METABOLISMENS OG DIÆTS ROLLE I UDVIKLING AF HJERNE SYGDOMMEN

MOLECULAR PHARMACOLOGY GROUP
AALBORG UNIVERSITY

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Agenda

- Hvem er jeg
- Hvordan startede de hele
- Hjerne sygdom
- Metabolisme
- Lipider i hjerne
- Medicin
- Effekt af Diæt og Stress på hjerne sygdomme
- Hvad kan du gøre selv til forbygge eller har det bedre

Hvem er jeg?

- Startede at arbejde som laborant, Universitet, PhD i Kræft og vaccine forskning
- USA arbejdede på HPV vaccine
- Tysk Biotek firma Medigene
- Flyttede til Danmark til en Biotek firma, Borean Pharma i Aarhus
- Aarhus Universitet underviste i Biotechnologi
- Aalborg Universitet forskning i Metabolisme og hjerne sygdomme
- Iværkkesat 2 biotek firmaer 2A Pharma og 2N Pharma

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Startede med et spørgsmål fra Medigene

- Kan man finde andre sygdomme man kan behandle med en medicin der bliver udviklet for hjerte sygdom?

- Hvad vidste vi om den medicin?

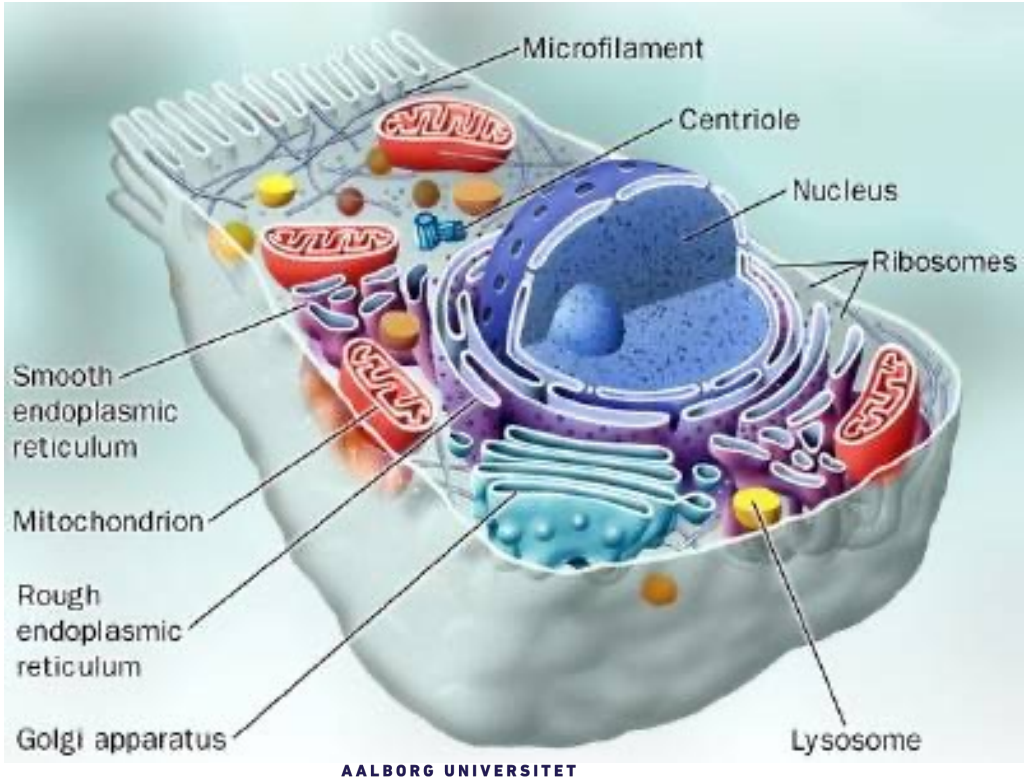
- Medicin hæmmer CPT1 en protein det er vigtig i lipid/fedt forbrænding

- CPT1A, CPT1B

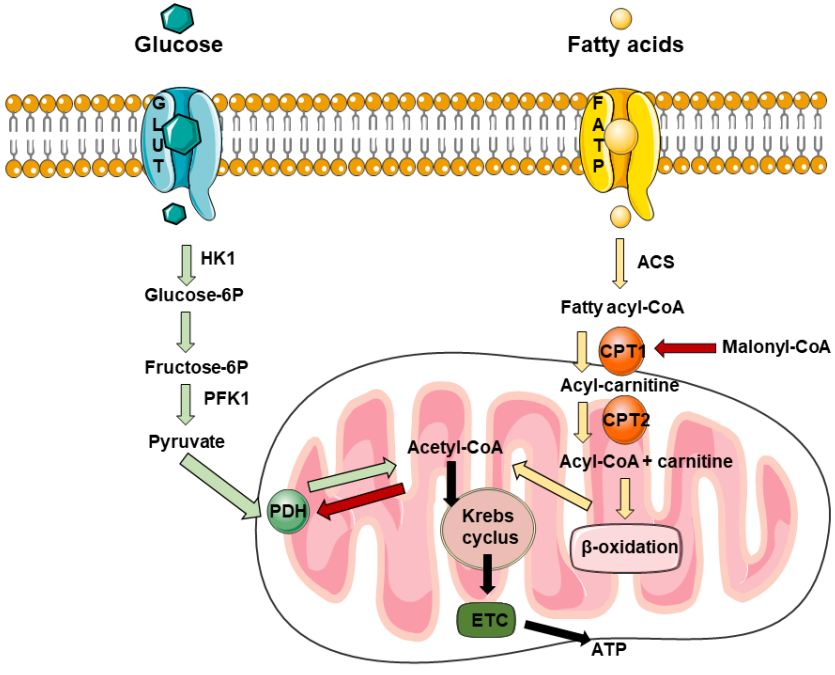
Field	Category	Affy ID	Genbank	Gene	GeneName	Tissue	Disease	CMean
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	AMYGDALA, NORMAL, CONTROL FOR SCHIZOPHRENIA	AMYGDALA, SCHIZOPHRENIA	12,18
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	AMYGDALA, NORMAL, CONTROL FOR SCHIZOPHRENIA	AMYGDALA, SCHIZOPHRENIA	19,86
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	AMYGDALA, NORMAL, CONTROL FOR SCHIZOPHRENIA	AMYGDALA, SCHIZOPHRENIA	55,51
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	AMYGDALA, NORMAL, CONTROL FOR SCHIZOPHRENIA	AMYGDALA, SCHIZOPHRENIA	60,82
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	AMYGDALA, SUICIDE WITH NO HISTORY OF DEPRESSION	AMYGDALA, SUICIDE WITH HISTORY OF DEPRESSION	14,45
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	AMYGDALA, SUICIDE WITH NO HISTORY OF DEPRESSION	AMYGDALA, SUICIDE WITH HISTORY OF DEPRESSION	18,21
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	AMYGDALA, NORMAL, CONTROL FOR SUICIDE	AMYGDALA, SUICIDE WITH HISTORY OF DEPRESSION	14,59
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	AMYGDALA, NORMAL, CONTROL FOR SUICIDE	AMYGDALA, SUICIDE WITH HISTORY OF DEPRESSION	20,03
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	AMYGDALA, SUICIDE WITH NO HISTORY OF DEPRESSION	AMYGDALA, SUICIDE WITH HISTORY OF DEPRESSION	30,47
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	AMYGDALA, SUICIDE WITH NO HISTORY OF DEPRESSION	AMYGDALA, SUICIDE WITH HISTORY OF DEPRESSION	53,08
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	AMYGDALA, NORMAL, CONTROL FOR SUICIDE	AMYGDALA, SUICIDE WITH HISTORY OF DEPRESSION	30,34
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	AMYGDALA, NORMAL, CONTROL FOR SUICIDE	AMYGDALA, SUICIDE WITH HISTORY OF DEPRESSION	50,85
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	AMYGDALA, NORMAL, CONTROL FOR SUICIDE	AMYGDALA, SUICIDE WITH NO HISTORY OF DEPRESSION	14,59
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	AMYGDALA, NORMAL, CONTROL FOR SUICIDE	AMYGDALA, SUICIDE WITH NO HISTORY OF DEPRESSION	20,03
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	AMYGDALA, NORMAL, CONTROL FOR SUICIDE	AMYGDALA, SUICIDE WITH NO HISTORY OF DEPRESSION	30,34
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	AMYGDALA, NORMAL, CONTROL FOR SUICIDE	AMYGDALA, SUICIDE WITH NO HISTORY OF DEPRESSION	50,85
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE NUCLEUS, ALZHEIMER DISEASE	14,76
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE NUCLEUS, ALZHEIMER DISEASE	21,78
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE NUCLEUS, ALZHEIMER DISEASE	46,36
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE NUCLEUS, ALZHEIMER DISEASE	55,46
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	14,76
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	21,78
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	46,36
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	55,46
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR SCHIZOPHRENIA	CAUDATE NUCLEUS, SCHIZOPHRENIA	9,54
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR SCHIZOPHRENIA	CAUDATE NUCLEUS, SCHIZOPHRENIA	21,08
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR SCHIZOPHRENIA	CAUDATE NUCLEUS, SCHIZOPHRENIA	57,11
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR SCHIZOPHRENIA	CAUDATE NUCLEUS, SCHIZOPHRENIA	72,14
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	15,65
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	25,03
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	14,76
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	21,78
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	42,4
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	55,93
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	46,36
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	55,46
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	15,65
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	25,03
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	15,2
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	27,15
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	14,76
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	21,78
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	42,4
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, POSSIBLE ALZHEIMER DISEASE (CERAD-4)	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	55,93
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	50,54
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE, DEFINITE ALZHEIMER DISEASE (CERAD-2)	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	61,55
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	46,36
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CAUDATE NUCLEUS, NORMAL, CONTROL FOR ALZHEIMER DISEASE	CAUDATE, PROBABLE ALZHEIMER DISEASE (CERAD-3)	55,46
Disease	Central Nervous System	203634_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CEREBELLAR HEMISPHERE, NORMAL, CONTROL FOR COCAINE ABUSE	CEREBELLAR HEMISPHERE, COCAINE ABUSE	11,78
Disease	Central Nervous System	210688_s_at	BC000185	CPT1A	carnitine palmitoyltransferase 1A (liver)	CEREBELLAR HEMISPHERE, NORMAL, CONTROL FOR COCAINE ABUSE	CEREBELLAR HEMISPHERE, COCAINE ABUSE	11,11
Disease	Central Nervous System	210069_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CEREBELLAR HEMISPHERE, NORMAL, CONTROL FOR COCAINE ABUSE	CEREBELLAR HEMISPHERE, COCAINE ABUSE	44,34
Disease	Central Nervous System	210070_s_at	BC021130	CPT1B	carnitine palmitoyltransferase 1B (muscle)	CEREBELLAR HEMISPHERE, NORMAL, CONTROL FOR COCAINE ABUSE	CEREBELLAR HEMISPHERE, COCAINE ABUSE	70,21

Hvordan kan men bruge det og hvordan passer det sammen?

Medicin hæmmer fedt forbranding



Mitochondriel metabolisme



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Glukose og Lipid metabolismen in hjerne sygdomme

Alzheimers Disease

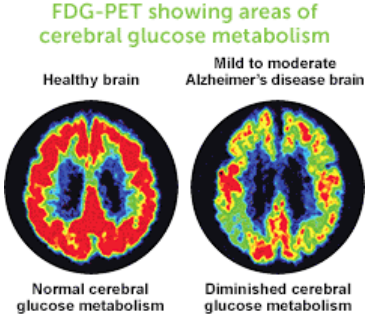
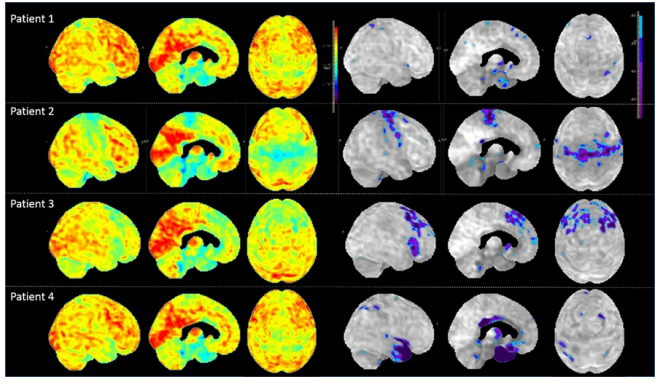
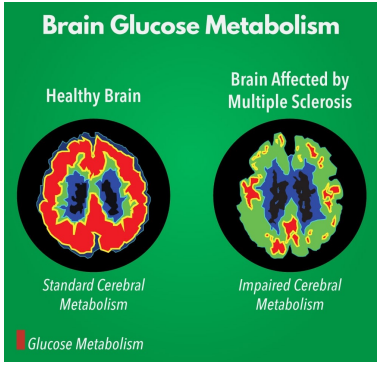


Image source: Small GW, Ercoli LM, Silverman DHS, et al. Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proc Natl Acad Sci USA*. 2000;97(11):6037-6042. Copyright 2013 National Academy of Sciences, U.S.A.

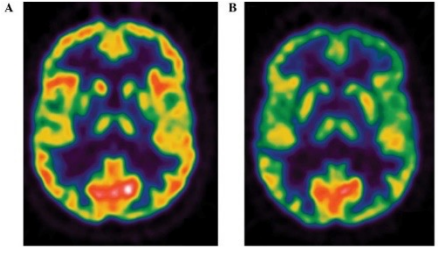
Amyotrophic lateral sclerosis



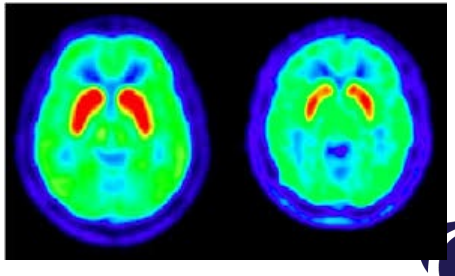
Multiple Sclerosis



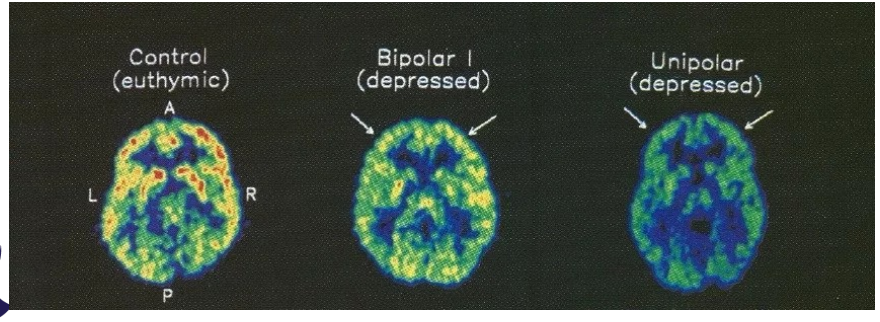
Hodgkins disease



Parkinson's disease



Depression



Er der en sammenhæng i de mekanismer?

Mechanism	Amyotophic lateral sclerosis	Parkinson's disease	Multiple sclerosis
Mitochondrial dysfunction	X	X	X
Inflammation	X	X	X
Oxidative stress	X	X	X
Demyelinering	X	(X)	X
Neurotransmitter forstyrrelser	X	X	X
Tarmbakterie forandringer	X	X	X
Ubalance i jern balance	X	X	X
hormon ændringer (stress)	X	X	X
Insulin resistens	X	X	X
Protein sammenklumpning	X	X	(X)
Nedsæt glukose metabolisme	X	X	X
forhøjet lipid metabolisme	X	X	X

Sygdommen; høne eller ægget spørgsmålet

Ilt mangel
Lipid peroxidation

Myelin sheath skade og demyelinering

.....

Amyotrophic lateral sclerosis, Parkinson's disease, Multiple sclerosis og andre sygdommen

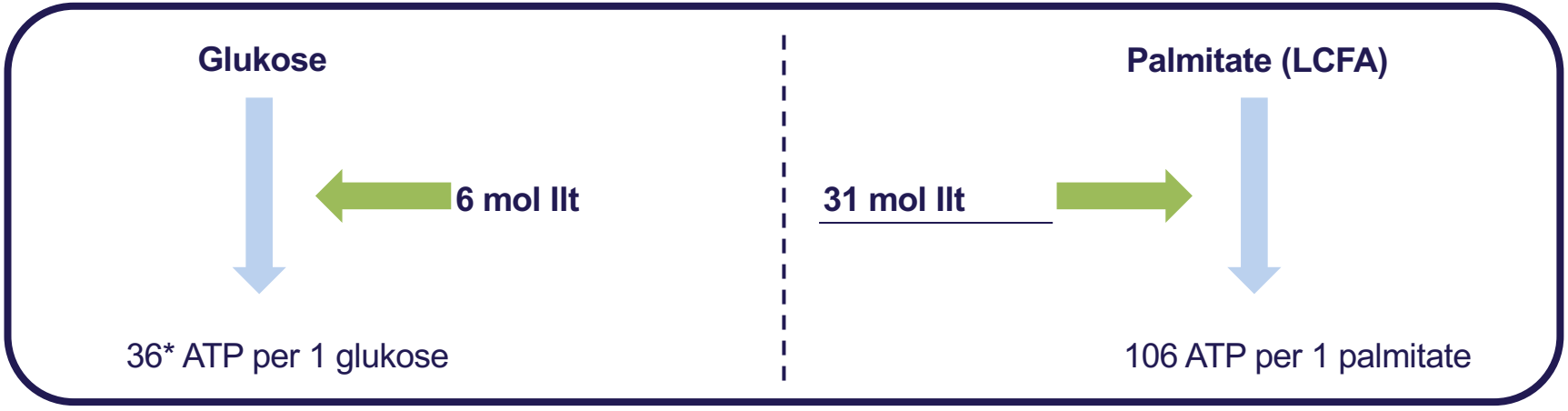
Inflammation

Akkumulering af misfolede proteiner

Tab af neuroner, og tab of function I neuroner

Ilt mangel
Lipid peroxidation

Glukose versus lipider in hjerne



- Hvis alt er i balancen bruger hjerne glukose
- Men i hjerne er der proteiner der sørger for forbrændingen af lipider
- Lipid metabolisme kan aktiveres hvis hjernen kommer i ubalance
- Lipid metabolisme bruger 2 gange så meget ilt (oxygen) per produceret ATP end glukose metabolisme gør

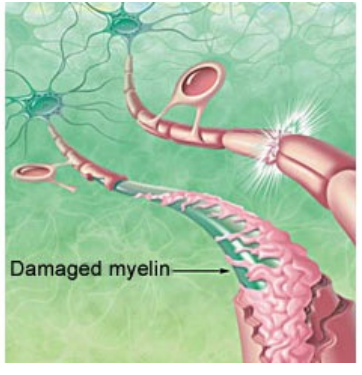
Ebert D, Haller RG, Walton ME. Energy contribution of octanoate to intact rat brain metabolism measured by 13C nuclear magnetic resonance spectroscopy. J Neurosci. 2003 Jul 2;23(13):5928-35.
Jernberg, J. N., Bowman, C. E., Wolfgang, M. J. & Scafidi, S. Developmental regulation and localization of carnitine palmitoyltransferases (CPTs) in rat brain. *J. Neurochem.* **142,** 407–419 (2017).
Bernier, L. P. *et al.* Microglial metabolic flexibility supports immune surveillance of the brain parenchyma. *Nat. Commun.* **11,** (2020).
Fecher, C. *et al.* Cell-type-specific profiling of brain mitochondria reveals functional and molecular diversity. *Nat. Neurosci.* **22,** 1731–1742 (2019).
Polyzos, A. A. *et al.* Metabolic Reprogramming in Astrocytes Distinguishes Region-Specific Neuronal Susceptibility in Huntington Mice. *Cell Metab.* **29,** 1258–1273.e11 (2019)

Myelin sheath skade og demyelinering

Tab af neuroner, og tab of function I neuroner

Lipider i hjernen

- Palmitat og andre lipider er 70% af Myelin hvilket isolerer neuroner
- Palmitat bundet til Myelin har en levetid af 3 dage
- Under stress og hypoxi konditioner, skifter cellerne metabolismen fra glukose til lipid forbrænding. Dermed vil lipid niveauet I hjerne synke
- Ingen lipider til at reparerer Myelin.
- Dette resulterer i:
  - Tab af nerve funktion
  - Problemer med at opbygge ny hukommelse
  - På lang sigt tab af lang tids hukommelsen
- Blokering af lipid metabolismen kunne måske omvender denne proces



Inflammation

Akkumulering af misfolede proteiner

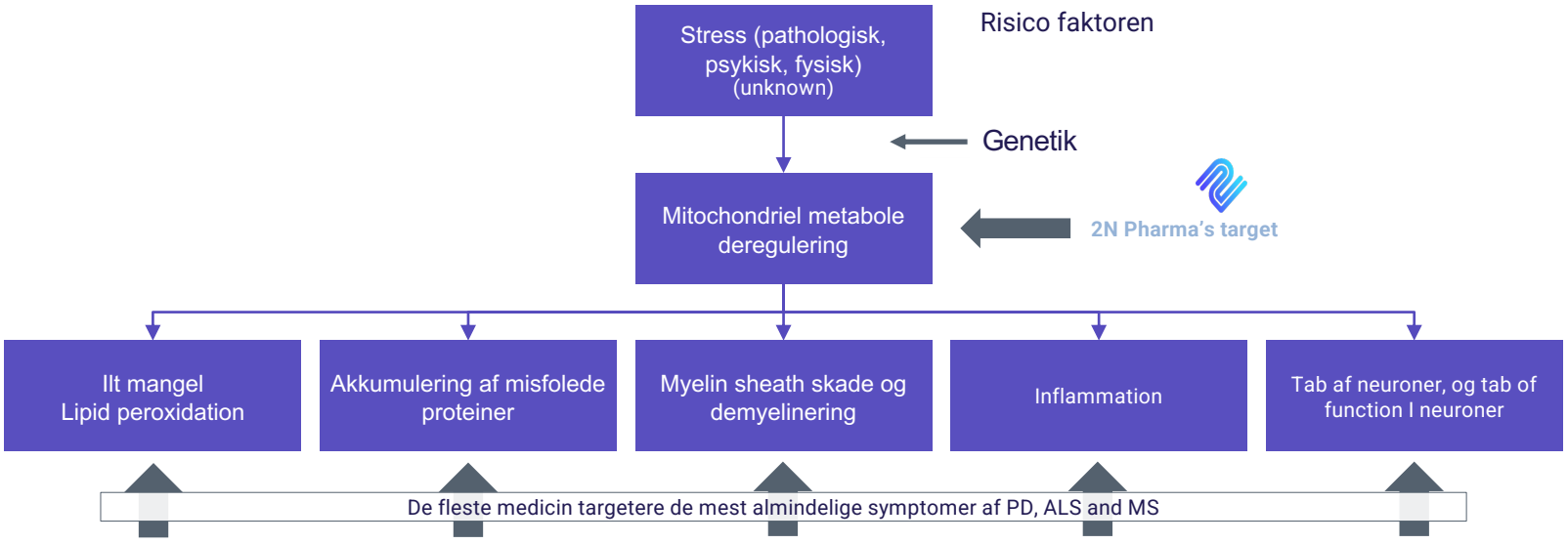
Inflammation og Protein sammenklumpning

- Ilt mangel + lipid metabolisme stimulere produktion af PGE2
- PGE2 aktivere celler af Immun forsvar

- Når men har iltmangel I Mitochondria starter den med at producere H_2O_2

- H_2O_2 inducere DNA skade og protein denaturering som alpha synuclein, beta amyloid, tau tangles, lewy bodies osv.

Behandling af hjerne sygdomme i dag



Eksempler af medicin det er tilladt (i italics) eller i de sidste stadie af test i kliniske studier
Tilpasset fraTrabjerg, M.S., Aalborg University Press, 2020

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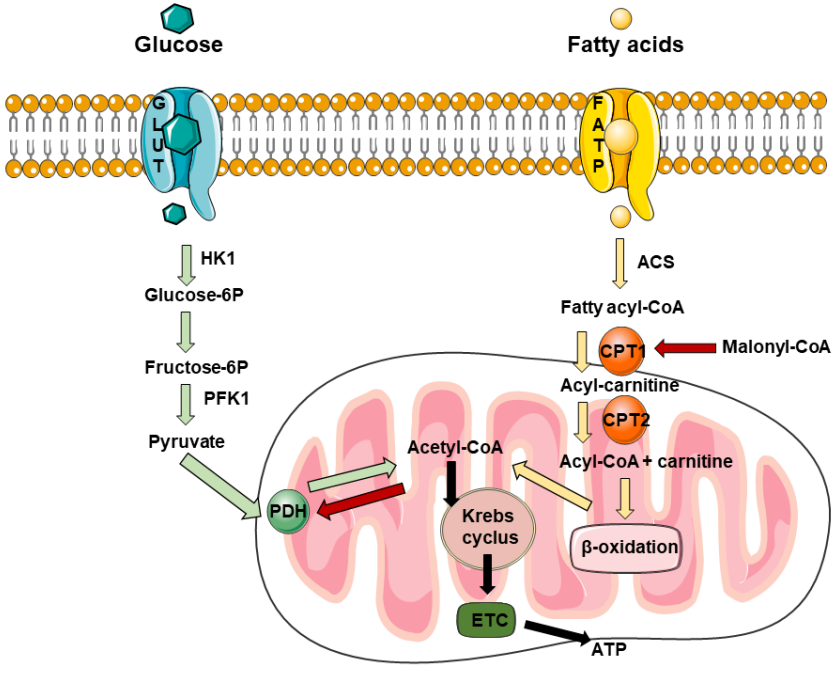
Mitochondrial metabolism



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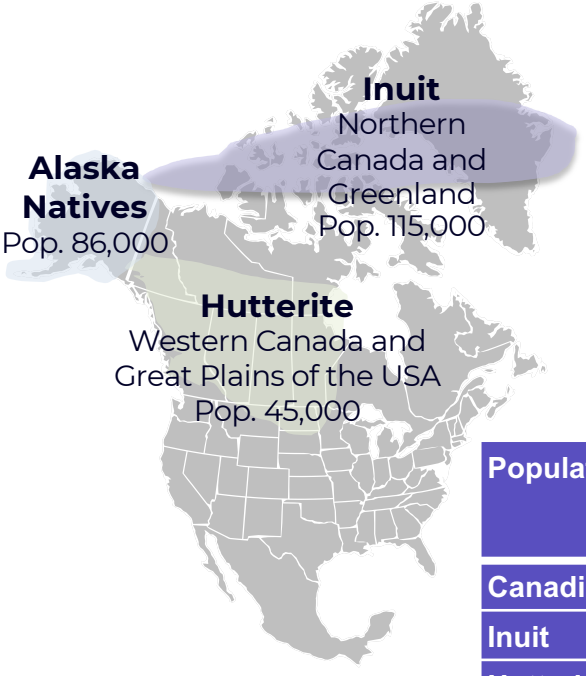
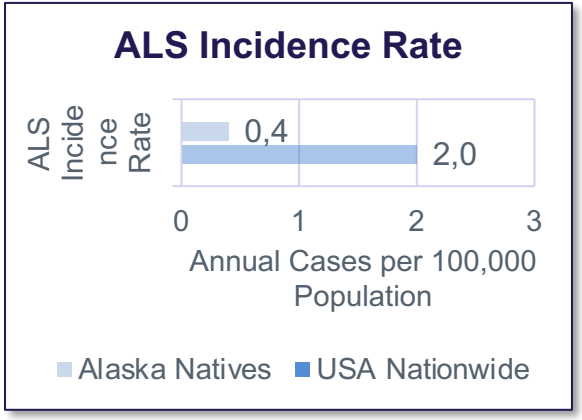
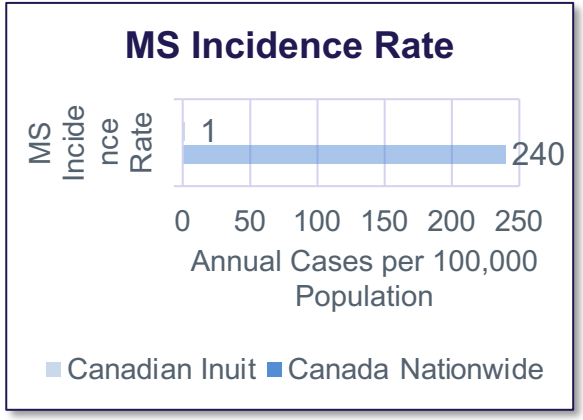
The genetic links: the Arctic and Hutterite CPT1A variants



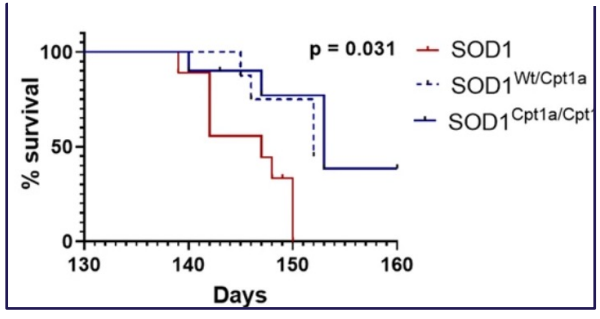




Population	CPT1A Activity Level	Frequency of at least one allele mutated	MS Incidence Rate	ALS Incidence Rate
Canadian	100%	≈0%	240 / 100,000	2 - 4 / 100,000
Inuit	22%	>90%	**1 / 100,000**	**0.4 / 100,000**
Hutterite	≈0%	30%	91 / 100,000	
United States	100%	≈0%	→	2 - 4 / 100,000
Alaska Natives	22%	>90%	→	**0.4 / 100.000**

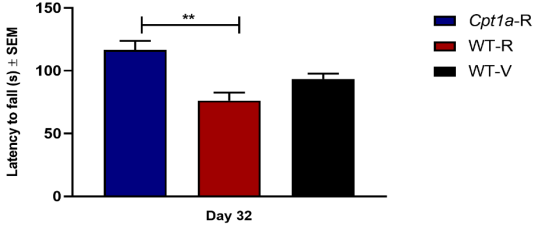
The CPT1A mutant mouse (Den arktisk mutation)

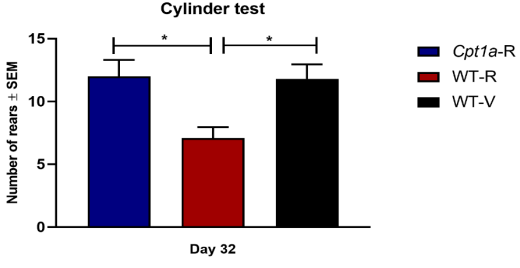
Overlevelse I ALS dyr



from Trabjerg, M.S., Andersen, D.C., Huntjens, P. et al. Downregulating carnitine palmitoyl transferase 1 affects disease progression in the SOD1 G93A mouse model of ALS. Commun Biol 4, 509 (2021)

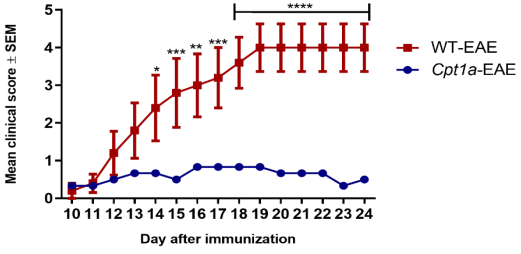
Sygdoms I Parkinson dyr





from Trabjerg, M.S., Andersen, D.C., Huntjens, P. *et al.* Inhibition of carnitine palmitoyl-transferase 1 is a potential target in a mouse model of Parkinson's disease. *npj Parkinsons Dis.* **9**, 6 (2023)

Sygdoms I MS dyr



from Mørkholt, A.S., Trabjerg, M.S., Oklinski, M.K.E. et al. CPT1A plays a key role in the development and treatment of multiple sclerosis and experimental autoimmune encephalomyelitis. Sci Rep 9, 13299 (2019)

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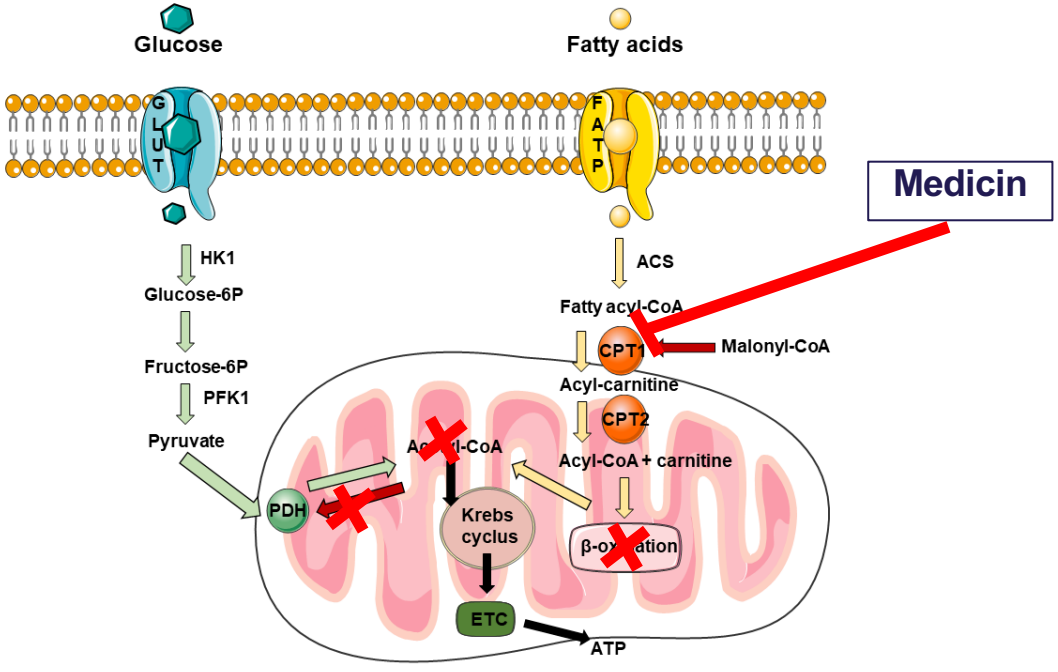
Hvad vider vi indtil nu?

- Mennesker det har nedsæt fedtforbrænding bliver ikke eller meget mindre syg af hjerne sygdommen
- Dyr med sammen nedsætte fedtforbrænding er beskyttet for hjerne sygdommen

- Finde medicin det kan gøre de samme

Medicinske behandling af mitochondriel metabolism



MS Trabjerg 2020. Aalborg University Press.

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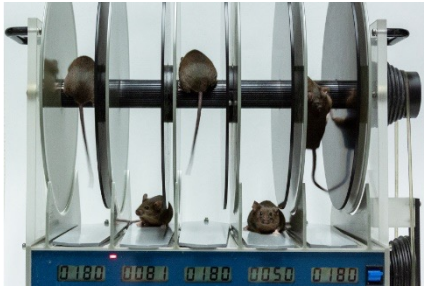
Eksperiment setup; hvordan tester vi sygdommen i mus?

Grip styrke test

https://www.bioseb.com/bioseb/anglais/default/item_id=48_Grip-Test.php

Rotarod test

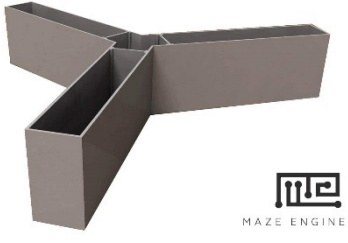


https://www.spectrumnews.org/news/toolbox/careful-mouse-tests-forecast-fate-angelman-drugs/

gitter test

https://www.jove.com/video/2610/measuring-the-strength-of-mice

Y-maze test



https://mazeengineers.com/portfolio/y-maze/

Cylinder test

https://www.pcrm.org/news/ethical-science/hundreds-diabetes-studies-mice-misinterpreted

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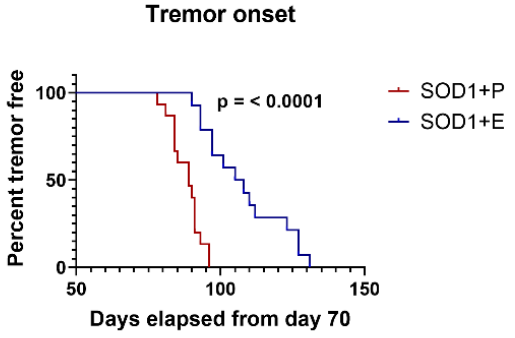
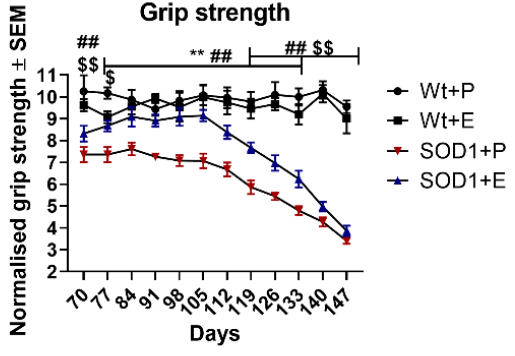
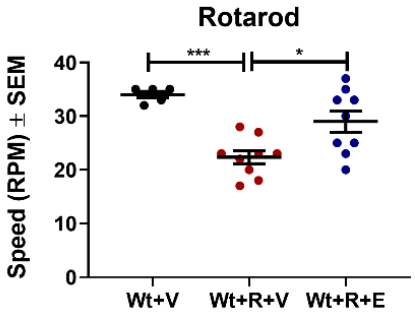
Behandling af ALS, Parkinson and EAE (MS) med CPT1 hæmmer

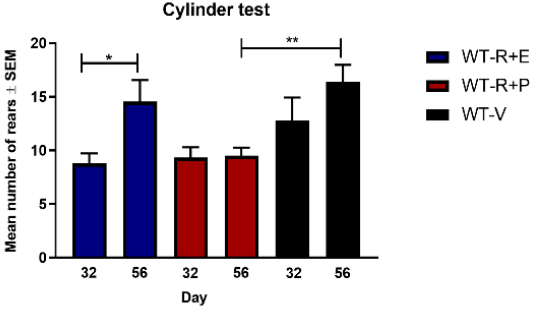
ALS



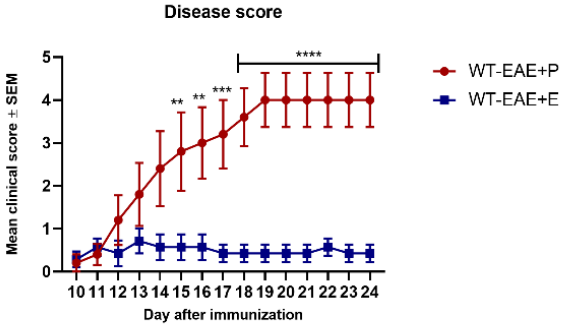


Parkinson

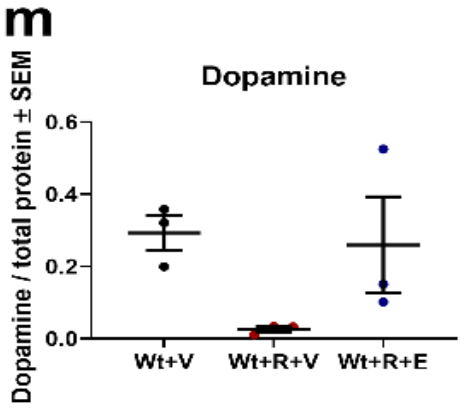


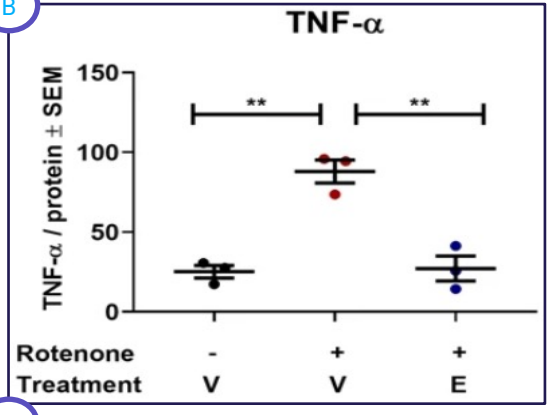


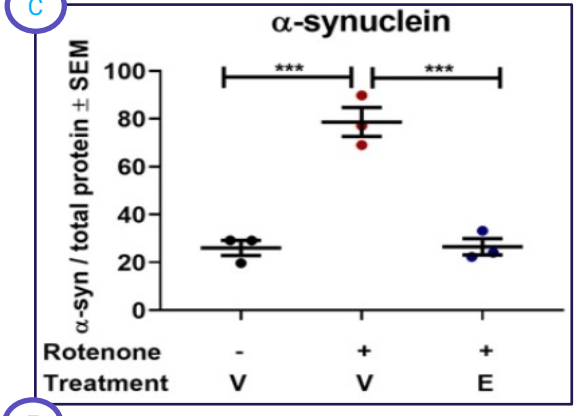
MS

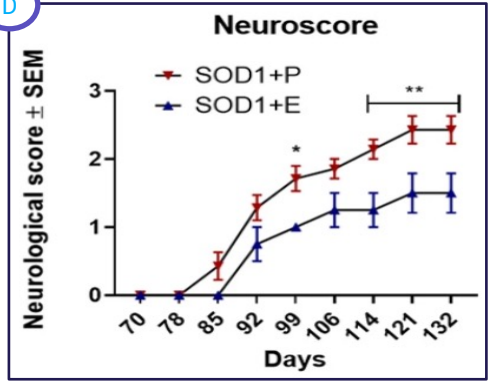


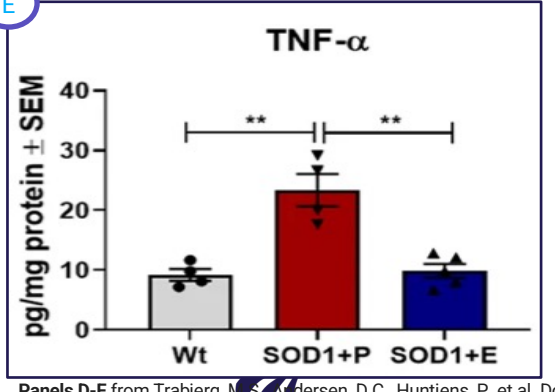
Tester I ALS og Parkinsons sygdom

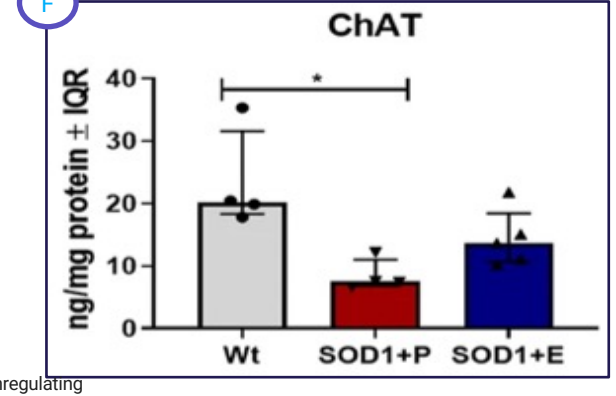








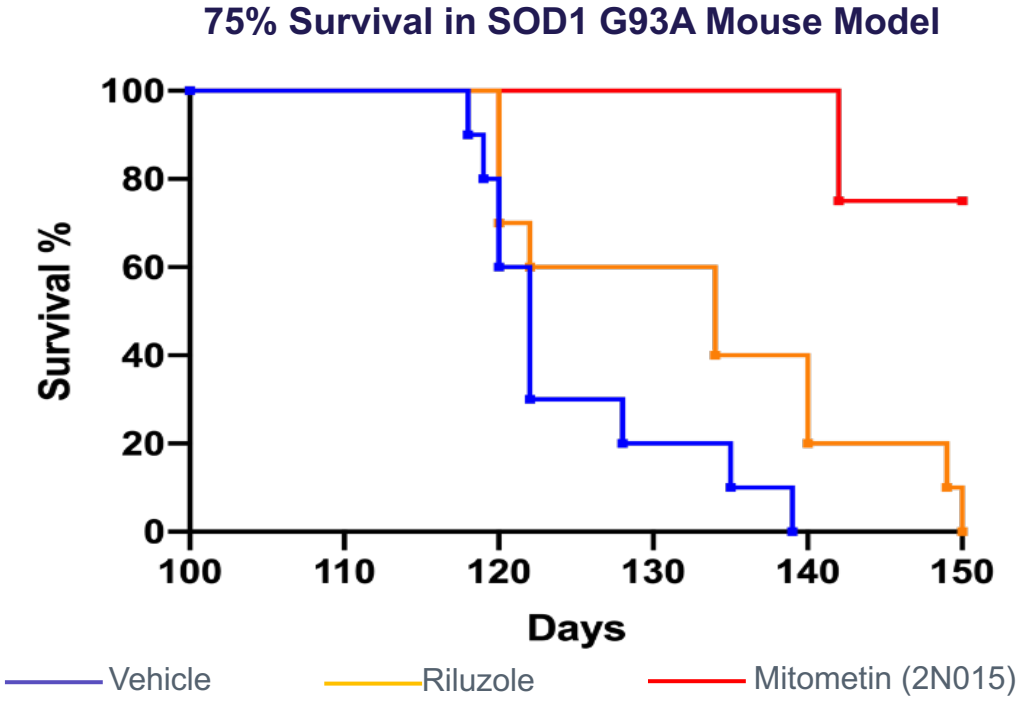




Panels A-C from Trabjerg, M.S., Andersen, D.C., Huntjens, P. *et al.* Inhibition of carnitine palmitoyl-transferase 1 is a potential target in a mouse model of Parkinson's disease. *npj Parkinsons Dis.* **9**, 6 (2023)

Panels D-F from Trabjerg, M.S., Andersen, D.C., Huntjens, P. et al. Downregulating carnitine palmitoyl transferase 1 affects disease progression in the SOD1 G93A mouse model of ALS. Commun Biol 4, 509 (2021)

Behandling af ALS med nyt CPT1 hæmmer



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Results: *Sod1 g93a*

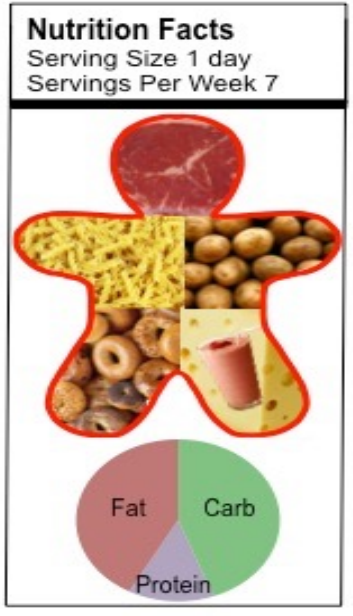
Video med 2 mus på det tidspunkt vi skal aflive dem.

Den ene er behandlet med medicin den anden er behandlet med placebo.

Medicinen blokere fedtstof forbrænding

Systemisk model

Illustration af Maria Rasmussen



FAT VS SUGAR:
The Culture of American Dieting

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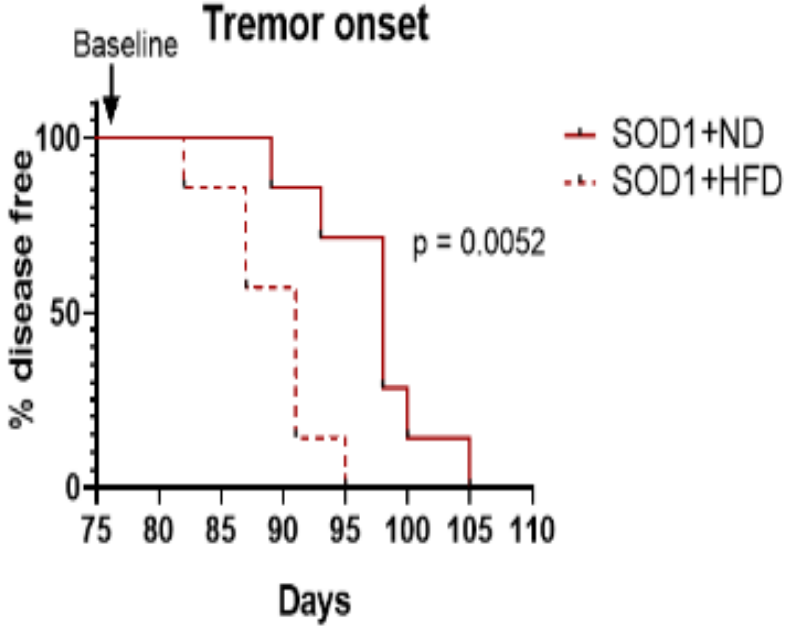
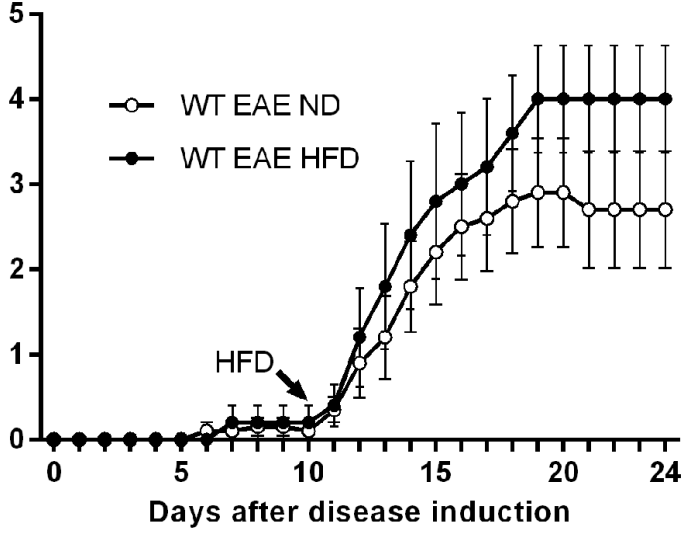
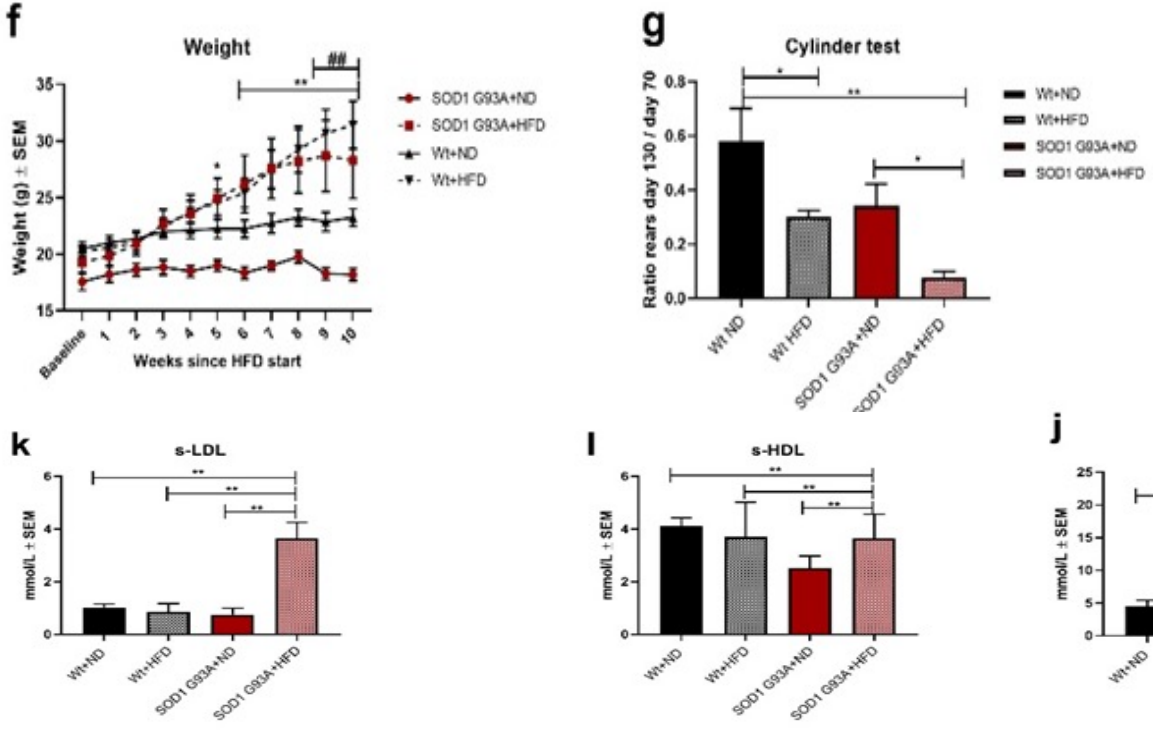
Effekt af vesterlige diæt på EAE (MS) og ALS





Sod1 g93a fed diæt

ND = Normal diæt
HFD = fed diæt



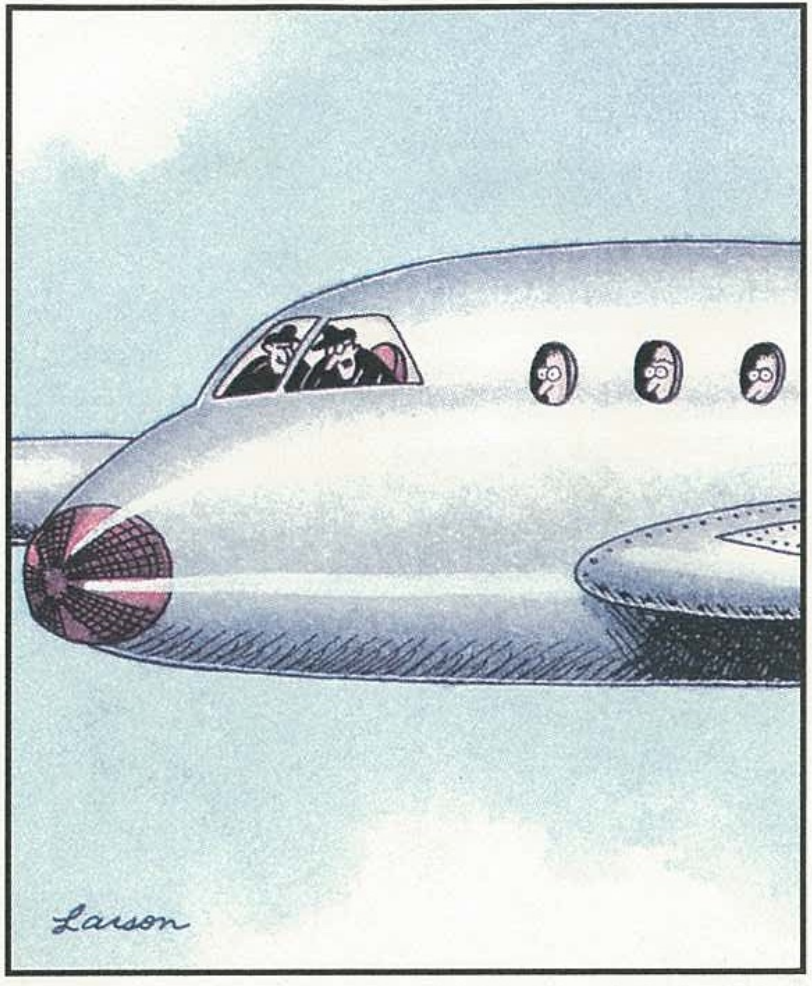

GOOD
Unsaturated Fats
VS
BAD
Saturated Fats
Butter
Butter

Glukose versus sukker

- Glukose giver Pyruvate

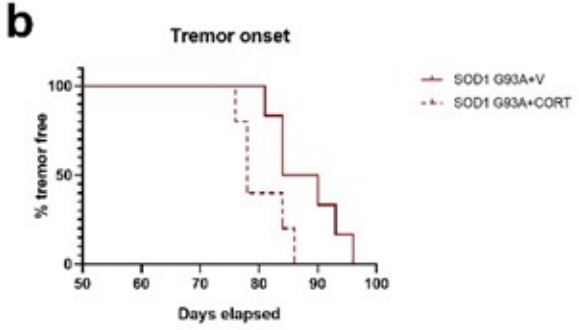
- Sukker= Sucrose = glukose + fruktose
- Fruktose bliver brugt i fedtsyre synthese

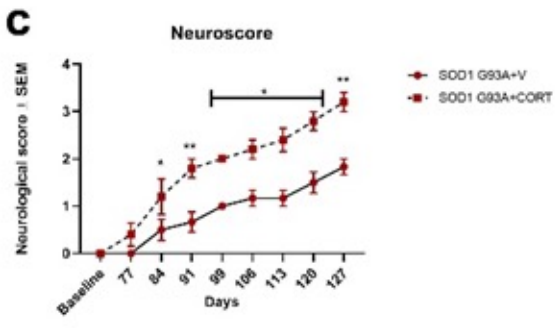
Stress and hjerne sygdom

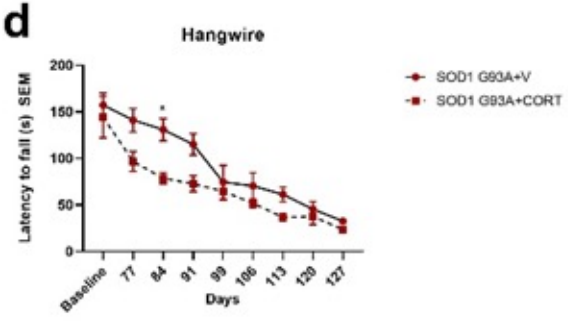


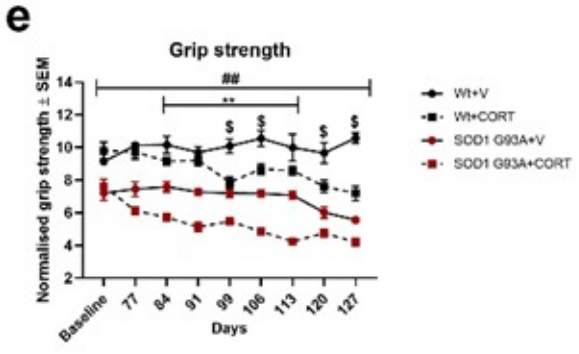
"The fuel light's on, Frank! We're all going to die! ... Wait, wait. ... Oh, my mistake—that's the intercom light."

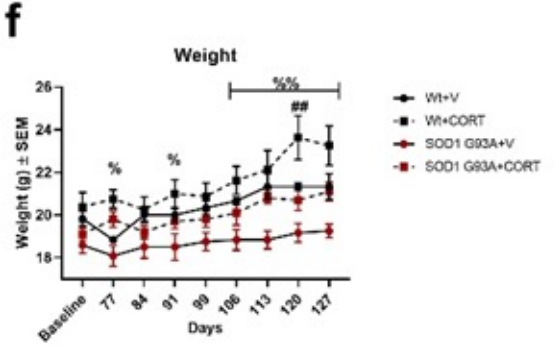
Sod1 g93a cortisone inducerer stress

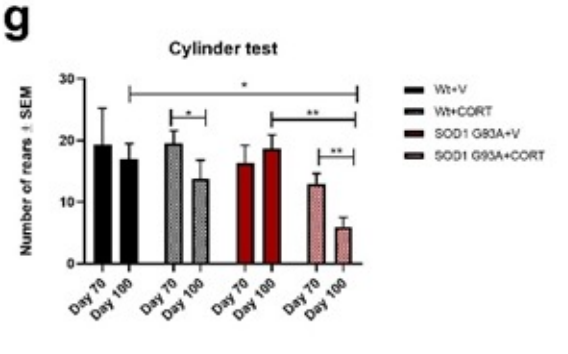












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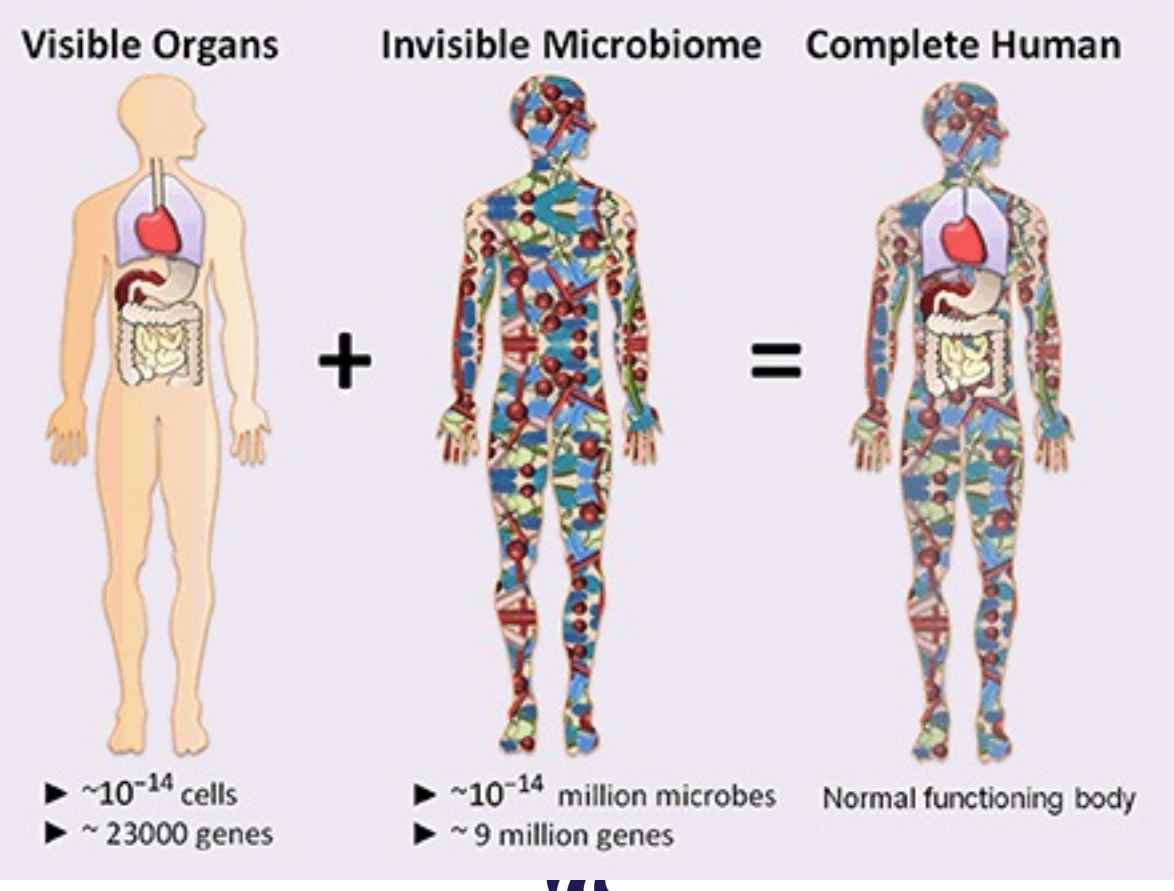
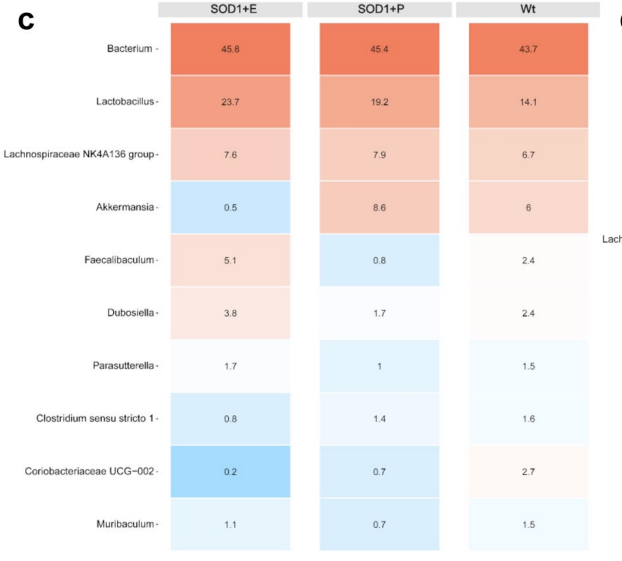
Microbiota og mennesker



Mikrobiota analyse

ALS Beh | ALS Placebo | Rask



ALS | ALS Inuit

ALS Fedt diæt | ALS norm diæt | Rask Fedt diæt | Rask norm diæt

John Dirk Vestergaard Nieland, jdn@hst.aau.dk

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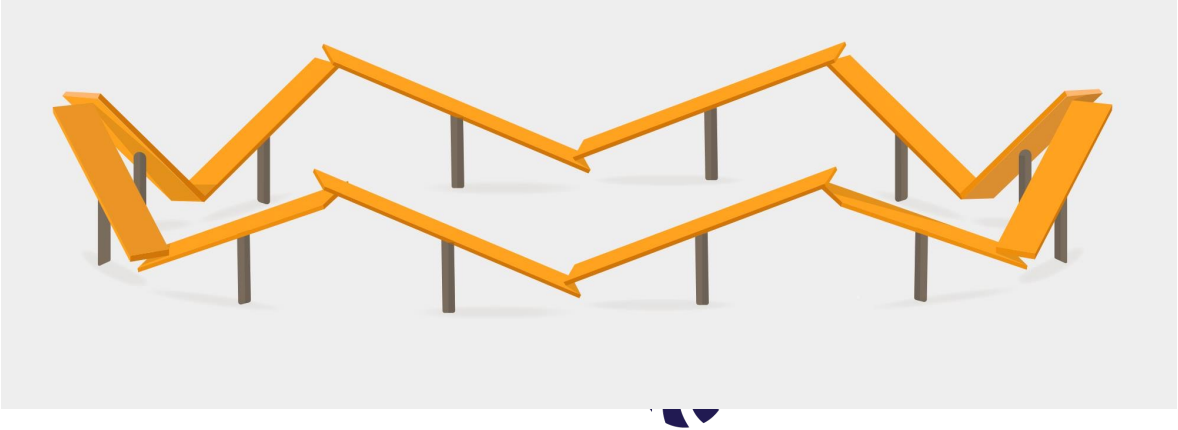
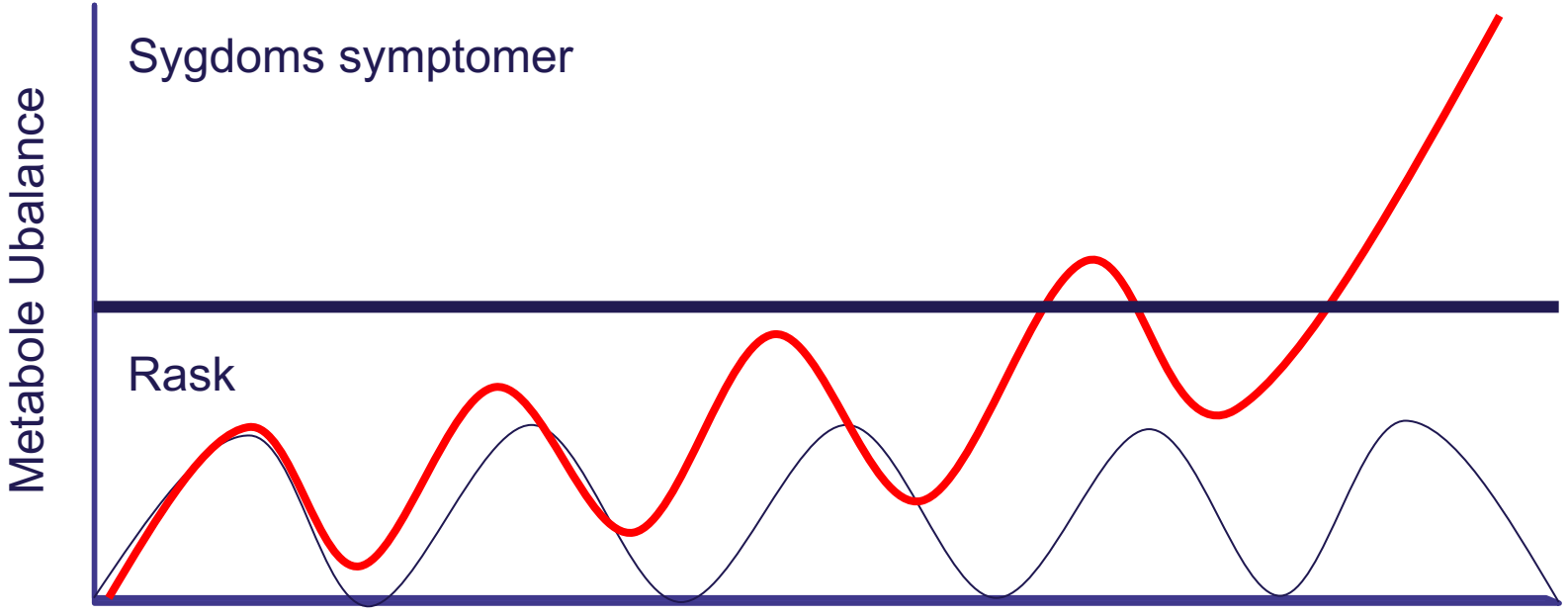
Balancen I kroppen

Fedt glukose ilt aminosyre gallesyre nukleinsyre

Antioxidanten hormonen mikrobiota immun forsvar ……




Metabole Ubalance
Sygdoms symptomer
Rask

Hvordan udvikler og frem skrider sygdommen sig?

- Ikke en enkelt ting/event kan få dig til at blive syg
- Forskellige biologiske mekanismen spiller sammen
- Stress, immun forsvar, tarm flora, hvad du spiser…..
- Hvad kan du gøre?

Diæt forslag udarbejdet af Umahro Cadogan
Pesco-vegetarisk og Mediterran-inspireret diæt

- Lavt indhold af mættet fedt (<5 % i alt kCal)
- Moderat enkelt- og flerumættede fedtstoffer (fisk, skaldyr, nødder, frø, mandler, rogn, kolduddrivningspressede vegetabilske olier)
- Højt indhold af omega-3 fedtsyrer (2,3-3 g/dag, både alfa-linolensyre, EPA, DPA og DHA)
- Tilstrækkeligt protein (1,2 gr/kg kropsvægt)
- Moderat indhold af kulhydrater fra uraffinerede kilder
- Mindst 600 gr grøntsager, bær, frugter og krydderurter på daglig basis
- Lavt tilsat sukker brug "naturlige" sødestoffer honning, ahornsirup osv.
- Udelade kunstige sødestoffer bortset fra stevia
- Lavt indhold af salt 5-6 g/dag
- Energiindtaget tilpasses den enkelte efter vægt
- Lavt til moderat koffeinindhold (5 kop kaffe eller 10 cup te /dag)
- Ingen eller meget lidt alkohol

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https://umahrouniverse.com

Diæt forslag udarbejdet af Umahro Cadogan

Specifikke fødevarer til at inkludere på daglig basis	Fødevarer, der skal udelukkes	Proteinkilder det kan inkluderes	Fedtkilder det kan inkluderes
-- Vegetariske omega-3 fedtsyrekilder (hørfrø, hørfrøolie, chiafrø, valnødder, valnøddeolie, afskallede hampefrø, hampefrøolie, koldpresset rapsolie, grønne bladgrøntsager, insekter **- Fordannet EPA og DHA dagligt fra fisk og rogn** **- Kakao i form af virkelig mørk chokolade (mindst 70 % kakao), rent kakaopulver og kakaonibs** **- "Frugt-grøntsager" såsom avocado, peberfrugt, rød peber og tomater** **- 600 gr. grøntsager, bær, frugter og krydderurter inklusive ovenstående** **- bælgplanter (linser)**	- Rødt kød - Fedtrige udskæringer af fjerkræ Mejeriprodukter (eller i det mindste alt andet end mejeriprodukter med meget lavt fedtindhold 0,7 % i mejeriprodukter og 18 % i ost) - Kokosolie - Palmeolie - Raffinerede vegetabilske olier og fedtstoffer - Transfedt af enhver art - Spæk (svinefedt) - Friturestegte fødevarer - Fastfood - Æg (men små mængder kan bruges til i opskrifter, så længe vi holder SAFA-indholdet på mindre end 5 % af det samlede kCal) - Fødevarer, der indeholder raffineret sukker	- Fisk eller rogn - Skaldyr - Magert fjerkræ (kyllingebryst uden hud, kalkun) - Tofu - Tempeh - bælgplanter - Sojabønne, linser, ærter og kikærtepastaer - Valleproteinpulver - Kaseinproteinpulver - Risproteinpulver - Ærteproteinpulver - Nødder, mandler og frø - Æggehvider	- Ekstra jomfru oliven olie - Uddrivningskoldpressede vegetabilske olier bortset fra ekstra jomfru olivenolie (NB: Ikke kokosolie, palmeolie og palmekerneolie) - Mandler, nødder, frø og kerner - Avocado - Fisk og skaldyr

Konklusion

- Nedsæt glukose metabolisme og opreguleret lipid metabolisme spiller en rolle i forskellige hjerne sygdommen
- Data fra vores og andres forskningsgrupper indikerer at nedregulering af lipid metabolisme spiller en vigtige rolle og er et mål til at behandle sygdommen
- Hvis man spise en tilpasset sund diæt kan man hjælpe med at forbygge sygdomme og muligvis nedregulere sygdommens fremskridt
- Prøve at undgå stress og spis sund
- Stadig flere studier er nødvendig for at forbedre behandlinger og få det store overblik

Hvad så nu?

- Forbedre medicin til behandling af Hjerne sygdomme
- Skal man give medicin resten af patientens liv eller kan kroppen tage over efter nogen behandlings tid
- Er det muligt at forbedre resultatet?

Samarbejde

Samarbejdspartner:

- AAU
  - Michael Trabjerg
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- DNAsense
  - Mads Søndergaard
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- NKI
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  - Colin Pritchard
  - Lona John Kroese

Støtte:

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- Louis-Hansen Foundation
- Gangsted Foundation
- Aalborg University
- Juchum Foundation
- Speciallæge Heinrich Kopps Legat
- Svend Andersen fonden

Tak

- 2N Pharma
- Meta-IQ
- DNAsense

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TAK FOR JERES OPMÆRKSOMHED

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References

Blocking carnitine palmitoyl transferase 1 in a chronic rotenone Parkinson mouse model ameliorate clinical symptoms. Michael Sloth Trabjerg, Dennis Christian Andersen, Kasper Mørk, Marie-Louise Nibelius Skjønnemand, Michal K. Oklinski, Anne Skøttrup Mørkholt, Lona J. Kroese, Colin E.J. Pritchard, Ivo J. Huijbers, Cecillie Fjord Mørre Pedersen, John Dirk Nieland. Accepted npj parkinson's disease 2022. Impact factor 9,014

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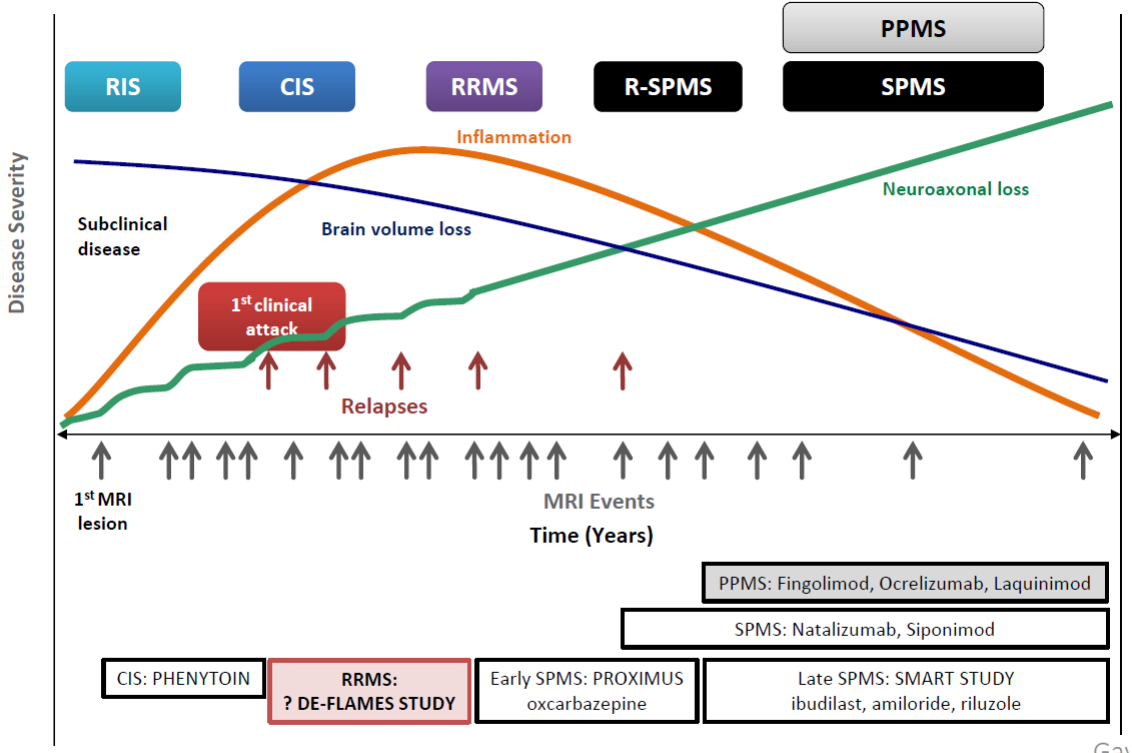
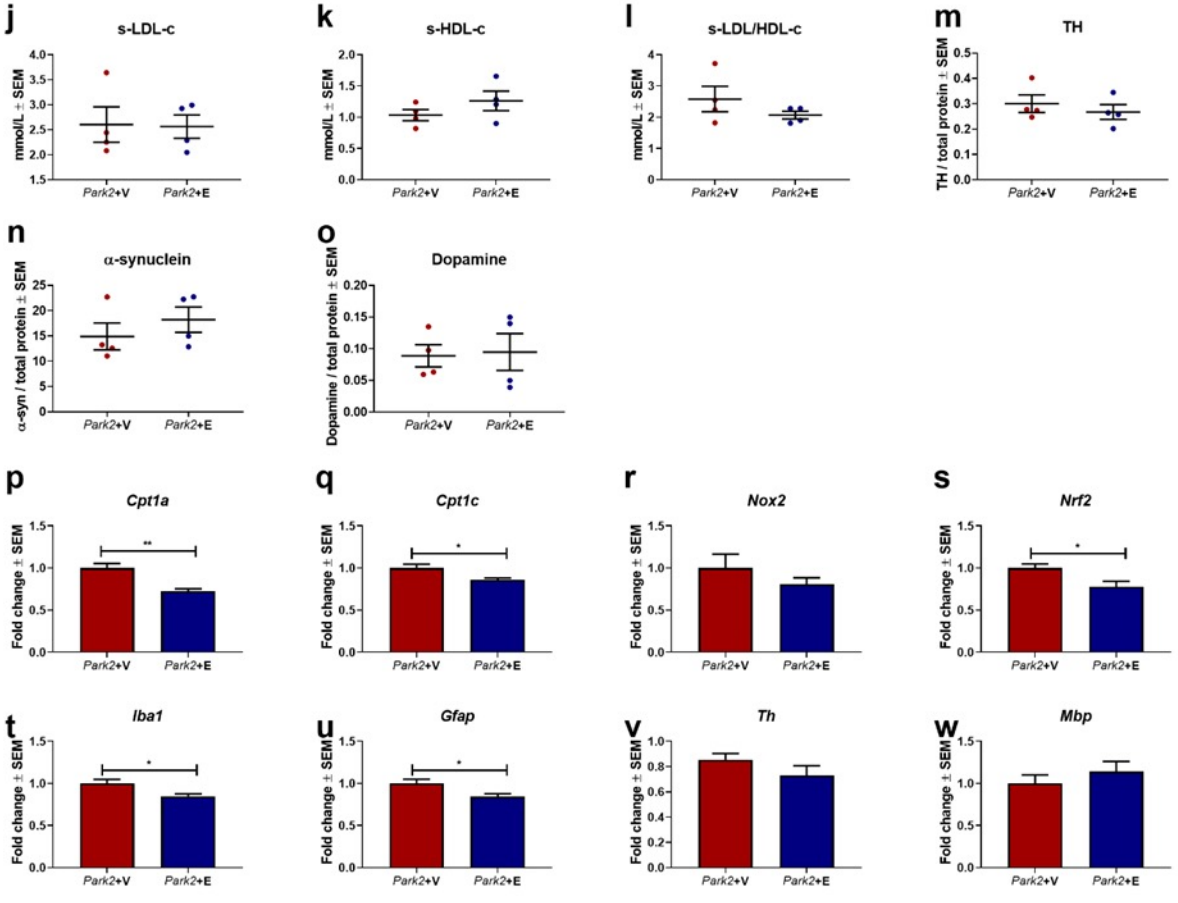
Progression and Inflammation do not correlate



RIS = radiologically isolated syndrome; CIS = clinically isolated syndrome, RRMS = relapsing-remitting MS;
R-SPMS = relapsing secondary progressive MS; SPMS = secondary progressive MS; PPMS = primary progressive MS

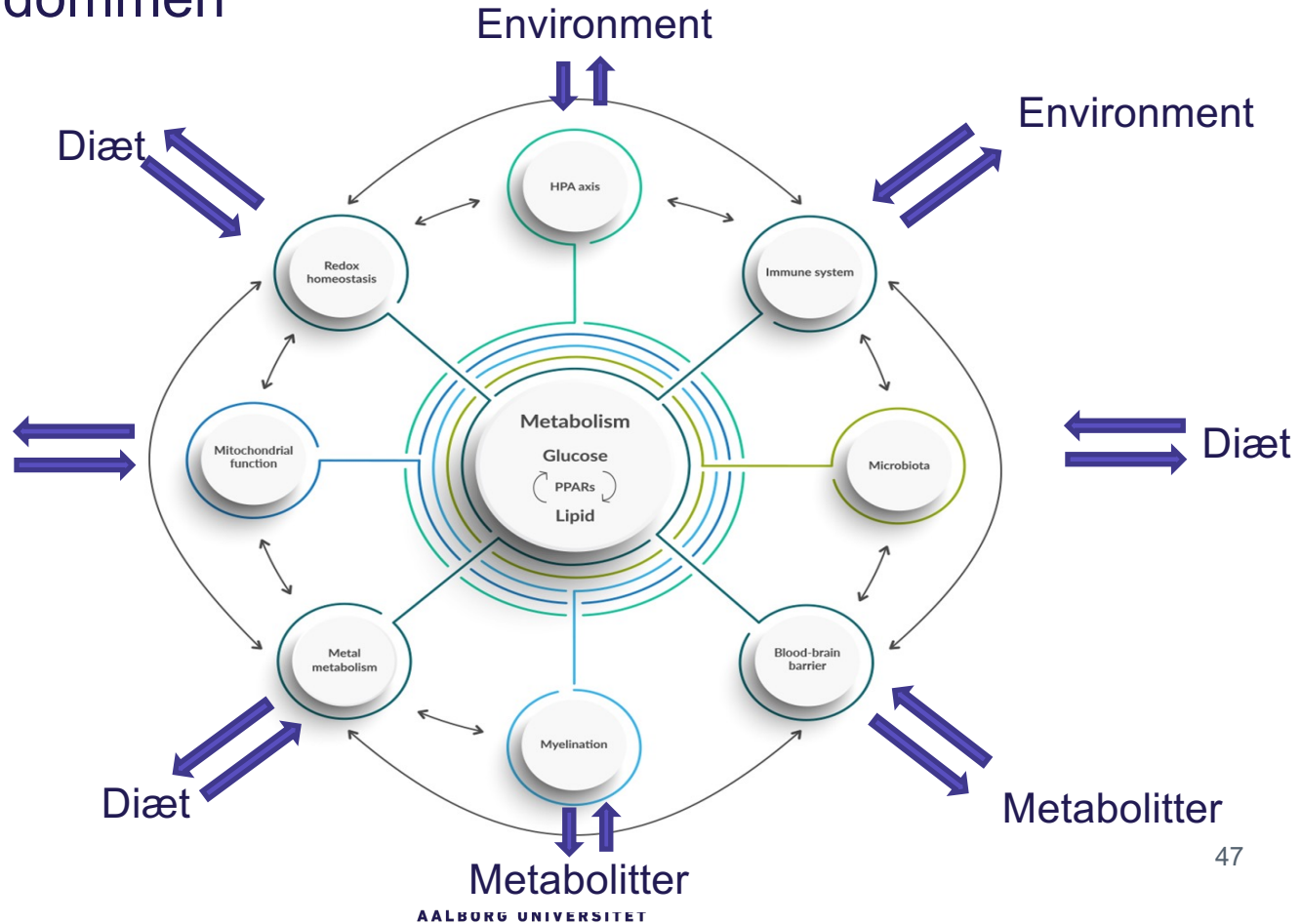
Gavin Giovannoni
Barts and The London

Parkinson's disease Park2 mouse model



Model af hjerne sygdommen
mindst 3 funktioner skal være ud af balance før men udvikler hjerne sygdommen

Genetisk er hver person forskellig derfor reagerer andeles på de forskellige stress faktorer



Parkinsons sygdom; CPT1 blokering