Intravenous Nicotinamide Adenine Dinucleotide and Clinical Applications

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What is NAD⁺ (Nicotinamide Adenine Dinucleotide)
What is NAD+ used for?

- Energy production (ATP)
- DNA repair (PARP)
- Gene expression (Sirtuins 1-7)
- Cell signalling (Immune-CD38, CD157)
- Neurotransmitter (NAD+)
- Enzyme activity (redox cofactor, NAD+:NADH NADP:NADPH)
- Increased Tankyrase activity
- Longer telomeres

Where does NAD+ come from (How is it made?)

- The body needs to make it (you can not absorb it from the diet)
- Every cell in the body needs it
- Main precursors:
  - Tryptophan
  - Vitamin B3 (nicotinic acid, nicotinamide, nicotinamide riboside or nicotinamide mononucleotide)
**Importantly**

1. NAD+ must come from dietary precursors
2. Too much NAD+ breakdown inhibits key enzymes
3. Inflammation switches tryptophan catabolism away from serotonin & melatonin production to making more NAD+

**Salvage pathway**

- Nicotinamide riboside (B3) to Nicotinamide mononucleotide to NAD+ to Nicotinic acid (B3)

**De novo pathway**

- Tryptophan → Quinolinic acid → Nicotinic acid mononucleotide → Nicotinic acid adenine dinucleotide → NAD+

**Renal Excretion**

- PARP1 (active) → DNA damage → SIRT (1, 6, 7) → acetylated protein → deacetylated protein
How do you raise NAD+ in the body?

**Oral**
- Nicotinamide riboside (NR)
- Nicotinamide mononucleotide (NMN)
- Nicotinic acid (Niacin)
- Nicotinamide (niacinamide)

**Intravenous (IV)**
- NAD+

Maintain NAD+ by:
1) Reducing oxidative damage &
2) Inflammation (CD38)
3) Increasing synthesis

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**NAD+, CD38 & Inflammation**

CD38 is one of the largest consumers of NAD+

CD38 is a glycoprotein found on the surface of many immune cells which also functions in cell adhesion, signal transduction and calcium signaling.

In humans, the CD38 protein is encoded by the CD38 gene which is located on chromosome 4.

- Uses NAD+ to generate Ca^{2+} mobilizing metabolites.

Important role in inflammation:

- CD38 induced Ca^{2+} release causes migration of neutrophils and monocytes toward sites of inflammation.
- Increased CD38 expression signals maturation of dendritic cells during inflammatory cytokine activation.
- Decreased CD38 function is associated with impaired immunity.


In conditions in which inflammation is increased CD38 activation is a potential cause of reduced cellular NAD+.
NAD⁺ and social behaviour (Autism-Oxytocin)

- OXT is involved in social interactions and may promote trust, generosity, increased emotional perception and parenting behaviour.
- Autism is a spectrum disorder (ASD), which is characterized by social and communication impairments, linked to significant defects in the OXT system.

[Diagram showing OXT release, CD38, and NAD⁺ mobilization]

Healthy social behavior

NAD⁺ & sleep / wake cycles

Biological rhythms are established and maintained by a central clock consisting of around 20,000 pacemaker neurons in the supra-chiasmatic nucleus (SCN)¹.

NAMPT/NAD drives the circadian clock feedback cycle through SIRT1 and CLOCK:BMAL1².

As the levels of NAD⁺ oscillate over the circadian cycle, the activity of SIRT1 oscillates, linking the metabolic state of the cell through an epigenetic mechanism to the circadian clock³.

Circadian dysfunction has been linked to sleep disorders, depression, bipolar disorder and changes in cognitive function and memory formation¹.

What happens as we age

Cumulative tissue damage results in:

- structural degeneration
- functional decline, and
- age-related diseases
- Increased telomere shortening

Oxidative Stress:

- Reflects an imbalance between the systemic manifestation of reactive oxygen species and a biological system's ability to readily detoxify the reactive intermediates or to repair the resulting damage.
**Oxidative Stress**

- **Reactive Oxidative Species (ROS):**
  - Free radicals with at least one unpaired electron in their atomic structure
  - Harmful at supra physiological concentrations
  - A delicate balance between the generation and the elimination of reactive oxidative species

Superoxide ($O_2^-$) radicals,
- hydroxyl radical (OH⁻),
- hydrogen peroxide ($H_2O_2$)
- the peroxynitrite ($OONO^-$) radical

Free radicals can produce cumulative tissue damage to major cell components such as DNA

The higher the rate of DNA damage the faster the ageing process
**Brain oxidative damage, age and NAD⁺**

- Oxidative Damage
  - Mean CSF 12 lipoproteins (nmol/L)
  - < 45 years vs > 45 years
- Inflammation
  - Mean CSF IL-6 (ng/ml)
  - < 45 years vs > 45 years

(data from Table 1)

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**NAD⁺ & telomere length**

Increased NAD⁺ availability can increase tankyrase removal of TRF1 improving telomerase access

- Telomere length shortens with age.
- Critically short telomeres trigger senescence and eventually cell death.
- Shorter telomeres have been linked to:
  - a) increased incidence of disease,
  - b) poor survival.
Conditions in which NAD\(^+\) can be depleted

↑ oxidative damage (with age)

Alcohol ↓ brain NAD\(^+\) & ↑ inflam.
**EtOH effect on cultured human brain astroglial cells**

- **Ox stress**
  - [Graph showing Ox stress affected by Ethanol concentration]

- **PARP**
  - [Graph showing PARP affected by Ethanol concentration]

- **NAD(H)**
  - [Graph showing NAD(H) affected by Ethanol concentration]

- **Sirt 1**
  - [Graph showing Sirt 1 affected by Ethanol concentration]

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**Importantly: additional NAD+ prevents synaptic disconnection**

- **Implications for neurodegenerative disease (e.g. alcoholism, AD)**

- **NAD+ prevents axon (Wallerian) degeneration**

- **Quantification of cortical presynaptic structures affixed to MAP-2-positive striatal dendrites after cortical axotomy. NAD+ delays cortical synaptic loss (ANOVA 2, *p*-value,0.05, **p*-value,0.01).**

- **% Axonal degeneration at different time points in presence of absence of [NAD]. In vitro-Dorsal root ganglion cells (DRG).**

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Calliari et al. Experimental Neurology 251 (2014) 91–100*
Figure 2. NAD Significantly Reduces Craving Ratings Associated With Opiate and Alcohol Withdrawal At Five And Ten Days of Treatment

Pairwise T-tests Conducted on Day 1 vs Day 5 and Day 1 vs Day 10 in Opiate (n=29) and Alcohol (n=24) Groups. * indicates p < 0.01.

Figure 3. Severity Of Cravings Associated With Alcohol and Opiate Withdrawal at 12-20 Months Post NAD Treatment

Severity of cravings (+SEM) reported for Opiate and Alcohol respondents to follow up surveys conducted from 12-20 months post NAD treatment.
Isoprostanes

- The isoprostanes are prostaglandin-like compounds formed *in vivo* from the free radical-catalyzed peroxidation of essential fatty acids (primarily arachidonic acid) without the direct action of cyclooxygenase (COX) enzymes.

- **8-Isoprostane** is a prostaglandin (PG)-F₂-like compound belonging to the F₂ isoprostane class that is produced *in vivo* by the free radical-catalyzed peroxidation of arachidonic acid. 8-Isoprostane is a biomarker of oxidative stress.
Plasma 8-Isoprostane following IV NAD BR+ Therapy

Baseline

Plasma 8-Isoprostane (nM)

Healthy Alcohol Abuse Opiate Abuse

Baseline Draw 2 Draw 3

Alcohol Abuse (n = 26) Opiate Abuse (n = 19)

Plasma TNF-alpha following IV NAD BR+ Therapy

Baseline

TNF-alpha (pg/mL)

Healthy Alcohol Abuse Opiate Abuse

Baseline Draw 2 Draw 3

Alcohol Abuse (n = 18) Opiate Abuse (n = 14)
Baseline NAD(H) Levels in Alcohol and Opiate Abuse Subjects

Response to Intravenous NAD BR⁺ Therapy in Subjects Treated for Alcohol Abuse

(n = 19 Subjects)
Luminosity Test Results
Measures of Memory, Attention, and Mental Flexibility
What research is still needed to be done?

We do not yet know:
1. The best dose regimen (how much and for how long) for many conditions and any of the NAD+ enhancing substances.
2. If there are combinations of treatments (molecules) that may enhance the NAD+ effect.

Need to assess the effectiveness of NAD+ therapy alone (or in combination) in multiple clinical/health/performance conditions/situations such as:
- Addiction medicine
- Neurodegenerative disease (AD, PD)
- Depression
- Chronic fatigue
- PTSD
- Traumatic Brain Injury - CTE
- Metabolic disease (Diabetes, mitochondrialopathies)

END PRESENTATION ~ Questions?

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The human body is made of cells

Organs

DNA

Cells

Figure 1. NTR™ Significantly Reduced Craving Ratings for Stimulants, Opiates and Alcohol Groups.

Data from Previous Experiment (2008). Pairwise T-tests Conducted on Stimulant s (n=10), Opiates (n=11), Alcohol (n=12), and Other/Poly (n=7) Groups Following 10 Days of NTR™ Treatment. * indicates p < 0.01.
Introduction: Treatment of substance abuse disorders continues to challenge clinicians and “cravings” for the abused substance are often impediments to sobriety. Nicotinamide Adenine Dinucleotide (NAD) has been used in the past with claims of having anti-craving properties. Previous data from this clinic using a similar formulation of NAD support the use of NAD as a valid treatment for drug cravings. This pilot study retrospectively examined the anti-craving properties of NAD in a group of 60 patients. Additionally, patients were assessed on severity of cravings and relapse episodes at 12-20 months post treatment.

Method
The patients were adult males and females with addictions to primarily opiates or alcohol (N=60). Six patients were omitted due to incomplete data. The treatment Brain Restoration Plus (BR+) comprised of IV infusions of NAD as well as vitamins, oral amino acids, NAC and variable PRN medications for an average of 10 consecutive days ranging from 5 to 10 hours daily at a dose range of 500mg-1500mg each day. Self-reported craving ratings (0-10 Scale) were collected on Day 1 (before starting treatment), Day 5, and on Day 10 (last day of treatment). Follow-up phone surveys were conducted from 12-20 months post treatment (N=27). Patients reported severity of cravings (1-5) and number of relapse episodes at the present time.

Results
1) NAD is an effective detox treatment for alcohol and opiate addicts as evidenced by a significant reduction in craving ratings.
2) NAD was effective in reducing and maintaining the number of relapse episodes, as well as severity of drug cravings.
3) NAD shows potential as a long-term therapy in maintaining sobriety through minimizing drug cravings and preventing relapse.

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Response to Intravenous NAD BR+ Therapy in Subjects Treated for Alcohol Abuse

(n = 12 Subjects)
Response to Intravenous NAD BR⁺ Therapy in Subjects Treated for Opiate Abuse

(n = 10 Subjects)

Aging: Lifespan

Ataxia-telangiectasia (A-T) is a rare "accelerated aging" degenerative disorder affecting multiple body systems but especially the brain and the immune system.

NAD⁺ therapy improves A-T (animal model)
- NAD⁺ is low in brain and tissue in A-T

NAD⁺ therapy (NR/NMN) increased
- DNA repair
- Mitophagy
- Mitochondrial function
- NAD⁺ ameliorated neurodegeneration
- Restored behaviour and memory to normal levels
- Markedly extending lifespan
Human skin DNA damage

Decrease in Sirtuin

Response to Intravenous NAD\(^+\) Therapy in Subjects Treated for Opiate Abuse

(\(n = 10\) Subjects)
Response to Intravenous NAD⁺ Therapy in Subjects Treated for Alcohol Abuse

(n = 12 Subjects)

8-Isoprostane (% Change From BL)

Baseline  Draw 2  Draw 3

END PRESENTATION

Questions?