Brainstem Origins of ASD

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Neurotoxic brainstem impairment as proposed threshold event in autistic regression.

Early hypothesis

1. Regression after 12 months is triggered by selective toxic effects on brainstem regions lacking BBB.
2. Earlier impairment of the same brainstem structures could predispose to regression, or result in early-onset autism.
Proposed toxic and hypoxic impairment of a brainstem locus in autism.

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Abstract

Electrophysiological findings implicate site-specific impairment of the nucleus tractus solitarius (NTS) in autism. This invites hypothetical consideration of a large role for this small brainstem structure as the basis for seemingly disjointed behavioral and somatic features of autism. The NTS is the brain's point of entry for visceral afference, its relay for vagal reflexes, and its integration center for autonomic control of circulatory, immunological, gastrointestinal, and laryngeal function. The NTS facilitates normal cerebrovascular perfusion, and is the seminal point for an ascending noradrenergic system that modulates many complex behaviors. Microvascular configuration predisposes the NTS to focal hypoxia. A subregion—the "pNTS"—permits exposure to all blood-borne neurotoxins, including those that do not readily transit the blood-brain barrier. Impairment of acetylcholinesterase (mercury and cadmium cations, nitrates/nitrites, organophosphates, monosodium glutamate), competition for hemoglobin (carbon monoxide, nitrates/nitrites), and higher blood viscosity (net systemic oxidative stress) are suggested to potentiate microcirculatory insufficiency of the NTS, and thus autism.
Hypothesis formation

Integrate data

No taboos

Cross disciplines
Assumptions

1. Widespread brain pathology in ASD does not preclude a primary site.

2. ASD is inherently a somatobehavioral syndrome.
Hypothesis statement

The autistic phenotype, both behavioral and visceral, largely results from primary injury to nucleus tractus solitarius, via the direct effect of:

A) Circulating toxin(s), OR
B) hypoxic/ ischemic insult.
Dual vulnerabilities

No BBB, so concentrates toxic cations.

Unique microvascular configuration, so prone to focal hypoxia/ischemia.
Lecture outline

I. Known BS abnormalities
II. NTS susceptibility to toxins
III. NTS susceptibility to ischemia
IV. Potentiation of hypoxia by toxins
V. Deafferentation and A2 impairment match ASD phenotype
VI. Therapeutic implications
Brainstem is suspect

Bernard Rimland 1964.

5-HT developmental flexibility 16283875

Lowest GSH and GR, high microglia
MacFabe D, AJBB 4(2) 146-166, 2008.

Affects development of higher brain.
18771507

Many consistent findings in autism.
Abnormal morphology

Small medulla / midbrain 8213050

Hypoplastic BS on MRI 9142760

Ectopic neurons, aberrant tracts, inferior olives ↑ then ↓ 8441369

Swollen axon terminals ("spheroids") in medulla and hypothalamus in 5/6 1173276
Abnormal biochemistry

↓ Melatonin and lack normal circadian rhythm  11455326

↓ Oxytocin, predominantly non-amidated  11690596
Abnormal function

Post-rotatory response  6874265

Auditory brainstem response, HR, respiratory and vascular.

Abnormal BS transcription of speech  1935083

Site-specific NTS impairment  16198209
Portals for toxins
Early leads to NTS

Highest binding IV secretin 14715495

IVC secretin binds pNTS 6129683

Parental reports of potty-training after secretin consistent with NTS effect.
Early leads to NTS

Thalidomide: Days 20-24 critical period for ASD corresponds days 11.5-12.5 in rats.

NTS neuronal activity rats starts day 13.
NTS basics

1. First central synapse for visceral afference.
2. Modulates brain perfusion via baroreflex and autoregulation.
3. Seminal point for ascending noradrenergic system: social, arousal, mood, emotion, pain.
Regression as clue

Now widely recognized.

Subtle earlier problems in some cases.

An acute (days to weeks) loss of function, often extreme.
Brain findings in autism are consistent with toxicity

Oxidative stress
Inflammation
Gliosis
Neuronal loss
Is regression a poisoning?
ARI Database

Sample Size

onset at 18 mos.--->

onset at birth--->

YEAR OF BIRTH
Epidemiology

Parallel increase in autism and global toxins

Autism rates correlate with:

- Landfills
- Estimated Cd and Hg
- Proximity to Hg
- Estimated Hg

Lathe AJBB 2008

Nurses Health II 2008
Inorganic mercury

MSG

Endotoxin

Cadmium

Paraquat

Fluoride
permissiveNTS (pNTS)
Ionic mercury (Hg\(^{++}\))

Pink Disease 1890-1950
Of concern in food, air, water and soil. 19171026, 11569621

Accumulation in CVO associates with ↑ microglia, persists years. 8122267

Hallmarks are inflammation and autoimmunity. 17399758, 174554560
Daily organic mercury

In 6 brain areas, Hg^{++} averaged x30 at 6 months, x60 at 18 months.

By far, highest Hg^{++} at pituitary, only CVO examined.

Stop at 6 months, Hg^{++} in pituitary doubled at 12 months

8122267
Cadmium

Injections accumulate only in CVO (AP, pineal) 3822264

Strong oxidant, blocked by antioxidants 12927359, 18629305

Highly inflammatory (TNF-α) 15033544

Strongly inhibits NE uptake 6326468
Paraquat

Injections accumulate only in CVO, (AP, pineal) 7576891

Oxidative stress 8553365

↑TNF-α production, including LPS-stimulated monocyte TNF-α 18-fold

15890010, 1414690
Monosodium Glutamate (MSG)

Injections accumulate only in CVO (AP / ME). 2415686, 2569986

Persistent oxidative effect. 12619899

TNF-α / neuronal death. 12419489
MSG effect on pNTS
Endotoxin (LPS)

LPS induces immediate robust TNF-\(\alpha\) only in CVO and adjacent structures, most intensely in AP and ME.

TNF-\(\alpha\) expression in NTS at 1.5 hours, marked by 18 hours.

No TNF-\(\alpha\) in DMV until 18 hours.
Chelation as clue

DMSA does not transit BBB.

Significant behavioral improvements in ASD after oral DMSA.

Pronounced effects on verbal communication and taste aversion.

19852790, 23400264
Case study: R.K.

Amalgam-associated regression consistent with laryngeal deafferentation.

• Age 4: Six amalgams
• Somnolent for 2 days
• Social and vocal decline; at 2 months whispered, “I am shouting,” then mute.
Case study: RK

- 5 years: Dx LKS; few words, touch/sound sensitive, poor social.
- 6 years: More alert and talkative after secretin.
- 6 years 8 months: ~100 words; High Hg in serum, hair, urine. Lymphocytes very sensitive to Hg.
Case study: RK

- Age 7 amalgams removal without precautions
- “Band-aid” that night, mute in 48h
- Alert and cheerful on DMSA
- Low function age 16, surprising keyboard results
Case study: RK

- Consistent with amalgam-triggered regression
- Amalgam-Hg circulates as ionic
- Does whisper associate with regression?
Amalgam removal decreased plasma and red-cell ionic mercury levels by 73%
Whisper in regression

ARI data-base: whisper replaced baseline vocal X1 week in 4,029 ASD; of these 42% lost all vocal, 16% long-term whisper.

Surgical deafferentation→ severe vocal impairment; reduced GCF
Laryngeal deafferentation

Unilateral division of SLN ↓ GCF 43%
15895781

Hyperthermia restored GCF 22097153

Temperature-sensitive vanilloid receptors in afferent terminals of NTS at level of AP 21734101
Reduced GCF → whisper
Parkinson’s

Toxins suspected, inflammation is prominent.

GI symptoms: ↓ motility, reflux 61%.

↓ GCF and associated whisper.

DMV proposed as first site of pathology
Ramifying pathology of PD
Ramifying pathology of PD
Key realization

Afferent-block at NTS alters visceral function.
Gut deafferentation

Selective vagotomy → ↓ gut secretory function 36992305

Opioid microinjection pNTS → ↓ gastric motility 22796075
Splenic deafferentation

VNS studies of ACh knock-outs demonstrate that interruption of splenic afference shifts lymphocytes to proinflammatory, including increased TNFα.

21840939
pNTS and CBF

pNTS stimulation increases CBF.

11172744, 6727069

Lesions block baroreflex rapid adjustment of pulse to BP.

6697447, 10683503

Lesions block autoregulation of capillaries to local needs. 3090898
pNTS viscerotopy

- Baroreflex
- Autoregulation
- Stomach
- Intestine
- Larynx  [Multiple refs in 24336025]

Experimental lesion increases salt and water intake, as in ASD 19448907, 10206527, McGinnis CRC 2010
NTS has borderline circulation

Localized NTS infarcts after hypoxic or hypotensive events 16167549, 10797184
High NMDA →hypoxic sensitive 10336064
Lower capillary density 2040734
Re-entrant blood from AP 17451045
Hypovascular pNTS
Hypoxic pNTS

AChE pro-dilatory and prominent

Ionic mercury, cadmium, MSG and nitrite reduce AChE

Oxidative stress increases blood viscosity

Freeways and CO?
SHR: NTS inflammation

Ischemia/hypoxia $\rightarrow$ microvascular inflammation 18585782, 10203141

Marked inflammation, high pro-inflammatory JAM-1 in NTS microvasculature of SHR 17420334

Potent vasodilator CGRP $\uparrow\uparrow$ in blood of SHR and neonates later diagnosed ASD 1742763, 11357950
NTS as cytokine epicenter?

Proposed long-distance ascent of cytokines from CSF along nerve bundles

TNF-α known to diffuse via small channels outside myelinated axons
Carboxyethylpyrrole (CEP)

ASD and fetal hypoxia

Fetal distress, prolonged labor, cords, Apgars, C-section

Low fetal pH

Newborn encephalopathy X6 ASD
A2 neurons

Ascending NA system: affect, social, learning, sickness behavior 20962208

NE compensatory in ischemia and excitotoxicity 19279246

Clinical response to clonidine suggests central NE deficit 19059284

Clonidine acts at NTS to increase vagal tone 20553874
A₂ and hypoxia

Hypoxic insult to A₂ may depress vasodilatory adenosine? 24336025

Hypoxic/ischemic pups: ↓ A₂ 18356740

Neonatal asphyxia: persistent change in A₂ function 9443281,14577519

Perinatal MSG depressed NE from A₂ long-term, no morphologic change. 14738902
Vitamin B₆ and NTS

CBS is alternative pathway for H₂S

H₂S ↑ afferent Transmission in NTS
Potential treatments

Detoxification

Immune modulation

Regenerative factors

VNS, including auricular

Anmian point
NTS studies

Clinical Morphology
Receptor density
Oxidative modification
Cytokine levels
Toxin levels
Vagus
NTS impairment

Toxins

Hypoxia

ASD

Visceral

ASD

Behavior