Adulthood dietary choline deficiency; a risk factor for obesity, impaired glucose tolerance, cardiac pathology and subsequent Alzheimer's disease.

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Introduction

- Alzheimer's Disease (AD) is a neurodegenerative disorder marked by cognitive decline and a decrease of functional skills that currently affects 6 million Americans and is projected to increase to 15 million by 2050 [1]
- AD risk has been associated with environmental components such as **dietary nutrients** [1,2,3].
- Choline, a B-like vitamin nutrient found in common foods, is necessary for brain, muscle, and liver function[4]. [4,5,6].
- While humans can produce endogenous choline, it is not sufficient to meet bodily demands. Current recommended daily adequate intake (AI) for adults are 425mg/kg (women) and 550mg/kg (men).

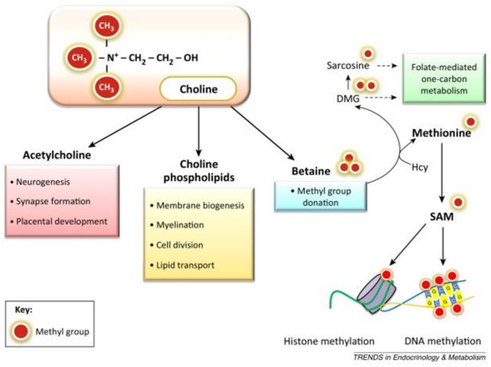


Figure 1: Choline functions, pathways, and metabolites. Image from (Jiang et al., 2014)

- Notably, a report shows that 90% of Americans are deficient in dietary choline [4].

The overall goal of this project is to determine whether choline deficiency throughout adulthood exacerbates AD pathology.

Hypothesis: *We hypothesize that a choline deficient diet (Ch-) will dysregulate peripheral body functions and exacerbate AD-like neuropathology in the 3xTg-AD mouse model of AD.*

Timeline & Methodology

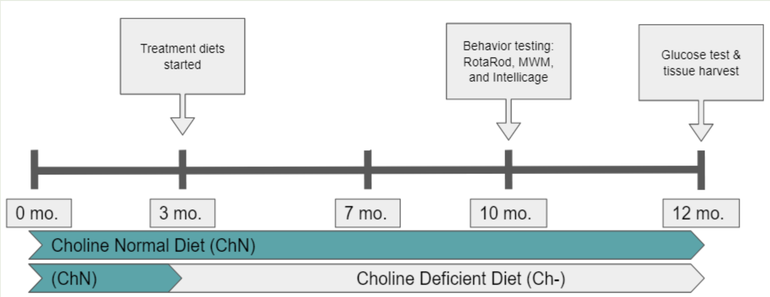


Figure 2: Experimental timeline for NonTg (control) and 3xTg-AD mice.

Diet Compositions

Formula g/Kg			
Control Diet (76A, Blue) TD.180228		Choline Deficient Diet (Adj. for Irrad.) TD.110617	
Casein	200.0	Casein	200.0
DL-Methionine	3.0	DL-Methionine	3.0
Sucrose	494.89	Sucrose	496.99
Corn Starch	150.0	Corn Starch	150.0
Corn Oil	50.0	Corn Oil	50.0
Cellulose	50.0	Cellulose	50.0
Mineral Mix, AIN-76 (170915)	35.0	Mineral Mix, AIN-76 (170915)	35.0
Vitamin Mix, AIN-76A (40077)	15.0	Vitamin Mix, AIN-76A (40077)	15.0
Choline Bitartrate	2.0	Choline Bitartrate	0.0
Ethoxyquin, antioxidant	0.01	Ethoxyquin, antioxidant	0.01

Table 1: Formula of diets used for control groups and deficient groups. Composition is nearly identical besides a slight difference in sucrose and the absence of Choline Bitartrate in the deficient diet.

Selected Nutrient Information[1]					
Control Diet (76A, Blue) TD.180228			Choline Deficient Diet (Adj. for Irrad.) TD.110617		
	% by weight	% kcal from		% by weight	% kcal from
Protein	17.7	18.8	Protein	17.7	18.7
Carbohydrate	64.9	68.8	Carbohydrate	65.1	68.9
Fat	5.2	12.4	Fat	5.2	12.4
Kcal/g: 3.8			Kcal/g: 3.8		

[1]Values are calculated from ingredient analysis or manufacturer data

Table 2: Nutrient information based upon manufacturer data by % weight and %kcal. Both diets that were utilized in this study have the same Kcal/g.

- We utilized the 3xTg-AD mouse model of AD, which develop Aβ, tau hyperphosphorylation and cognitive deficits by 9 months of age [7]. Wildtype (NonTg) mice served as controls.
- Starting at 3 months of age, NonTg and 3xTg-AD were placed on one of two diets varying in choline concentration.
- Mice were aged to 11 months and assessed for body weight, motor function, glucose metabolism, cardiac and AD-like pathology.

Figure Legend

- NonTg ChN
- NonTg Ch-
- 3xTg-AD Ch-
- 3xTg-AD ChN

Figure 4: Graph legend corresponding to the four groups in the study.

Results

The choline deficient (Ch-) diet leads to obesity in both 3xTgAD and NonTg mice.

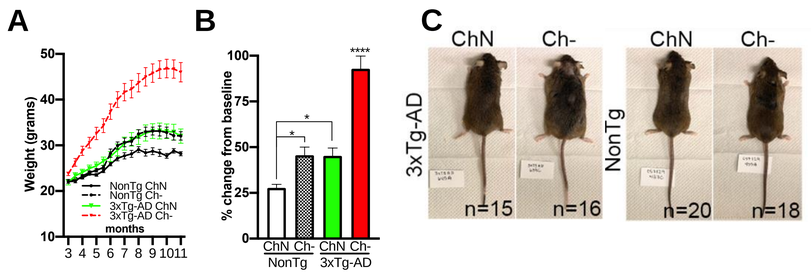


Figure 5. (A) Weight of mice as a function of months. **(B)** % weight change from baseline **(C)** Representative pictures of mice from the 4 groups. Data are means ± SE. ****p<0.0001, *p<0.05.

Figure 6: Visualization of Rotarod testing to assess motor function. Image from (Mahieu et al., 2012).

The choline deficient (Ch-) diet impair motor function and glucose metabolism in both NonTg and 3xTg-AD mice, with AD mice showing greater deficits

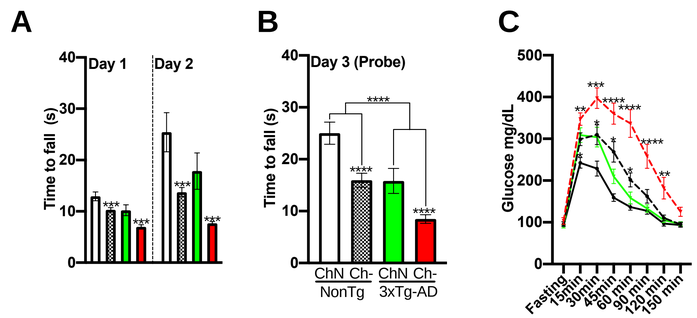


Figure 7. (A-B) Ch- mice are impaired on Day 1-2 training phases and the Day 3 probe, when the rod spins at 1rpm/sec **(C)** Glucose levels at 16hr fasting and after a 2.0g/kg glucose injection. Data are means ±SE. ****p<0.0001;***p<0.001; **p<0.01; *p<0.05.

Both 3xTg-AD diet groups and NonTg Ch- mice show increased expression of genes associated with cardiac pathology.

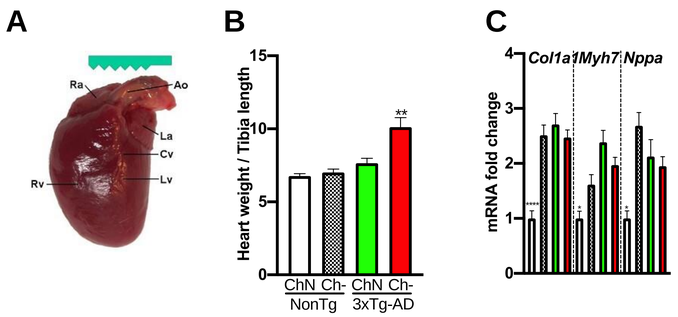
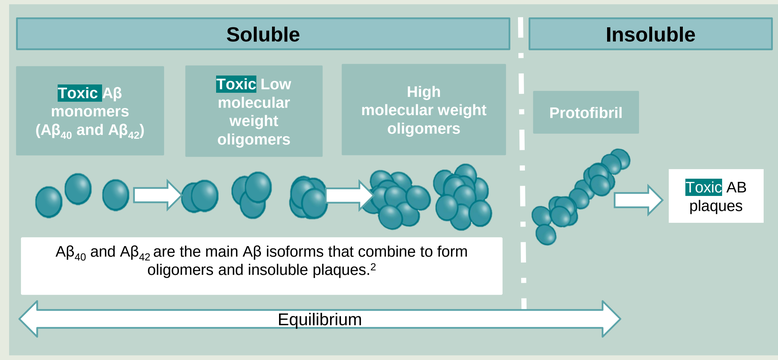


Figure 8. (A) Image of a mouse heart (Morawietz et al., 2004) **(B)** Heart weight / tibia length **(C)** Expression levels of *Col1a1, Myh7,* and *Nppa*. Data are means ± SE. ****p<0.000, **p<0.01; *p<0.05.



3xTg-AD Ch- mice show elevated levels of soluble, oligomers and insoluble Aß.

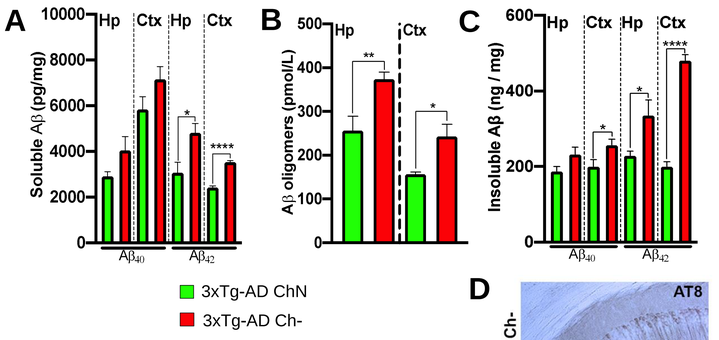


Figure 10: (A) Soluble Aß$_{40-42}$ levels in Cortex (Ctx) and Hippocampus (Hp) of 3xTg-AD mice. **(B)** Toxic soluble oligomer levels in the Hp and Ctx of 3xTg-AD mice. **(C)** Insoluble Aß$_{40-42}$ levels in the Hp and Ctx of 3xTg-AD mice. **(D)** Representative photomicrographs illustrating tau phosphorylated at Ser202/Thr205 (AT8) in the hippocampus of 3xTg-AD mice. Data are means ± SE. ****p<0.0001;**p<0.01; *p<0.05.

Conclusions

- Ch- diet increased the weight of NonTg mice to mimic a ChN AD mouse.
- Ch- diet fed mice show deficits in motor coordination and endurance.
- Ch- diet impaired glucose metabolism in both NonTg and AD mice.
- NonTg Ch- and both AD groups show elevated levels of *Col1a*, *Myh7*, *Nppa*, which are indicators of cardiac pathology.
- AD mice fed a Ch- diet had a higher amount of soluble, toxic oligomers and insoluble Aß in both the Cortex and Hippocampus.

Collectively, our data show that a choline deficient diet throughout adulthood leads to peripheral body dysfunctions and exacerbates AD-like pathology. This work suggests that simply modifying one's daily diet to include adequate choline may reduce one's risk of AD.

References

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