Mitochondrial dysfunction and redox balance alterations in the development of AD-like pathology in OXYS rats

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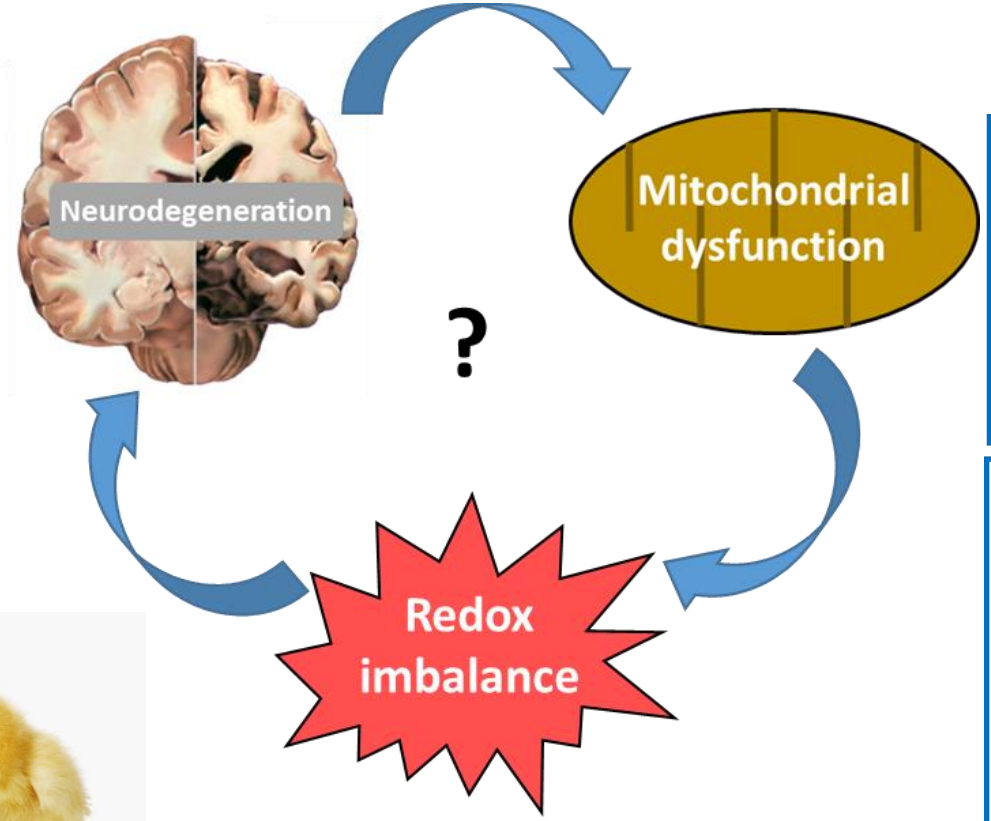
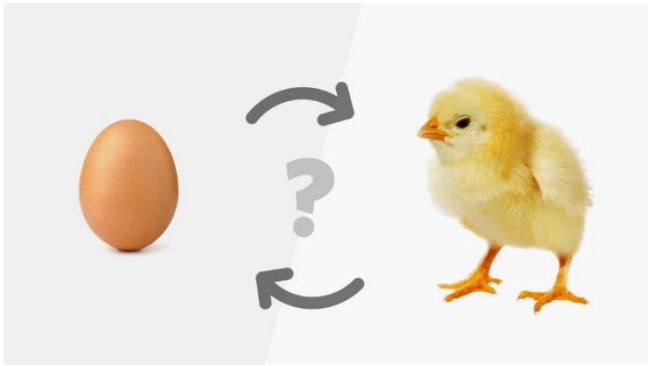
Mitochondrial dysfunction is assumed to be directly associated with oxidative stress and redox imbalance which are thought to be tightly connected to aging and thus to age-related diseases such as Alzheimer's disease

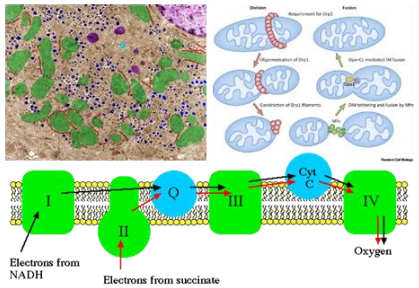
however…

Pathology timeline remains unclear





Assessing mitochondrial structure and function:
- Electron microscopy
- ELISA



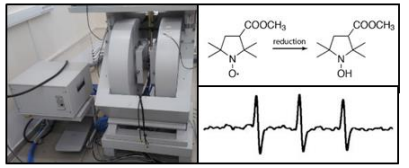
Creating genes of interest list:

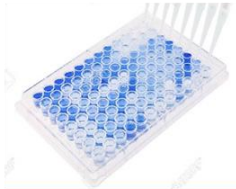
Wikipathways:
- Redox regulation
- Response to hypoxia

18 months	5 months	20 days
8.82E-103	4.43E-97	1.45E-13
6.40E-65	1.04E-67	5.74E-05
2.26E-47	2.31E-51	2.12E-13
2.41E-45	3.37E-47	2.24E-14
1.47E-37	3.28E-40	1.56E-36
3.47E-28	4.00E-34	2.99E-08
3.97E-28	1.89E-26	1.61E-43
4.18E-27	4.75E-56	6.80E-23
6.32E-27	7.32E-22	
6.33E-26	2.31E-24	1.92E-20
3.44E-25	7.17E-12	

Searching for OXYS DEGs in brain RNAseq data

Direct redox status measurement
- EPR spectroscopy
- biochemical assay





Mitochondrial dysfunction is present in OXYS rats starting from preclinical stage

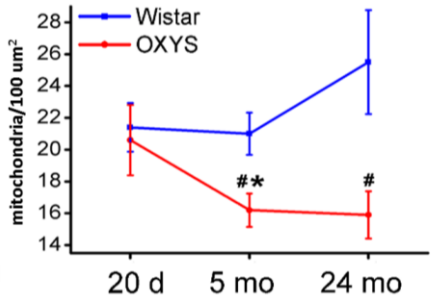
and…

OXYS brain experiences gradual activation of redox-regulating genes culminating in old age

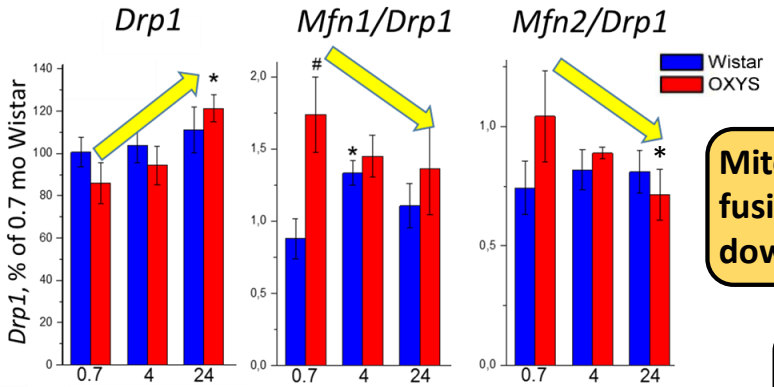
yet…

Biochemical signs of oxidative stress do not differ from control

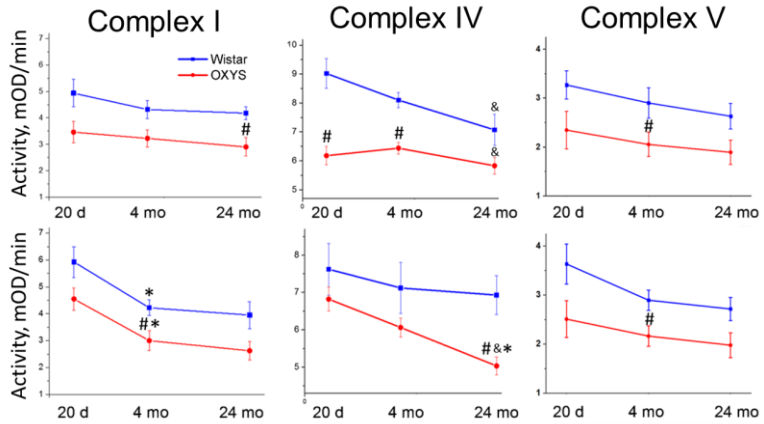
Mitochondrial quantity, by area



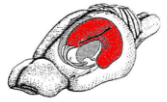
Neuronal mitochondria depleted

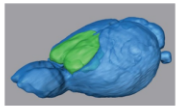


Mitochondrial fusion downregulated

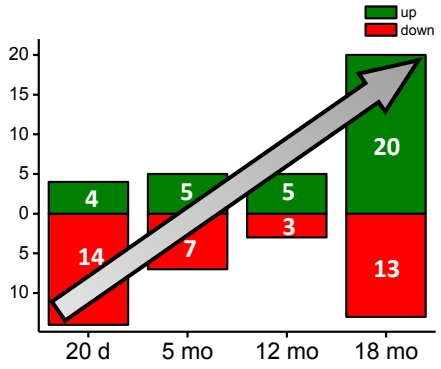


ETC activity decreased

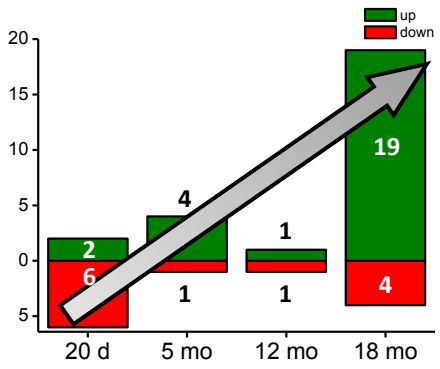

Hippocampus


Prefrontal cortex

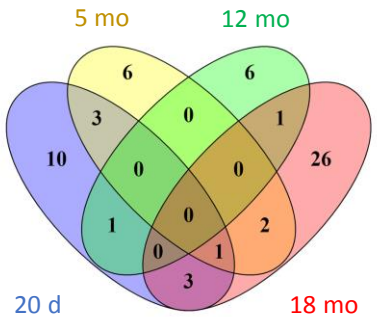
Redox-regulation



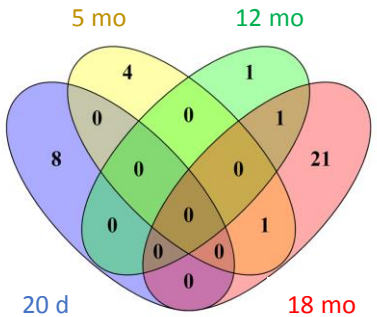
Hypoxia response



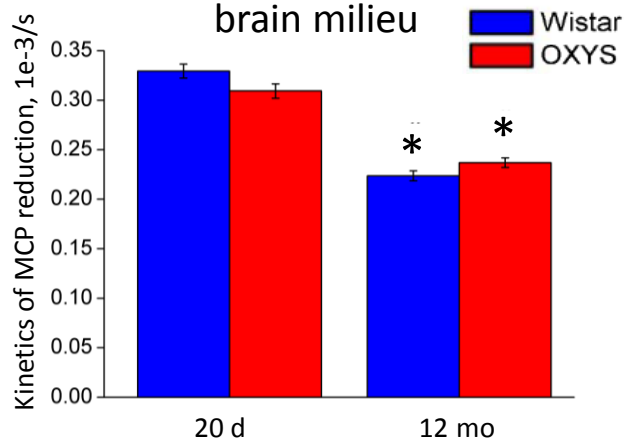
Redox-regulation



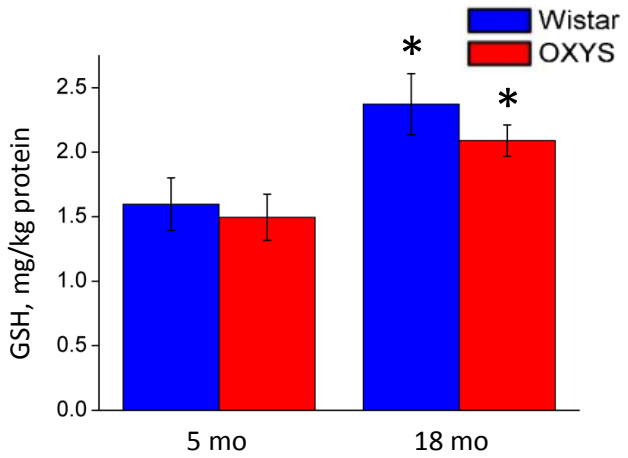
Hypoxia response



Redox status of the brain milieu



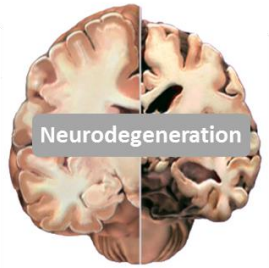
Brain GSH content



- p<0,05 interstrain difference
∗ - p<0,05 difference compared to previous age group
& - p<0,05 difference compared to 20-days-old animals of the same strain

MA Tyumentsev et al./ *Journal of Alzheimer's Disease* (2018)

<u>Mitochondrial dysfunction</u> precedes signs of Alzheimer's disease and occurs independently from <u>redox imbalance</u> which does not develop until later stages of neurodegeneration and remains moderate



Redox imbalance

Redox imbalance

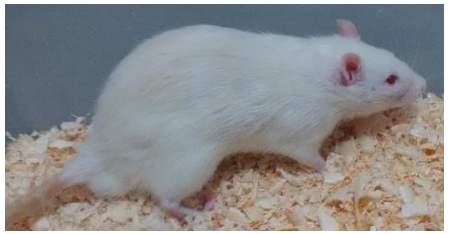
Mitochondrial dysfunction

Neurodegeneration

Mitochondrial dysfunction

20 days **5 months** **12 months** **18 months**

preclinical stage | manifestation stage | progression stage



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