Walter Bradford Cannon M.D., Sc.D.

1871-1945

1896 ..... First year medical student at Harvard

1906-1942 ..... Succeeded W. Bowditch as Higginson Professor and Chairman of Physiology at Harvard

1914-1916 ..... 6th President of the American Physiological Society

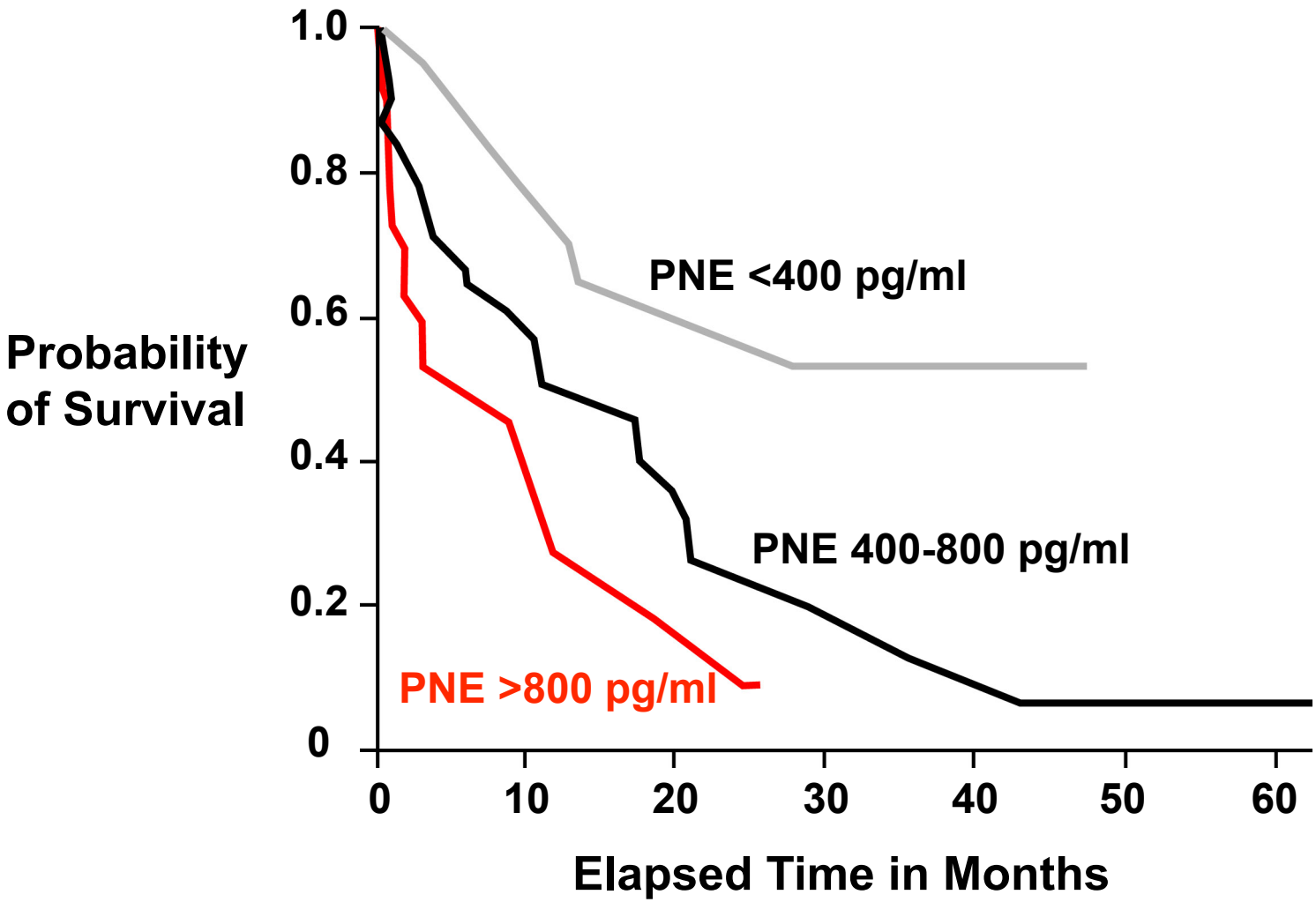
In Search of Autonomic Balance

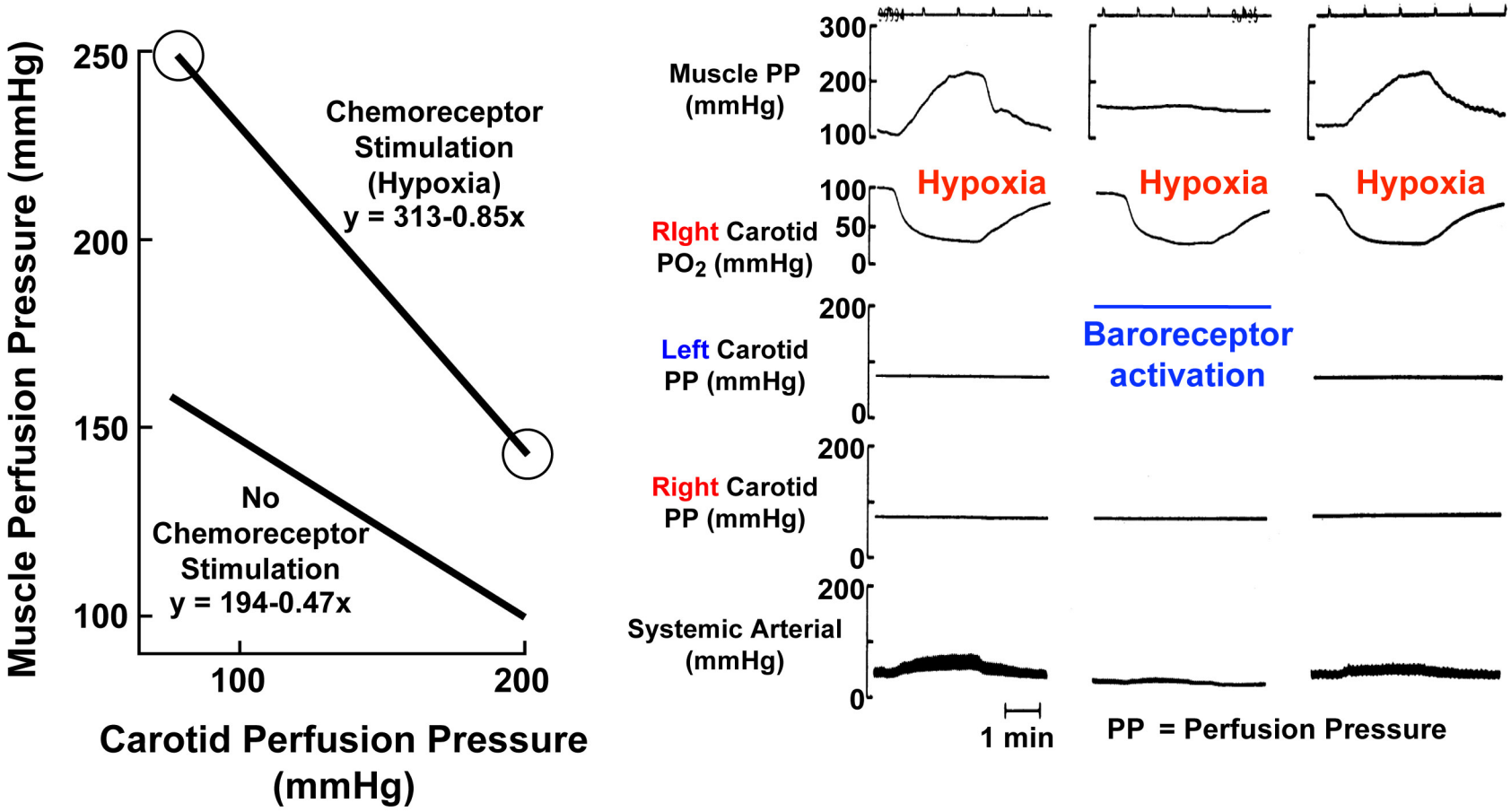
The Good, The Bad, and the Ugly

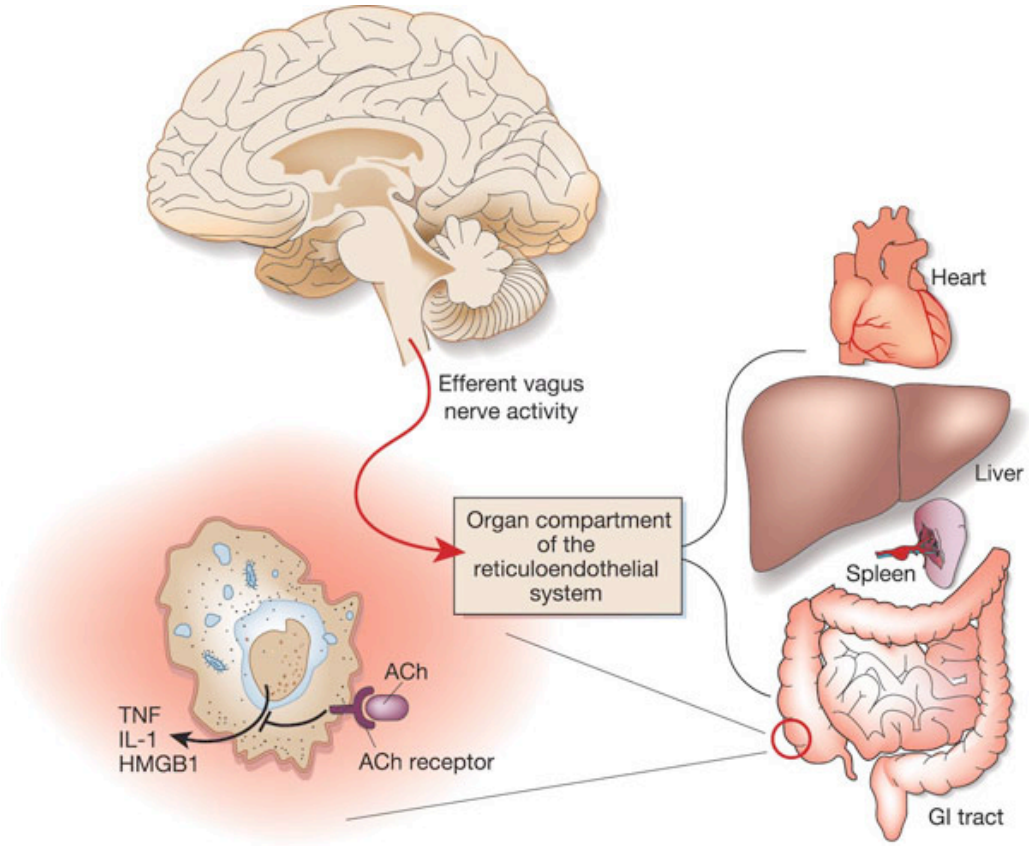
I. The Vagal – Sympathetic Imbalance and Reciprocal Dysautonomia in Heart Failure

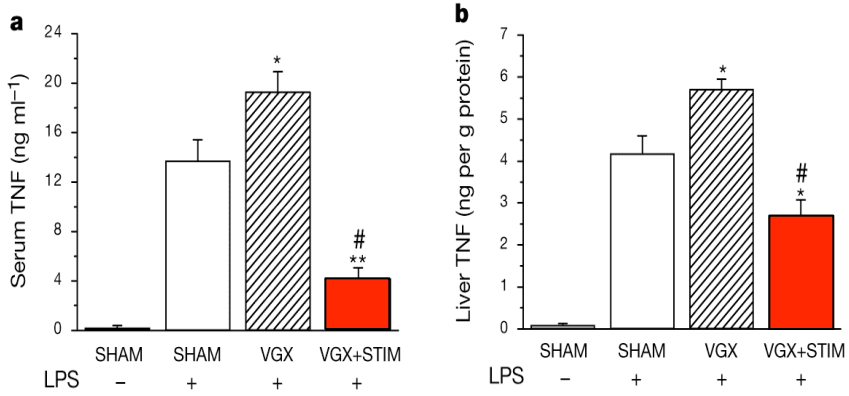
II. Molecular Components of Sensory Signals (ASICs as Mechano and Chemosensors)

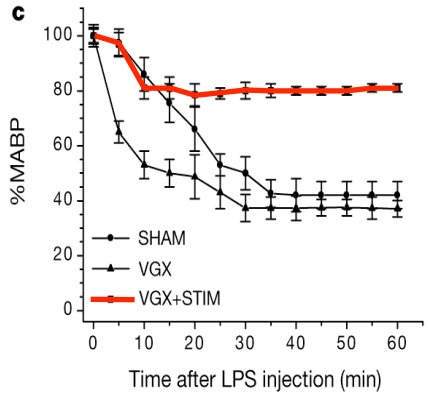
III. The ROS as the Insiduous Instigator of Sympathoexcitation

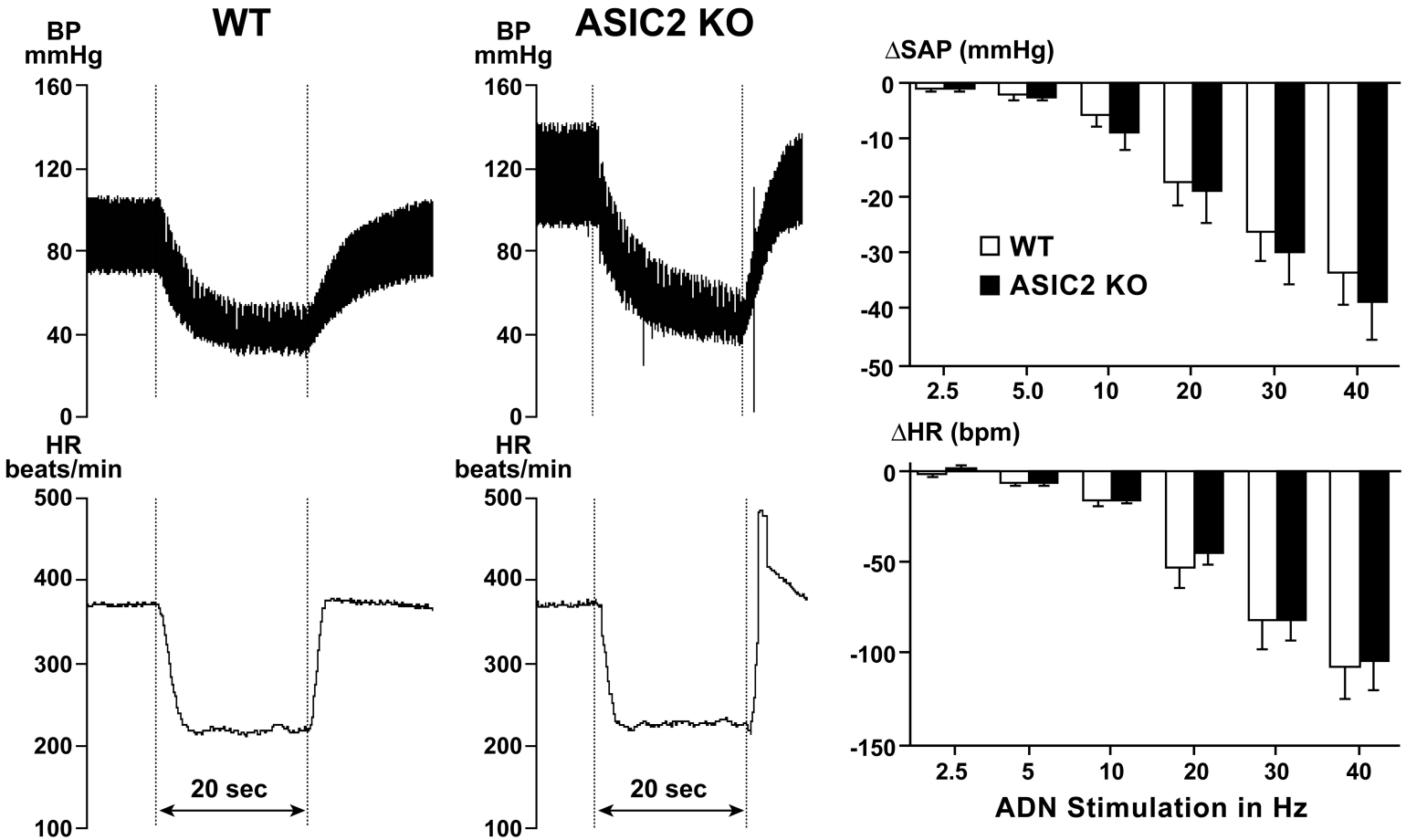

Probability of Survival
1.0
0.8
0.6
0.4
0.2
0
PNE <400 pg/ml
PNE 400-800 pg/ml
PNE >800 pg/ml
0
10
20
30
40
50
60
Elapsed Time in Months

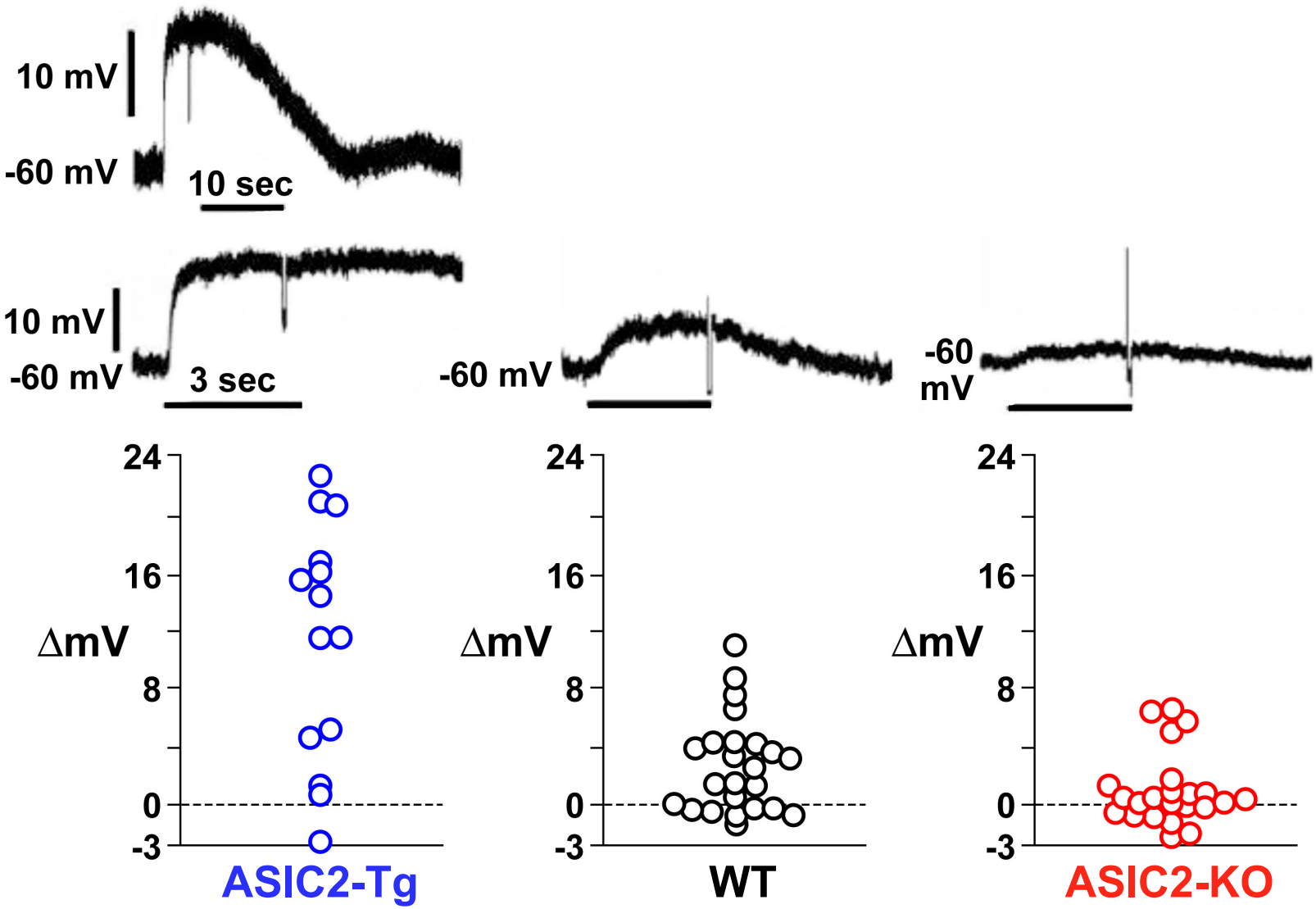

Muscle Perfusion Pressure (mmHg)
250
200
150
100
Chemoreceptor Stimulation (Hypoxia) y = 313-0.85x
No Chemoreceptor Stimulation y = 194-0.47x
100
200
Carotid Perfusion Pressure (mmHg)
Muscle PP (mmHg)
300
200
100
Hypoxia
Hypoxia
Hypoxia
RIght Carotid PO2 (mmHg)
100
50
0
Baroreceptor activation
Left Carotid PP (mmHg)
200
0
Right Carotid PP (mmHg)
200
0
Systemic Arterial (mmHg)
200
0
1 min
PP = Perfusion Pressure

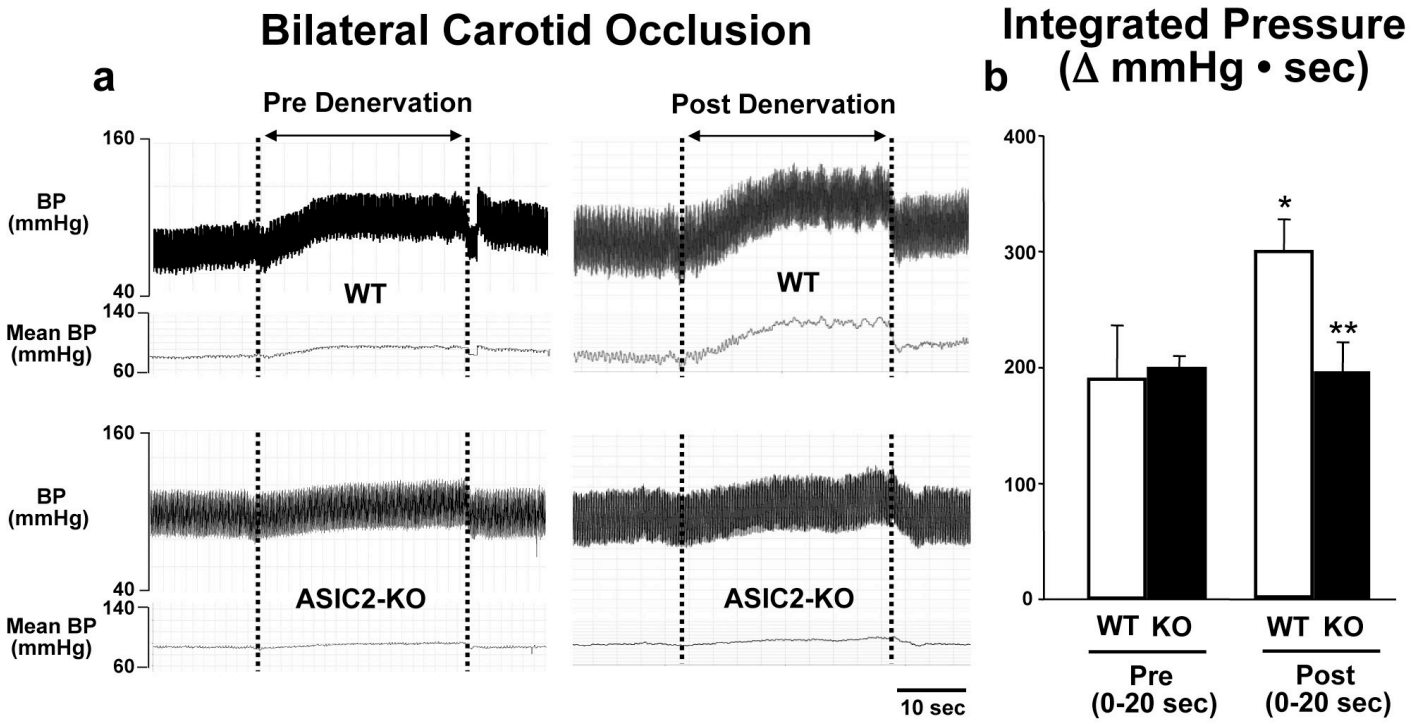

Efferent vagus
nerve activity
Organ compartment
of the
reticuloendothelial
system
Heart
Liver
Spleen
GI tract
ACh
ACh receptor
TNF
IL-1
HMGB1


a
Serum TNF (ng ml⁻¹)
24
20
16
12
8
4
0
SHAM
SHAM
VGX
VGX+STIM
LPS
–
+
+
+
*
#
**
b
Liver TNF (ng per g protein)
7
6
5
4
3
2
1
0
SHAM
SHAM
VGX
VGX+STIM
LPS
–
+
+
+
*
#
*

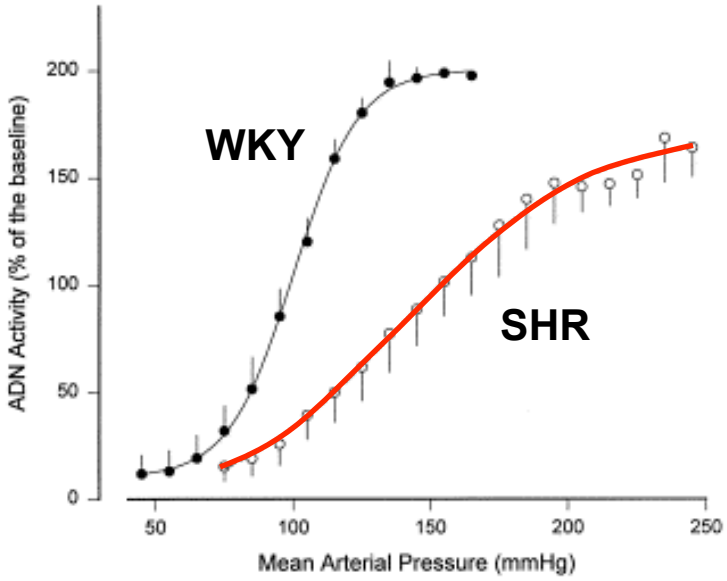

c
%MABP
100
80
60
40
20
0
SHAM
VGX
VGX+STIM
0
10
20
30
40
50
60
Time after LPS injection (min)


WT
ASIC2 KO
BP
mmHg
160
120
80
40
0
HR
beats/min
500
400
300
200
100
20 sec
ΔSAP (mmHg)
0
-10
-20
-30
-40
-50
WT
ASIC2 KO
2.5
5.0
10
20
30
40
ΔHR (bpm)
-50
-100
-150
2.5
5
ADN Stimulation in Hz

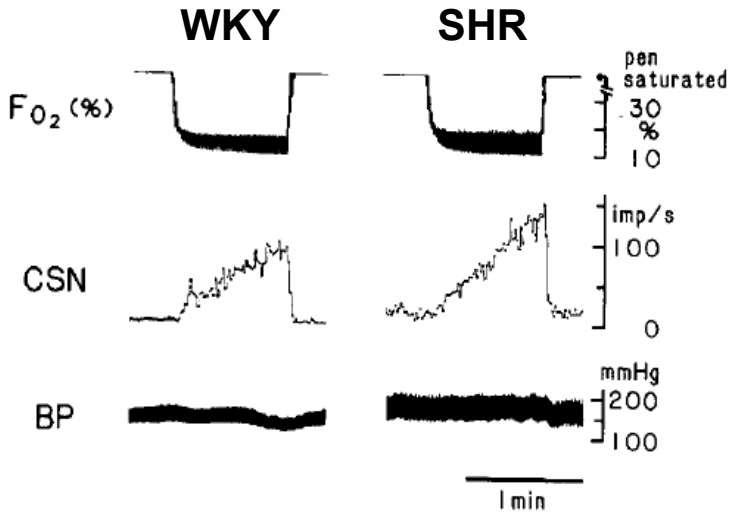

10 mV
-60 mV
10 sec
10 mV
-60 mV
3 sec
-60 mV
-60
mV
24
16
ΔmV
8
0
-3
ASIC2-Tg
24
16
ΔmV
8
0
-3
WT
24
16
ΔmV
8
0
-3
ASIC2-KO


Bilateral Carotid Occlusion
a
Pre Denervation
Post Denervation
160
BP
(mmHg)
40
WT
140
Mean BP
(mmHg)
60
160
BP
(mmHg)
40
ASIC2-KO
140
Mean BP
(mmHg)
60
10 sec
Integrated Pressure
b
(Δ mmHg • sec)
400
300
200
100
0
*
**
WT KO
WT KO
Pre
(0-20 sec)
Post
(0-20 sec)

Aortic Depressor Nerve Activity



Carotid Sinus Nerve (CSN) Activity



Supplementary Figure Legends

Supplementary Figure 1: Walter B. Cannon

Supplementary Figure 2: Outline of the lecture: The Good, The Bad, and The Ugly

Supplementary Figure 3: Survival of patients in heart failure. Life-Table Analysis of Survival, according to tircile based on level of plasma norepinephrine (PNE). Survival is less than 2 years in 90% of patients with PNE>800pg/ml whereas 60% of patients with PNE<400pg/ml survive 4 years [From Cohn et al. (10)].

Supplementary Figure 4: In dogs, the vasoconstrictor responses of the gracilis muscle perfused at constant flow, during stimulation of chemoreceptors by hypoxic blood, were suppressed during activation of the contralateral baroreceptors. Perfusion pressure (PP) was maintained at 75 mmHg in the right carotid artery where the chemoreceptors were stimulated by hypoxic blood. Simultaneously, the left carotid artery was perfused with normoxic blood and the baroreceptors were activated by raising perfusion pressure from 75 to 200 mmHg which inhibited the chemoreceptor reflex response to contralateral hypoxia [From Heistad et al. (30)].

Supplementary Figure 5: The sketches portray the vagal outflow to the reticulo-endothelial system and an inset of a macrophage with a cholinergic receptor that is activated by acetyl choline (Ach) to inhibit the release of TNF and 1L-1. The graphs portray the effects of LPS on TNF levels and on arterial blood pressure (MAP) [From Borovikova et al. (4) and Tracey (79)].

Supplementary Figure 6: Electrical stimulation of aortic depressor nerves (ADN) caused equivalent decreases in BP and HR in WT and ASIC2-KO mice indicating that deletion of ASIC2 did not alter the central mediation of the baroreceptor reflex [From Lu et al. (48)].

Supplementary Figure 7: Mechanically-induced depolarizations are greater in isolated nodose neurons from Tg ASIC2 mice and lesser in ASIC2 KO mice when compared to WT. Fewer neurons depolarized in ASIC2 KO compared to WT and the depolarizations of Tg neurons were greater and more prolonged than WT neurons [From Lu et al. (48)].

Supplementary Figure 8: (a) Bilateral carotid occlusion causes significantly greater increases in systemic arterial pressure (BP) in WT compared to ASIC2-KO following section of the aortic depressor nerves (post-denervation). (b) The bar graph shows the integrated increase in mech arterial pressure over a 20 sec. period of occlusion in WT (white bars) and KO (black bars) before (Pre) and after (Post) section of the aortic depressor nerves (ADNs) The ADN activity restrains the pressor response in WT but not in ASIC2 KO [From Lu et al. (48)].

Supplementary Figure 9: In spontaneously hypertensive rats (SHR) aortic depressor nerve activity (baroreceptors) is decreased in response to increases in arterial pressure, and

chemoreceptor nerve activity is enhanced in response to hypoxia when compared to WKY [From Fazan et al. (20) and Fukuda et al. (23)].