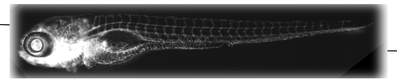
↑Adiponectin

Adiponectin is produced from adipose tissue in proportion to body fat. It is a negative feedback regulator of many of the effects of obesity. It is generally very beneficial. it is regulated by SIRT1 as well.



Endothelial

↑NADPH

↓Redox sensitive genes ↓MCP-1 & VCAM → ↓Vascular Inflammation

↓DGAT → ↓Triglycerides ↓Apo B ↓VLDL

↓beta ATP Synthase/HDL receptor/ATP5B
(HDL catabolism in a ADP dependent fashion... see Chirugi's lecture)

Note: The concentration of NA needed for this effect which was shown in hepatocytes to be involed in increasing ApoB catabolism seems unnaturally high according to Offermann/ARPT paper where he points out that the NA concentration achieved after NA is 100 fold less than that used in this experiment 0.3-3mM (this does not seem right to me.) This same argument was levied in the same article by Offermann against the idea that decreases in ApoA catabolism were seen at the high concentrations of nicotinic acid.

↓PKA → ↓HSL → Inhibition of lipolysis in adipose tissue.. decrease FFA mobilization. This is a unique action of NA and this decrease in FFA leads to decreased VLDL. Potentially very signficant.

? → ↓TNFα induction of inflammatory genes
Corrected lipodystrophy
Reduced cardiac disease mortality
neutrophil apoptosis

DP1 → PGD_2:DP1/smooth muscle cells .. vasodilation/flushing

$PPAR\gamma$ → Anti-inflammatory: ↓NFκβ, ↓AP-1, ↓TNF alpha,↓cytokines, ↓iNOS, ↓MMP, & ↓DC chemotaxis
Increased HDL-C with decreased cholesterol: ↑CD36 & ↑ABCA1 ↑ HDL-C
inhibition of neutrophil infiltration

Environmental:
Triclosan is polychlorinated biphenyl aromatic that is infused into soaps, toothpastes, deodorants, mouth washes, shaving creams, kitchen utensils, ... many other products to minimize bacterial contamination. It is made from partial oxidation of benzene or coal oxidation. The mechanism of microbicidal action involves the formation of a stable intermediate with the enzyme enoyl-acyl carrier protein:NAD:triclosan. This enoyl-acyl carrier protein is encoded by the gene FABI and ultimately this inhibits fatty acid synthesis. Humans do not have enoyl-acyl carrier protein, so this loss of fatty acid synthesis is not seen for humans. However, in 2006 it was determined to interfere with thyroid signaling in Xenopus based experiments. Also, chlorine reacts with triclosan to produce dinitrophenol and dioxins which are of obvious concern to people's health.

HM74a/GPR109a

↓cAMP/adipocytes & neutrophils

↑Ca^{+2} / APCs → PGD_2...PGJ_2, PGE_2...PGF_2, PGH_2, & PGI_2 → EP2 & EP4

(↑100-500x) (↑100x) (PGI2 can activate PPARδ)

(PGE2 increases in macrophages, not monocytes nor endothelial cells... big adipocytes?)

Endothelial
Epidermal
Langerhans Cells,
Lung,
Adipocytes,
& Macrophages
HM74a is also expressed in glia and neurons, but activities are unknown; PGD2 release was not detected in neutrophils

PGE_2:EP2 .. *IDO* induction with tolerogenesis & vasodilation/flushing. Also of potential interest, PGE2:EP3 inhibits lipolysis in adipoyctes [Johansson, 2007 #5000]. Whether a pathway exists for nicotinic acid-PGE2-EP3-anti-lipolysis is unknown as far as I can tell.

PGE_2:EP4 .. epidermal langerhans migration to lymph nodes

Role for ApoE?: Niacin can not raise HDL nor lower triglycerides in ApoE KO mouse [Declercq, 2005 #4543]. These observations suggest that niacin may work in part by altering the levels or activities of ApoE, however this does not appear to be examined as far as I can tell. CETP deficient individuals have increased cholesterol efflux only in a ApoE and ABCG1 dependent manner [Matsuura, 2006 #4542]. Only in CETP overexpressor mice can the corrective lipodystrophy effects be seen, where the assumption is that niacin is decreasing CETP expression [Hernandez, 2007 #4657]. Taken together it appears that CETP inhibition depends on ApoE. The ApoE KO mouse has hypercholesterolemia, ApoE:cholesterol is able to substitute for glia in conferring synaptogenic activity neuron to neuron, and ApoE mutations are associated with Alzheimer's Disease. All together these observations strongly suggest that niacin is likely to help against Alzheimer's Disease perhaps be mechanisms involving decreasing CETP.

Based on experimental data:
SLC22A13/hORCTL3./hOAT10 has higher affinity than SLC5A8 (Km=0.5μM vs 250μM respectively). Based on phylogenetic conservation from bacteria to man, not yet experimentally verified: SVAP (NiaP, bacterial name). Transporter in mammals to bacteria!. In mammals these have not been experimentally verified yet with regards to activity, but they have for bacteria. Others in bacteria only are PnuC, NiaX, & NiaY. There is also a high affinity NA specific transporter activity identified in hepatocytes, but the protein has not been identified [Said, 2007 #4532].)

(TnaP, high affinity nicotinic acid transporter in yeast)

Nicotinic Acid (Niacin)

Tryptophan → Serotonin → Melatonin

TDO2 (also expressed in neurons and glia, over-expressed in schizophrenia [Miller, 2004 #5118])

(+) / PAPCs endothelial?

IDO1 *IDO2* (Vit C-dependent)

DAP12/TYROBP, TREM2, or *Bin1*/Amphiphysin → Important Functions in Auto-immunity and Mental Health

kynurenine

CCBL1 *KAT2* → kynurenate

KMO (B2-dependent) → 3-hydroxykynurenine → formic acid

anthranilate

KYNU (B6-dependent)

3-hydroxyanthranilic acid → picolinic acid (*ACMSD*)

3HAAO

spontaneous reaction → quinolinic acid

(Tryptophan to NAD in yeast... Brn2, -3, -4, -5, -1, and QPT/Brn6)

NAPRT1
(*NPT1* required for CR-mediated increases in lifespan in yeast studies, but no change total NAD)

QPRT

Nicotinic Acid (Niacin) → Nicotinic Acid Mononucleotide (*PncA*, bacteria and mycobacteria)

Same as below (*PncB*, bacteria but not typically active in mycobacteria) → Nicotinic Acid Dinucleotide

Niacin
Raises HDL
Lowers LDL and VLDL
GPR109a activation decreases TGs in adipocytes which decreases FFA (however there is a rebound increase in FFA in humans)
Niacin also inhibits diacylglycerol transferase (DGAT2) which increases ApoB degradation and decreases ApoB secretion, thus explaining the decrease in VLDL and LDL.

HDL:
It has been shown that increased SIRT-1 activity through direct deacetylation of LXR leads to increased ABCA1 expression along with increases in HDL [Li, 2007 #3877]. NA is now known to activate LXR in adipocytes [Zhao, 2008 #5073]. Since NA leads to NAD which is the known activator of SIRT-1, this suggests that NA mediated increases in HDL may be through NA-NAD-SIRT1-LXR-ABCA1-HDL. Of course nicotinic acid/niacin also leads to local production of PGJ2 where nicotinamide does not and thus it would seem that this may be the most important unique aspect and perhaps somehow it is. Other PPAR agonists such as thiazolidinediones are well known for their ability to increase HDL and lower triglycerides. I think logically it has to be the combined greater delivery of NAD from nicotinic acid/niacin and the local production of PGJ2 that are involved in the unique ability to dramatically raise HDL, where nicotinamide/niacinamide can not. Kashyap has other ideas that are not as well accepted.

PNC1 (nicotinamidase/pyrazinamidase) - not present in mammals, but is present in *C. elegans* and can increase *C. elegans* lifespan
(necessary for CR life extension in yeast;
not present in mammals tremendously important in microbial pathogenesis;
also present in *M. tuberculosis* and is the mechanism of action for pyrazinamide which is bacteriostatic but bacteriocidal in replicating acidi *M. tb.* cells but can be bactericidal in dormant *Mtb.*
The PNC converts pyrazinamide to pyrazinoic acid... one belief is that the product pyrazinoic acid then inhibits fatty acid synthetase 1, *FASI*. This latter mechanism is debated, but what is clear is that *PNC1* mutations are definitely present in pyrazinamide resistant *M. tb. PNC1* is also present in *Drosophila* -Homologene.) Normally NA is made.

Nicotinamide Riboside (NAMR) (2004)

NRT1 (NAMR transporter; present in *C. glabrata* and other yeast thus far)

(Not present in bacteria, yeast, worms, or flies; +regulated by glucocorticoids, - reg'd TNFalpha)

NRK1, 2 (*NRK* lifespan / yeast)

NADS (*QNS* in yeast)

ADP-P2X7R → NAD mediated T cell death (physiological relevance/significance is unknown)

P2X7R NAD transporter

NMNAT1-3
(*NMNAT1 / Wld*^{S} mouse, *Nma1, 2* -nuclear- for yeast = increased lifespan)

NAMPT1/ PBEF1/ VISFATIN

Nicotinamide (Niacinamide) → Nicotinamide (Niacinamide) → Nicotinamide Mononucleotide → **NAD**

ART2

NADK → NADP

CD38 (*CD157*, also makes NAADP)

CD38: unknown biochemical function other than as a mechanism to control extracellular NAD levels, critical roles in immune function.

cADP → NAADP (nicotinic acid instead of nicotinamide)

NAADP is the most potent of all known endogenous calcium release agents !!
NAADP is known to be active in many cell types.

cADP has a very long half life

Intracellular calcium release is controlled by IP3, cADP, and NAADP, where least is understood regarding the function of cADP and NAADP in regulating intracellular calcium release.

Cellular:
Several nicotinic acid related precursors promote HL-60 cell apoptosis including picolinic acid, dipicolinic, isonicotinamide, and isonicotinic acid hydrazide (described in [Ida, 2008 #4594]). Nicotinamide was also shown to decrease c-myc and CD38 levels.

>500 Redox Reactions Rely on NAD as a Co-factor

Significantly, all cytochrome P450 phase 1 drug metabolizing ezymes control metabolism of the following molecules where CYP4A and CYP4B family members are transcriptionally induced in response to PPAR activation thus increasing the need for NAD cofactor where CYP4 family member substrate has accumulated ultimately regulating arterial hypertension. Generally, NAD(H) is involved in catabolic reactions, where NADP(H) is more frequently involved in anabolic reactions.

Drugs
Foreign Chemicals
Endogenous Prostaglandin / Eicosanoid / Arachidonate
Fatty Acids
Steroids / Cholesterol / Bile
Vitamin D
Vitamin A
Orphan Molecules (e.g. CYP20A1)

Deacetylation
c-myc... decreased c-myc stability
WRN... increased helicase activity during DNA damage
PGC1α (trans-activation)... mitochondrial biogenesis
FOXO1, FOXO3A (trans-activation)
Histones (general repression)
NFκβ (repression)... decreased TNFα
p53.. decreased function

Functional Endpoints:
Increased Lifespan
Decreased Inflammation
Increased Tumor Cell Apoptosis
Fat Reduction

Interferon gamma highly increases transcription of *IDO* and *HM74a/gPR109a*

Resveratrol (+) → SIRT1

(in yeast these are sir2, hst1, hst2, hst3, and hst4; hst1 sensor of NAD that controls NAD biosynthetic enzymes)

PARP1 (-) (+)
(Minocycline, PJ34, DHIQ, ...)

Inhibited PARP1 Activity:
Prevention of DNA Damage Associated Cell Death

ADP-ribosylation of: NF-kb, PARP-1, others, ...

ERK1/2 or JNK1/MAPK8

definitely: any DNA damage, insulin likely: cytokines, growth factors

PAR

PARG or PD1 (Immune System Cells)

NAD IN INFECTIOUS DISEASE

TUBERCULOSIS
The first tests involved detection of nicotinic acid production [Konno, 1967 #4525]. Structurally related to NA/NAM are the first major anti-Tb drugs, pyrazinamide and isoniazide. There development stemmed from initial promising anti-Tb results using nicotinamide.
Isoniazid can cause pellagra by somehow interfereing with endogenous pathways to NAD biosynthesis. This is rescable with niacin administration [Darvay, 1999 #3850]. Isoniazid requires bacterial catalase-peroxidase to generate isonicotinic acyl anion or radical which then reacts with NADH to generate isonicotinic acyl anion or radical which will bind tightly to ketoenoylreductase known as InhA to inhibits the synthesis of mycolic acid in the mycobacterial cell wall.Isoniazid is inactivated by NAT2 (N-acetyltransferases). For pyrazinamide it requires Pnc1 (a gene not present in mammals; see left part of figure). M. tb. that are resistant to nicotinamide and pyrazinamide have PNC1 mutations in [Konno, 1967 #4525]. Interestingly, both isoniazid [Darvay, 1999 #3850] and pyrazinamide [Jorgensen, 1983 #4526] have been shown to cause pellagra in people. Application of isoniazid to tubercule bacili leads to dramatic lowering of NAD levels [Bekierkunst, 1966 #4582] and this just may be the primary mechanism of action for isoniazid -simple inhibition of the NAD salvage pathway of tuberculosis. Isoniazid has also been shown to cause psychosis, an increase in triglycerides, and kynurenines by uncertain mechanisms (inhibition of NAD-SIRT-LXR-triglycerides or GPR109a/HM74a signaling? does isoniazid/alternative name or pyrazinamide/alternative name bind GPR109a ? Well pyrazinoate which is produced from PNCa mediated catalysis starting from pyrazinamide, does [Gharbaoui, 2007 #4945]).

MALARIA
RBCs infected with *Plasmodiaum falciparium* have 10x greater NAD, where RBCs normally can only make NAD from NA, *P. falciparium* infected red blood cells can make NAD from NAM [Zerez, 1990 #4506]. Also NPT1 activity is increased by 3 fold, such that both NA and NAM pathways to NAD are increased. Interestingly the *Fp*Sir2 uniquely possesses ADP ribosyltransferase activity where the HDAC activity is dependent on ADP rribosyltransferase activity and NAM inhibits it but other sirtuin inhibitors do not [Merrick, 2007 #4507]
Metabolomics analysis reveals a critical role for NAD in susceptibility to cerebral malaria [Parekh, 2006 #4508] Other HDAC inhibitors are showing greater promise than *Pf*Sir inhibitors [Andrews, 2008 #4540]. However, *Pf*Sir definitely has roles in repressing *var* (variant surface) gene expresion [Freitas-Junior, 2005 #4541].

CA NDIDIASIS
Sir2p mediated repression of *EPA* pathogenic genes in *C. glabrata*. Niacin auxotroph that in the absence of NAD

YERSINIA
Pyrazinamidase/nicotinamidase production or acitivity is used as an assay of virulence factor. Yersinia are facultative anaerobes, gram negative bacteria, pretty hardy/resistant to cold/heat, Yersinia enterocolitica is the most prevalent one connected with human disease.

CORYNEBACTERIUM
Gram positive, facultative anaerobe, *Corynebacterium diptheriae* is cause of diptheria, most are non-pathogenic, but there are strains that are a serious problem in immunocompromised individuals, e.g. endocarditis! Diptheria toxin works via ADP ribosylation of eEF-2, thus inhibiting eukaryotic protein translation. Multi-drug resistant *Corynebacterium* causing lethal human infections has been recently isolated and determined to contain a mutation in PNC1 [Otsuka, 2005 #4527].

Vibrio cholera
Cholera toxin interactS with the human protein mono-adp ribosyl transferase ARF6, using NAD to ADP ribosylate adenylate cyclase causing tremondous cAMP production that results in electrolyte efflux characteristic of cholera. This mechanism of NAD dependent ADP ribosylation causing dysregulation of signal transduction continues to be an expanding field of research as there are now known to be 18 different PARP1 related proteins based purely on sequence gazing, where we only understand the function of roughly the first 5. ARF6 itself is interesting: ras family member superfamily (it can bind guanine nucleotide), interacts with beta arrestin after GPCR activation, and is involved in vessicle trafficing.

Brucella abortus
Facultative intracellular anaerobe that can live in phagocytic cell types. Can cause undulant fever in people in premature abortions. PNC1 is required and key in its ability to perform intracellular replication. For the PNC1 mutant *Brucella*, the addition of nicotinic acid helped it replicate in hela cells and macrophages, while nicotinamide could not.

Neurodegenerative Disease
Alzheimer's Disease - beat amyloid & tauopathy
Parkinson's Disease - Alpha synucleinopathy
Amyotrophic lateral sclerosis - TDP-43 proteinopathy
Huntington Disease - huntingtin proteinopathy

NAD boosts HST1 which directs expression of HSPs and chaperons, while NMNAT2 is a chaperone itself, all contributing to reducing the accumulation of these proteinopathies.

Clostridium thermoaceticum
Nicotinic acid can function as the sole vitamin essential for minimal media for *Clostridium thermoaceticum* [Lundie, 1984 #4576]. I do not know how relevant this may be for the other species, but the other related species are involved in tetanus (*C. tetani*), botulism (*C. botulinum*), pseudomembranous colitis (*C. dificile*), and gangrene (*C. perfringens*).

HIV & Dyslipidemia
Dilipidemia is commonly connected with HIV pathogenesis and increasingly more research is focused on this including niacin, niaspan, and acipomox [Oh, 2007 #4528].

NAD Sensitive Transcription Factors & Evolution
NrtRs are trans-factors that positively regulate NAD biosynthetic pathway enzymes (*nadA, nadB, nadC, nadD, nadE, pncB, nadR, tkt, tal, rpe, xylAB*, arabinose, and xylanose p-way enzymes all shown in fig. 1 [Rodionov, 2008 #4529]). DNA binding by NrtR family of transcription factors is inhibited by ADP-ribose (product of PARG reactions). This study reveals a new role for ADP-ribose in bacteriology. These studies demonstrated significant variability in the way different bacteria regulate NAD metabolism. Still however, we do not know what the target genes are in these pathways.
YrxA/NiaR family of transcription factors are are niacin responsive repressors of NAD biosynthetic pathway enzymes (e.g. *nadA, nadB, nadC*), salvage p-way (*pncA*), and transporters (*niaX, niaY, niaP, pnuC*) [Rodionov, 2008 #4534]. These are found in *Clostridium/Bacillus* bacteria.

Vancomycin-resistant *enterococci*
Pyrazinamidase/nicotinamidase/PNC1 assay is used to rapidly somewhat reliably identify vancomycin resistant strains of enterococci.