Evidence for histamine as a neurotransmitter in the cardiac sympathetic nervous system

A journey from hypothesis to theory

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2010.12  Xian
You listen, you forget.
You read, you remember.
You do, you understand.

PPA  Persistent
     Patient
     Aggressive
论文数量 ≠ 产生新的学术思想
指标堆积 ≠ 证明问题关键
少量指标 ≠ 论文质量不高

科学研究的目的？

So what？
Who cares？
Asian-Pacific research assessment

Giant planets
Origins of oxygen?

p73
The new p53?

Quantum Hall effect
Observing a fractional change
# Betz’s publications on vesicle cycling

<table>
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<tr>
<th>Year</th>
<th>Journal</th>
<th>Pages</th>
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<tr>
<td></td>
<td>Neuron.</td>
<td>51:317-25.</td>
</tr>
<tr>
<td>2004</td>
<td>Science.</td>
<td>303:2037-9</td>
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</table>

37年 66篇 1.7篇/年

William J. Betz  
Professor and Chairman  
Department of Physiology  
and Biophysics  
UCSHC

Michael Galfield  
Joseph Johnson

Leah Sheridan
What is a story?
Cardiac sympathetic neurotransmission

Sympathetic varicosities

Myocardium

α₂

NE

+ NE

β₁

H₂

NE
Hyperactivity of sympathetic nervous system and abnormal cardiac function

**A**

<table>
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<tr>
<th></th>
<th>WT</th>
<th>DKO</th>
<th>AKO</th>
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<tbody>
<tr>
<td>Blood Pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>120</td>
<td>110</td>
<td>100</td>
</tr>
<tr>
<td>4 months</td>
<td>130</td>
<td>120</td>
<td>110</td>
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**B**

<table>
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<tr>
<th></th>
<th>WT</th>
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<tbody>
<tr>
<td>Heart Rate (bpm)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>700</td>
<td>600</td>
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<tr>
<td>4 months</td>
<td>800</td>
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**Inotropy**

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<tr>
<td>+ dP/dt (mmHg/s)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
<td>6000</td>
<td>5000</td>
<td>4000</td>
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<tr>
<td>Propranolol</td>
<td>7000</td>
<td>6000</td>
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**Lusitropy**

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<tr>
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<td>- dP/dt (mmHg/s)</td>
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<tr>
<td>Control</td>
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<td>3000</td>
</tr>
<tr>
<td>Propranolol</td>
<td>6000</td>
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</table>

* Significant difference

Am J Physiol Heart Circ Physiol 2002; 283:1838-1845
Exercise capacity of wild-type (WT), 2A-adrenoceptor (AR) knockout (AKO), and 2A/2C-AR knockout (DKO) mice
<table>
<thead>
<tr>
<th></th>
<th>WT</th>
<th></th>
<th>DKO</th>
<th></th>
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<tr>
<td></td>
<td>1 mo</td>
<td>6 mo</td>
<td>1 mo</td>
<td>6 mo</td>
</tr>
<tr>
<td>FS, %</td>
<td>56 ± 3</td>
<td>52 ± 4</td>
<td>63 ± 3</td>
<td>29 ± 3*†</td>
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<td>ESD, mm</td>
<td>1.7 ± 0.1</td>
<td>2.1 ± 0.3</td>
<td>1.5 ± 0.2</td>
<td>3.6 ± 0.3*†</td>
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<tr>
<td>EDD, mm</td>
<td>3.9 ± 0.3</td>
<td>4.2 ± 0.3</td>
<td>4.0 ± 0.3</td>
<td>5.1 ± 0.3*†</td>
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<tr>
<td>n</td>
<td>5</td>
<td>4</td>
<td>4</td>
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</table>

Table 1. Echocardiographic characteristics of 1- and 6-mo-old WT and DKO mice
Kaplan-Meier survival curves for the composite of all cause mortality and vascular events in patients below (MSNA < 36 bursts/min) and above or in (MSNA ≥ 36 bursts/min) the 75th percentile of baseline MSNA (log-rank: p=0.002).
Histamine receptors:  $H_1, H_2, H_3, H_4$

Functions of histamine $H_3$ receptors:

**CNS:**  Presynaptic homoreceptor

  inhibit --- histamine release from
  histaminergic neuron
  --- histamine synthesis and
  biotransformation

**PNS:**  Presynaptic heteroreceptor

  inhibit --- neurotransmission
Cardiac Effects of Histamine

- Direct effects on the heart (complex)
  
  H-2: positive inotropic and chronotropic effects
  
  H-1: slowed AV conduction

- Indirect effects on the heart
  
  H-3: inhibit sympathetic neurotransmission, secondary to negative inotropic and chronotropic actions
ECG tracings from both H3R \(^{+/-}\) and H3R\(^{-/-}\) hearts during reperfusion.

<table>
<thead>
<tr>
<th>Reperfusion time (sec)</th>
<th>(H_3R^{+/+})</th>
<th>(H_3R^{-/-})</th>
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<td>48-60</td>
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<tr>
<td>168-180</td>
<td><img src="image" alt="Waveform" /></td>
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</tbody>
</table>

QUESTIONS

Where?  Endogenous histamine

How?  Histamine $H_3$ receptor works
The proposed negative-feedback loop linking sensory C-fiber terminals to mast cells in the heart: (1) Antidromic stimulation of afferent C fibers by bradykinin or capsaicin causes the release of CGRP in an efferent direction. (2) Released CGRP stimulates local mast cell to release histamine (HA). (3) Released histamine stimulates prejunctional inhibitory H₃-receptors (H₃R) on C fibers. (4) H₃-Receptors negatively modulate CGRP release. Released histamine contributes in part to the chronotropic effects of CGRP.

Scheme of proposed mechanisms explaining the interactions between cholinergic fibers, C-fibers and mast cells in tracheally perfused rabbit lungs and the localization of histamine H₃ receptors. SP released by capsaicin can activate cholinergic fibers, leading to cholinoreceptor stimulation with subsequent activation of the C-fibers and mast cells.

Hypothesis

SYMPATHETIC NERVE TERMINAL

NE

NE

HA

HA

H_3

NE

NE

HA

HA

α/β

HA

HA

HA

Mast cell

EFFECTOR

β_1R

H_2R
Distribution of histidine decarboxylase (HDC) in the superior cervical ganglion of guinea pig.
Fluorescence photomicrographs of sections showing the coexistence of TH and NE in neurons of sympathetic ganglia
Coexistence of D-βH and HA in SCG

A: D-β-H
B: HA
C: D-β-H+HA
D: D-β-H (SIF cell)
E: HA (SIF cell)
F: D-β-H+HA (SIF cell)
G: D-β-H
H: HA
I: D-β-H+HA

Auto Autac Pharm 2004; 23:327-33
Schematic diagram of a sympathetic neuron and images of immunostainings for NE and HA in soma, axon and varicosities of guinea pig SCG

Fluorescence photomicrographs of sections showing the coexistence of HA and NE in neurons of sympathetic ganglia.

The coexistence of HA and NE in sympathetic axon terminals

Double immunostainings for NE and HA in the SCG of monkey

Li M et al., Auton. Neurosci. 2007; 137:37-43
An electron micrograph showing HA-like immunoreactivity in synaptic vesicles of sympathetic axon terminals in the guinea pig vas deferens.

NE and HA release from cardiac sympathetic nerve endings (synaptosomes) and their inhibitions by pretreatment with 6-OHDA

Effects of compound 48/80, ω-CTX and lacidipine on cardiac synaptosome HA release evoked by 50 mM K⁺.
Effects of histidine, FMH and quinacrine on HA release from cardiac synaptosomes, evoked by 50 mM K+.

**A**

![Bar chart showing the effect of histidine, FMH, and α-FMH on HA release](chart)

- **K**
- **Histidine**
- **α-FMH**

**B**

![Bar chart showing the effect of quinacrine and histidine on HA release](chart)

- **K**
- **Quinacrine**
- **Histidine**

Effects of MeHA, and thioperamide (Thio) on HA release from cardiac synaptosomes of guinea pig evoked by 50 mM K+.

Effects of endogenous HA on K+-evoked exocytosis of endogenous NE from cardiac synaptosomes.
Proposed mechanisms of the negative feedback modulation of sympathetic neurotransmission through HA and histamine H₃ receptors.

The effects of EFS on the release of HA from isolated guinea pig vas deferens.

The effects of compound 48/80 and cromolyn on the release of HA from isolated guinea pig vas deferens.

The effects of Thio and CPM on the contraction of isolated guinea pig vas deferens evoked by EFS.

The effects of $\alpha \beta$-meATP, prazosin and CPM on the contraction of isolated guinea pig vas deferens evoked by EFS.
The effects of exogenous HA and αMeHA on the contraction of isolated guinea pig vas deferens evoked by EFS
The effects of exogenous HA on the contraction of isolated guinea pig vas deferens evoked by exogenous ATP and NE.
Proposed mechanisms of the negative feedback modulation of sympathetic neurotransmission through HA and histamine $H_3$ receptors.
Effect of global stop-flow ischemia on ventricular arrhythmias in mice isolated hearts during 30-min reperfusion. Ischemia was applied for 10 min after an initial stabilization period of 30 min.
Criteria to identify a neurotransmitter

1. The substance must be present within the presynaptic neuron.

Li MK., et al. Auto Autac Pharm 2003; 23: 327–33

2. The enzymes for synthesising the transmitter exist in the presynaptic terminals;

李明凯等. 解剖学报 2004; 35:18–21
3. The substance must be released in response to presynaptic depolarization, and the release must be Ca^{2+}-dependent;

Li MK., et al. Auto Autac Pharm 2003; 23: 327–33

4. Specific receptors for the substance must be present on the postsynaptic cell.

5. Experimental application of appropriate amounts of the chemical at the synapse produces changes in postsynaptic potentials

He GH., et al. J Neurochem 2008; 106;1710
Blandina P., Br J Pharmacol. 1987; 90:459-66
CONCLUSIONS

1. Histamine in sympathetic neuron comes close to satisfying the criteria, therefore

   **Sympathetic histamine is a newly recognized sympathetic neurotransmitter**

2. Presynaptic histamine $H_3$ receptors on sympathetic terminals are

   **Homereceptors** rather than **heteroreceptors**
Are we making an impact?
Fine Tuning of Sympathetic Transmitter Release via Ionotropic and Metabotropic Presynaptic Receptors

STEFAN BOEHM AND HELMUT KUBISTA

TABLE 6
Presynaptic histamine receptors mediating modulation of sympathetic transmitter release

<table>
<thead>
<tr>
<th>Species</th>
<th>Tissue</th>
<th>Parameter Determined</th>
<th>Effect of Receptor Activation</th>
<th>Receptor Subtype</th>
<th>Reference</th>
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<tbody>
<tr>
<td>Guinea pig</td>
<td>Small intestine</td>
<td>IPSP</td>
<td>Inhibition</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Liu et al., 2000</td>
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<td>Guinea pig</td>
<td>Ileum</td>
<td>NA release</td>
<td>Inhibition</td>
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<td>Blandizzi et al., 2000</td>
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<td>Dog</td>
<td>Heart</td>
<td>NA release</td>
<td>Inhibition</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Mazenot et al., 1999b</td>
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<td>Pulmonary artery</td>
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<td>Inhibition</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Hey et al., 1998</td>
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<td>Guinea pig</td>
<td>Cardiac synaptosomes</td>
<td>NA release</td>
<td>Inhibition</td>
<td>H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Tedford et al., 1998</td>
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<td>Human</td>
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<td>Hatta et al., 1997</td>
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<td>Seyedi et al., 1997</td>
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<td>Heart</td>
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<td>H&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Luo et al., 1996</td>
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<td>Pressor response</td>
<td>Inhibition</td>
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<td>Eakum et al., 1996</td>
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<td>Imamura et al., 1996</td>
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<tr>
<td>Chicken</td>
<td>Heart</td>
<td>Positive inotropic response</td>
<td>Stimulation</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Tanaka et al., 1995b</td>
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<td>Mouse</td>
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<td>Imamura et al., 1994</td>
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<td>H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Endou et al., 1994</td>
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<td>Koss, 1994</td>
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<td>Vas deferens</td>
<td>Neurogenic contraction</td>
<td>Inhibition</td>
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<td>Poli et al., 1994</td>
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<td>Inhibition</td>
<td>H&lt;sub&gt;2&lt;/sub&gt;</td>
<td>Luo et al., 1994</td>
</tr>
</tbody>
</table>

IPSP, inhibitory postsynaptic potential; NA, noradrenaline.
Synaptic Neurotransmission

Symphony of Presynaptic receptors

Presynaptic Terminals

Action Potentials

Postsynaptic membrane

$\alpha R$

$\beta_1 R$

$H_2 R$

SYMPHONY OF PRESYNAPTIC RECEPTORS

$\alpha R$

$\beta_2 R$

$A_1 R$

$H_3 R$

$A_2 R$

$\mu - R$

$P2Y R$

$\beta_1 R$

$M_2 R$

$\alpha R$

$AT_1 R$

$H_2 R$

$\beta_2 R$

$A_1 R$

$\alpha_2 R$
要论文，就根据一二个数据写论文；要成果，有一二点苗头就作为阶段性成果申报。

“把刚想做的，说成做了；把刚看到的苗头说成成果已经到手了；把刚做完的，说成是完美无缺了。似乎这么一来就真的是创新了”。

“这种浮躁状态已经明显影响国家的可持续发展。满足于花花哨哨、热热闹闹，不深谋远虑，不未雨绸缪，不研究解决发展我国科技的深层问题，早晚会暴露科技浮躁带来的严重后果”。

可持续发展的大敌——社会浮躁

《漫说科教》秦伯益著，新世纪出版社，2004；第1版
1994年诺贝尔经济学奖获得者纳什

John Nash

**Publications by John Nash**


In addition, there were also a number of Rand Corporation memoranda written by Nash on diverse subjects such as machine memories and parallel control (Nasar, pp. 403, 407, 411, 430), as well as an unpublished lecture at the World Congress of Psychiatry in Madrid in 1996.
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