CNS Effects of Aldosterone: Critical Roles in salt-sensitive hypertension and CHF.

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Renin–Angiotensin – Aldosterone System

- Circulatory RAAS
- Tissue RAAS: - arteries, heart
  - kidneys
  - brain
Aldosterone, Ang II and the CNS

- **Source:** circulation or locally produced?

- **Function:** irrespective of source

**Salt – Sensitive hypertension:**
- circulatory RAAS ↓
- brain RAAS ↑

**CHF post MI:**
- circulatory & cardiac RAAS ↑
- brain RAAS ↑
Salt and Circulatory RAAS in Dahl R and S rats.

**Plasma Aldosterone**

- **Reg Salt**
- **High Salt for 4 weeks**

**Plasma Ang II**

- **Reg Salt**
- **High Salt for 4 weeks**
Salt and tissue RAAS in Dahl S

Angiotensin II

Aldosterone

Control
8% for 3 wks

(Bayorh et al. Clin Exper Hypertens 2005)
Salt and hypothalamic aldosterone and corticosterone in Dahl S

Aldosterone

Corticosterone

* p<0.05 vs RNa

RNa
HNa
CSF [Na⁺] & MAP on high salt in Dahl S versus R

**Graphs showing:**
- CSF Na⁺ (mol/L) over Days:
  - Dahl S: Red circles with bars indicating standard error of the mean.
  - Dahl R: Blue squares with bars indicating standard error of the mean.

- MAP (mmHg) over Days:
  - Dahl S: Red circles with bars indicating standard error of the mean.
  - Dahl R: Blue squares with bars indicating standard error of the mean.

Significant differences indicated by asterisks (* p<0.05 vs RNa).

Plasma [Na⁺] levels also shown:
- RNa: Red bars
- HNa: Blue bars

*(Huang et al. Am J Physiol 2004)*
CSF [Na⁺] ↑ and hypothalamic aldosterone and corticosterone

**Aldosterone**

- Icv aCSF
- Icv Na⁺ rich aCSF for 2 weeks

**Corticosterone**

- Icv aCSF
- Icv Na⁺ rich aCSF for 2 weeks

* p<0.05 vs others
Enhanced BP ↑ to CSF [Na⁺] in Dahl S vs R

Resting MAP

CSF [Na⁺]

* p< 0.05 vs other
a: p< 0.05 vs aCSF

(Huang et al. Am J Physiol 2001)
Activation of neural mechanisms by high salt in Dahl S

- Genetic dysregulation of CNS Na⁺-homeostasis:
  - Enhanced Na⁺ transport from blood into CSF
  - CNS aldosterone
  - Neuronal activation
  - Sympathetic activity
  - Hypertension
Functional role of aldosterone in the CNS

- Central MR Blockade
  - Limitations: not specific for aldosterone
    not specific for locally produced steroid

- Aldosterone synthase inhibition

- 1 vs 2 MR activation due to locally produced aldosterone.
Aldosterone synthase inhibitor

(+)-(5R)-4-(5,6,7,8-terahydroimidazo[1,5-a]pyridin-5-yl) benzonitrile hydrochloride

FAD 286 is a single (+) -enantiomer

(Fiebeler et al. Circulation 2005)
CSF [Na$^+$] $\uparrow$ and hypothalamic aldosterone and corticosterone

Central aldosterone synthase inhibition

**Aldosterone**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Value (pg/g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Icv aCSF +veh</td>
<td></td>
</tr>
<tr>
<td>Icv Na$^+$ rich aCSF AS inh</td>
<td></td>
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**Corticosterone**

<table>
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<tr>
<th>Condition</th>
<th>Value (ng/g)</th>
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<td>Icv aCSF +veh</td>
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* p<0.05 vs others

100 µg/kg/day
CSF [Na+] and sympathetic activity

Central aldosterone synthase inhibition

Air Stress

Baroreflex control of RSNA

**Max. slope (%/mmHg)**
- **CSF** 3.6±0.2
- **CSF AS inh** 3.7±0.3
- **(Na)aCSF** 2.3±0.3*
- **(Na)aCSF AS inh** 3.3±0.3

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* p<0.05, vs aCSF with/without AS inh; a: p<0.05, vs Na+ -rich aCSF+veh

* p<0.05, vs others
Dahl S on HNa for 4 weeks

Central aldosterone synthase inhibition

Aldosterone

Corticosterone

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<tr>
<th></th>
<th>pg/g</th>
<th></th>
<th>ng/g</th>
</tr>
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<tbody>
<tr>
<td>RNa</td>
<td>200</td>
<td>HNa</td>
<td>100</td>
</tr>
<tr>
<td>+veh</td>
<td>300</td>
<td>AS inh</td>
<td>80</td>
</tr>
</tbody>
</table>

80 µg/kg/day
BP and HR in Dahl S on high salt

Central aldosterone synthase inhibitor vs MR blocker

Resting MAP

MAP (mmHg)

180
160
140
120
100

icv aCSF AS inh spir

* p<0.05 vs others
b: vs RNa+aCSF

Resting HR

HR (bpm)

550
500
450
400
350
300

icv aCSF AS inh spir

RNa

HNa
CONCLUSION

- Central blockade of aldosterone synthesis or MR prevents to a large extent the salt-induced hypertension in Dahl S.

  - locally in the CNS produced aldosterone via MR plays a major role

New Paradigm:

- High salt diet via CSF \([\text{Na}^+]\) activates aldosterone – MR and sodium transport in the CNS.
Shift in Paradigm from Kidney to CNS

**Old Paradigm:**
- Intrinsic changes in renal function lead to a defect in the kidneys’ ability to excrete salt and to an increase in BP until sodium balance is restored.
  "the Guyton Dogma"

**New Paradigm:**
- Kidneys of genetic models of salt – induced hypertension do not require hypertension, and the animals live happy (*happier ?*) without.
- Kidneys are a "sensor and /or effector" organ like the arteries and the heart, and in general the CNS determines the set – point of BP.
Changing Face of CHF

Past and Present

Hypertension → LVH → LV dysfunction → CHF

Present and Future

Hypertension
Dyslipidemia → Atherosclerosis → MI → LV remodeling/dysfunction
Diabetes
Smoking

↓
CHF
CHF mortality still very high

(Davis et al. Circulation, 2006)
LV remodeling following MI
Stimuli for cardiac remodeling post MI

**Cardio-centric view:** diastolic wall stress ➰
- systolic wall stress ➰
- progressive LV dilation and hypertrophy

**Cardio-renal view:** reduced cardiac output and renal perfusion
- activation of circulatory RAAS
- salt and water retention

**Neuro-hormonal view:** sympathetictic hyperactivity
- circulatory, cardiac, renal RAAS ➰
- vasopressin ➰
- pro-inflammatory cytokines ➰
CNS and CHF Post MI

Brain RAAS: locally produced aldosterone
→ MR & AT₁–rec stimulation

- sympathetic activity
  & other peripheral mechanisms

- cardiac remodeling / dysfunction post MI
Myocardial Infarction

Circulation → Aldosterone → Min. Cort. Receptor → Ang II → Peripheral Mechanisms → CHF

Local Synthesis → AS inh

Spironolactone

Losartan / Transgenic Rats
Transgenic Rats

To assess the role of Angiotensins locally produced in the brain

Glial fibrillary acidic protein promoter

Angiotensinogen Antisense DNA

Angiotensinogen antisense RNA (glia only)

Angiotensinogen mRNA Angiotensinogen

SD TG Rats

Hypothalamic Angiotensinogen, pmol/mg protein

1.5 0.1

Plasma Angiotensinogen, nmol/ml

1.4 1.4

(Schinke et al. PNAS, 1999)
CNS aldosterone post MI

Central aldosterone synthase inhibitor

Hypothalamus

<table>
<thead>
<tr>
<th></th>
<th>2 weeks</th>
<th>4 weeks</th>
<th></th>
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<tbody>
<tr>
<td>Sham</td>
<td>MI</td>
<td>MI Icv</td>
<td>MI Icv</td>
</tr>
<tr>
<td>pg/g</td>
<td>*</td>
<td>a</td>
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Hippocampus

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<tr>
<th></th>
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*p ≤ 0.05
Sympathetic Hyperactivity in CHF post MI

- set point $\uparrow$
- reactivity $\uparrow$
- baroreflex-control $\downarrow$
Blockade of Brain MR–AT$_1$-rec prevents sympathetic hyperactivity post MI

*Resting RSNA

Air-stress

Maximal Gain of baroreflex

(Francis et al. AJP, 2003)
(Huang et al. AJP, 2005)
Blockade of brain RAAS prevents plasma Ang II and aldosterone ↑ post MI

Blockade of brain RAAS prevents LV aldosterone → post MI

Wistar rats with icv spironolactone

![Graph showing aldosterone levels in TG rats and Wistar rats with icv spironolactone]

(Lal et al. JMCC, 2005)

* p<0.05 vs other
Blockade of brain MR prevents plasma TNF-α ↑ post MI

* p<0.05, vs other

(Francis et al, AJP, 2004)
CNS and CHF Post MI

Brain RAAS: locally produced aldosterone
- MR & AT$_1$–rec stimulation

- sympathetic activity
  - & other peripheral mechanisms

- cardiac remodeling / dysfunction post MI
Parameters of LV remodeling

- LV diameter
- cardiomyocyte numbers and size
- extracellular matrix - collagen

Parameters of LV dysfunction and CHF

- LVEDP, LVPSP, LV dP/dt max
- lung weight
- RV weight and diameter
LV dimensions at 4 weeks post MI
Central Blockades

Diastolic

Systolic

EF (%)

* p<0.05 vs sham; \( ^a \)p<0.05 vs MI +veh
LV pressure-volume curves in transgenic vs. SD rats at 8 wks post MI

* P<0.05 vs sham; # P<0.05 vs SD MI

MI size : 40 ± 3 for TG and 40 ± 4 for SD

Interstitial Fibrosis in Peri-infarct Zone

Effect of central MR blocker

Interstitial fibrosis (magnification X400)

Fibrillar collagen by SEM (magnification X8000)


Sham  MI  MI + Icv Spironolactone
Oral vs icv spironolactone and MI-Induced changes in hemodynamics

- **LVPSP**
  - Oral: [Graph data]
  - ICV: [Graph data]

- **LVEDP**
  - Oral: [Graph data]
  - ICV: [Graph data]

- **LV +dP/dt max**
  - Oral: [Graph data]
  - ICV: [Graph data]

* p< 0.05 vs sham; a p<0.05 vs MI+Vehicle

LV function at 4 weeks post MI
Icv losartan versus icv spironolactone

LVPSP

LVEDP

dP/dt_{max}

* p<0.05 vs sham; a p<0.05 vs MI +veh

(Huang et al. JMCC 2007)
LV function 4 weeks post MI
Central aldosterone synthase inh

**LV function 4 weeks post MI**

**Central aldosterone synthase inh**

**LVPSP**

**LVEDP**

**dP/dt_max**

* p<0.05 vs sham;  a p<0.05 vs MI +veh
CNS and LV dysfunction post MI

Clinical CHF

Pre 1 day MI
Post MI

weeks/months

CNS
RAAS
Sympathetic activity post MI
Effects of systemic losartan

Air Stress

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Veh</th>
<th>L15</th>
<th>L100</th>
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<tbody>
<tr>
<td>% resting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RSNA</td>
<td>*</td>
<td>* a</td>
<td>a</td>
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<tr>
<td>MAP (% resting)</td>
<td>* a</td>
<td>a</td>
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<tr>
<td>mmHg</td>
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<tr>
<td>MAP (mmHg)</td>
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<td>HR (bpm)</td>
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<td>L100</td>
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Maximal Slope (%)

- Sham: 3.4 ± 0.2
- Veh: 2.1 ± 0.2*
- L15: 2.8 ± 0.2*a
- L100: 3.4 ± 0.3

(Huang et al. JMCC, 2007)
Losartan and sympathetic activity in patients with CHF

\[ \text{MSNA Plasma Norepinephrine} \]

- **Msna** bar graph:
  - Y-axis: bursts/100 beats
  - X-axis: pg/ml
  - Comparison between:
    - Losartan 50 mg/day
    - Losartan 200 mg/day

- **Plasma Norepinephrine** bar graph:
  - Y-axis: pg/ml
  - X-axis: pg/ml
  - Comparison between:
    - Losartan 50 mg/day
    - Losartan 200 mg/day

\# p<0.05 vs baseline

+ p< 0.05 compared to losartan 50 mg/day

(Ruzicka et al. ESC, 2007)
The Brain: The forgotten target in Heart Failure

SFO

Brain RAAS

'Ouabain'

Cytokines

PVN

SON

LC

RVLM

Sympathetic hyperactivity

Cytokines

Cardiac RAAS

Remodeling Dysfunction

HEART FAILURE

Infarct

Cardiac afferents

Circulating RAAS

BP

↑ Cytokines

↑ Cytokines

Cardiac RAAS

vasopressin

Other factors?