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Moderate differences in common feeding diets change lipid composition in the hippocampal dentate gyrus and affect spatial cognitive flexibility in male rats

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ABSTRACT

There is growing evidence that lipids play a fundamental role in neuronal plasticity and learning and memory. Effects of nutrition on brain lipid composition and neuronal functioning are known, but the feeding interventions are often severe and may not reflect nutritional effects below clinical relevance. Therefore, we tested two commercially available rat feeding diets with only moderate differences in the food compositions, a standard diet (gross energy metabolizable 12.8 MJ/kg) and a energy reduced diet (gross energy metabolizable 8.9 MJ/kg) on possible effects upon dentate gyrus lipid composition, spatial learning and memory in a water maze and corticosterone release (blood serum concentrations) in adult male rats. Rats were fed with the standard diet up to an age of 8 weeks. One group was further fed with the standard and another with the energy reduced diet until an age of 5 months. We did not found differences in serum corticosterone levels. We found group differences in a variety of lipids in the hippocampal dentate gyrus.. Most of the lipid levels were lower in energy reduced diets, namely glycerophosphoethanolamines, sphingomyelins and hexosyceramides, whereas some ceramides (Cer18:0 and Cer24:1) and glycerophosphocholines (PC34:3 and PC36:2) were upregulated compared to the standard diet group. The performance in a common reference memory water maze task was not different between groups, however during reversal learning (platform in a different position) after the initial training, the standard diet fed rats learned better and spatial memory was improved compared to the energy reduced diet group. Thus, moderate differences in feeding diets have effects specifically upon spatial cognitive flexibility. Possible relations between differences in lipid composition and cognitive flexibility are discussed.

1. Introduction

Lipids play an important role in neuronal cellular signalling and plasticity that underlie mechanism of learning and memory (Saleem et al., 2013; Huston et al., 2016; Xing et al., 2016), depression and anxiety disorders (Müller et al., 2015) and dementia (Grimm et al., 2017). Feeding interventions to study the effects of nutrition on brain or peripheral lipid composition are often severe in order to induce alterations that are of clinical relevance. This involves long-lasting food restriction, high fat diet or the exclusion of essential nutrients (Boitard et al., 2014; Berrocal-Zaragoza et al., 2014; Lépinay et al., 2015; De Luca et al., 2016). Studies addressing nutrition effects below clinical relevance are rare, however may address non-pathological but significant effects of nutrition causing learning and memory modulations during everyday life.

Brain lipid compositions can affect cognitive processes negatively (Xing et al., 2016; Saleem et al., 2013; Chan et al., 2018) and positively (Huston et al., 2016). However, chronic stress, also affects the brain lipidome in a region dependent manner (Babenko et al., 2016; Oliveira et al., 2016).

Involuntary prevention of access to food causes chronic stress indicated by long-lasting elevation of corticosterone release from the adrenal glands (Han et al., 2001; Pesic et al., 2010; McDonald et al., 2014). Corticosterone easily passes the blood brain barrier and level

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increases can be measured in the brain within minutes after stress (Wang et al., 2013). Brain corticosterone affects behavior (Duclos et al., 2009) and neuronal and synaptic plasticity (Pavlides et al., 1993).

Long-lasting feeding with *ad libitum* access to a low caloric diet may prevent chronic stress. Facilitating effects in the water maze and passive avoidance performance have been found in aged rats after life-long feeding with a low caloric diet *ad libitum* (Pitsikas et al., 1990, 1991), however possible stress effects were not considered. Therefore, we tested *ad libitum* feeding of a standard and a energy reduced diet, both containing the same components but at different amounts, on stress, learning and cognitive flexibility in the water maze in adult rats.

2. Materials and methods

2.1. Subjects

Male Sprague–Dawley rats (8 weeks old), bred and maintained in the Core Unit of Biomedical Research, Division of Laboratory Animal Science and Genetics, Medical University of Vienna were used. The housing conditions and euthanasia were published previously (Maliković et al., 2018). Briefly, animals lived in the separate experimental room one week before and throughout the experiment. Rats were housed individually in standard Makrolon cages filled with autoclaved wood chips (temperature: 22 ± 2 °C; humidity: 55 ± 5%; 12 h artificial light/12 h dark cycle: light on at 7:00 a.m.). All rats were housed in the same room with cages close together, thus there was no social isolation, only a tactile but not a olfactory or acoustic isolation. Rank order interferences with learning was thereby avoided. The experiments have been according to the guidelines of the European Communities Council Directive of 24 November 1986 (86/609/EEC) and approved prospectively by The Ethics committee, Medical University of Vienna and by the Federal Ministry of Education, Science and Culture, Austria. Approval number: BMWFW-66.009/0206-WF/V/3b/2015. Animals were anaesthetized by exposition to carbon dioxide and were subsequently immediately decapitated.

2.2. Feeding regimen

All rats (n = 20) were fed with the standard diet R/M-H until they reached an age of 8 weeks. Thereafter they were separated randomly in two groups, one fed with the standard diet and one with the energy reduced diet R/M-H Ered II over 3 months *ad libitum* and then tested in the water maze. Different feeding was maintained during the water maze procedure. Both diets were from ssniff®, Soest; Germany. For the food compositions and the diet energy contents see Table 1). Tap water was available *ad libitum* during housing and training.

2.3. Water maze

The paradigm was performed according to previously described procedure with some modifications (Bezu et al., 2017). Before the training phase rats were handled 2 days for 15 min each, and thereafter habituated to the pool at the following day by a 120 s swim without platform. Training consisted of 20 trials (5 trials/day) over 4 days, followed by a 60 s probe trial 24 h later without platform. Reversal training started 24 h after the probe trial with the platform located in the opposite quadrant of that used in the learning phase. Reversal training followed the same protocol as the learning training. In case the animals did not find the platform during both phases, they were guided by hand and allowed to remain on it for 30 s. Starting positions for all trials varied pseudorandomly. Baseline performance of rats were not tested because this may cause interferences with later testing. Animals are from the same breeding colony and litters were mixed between groups.

Animals were decapitated 1 h after the last trial, the brains rapidly removed and the dentate gyrus of the hippocampal formation was dissected on a Para Cooler (RWW Medizintechnik, Hallerndorf, Germany) at 4 °C and immediately stored at −80 °C until further analysis. The lipid composition of the hippocampal dentate gyrus region was analyzed.

Table 1
Composition of the standard diet (STD) and the low energy diet (LED) according to the informations provided by the manufacturer.

Energy (MJ/kg)	STD	LED	**Fatty acids (%)**	STD	LED
Gross energy	16.3	16.6	C14:0	0.01	0.01
metabolizable	12.8	8.9	C16:0	0.47	0.54
from Carbohydrates (%)	58.0	46.0	C16:1	0.01	0.02
from fat (%)	9.0	12.0	C18:0	0.08	0.10
from protein (%)	33.0	42.0	C18.1	0.62	0.54
Cruide Nutrients (%)			C18.2	1.79	1.57
Dry matter	87.8	89.3	C18:3	0.23	0.34
Protein (Nx6.25)	19.0	16.5	C20:0	0.01	0.01
Fat	3.3	3.2	C20:1	0.02	0.01
Fibre	4.9	15.5	C20:5	–	–
Ash	6.4	7.2	C22:6	–	–
N free extracts	54.2	46.9	**Trace elements (mg/kg)**		
Starch	36.6	19.3	Iron	176	294
Sugar	4.7	4.5	Manganese	69	66
Minerals (%)			Zin	94	89
Calcium	1.00	1.10	Copper	16	17
Phosphorus	0.70	0.60	Iodine	2.2	2.1
Sodium	0.24	0.20	Selenium	0.3	0.4
Magnesium	0.23	0.25	Cobalt	0.1	2.1
Potassium	0.92	1.72			
Amino acids (%)			**Vitamins (per kg)**		
Lysine	1.10	0.80	Vitamin A	25.000 IU	15.000 IU
Methionine	0.35	0.35	Vitamin D3	1000 IU	1000 IU
Met + Cys	0.70	0.63	Vitamin E	135 mg	125 mg
Threonine	0.68	0.64	Vitamin K	20 mg	5 mg
Trypthophan	0.25	0.20	Thiamin (B1)	86 mg	17 mg
Arginine	1.16	0.89	Riboflavin (B2)	32 mg	25 mg
Histidine	0.45	0.36	Pyridoxine (B6)	32 mg	21 mg
Valine	0.90	0.83	Cobolamin (B12)	150 µg	100 µg
Isoleucin	0.78	0.69	Nicotinic acid	165 mg	123 mg
Leucine	1.33	1.21	Pantothenic acid	62 mg	45 mg
Phenylalanine	0.87	0.74	Folic acid	10 mg	8 mg
Phe + Tyr	1.47	1.18	Biotin	730 µg	715 µg
Glycine	0.82	0.75	Choline-Cholide	3.000 mg	2.900 mg
Glutamic acid	3.97	2.79	Inositol	100 mg	100 mg
Aspartic acid	1.66	1.43			
Proline	1.28	1.07			
Alanine	0.81	0.81			
Serin	0.92	0.73			

2.4. Analysis of lipids

The lipidomic analysis followed the previously published procedure (Smidak et al., 2017). Briefly, lipids were extracted by a methyl-tert-butyl ether (MTBE) protocol (Matyash et al., 2008) and analyzed on an LTQ Orbitrap Velos Pro instrument (Thermo Scientific) coupled to a Dionex Ultimate 3000 UHPLC (Thermo Scientific). Each sample was measured in positive and negative mode. The data were analyzed using SIEVE™ software (version 1.3, Thermo Scientific) with manual feature identification of the significantly changed lipids (P-Value < 0.05) as previously described (Smidak et al., 2017). The results are presented as ratio values between energy reduced and standard diet rats of peak areas averaged across the samples within one group ± SEM. Annotation of lipids was based on the Lipid MAPS shorthand nomenclature (Liebisch et al., 2013). Individual lipid species were denoted as AA X:Y representing the abbreviation of lipid molecule (AA), the total number of carbons (X) and the total number of double bonds (Y) in their acyl side chains.

2.5. Blood serum corticosterone measures

Trunk blood was collected from the same animals as used for the lipid analysis. Blood was collected in vials and allowed to coagulate for 30 min and then centrifuged for 15 min at 9000 rpm. The serum was pipetted into vials and stored at −80 °C until the assay was performed.

An enzyme-linked immunosorbent assay (ELISA) was used to measure corticosterone levels (Corticosterone ELISA by IBL Hamburg, Germany). Samples were diluted 1:5 with the standard zero of the standard curve and applied in duplicate. Sample preparation was done according to the manufacturer's instructions. OD values were measured at 450 nm in a micro plate reader (Tecan Infinite 200 pro). The assay has little interference with other steroids, thus being highly specific (Cross reactivity: corticosterone 100%, progesterone 7.4%, deoxycorticosterone 3.4%, 11-dehydrocorticosterone 1.6%, cortisol 0.3%, pregnenolone 0.3%, other steroids < 0.1%). The minimum detectable dose of corticosterone was 1.631 nmol/L and the mean intra-assay and inter-assay coefficients of variation were 3.1% and 6.01%, respectively. The analysis was done using a four parameter logistics curve. One animal from the water maze reduced diet group was excluded from the statistical comparison because of a concentration of only 0.5 ng/ml serum, which is obviously based on technical mistakes.

2.6. Statistics

Behavior during training and body weights were compared by the linear general model for repeated measures. Probe trial performance and corticosterone levels were analyzed with a one way ANOVA. One animal from the standard diet group was removed from the analyses because of blindness. Group comparisons of lipids were done by Student's t-tests.

3. Results

3.1. Behavior

We found no difference between standard and energy reduced diet fed animals in the initial learning task for the latencies to reach the platform ($F_{1,17} = 2.20$, $p = 0.156$), a significant trial effect ($F_{19,323} = 11.51$, $p < 0.001$), and no trial × diet interaction ($F_{19,323} = 0.71$, $p = 0.803$), thus both groups learned equally (Fig. 1 A). During the probe trial (Fig. 1 B) there was no difference in the percentage of time the animals of the two groups spent in the target quadrant ($F_{1,17} = 0.99$, $p = 0.334$) or the other quadrants ($p > 0.1$, each)..

In contrast, during the reversal learning there was a significant diet effect (Fig. 1C), when escape latencies were compared ($F_{1,17} = 7.10$, $p = 0.016$); a significant trial effect ($F_{19,323} = 11.63$, $p < 0.001$) and no trial × diet interaction ($F_{19,323} = 1.30$, $p = 0.182$). There was also a significant difference between groups (Fig. 1 D) in the percentage of time the animals spent in the target quadrant during the probe trial ($F_{1,17} = 7.05$, $p = 0.017$) but not the other quadrants ($p > 0.1$, each).

When swim velocities were compared we found no diet effect during learning ($F_{1,17} = 0.88$, $p = 0.361$), a significant trial effect ($F_{19,323} = 2.82$, $p < 0.001$) and no diet × trial interaction ($F_{19,323} = 1.38$, $p = 0.134$; Fig. 1 E). Similar results were obtained during reversal training, swim velocities did not differ between groups ($F_{1,17} = 0.31$, $p = 0.587$), but there was again a significant trial effect ($F_{19,323} = 2.17$, $p = 0.004$) and no diet trial interaction ($F_{19,323} = 0.65$, $p = 0.863$; Fig. 1 F).

3.2. Body weight and food consumption

The body weight before the water maze experiments (Fig. 2 A) differed significantly between groups ($F_{1,38} = 23.32$, $p < 0.001$), with a significant time effect ($F_{24,912} = 471.42$, $p < 0.001$) and an diet × time interaction ($F_{24,912} = 7.90$, $p < 0.001$), this difference (Fig. 2 B) remained during the experiment ($F_{1,17} = 30.27$, $p < 0.001$). However, animals fed with the standard diet lost significantly more body weight (Fig. 2 C) as compared to rats with the energy reduced diet ($F_{1,17} = 13.02$, $p = 0.002$) during the water maze training.

3.3. Corticosterone

There was no significant difference in blood serum corticosterone levels between groups ($t = 0.64$, $df = 16$, $p = 0.53$; Fig. 2 D).

3.4. Lipids

Table 2 lists the lipid species which are significantly (Adj. p value < 0.05) up- or down regulated when comparing rats on energy reduced diet versus rats on standard diet. Most of the significantly regulated phospholipids are downregulated in rats fed with the energy reduced diet as compared to rats fed with the standard diet, particularly phospholipids with an alkyl (ether) bond, which are presumably plasmalogens. However, the glycerophosphocholines PC34:3 and PC 36:2 are upregulated in the former. While in the realm of sphingolipids some sphingomyeline and hexosyl (either Gluc or Gal) ceramide species (Fig. 3) are also down regulated in the energy reduced diet group, unmodified ceramides without any carbohydrate or phosphocholine headgroup are up regulated on the contrary.

4. Discussion

We found impaired reversal learning in rats fed with a diet moderately reduced in energy delivery as compared with rats fed with a standard diet, while a standard water maze reference memory. The procedure was unaffected by the different diets. Body weight was significantly reduced in the low energy diet group as compared to the standard diet group, but both groups showed a significant increase of body weight over time. Standard diet animals show a higher loss of body weight during the water maze training as compared to the energy reduced diet group.

A possible effect of this difference in the loss of body weights upon behavioral performance or brain lipid composition is difficult to verify, however unlikely. The difference is more likely to depend on a loss of body fat, which is apparently higher in the standard diet rats. Water maze training is a motor demanding task and in addition related to higher stress as indicated by increased levels of corticosterone briefly after the training (Schulz and Korz, 2010). In a previous study (Maliković et al., 2018), related to age dependent effects of these diets, control groups of young male rats did not show diet dependent differences in a less stressful spatial holeboard task. Thus, the here observed differences may be task specific. We did not found differences in corticosterone levels. Thus, differences in lipid composition between groups due to different stress can be excluded. Sphingomyelins have been found to be negatively correlated with corticosterone in the prefrontal cortex and the Lysophosphatidylcholine 20:4 positively in the hippocampus (Oliveira et al., 2016). Hippocampal levels of ceramides are increased after chronic stress in rats, whereas hippocampal Sphingomyelin levels are lowered (Babenko et al., 2016). For the present study we can exclude stress induced differences between the standard and energy reduced diet groups based on the corticosterone data. Thus, the significantly higher levels of Sphingomyelins in standard diet rats are likely related to the learning performance in the water maze. Ceramides in general seem to be related to impaired learning and memory. C22:0, C20:0 and C18:0 increases were correlated with decreased memory function in Parkinson patients (Xing et al., 2016) and increased levels of ceramides (C22:0, C24:0, C18:0) were correlated with worse verbal memory performance (Saleem et al., 2013; Parco et al., 2018). Ceramides (besides de novo synthesis) are produced from the hydrolysis of sphingomyelins by the enzyme acid sphingomyelinase (ASM). It has

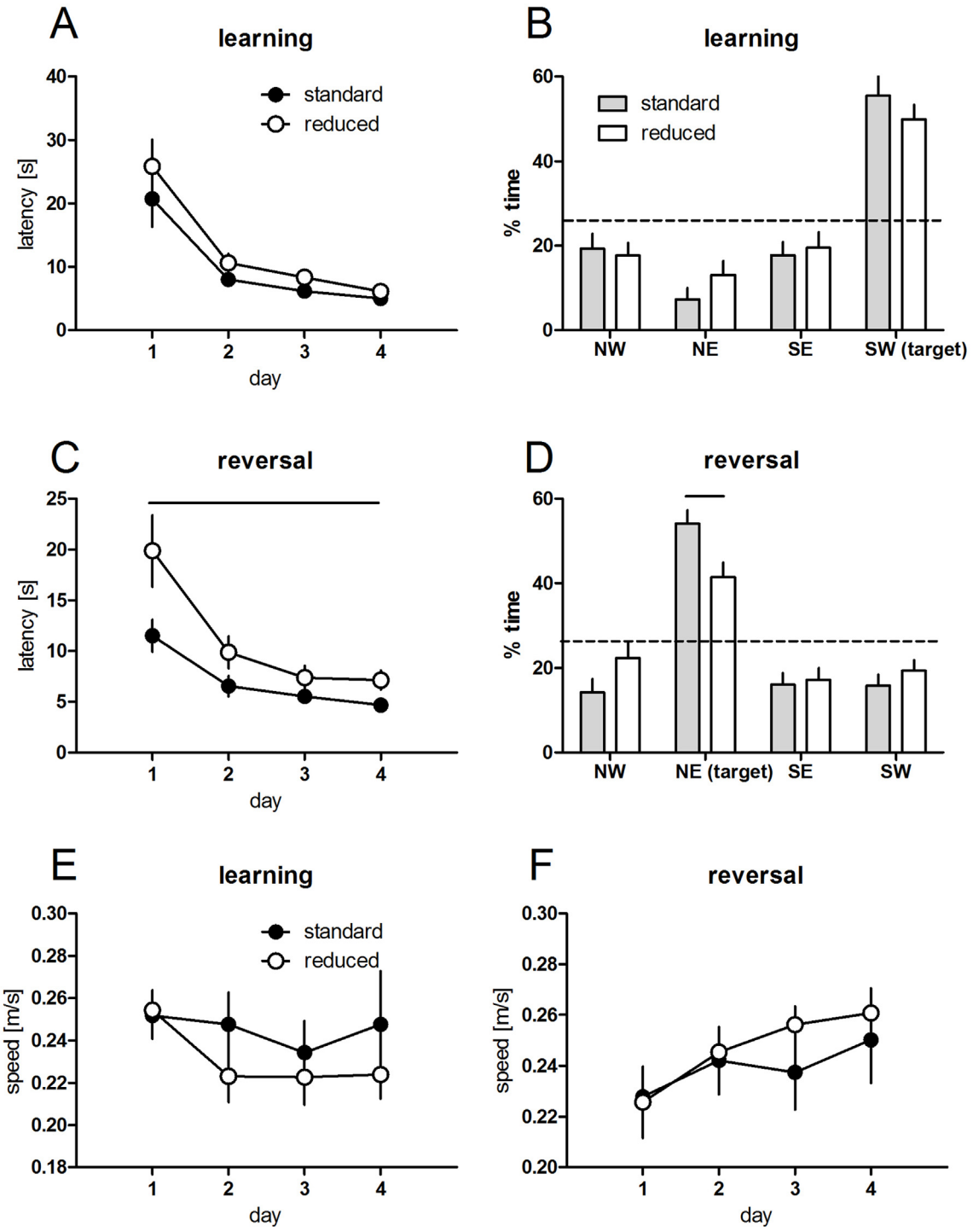

Fig. 1. Water maze performance of rats fed with the standard (n = 9) or the energy reduced (n = 10) diet. There is no difference in escape latencies over training (A) or in the probe trial (B) between the groups during learning. During the reversal training standard diet fed rats performed significantly better than energy reduced diet fed rats with lower escape latencies (C) and more time spent in the target quadrant (D). Swim velocities did not significantly differ between groups during learning (E) or reversal training (F). The mean of escape latencies and velocities of the 5 trials/day was calculated and presented. Vertical broken lines indicate the random values of time spent in the quadrants (25%) during probe trials. Vertical solid lines indicate statistically significant differences. Given are the means and standard errors of means.

been shown that a decrease in the ASM activity was inversely correlated with extinction of an operant behavioral task in rats (Huston et al., 2016). The improvement in extinction was paralleled with a decrease of ceramides in the dorsal hippocampus, whereas the amount of Sphingomyelins remained the same. Specifically, Cer16, Cer24 and Cer24:1 levels were reduced in extinction trained rats. Rapid extinction indicates effective relearning of a novel task, thus a similar mechanism indicated by the increased Cer24:1 in energy reduced diet rats may explain, at least in part, the impaired reversal learning of this group. Here, this view is additionally supported by the fact that the increase of ceramides in rats with energy reduced diet is related to a decrease of sphingomyelins, thus indicating a putative high activity of ASM.

However, other pathways are also feasible. Ceramides are considered to mediate cellular signals to induce apoptosis (Tserng and

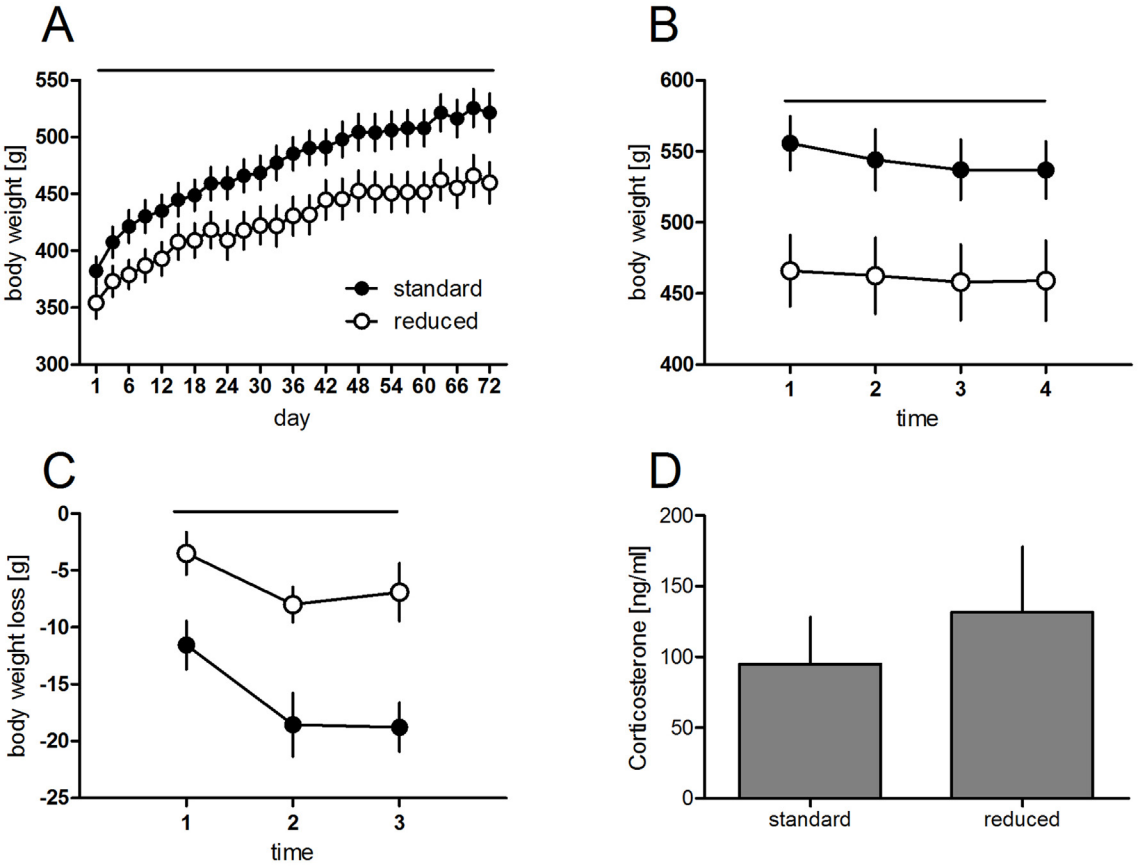

Fig. 2. Development of body weights and corticosterone levels during the experimental conditions.
The body weights were recorded during the keeping (A) and during entire water maze training (B) of standard and energy reduced diet fed rats. Loss of body weights of both groups during water maze training as percent decrease from the start day (C). Corticosterone levels of trained animals under standard and reduced diets were not statistically significant different (D). Vertical solid lines indicate statistically significant differences. Given are the means and standard errors of means.

Table 2
Statistically significantly differences in dentate gyrus lipids between rats fed with the standard (ST) and rats fed with the energy reduced (ER) diet.

Lipid MAPS classification	Lipid Molecule	Ratio ER/ST	Adjusted p-value
Glycerophosphocholines	aPC 36:3	0.535	0.0181
	aPC34:1	0.681	0.0008
	aPC36:1	0.728	0.0306
	aPC32:1	0.774	0.0267
	aPC40:1	0.857	0.0379
	PC36:1	0.754	0.0042
	PC34:3	1.116	0.0240
	PC36:2	1.334	0.0271
Glycerophosphoethanolamines	aPE38:2	0.754	0.0052
	aPE34:2	0.688	0.0149
	aPE38:3	0.855	0.0271
	PE40:4	0.666	0.0149
	PE38:4	0.802	0.0019
	PE36:1	0.264	0.0021
	PE36:2	0.518	0.0008
	PE40:6	0.842	0.0239
Ceramides	Cer18:0	1.603	0.0211
	Cer24:1	1.503	0.0123
Hexosyceramides	HexCer22:0	0.484	0.0008
	Hexcer24:2	0.629	0.0052
	HexCer20:0	0.651	0.0093
Sphingomyelins	SM18:0	0.744	0.0046
	SM20:0	0.820	0.0308
	SM24:0	0.278	0.0049

Griffin, 2004). Anacker and Hen (2017) propose an improvement of cognitive flexibility by inhibition of the overall activity of the dentate gyrus by new adult born neurons, which recruit local interneurons. Pattern separation, a fundamental feature of information processing within the dentate gyrus based on sufficient novel information to discriminate between different contexts is improved by adult neurogenesis (Sahay et al., 2011). Lipid nutrition is largely affecting neural stem/progenitor cells and neurogenesis (Knobloch et al., 2013; Sakayori et al., 2013), e.g. the sphingomyelinase/ceramide system (Gulbins et al., 2015) for which we found some significant differences between groups. New dentate gyrus cells at an age of 4 weeks or older are more likely recruited into spatial memory circuits in adult animals than existing neurons as shown in the water maze (Kee at al., 2007).

Further mechanisms for the impaired cognitive flexibility of the low energy diet group may be based on the efficiency of dentate gyrus neuronal circuits. Individual hippocampal dentate gyrus granule cells differ in a number of lipids in a resting state or after electrical stimulation, i.e. SM24:0, PE36:2 are upregulated after stimulation (Merril et al., 2017). These lipids are downregulated in our study in reduced energy diet fed rats compared to standard diet rats, which may, to a certain extent, point to less activity of specific neurons/circuits in the dentate gyrus in the former which may underlie diminished cognitive flexibility in this group. PC34:1 and PE40:6 levels were downregulated in stimulated granule cells, however upregulated in standard diet fed rats. Although the conclusions that can be drawn from these comparisons are limited, it points to a concerted regulation of different lipids with different functions in response to electrical stimulation or memory formation. Since there is no difference in memory strengths between the groups in the learning task, impaired reversal learning in the energy

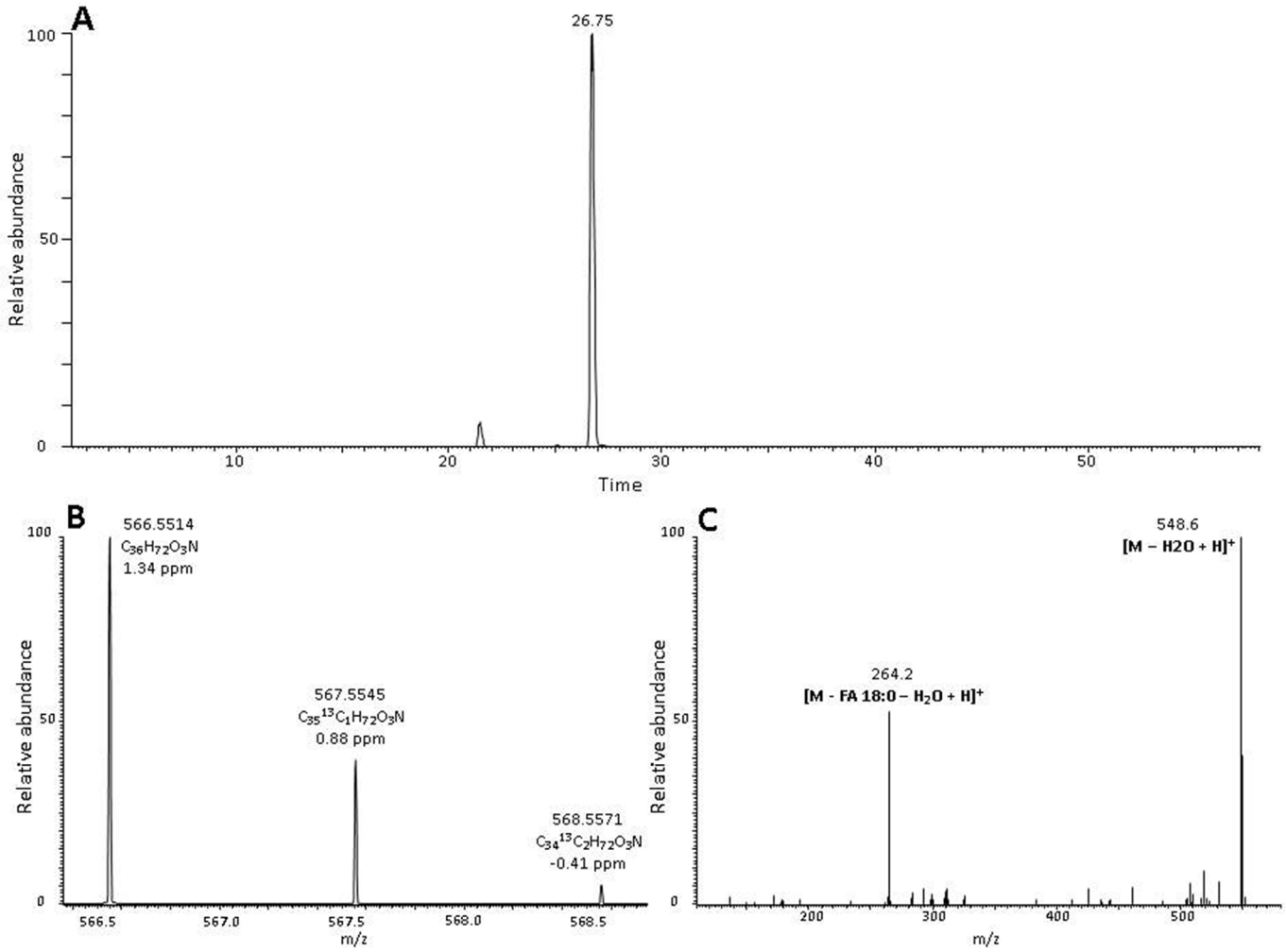

Fig. 3. Chromatogram of Cer 18:0

The upper panel (**A**) shows an extracted ion chromatogram of m/z 566.0–567.0 corresponding to the mass of Cer 18:0. In the lower left panel (**B**) the associated mass spectrum at retention time 26.75 shows the observed exact mass of Cer 18:0 at m/z 566.5514 with 1.34 ppm deviation from the theoretical mass (m/z 566.5507). The M + 1 and the M + 2 ^{13}C isotopic peaks are also well within 1 ppm mass deviation. The lower left panel (**C**) depicts the CID fragment spectrum of m/z 566.5 at 26.75 min. The fragment ions at m/z 264.2 and 548.6 are indicative for ceramides.

reduced diet group may be based on delayed extinction of the first memory trace or weaker formation of the second memory due to these differences in dentate gyrus plasticity.

Although we focused on the dentate gyrus, a hippocampal subregion involved in water maze learning, which neuronal plasticity is in turn changed in a water maze learning and memory dependent manner (Schulz and Korz, 2010), other hippocampal subregions or extra-hippocampal brain regions may also be involved and respond with a different lipid composition to the feeding regimen. However, we were able to show that a moderate difference in feeding diets that are commonly used as food for laboratory rats can cause massive and specific effects on dentate gyrus lipid composition and spatial cognitive flexibility.

Declaration of interest

None.

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