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International Child Development Resource Center
Opening windows of hope for children with developmental disorders.

Link between the Vagus Nerve, Cholinergic Deficit, Inflammation, Cognitive Deficits and Inattention: the Soul of the Gut – Brain Connection

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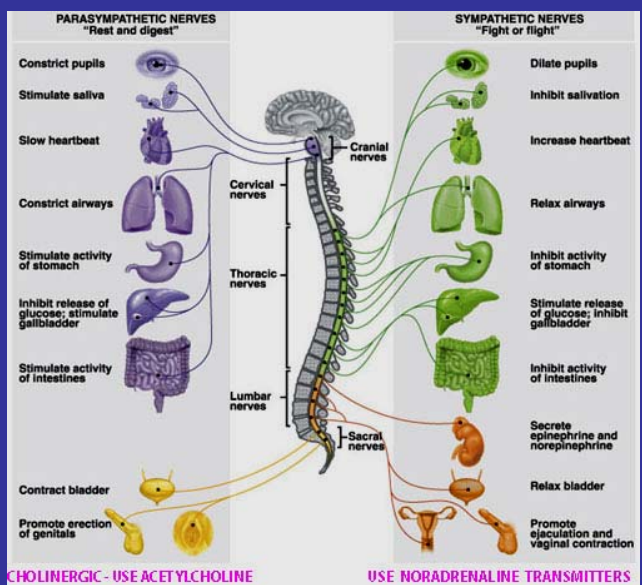
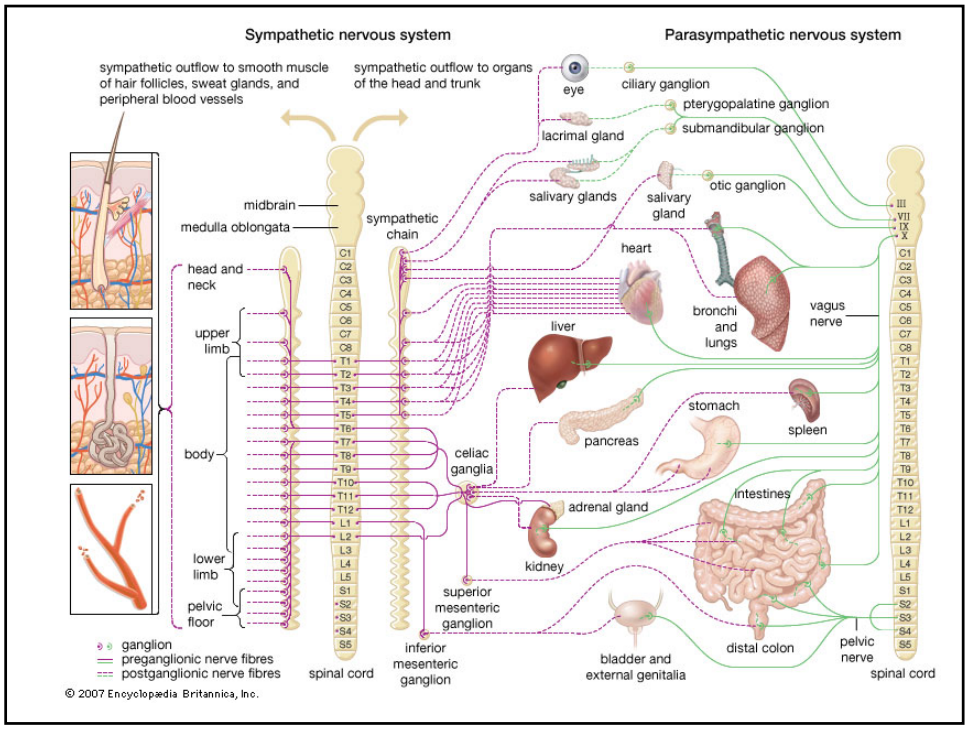
Autonomic Nervous System



Nicotine effect Adrenaline effect



The Very Important Vagus Nerve

- The vagus nerve supplies motor parasympathetic fibers to all the organs except the adrenal glands, from the neck down to the second segment of the transverse colon. Throat, pharyngeal constrictors
- Muscles of the larynx (speech).
- This means that the vagus nerve is responsible for such varied tasks as heart rate, gastrointestinal peristalsis, sweating, and quite a few muscle movements in the mouth,and keeping the larynx open for breathing.

Vagus nerve stimulation (VNS)

- VNS therapy uses a pacemaker-like electrical device implanted in the chest to control seizures in epilepsy patients
- Now also approved for treating drug-resistant cases of clinical depression.
- Future uses may impact cognition and Alzheimer's disease.

Subclinical effects of prenatal methylmercury exposure on cardiac autonomic function in Japanese children.

Int Arch Occup Environ Health. 2006 May;79(5):379-86. Epub 2005 Dec 20.
Murata K, **Sakamoto M**, **Nakai K**, **Dakeishi M**, **Iwata T**, **Liu XJ**, **Satoh H**

Department of Environmental Health Sciences, Akita University School of Medicine, 010-8543, Akita, Japan, winestem@med.akita-u.ac.jp.

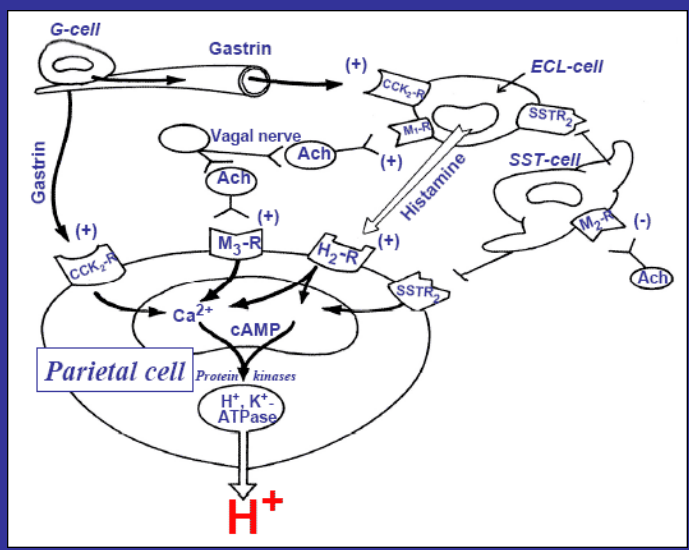
Conclusions: Despite the potential limitations involved in the retrospective study, **these findings suggest that prenatal methylmercury exposure (median of estimated maternal hair mercury at parturition, 2.24 mug/g) may be associated with reduced parasympathetic activity and/or sympathovagal shift**.

Reduced cardiac parasympathetic activity in children with autism.

Brain Dev. 2005 Oct;27(7):509-16
Ming X, et al
Department of Neuroscience, New Jersey Medical School, UMDNJ, Newark, 90 Bergen Street, DOC 8100, NJ 07103, USA. mingxu@umdnj.edu

Many of the clinical symptoms of autism suggest autonomic dysfunction. **results suggest that there is low baseline cardiac parasympathetic activity with evidence of elevated sympathetic tone in children with autism whether or not they have symptoms or signs of autonomic abnormalities.**

Vagus nerve and histamine help regulate acid production in stomach as well as motility



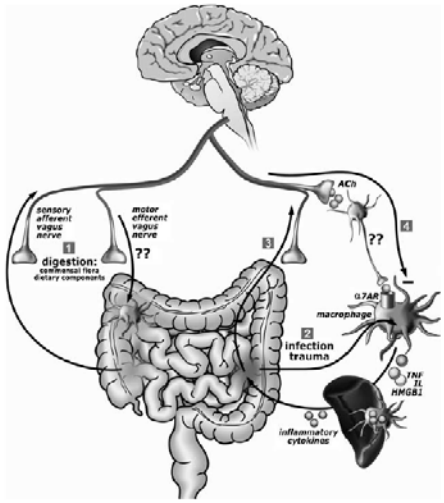
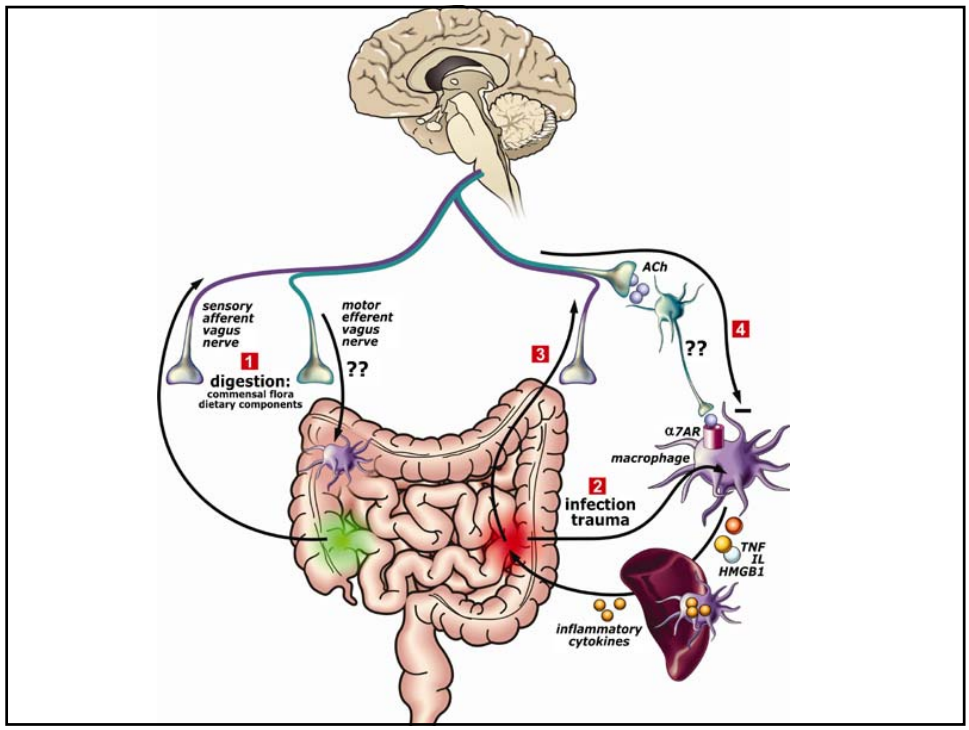
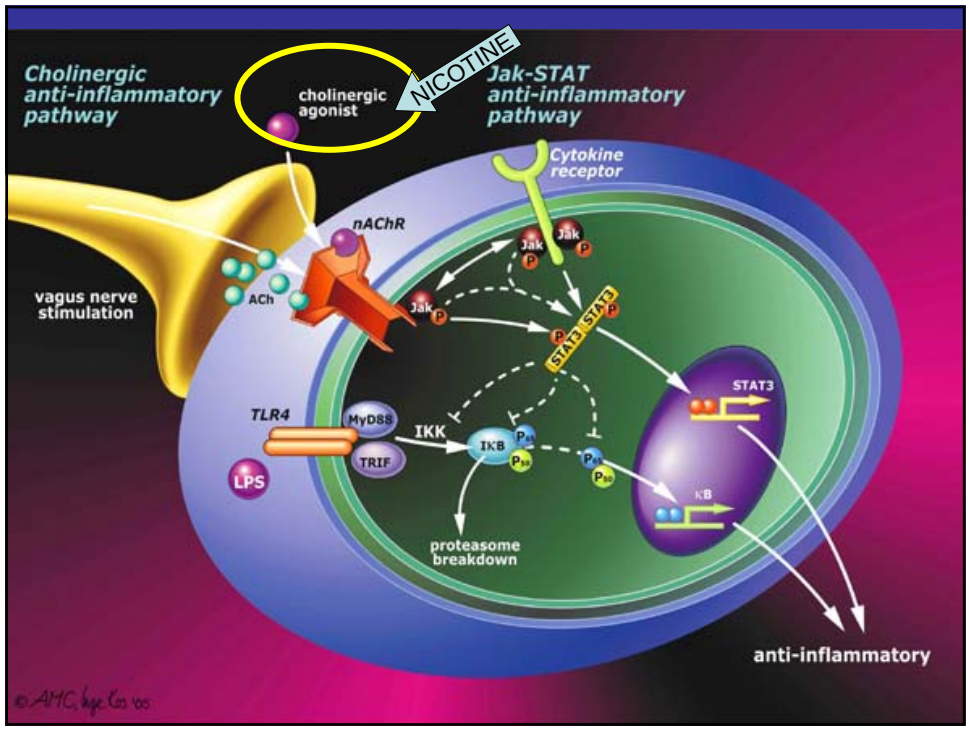


Figure 1 The cholinergic anti-inflammatory surveillance. Hypothetical scheme of the vagus nerve continuously monitoring and modulating innate immune activation following ingestion, infection, and trauma. (1) During digestion, the commensal flora and dietary components activate the sensory afferent vagus nerve, which will transmit the information to the brain. In return, the brain may activate the efferent vagus nerve to modulate gastrointestinal macrophages. (2) The efferent vagus nerve also modulates systemic inflammatory responses through a mechanism involving an intact spleen. Upon infection or trauma, bacterial components or intracellular mediators (HMGB1, heat shock proteins, etc) activate macrophages to produce proinflammatory cytokines. (3) This will trigger afferent vagus nerve signaling. (4) In return, the brain will activate efferent vagus nerve to release acetylcholine, which can bind to the $\alpha 7$ acetylcholine receptor on macrophages and inhibit the production of proinflammatory cytokines. Interrogation marks indicate that although macrophages are found in the proximity of cholinergic fibers in the spleen and the intestine (De Jonge *et al.*, 2005) there is currently no evidence demonstrating that parasympathetic neurons indeed innervate immune cells and further studies are needed to determine the physiological interaction between the vagus nerve and immune cells. HMGB1, high-mobility group box 1.

British Journal of Pharmacology (2007) 151 915–929





The alpha7 nicotinic acetylcholine receptor as a pharmacological target for inflammation

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The physiological regulation of the immune system encompasses comprehensive anti-inflammatory mechanisms that can be harnessed for the treatment of infectious and inflammatory disorders. Recent studies indicate that the vagal nerve, involved in control of heart rate, hormone secretion and gastrointestinal motility, is also an immunomodulator. In experimental models of inflammatory diseases, vagal nerve stimulation attenuates the production of proinflammatory cytokines and inhibits the inflammatory process. Acetylcholine, the principal neurotransmitter of the vagal nerve, controls immune cell functions via the alpha7 nicotinic acetylcholine receptor (alpha7nAChR). From a pharmacological perspective, nicotinic agonists are more efficient than acetylcholine at inhibiting the inflammatory signaling and the production of proinflammatory cytokines. This 'nicotinic anti-inflammatory pathway' may have clinical implications as treatment with nicotinic agonists can modulate the production of proinflammatory cytokines from immune cells. Nicotine has been tested in clinical trials as a treatment for inflammatory diseases such as ulcerative colitis, but the therapeutic potential of this mechanism is limited by the collateral toxicity of nicotine. Here, we review the recent advances that support the design of more specific receptor-selective nicotinic agonists that have anti-inflammatory effects while eluding its collateral toxicity.
British Journal of Pharmacology (2007) **151**, 915–929; doi:10.1038/sj.bjp.0707264; published online 14 May 2007

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ARTICLE

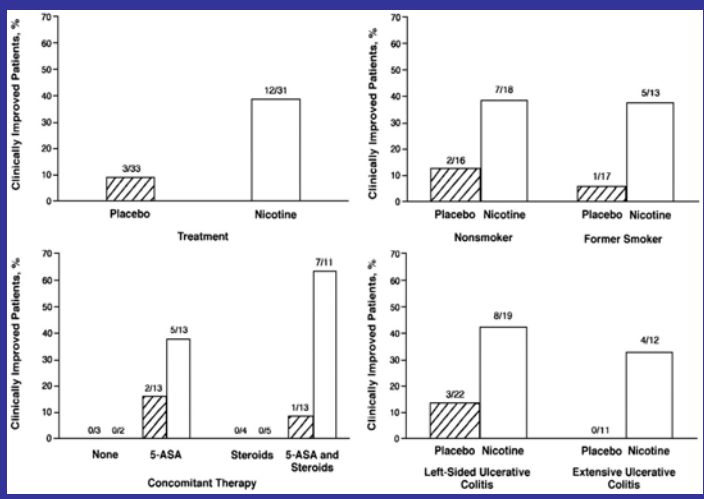
Transdermal Nicotine for Mildly to Moderately Active Ulcerative Colitis

A Randomized, Double-Blind, Placebo-Controlled Trial

William J. Sandborn, MD; William J. Tremaine, MD; Kenneth P. Offord, MS; George M. Lawson, PhD; Bret T. Petersen, MD; Kenneth P. Batts, MD; Ivana T. Croghan, PhD; Lowell C. Dale, MD; Darrell R. Schroeder, MS; and Richard D. Hurt, MD

1 March 1997 | Volume 126 Issue 5 | Pages 364-371

Percentage of patients with clinically improved ulcerative colitis at week 4



Sandborn, W. J. et. al. Ann Intern Med 1997;126:364-371

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Nicotinic receptor mechanisms and cognition in normal states and neuropsychiatric disorders

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Abstract

Cigarette smoking rates in the American population are approximately 23%, whereas rates of smoking in clinical and population studies of individuals with neuropsychiatric disorders are typically two- to four-fold higher. Studies conducted in a variety of neuropsychiatric populations [e.g. attention-deficit hyperactivity disorder (ADHD), Alzheimer's disease, schizophrenia] have collectively suggested that nicotine may be efficacious in remediating selected cognitive deficits associated with these disorders, thus providing a framework for understanding the specific vulnerability of these patients to smoking initiation and maintenance. However, the specific gain in cognitive performance produced by nicotine administration in healthy subjects with normal cognitive function is less clear. This article reviews our current understanding of central nicotinic acetylcholine receptor (nAChRs) systems in normal and neuropsychiatric disease states and, specifically, their role with respect to cognitive dysfunction and clinical symptoms in several specific neuropsychiatric populations, including ADHD, Alzheimer's disease, Parkinson's disease, Tourette's Disorder, schizophrenia and affective disorders. The potential benefits of nicotinic agents for therapeutic use in neuropsychiatric disorders is discussed, as well as directions for further research in this area.

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Pharmacology, Biochemistry and Behavior 88 (2008) 407–417

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Acute nicotine improves cognitive deficits in young adults with attention-deficit/hyperactivity disorder

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Abstract

Objective: The strong association between ADHD and cigarette smoking and the known effects of nicotine on cognition has lead to interest in the role of cholinergic function in ADHD cognitive deficits. We have previously demonstrated that acute nicotine improves behavioral inhibition in adolescents with ADHD. This study examined acute nicotine in young adults with ADHD-Combined type on cognitive domains including behavioral inhibition, delay aversion, and recognition memory.
Methods: 15 non-smoking young adults (20±1.7 years) diagnosed with ADHD-C received acute nicotine (7 mg patch for 45 min) and placebo on separate days. Cognitive tasks included the Stop Signal Task, Choice Delay task, and the High–Low Imagery Task (a verbal recognition memory task). Three subjects experienced side effects and their data was excluded from analysis of cognitive measures.
Results: There was a significant ($p<.05$) positive effect of nicotine on the Stop Signal Reaction Time measure of the Stop Signal Task. The SSRT was improved without changes in GO reaction time or accuracy. There was a trend ($p=.09$) for nicotine to increase tolerance for delay and a strong trend ($p=.06$) for nicotine to improve recognition memory.
Conclusions: Non-smoking young adults with ADHD-C showed improvements in cognitive performance following nicotine administration in several domains that are central to ADHD. The results from this study support the hypothesis that cholinergic system activity may be important in the cognitive deficits of ADHD and may be a useful therapeutic target.

Adverse Reactions to 7 mg/24hr Nicotine patch in young adults with ADHD

Reaction	Nicotine Group (n = 31)	Placebo Group (n = 33)	P Value*
	%		
Skin irritation, erythema, or contact dermatitis	58	12	<0.001
Lightheadedness or dizziness	29	3	0.005
Nausea	29	0	<0.001
Vomiting	6	0	>0.05
Headaches	10	0	>0.05
Sleep disturbance or violent or sexual dreams	6	3	>0.05
Stimulation of central nervous system	3	3	>0.05
Diaphoresis or sweating	3	0	>0.05
Shakiness or tremor	3	0	>0.05
Tachycardia	3	0	>0.05
Miscellaneous	23	15	>0.05
Any adverse reaction	77	30	<0.001

* By the Fisher exact test.

NS ???

Case Response: 6 yo male w/ASD

- Positive antibodies to brain endothelium
- Elevated Neopterin
- Intestinal Dysbiosis
- Stereotypia, verbal stimming, cognitive deficits, socially withdrawn, auditory processing delays and both expressive and receptive language deficits.
- Hypotonia and sensory processing issues
- Huge bowel movements

Email from Mom after first dose

Dear Dr. Bradstreet,

The Nicoderm patch (1/4 of 7 mg patch) really made a difference for our son. We just got reports back from his teachers that have us jumping up and down. They report improved eye contact, improved attention and focus, class participation, reduced anxiety, significant decrease in hyperactivity and more.

His school has no idea what we have done -- or what to look for. Hence, the report is unbiased and quite reliable. We have seen the same at home:0)

This is REALLY exciting. But, I have been online reading quite a bit about the downside of the patch. Of course I am concerned about Nicotine addiction, long term use, carcinogenic effects, etc.... So the next question is what do we do now? Should I continue w/ the patch for now? How long can we safely do this?

I have never been more excited in my life. This is without a doubt the most significant change we have seen in all our efforts thus far.

Thanks for your time.
Warmest Regards

Nicoderm CQ Clear

- Step 1 = 21 mg
- Step 2 = 14 mg
- Step 3 = 7 mg
- Manufacturer warns NOT to cut the patch, but in practice thus far it has worked extremely well.
- Skin reactions #1 issue
- Nausea and dizziness next