Effects of interventions with short-chain fatty acids on brain function and structure in obese LDLr-/-Leiden male mice

Marloes M. Hoogstad¹, Anouk C. Tengeler¹, Maaike H. G. Lamers¹, Martine C. Morrison², Robert Kleemann², Tamas Kozicz^{1,3}, Amanda J. Kiliaan¹

¹Department of Anatomy, Radboud university medical center, Centre for Medical Neuroscience, Donders Institute for Brain, Cognition and Behaviour, Preclinical Imaging Centre PRIME, Nijmegen, The Netherlands. ²Department of Metabolic Health Research, The Netherlands Organization for Applied Scientific Research (TNO), Leiden, Netherlands. ³Department of Clinical Genomics, Center For Individualized Medicine, Mayo Clinic, Rochester, MN, USA

Introduction

- Worldwide 39% of adults are overweight and 13% are obese
 - Associated with metabolic diseases, structural brain changes, cognitive dysfunction and impairment
- Gut microbiota altered by high fat diet (HFD)
 - Associated with behavioral change and cognitive dysfunction
 - Produce short-chain fatty acids (butyrate, propionate, caproic acid)

Objective

Investigate the effects of dietary interventions containing butyrate, propionate or caproic acid on HFD induced metabolic, cerebrovasculature and cognitive dysfunction

DONDERS INSTITUTE

P2.81

SCFA believed to mainly exert beneficial effects in HFD induced obesity

Material & Methods

Age (weeks)	0 1	2	3 4	- 5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	3	73	8 3	39	40	41	42) -	
Male LDLR ^{-/-} mice (N=15)													1														2	3	4										2	3	4	5		
Male LDLR ^{-/-} mice (N=15)													1														2	3	4										2	3	4	5	, e	ע כ
Male LDLR ^{-/-} mice (N=15)													1														2	3	4										2	3	4	5	crifi	
Male LDLR ^{-/-} mice (N=15)													1														2	3	4										2	3	4	5	Sa	0 a
Male LDLR ^{-/-} mice (N=15)													1														2	3	4										2	3	4	5	,	
	Birth		Wear	ning										Sta	rt H	=D														Sta	rt int	terve	ntior	าร										
Chow HFD (24% w/w)		HFD + 2 HFD + 2	2.5% pr 2.5% bu	opiona tyrate	te		HFI	D + 2.	5% cap	proic a	icid			1: Bl 2: Fe	ood s ecal sa	ample imples	es s, bloc	od pres	ssure,	blood	samp	es						3: 4:	Rota Mori	irod, c ris Wa	open f iter N	field, s 1aze	ocial	intera	ction						5	: MR	1	

Figure 1. Study design. 3 cohorts consisting of 25 male LDLr-/-Leiden male mice . Each cohort is divided into 5 smaller group). Mice in group 1 will stay on standard Chow diet, mice in group 2 will stay on HFD diet. Mice in group 3-5 will switch to an HFD enriched with propionate (2.5% wt/wt), butyrate (2.5% wt/wt) (N=15 per group). From week 3 to week 14 the mice will be fed Chow. They switch to HFD from 15 weeks until 42 weeks of age. The interventions with SCFAs will be added to the HFD when the mice are 31 weeks of age.

Preliminary Results 9,0 Butyrate *** 50 * 45 8,0 (mmol/L) 40 7,0 35 6,0 **/eight (g)** 5,0

Expected Outcomes

- Enhances cognition
- Exerts anti-inflammatory effects
- Exerts neuroprotective effects



Figure 2. Bodyweight at 30 weeks of age after 16 weeks of HFD. *N*=15 for each diet. Data are presented as mean ± SEM. No statistically significant difference was found between the HFD groups. Statistically significant difference between HFD and *Chow (p<0.000; n=15)*



Statistically significant difference between HFD and caproic acid 2.5% (p<0.016; n=5)



Figure 4. Average food intake per mouse/day. Currently week 13-15 and week 34 - 39 are n=5, week 16-21 and week 31-33 are n=10, and week 22-30 n=15. At the end of the study weeks 22-41 will be n=15.

Propionate

- Decreases food intake by stimulating leptin expression
- Causes cognitive deficits
- Decreases social interaction
- Induces abnormal motor activity

Caproic acid

Decreases body weight

Preliminary Conclusions

- Supplementation of 2,5% caproic acid to HFD increases insulin sensitivity.
- Decreased motor skills in HFD fed mice compared to chow

а.



Figure 5. Motor skills were measured with rotarod. Data are presented as mean ± SEM and statistical significanse was calculated with a student T-test.a. Distance walked. Chow-fed mice walked larger distance compared to mice on HFD (p<0.000; n=15) b. Walking speed (4-40 rpm). Chow-fed mice walked faster compared to mice on HFD (p<0.009; n=15)

Post-mortem analysis

• Brain, liver, adipose tissue, heart, aorta, intestines, femur muscle, feaces and blood

• qPCR

- Focus on neurogenesis
- Immunohistochemical stainings
 - Focus on neurogenesis

Radboud University Nijmegen



