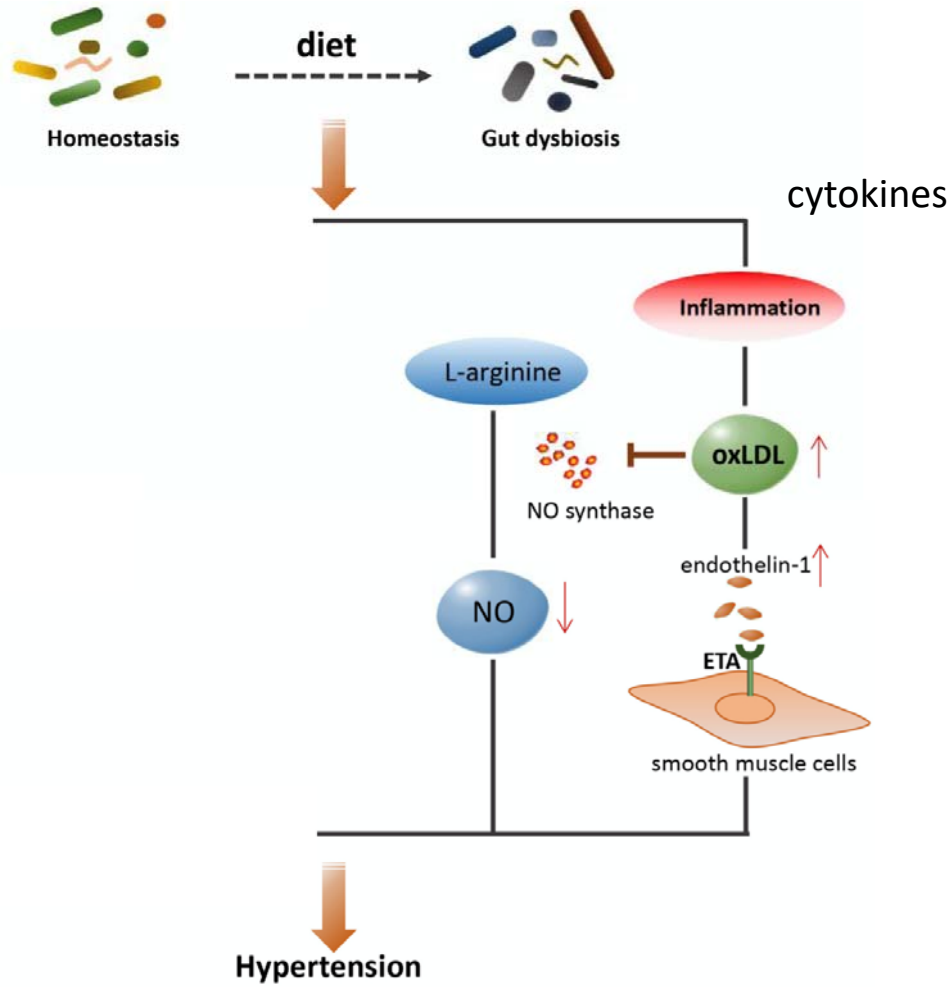
  →stimulate oxidation of LDL

- Ox-LDL (Oxidized Low-Density Lipoprotein)

  →inhibiting the production of NO

- Ox-LDL decreases the production of NO and reduces the degree of vasodilation
- Gut dysbiosis contributes to HTN through vasoconstriction mediated by oxidation of LDL(Ox-LDL)

Junli Ma and Houkai Li. 2018



Office5 Spell it out LDL
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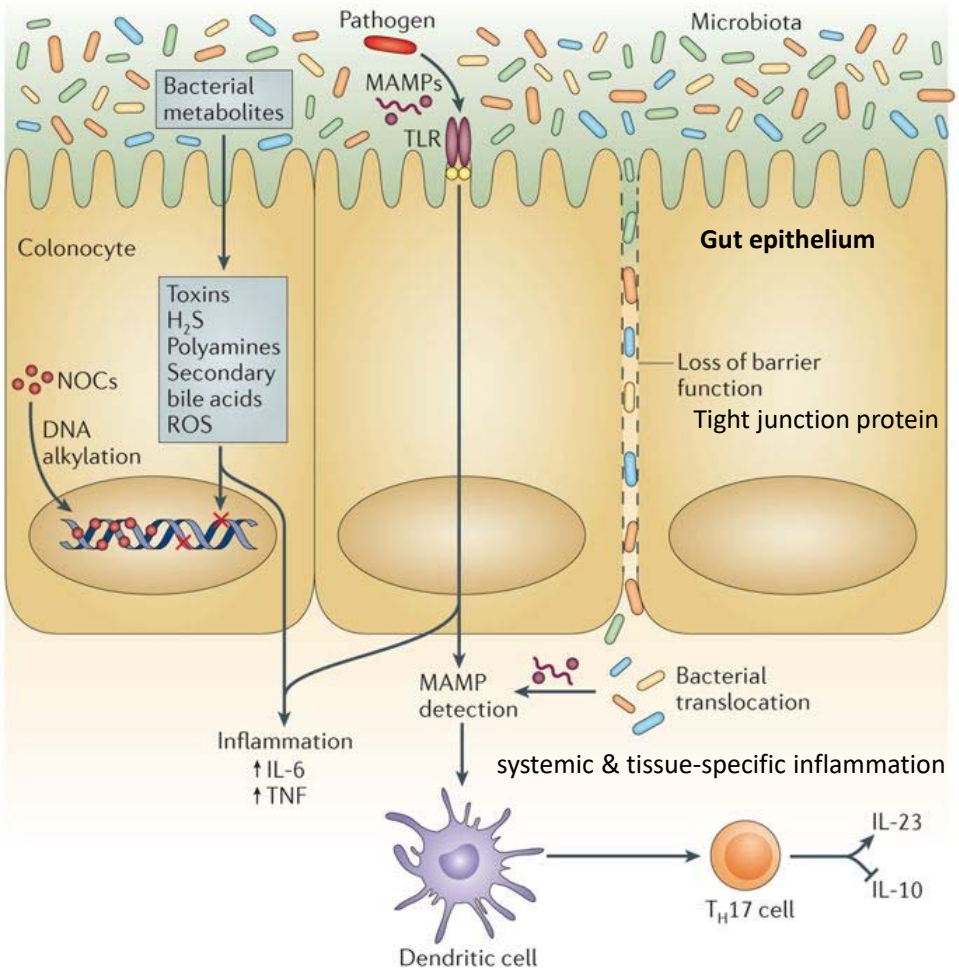
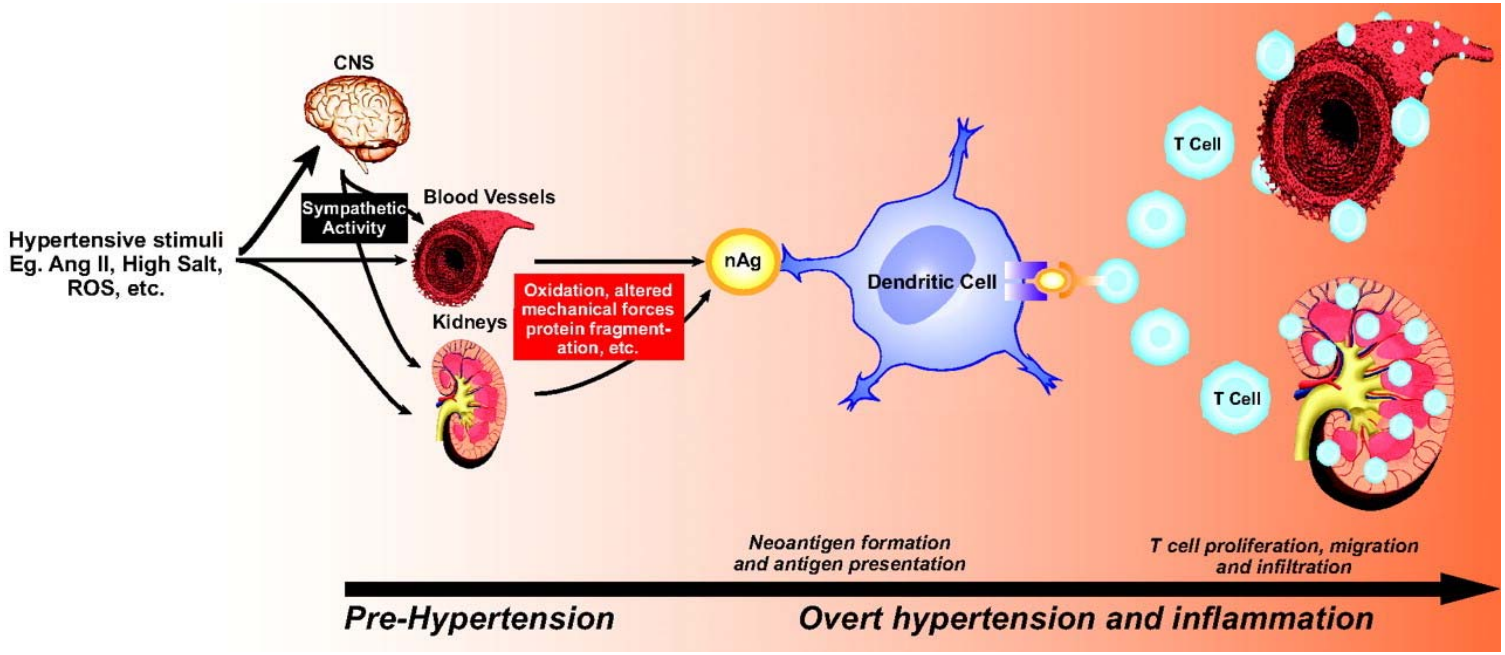
2. Low-grade Inflammation

Gut dysbiosis



Petra Louis et el. 2014

Low-grade Inflammation

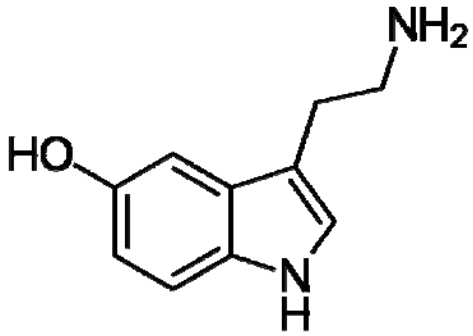


- Activated T cells enter the kidney and vasculature
- T cell–derived signals (IL-17) promote entry of other inflammatory cells (macrophages)
  →Release cytokines
    →cause vasoconstriction
    →promote sodium and water absorption
      →severe hypertension.

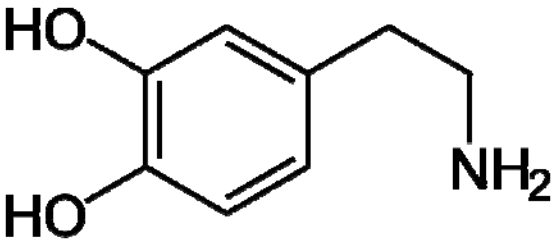
David. G. Harrison et el. 2010

3. Hormones

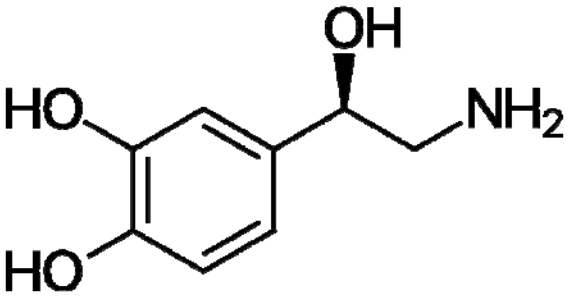
- Gut microbiota influence production of various hormones



serotonin



dopamine



norepinephrine

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Serotonin (5-HT)

Tryptophan + tryptophan hydroxylase
→Form 5-hydroxytryptamine (5-HT), or serotonin

Neurotransmitter/hormone
-Produced in the intestines and the brain
-Also present in blood platelets & central nervous system (CNS)

Important chemical and neurotransmitter in the human body

Help regulate mood and social behavior, appetite and digestion, sleep, memory, and sexual desire and function

Office7 Larger fond size

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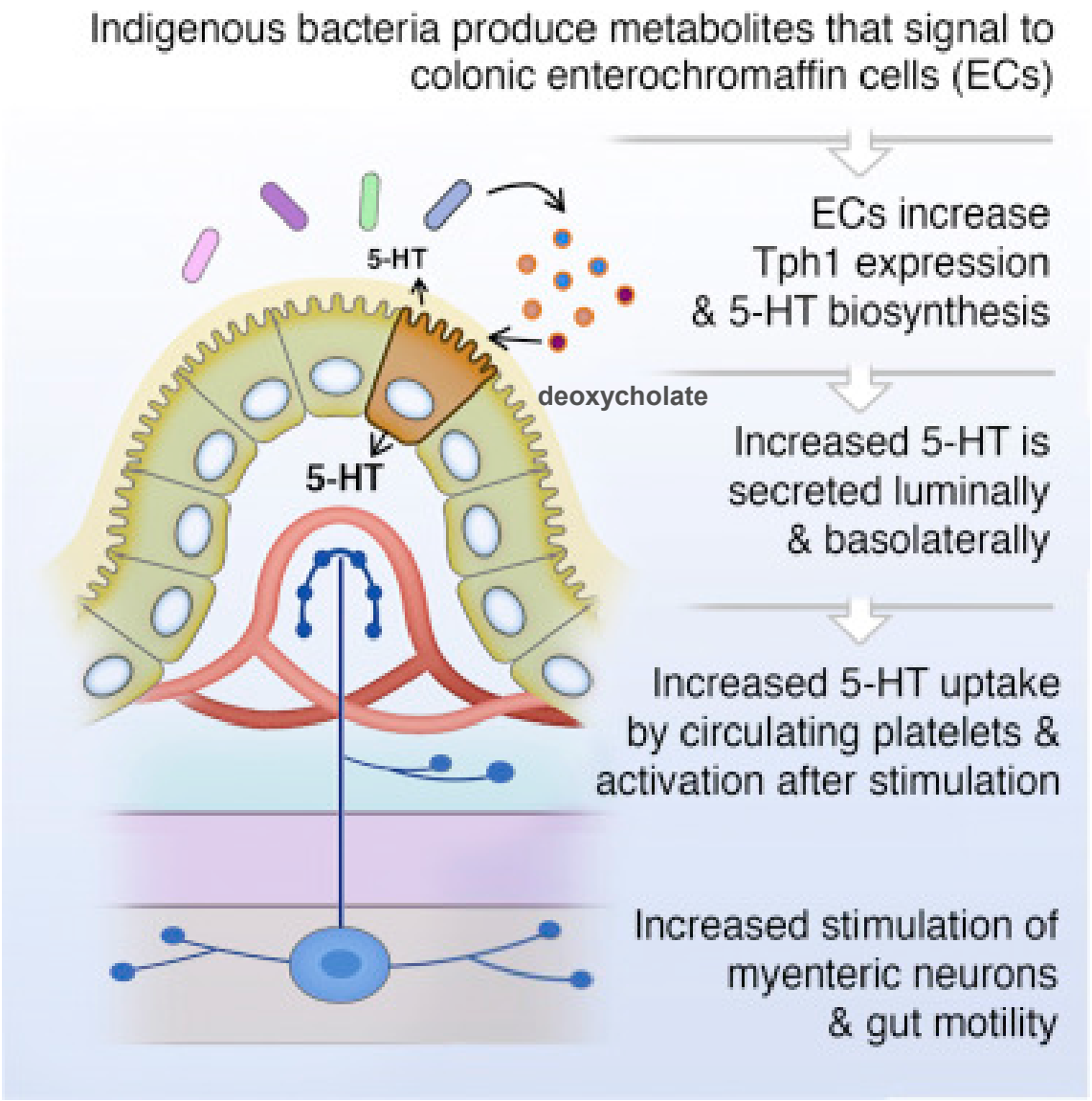
Serotonin

5-HT_2 receptor

1. Vasoconstriction — Increase BP
2. Facilitation of platelet aggregation
3. Augmentation of other vasoconstrictors: prostaglandin $F_{2\alpha}$, norepinephrine, angiotensin II, histamine

Serotonin



Jessica M. Yano et el. 2014

Probiotics Therapy

What is Probiotics?

-Live bacteria and yeasts

- good for you, especially your digestive system

-keep your gut healthy

Probiotics in supplements & foods, like yogurt

Dr.s often suggest them to help digestive problems

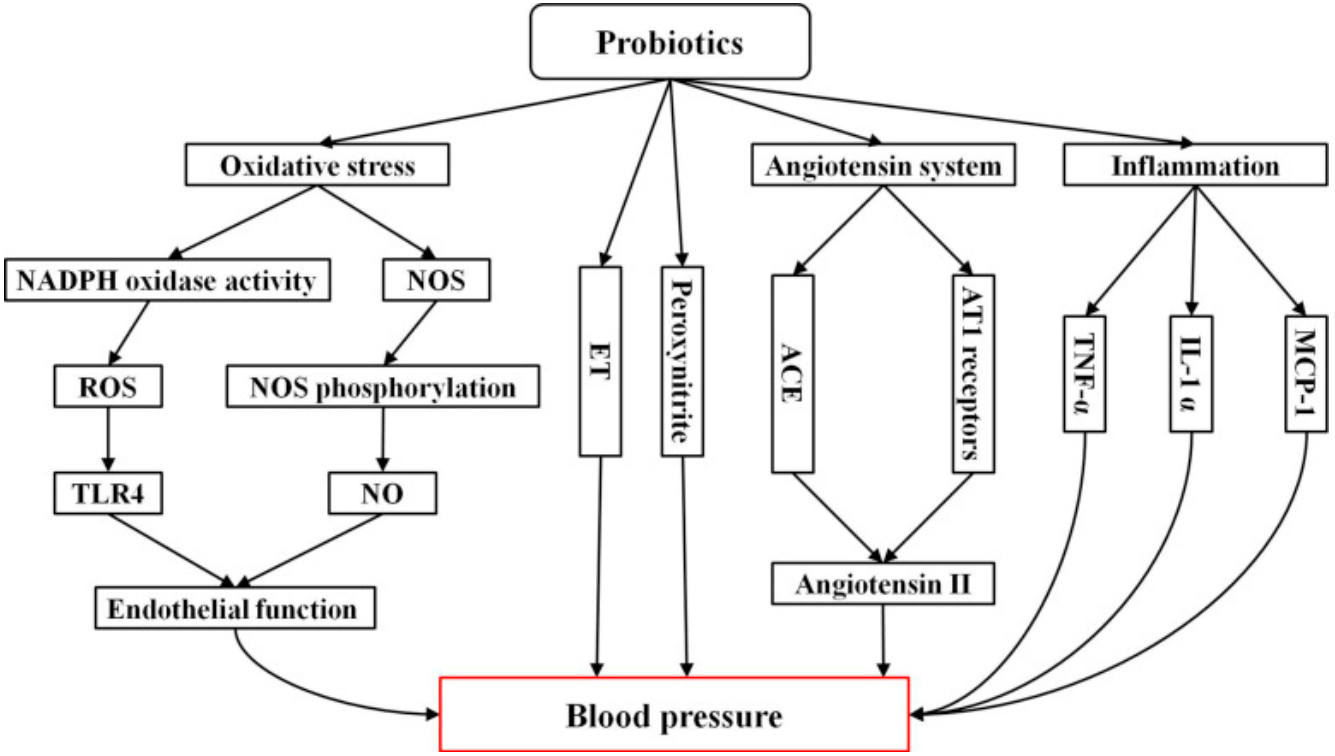
Probiotics Therapy

- Probiotics are widely studied in medical application to prevent or treat many diseases

- such as rheumatism arthritis, diabetes, obesity, allergies and asthma

- Therapeutic effects of probiotics on HTN have also been confirmed in animal and humans

Probiotics Therapy



Probiotics Therapy

Lactobacilli

- Enhance release of anti-inflammatory factors
- Protect against invasion of pathogenic bacteria
  - Competition & lactic acid produced

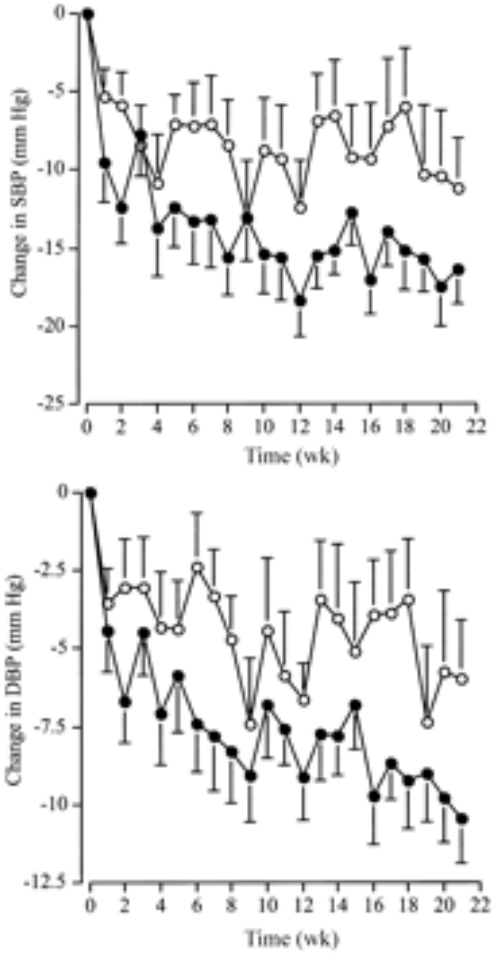
Probiotics Therapy

Randomized

placebo-controlled study

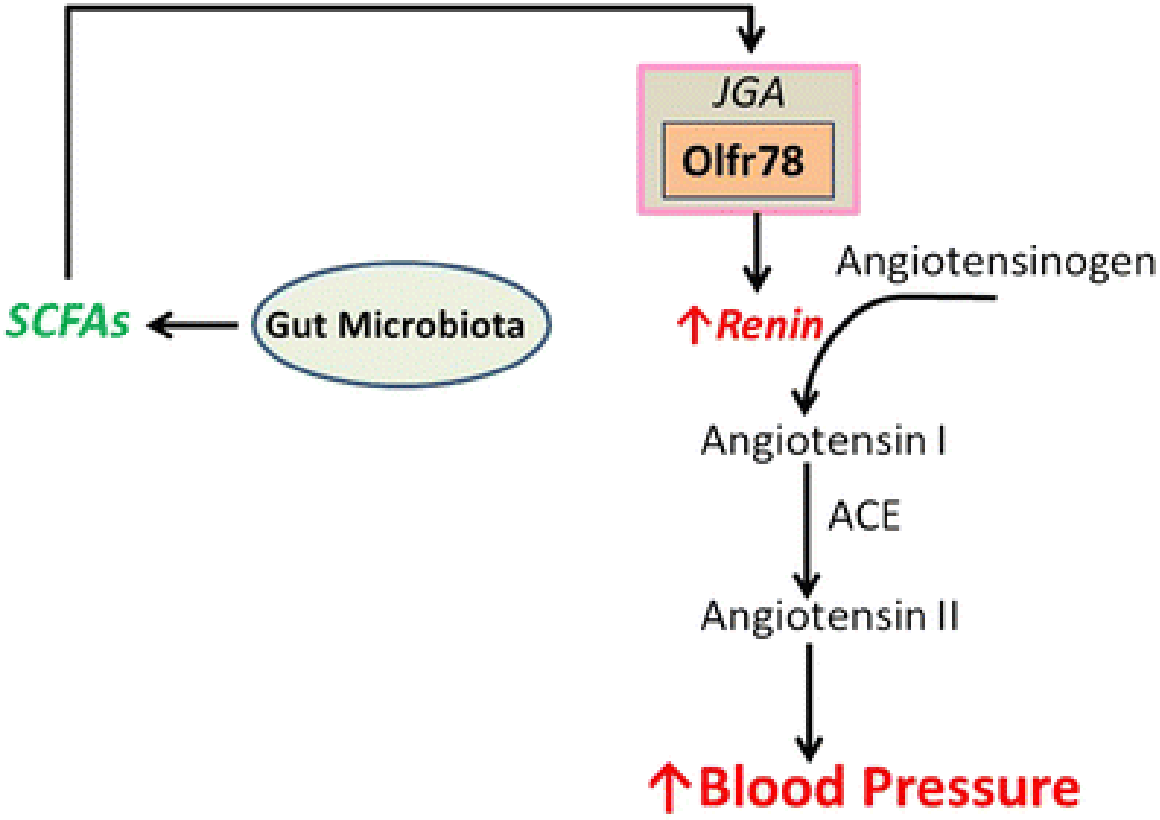
Lactobacillus helveticus LBK-16H fermented milk containing bioactive peptides in normal daily use has a **blood pressure-lowering** effect in HTN subjects

It has been suggested that the mechanism of the antihypertensive effect of these tripeptides may at least, in part, be the inhibition of the angiotensin-converting enzyme (ACE)


Change in SBP (mm Hg)
0
-5
-10
-15
-20
-25
0 2 4 6 8 10 12 14 16 18 20 22
Time (wk)
Change in DBP (mm Hg)
0
-2.5
-5
-7.5
-10
-12.5
0 2 4 6 8 10 12 14 16 18 20 22
Time (wk)

Probiotics Therapy

- Recombinant L. plantarum(model of spontaneously hypertensive rats (SHRs)
- Expressing angiotensin converting enzyme inhibitory peptide (ACEIP) significantly **decreased systolic blood** in the model of spontaneously hypertensive rats (SHR)
- Maintenance of the gut microbiota balance



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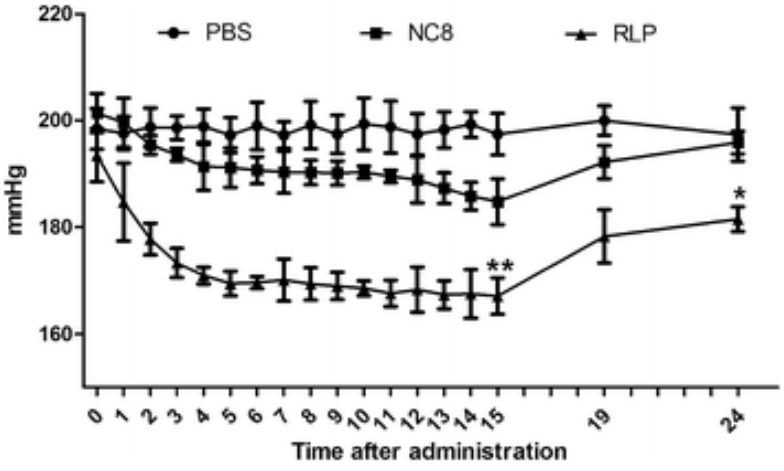
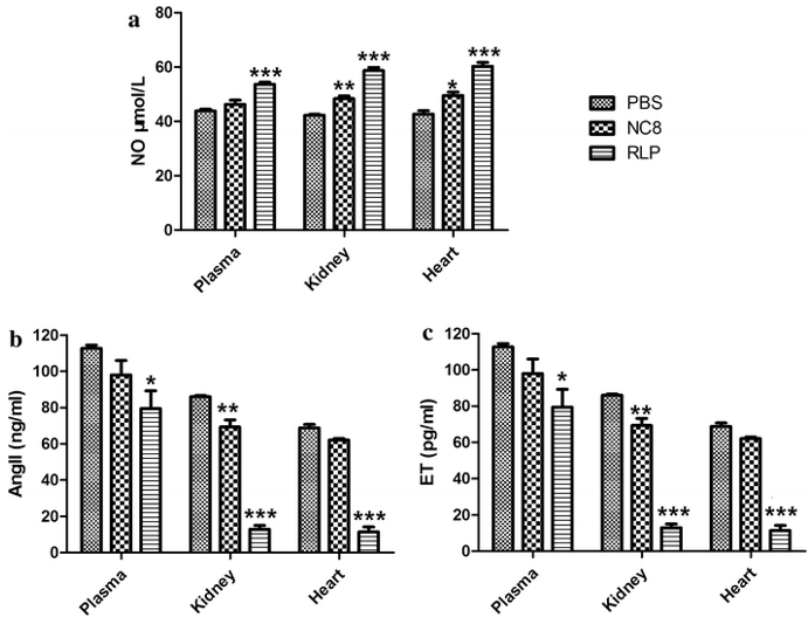

PBS
NC8
RLP
mmHg
220
200
180
160
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 19 24
Time after administration
**
*


a
NO μmol/L
80
60
40
20
0
***
**
*
***
***
Plasma
Kidney
Heart
PBS
NC8
RLP
b
AngII (ng/ml)
120
100
80
60
40
20
0
*
**
***
***
Plasma
Kidney
Heart
c
ET (pg/ml)
120
100
80
60
40
20
0
*
**
***
***
Plasma
Kidney
Heart

Office9 Combine slides

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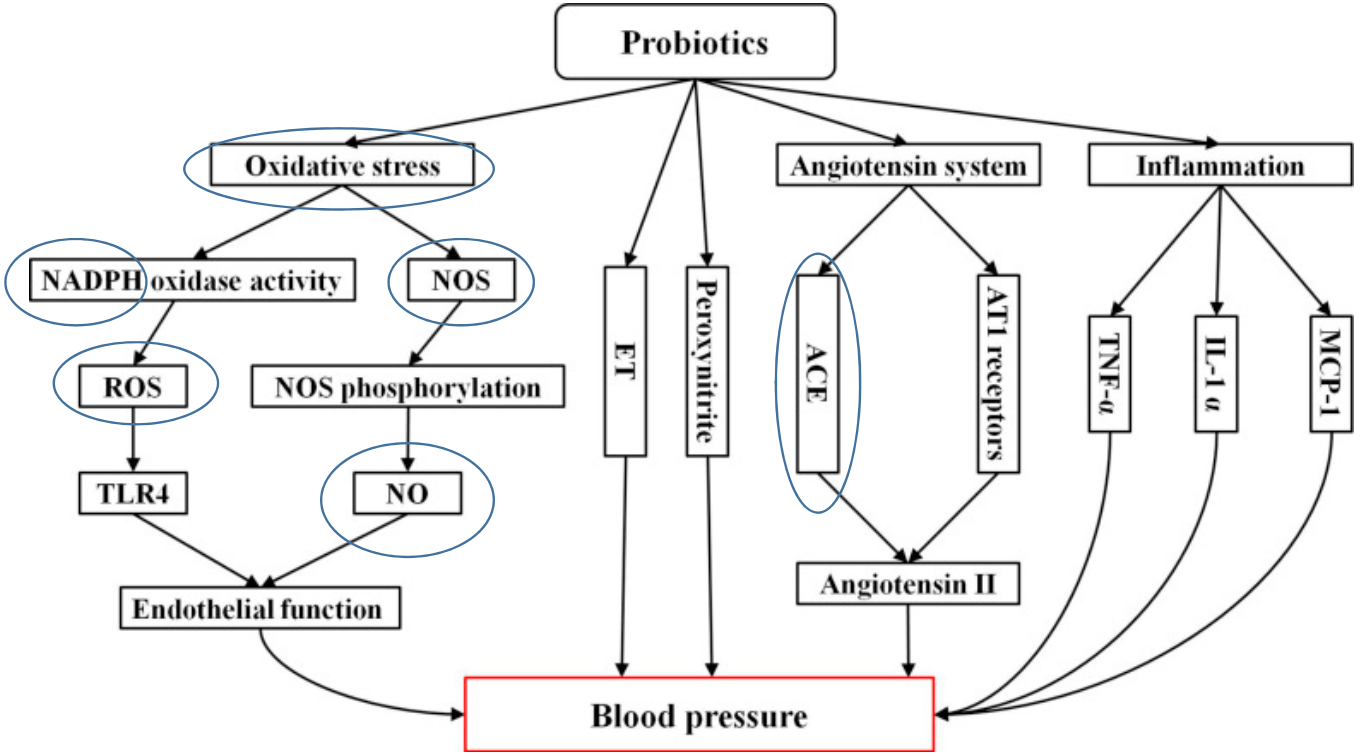
Office9

Probiotics Therapy

VSL#3 (Streptococcus thermophilus, B. longum, B. breve, B. infantis, L. acidophilus, L. plantarum, L. casei, L. bulgaricus)



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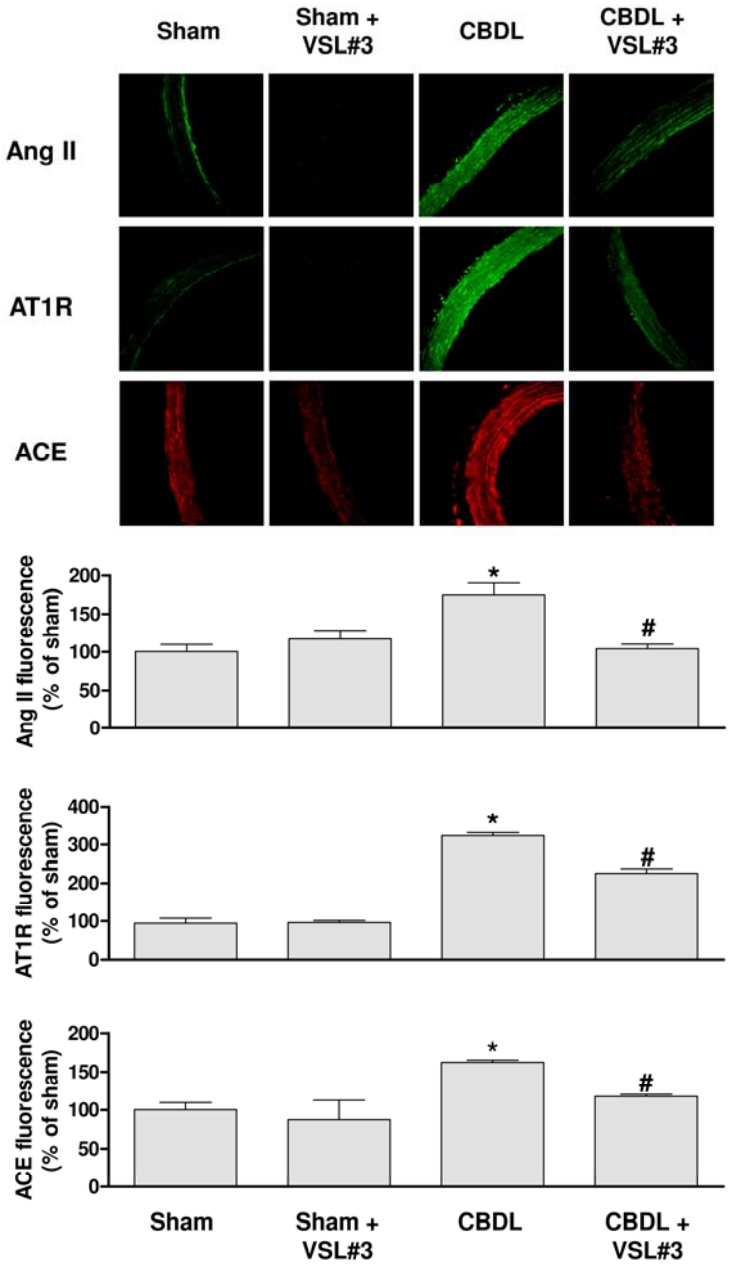
Sham
Sham + VSL#3
CBDL
CBDL + VSL#3
Ang II
AT1R
ACE
Ang II fluorescence (% of sham)
AT1R fluorescence (% of sham)
ACE fluorescence (% of sham)
0
50
100
150
200
300
400
*
#
Sham
Sham + VSL#3
CBDL
CBDL + VSL#3

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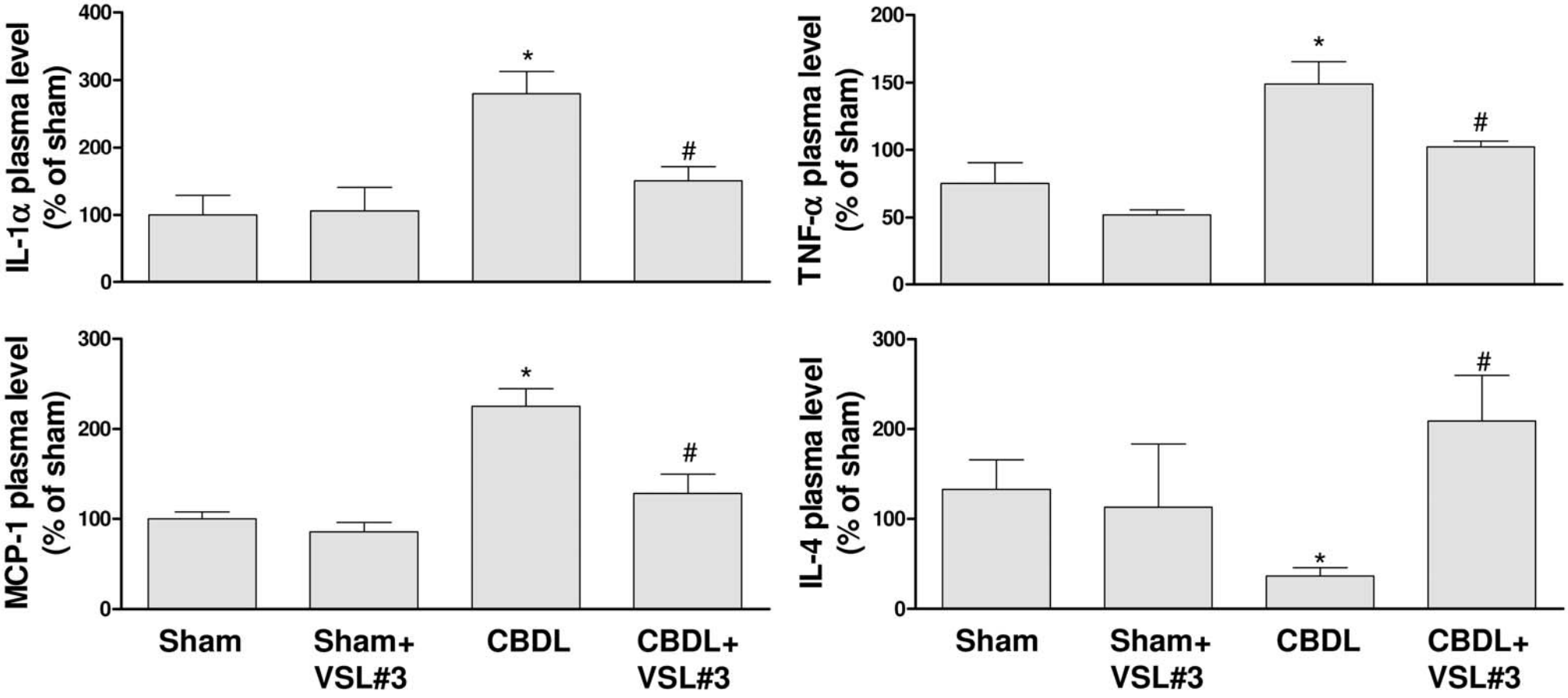
IL-1α plasma level (% of sham)
400
300
200
100
0
*
#
TNF-α plasma level (% of sham)
200
150
100
50
0
*
#
MCP-1 plasma level (% of sham)
300
200
100
0
*
#
IL-4 plasma level (% of sham)
300
200
100
0
*
#
Sham
Sham+ VSL#3
CBDL
CBDL+ VSL#3
Sham
Sham+ VSL#3
CBDL
CBDL+ VSL#3

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Summary:

1. There is relationship between gut microbiota and HTN
2. Gut microbiota have potential mechanism to alter BP
3. Probiotics therapy improve HTN by modulating gut microbiota

Thank you