Presentation 2 - Kevin Tracey

The Feinstein Institute for Medical Research
North Shore-Long Island Jewish Health System

The Cholinergic Anti-inflammatory Pathway In the Inflammatory Reflex

14 August 2006

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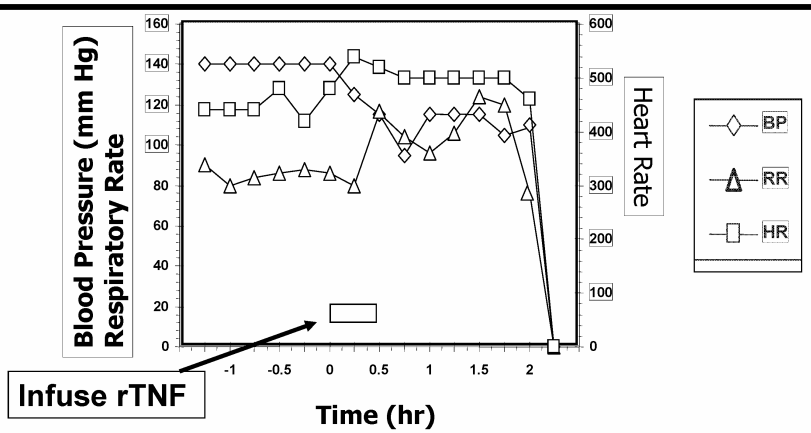
CEO, Feinstein Institute
Vice President, Research, NSLIJHS

Janice

- Friday, May 3, 1985, 5:35 pm
  - 11 month old girl transported to ER via ambulance
  - Crying and clutching her pink teddy-bear blanket
  - 75% of her total skin surface injured with full and partial thickness scald
- Monday, May 6, 1985
  - Tangential excision and skin grafting
- Tuesday, May 7th, 1985, 9:45 PM
  - Acute septic shock
  - Renal failure
  - Respiratory failure

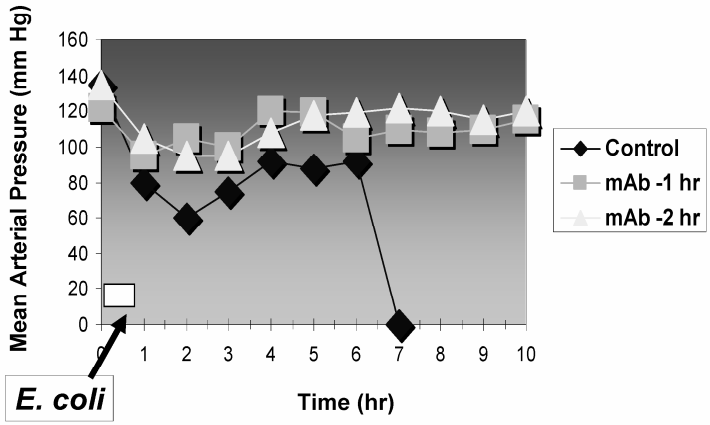
Tracey, KJ. Fatal Sequence, Dana Press, Washington, 2005

Shock and Tissue Injury Induced by TNF



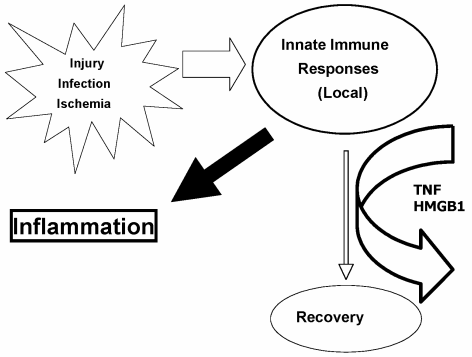
Tracey, et al., *Science* 234:470, 1986

Anti-TNF Prevents Lethal Septic Shock



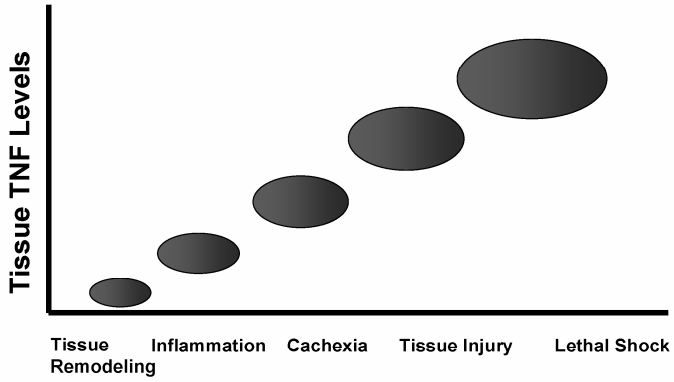
Tracey, et al., *Nature* 330:662-4, 1987

Cytokine Theory of Disease

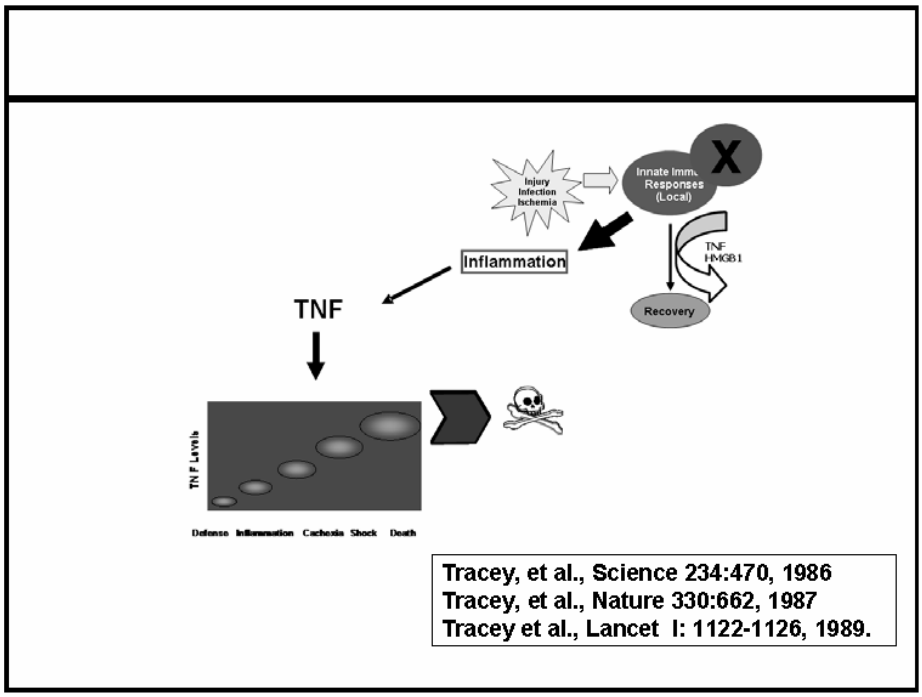


Tracey, KJ. Fatal Sequence, Dana Press, Washington, 2005

Biology of TNF



Tracey et al., *Lancet I*: 1122-1126, 1989



Conserved Mechanisms Protect Against Cytokine Excess

Molecular

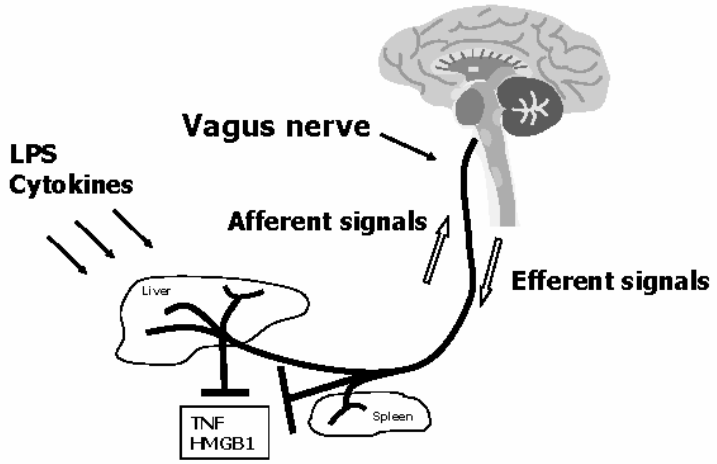
- Transcriptional
- Translational
- Release
- Refractory period

Humoral

- Glucocorticoids
- IL-10
- TGF-β
- Soluble receptors

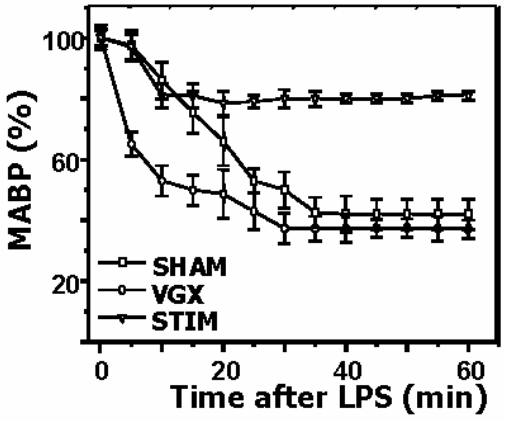
Neural

The Inflammatory Reflex



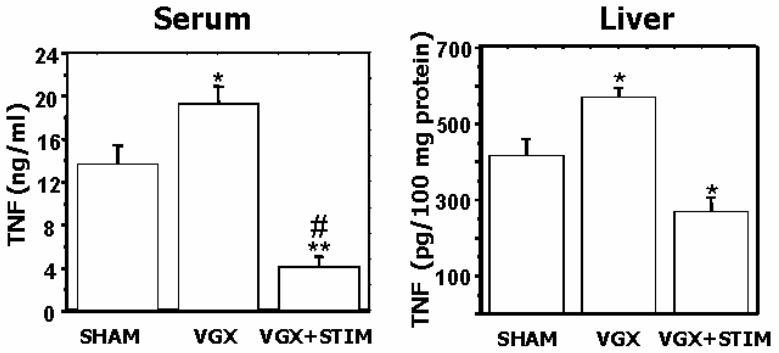
Tracey, KJ. *Nature* 420: 853-859, 2002

Vagus Nerve Stimulation Attenuates Endotoxic Shock

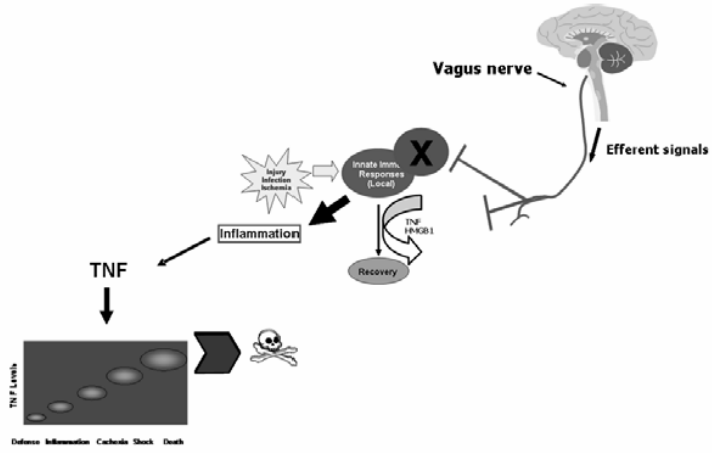


Borovikova et al., *Nature* 405:458-62, 2000

Vagus Nerve Stimulation Attenuates TNF

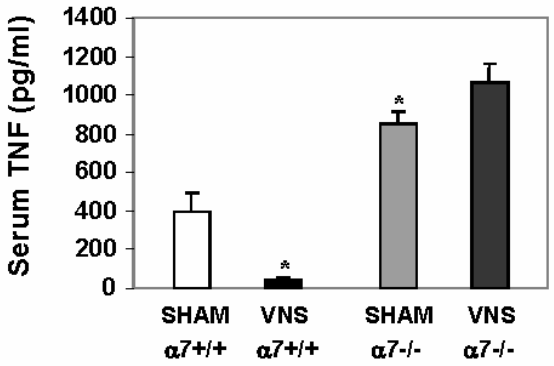


Borovikova et al., *Nature* 405:458-62, 2000



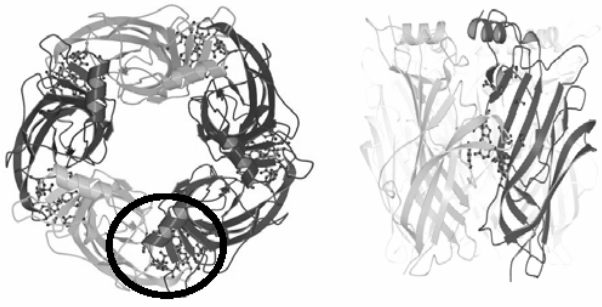
Tracey, KJ. *Nature* 420: 853-859, 2002

Nicotinic Acetylcholine Receptor α7 Subunit is an Essential Regulator of Inflammation



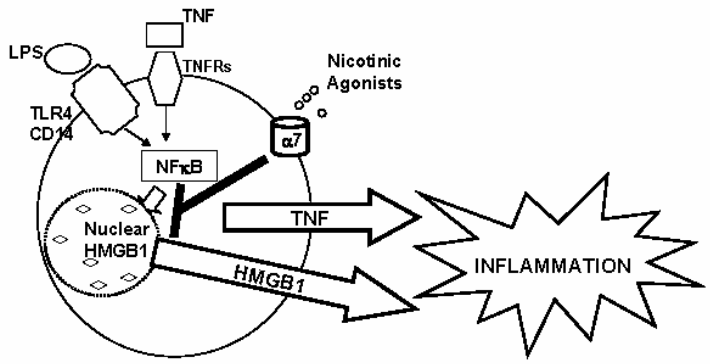
Wang et al., *Nature*, 421: 384-388, 2003

Pentameric Structure of Nicotinic Acetylcholine Receptor

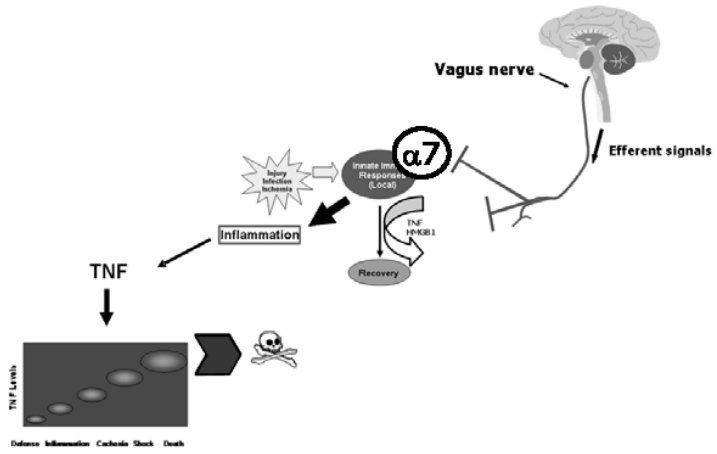


Brejc, K. *Nature* 411: 269-276, 2001

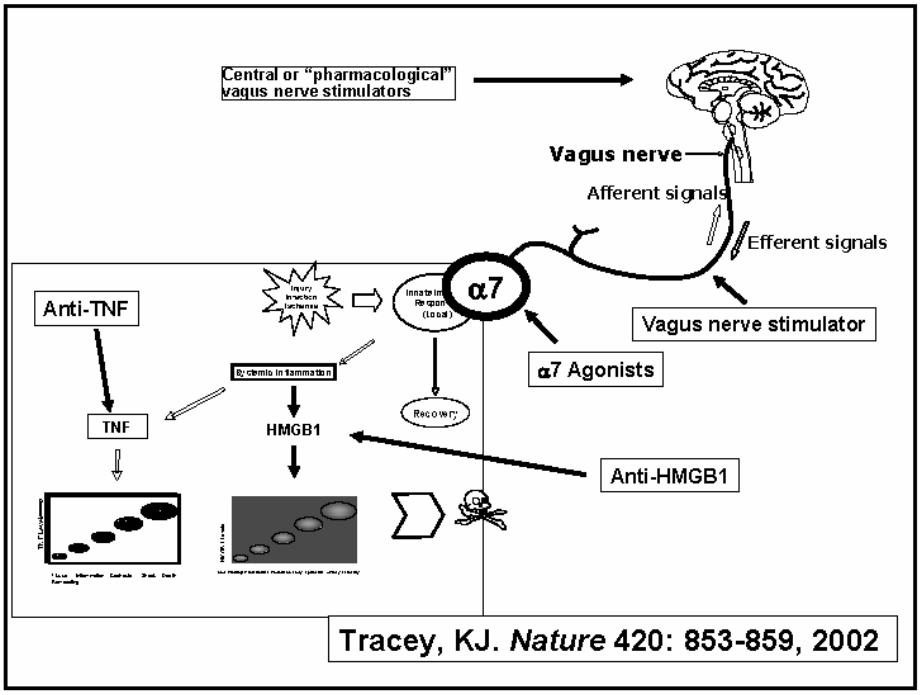
α7 Inhibition of Cytokine Release in Macrophages



Wang et al, *Nat Med*, 10:1216-21, 2004



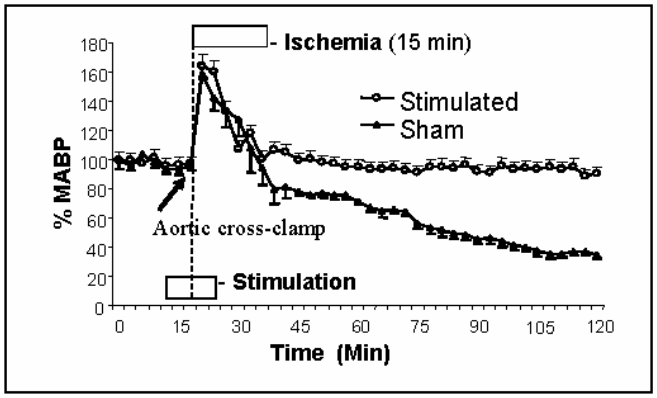
Tracey, KJ. *Nature* 420: 853-859, 2002



Efficacy of VNS and α7 Agonists

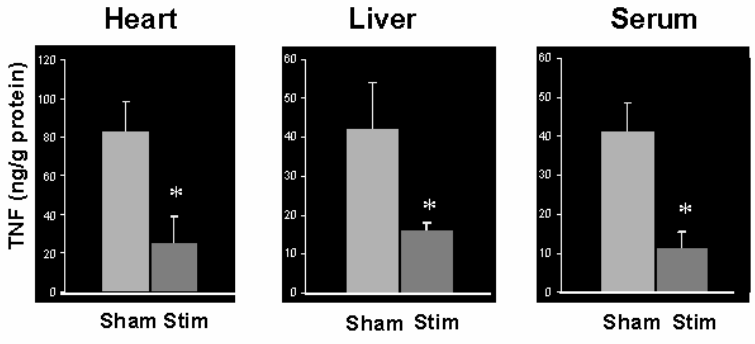
Disease	VNS	α7
Endotoxemia	X	X
Sepsis	X	X
Arthritis	X	X
Hemorrhagic Shock	X	X
Ischemia-reperfusion	X	X
Subcutaneous inflammation	X	X
Pancreatitis	X	X
Autoimmune diabetes		X
Ileus	X	X
Colitis		X

Vagus Nerve Stimulation Attenuates Ischemia Reperfusion



Bernik et al., *J. Exp. Med.* 195:781-788, 2002
Bernik et al., *J. Vasc. Surg.* 36:1231-6, 2002

Vagus Nerve Stimulation Attenuates TNF in Ischemia Reperfusion



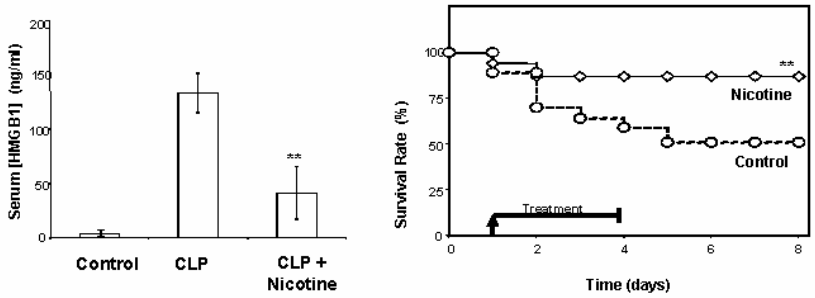
Bernik et al., *J. Exp. Med.* 195:781-788, 2002
Bernik et al., *J. Vasc. Surg.* 36:1231-6, 2002

Development of α7 Agonists as Anti-inflammatory Agents: Inhibition of TNF Release

Compound	EC_{50} (μM)
CAP13	< 1
CAP15	< 1
CAP22	~ 1
CAP17	< 10
CAP19	< 10
CAP25	< 10
CAP26	< 10
CAP02	< 25
CAP11	< 25
CAP06	< 50
CAP03	Inactive
CAP12	Inactive
CAP27	Inactive
CAP23	Inactive

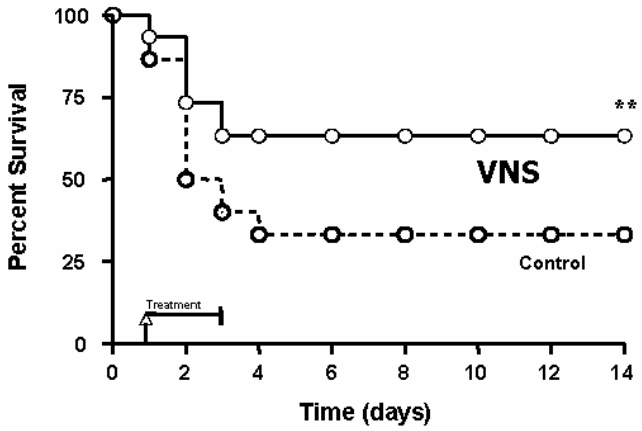
Y. Al-Abed, 2002-5

Cholinergic Agonists Suppress HMGB1 During Severe Sepsis (CLP)



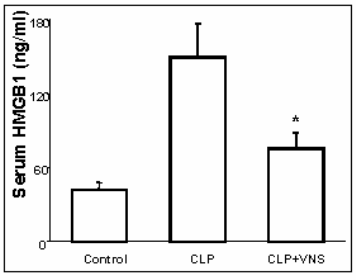
Nature Medicine, 10:1216-21, 2004

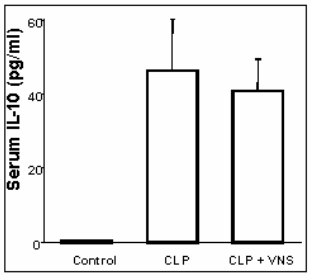
Murine Vagus Nerve Stimulation in Sepsis



Huston et al., 2005

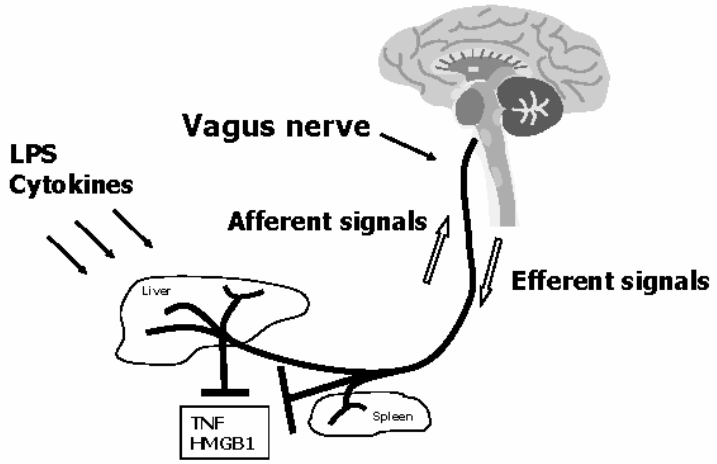
Murine Vagus Nerve Stimulation in Sepsis





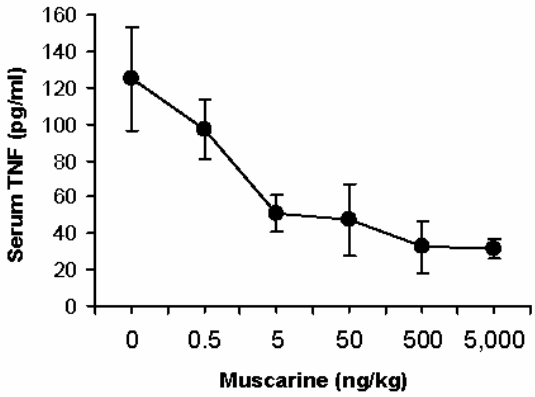
Huston et al., 2006

The Inflammatory Reflex



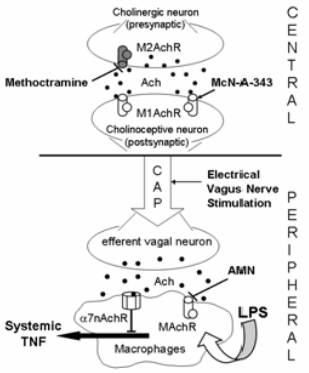
Tracey, KJ. *Nature* 420: 853-859, 2002

Central Cholinergic Activation of the Vagus Nerve



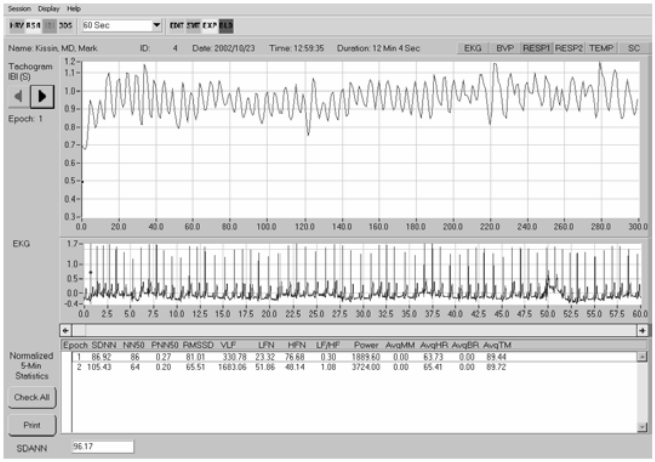
Pavlov et al., ***Proc. Nat'l. Acad. Sci.*** 103:5219-23, 2006

Central Cholinergic Activation of the Vagus Nerve



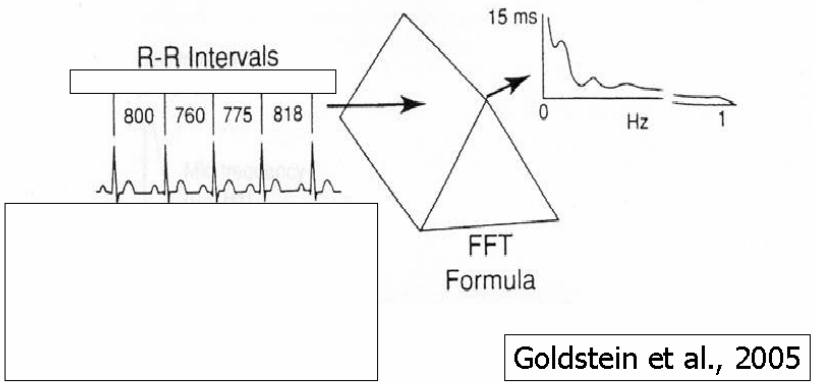
Pavlov et al., ***Proc. Nat'l. Acad. Sci.*** 103:5219-23, 2006

Instantaneous Heart Rate: Tachogram



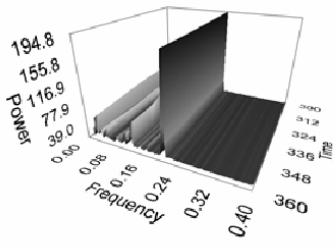
Goldstein et al., 2005

Fast Fourier Transform of Tachogram

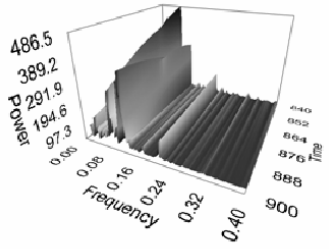


Goldstein et al., 2005

Vagus Nerve Activity in Volunteers



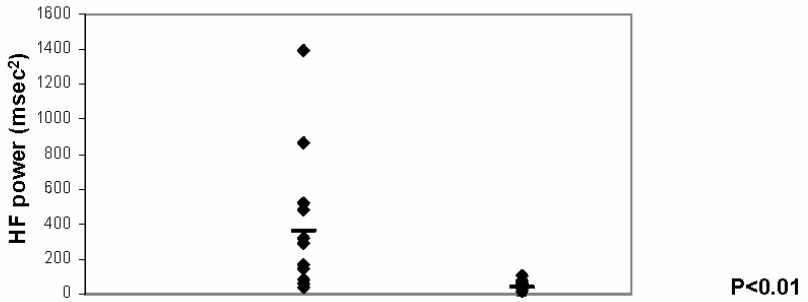
Vagus Predominate



Sympathetic Predominate

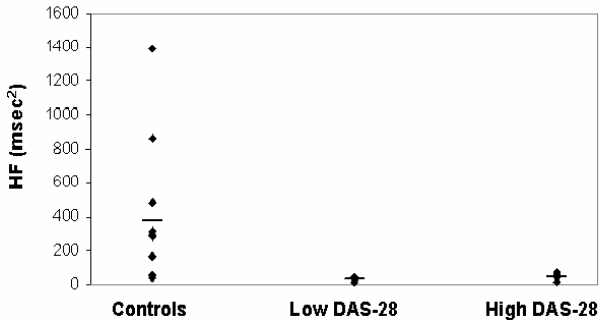
Goldstein, Czura et al., 2003

Vagus Nerve Activity is Depressed in Rheumatoid Arthritis



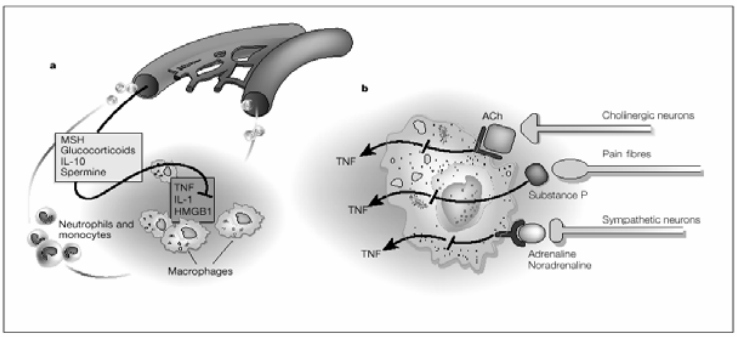
Goldstein et al., 2006

Vagus Nerve Activity in Rheumatoid Arthritis



Goldstein et al., 2006

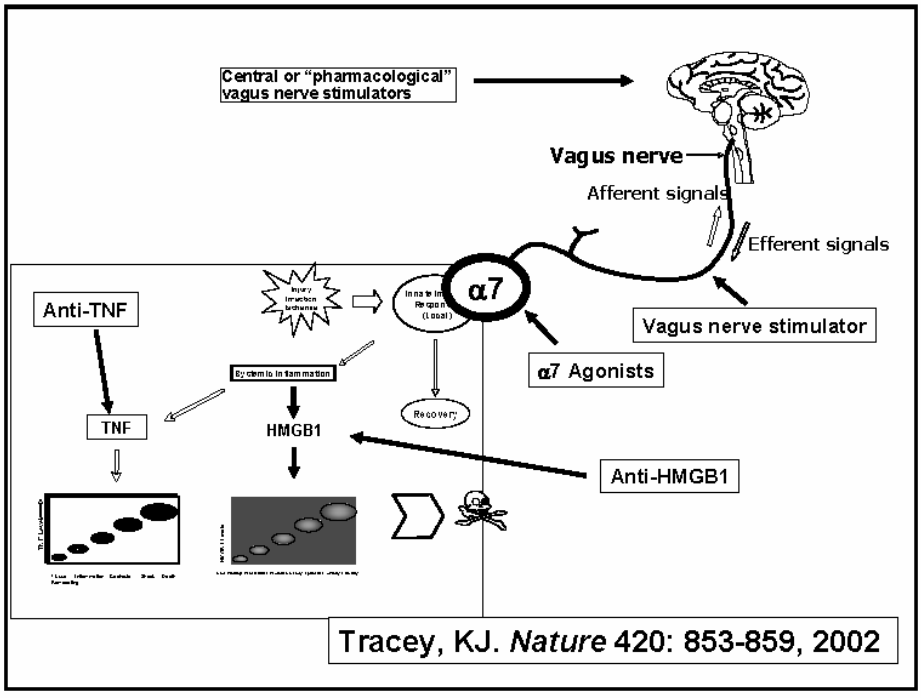
Humoral vs. Neural Anti-inflammatory Pathways



- Concentration gradient
- Slow
- Not-integrated

- Local
- Fast
- Integrated

Tracey, KJ. *Nature* 420: 853-859, 2003



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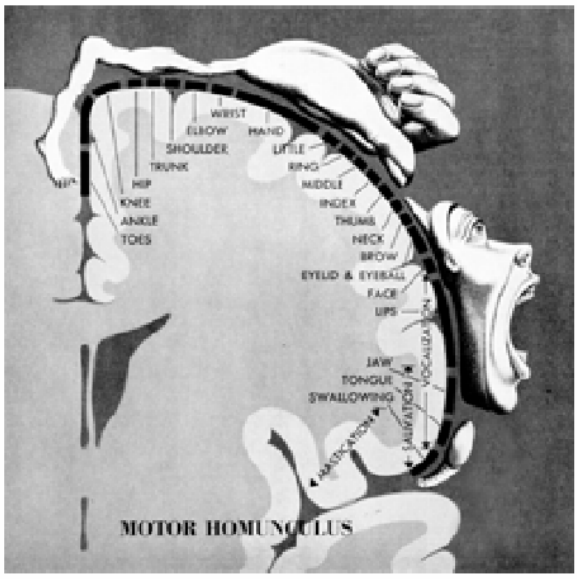
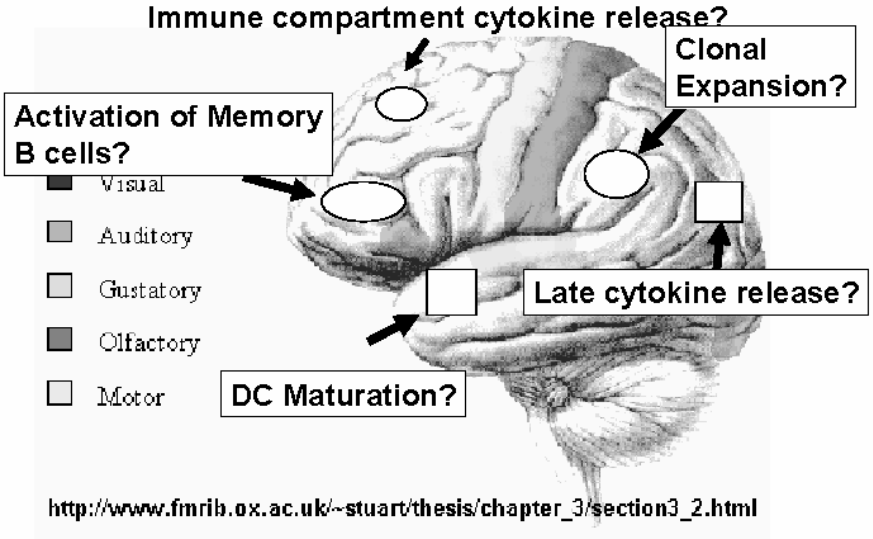

WRIST
ELBOW
HAND
SHOULDER
LITTLE
TRUNK
RING
HIP
MIDDLE
KNEE
INDEX
ANKLE
THUMB
TOES
NECK
BROW
EYELID & EYEBALL
FACE
LIPS
JAW
TONGUE
SWALLOWING
MOTOR HOMUNCULUS


Immune compartment cytokine release?
Clonal Expansion?
Activation of Memory B cells?
Visual
Auditory
Gustatory
Olfactory
Motor
Late cytokine release?
DC Maturation?
http://www.fmrib.ox.ac.uk/~stuart/thesis/chapter_3/section3_2.html