The Vagus Nerve, Heart Rate Variability, Cholinergic Anti-Inflammatory Pathway Nexus

Started by HighDesertWizard , May 24 2012 11:20 PM

vagus, cholinergic, anti-inflammatory, heart rate variability, spleen,

HighDesertWizard

Posted 24 May 2012 - 11:20 PM

THIS TOPIC IS MODERATED BY THE THREADSTARTER

The systematic study of the Vagus Nerve, Heart Rate Variability, and Cholinergic Anti-Inflammatory Pathway Nexus has been among the most profound developments in disease and aging research since the year 2000.

I've established this thread to describe and discuss the science underlying this development. I believe Dr. Kevin Tracey to be the leading student of the Vagus Nerve and the Cholinergic Anti-Inflammatory Pathway (hereafter CAIP). The literature about Heart Rate Variability (HRV) has a longer history. Lower HRV is inversely correlated with disease incidence of most of the most serious diseases, morbidity, and mortality.

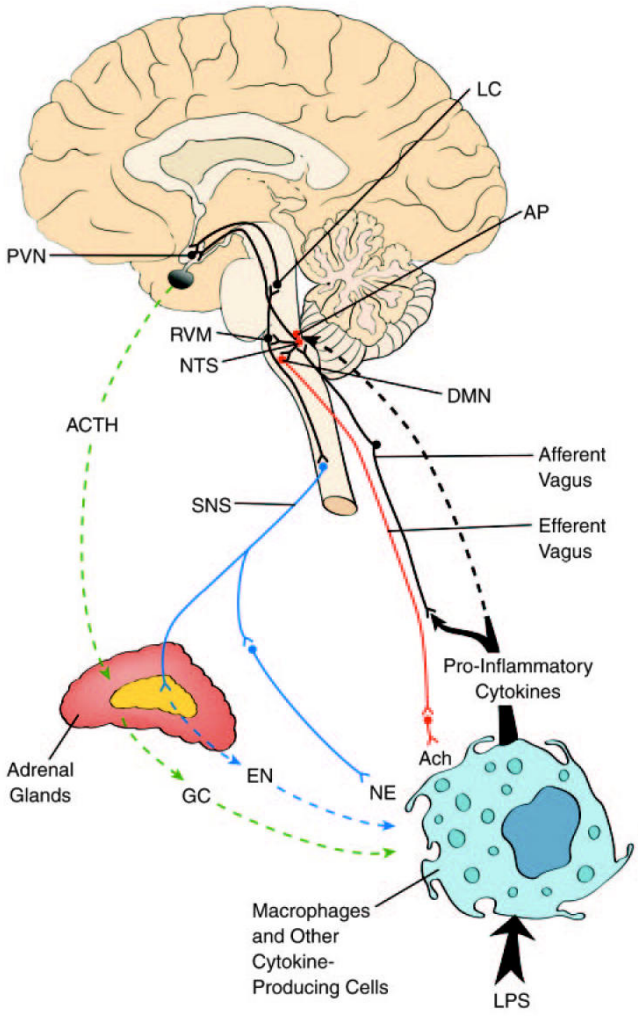
I first began to examine the literature of HRV in 2008. At that time, I hadn't come across the literature, which had already been published, about the Vagus Nerve and the CAIP which is associated by causation to higher and lower HRV. When I stumbled on the literature of the Vagus Nerve and the CAIP I was astounded. I couldn't believe that, in all my health science related travels, I had never come across it. I think it must be one of the most important topics that many of us don't know anything about.
I'll begin to lay out the literature about it by referencing the abstracts and graphic figures of Dr. Kevin Tracey and his colleagues. His primary focus is on the Vagus Nerve and the CAIP. Remember, while you're looking at his work, that Low HRV is strongly correlated with serious disease incidence, morbidity, and mortality.

I look forward to discussion and new insight about this biological lever we have to improve our lives and our health!

The Cholinergic Anti-inflammatory Pathway: A Missing Link in Neuroimmunomodulation (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1430829/)

This review outlines the mechanisms underlying the interaction between the nervous and immune systems of the host in response to an immune challenge. The main focus is the cholinergic anti-

inflammatory pathway, which we recently described as a novel function of the efferent vagus nerve. This pathway plays a critical role in controlling the inflammatory response through interaction with peripheral α7 subunit–containing nicotinic acetylcholine receptors expressed on macrophages. We describe the modulation of systemic and local inflammation by the cholinergic anti-inflammatory pathway and its function as an interface between the brain and the immune system. The clinical implications of this novel mechanism also are discussed.



Edited by HighDesertWizard, 20 March 2015 - 03:05 AM.
topic moderator

like x 1

HighDesertWizard

Posted 24 May 2012 - 11:22 PM

Kevin Tracey and a collegue wrote an overview of the literature about this topic, published in 2007. This post contains the abstract from the overview article and 3 graphic figures from it. I recommend studying the article, which is available in its entirety for free, and the figures in detail.

Dr. Tracey did a video presentation of the content of this article in an hour lecture to the NIH a few years ago. The video quality is not great but, if you're like me, and once it dawns on you how important this topic is, you'll want to see it... Or so I'd bet... Here's the link to the video...

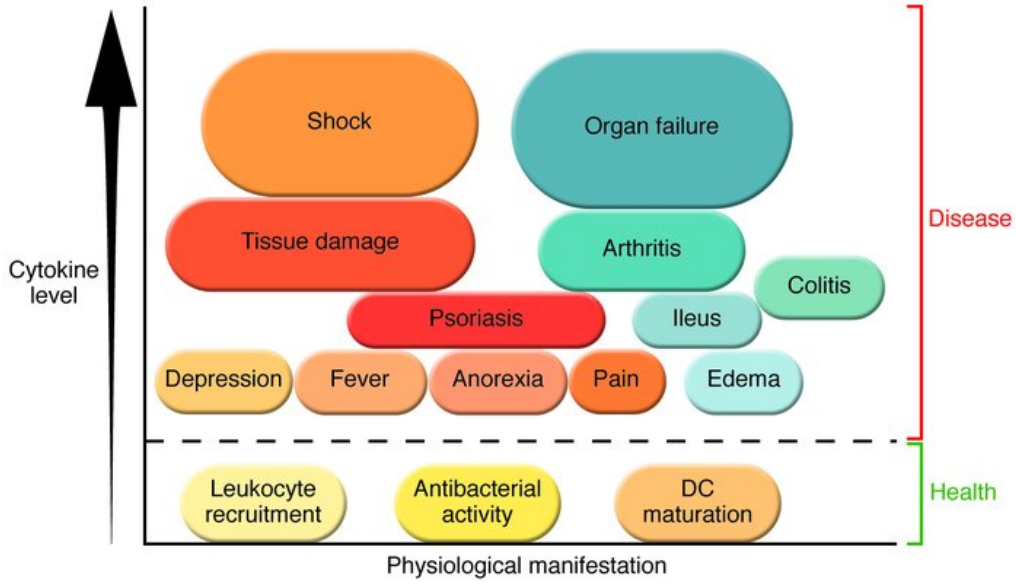
http://videocast.nih...y.asp?live=6197 (http://videocast.nih.gov/summary.asp?live=6197)

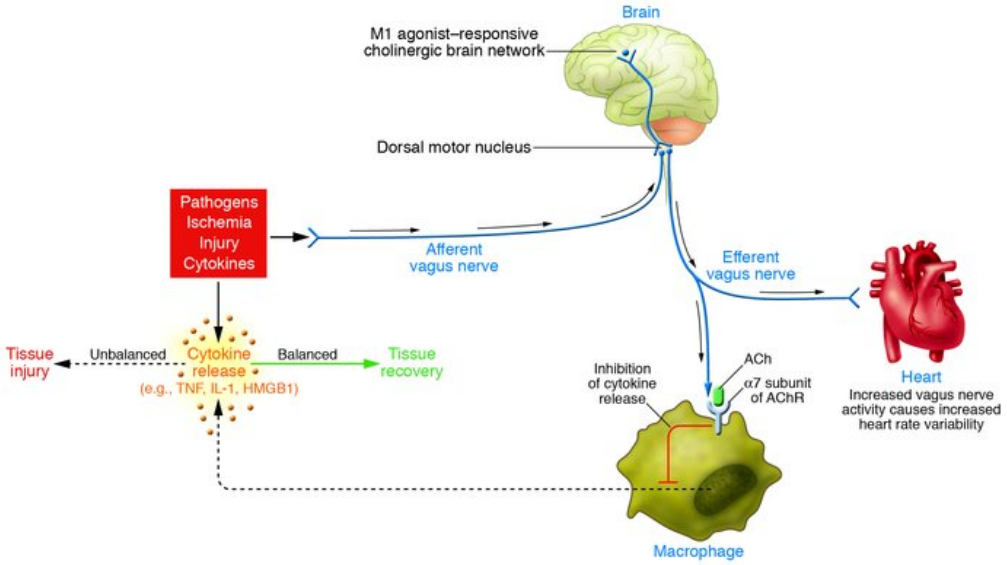
2007

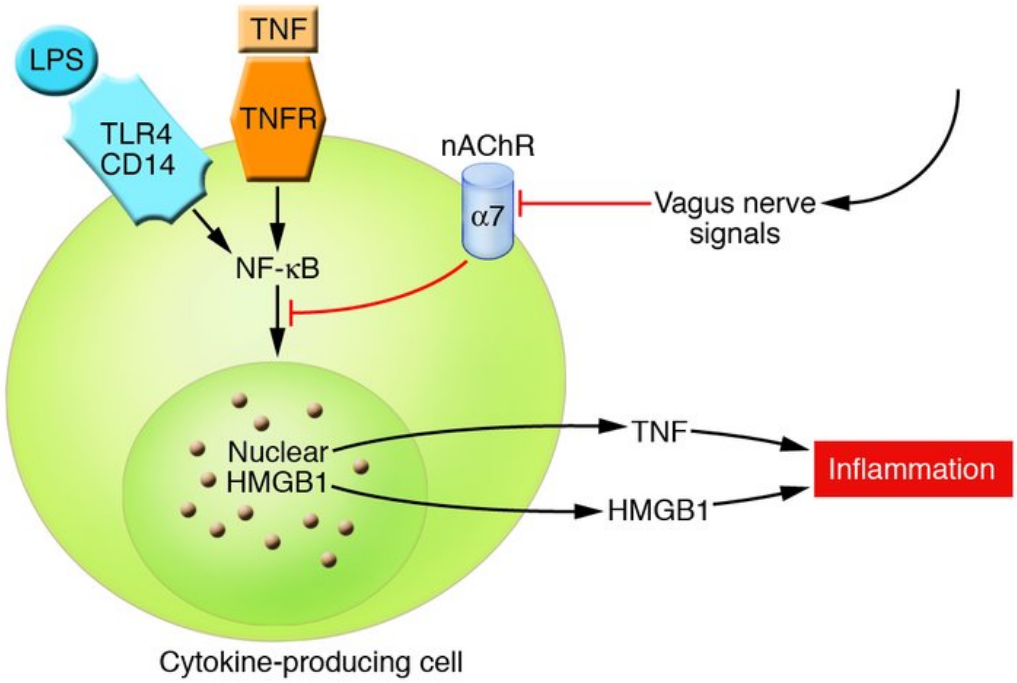
The entire article is available for free at the link

Physiology and immunology of the cholinergic antiinflammatory pathway (http://www.jci.org/articles/view/30555)

Cytokine production by the immune system contributes importantly to both health and disease. The nervous system, via an inflammatory reflex of the vagus nerve, can inhibit cytokine release and thereby prevent tissue injury and death. The efferent neural signaling pathway is termed the*cholinergic antiinflammatory pathway***. Cholinergic agonists inhibit cytokine synthesis and protect against cytokine-mediated diseases. Stimulation of the vagus nerve prevents the damaging effects of cytokine release in experimental sepsis, endotoxemia, ischemia/reperfusion injury, hemorrhagic shock, arthritis, and other inflammatory syndromes. Herein is a review of this physiological, functional anatomical mechanism for neurological regulation of cytokine-dependent disease that begins to define an immunological homunculus.**







Edited by wccaguy, 24 May 2012 - 11:31 PM.

HighDesertWizard

Posted 24 May 2012 - 11:22 PM

Among the first and most important articles Dr. Tracey has written about the Cholinergic Anti-Inflammatory Pathway (CAIP) is the one that appeared in Nature in 2002.

It's a free and truly great introduction to the topic and contains graphics that make the scientific concepts he's communicating clear. A must read...

Be sure to open the document to view the graphic figures...

2002
A downloadable PDF

[The Inflammatory Reflex](http://www.tedpriebe.com/documents/the_inflammatory_reflex.pdf)

Inflammation is a local, protective response to microbial invasion or injury. It must be fine-tuned and regulated precisely, because deficiencies or excesses of the inflammatory response cause morbidity and shorten lifespan. The discovery that cholinergic neurons inhibit acute inflammation has qualitatively expanded our understanding of how the nervous system modulates immune responses. The nervous system reflexively regulates the inflammatory response in real time, just as it controls heart rate and other vital functions. The opportunity now exists to apply this insight to the treatment of inflammation through selective and reversible 'hard-wired' neural systems.

Edited by wccaguy, 24 May 2012 - 11:36 PM.

HighDesertWizard

Posted 24 May 2012 - 11:22 PM

Ok... Enough of the overviews of the literature for now, right? How about some actual, harder scientific studies of the subject...

I first came across the literature of the Cholinergic Anti-Inflammatory Pathway because I was increasing my Acetylcholine precursor dose while using HeartMath's emWave2 product to practice increasing my Heart Rate Variability. I noticed that it was dramatically easier to raise my HRV while supplementing Acetylcholine than when I wasn't. I didn't understand why that should be. So I began to investigate and that led me to find the work of Kevin Tracey... 8-)

2002
Complete study is available for review for free

Pharmacological Stimulation of the Cholinergic Antiinflammatory Pathway (http://jem.rupress.org/content/195/6/781.full)

Efferent activity in the vagus nerve can prevent endotoxin-induced shock by attenuating tumor necrosis factor (TNF) synthesis. Termed the "cholinergic antiinflammatory pathway," inhibition of TNF synthesis is dependent on nicotinic α-bungarotoxin-sensitive acetylcholine receptors on macrophages. Vagus nerve firing is also stimulated by CNI-1493, a tetravalent guanylhydrazone molecule that inhibits systemic inflammation. Here, we studied the effects of pharmacological and electrical stimulation of the intact vagus nerve in adult male Lewis rats subjected to endotoxin-induced shock to determine whether intact vagus nerve signaling is required for the antiinflammatory action of CNI-1493. CNI-1493 administered via the intracerebroventricular route was 100,000-fold more effective in suppressing endotoxin-induced TNF release and shock as compared with intravenous dosing. Surgical or chemical vagotomy rendered animals sensitive to TNF release and shock, despite treatment with CNI-1493, indicating that an intact cholinergic antiinflammatory

pathway is required for antiinflammatory efficacy in vivo. Electrical stimulation of either the right or left intact vagus nerve conferred significant protection against endotoxin-induced shock, and specifically attenuated serum and myocardial TNF, but not pulmonary TNF synthesis, as compared with sham-operated animals. Together, these results indicate that stimulation of the cholinergic antiinflammatory pathway by either pharmacological or electrical methods can attenuate the systemic inflammatory response to endotoxin-induced shock.

Edited by wccaguy, 24 May 2012 - 11:42 PM.

HighDesertWizard

Posted 24 May 2012 - 11:22 PM

Another harder science post about the CAIP... The control of the bodies innate, systemic and organ specific immune system inflammation fighting effort is controlled by acetylcholinesterase...

2009
Haven't found a free version of entire study

Brain acetylcholinesterase activity controls systemic cytokine levels through the cholinergic anti-inflammatory pathway
(http://www.sciencedirect.com/science/article/pii/S0889159108003000)

The excessive release of cytokines by the immune system contributes importantly to the pathogenesis of inflammatory diseases. Recent advances in understanding the biology of cytokine toxicity led to the discovery of the “cholinergic anti-inflammatory pathway,” defined as neural signals transmitted via the vagus nerve that inhibit cytokine release through a mechanism that requires the α7 subunit-containing nicotinic acetylcholine receptor (α7nAChR). Vagus nerve regulation of peripheral functions is controlled by brain nuclei and neural networks, but despite considerable importance, little is known about the molecular basis for central regulation of the vagus nerve-based cholinergic anti-inflammatory pathway. Here we report that brain acetylcholinesterase activity controls systemic and organ specific TNF production during endotoxemia. Peripheral administration of the acetylcholinesterase inhibitor galantamine significantly reduced serum TNF levels through vagus nerve signaling, and protected against lethality during murine endotoxemia. Administration of a centrally-acting muscarinic receptor antagonist abolished the suppression of TNF by galantamine, indicating that suppressing acetylcholinesterase activity, coupled with central muscarinic receptors, controls peripheral cytokine responses. Administration of galantamine to α7nAChR knockout mice failed to suppress TNF levels, indicating that the α7nAChR-mediated cholinergic anti-inflammatory pathway is required for the anti-inflammatory effect of galantamine. These findings show that inhibition of brain acetylcholinesterase suppresses systemic inflammation through a central muscarinic receptor-mediated and vagal- and α7nAChR-dependent mechanism. Our data also indicate that a clinically used centrally-acting acetylcholinesterase inhibitor can be utilized to suppress abnormal inflammation to therapeutic advantage.

Edited by wccaguy, 25 May 2012 - 12:14 AM.

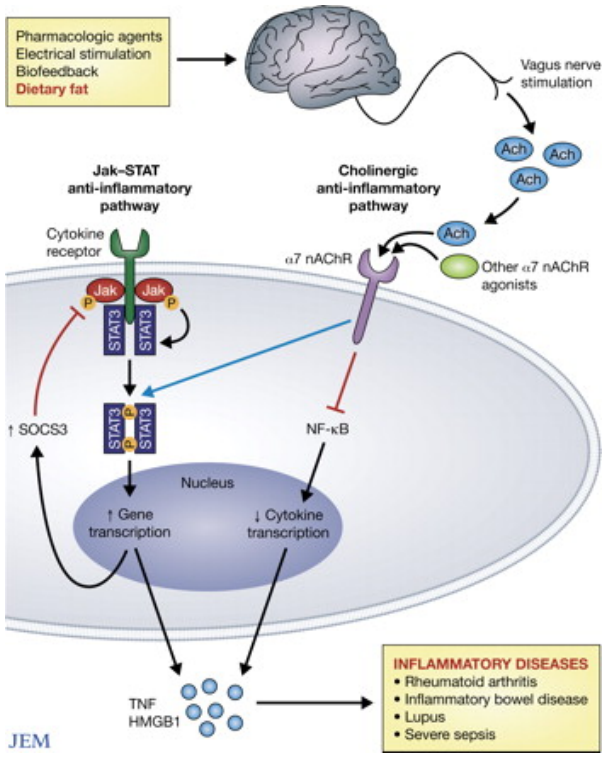
HighDesertWizard

Posted 24 May 2012 - 11:43 PM

2005
Free access to complete text

Fat meets the cholinergic antiinflammatory pathway
(http://jem.rupress.org/content/202/8/1017.full)

The cholinergic antiinflammatory pathway is a neural mechanism that is controlled by the vagus nerve and inhibits local cytokine release, thereby preventing the damaging effects of cytokine overproduction. A new study now shows that dietary fat can activate this pathway, a finding that may help explain the immune system's failure to react to food antigens and commensal bacteria. Here we discuss this new data and its potential implications for dietary intervention in the treatment of inflammatory diseases.



Edited by HighDesertWizard, 31 January 2015 - 11:15 PM.

HighDesertWizard

Posted 24 May 2012 - 11:49 PM

Evidence from someone other than Kevin Tracey that this CAIP exists and has a relationship to Heart Rate Variability...

2009
Free access

Heart rate variability, overnight urinary norepinephrine and C-reactive protein: evidence for the cholinergic anti-inflammatory pathway in healthy human adults (http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2796.2008.02023.x/full)

Objectives. C-reactive protein (CRP) has been identified as an independent predictor of cardiovascular mortality and morbidity in population-based studies. Recent advances have suggested a prominent role for the autonomic nervous system (ANS) in the regulation of inflammation. However, no *in vivo* human studies have examined indices of sympathetic and parasympathetic nervous system activity simultaneously in relationship to inflammatory markers in apparently healthy adults. Therefore, the objective of this study was to assess the immunomodulatory effects of the ANS.

Methods and results. The study population comprised 611 apparently healthy employees of an airplane

manufacturing plant in southern Germany. Urinary NE was positively associated with white blood cell count (WBC) in the total sample. We found an inverse association between indices of vagally mediated heart rate variability and plasma levels of (CRP), which was significantly larger in females than in males after controlling for relevant covariates including NE. Similar results were found using the percentage of interbeat interval differences >50 ms and WBC.

Conclusions. We report here for the first time, in a large sample of healthy human adults, evidence supporting the hypothesis of a clinically relevant cholinergic anti-inflammatory pathway after controlling for sympathetic nervous system activity. This suggests an important role for the vagal control of systemic inflammatory activity in cardiovascular disease.

Edited by wccaguy, 25 May 2012 - 12:22 AM.

HighDesertWizard

Posted 25 May 2012 - 12:18 AM

An attempt to falsify Tracey's CAIP hypothesis finds that, indeed, HRV varies inversely with inflammation...

2007
Free access to study text available

Stimulated Production of Proinflammatory Cytokines Covaries Inversely With Heart Rate Variability (http://www.psychosomaticmedicine.org/content/69/8/709.full)

Objective: To examine whether high-frequency heart rate variability, an indirect measure of parasympathetic (vagal) control over variations in heart rate, is associated with immune reactivity to an in vitro inflammatory challenge. Convergent evidence from the animal literature shows that the autonomic nervous system plays a key role in regulating the magnitude of immune responses to inflammatory stimuli. Signaling by the parasympathetic system inhibits the production of proinflammatory cytokines by activated monocytes/macrophages and thus decreases local and systemic inflammation. As yet, no direct human evidence links parasympathetic activity to inflammatory competence.
Methods: We examined the relationship of variations in heart rate, recorded during paced respiration, to lipopolysaccharide-induced production of the inflammatory cytokines interleukin (IL)-1ß, IL-6, tumor necrosis factor (TNF)-α, and IL-10 among a community sample of 183 healthy adults (mean age = 45 years; 59% male; 92% White, 7% African-American).
Results: Consistent with animal findings, higher derived estimates of vagal activity measured during paced respiration were associated with lower production of the proinflammatory cytokines TNF-α and IL-6 (r = –.18 to –.30), but were not related to production of the anti-inflammatory cytokine IL-10. These associations persisted after controlling for demographic and health characteristics, including age, gender, race, years of education, smoking, hypertension, and white blood cell count.
Conclusions: These data provide initial human evidence that vagal activity is inversely related to inflammatory competence, raising the possibility that vagal regulation of immune reactivity may represent a pathway linking psychosocial factors to risk for inflammatory disease.

Edited by wccaguy, 25 May 2012 - 12:29 AM.

HighDesertWizard

Posted 25 May 2012 - 12:24 AM

All that we are is the result of what we have thought. The mind is everything. What we think we become. -- Gautama Siddharta, the Buddha

Among the most amazing things to me about the science of the CAIP is this... In the years between 1000 BCE and 400 BCE, the peoples inhabiting current day South Central India had discovered profound truths about human life and health.

- the Buddha and his spiritual comrades had discovered the meditation and mindfulness practices that our science only in the last 10 years has receognized as being valid.
- religious texts of this period also began to describe the healthful effects of the gum resin of the Frankincense tree (Boswellia Serata (AKBA)). (I've spent a lot of time studying the science of Boswellia and how it inhibits the 5-Lipoxygenase Inflammatory Pathway. Just a few months ago, the LEF, for the first time, published an editorial (http://www.lef.org/magazine/mag2011/ss2011_Neutralize-a-Lethal-Enzyme_01.htm) stating that 5-LO was involved in 7 out of the 10 most lethal diseases in the US.

Here is Dr. Barbara Fredrickson, the leading student in the world of Positive Human Emotions, about Positive Emotions and "Vagal Tone"...

2010
free download

Upward spirals of the heart: Autonomic flexibility, as indexed by vagal tone, reciprocally and prospectively predicts positive emotions and social connectedness (http://www.unc.edu/peplab/publications/Kok%20&%20Fredrickson%202010.pdf)

Vagal tone (VT), an index of autonomic flexibility, is linked to social and psychological well-being. We posit that the association between VT and well-being reflects an “upward spiral” in which autonomic flexibility, represented by VT, facilitates capitalizing on social and emotional opportunities and the resulting opportunistic gains, in turn, lead to higher VT. Community-dwelling adults were asked to monitor and report their positive emotions and the degree to which they felt socially connected each day for 9 weeks. VT was measured at the beginning and end of the 9-week period. Adults who possessed higher initial levels of VT increased in connectedness and positive emotions more rapidly than others. Furthermore, increases in connectedness and positive emotions predicted increases in VT, independent of initial VT level. This evidence is consistent with an “upward spiral” relationship of reciprocal causality, in which VT and psychosocial well-being reciprocally and prospectively predict one another.

Edited by wccaguy, 25 May 2012 - 12:48 AM.

HighDesertWizard

Posted 25 May 2012 - 12:31 AM

There's more to come... The devil is in the details right? And there are lots more details...

When I have more time, I'll talk about my experience with HeartMath's emWave2 product... An amazing tool. It was the tool that led me to try to figure out why Acetylcholine helped me raise my HRV and keep it high...

In the meantime, has your mind gone there yet? I mean, you know, about the Placebo Effect? Take the scientific findings of folks like Kevin Tracey and combine it with the insight and findings of Barbara Fredrickson and you can derive something close to a relatively strong Hypothesis about what lies behind the Placebo Effect. And studies could be done to try to Falsify the Hypothesis.

So help me out... Before I go and post the following Figure as my Facebook Cover Photo, tell me what I got wrong, so I don't embarrass myself...

Enjoy healing yourself!

Explanations that transform the world are the beginning of Infinity -- David Deutsch

Edited by wccaguy, 25 May 2012 - 01:13 AM.

HighDesertWizard

Posted 25 May 2012 - 01:20 AM

Two pics that didn't make the post about Fredrickson's Positive Emotions point before I lost edit capability on the post....

A great figure illustrating "upward positive" and "downward negative" spirals of the mind and heart. I believe the science is established and actual practiced has confirmed that autonomic flexibility (aka "positive vagal tone" or "parasympathetic nervous system dominance") is difficult or impossible to achieve without some degree of Positive Mental State...

These figures are from the Fredrickson, et al, study...

Upward spirals of positive emotions counter downward spirals of negativity: Insights from the broaden-and-build theory and affective neuroscience on the treatment of emotion dysfunctions and deficits in psychopathology (http://www.unc.edu/peplab/publications/Garland%20et%20al%202010.pdf)

That image of the chalkboard with Fredrickson's list of Positive Emotions was fuzzy. Here's a better one...

Edited by wccaguy, 25 May 2012 - 02:13 AM.

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niner

Posted 25 May 2012 - 02:18 AM

> *'wccaguy', on 25 May 2012 - 02:31 AM, said:*
>
> Before I go and post the following Figure as my Facebook Cover Photo, tell me what I got wrong...

Is the wording right on the 7/8 box? It sounds odd...

HighDesertWizard

Posted 25 May 2012 - 02:25 AM

> *'niner', on 25 May 2012 - 04:18 AM, said:*
>
> Is the wording right on the 7/8 box? It sounds odd...

Hey niner... Thanks, you're right. I'm thinking it should be "Reducing Serious Disease, Morbidity, and Mortality".

Thanks for spotting that!

HighDesertWizard

Posted 27 May 2012 - 08:32 PM

Heart Rate Variability (HRV) is computed and measures "Vagal Tone," "Parasympathetic Dominance," "Autonomic Balance," etc.

Higher HRV is healthier and indicative of Vagus Activation/Stimulation. Lower HRV is implicated in more serious disease, morbidity, and death. Kevin Tracey's work on the Vagus/CAIP Nexus explains the physiology and biology of HRV.

In fact, the scientific evidence is clear that numerous vagus mutations must have arisen over thousands of years (because they exist in other mammals) and it is recognized as an independent predictor of extreme longevity, **by means of Heart Rate Variability measurement**.

What follows below are snippets from numerous studies about the importance of HRV in aging, disease, and mortality.

Relation of high heart rate variability to healthy longevity (http://www.ncbi.nlm.nih.gov/pubmed/20381674)

The population's aging underscores the need to understand the process and define the physiologic markers predictive of healthy longevity. The findings that aging is associated with a progressive decrease in heart rate variability (HRV), an index of autonomic function, suggests that longevity might depend on preservation of autonomic function. However, little is known about late life changes.... The HRV-sympathetic function continues to decrease throughout life. In contrast, the decrease in HRV-parasympathetic function reaches its nadir in the eighth decade, followed by reversal and a progressive increase to higher levels ($p < 0.05$), more characteristic of a younger population. In conclusion, healthy longevity depends on preservation of autonomic function, in particular, HRV-parasympathetic function, despite the early age-related decrease. The eighth decade reversal of the decrease in HRV-parasympathetic function and its subsequent increase are key determinants of longevity. Persistently high HRV in the elderly represents a marker predictive of longevity.

We studied the significance for further survival of heart rate variability and other variables in the very elderly... (http://cat.inist.fr/?aModele=afficheN&cpsidt=13491211)
Logistic regression analysis using backward elimination detected three factors, dementia, LF/HF , and age, that independently influenced mortality. Mortality risk increased with greater age..., more severe dementia, or lower LF/HF [i.e., HRV]. (http://cat.inist.fr/?aModele=afficheN&cpsidt=13491211)

Consequently, the low-frequency/high-frequency ratio (0.43±0.07 compared with 0.91±0.05; $P < 0.02$) was also lower in the healthy centenarians than in the aged subjects. Our study demonstrates that the basal low-frequency/high-

frequency ratio, an indirect index of cardiac sympathovagal balance, is lower in healthy centenarians than in aged subjects. (http://submit.clinsci.org/cs/097/0579/cs0970579.htm)

These data confirm an age-related decline in sympathetic activity. Compared with elderly subjects from 81 to 100 years of age ultra-centenarians have significantly higher spectral parasympathetic indexes. (http://www.sciencedirect.com/science/article/pii/S0167527397002829) Parasympathetic predominance may be the neuroautonomic feature that helps to protect ultra-centenarians against cardiovascular disease (http://www.sciencedirect.com/science/article/pii/S0167527397002829) . (http://www.sciencedirect.com/science/article/pii/S0167527397002829)

This study demonstrated that age had a greater impact on HRV than sex. The older age group had consistently lower HRV than younger people. The values generated in this study may be useful in health care settings to determine abnormal ranges of HRV under different clinical and experimental conditions. (http://www.sciencedirect.com/science/article/pii/S0161475407001224)

Power-law relationship of 24-hour HR variability is a more powerful predictor of death than the traditional risk markers in elderly subjects. Altered long-term behavior of HR implies an increased risk of vascular causes of death rather than being a marker of any disease or frailty leading to death. (http://circ.ahajournals.org/content/97/20/2031.short)

HR variability remained a significant predictor of mortality after adjusting for clinical, demographic, other Holter features and ejection fraction. A hypothesis to explain this finding is that decreased HR variability correlates with increased sympathetic or decreased vagal tone, which may predispose to ventricular fibrillation. (http://www.sciencedirect.com/science/article/pii/0002914987907958)

Decreased heartratevariability (HRV) is associated with congestive heart failure, post-myocardial infarction, ventricular arrhythmias, sudden cardiac death, and advancing age. (http://www.sciencedirect.com/science/article/pii/S0002914997010199)

Physiological ageing is associated with a reduction in parasympathetic control of the heart; this decline in parasympathetic activity can be reduced by regular endurance exercise. (http://www.ingentaconnect.com/content/adis/smd/2003/00000033/00000001/art00003)

Intensive endurance training in elderly men enhanced parasympathetic parameters of HRV and, interestingly, of SBR. Physiological mechanisms and long-term clinical effects on health status should be further investigated. (http://www.springerlink.com/content/ju5muugp8p267807/)

Low HRV was associated with increased risk of CHD and death from several causes. It is hypothesized that low HRV is a marker of less favorable health. (http://circ.ahajournals.org/content/102/11/1239.short)

ATRAMI provides clinical evidence that after myocardial infarction the analysis of vagal reflexes has significant prognostic value independently of LVEF and of ventricular arrhythmias and that it significantly adds to the prognostic value of heart-rate variability. (http://ukpmc.ac.uk/abstract/MED/9482439)

CHF is associated with autonomic dysfunction, which can be quantified by measuring HRV. A reduction in SDNN identifies patients at high risk of death and is a better predictor of death due to progressive heart failure than other conventional clinical measurements. (http://www.ncbi.nlm.nih.gov/pubmed/9769304)

During a mean follow-up of 3.5 years, cardiac events occurred in 58 subjects. After adjustment for age, sex, cigarette smoking, diabetes, left ventricular hypertrophy, and other relevant risk factors, all HRV measures except the ratio of low-frequency to high-frequency power were significantly associated with risk for a cardiac event. (http://circ.ahajournals.org/content/94/11/2850.short)

Relationships between measures of inflammation and autonomic function are stronger among depressed than non-depressed cardiac patients. Interventions targeting regulation of both autonomic control and inflammation may be of particular importance. (http://www.sciencedirect.com/science/article/pii/S0889159109003833)

Substantial evidence exists to support the notion that decreased HRV precedes the development of a number of risk factors and that lowering risk profiles is associated with increased HRV. We close with a suggestion that a model of autonomic imbalance may provide a unifying framework within which to investigate the impact of risk factors, including psychosocial factors and work stress, on cardiovascular disease. (http://www.sciencedirect.com/science/article/pii/S0167527309014879)

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heart rate variability may offer an inexpensive, non-invasive method of monitoring neuropathological processes following CA. The inverse linear relationships between heart rate variability and brain damage after CA also may partially explain why low heart rate variability is associated with increased morbidity and mortality in myocardial infarction patients. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3349244/)

The components of the heart rate variability indicated that men with a large prostate had increased sympathetic activity. (http://onlinelibrary.wiley.com/doi/10.1046/j.1464-410X.2003.04277.x/full)

Exposures to Air Pollution is associated with decreased HRV, and history of IHD, hypertension, and diabetes may confer susceptibility to autonomic dysfunction by air pollution. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1253756/)

TNF is an independent predictor of depressed heart rate variability in patients with heart failure. (http://chestjournal.chestpubs.org/content/123/3/716.short)

We concluded that power spectral analysis of heart rate variability offers a possible means of identifying episodes of sleep-related breathing disorders or periodic leg movements. (http://ukpmc.ac.uk/abstract/MED/9176031)

Hemispheric brain infarction seems to cause significant long-lasting damage to the cardiovascular autonomic regulatory system manifested as abnormalities of heart rate variability. Distorted heart rate variability in the acute phase of stroke may be prognostically unfavorable. (http://stroke.ahajournals.org/content/27/11/2059.short)

During the awakening period, global HRV and the parasympathetic tone were significantly lower in the worsened neurologic state group. In conclusion, HRV could be helpful as a predictor of imminent brain death and a useful adjunct for predicting the outcome of patients with severe head injury. (http://journals.lww.com/jnsa/Abstract/2001/07000/Could_Heart_Rate_Variability_Predict_Outcome_In.16.aspx)

HRV time and domain parameters were lower in patients with AD than in patients with MCI and controls.... QTD and HRV were found to be significantly correlated with the degree of cognitive impairment. (http://onlinelibrary.wiley.com/doi/10.1111/j.1532-5415.2005.00508.x/abstract?)

Habitual tuna/other fish and marine ω-3 consumption are associated with specific HRV components in older adults, particularly indices of vagal activity, baroreceptor responses, and sinoatrial node function. (http://circ.ahajournals.org/content/117/9/1130.short)

These findings suggest that higher intake of green leafy vegetables may reduce the risk of cardiovascular disease through favorable changes in cardiac autonomic function. (http://www.ajcn.org/content/89/3/778.short)

Edited by wccaguy, 27 May 2012 - 08:35 PM.

HighDesertWizard

Posted 28 May 2012 - 03:40 PM

Deleted...

Edited by HighDesertWizard, 27 January 2015 - 03:29 AM.

HighDesertWizard

Posted 11 September 2014 - 04:33 PM

I noticed the following story...

Silicon Valley Investor Backs $1 Million Prize to End Death (http://www.businessweek.com/articles/2014-09-09/silicon-valley-investor-backs-1-million-longevity-prize)

When you read the story, notice that 1/2 the Prize will go "to a team that can take an older mammal and bring its Heart Rate Variability (HRV) characteristics back to those of a young adult mammal."

If you work through the abstracts I've summarized in this threads, you'll see have a better understanding of HRV.

I summarized key findings about HRV and disease, aging, and longevity in post #14 of this thread here (http://www.longecity.org/forum/topic/56529-the-vagus-nerve-heart-rate-variability-cholinergic-anti-inflammatory-pathway-nexus/?view=findpost&p=516755)...

HighDesertWizard

Posted 02 February 2015 - 03:52 AM

Want to keep this thread current with discussion and study links related to the Vagus-HRV-CAIP Nexus...

> *HighDesertWizard, on 01 Feb 2015 - 02:02 AM, said:*

Neuronal control of NF-kB and aging intersect in another way, founded in Settled Science, that sometimes also involves the Hypothalamus.

The Vagus Nerve, Heart Rate Variability, Cholinergic Antiinflammatory Pathway Nexus (http://www.longecity.org/forum/topic/56529-the-vagus-nerve-heart-rate-variability-cholinergic-anti-inflammatory-pathway-nexus/) is, to my knowledge, our bodies' major, Innate mechanism for inflammation inhibition. A while back, I tried to summarize a bit of the literature about it at that Longecity link...

Kevin Tracey, the scientist most important to the research effort focused on this Innate Immunity Modulating Mechanism, is the lead author of a couple more recent study summaries that provide more significant insight. Links to the full articles follow...

Reflex Principles of Immunological Homeostasis (http://www.utdallas.edu/~mxa049000/lessons/research/IL-6%20literature/may%202012/Tracey%20annurev-immunol%202011.pdf)
Neural reflexes in inflammation and immunity (http://jem.rupress.org/content/209/6/1057.full)

If you believe that NF-kB is important and, yet, aren't familiar with the Vagus-HRV-CAIP Nexus, you're missing a big piece of the NF-kB puzzle...

Please allow me to press you to pay attention to this Nexus (http://www.longecity.org/forum/topic/56529-the-vagus-nerve-heart-rate-variability-cholinergic-anti-inflammatory-pathway-nexus) in the following two ways...

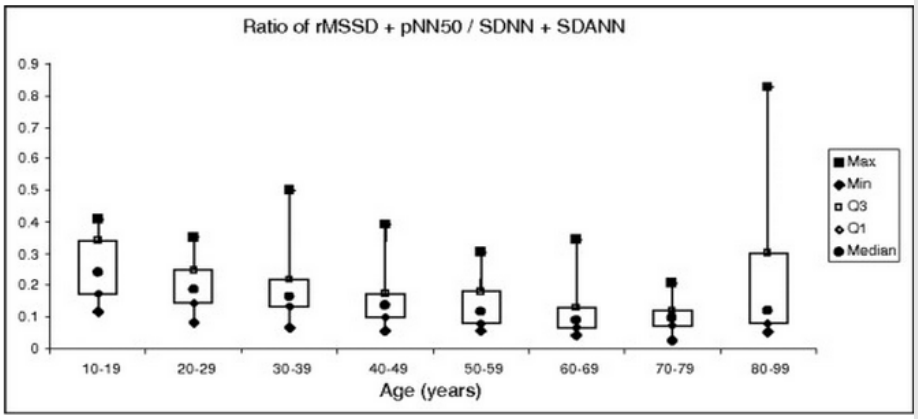
- Vagus Nerve Stimulation results in High Heart Rate Variability (HRV) coincident with triggering of the Cholinergic Antiinflammatory Pathway (CAIP).

  That Lower HRV is associated with increased Morbidity and Mortality (http://www.longecity.org/forum/topic/56529-the-vagus-nerve-heart-rate-variability-cholinergic-anti-inflammatory-pathway-nexus/?view=findpost&p=516755) is, by now, Settled Science. Meanwhile, Higher HRV is associated with increased healthy aging. No time to get at evidence about that point?

  How about a Single Study (http://www.sciencedirect.com/science/article/pii/S0002914909028525) Graphic Figure illustrating a fact-anomaly that the Vagus-HRV-CAIP Nexus and its impact on NF-kB can completely explain?

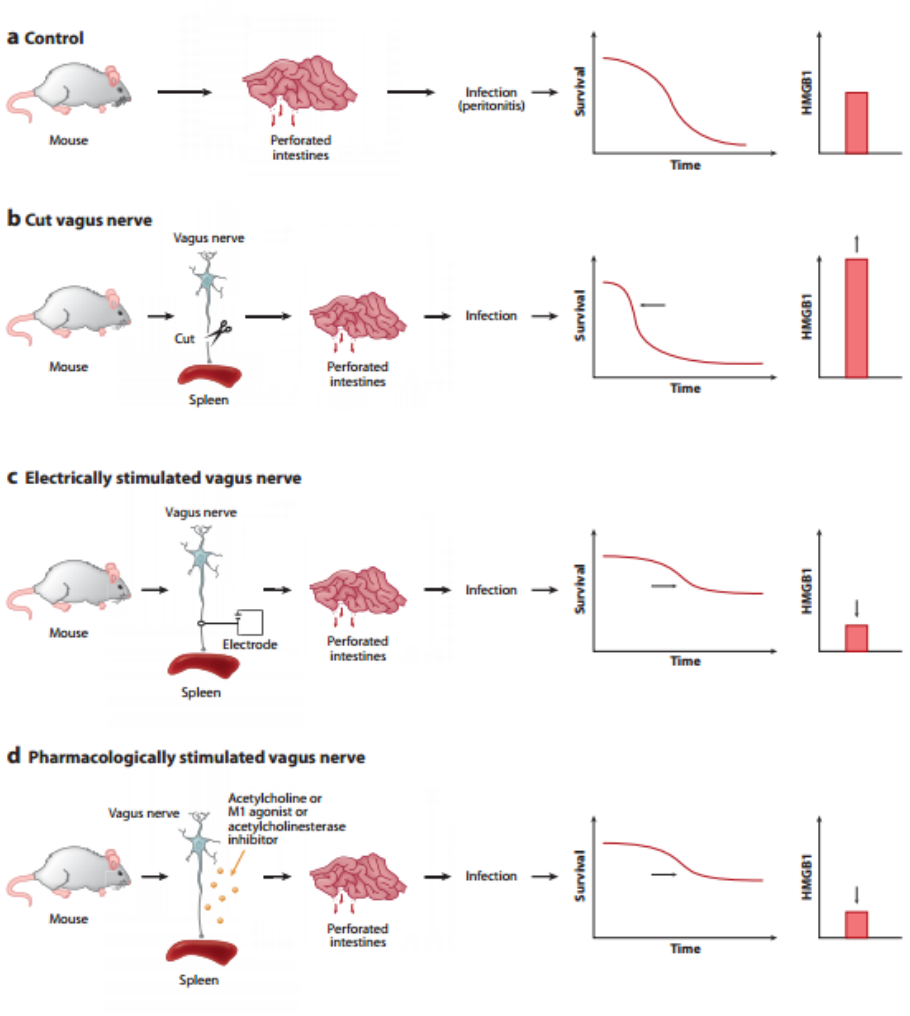
  Relation of High Heart Rate Variability to Healthy Longevity, 2010

  "The HRV of all measures decreases rapidly from the second to fifth decades. It then slows. The HRV–sympathetic function continues to decrease throughout life. In contrast, the decrease in HRV–parasympathetic function reaches its nadir in the eighth decade, followed by reversal and a progressive increase to higher levels ($p < 0.05$), more characteristic of a younger population. In conclusion, healthy longevity depends on preservation of autonomic function, in particular, HRV–parasympathetic function, despite the early age-related decrease. The eighth decade revers of the decrease in HRV–parasympathetic function and its subsequent increase are key determina of longevity. Persistently high HRV in the elderly represents a marker predictive of longevity."

- And if that isn't enough to get your attention, how about a set of good old fashioned Population Survival Curves, in which a functioning Vagus Nerve is the Independent Variable? (From Reflex Principles of

Immunological Homeostasis (http://www.utdallas.edu/~mxa049000/lessons/research/IL-6%20literature/may%202012/Tracey%20annurev-immunol%202011.pdf) .)



- A third Study Snapshot about HRV, and, by implication, Vagus-CAIP-NF-kB, just for the fun of it...

Power-Law Relationship of Heart Rate Variability as a Predictor of Mortality in the Elderly

Abstract

Background—The prognostic role of heart rate (HR) variability analyzed from 24-hour ECG recordings in the general population is not well known. We studied whether analysis of 24-hour HR behavior is able to predict mortality in a random population of elderly subjects.

Conclusions—Power-law relationship of 24-hour HR variability is a more powerful predictor of death than the traditional risk markers in elderly subjects. Altered long-term behavior of HR implies an increased risk of vascular causes of death rather than being a marker of any disease or frailty leading to death.

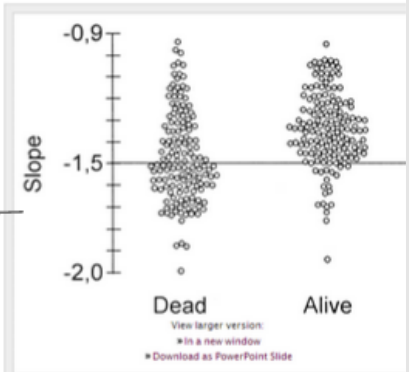


Figure 1.

Individual values of the slope of power-law regression line computed over frequencies between 10^{-2} and 10^{-4} for subjects who were alive and for those who died during the 10-year follow-up.

Informative x 1

HighDesertWizard

Posted 04 February 2015 - 01:07 PM

I noted the existence of a discontinuity in the literature just a few days ago here (http://www.longecity.org/forum/topic/63294-hypothalamus-key-to-aging/) ...

> *HighDesertWizard, on 01 Feb 2015 - 6:15 PM, said:*
>
> About NF-kB science, notice the existence of profound discontinuity in the literature...
>
> From the Opening Post, about a study published in 2013...
>
> > *Quote*
> >
> > In the current study, Dr. Cai and his team demonstrated that activating the NF-κB pathway in the hypothalamus of mice significantly accelerated the development of aging, as shown by various physiological, cognitive, and behavioral tests. "The mice showed a decrease in muscle strength and size, in skin thickness, and in their ability to learn -- all indicators of aging. Activating this pathway systemic aging that shortened the lifespan," he said. Conversely, Dr. Cai and his group found that blocking the NF-κB pathway in the hypothalamus of mouse brains slowed aging and increased median longevity by about 20 percent, compared to controls.
>
> Meanwhile, led by Karolinska Institute Honorary Doctorate, Kevin Tracey (http://ki.se/en/news/three-new-honorary-doctors-at-karolinska-institutet-2009) , dozens of others, in at least a hundred studies, with a first milestone study published in 2002 (http://www.researchgate.net/profile/Kevin_Tracey/publication/10983143_The_inflammatory_reflex/links/02bfe , have been Settling the Science of our Innate Antiinflammatory process for Modulating Innate Immunity, the Cholinergic Antiinflammatory Pathway. It's Triggered by Vagus Nerve Stimulation, is Controlled by Neuronal Muscarinic M1 Receptors, Inhibits NF-kB, and its effect can be measured by a computed statistic, Heart Rate Variability. And that measure, HRV, has been shown, in innumerable studies (http://www.longecity.org/forum/topic/56529-the-vagus-nerve-heart-rate-variability-cholinergic-anti-inflammatory-pathway-nexus/?view=findpost&p=516755) to be profoundly associated with Morbidity and Mortality.
>
> And, yet, the scientists quoted in the opening post, writing in 2013, are unfamiliar with the CAIP or didn't think it important enough to include a reference to it? And they are not alone in ignoring the CAIP... There are dozens, increasingly fewer, who are either ignorant of it or who choose to ignore it.
>
> I believe we are close to new insight about the importance of NF-kB for aging and longevity as this discontinuity in the literature diminishes and new knowledge grows...

Talk about timing... I notice that Anti-Aging Firewalls has just posted a truly great summary of the importance of Heart Rate Variability (http://www.anti-agingfirewalls.com/2015/02/03/digital-health-health-and-fitness-wearables-part-3-heart-rate-variability-principles-and-science-and-practical-measuring-devices/) ... I found the link to the Watson/Guiliano article at the LongeCity bot link here (http://www.longecity.org/forum/topic/76551-anti-aging-firewalls-digital-health-%E2%80%93-health-and-fitness-wearables-part-3-heart-rate-variability-principles-and-s/) .

But the discontinuity in the literature I described above continues... Watson and Guiliano completely missed Kevin Tracey's, and other's, work about the settled science of the Cholinergic Antiinflammatory Pathway...

It's not difficult to point out to Watson and Giuliano what they've missed. And new understanding of the importance of NF-kB Inhibition and the CAIP will spread... I anticipate more breakthrough studies as more smart people become familiar with this important science...

Edited by HighDesertWizard, 04 February 2015 - 01:19 PM.

Razor444

Posted 27 March 2015 - 07:46 PM

Regarding alpha-7 nicotinic acetylcholine receptors.

Melatonin regulates the autophagic flux via activation of alpha-7 nicotinic acetylcholine receptors. (http://www.ncbi.nlm.nih.gov/pubmed/25808024?dopt=Abstract)

> *Quote*
>
> Our previous study suggested that melatonin-mediated neuro-protective effects are related with the activation of autophagy. However, the mechanism of melatonin-mediated autophagic activation in prion-mediated mitochondrial damage is not reported. Alpha 7 Nicotinic acetylcholine receptors (α7nAchR) is a member of nicotinic acetylcholine receptors and α7nAchR activation is regulates via melatonin. Thus, we hypothesized that melatonin-mediated neuroprotective effect related with to autophagy pathway as a result of α7nAchR regulation. Inactivation of α7nAchR inhibited melatonin-mediated autophagic activation and protective effect against prion-mediated mitochondrial neurotoxicity. Also, knock-down of ATG5 blocked the melatonin-mediated neuroprotection and did not influence to the activation of α7nAchR caused by melatonin. This report is the first study demonstrating that melatonin-mediated autophagic activation regulates via modulation of α7nAchR signals, a**nd up-regulation of α7nAchR signals induced by melatonin plays a pivotal role** in neuro-protection of prion-mediated mitochondrial neurotoxicity. **Our results suggested that regulator of α7 nAChR signals including melatonin** may have used for neuroprotective strategies for the neurodegenerative disorders including prion diseases.

nightlight

Posted 27 March 2015 - 09:23 PM

Thanks, it's a very collection of links.

HighDesertWizard

Posted 28 March 2015 - 02:56 PM

Razor444, thanks for that study link...

Much of what's going on with the science of CAIP is the mere rolling out of what it is, how it works, how far its reach is. Haven't posted much lately here but this topic is always on my mind. There have been a number of studies since 2011 that have greatly expanded the implications of the CAIP for the Life Extension Movement. Knowledge is increasing at an exponential rate. Given that fact, how likely is it that ALL our cherished understandings and beliefs are actually good Explanations? It's important we remain open to new evidence and paradigm shifts... :-)

IMO, there is a surprising lack of knowledge among LE Movement Thought Leaders about the Vagus-HRV-CAIP nexus. It is a symptom of a larger fracture in Scientific Community Knowledge about NF-kB.

A few latest thoughts and a conclusion below... An (DTF) following a point means I believe the point is now Difficult to Falsify. An (DTF-) means I believe there is some Science to support the point but that the Science is recent enough that it might be Falsified. An (MS) means My Speculation.

- Aging is an outcome of Epigenetic changes (DTF-) and cells know how they should behave via their external context (the blood Circulation System). (DTF) I believe Katcher has expressed (http://www.longecity.org/forum/index.php?app=core&module=attach&section=attach&attach_id=12864) something important in characterizing the meaning of Parabiosis studies. (DTF-)

- The Vagus-HRV-CAIP nexus is only one element of a larger process for managing Immune (Inflammation) Expression throughout the body. The Vagus-HRV-CAIP nexus impacts aging throughout the body mostly via access to the Blood Circulatory System via the Spleen (http://www.nature.com/mi/journal/v7/n2/full/mi201352a.html) , but not the Intestine (http://gut.bmj.com/content/early/2013/08/08/gutjnl-2013-304676.abstract) . (DTF)

Now, let's think through the facts we know...

- The Vagus-HRV-CAIP nexus profoundly impacts life and health. (See the last 3 graphic figures I posted.) (DTF)

- HRV can be considered a Life-Health Clockface demonstrating the health of Vagus-CAIP Signaling. That first graphic figure clearly shows Vagus-CAIP Signaling Function damage over time. (DTF-)

- The Spleen is a part of the Blood Circulatory System. One early study (http://www.ncbi.nlm.nih.gov/pubmed/8292450) showed human blood flowing through the Spleen at 168.0 ml/min per 100 grams of Spleen weight. That's fast... Can't find it now, but I've read that most/all of our blood flows through the Spleen every 3 to 10 minutes. (DTF)

- The Spleen is the major organ through which the Vagus-HRV-CAIP nexus provides a less (aka, resets the) inflammatory context throughout the Blood Circulation System. (DTF)

- Some Parabiosis Studies, that many people are excited about, have shown Improved Health and even Rejuvenation in older mice. (DTF-)

- Sewing the two Circulatory Systems together of an old mouse and a new mouse, By Definition, means that they share Spleens. The result being that the old mouse benefits from the younger mouse's better Vagus-HRV-CAIP signaling. (DTF-)

"The functionality of the Vagus-HRV-CAIP-Spleen nexus is the Best Explanation of Parabiotic Rejuvenation..."
-- HDW, 2015

I have great respect for Dr. Katcher. His ideas have impacted mine profoundly. He got me thinking about the blood. And the It's-All-About-The-Damage minds have nothing to say about Parabiosis. Obviously, they can't, for reasons Dr. Katcher outlines. But Katcher's suggestion that we do Human Blood Transfusions experiments to provide benefit is of questionable worth because it is proposed, I believe, without knowledge and sharing the functions of the Vagus-HRV-CAIP-Spleen nexus.

There is a way to improve the Human Blood Transfusions experiment idea. I'll have more on that later...

Cheers!

Edited by HighDesertWizard, 31 March 2015 - 01:40 PM.

like x 2 dislike x 1

HighDesertWizard

Posted 29 March 2015 - 09:41 PM

In my last post, I said I now believe that t**he functionality of the Vagus-HRV-CAIP-Spleen nexus is the Best Explanation of Parabiotic Rejuvenation.** I have an Hypothesis Statement and Experiment in mind that would be useful to determine whether that statement can be Falsified. Here it is...

Hypothesis: Parabiosis rejuvenation takes place in the older mouse because it has access to more youthful Vagus-CAIP Signaling via acess to the younger mouse's spleen.

Experiment: Establish 5 Groups of Old/Young mice for a standard Parabiosis experiment. All 5 groups have the standard parabiosis operation performed on them. In addition, the 5 groups are the same groups as shown in the graphic figure below.

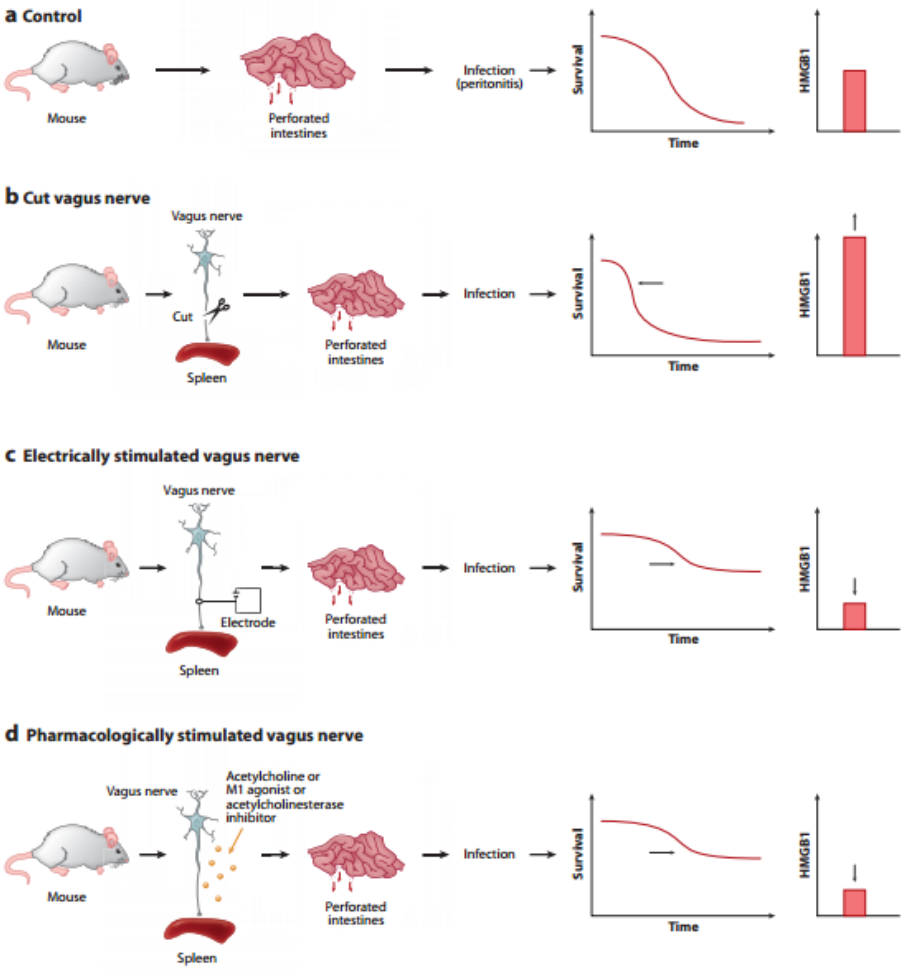
1. Control = Standard Parabiosis Only
2. Splenectomy... Remove the younger mice spleen and see if the older mice still experience rejuvenation
3. Cut the efferent Vagus Nerve to the Spleen in the younger mice along with Standard Parabiosis.
4. Electrically stimulate the Vagus Nerve in the younger mice along with Parabiosis.
5. Use an acetylcholine agonist to trigger the CAIP in the younger mice along with Parabiosis.

Maybe there are some Vagus-CAIP Stimulation related things to do to the older mice too. Dunno...

Take a close look at the graphic figure below. Given that blood circulates through the Spleen, I believe this experiment would be valuable one to perform to relatively quickly determine if the Hypothesis statement can be Falsified.

Any suggested upgrades to the Hypothesis Statement and/or Experiment idea appreciated.

From Reflex Principles of Immunological Homeostasis (http://www.utdallas.edu/~mxa049000/lessons/research/IL-6%20literature/may%202012/Tracey%20annurev-immunol%202011.pdf)



Edited by HighDesertWizard, 29 March 2015 - 10:10 PM.

HighDesertWizard

Posted 03 April 2015 - 04:18 PM

Among the problems with the Baati, 2012, study, [The prolongation of the lifespan of rats by repeated oral administration of [60] fullerene (http://www.sciencedirect.com/science/article/pii/S0142961212003237)](http://www.sciencedirect.com/science/article/pii/S0142961212003237) is a problem with accurately expressing what the data in Table 2 clearly shows... It's not a misstatement of fact, but a confused and misleading interpretation of the data based on, what I believe, was a preconceived notion of what drove the C60 longevity effects.

Here's the study paragraph where the unconscious, unknowing, but, nevertheless, misleading statement takes place...

"The differences in C60 contents in livers and spleens (Table 2) can be obviously assigned to the differences in the absorbed doses. However, the delay of elimination which is somewhat larger after i.p. administration could also play a non negligible role. The presence of C60 crystals inside the cells after i.p. administration (Fig. 2) supports the hypothesis according to which the precipitation of part of the administered C60 in the injection site may contribute to the observed delay of elimination after i.p. administration. ***Nevertheless, the weakness of organ concentrations notably at D8 after 7 daily successive administrations of C60 dissolved in olive oil clearly shows that C60 molecules are eliminated from the organs in a few hours after both oral and i.p. administrations."***

A snapshot of Table 2 is pasted in below. Notice that, in fact, **C60 was Accumulating in the Spleen and Not being Eliminated.**

Table 2
Biodistribution of C_{60}. C_{60} concentrations in whole blood (WB), liver, spleen and brain of rats daily treated with a single dose of C_{60} dissolved in olive oil (4 mg/kg body weight) by oral gavages or i.p. route (IP, Mean ± SD, $n = 3$) (Lw = liver weight; Sw = spleen weight; Bw = brain weight; TAD = total administered dose).

	Oral (D_1)	Oral (D_8)	IP (D_1)	IP (D_8)
WB (C_{60}, μg/ml)	0.03 ± 0.01	0.18 ± 0.06	0.36 ± 0.06	0.56 ± 0.17
Liver (C_{60}, μg/g)	0.21 ± 0.04	2.92 ± 0.82	4.91 ± 1.52	31 ± 12
Lw (g)	5.2 ± 0.6	7.5 ± 0.8	7.7 ± 0.8	10.0 ± 1.1
C_{60} (%/TAD)	0.14	0.39	4.73	5.54
Spleen (C_{60}, μg/g)	2.99 ± 1.37	51 ± 14	23 ± 6	191 ± 40
Sw (g)	0.48 ± 0.10	0.56 ± 0.13	0.54 ± 0.17	0.70 ± 1.3
C_{60} (%/TAD)	0.18	0.51	1.55	2.39
Brain (C_{60}, μg/g)	0.013 ± 0.003	0.20 ± 0.08	0.54 ± 0.17	3.78 ± 1.25
Bw (g)	1.81 ± 0.03	1.83 ± 0.03	1.85 ± 0.05	1.82 ± 0.04
C_{60} (%/TAD)	0.003	0.007	0.125	0.123

Baati, et al, also say...

"Microscopic examination at D8 of the spleen reticuloendothelial system (RES), where the highest concentrations are observed, shows the presence of some C60 aggregates that are larger and more numerous after i.p. administration (Fig. 2c and d) than after o.g. (Fig. 2a, b): thus ***C60 concentrations reached the limit of solubility in spleens****. In contrast there are no observable deposits inside the livers in all cases indicating that C60 concentrations in these organs are not high enough to trigger precipitation. While transmission electron microscopy (TEM) at D8 after* ***i.p. administration shows numerous spleen macrophages laden C60 crystals (Fig. 2e) only some C60 crystals were observed inside liver macrophages and very rare crystals in lung (Fig. 2f) and kidney cells (Fig. 2g).****"*

Let's be clear about the significance of these Baati study data and statements summarizing the data for the science of the Vagus-HRV-CAIP Nexus...

The Vagus-HRV-CAIP Nexus Science suggests that Spleen Macrophage Inflammation is an important variable for Morbidity, Mortality, and Longevity. The Baati Study explicitly highlights the C60 study data about Spleen Macrophages. "Something different is going on with C60 in Baati Study Spleen Macrophages**," they say. And, yet, Baati, et al, don't ask the question... What does this C60 Spleen data mean?**

We need to work to figure out what it means...

I ingest and apply C60-OO and I have experienced many of the same Rejuvenation effects others have. We're all grateful for Baati and his team for doing and publishing that 2012 study. And I grant that the Baati study, taken by itself, doesn't implicate the Spleen data as meaning anything especially important for the Longevity effect.

That said, we now have too many other studies implicating the Spleen as important to Rejuvenation to ignore the data of Table 2.

- I don't have any more specific evidence about how C60 Accumulation in the Spleen might have had a Longevity effect. But I doubt that C60 triggered the CAIP. Instead, my hunch is that C60

triggered an effect in Splenic Macrophages that the CAIP itself triggers. But that's just a hunch.

- I do have a specific experiment idea in mind that could be done in a relatively short time to test an hypothesis about it. I'll post that experiment idea soon in this forum thread.

I should say also... I've been making larger scoped statements lately without specific reference to scientific studies for each point made. I understand the importance of providing specific references and I will circle back around at some point soon to provide them.

Edited by HighDesertWizard, 06 April 2015 - 03:59 PM.

Informative x 2

HighDesertWizard

Posted 06 April 2015 - 03:57 PM

I've updated my previous post (http://www.longecity.org/forum/topic/56529-the-vagus-nerve-heart-rate-variability-cholinergic-anti-inflammatory-pathway-nexus/?view=findpost&p=721820) about the Baati Study and the Vagus-HRV-CAIP nexus science. The argument is now more pointed and if you're into this science, you'll want to take another look...

HighDesertWizard

Posted 19 April 2015 - 07:36 PM

A few posts back (http://www.longecity.org/forum/topic/56529-the-vagus-nerve-heart-rate-variability-cholinergic-anti-inflammatory-pathway-nexus/?view=findpost&p=721119) I proposed an Hypothesis vis-a-vis the Mechanism underlying Heterochronic Parabiotic Rejuvenation...

> *HighDesertWizard, on 29 Mar 2015 - 11:41 PM, said:*
>
> **Hypothesis:** Parabiotic rejuvenation takes place in the older mouse because it has access to more youthful Vagus-CAIP Signaling via acess to the younger mouse's spleen.

I believe I've now found evidence that makes the case for that Hypothesis stronger. What do you think?.

Harold Katcher has emphasized (http://www.longecity.org/forum/index.php?app=core&module=attach&section=attach&attach_id=12864) the importance of the 2011 Villeda study. There is also a great 2014 note entirled Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4224436/) ... The key finding...

> *... we examined **phosphorylated Creb** in the DG of aged animals systemically treated with plasma from young or aged mice by immunohistochemistry. Creb phosphorylation increased in the DG after administration of young plasma.*
>
> *Taken together, our data demonstrate that exposure to young blood counteracts aging at the molecular, structural, functional and cognitive levels in the aged hippocampus. **Mechanistically, we identified Creb as one member of the regulatory network underlying structural and cognitive enhancements by young blood.***

Here's a graphic depiction of the Mechanism from a study summary (http://web.stanford.edu/group/twclab/cgi-

bin/images/TWClab/publications/2014_villeda_natmed_newsviews.pdf) . Notice that both Creb and c-Fos are referenced in the figure...

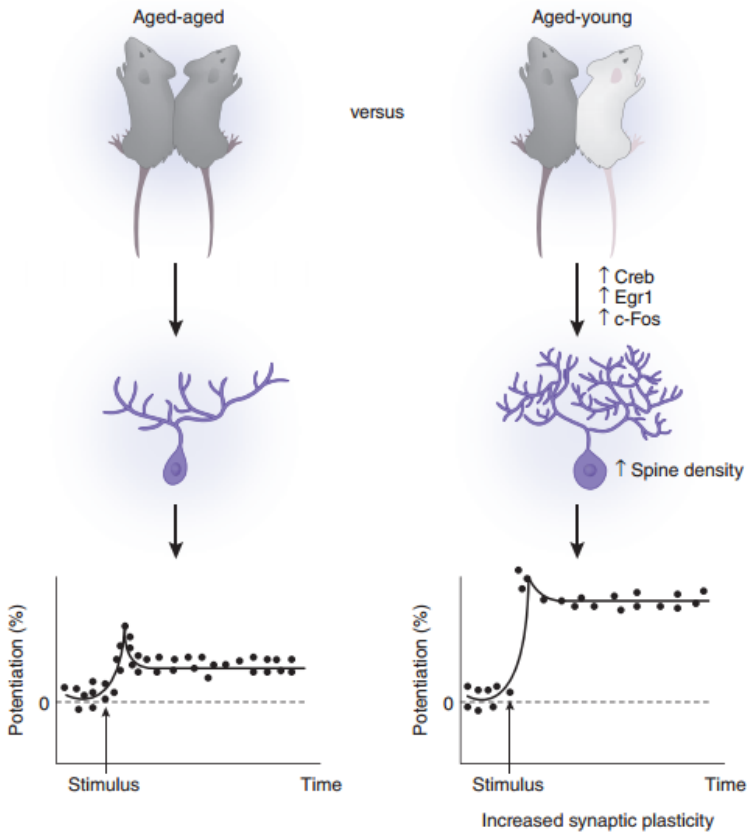


Figure 1 Young mouse blood is able to rejuvenate aged mouse brains. Villeda *et al.*[4] show that young blood contains a factor that reverses some aspects of age-related cognitive impairment in mice. Parabiosis in which aged mice are conjoined with aged mice such that their circulatory systems are connected results in no change in synaptic plasticity. However, parabiois between aged and young mice results in increased expression of proteins involved in synaptic plasticity, and an increased number of dendritic spines and synaptic plasticity in aged mice, as measured by enhanced long-term potentiation in these mice.

Meanwhile, as described up thread, we know that the positive Longevity effects of High Heart Rate Variability **in Humans** are related to triggering of the Cholinergic Antiinflammatory Pathway, primarily via Vagus Nerve Stimulation. And what is the more specific Mechanism driving NF-kB inhibition prior to Cytokine Transcription, especially in the Spleen as it sets the Context of the blood of the circulatory system? Here's Tracey about that question in his 2012 study summary (http://www.utdallas.edu/~mxa049000/lessons/research/IL-6%20literature/may%202012/Tracey%20annurev-immunol%202011.pdf) ...

> *The molecular signaling mechanism of α7 inhibition of TNF occurs through a physical interaction between α7 and adenylate cyclase 6, which generates increased levels of intracellular cAMP.* ***This activates phosphorylation of CREB, which increases expression of cfos, a member of the immediate early gene family of transcription factors. Activation of cfos inhibits NF-κB activity, effectively shutting down the transcription of cytokines.***

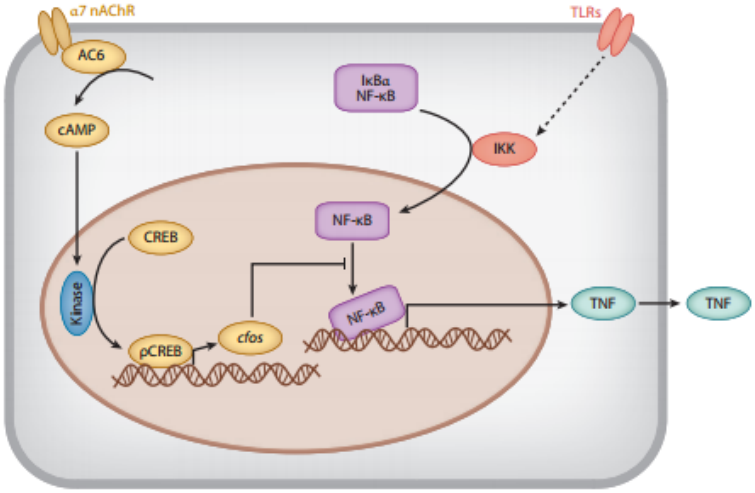


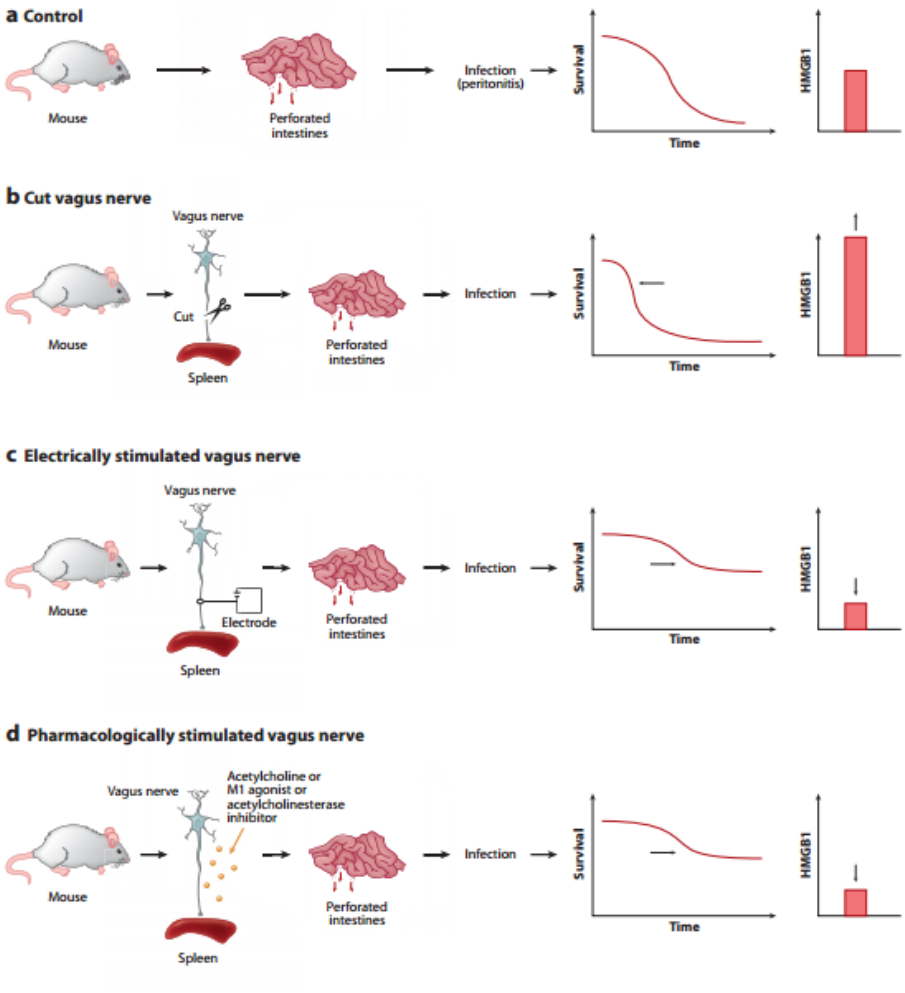
Figure 2

Mechanism of inhibition of cytokine release mediated by α7 nicotinic acetylcholine receptor (α7 nAChR).

In short, the existing science of the Vagus-HRV-CAIP nexus not only provides a general explanation of Parabiotic Rejuvenation, it also establishes a more complete Physiological/Biological Explanatory Context for that CREB -> c-fos Mechanism discovered important in the Villeda study.

I believe the coincidence of the Mechanism is reason enough to warrant prioritizing something like the experiment I've suggested up thread.

> *HighDesertWizard, on 29 Mar 2015 - 11:41 PM, said:*
>
> **Experiment:** Establish 5 Groups of Old/Young mice for a standard Parabiosis experiment. All 5 groups have the standard parabiosis operation performed on them. In addition, all 5 groups have the Perforated Intestine procedure done on them as well. The 5 groups closely resemble the groups as shown in the graphic figure below, except they have Parabiosis performed on them...
>
> 1. Control = Standard Parabiosis Only
> 2. Splenectomy... Remove the younger mice spleen along with Parabiosis
> 3. Cut the efferent Vagus Nerve to the Spleen in the younger mice along with Standard Parabiosis.
> 4. Electrically stimulate the Vagus Nerve in the younger mice along with Parabiosis.
> 5. Use an acetylcholine agonist to trigger the CAIP in the younger mice along with Parabiosis.
>
> Maybe there are some Vagus-CAIP Stimulation related things to do to the older mice too. Dunno...
>
> << SNIP >>
>
> From Reflex Principles of Immunological Homeostasis (http://www.utdallas.edu/~mxa049000/lessons/research/IL-6%20literature/may%202012/Tracey%20annurev-immunol%202011.pdf)



Thoughts?

Edited by HighDesertWizard, 28 April 2015 - 11:49 AM.

HighDesertWizard

Posted 29 April 2015 - 12:44 PM

A New York Times Magazine article about the Cholinergic Anti-Inflammatory Pathway and leveraging it in treating Arthritis...

Can the Nervous System be Hacked? (http://nytimes.com/2014/05/25/magazine/can-the-nervous-system-be-hacked.html)

We're way past the time when the Life Extension Science Movement can afford to have Thought Leadership uninformed about the Vagus-HRV-CAIP nexus...

Just sayin'...

sthira

Posted 29 April 2015 - 07:30 PM

> *HighDesertWizard, on 29 Apr 2015 - 2:44 PM, said:*
>
> A New York Times Magazine article about the Cholinergic Anti-Inflammatory Pathway and leveraging it in treating Arthritis...
>
> Can the Nervous System be Hacked? (http://nytimes.com/2014/05/25/magazine/can-the-nervous-system-be-hacked.html)
>
> We're way past the time when the Life Extension Science Movement can afford to have Thought Leadership uninformed about the Vagus-HRV-CAIP nexus...
>
> Just sayin'...

Bioelectronics is fascinating. I wonder why Dr Tracey's study was terminated in 2011? https://www.clinical...859?term=Tracey (https://www.clinicaltrials.gov/ct2/show/NCT00859859?term=Tracey)

niner

Posted 29 April 2015 - 08:55 PM

> *HighDesertWizard, on 29 Apr 2015 - 2:44 PM, said:*
>
> We're way past the time when the Life Extension Science Movement can afford to have Thought Leadership uninformed about the Vagus-HRV-CAIP nexus...
>
> Just sayin'...

Can you point to any significant life extension that's been shown to occur due to manipulation of the Vagus-HRV-CAIP axis? We've seen that HRV can be a marker of poor health in old age, and we see that Vagal stimulators significantly improved symptoms of RA in at least one person, but so do anti-tnf Mabs.

I think that the connection between c6000 and the CAIP is particularly tenuous. Baati saw a 90% life extension with c6000, but as far as I know, there has never been life extension shown due to the spleen catching a bit of particulate matter from circulation, no matter what the particles were, including aggregated forms of c60.

HighDesertWizard

Posted 01 May 2015 - 12:39 PM

> *niner, on 29 Apr 2015 - 10:55 PM, said:*
>
> > *HighDesertWizard, on 29 Apr 2015 - 2:44 PM, said:*

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niner... Appreciate your questions... I'll take the first paragraph questions first... I stand by the statement I made above...

We're way past the time when the Life Extension Science Movement can afford to have Thought Leadership uninformed about our Innate, Evolution Established, Mechanism for Inhibiting NF-kB Cytokine Transcription. And that Mechanism is the Vagus-HRV-CAIP Nexus...

Evidently, there's a Silicon Valley Investor willing to put up $500,000 "to a team that can take an older mammal and bring its Heart Rate Variability characteristics back to those of a young adult mammal."

Silicon Valley Investor Backs $1 Million Prize to End Death (http://www.businessweek.com/articles/2014-09-09/silicon-valley-investor-backs-1-million-longevity-prize)

Your statement above that "**HRV can be a marker of poor health in old age**" gives away that you're Unfamiliar with the science of HRV. No one familiar with the science would frame a sentence that way. Here are better summary statements about HRV...

- Taken together, the graphic figures below, from different studies, show a Longevity effect for High HRV. Taken together, the effect looks to be about 5 to 15 years depending on you count it. The important point is that these studies of the impact of High HRV were of **In The Wild Humans**, i.e., In Humans Not Making a Conscious and Deliberate effort to Raise HRV. The Method of that 2nd study is pretty amazing. I encourage a close look at it.

  I've included the 3 graphic figures below in a set of 8 slides here (https://drive.google.com/open?id=1LpZvpSRziiCTNJIP-xjy1pQqanLXT6WqCdvgIRJ8gig&authuser=0) . The additional slides highlight the Mechanism of the High HRV Longevity effect, especially the NF-kB Cytokine Inhibition effect.

  There have also been studies showing Health Statistic related impacts of High HRV like, for example, longer Telomeres for those with High HRV. I'll post that evidence when I address your second question.

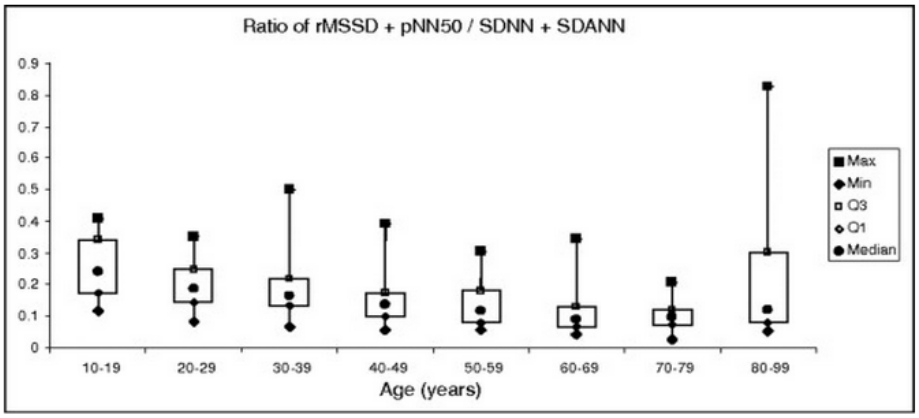
  niner... Are you one of those folks who says a 5 to 15 year Life Extension benefit is nothing? For some of us, 5 to 15 years is important so that we will have a greater probability of participating in even more promising LE science down the road.

- I've posted something like 25 references to studies showing profound Morbidity, Mortality, and Longevity effects of Low and High HRV, respectively, here

(http://www.longecity.org/forum/topic/56529-the-vagus-nerve-heart-rate-variability-cholinergic-anti-inflammatory-pathway-nexus/?view=findpost&p=516755) . The science about HRV is broad and deep.

Relation of High Heart Rate Variability to Healthy Longevity, 2010

"The HRV of all measures decreases rapidly from the second to fifth decades. It then slows. The HRV–sympathetic function continues to decrease throughout life. In contrast, the decrease in HRV–parasympathetic function reaches its nadir in the eighth decade, followed by reversal and a progressive increase to higher levels ($p < 0.05$), more characteristic of a younger population. In conclusion, healthy longevity depends on preservation of autonomic function, in particular, HRV–parasympathetic function, despite the early age-related decrease. The eighth decade reversal of the decrease in HRV–parasympathetic function and its subsequent increase are key determinants of longevity. Persistently high HRV in the elderly represents a marker predictive of longevity."



Power-Law Relationship of Heart Rate Variability as a Predictor of Mortality in the Elderly

Abstract

Background—The prognostic role of heart rate (HR) variability analyzed from 24-hour ECG recordings in the general population is not well known. We studied whether analysis of 24-hour HR behavior is able to predict mortality in a random population of elderly subjects.

Conclusions—Power-law relationship of 24-hour HR variability is a more powerful predictor of death than the traditional risk markers in elderly subjects. Altered long-term behavior of HR implies an increased risk of vascular causes of death rather than being a marker of any disease or frailty leading to death.

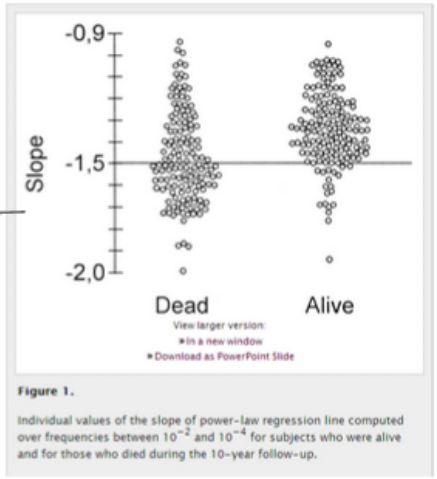
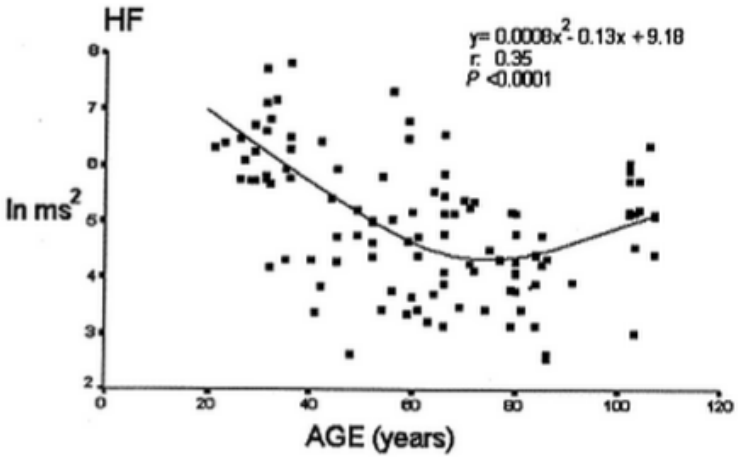


Figure 1.

Individual values of the slope of power-law regression line computed over frequencies between 10^{-2} and 10^{-4} for subjects who were alive and for those who died during the 10-year follow-up.



From... Power spectral analysis of heart rate in subjects over a hundred years old

"Altered autonomic regulation of cardiac function may contribute to the onset of cardiovascular disease and provide a substrate for malignant ventricular arrhythmias. This study was designed to assess cardiovascular neuroautonomic status in healthy subjects with short-term power spectral analysis of heart rate variability, including a group over 100 years of age, to identify a neuroautonomic pattern that could help to protect ultra-centenarians against cardiovascular disease.... Compared with elderly subjects from 81 to 100 years of age ultra-centenarians have significantly higher spectral parasympathetic indexes. Parasympathetic predominance may be the neuroautonomic feature that helps to protect ultra-centenarians against cardiovascular disease."

Edited by HighDesertWizard, 01 May 2015 - 01:21 PM.

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