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Prolonged saturated, but not monounsaturated, high-fat feeding provokes anxiodepressive-like behaviors in female mice despite similar metabolic consequences

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ABSTRACT

Obesity significantly increases the risk for anxiety and depression. Our group has recently demonstrated a role for nucleus accumbens (NAc) pro-inflammatory nuclear factor kappa-B (NFkB) signaling in the development of anxiodepressive-like behaviors by diet-induced obesity in male mice. The NAc is a brain region involved in goal-oriented behavior and mood regulation whose functions are critical to hedonic feeding and motivation. While the incidence of depression and anxiety disorders is significantly higher in women than in men, the use of female animal models in psychiatric research remains limited. We set out to investigate the impact of chronic intake of saturated and monounsaturated high-fat diets (HFD) on energy metabolism and on anxiety- and despair-like behaviors in female mice and to ascertain the contribution of NAc NFkB-mediated inflammation herein.

Adult C57Bl6N female mice were fed either a saturated HFD, an isocaloric monounsaturated HFD or a control low-fat diet for 24 weeks, after which metabolic profiling and behavioral testing for anxiodepressive-like behaviors were conducted. Plasma was collected at time of sacrifice for quantification of leptin, inflammatory markers as well as 17 β-estradiol levels and brains were harvested to analyze NAc expression of pro-inflammatory genes and estrogen-signaling molecules. In another group of female mice placed on the saturated HFD or the control diet for 24 weeks, we performed adenoviral-mediated invalidation of the NFkB signaling pathway in the NAc prior to behavioral testing.

While both HFDs provoked obesity and metabolic impairments, only the saturated HFD triggered anxiodepressive-like behaviors and caused marked elevations in plasma estrogen. This saturated HFD-specific behavioral phenotype could not be explained by NAc inflammation alone and was unaffected by NAc invalidation of the NFkB signaling pathway. Instead, we found changes in the expression of estrogen signaling markers. Such results diverge from the inflammatory mechanisms underlying diet- and obesity-induced metabolic dysfunction and anxiodepressive-like behavior onset in male mice and call attention to the role of estrogen signaling in diet-related anxiodepressive-like phenotypes in female mice.

1. Introduction

Obesity increases the odds of depression and anxiety in both men and women (Amiri and Behnezhad, 2019; Luppino et al., 2010). Several lines of evidence link the development of depression and anxiety to features of metabolic syndrome such as visceral adiposity, poor glucose tolerance and elevated circulating levels of pro-inflammatory markers (Dunbar et al., 2008; Hamer et al., 2012; Hinnouho et al., 2017; Pierce et al., 2016; Schmitz et al., 2016). The subtype of depression related to obesity and poor cardiometabolic health is most often 'atypical depression', characterized by hyperphagia, lethargy and hypersomnia. This form of depression is, in turn, predictive of weight gain and obesity (Lasserre

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et al., 2014), thus creating a vicious circle of overeating and depressive symptomatology. In addition to a 2-fold increased diagnostic risk for depression and anxiety in women, starting at puberty (Burt and Stein, 2002; Li and Graham, 2017), the clinical presentation of depression can also be influenced by sex. For example, symptoms of increased appetite and weight gain are more commonly reported by women (Kokras and Dalla, 2017). The correlation between adiposity and depressive symptoms is stronger for women (Ul-Haq et al., 2014) and the prevalence of depression in individuals with type 2 diabetes is also especially increased in women (Anderson et al., 2001). Although less studied, female rodent models are essential to shed light on the mechanistic attributes of increasing depression and anxiety prevalence in obese women.

Obesity is characterized by a chronic state of low-grade inflammation from which the brain is not immune (Thaler et al., 2012). Pro-inflammatory signaling is enhanced in at least a subset of patients with depression and anxiety (Dowlati et al., 2010; Pierce et al., 2016), and is more strongly present in those with the atypical subtype of depression (Milaneschi et al., 2017). In addition, circulating levels of pro-inflammatory markers such as C-reactive protein are predictive of depressive symptomatology in obese individuals (Daly, 2013; Tayefi et al., 2017). Interestingly, depressive symptoms related to loss of pleasure and motivation are associated with decreased functional connectivity between the cortex and the nucleus accumbens (NAc) (Felger et al., 2016). Our group has previously shown that saturated high-fat feeding, in male mice, promotes anxiodepressive-like behaviors via recruitment of the pro-inflammatory nuclear factor kappa-B (NFkB) signaling pathway in the NAc (Décarie-Spain et al., 2018). While others have evidenced a role for the NAc in mediating the enhanced susceptibility of female mice in a stress-induced depression paradigm (Hodes et al., 2015), the relative contribution of NAc inflammation to anxiodepressive-like behaviors induced by high-fat feeding in female mice has not been addressed.

It is not always clear whether or not the association of depression to obesity derives from metabolic impairments, peripheral inflammation (Ambrósio et al., 2018) or even dietary fatty acids crossing the blood-brain barrier to directly influence neural function (Fulton and Alquier, 2019). Dietary fatty acids differentially impact cardiometabolic health, for instance, the saturated fatty acid palmitate has pro-inflammatory properties (Huang et al., 2012) that can directly impair hypothalamic function and hinder metabolism (Benoit et al., 2009). On the other hand, the monounsaturated fatty acid oleate exerts anti-inflammatory actions (Carrillo et al., 2012; Oh et al., 2009) and consumption of a Mediterranean diet, rich in oleate, is associated to improved metabolic function and lower risk for depression (García-Toro et al., 2016; Martínez-González et al., 2015; Sánchez-Villegas et al., 2013; Teres et al., 2008). We have previously demonstrated that saturated, but not monounsaturated, high-fat feeding, promotes adaptations in the reward circuitry of male rodents (Décarie-Spain et al., 2018; Hryhorczuk et al., 2015) even independently of significant weigh gain (Hryhorczuk et al, 2015, 2017a). In female mice, however, the long-term effects of such diets remain to be elucidated. Thus, we aimed to investigate the metabolic and behavioral consequences of prolonged and excessive intake of different dietary fats in female mice. In addition, as estrogen can exert neuroprotective effects (Maggioli et al., 2016; Spence et al., 2011), we set out to verify whether the association between neuroinflammation and obesity-related anxiodepressive-like behaviors was present in females and/or if changes pertaining to estrogen signaling could be observed.

2. Materials and methods

2.1. Animals and diets

All procedures involving animals were approved by the CRCHUM Animal Care Committee in accordance with the Canadian Council on Animal Care's guidelines. Females from our in-house NFkB/LacZ reporter mice colony (C57BL/6 N background) were housed (n = 2–5/cage except for food intake measurements where mice were single housed) in a reverse 12 h light-dark cycle (lights off at 10am) with *ad libitum* access to food and water. At 8 weeks of age, mice were assigned one of three custom, ingredient-matched diets (Table 1) (Hryhorczuk et al., 2015), for a duration of 24 weeks: a soybean oil-based low-fat diet (Control), a palm-oil based saturated high-fat diet (Palm) or an isocaloric olive-oil based monounsaturated high-fat diet (Olive). This diet duration was required in order to induce obesity, which is consistent with the reduced susceptibility of female rodents to diet-induced obesity (Pettersson et al., 2012).

2.2. Metabolic assessments

Food intake was measured weekly and number of grams consumed were multiplied by the caloric density of each respective diet. Final body weights were recorded at the end of the 24th week of diet, followed by fat and lean mass measures by EchoMRI. For the oral glucose tolerance test (OGTT) (cohort 1, n = 8–10/diet), 4 h-fasted mice were given a dextrose solution (2 g/kg) by oral gavage. Tail blood glucose measures were obtained 0, 15, 30, 60 and 90 min following dextrose administration using a glucometer. For the insulin tolerance test (ITT), a second cohort of mice (cohort 2, n = 8–10/diet) were fasted for 4 h prior to intraperitoneal injection of insulin. Tail blood glucose levels were monitored 0, 15, 30, 60 and 90 min post-injection using a glucometer. At the time of sacrifice, mice were anesthetized under isoflurane and quickly decapitated to harvest brain and blood. White subcutaneous and perirenal as well as brown interscapular adipose tissue depots were dissected and weighed. Plasma was extracted from blood samples and used for immunoassays to quantify circulating levels of leptin (Leptin (mouse) AlphaLISA detection kit, PerkinElmer, Woodbridge, ON, Canada), tumour necrosis-factor (TNF) (TNFa (mouse) AlphaLISA detection kit, PerkinElmer), C-reactive protein (CRP) (Mouse CRP ELISA kit, Life Diagnostics Inc, West Goshen, PA, USA) and estradiol (17β-Estradiol high sensitivity ELISA kit, Enzo Life Sciences, Farmingdale, NY, USA).

2.3. Anxiety and despair-like behavioral measures

Behavioral procedures (cohorts 1 and 2) were performed one day apart, under white light conditions and towards the end of the light phase, as described previously (Décarie-Spain et al., 2018; Hryhorczuk et al., 2017a; Sharma and Fulton, 2013). As an assessment of anxiety-like behavior, mice were placed in the centre of the elevated-plus maze (EPM) and left to explore all arms of the maze for 5 min. The proportion of time spent in the open arms of the maze was used as a read out of anxiety-like behavior and total distance travelled as an indication of overall locomotion. To evaluate behavioral despair, we used the forced swim test (FST), where mice were placed in a 2000 mL water-filled (23 ± 1 °C) glass container for 6 min. The mean velocity during the first 2 min of the test was used as an indication of swimming ability, while the proportion of time spent immobile during the remaining 4 min of the test served as a read-out of behavioural despair.

Table 1
Diets composition.

Nutrients	Control	Palm	Olive
Source of fat	Soybean oil	Palm oil	Olive oil
Fat (g/kg)	70	270	270
Casein (g/kg)	200	200	200
Sucrose (g/kg)	100	100	100
Cornstarch (g/kg)	397.5	197.5	197.5
Mineral mix (g/kg)	35	35	35
Vitamin mix (g/kg)	10	10	10
% kcal from fat	17	50	50
Total kcal/g	3.8	4.8	4.8
% palmitic acid (C16:0)	10.2	44.5	10.512
% oleic acid (C18:1)	22.7	39.4	77
% saturated fat	15	51.1	17.1
% monounsaturated fat	23.4	38.8	72.3

2.4. Quantitative PCR

At time of sacrifice, brains were snap-frozen in isopentane and 250 μm coronal sections were obtained with a cryostat. RNA was extracted from NAc microdissections using TRIzol (Invitrogen, Carlsbad, CA, USA) and cDNA was synthetized from 700 ng of total RNA with random hexamers and the M-MLV Reverse Transcriptase (Invitrogen), as described previously (Décarie-Spain et al., 2018). Rotor Gene SYBR Green PCR kits (Qiagen) were employed for real-time PCR. Primers (Table 2) were designed via BLAST (U.S. National Library of Medicine) and synthetized by Integrated DNA Technologies (Coralville, IA, USA). Gene copies were extrapolated from standard curves and absolute values for each gene of interest were normalized to the absolute values for the housekeeping gene found to be the most stable across diet conditions; cyclophilin (Cyclo) for the cohort used to measure pro-inflammatory makers (cohort 1, n = 8–10/diet) and beta-actin (*Bactin*) for the cohort in which expression of genes related to estrogen signaling was measured (cohort 2, n = 8–10/diet). For aromatase gene expression, gene copies for CYP2S1 and CYP4X1, the two most expressed isoforms in the female rodent brain (Stamou et al., 2014), were combined and normalized to Bactin. Values for each group are expressed as fold change relative to Control (1.0).

2.5. Beta-galactosidase histochemistry

Following a lethal injection of pentobarbital (intraperitoneal; ip), a transcardiac perfusion of phosphate buffered saline (PBS) followed by formalin was performed on a third cohort of mice (cohort 3, n = 4/diet). Brains were placed in formalin for 6 h and then in a 30% sucrose solution for 24 h. Coronal sections of 25 μm were obtained using a microtome (Leica SM2000R). Staining against beta-galactosidase (βgal) was performed as previously described (Décarie-Spain et al., 2018). Briefly, sections were washed in PBS, blocked for 2 h in a 3% normal goat serum solution, permeabilized with Tween and incubated overnight with a polyclonal chicken βgal antibody (Ab9361, 1:1000; Abcam, Cambridge, UK) at 4 °C. The next day, sections were washed in PBS, incubated with an Alexa Fluor® 568-conjugated goat anti-chicken IgG antibody (Abcam, 1:1000), mounted on microscope slides with a DAPI mounting media (Vectashield, Vector Labs, Burlingham, CA, USA) and visualized on the fluorescent microscope (Zeiss AxioImager.M2 ApoTome.2). βgal-labeled cells within the NAc (core and shell combined) were quantified from coronal slices (anterior/posterior coordinates relative to bregma ranging from +1.42 mm to +0.845 mm; n = 4/diet) using the "analyze particles" function of ImageJ (Schneider et al., 2012).

2.6. Viral-mediated inhibition of NFkB signaling

The NFkB signaling pathway was inhibited via NAc infusion of an adenoviral construct (serotype 5) containing the coding sequence for a dominant negative mutation of the inhibitor of kappa-B kinase (IKK) beta subunit under the control of a cytomegalovirus promoter, an approach previously validated (Décarie-Spain et al., 2018). Briefly, after 20 weeks on diets, female mice were placed into a mouse ultraprecise stereotaxic instrument (Kopf, Inc.) for bilateral delivery (0.5μL/side; 3.0×10^7 PFU/side) of either the adenoviral construct for the dominant negative mutation of IKK (Ad^{IKKdn}) or green fluorescent protein (Ad^{GFP}) into the NAc (AP:+1.7 mm, ML:±1.1 mm, DV: 4.5 mm, relative to bregma and skull surface) using a 0.5 μL Neurosyringe (Hamilton, Reno, NV, USA). Mice were maintained on their respective diets for 4 additional weeks following surgery to allow recovery and viral recombination prior to behavioral testing in our 4 experimental groups: $Control^{GFP}$, $Control^{IKKdn}$, $Palm^{GFP}$ and $Palm^{IKKdn}$ (n = 6–9/group).

Table 2
Primers sequences.

Gene	Forward	Reverse
Cyclo	GCTTTTCGCCGCTTGCTGCA	TGCAAACAGCTCGAAGGAGACGC
Gfap	AACGACTATCGCCGCCAACTG	CTCTTCCTGTTCGCGCATTTG
Iba1	GGATTTGCAGGGAGGAAAAG	TGGGATCATCGAGGAATTG
Ifng	AAGTTTGAGGTCAACAACCCAC	AATCTCTTCCCCACCCCGAA
Mhc-i	GTGATCTCTGGCTGTGAAGT	GTCTCCACAAGCTCCATGTC
Mhc-ii	CAACCGTGACTATTCCTTCC	CCACAGTCTCTGTCAGCTC
Cd45	TGAGCACAACAGAGAATGCCC	AACACACCTGGATGATATGTGGT
Cd11b	CCCAGAACCTCTCAAGTGCC	CTGCAACAGAGCAGTTCAGC
Era	AGCAAGCCCCGATGGA	GAGATGCCTGGGATGCTCTT
Erb	CTATATCTGTCCAGCCACGAATC	CCACACTTGACCATTCCTACTT
Cyp2s1	TCGGGGCTTTTGCGGCTAAGT	CAACCAGGACCACCACGCGG
Cyp4x1	CACCCTTGTGCCTTCCCCTGC	CCTCGTCCAATGCATGGAGTCAGG

2.7. Statistical analyses

Data were analysed using the GraphPad Prism 9 software and results are presented as mean ± standard error of the mean (SEM). A one-way ANOVA with Bonferonni post-hoc was employed to compare the 3 diet conditions, except when the distribution was non-Gaussian, in which case a Kruskal Wallis test with Dunn post-hoc was performed. A two-way ANOVA, repeated measures, with Bonferonni post-hoc, as well, was used to assess the impact of diet across time in the OGTT and ITT. In addition, a two-way ANOVA with Bonferonni post-hoc was employed to analyze the impact of viral-mediated inhibition of NFkB signaling in animals fed the Control or Palm diets. Criterion for significance was set to $p < 0.05$ for all comparisons.

3. Results

3.1. Prolonged saturated and monounsaturated high-fat feeding favor adipose accumulation and metabolic impairments

Our first aim was to investigate the impact of high-fat feeding and the differential effects of dietary fats on parameters of energy balance in female mice. While there was an overall treatment effect of diets on caloric intake ($F_{(2, 14)} = 5.044$, $p = 0.0224$), the average caloric intake relative to the Control condition was only significantly greater in the Palm ($t_{(14)} = 2.937$, $p = 0.0325$) and not the Olive ($t_{(14)} = 2.464$, $p = 0.0819$) HFD group (Fig. 1A). Body weight was also influenced by diet condition ($F_{(2, 49)} = 23.98$, $p < 0.0001$), with higher values relative to Control-fed animals in both the Palm ($t_{(49)} = 6.254$, $p < 0.0001$) and Olive ($t_{(49)} = 5.540$, $p < 0.0001$) HFD groups (Fig. 1B). Diets did not impact lean mass ($F_{(2, 30)} = 0.7897$, $p = 0.4632$) (Fig. 1C), but had an impact on fat mass ($F_{(2, 30)} = 20.63$, $p < 0.0001$) with enhanced adiposity relative to Controls in both the Palm ($t_{(30)} = 5978$, $p < 0.0001$) and Olive ($t_{(30)} = 4.638$, $p = 0.0002$) conditions (Fig. 1D). Concurrently, circulating levels of leptin varied across diet conditions ($H_{(2, 20)} = 12.38$, $p = 0.0021$) as levels were increased with the Palm ($z_{(20)} = 3.391$, $p = 0.0021$) and Olive ($z_{(20)} = 2.457$, $p = 0.04$) diet relative to the Control group (Fig. 1E). The diet condition influenced the mass of subcutaneous ($H_{(2, 30)} = 20.46$, $p < 0.0001$), visceral ($H_{(2, 30)} = 17.78$, $p = 0.0001$) and brown ($H_{(2, 30)} = 14.57$, $p = 0.0007$) adipose tissue depositions with the mass of all depositions increased in both the Palm (subcutaneous $z_{(30)} = 3.965$, $p = 0.0002$; visceral $z_{(30)} = 3.612$, $p = 0.0009$; brown $z_{(30)} = 2.720$, $p = 0.0196$) and Olive (subcutaneous $z_{(30)} = 3.548$, $p = 0.0012$; visceral $z_{(30)} = 3.411$, $p = 0.0019$; brown $z_{(30)} = 3.525$, $p = 0.0013$) conditions (Fig. 1F). There was an overall diet effect on plasma concentrations of estradiol ($F_{(2, 16)} = 4.761$, $p = 0.0239$), with only the Palm group showing greater values relative to Control $t_{(16)} = 2.994$, $p = 0.0258$) and a trend for an increase relative to the Olive ($t_{(16)} = 2.353$, $p = 0.0951$) condition (Fig. 1G). However, plasma TNF was unchanged by diet ($F_{(2, 19)} = 1.650$, $p = 0.2184$) (Fig. 1H) and while the CRP marker levels were influenced by diet ($H_{(2, 32)} = 7.966$, $p = 0.0186$), plasma concentrations were only elevated relative to Control in the Olive ($z_{(32)} = 2.607$, $p = 0.0274$) condition (Fig. 1I). Nonetheless, the OGTT revealed an interaction effect between time and diet ($F_{(8, 100)} = 2.287$, $p = 0.0272$), with blood glucose levels

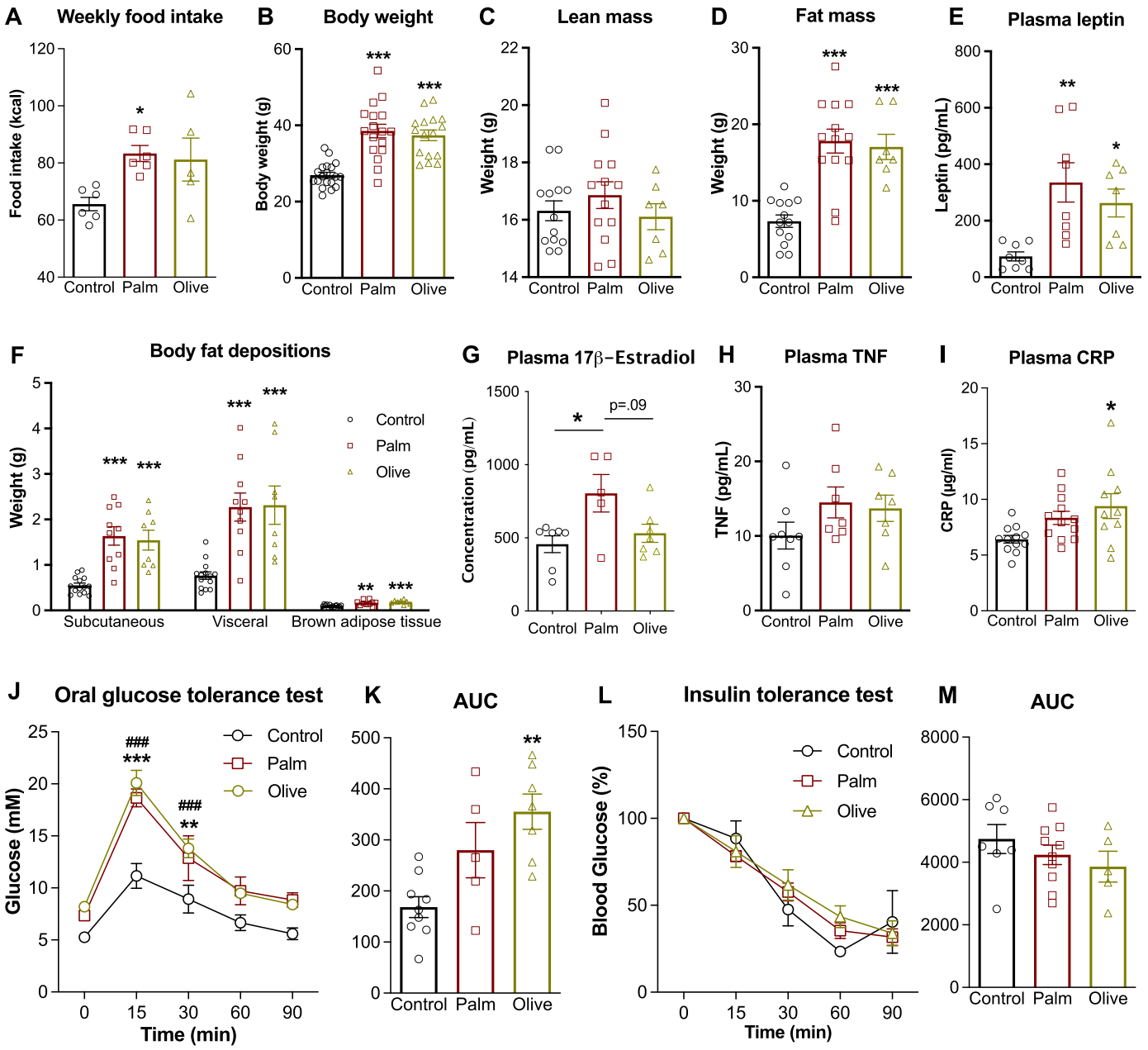

Fig. 1. Both saturated and monounsaturated high-fat feeding promote adiposity and metabolic impairments. (A) Average weekly food intake (n = 5–6/diet), (B) final body weight (n = 16–19/diet), (C) lean and (D) fat mass (n = 7–13/diet), as well as (E) plasma leptin levels (n = 7–8/diet), (F) adipose tissue distribution (n = 7–13/diet), (G) plasma estradiol (n = 5–7/diet), (H) tumor necrosis factor (TNF) (n = 7–8/diet) and (I) C-reactive protein (CRP) (n = 10–12/diet) levels following 24 weeks of low-fat (Control), saturated (Palm) or monounsaturated (Olive) high-fat feeding. (J, K) Oral glucose tolerance test in 4 h fasted mice receiving 2 mg/kg of dextrose (n = 6–10/diet). (L, M) Insulin tolerance test in 4 h fasted mice injected with insulin (n = 6–10/diet). Data presented as mean ± SEM. One-way (A-I, K, M) and two-way (J, L) ANOVA, Bonferonni post hoc; *p < 0.05, **p < 0.01, ***p < 0.005.

higher than controls at the 15 and 30 min time points by both Palm (15 min $t_{(100)} = 5.34$, $p < 0.0001$; 30 min $t_{(100)} = 2.819$, $p = 0.0894$) and Olive (15 min $t_{(100)} = 6.678$, $p < 0.0001$; $t_{(100)} = 3.641$, $p = 0.0065$) HFDs (Fig. 1J). Analysis of the area under the curve revealed a diet effect ($F_{(2, 18)} = 9.126$, $p = 0.0018$) with values specifically enhanced by the Olive condition ($t_{(18)} = 4.220$, $p = 0.0015$) relative to controls (Fig. 1K). This impairment was not associated to any effect of the interaction between diet and time on blood glucose values ($F_{(8, 76)} = 1.306$, $p = 0.2534$) or diet on area under the curve ($F_{(2, 19)} = 1.001$, $p = 0.3862$) in the ITT (Fig. 1L and M).

3.2. Saturated, but not monounsaturated, high-fat feeding provokes anxiodepressive-like behaviors

We then sought to assess the consequences of high-fat feeding on anxiodepressive-like behaviors. Time spent in the open arms of the EPM was influenced by diet ($H_{(2, 46)} = 11.73$, $p = 0.0028$) with Palm HFD mice showing a reduction relative to both the Control ($z_{(46)} = 2.478$, $p = 0.0396$) and Olive ($z_{(46)} = 3.283$, $p = 0.0031$) groups (Fig. 2A). Diet condition had no impact on locomotor activity as total distance travelled did not vary across groups ($F_{(2, 46)} = 0.2765$, $p = 0.7597$) (Fig. 2B). Similarly, a diet effect was observed for immobility time in the FST ($F_{(2,}$

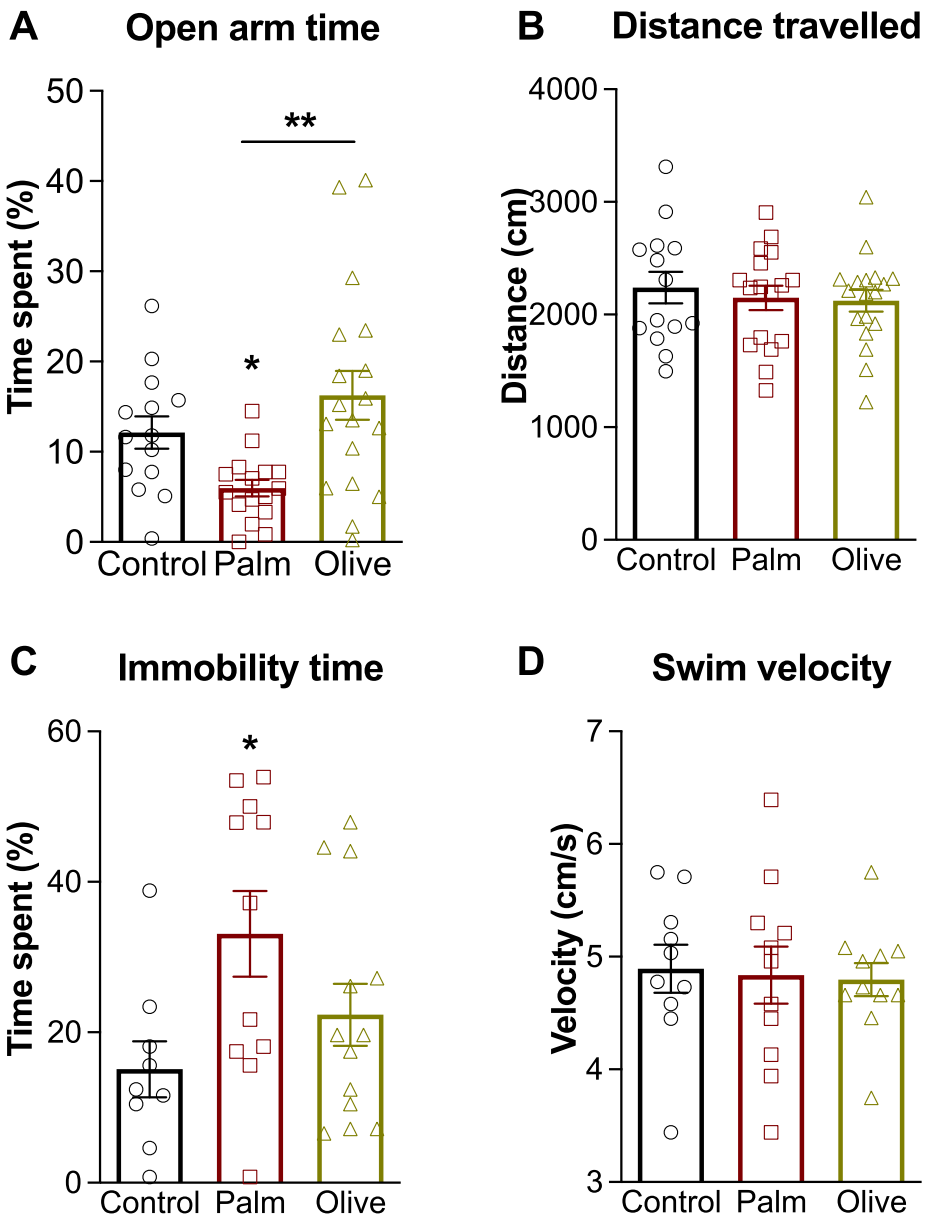

Fig. 2. Saturated, but not monounsaturated, high-fat feeding promotes anxiodepressive-like behaviors. (A) Time spent in the open arms and (B) total distance travelled in the elevated-plus maze (n = 14–18/diet). (C) Time spent immobile and (D) swim velocity during the first 2 min of the forced swim test (n = 10–11/diet). Data presented as mean ± SEM. One-way ANOVA, Bonferonni post hoc; *p < 0.05, **p < 0.01.

$_{30)}$ = 3.462, p = 0.0444) with increased immobility time in the Palm group relative to controls ($t_{(30)}$ = 2.587, p = 0.0443) (Fig. 2C). This was not attributable to locomotion as average swim velocity was not influenced by diet ($F_{(2, 29)}$ = 0.05203, p = 0.9494) (Fig. 2D).

3.3. Saturated and monounsaturated differentially impact the expression of nucleus accumbens genes affecting estrogen signaling

Our next step was to ascertain if anxiodepressive-like behaviors elicited by the palm HFD were associated with markers of inflammation and estrogen signaling in NAc microdissections (Fig. 3A). We measured gene expression levels of glial fibrillary acidic protein (*Gfap*) and ionized calcium binding adaptor molecule-1 (*Iba1*), markers of astrocytes and microglia respectively, the pro-inflammatory cytokine interferon gamma (*Ifng*), major histocompatibility complex-1 (*Mhc-i*) and 2 (*Mhc-ii*) involved in antigen response, the myeloid cell marker *Cd45* and the monocyte marker *Cd11b*. While diet condition had no impact on *Cyclo* (reference gene) ($F_{(2, 21)}$ = 0.3375, p = 0.7173), *Gfap* ($F_{(2, 21)}$ = 0.3056, p = 0.7399), *Iba1* ($F_{(2, 21)}$ = 0.9032, p = 0.4204), *Mhc-i* ($F_{(2, 20)}$ = 1.417, p = 0.2659) and *Cd11b* ($F_{(2, 21)}$ = 2.121, p = 0.1448) expression levels (Fig. 3B), a main effect was found for the relative gene expression of *Ifng* ($F_{(2, 20)}$ = 5.464, p = 0.0128), *Cd45* ($F_{(2, 20)}$ = 5.444, p = 0.0130) and *Mhc-ii* ($F_{(2, 20)}$ = 7.465, p = 0.0038). NAc gene expression of *Ifng* was higher in both the Palm ($t_{(20)}$ = 2.615, p = 0.0498) and Olive ($t_{(20)}$ = 3.105, p = 0.0167) conditions compared to controls. While *Cd45* levels were only significantly increased in the Palm group ($t_{(20)}$ = 3.231, p = 0.0126), there was a trend for greater expression in the Olive group ($t_{(20)}$ = 2.291, p = 0.0989) relative to controls. In contrast, *Mhc-ii* was significantly increased by the Olive diet ($t_{(20)}$ = 3.848, p = 0.0030) and trending in the Palm group ($t_{(20)}$ = 2.352, p = 0.0871). In view of elevated estradiol levels in Palm-fed mice, we also sought to verify the markers related to estrogen signaling in the NAc (Fig. 3C). Although gene expression levels for *Bactin* (reference gene) ($F_{(2, 19)}$ = 1.527, p = 0.2427) and estrogen receptor alpha (*Era*) ($F_{(2, 19)}$ = 0.5142, p = 0.6061) did not vary across diet conditions, a main effect was found for estrogen receptor beta (*Erb*) expression ($H_{(2, 20)}$ = 11.07), p = 0.0013). In fact, the Olive

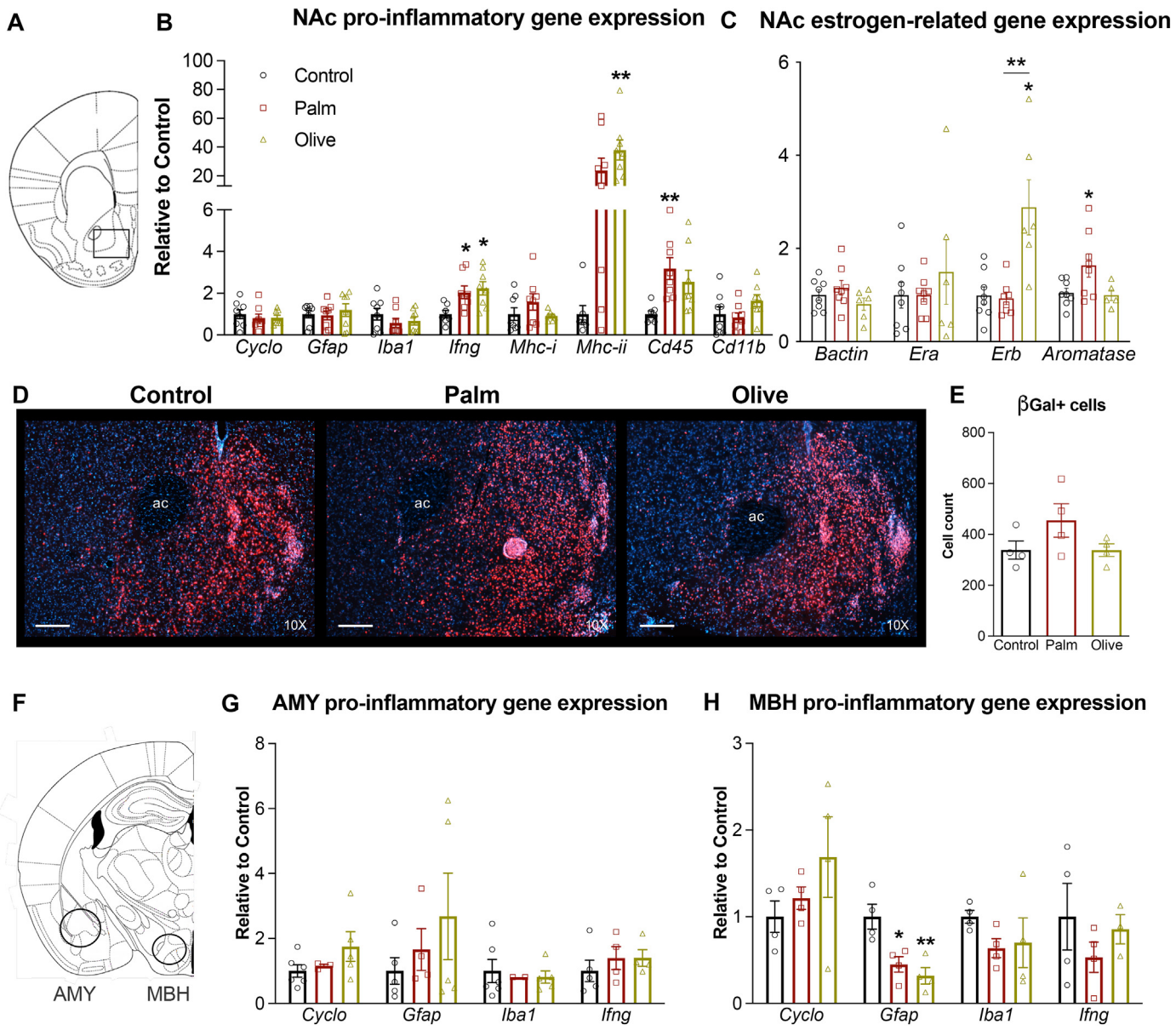

Fig. 3. Saturated and monounsaturated high-fat feeding differ by nucleus accumbens expression of estradiol-related genes. (A) Nucleus accumbens microdissections on coronal slices. (B) Relative nucleus accumbens gene expression of cyclophiline (*Cyclo*), glial fibrillary acidic protein (*Gfap*), ionized calcium binding adaptor molecule-1 (*Iba1*), interferon gamma (*Ifny*), major histocompatibility complex-1 (*Mhc-I*) and 2 (*Mhc-II*), *Cd45* and *Cd11b* (n = 8/diet). (C) Relative nucleus accumbens gene expression of beta-actin, estrogen receptor alpha, estrogen receptor beta and aromatase (n = 6–8/diet). (D) βgal (red) immunofluorescence on nucleus accumbens coronal sections from NFkB-LacZ reporter mice (n = 4/diet); 10X magnification, 200 μm scale bars. (E) Cell count of βgal-positive cells on nucleus accumbens coronal sections from NFkB-LacZ reporter mice (n = 4/diet). (F) Amygdala and mediobasal hypothalamic microdissections on coronal slices. Relative (G) amygdala and (H) mediobasal hypothalamus expression of *Cyclo*, *Gfap*, *Iba1* and *Ifng* (n = 3–6/diet). Data presented as mean ± SEM. One-way ANOVA, Bonferonni post hoc; *p < 0.05, **p < 0.01. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

HFD increased gene expression for NAc ERβ compared to both the Control ($z_{(20)} = 2.834$, $p = 0.0138$) and Palm ($z_{(20)} = 3.048$, $p = 0.0069$) conditions. In addition, there was an influence of diet on NAc gene expression of the testosterone to estrogen converting enzyme aromatase ($F_{(2, 18)} = 3.897$, $p = 0.0392$), with increased expression in the Palm HFD group relative to controls ($t_{(18)} = 2.422$, $p = 0.0517$) and a trend for greater expression in the Palm versus the Olive HFD condition ($t_{(18)} = 2.310$, $p = 0.0649$).

Given enhanced gene expression of markers related to inflammation in the NAc of mice fed the Palm and Olive HFDs, we also examined NAc NFkB transcriptional activity using NFkB-LacZ reporter mice to verify if diet condition influenced the recruitment of this pro-inflammatory transcription factor. NAc NFkB transcriptional activity was visualized via immunofluorescence using an antibody against beta-galactosidase (βgal) (Fig. 3D) and βgal-labeled cells counts did not vary across diet conditions ($F_{(2, 9)} = 2.208$, $p = 0.1659$) (Fig. 3E). As diet-induced obesity can trigger inflammatory processes in brain regions other than the NAc, we investigated gene expression levels for inflammatory markers in the amygdala (AMY) and the mediobasal hypothalamus (MBH) (Fig. 3F). Diet conditions had no impact on AMY gene expression of *Cyclo* ($F_{(2, 11)} = 1.710$, $p = 0.2256$), *Gfap* ($F_{(2, 11)} = 0.9016$, $p = 0.4339$), *Iba1* ($F_{(2, 10)} = 0.1266$, $p = 0.8825$) and *Ifng* ($F_{(2, 10)} = 0.5390$, $p = 0.5994$) (Fig. 3G). Similarly, MBH expression levels for *Cyclo* ($F_{(2, 9)} = 1.404$, $p = 0.2947$), *Iba1* ($F_{(2, 9)} = 1.141$, $p = 0.3616$) and *Ifng* ($H_{(2, 9)} = 1.394$, $p = 0.5387$) were unaffected by diet and despite a diet effect for MBH *Gfap* ($F_{(2, 9)} = 10.46$, $p = 0.0045$), expression was decreased by Palm

($t_{(9)} = 3.483$, $p = 0.0207$) and Olive ($t_{(9)} = 4.309$, $p = 0.0059$) conditions relative to Control (Fig. 3H).

3.4. Saturated high-fat feeding promotes anxiodepressive-like behaviors independently of nucleus accumbens IKK-NFkB signaling

Gene expression for inflammatory markers in the NAc revealed indices of inflammation in animals fed the HFDs and our previous work identified NAc NFkB signaling to mediate the anxiodepressive-like behaviors and NAc inflammation induced by saturated high-fat feeding (Décarie-Spain et al., 2018). In addition, NAc NFkB activity is involved in depressive behaviors and reward function even in the absence of diet-related inflammatory conditions (Christoffel et al, 2011, 2012). Thus, we sought to determine the impact of NAc-specific viral-mediated invalidation of inhibitor of kappa-B kinase (IKK)-mediated NFkB signaling on palm HFD-induced anxiodepressive-like behaviors. In mice fed either the Control diet or the Palm HFD and injected with the adenoviral construct coding for a dominant negative mutation of the IKK beta subunit (Ad^{IKKdn}) or green fluorescent protein (Ad^{GFP}) (Fig. 4A), neither diet ($F_{(1, 26)} = 2.051$, $p = 0.1640$), virus ($F_{(1, 26)} = 0.1957$, $p = 0.6618$) or their interaction ($F_{(1, 16)} = 0.2041$, $p = 0.6551$) had an effect on cumulative food intake over the 4 weeks of recovery (Fig. 4B). Body weight was influenced by the diet ($F(1, 24) = 20.68$, $p = 0.0001$), but not the virus ($F_{(1, 24)} = 0.3340$, $p = 0.5687$) nor the interaction between diet and virus ($F_{(1, 24)} = 0.04873$, $p = 0.8272$), as palm HFD-fed mice weighed significantly more than Control-fed animals, regardless of whether they were injected with the Ad^{GFP} ($Control^{GFP}$ vs. $Palm^{GFP}$; $t_{(24)} = 3.164$, $p = 0.0084$) or Ad^{IKKdn} ($Control^{IKKdn}$ vs. $Palm^{IKKdn}$; $t_{(24)} = 3.289$, $p = 0.0062$) (Fig. 4C). In the EPM, a main diet effect ($F_{(1, 24)} = 6.448$, $p = 0.0180$) was found with a reduction in time spent in the open arms by the Palm HFD, indicative of an anxiety-like phenotype, but no main impact of the viral intervention ($F_{(1, 24)} = 0.08310$, $p = 0.7756$) or its interaction with diet ($F_{(1, 24)} = 0.2331$, $p = 0.6336$) could be observed (Fig. 4D) and no differences in locomotor activity was displayed

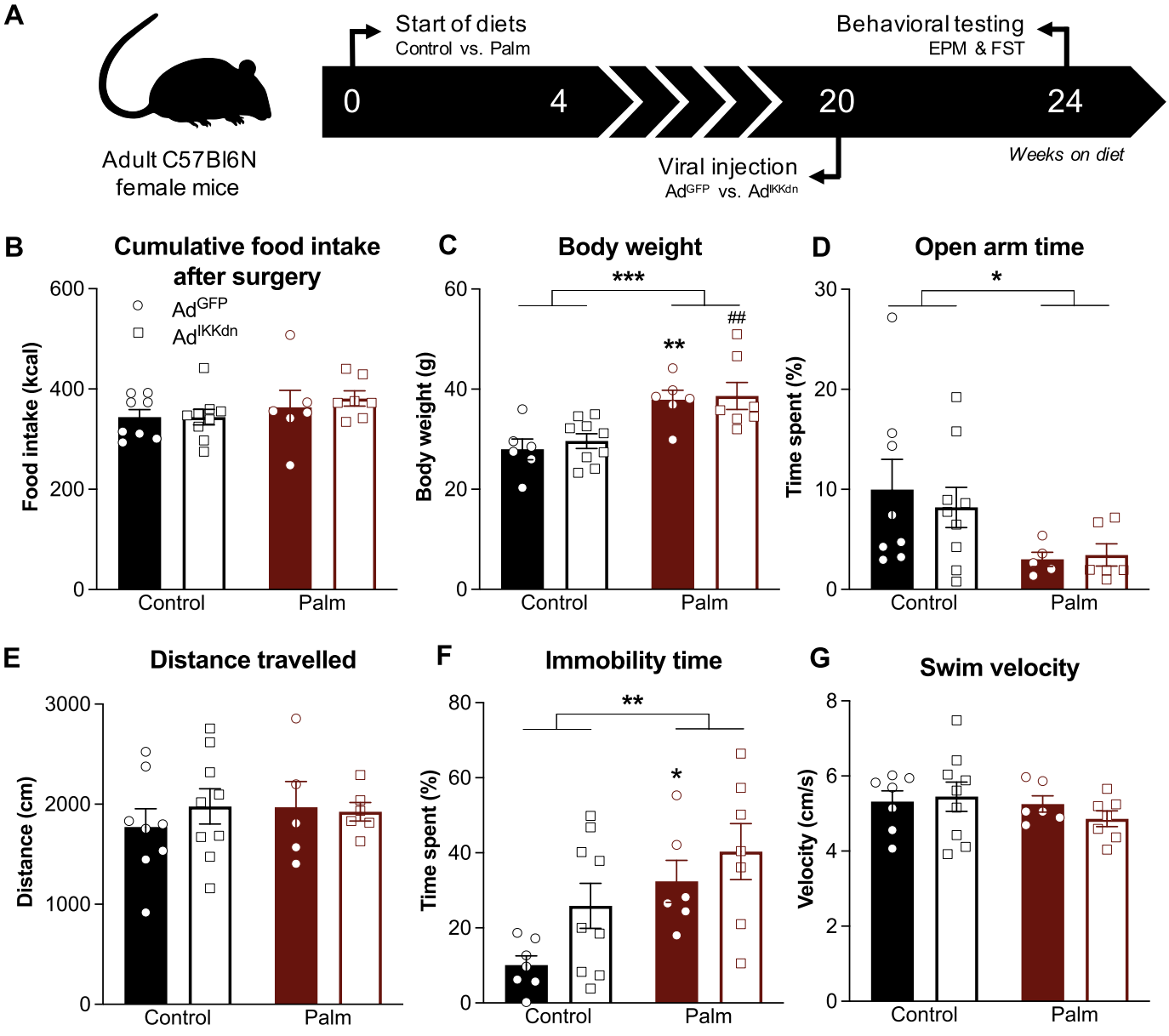

Fig. 4. Saturated high-fat feeding promotes anxiodepressive-like behaviors independently of nucleus accumbens IKK-NFkB signaling. (A) Timeline for experiment. (B) Cumulative food intake after surgery and (C) final body weight. (D) Time spent in open arms and (E) distance travelled in the elevated-plus maze. (F) Time spent immobile and (G) swim velocity during the first 2 min of the forced swim test. (n = 6–9/group). Data presented as mean ± SEM. Two-way ANOVA, Diet effect; *p < 0.05, **p < 0.01, ***p < 0.005 and Bonferonni post hoc; *p < 0.05, **p < 0.005 relative to $Control^{GFP}$, ##p < 0.005 relative to $Control^{IKKdn}$.

across diet ($F_{(1, 24)} = 0.1392$, $p = 0.7124$), virus ($F_{(1, 24)} = 0.1795$, $p = 0.6756$) or their interaction ($F_{(1, 24)} = 0.4358$, $p = 0.5154$) (Fig. 4E). Similarly, in the FST, a main diet effect was found for immobility time ($F_{(1, 25)} = 9.805$, $p = 0.0044$), in addition to a trend for a viral effect ($F(1, 25) = 4.052$, $p = 0.0550$) and $Palm^{GFP}$ mice displaying significantly greater time immobile relative to the $Control^{GFP}$ animals ($t_{(25)} = 2.566$, $p = 0.0333$) (Fig. 4F). However, there was no effect of the viral-mediated knockdown of IKK-NFkB signaling on immobility time ($Control^{IKKdn}$ vs. $Palm^{IKKdn}$; $t_{(24)} = 1.831$, $p = 0.1581$) and neither diet ($F_{(1, 25)} = 1.070$, $p = 0.3109$), viral intervention ($F_{(1, 25)} = 0.1729$, $p = 0.6811$) nor their interaction ($F_{(1, 25)} = 0.6858$, $p = 0.4151$) had an effect on swim velocity (Fig. 4G).

4. Discussion

Lifetime prevalence for mood and emotional disorders is greater in women and the relationship between metabolic impairments and depression may be stronger in women than in men (Anderson et al., 2001; Ul-Haq et al., 2014). The goal of this study was to compare the consequences of saturated versus monounsaturated high-fat feeding on metabolic and behavioral endpoints in female mice as well as to verify the contribution of NAc inflammation in mediating diet-induced anxiodepressive-like behaviors. Our findings demonstrate that both a saturated and monounsaturated HFD promote adiposity gain and glucose intolerance. Strikingly, despite similar metabolic profiles after 24 weeks of HFD, anxiodepressive-like behaviors were solely observed in mice fed the palm HFD. While some indices of NAc inflammation were observed with both the Palm and Olive HFDs, only mice fed the Palm HFD presented elevated circulating estradiol, in addition to alterations in NAc expression of estrogen-related genes.

Metabolic impairments are thought to mediate the risk for depression in obese individuals (Hamer et al., 2012) and consumption of a Mediterranean diet, rich in unsaturated fatty acids, is typically associated to positive outcomes on metabolic health (Martínez-González et al., 2015; Ros et al., 2014; Soriguer et al., 2013). The impairments observed in our olive HFD group may derive from the especially long duration of diet study which was required to bypass the typical resistance of female rodents to diet-induced obesity (Palmisano et al., 2017; Pettersson et al., 2012; Saito et al., 2016). Our model of obesity and glucose intolerance induced by prolonged monounsaturated high-fat feeding is compatible with protective effect of oleate on anxiodepressive-like behaviors, which is in accordance with the beneficial effects of the Mediterranean diet on mental health (García-Toro et al., 2016; Sánchez-Villegas et al., 2013). A possible explanation for this discrepancy between the periphery and the central nervous system could be direct actions of dietary fatty acids on brain function. In fact, saturated and monounsaturated dietary fatty acids have been shown to decrease and increase cortical activity, respectively (Sartorius et al., 2012) and infusion of oleate, but not palmitate, into the ventral tegmental area impacts both motivated behaviors and mesolimbic dopamine signaling (Hryhorczuk et al., 2017b). While the contribution of other diet-induced peripheral adaptations to the behavioral phenotype cannot be excluded, our findings indicate monounsaturated high-fat feeding protects against obesity-induced anxiodepressive-like behaviors in spite of its actions to increase adiposity, glucose intolerance and stimulate inflammation in female mice.

In male mice, we showed that saturated high-fat feeding induces anxiodepressive-like behaviors via NAc NFkB-mediated inflammation (Décarie-Spain et al., 2018). In the present study however, minimal indices of neuroinflammation were observed, with only *Ifng* and *Mhc-ii* upregulated by both the saturated and monounsaturated HFDs, and *Cd45* only increased in the saturated HFD condition. Interestingly, unlike glia-related markers *Gfap* and *Iba1*, present in resident brain cells, *Ifng*, *Mhc-ii* and *Cd45* are highly expressed in peripheral immune cells (Ransohoff and Brown, 2012). As the methods employed in this study do not allow us to determine the origin of these *Ifng*, *Mhc-ii* and *Cd45* expressing cells, future work should investigate whether the indices of neuroinflammation observed in the Palm and Olive HFDs are mainly driven by infiltration of peripheral immune cells to the central nervous system. Another contrast with observations in male mice is the increased expression of some inflammatory markers in the female mice fed the Olive HFD. This finding is in accordance with the impaired glucose tolerance observed in these animals. While female rodents may typically be less susceptible to diet-induced inflammation, specific immune processes may be triggered by prolonged overnutrition, such as the 24 week period applied here, independently of dietary fat composition.

In addition, invalidation of the IKK-NFkB signaling pathway in the NAc had no impact on anxiodepressive-like behaviors. High-fat feeding has been shown to affect brain lipid metabolism differently in female rodents (Morselli et al., 2016; Rodriguez-Espinosa and Fernandez-Espejo, 2015) and others have detected no indications of immune activation in the hypothalamus (Dorfman et al., 2017; Morselli et al., 2014). While inhibition of IKK-NFkB activity in the NAc was shown to protect against stress-induced depressive phenotypes in male mice, overexpression of NAc IKK-NFkB signaling reduced susceptibility to stress-induced depression in gonadally intact female mice (LaPlant et al., 2009). Thus, the IKK-NFkB signaling pathway may act via non-inflammatory mechanisms to protect against pro-depressant stress-induced adaptions in the NAc in female mice with intact activity of reproductive hormones.

Interestingly, while some studies report serum concentrations of pro-inflammatory markers and adipokines to predict anxiety and depressive symptoms in obese women (Capuron et al., 2011; Kohn et al., 2019), others observed no association between these same markers and depressive symptoms in obese women (Olszanecka-Glinianowicz et al., 2009). In addition, other groups have the relationship between circulating levels of CRP and depressive symptoms to be only present in obese men (Vetter et al., 2013) or stronger in obese men than obese women (Tayefi et al., 2017). These findings suggest the correlation between diet-induced inflammation and depression to be influenced by sex in humans. It is worth mentioning that factors other than body mass index or inflammatory markers, such as methylation of clock genes, have been shown to predict severity of depressive symptoms in overweight and obese women (Iodice et al., 2021). Similarly to the indices of change in estrogen signaling observed in our study, neuroendocrine adaptations to chronic saturated high-fat feeding rather than inflammation per se may mediate susceptibility to anxiety and depression in women.

The lack of a strong neuroimmune response to the saturated high-fat diet in female mice could result from the anti-inflammatory properties of estradiol, whose circulating levels were enhanced by the Palm HFD. The increase in estradiol cannot be attributed solely to a change in body weight as this finding was not present in animals fed the olive HFD. Estradiol is shown to dampen pro-inflammatory signaling in astrocytes and microglia and to promote the secretion of IFN in T cell lymphocytes (Straub, 2007). This is consistent with indices of brain immune infiltration, especially in the Palm HFD group. In addition, mice fed the saturated HFD presented greater NAc gene expression for the two main isoforms of aromatase, which has been shown to be upregulated in response to brain ischemia and correlate negatively with microglial activation (Zhong et al., 2017). Thus, the neuroinflammatory patterns observed in our female mice may result from an interaction between estradiol and diet-induced obesity.

Importantly, changes in the expression of markers involved in estrogen signaling in the NAc were associated to the differential impact of dietary fatty acids on anxiodepressive-like behaviors. While ERα has been recently shown to regulate resiliency to stress-induced depression (Lorsch et al., 2018), we found NAc ERβ gene expression to be increased by the olive HFD in comparison to both the control and palm conditions. Interestingly, estrogen appears to mediate its anxiolytic and anti-depressant functions preferentially via ERβ (Sasayama et al., 2017; A A Walf et al., 2009; Alicia A Walf et al., 2009) which may contribute to the protection of female mice fed the olive HFD to the anxiodepressive-like phenotype. Neural-derived estradiol is known to

promote neuroplasticity (Azcoitia et al., 2016) and enhanced NAc gene expression of aromatase in the Palm HFD group could suggest neural adaptations promoting the expression of anxiodepressive-like behaviors. Furthermore, palmitic acid partakes in the stabilization of membrane estrogen receptors and association with other receptors (Fukata et al., 2004; Meitzen et al., 2013), a process mediating the influences of estradiol on NAc neuroplasticity and activity (Tonn Eisinger et al., 2018a, 2018b). Therefore, alterations in peripheral and central estradiol signaling may dictate the differential impacts of dietary fatty acids anxiodepressive-like behaviors.

A limitation of this work is the use of a single task to assess either anxiety-like behavior or behavioral despair. The inclusion of a second exploration-based anxiety-like behavior array as well as adding a task assessing hedonic processes would have solidified the behavioral phenotype observed. In addition, while we observe significant behavioral and molecular alterations across diet conditions, without controling for hormonal status, determination of estrus cycle at time of behavior and sacrifice would have added information about potential sex hormone modulation of NAc-mediated function. Finally, G protein-coupled estrogen receptor 1 (GPER1) is also expressed in the NAc (Proañ and Meitzen, 2020) and shown to influence anxiodepressive-like behaviors (Wang et al., 2019) – has not been investigated in this study and could play a role in saturated high-fat feeding-induced anxiodepressive-like behaviors in female mice.

In conclusion, this work in females evidences differential behavioral consequences of saturated and monounsaturated high-fat feeding that occur independently of obesity-induced metabolic impairments and peripheral and central inflammation. While saturated high-fat feeding induces anxiodepressive-like behaviors in female mice, as we have shown previously in males, inflammatory processes and over-recruitment of the IKK-NFkB signaling pathway in the NAc of female mice do not contribute to the behavioral phenotype. Given the higher prevalence of treatment-resistant depression in individuals suffering from comorbid obesity and metabolic impairments (Rizvi et al., 2014) as well as growing interest in the addition of anti-inflammatory agents to pharmacotherapy against depression (Kohler et al., 2014; Raison et al., 2013; Strawbridge et al., 2015), our recent results add weight to the need for sex-specific therapeutic considerations. Despite similar behavioral phenotypes in saturated HFD-fed male and female mice, this study highlights minimal contribution of NAc inflammation to anxiodepressive-like behaviors elicited by a saturated high-fat diet in female mice. Future directions in the field of psychoneuroimmunology should strengthen knowledge on female-specific mechanisms in view of developing therapeutic approaches that are both safe and effective in women, especially for disorders where women are over-represented. In addition to considering sex as a variable, unraveling the channels through which female reproductive hormones influence immuno-metabolism and brain functions could give rise to novel therapies.

Declaration of competing interest

The authors declare no conflict of interest.

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References

Ambrósio, G., Kaufmann, F.N., Manosso, L., Platt, N., Ghisleni, G., Rodrigues, A.L.S., Rieger, D.K., Kaster, M.P., 2018. Depression and peripheral inflammatory profile of patients with obesity. Psychoneuroendocrinology. https://doi.org/10.1016/j.psyneuen.2018.03.005.

Amiri, S., Behnezhad, S., 2019. Obesity and anxiety symptoms: a systematic review and meta-analysisAdipositas und Angstsymptome: systematische Review und Metaanalyse. neuropsychiatrie. https://doi.org/10.1007/s40211-019-0302-9.

Anderson, R.J., Freedland, K.E., Lustman, P.J., 2001. The prevalence of comorbid depression in adults with diabetes: a meta-analysis. Diabetes Care 24, 1069–1078. https://doi.org/10.2337/diacare.24.6.1069.

Azcoitia, I., Arevalo, M.A., Garcia-Segura, L.M., 2016. Neural-derived estradiol regulates brain plasticity. J. Chem. Neuroanat. https://doi.org/10.1016/j.jchemneu.2017.04.004.

Benoit, S.C., Kemp, C.J., Elias, C.F., Abplanalp, W., Herman, J.P., Migrenne, S., Lefevre, A.L., Cruciani-Guglielmacci, C., Magnan, C., Yu, F., Niswender, K., Irani, B.G., Holland, W.L., Clegg, D.J., 2009. Palmitic acid mediates hypothalamic insulin resistance by altering PKC-theta subcellular localization in rodents. J. Clin. Invest. 119, 2577–2589. https://doi.org/10.1172/JCI36714.

Burt, V.K., Stein, K., 2002. Epidemiology of depression throughout the female life cycle. J. Clin. Psychiatr. 63, 9–15.

Capuron, L., Poitou, C., MacHaux-Tholliez, D., Frochot, V., Bouillot, J.L., Basdevant, A., Layà, S., Clément, K., 2011. Relationship between adiposity, emotional status and eating behaviour in obese women: role of inflammation. Psychol. Med. 41, 1517–1528. https://doi.org/10.1017/S0033291710001984.

Carrillo, C., Cavia Mdel, M., Alonso-Torre, S., 2012. Role of oleic acid in immune system; mechanism of action; a review. Nutr. Hosp. 27, 978–990. https://doi.org/10.3305/nh.2012.27.4.5783.

Christoffel, D.J., Golden, S.A., Dumitriu, D., Robison, A.J., Janssen, W.G., Ahn, H.F., Krishnan, V., Reyes, C.M., Han, M.H., Ables, J.L., Eisch, A.J., Dietz, D.M., Ferguson, D., Neve, R.L., Greengard, P., Kim, Y., Morrison, J.H., Russo, S.J., 2011. IkappaB kinase regulates social defeat stress-induced synaptic and behavioral plasticity. J. Neurosci. 31, 314–321. https://doi.org/10.1523/JNEUROSCI.4763-10.2011.

Christoffel, D.J., Golden, S.A., Heshmati, M., Graham, A., Birnbaum, S., Neve, R.L., Hodes, G.E., Russo, S.J., 2012. Effects of inhibitor of kappaB kinase activity in the nucleus accumbens on emotional behavior. Neuropsychopharmacology 37, 2615–2623. https://doi.org/10.1038/npp.2012.121.

Daly, M., 2013. The relationship of C-reactive protein to obesity-related depressive symptoms: a longitudinal study. Obesity 21, 248–250. https://doi.org/10.1002/oby.20051.

Décarie-Spain, L., Sharma, S., Hryhorczuk, C., Issa-Garcia, V., Barker, P.A., Arbour, N., Alquier, T., Fulton, S., 2018. Nucleus accumbens inflammation mediates anxiodepressive behavior and compulsive sucrose seeking elicited by saturated dietary fat. Mol. Metab. 10, 1–13. https://doi.org/10.1016/j.molmet.2018.01.018.

Dorfman, M.D., Krull, J.E., Douglass, J.D., Fasnacht, R., Lara-Lince, F., Meek, T.H., Shi, X., Damian, V., Nguyen, H.T., Matsen, M.E., Morton, G.J., Thaler, J.P., 2017. Sex differences in microglial CX3CR1 signalling determine obesity susceptibility in mice. Nat. Commun. 8, 14556. https://doi.org/10.1038/ncomms14556.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E.K., Lanctot, K.L., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatr. 67, 446–457. https://doi.org/10.1016/j.biopsych.2009.09.033.

Dunbar, J.A., Reddy, P., Davis-Lameloise, N., Philpot, B., Laatikainen, T., Kilkkinen, A., Bunker, S.J., Best, J.D., Vartiainen, E., Kai Lo, S., Janus, E.D., 2008. Depression: an important comorbidity with metabolic syndrome in a general population. Diabetes Care 31, 2368–2373. https://doi.org/10.2337/dc08-0175.

Felger, J.C., Li, Z., Haroon, E., Woolwine, B.J., Jung, M.Y., Hu, X., Miller, A.H., 2016. Inflammation is associated with decreased functional connectivity within corticostriatal reward circuitry in depression. Mol. Psychiatr. 21, 1358–1365. https://doi.org/10.1038/mp.2015.168.

Fukata, M., Fukata, Y., Adesnik, H., Nicoll, R.A., Bredt, D.S., 2004. Identification of PSD-95 palmitoylating enzymes. Neuron 44, 987–996. https://doi.org/10.1016/j.neuron.2004.12.005.

Fulton, S., Alquier, T., 2019. Lipid signalling in the mesolimbic dopamine pathway. Neuropsychopharmacology 44, 221–222. https://doi.org/10.1038/s41386-018-0188-4.

García-Toro, M., Vicens-Pons, E., Gili, M., Roca, M., Serrano-Ripoll, M.J., Vives, M., Leiva, A., Yáñez, A.M., Bennasar-Veny, M., Oliván-Blázquez, B., 2016. Obesity, metabolic syndrome and Mediterranean diet: impact on depression outcome. J. Affect. Disord. 194, 105–108. https://doi.org/10.1016/j.jad.2015.12.064.

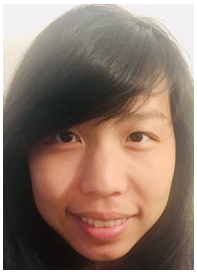
Hamer, M., Batty, G.D., Kivimaki, M., 2012. Risk of future depression in people who are obese but metabolically healthy: the English longitudinal study of ageing. Mol. Psychiatr. 17, 940–945. https://doi.org/10.1038/mp.2012.30.

Hinnouho, G.M., Singh-Manoux, A., Gueguen, A., Matta, J., Lemogne, C., Goldberg, M., Zins, M., Czernichow, S., 2017. Metabolically healthy obesity and depressive symptoms: 16-year follow-up of the Gazel cohort study. PloS One 12, e0174678. https://doi.org/10.1371/journal.pone.0174678.

Hodes, G.E., Pfau, M.L., Purushothaman, I., Ahn, H.F., Golden, S.A., Christoffel, D.J., Magida, J., Brancato, A., Takahashi, A., Flanigan, M.E., Menard, C., Aleyasin, H., Koo, J.W., Lorsch, Z.S., Feng, J., Heshmati, M., Wang, M., Turecki, G., Neve, R., Zhang, B., Shen, L., Nestler, E.J., Russo, S.J., 2015. Sex differences in nucleus accumbens transcriptome profiles associated with susceptibility versus resilience to

subchronic variable stress. J. Neurosci. 35, 16362–16376. https://doi.org/10.1523/JNEUROSCI.1392-15.2015.
Hryhorczuk, C., Décarie-Spain, L., Sharma, S., Daneault, C., Rosiers, C. Des, Alquier, T., Fulton, S., 2017a. Saturated high-fat feeding independent of obesity alters hypothalamus-pituitary-adrenal axis function but not anxiety-like behaviour. Psychoneuroendocrinology 83, 142–149. https://doi.org/10.1016/j.psyneuen.2017.06.002.
Hryhorczuk, C., Florea, M., Rodaros, D., Poirier, I., Daneault, C., Des Rosiers, C., Arvanitogiannis, A., Alquier, T., Fulton, S., 2015. Dampened mesolimbic dopamine function and signaling by saturated but not monounsaturated dietary lipids. Neuropsychopharmacology. https://doi.org/10.1038/npp.2015.207.
Hryhorczuk, C., Sheng, Z., Decarie-Spain, L., Giguere, N., Ducrot, C., Trudeau, L.-E., Routh, V.H., Alquier, T., Fulton, S., 2017b. Oleic acid in the ventral tegmental area inhibits feeding, food reward, and dopamine tone. Neuropsychopharmacology. https://doi.org/10.1038/npp.2017.203.
Huang, S., Rutkowsky, J.M., Snodgrass, R.G., Ono-Moore, K.D., Schneider, D.A., Newman, J.W., Adams, S.H., Hwang, D.H., 2012. Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways. J. Lipid Res. 53. https://doi.org/10.1194/jlr.D029546, 2002–2013.
Iodice, S., Ceresa, A., Esposito, C.M., Mucci, F., Conti, D.M., Pergoli, L., Tarantini, L., Vigna, L., Bollati, V., Buoli, M., Serati, M., 2021. The independent role of body mass index (Bmi) and severity of depressive symptoms on biological changes of women affected by overweight/obesity. Int. J. Environ. Res. Publ. Health 18, 1–11. https://doi.org/10.3390/ijerph18062923.
Kohler, O., Benros, M.E., Nordentoft, M., Farkouh, M.E., Iyengar, R.L., Mors, O., Krogh, J., 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatry 71, 1381–1391. https://doi.org/10.1001/jamapsychiatry.2014.1611.
Kohn, J.N., Cabrera, Y., Dimitrov, S., Guay-Ross, N., Pruitt, C., Shaikh, F.D., Hong, S., 2019. Sex-specific roles of cellular inflammation and cardiometabolism in obesity-associated depressive symptomatology. Int. J. Obes. 43, 2045–2056. https://doi.org/10.1038/s41366-019-0375-3.
Kokras, N., Dalla, C., 2017. Preclinical sex differences in depression and antidepressant response: implications for clinical research. J. Neurosci. Res. 95, 731–736. https://doi.org/10.1002/jnr.23861.
LaPlant, Q., Chakravarty, S., Vialou, V., Mukherjee, S., Koo, J.W., Kalahasti, G., Bradbury, K.R., Taylor, S.V., Maze, I., Kumar, A., Graham, A., Birnbaum, S.G., Krishnan, V., Truong, H.T., Neve, R.L., Nestler, E.J., Russo, S.J., 2009. Role of nuclear factor kappaB in ovarian hormone-mediated stress hypersensitivity in female mice. Biol. Psychiatr. 65, 874–880. https://doi.org/10.1016/j.biopsych.2009.01.024.
Lasserre, A.M., Glaus, J., Vandeleur, C.L., Marques-Vidal, P., Vaucher, J., Bastardot, F., Waeber, G., Vollenweider, P., Preisig, M., 2014. Depression with atypical features and increase in obesity, body mass index, waist circumference, and fat mass: a prospective, population-based study. JAMA Psychiatry. https://doi.org/10.1001/jamapsychiatry.2014.411.
Li, S.H., Graham, B.M., 2017. Why are women so vulnerable to anxiety, trauma-related and stress-related disorders? The potential role of sex hormones. The Lancet Psychiatry. https://doi.org/10.1016/S2215-0366(16)30358-3.
Lorsch, Z.S., Loh, Y.H.E., Purushothaman, I., Walker, D.M., Parise, E.M., Salery, M., Cahill, M.E., Hodes, G.E., Pfau, M.L., Kronman, H., Hamilton, P.J., Issler, O., Labonté, B., Symonds, A.E., Zucker, M., Zhang, T.Y., Meaney, M.J., Russo, S.J., Shen, L., Bagot, R.C., Nestler, E.J., 2018. Estrogen receptor α drives pro-resilient transcription in mouse models of depression. Nat. Commun. 9, 1116. https://doi.org/10.1038/s41467-018-03567-4.
Luppino, F.S., de Wit, L.M., Bouvy, P.F., Stijnen, T., Cuijpers, P., Penninx, B.W., Zitman, F.G., 2010. Overweight, obesity and depression: a systematic review and meta-analysis of longitudinal studies. Arch. Gen. Psychiatr. 67, 10.
Maggioli, E., McArthur, S., Mauro, C., Kieswich, J., Kusters, D.H.M., Reutelingsperger, C.P.M., Yaqoob, M., Solito, E., 2016. Estrogen protects the blood-brain barrier from inflammation-induced disruption and increased lymphocyte trafficking. Brain Behav. Immun. 51, 212–222. https://doi.org/10.1016/j.bbi.2015.08.020.
Martínez-González, M.A., Salas-Salvadó, J., Estruch, R., Corella D, D., Fitó, M., Ros, E., 2015. Benefits of the mediterranean diet: insights from the PREDIMED study. Prog. Cardiovasc. Dis. 58, 50–60. https://doi.org/10.1016/j.pcad.2015.04.003.
Meitzen, J., Luoma, J.I., Boulware, M.I., Hedges, V.L., Peterson, B.M., Tuomela, K., Britson, K.A., Mermelstein, P.G., 2013. Palmitoylation of estrogen receptors is essential for neuronal membrane signaling. Endocrinology 154, 4293–4304. https://doi.org/10.1210/en.2013-1172.
Milaneschi, Y., Lamers, F., Peyrot, W.J., Baune, B.T., Breen, G., Dehghan, A., Forstner, A.J., Grabe, H.J., Homuth, G., Kan, C., Lewis, C., Mullins, N., Nauck, M., Pistis, G., Preisig, M., Rivera, M., Rietschel, M., Streit, F., Strohmaier, J., Teumer, A., Van Der Auwera, S., Wray, N.R., Boomsma, D.I., Penninx, B.W.J.H., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E.M., Abdellaoui, A., Adams, M.J., Agerbo, E., Air, T.M., Andlauer, T.F.M., Bacanu, S.A., Bakvad-Hansen, M., Beekman, A.T.F., Bigdeli, T.B., Binder, E.B., Blackwood, D.H.R., Bryois, J., Buttenschon, H.N., Bybjerg-Grauholm, J., Cai, N., Castelao, E., Christensen, J.H., Clarke, T.K., Coleman, J.R.I., Colodro-Conde, L., Couvy-Duchesne, B., Craddock, N., Crawford, G.E., Davies, G., Deary, I.J., Degenhardt, F., Derks, E.M., Direk, N., Dolan, C.V., Dunn, E.C., Eley, T.C., Escott-Price, V., Kiadeh, F.F.H., Finucane, H.K., Frank, J., Gaspar, H.A., Gill, M., Goes, F.S., Gordon, S.D., Grove, J., Hall, L.S., Hansen, C.S., Hansen, T.F., Herms, S., Hickie, I.B., Hoffmann, P., Horn, C., Hottenga, J.J., Hougaard, D.M., Ising, M., Jansen, R., Jorgenson, E., Knowles, J.A., Kohane, I.S., Kraft, J., Kretzschmar, W.W., Krogh, J., Kutalik, Z., Li, Y., Lind, P.A., MacIntyre, D.J., MacKinnon, D.F., Maier, R.M., Maier, W., Marchini, J., Mbarek, H., McGrath, P., McGuffin, P., Medland, S.E., Mehta, D., Middeldorp, C.M., Mihailov, E., Milani, L., Mondimore, F.M., Montgomery, G.W., Mostafavi, S., Ng, B., Nivard, M.G., Nyholt, D.R., O'Reilly, P.F., Oskarsson, H., Owen, M.J., Painter, J.N., Pedersen, C.B., Pedersen, M.G., Peterson, R.E., Pettersson, E., Posthuma, D., Quiroz, J.A., Qvist, P., Rice, J.P., Riley, B.P., Mirza, S.S., Schoevers, R., Schulte, E.C., Shen, L., Shi, J., Shyn, S.I., Sigurdsson, E., Sinnamon, G.C.B., Smit, J.H., Smith, D.J., Stefansson, H., Steinberg, S., Tansey, K.E., Teismann, H., Thompson, W., Thomson, P.A., Thorgeirsson, T.E., Traylor, M., Treutlein, J., Trubetskoy, V., Uitterlinden, A.G., Umbricht, D., Van Hemert, A.M., Viktorin, A., Visscher, P.M., Wang, Y., Webb, B.T., Weinsheimer, S.M., Wellmann, J., Willemsen, G., Witt, S.H., Wu, Y., Xi, H.S., Yang, J., Zhang, F., Arolt, V., Berger, K., Cichon, S., Dannlowski, U., De Geus, E.J.C., DePaulo, J.R., Domenici, E., Domschke, K., Esko, T., Hamilton, S.P., Hayward, C., Heath, A.C., Kendler, K.S., Kloiber, S., Lewis, G., Li, Q.S., Lucae, S., Madden, P.A.F., Magnusson, P.K., Martin, N.G., McIntosh, A.M., Metspalu, A., Mors, O., Mortensen, P.B., Muller-Myhsok, B., Nordentoft, M., Nothen, M.M., O'Donovan, M.C., Paciga, S.A., Pedersen, N.L., Perlis, R.H., Porteous, D.J., Potash, J.B., Schaefer, C., Schulze, T.G., Smoller, J.W., Stefansson, K., Tiemeier, H., Uher, R., Volzke, H., Weissman, M.M., Werge, T., Levinson, D.F., Borglum, A.D., Sullivan, P.F., 2017. Genetic association of major depression with a typical features and obesity-related immunometabolic dysregulations. JAMA Psychiatry 74, 1214–1225. https://doi.org/10.1001/jamapsychiatry.2017.3016.
Morselli, E., Frank, A.P., Palmer, B.F., Rodriguez-Navas, C., Criollo, A., Clegg, D.J., 2016. A sexually dimorphic hypothalamic response to chronic high-fat diet consumption. Int. J. Obes. 40, 206–209. https://doi.org/10.1038/ijo.2015.114.
Morselli, E., Fuente-Martin, E., Finan, B., Kim, M., Frank, A., Garcia-Caceres, C., Navas, C.R., Gordillo, R., Neinast, M., Kalainayakan, S.P., Li, D.L., Gao, Y., Yi, C.-X., Hahner, L., Palmer, B.F., Tschöp, M.H., Clegg, D.J., 2014. Hypothalamic PGC-1α protects against high-fat diet exposure by regulating ERα. Cell Rep. 9, 633–645. https://doi.org/10.1016/j.celrep.2014.09.025.
Oh, Y.T., Lee, J.Y., Lee, J., Kim, H., Yoon, K.S., Choe, W., Kang, I., 2009. Oleic acid reduces lipopolysaccharide-induced expression of iNOS and COX-2 in BV2 murine microglial cells: possible involvement of reactive oxygen species, p38 MAPK, and IKK/NF-κB signaling pathways. Neurosci. Lett. 464, 93–97. https://doi.org/10.1016/j.neulet.2009.08.040.
Olszanecka-Glinianowicz, M., Zahorska-Markiewicz, B., Koceak, P., Janowska, J., Semik-Grabarczyk, E., Wikarek, T., Gruszka, W., Dbrowski, P., 2009. Is chronic inflammation a possible cause of obesity-related depression? Mediat. Inflamm. 2009. https://doi.org/10.1155/2009/439107.
Palmisano, B.T., Stafford, J.M., Pendergast, J.S., 2017. High-Fat feeding does not disrupt daily rhythms in female mice because of protection by ovarian hormones. Front. Endocrinol. 8. https://doi.org/10.3389/fendo.2017.00044.
Pettersson, U.S., Waldén, T.B., Carlsson, P.O., Jansson, L., Phillipson, M., 2012. Female mice are protected against high-fat diet induced metabolic syndrome and increase the regulatory T cell population in adipose tissue. PloS One 7. https://doi.org/10.1371/journal.pone.0046057.
Pierce, G.L., Kalil, G.Z., Ajibewa, T., Holwerda, S.W., Persons, J., Moser, D.J., Fiedorowicz, J.G., 2016. Anxiety independently contributes to elevated inflammation in humans with obesity. Obesity. https://doi.org/10.1002/oby.21698.
Proañ, S.B., Meitzen, J., 2020. Estradiol decreases medium Spiny neuron excitability in female rat nucleus accumbens core. J. Neurophysiol. 123, 2465–2475. https://doi.org/10.1152/JN.00210.2020.
Raison, C.L., Rutherford, R.E., Woolwine, B.J., Shuo, C., Schettler, P., Drake, D.F., Haroon, E., Miller, A.H., 2013. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry 70, 31–41. https://doi.org/10.1001/2013.jamapsychiatry.4.
Ransohoff, R.M., Brown, M.A., 2012. Innate immunity in the central nervous system. J. Clin. Invest. https://doi.org/10.1172/JCI58644.
Rizvi, S.J., Grima, E., Tan, M., Rotzinger, S., Lin, P., Mcintyre, R.S., Kennedy, S.H., 2014. Treatment-resistant depression in primary care across Canada. Can. J. Psychiatr. 59, 349–357. https://doi.org/10.1177/070674371405900702.
Rodriguez-Espinosa, N., Fernandez-Espejo, E., 2015. Effects of acute and repeated cocaine on markers for neural plasticity within the mesolimbic system in rats. Psychopharmacology (Berlin) 232, 57–62. https://doi.org/10.1007/s00213-014-3632-0.
Ros, E., Martinez-Gonzalez, M.A., Estruch, R., Salas-Salvado, J., Fito, M., Martinez, J.A., Corella, D., 2014. Mediterranean diet and cardiovascular health: teachings of the PREDIMED study. Adv. Nutr. An Int. Rev. J. 5, 330S–336S. https://doi.org/10.3945/an.113.005389.
Saito, K., He, Y., Yang, Y., Zhu, L., Wang, C., Xu, P., Hinton, A.O., Yan, X., Zhao, J., Fukuda, M., Tong, Q., Clegg, D.J., Xu, Y., 2016. PI3K in the ventromedial hypothalamic nucleus mediates estrogenic actions on energy expenditure in female mice. Sci. Rep. 6. https://doi.org/10.1038/srep23459.
Sánchez-Villegas, A., Martínez-González, M., Estruch, R., Salas-Salvadó, J., Corella, D., Covas, M., Arós, F., Romaguera, D., Gómez-Gracia, E., Lapetra, J., Pintó, X., Martínez, J., Lamuela-Raventós, R., Ros, E., Gea, A., Wärnberg, J., Serra-Majem, L., 2013. Mediterranean dietary pattern and depression: the PREDIMED randomized trial. BMC Med. 11, 208. https://doi.org/10.1186/1741-7015-11-208.
Sartorius, T., Ketterer, C., Kullmann, S., Balzer, M., Rotermund, C., Binder, S., Hallschmid, M., Machann, J., Schick, F., Somoza, V., Preissl, H., Fritsche, A., Häring, H.-U., Hennige, A.M., 2012. Monounsaturated fatty acids prevent the aversive effects of obesity on locomotion, brain activity, and sleep behavior. Diabetes 61, 1669–1679. https://doi.org/10.2337/db11-1521.
Sasayama, D., Sugiyama, N., Yonekubo, S., Pawlak, A., Murasawa, H., Nakamura, M., Hayashi, M., Ogawa, T., Moro, M., Washizuka, S., Amano, N., Hongo, K., Ohnota, H., 2017. Novel oestrogen receptor β-selective ligand reduces obesity and depressive-like

behaviour in ovariectomized mice. Sci. Rep. 7, 1–8. https://doi.org/10.1038/s41598-017-04946-5.
Schmitz, N., Deschênes, S., Burns, R., Smith, K., Lesage, A., Strychar, I., Rabasa-Lhoret, R., Freitas, C., Graham, E., Awadalla, P., Wang, J., 2016. Depression and risk of type 2 diabetes: the potential role of metabolic factors. Mol. Psychiatr. 217, 1726–1732. https://doi.org/10.1038/mp.2016.7.
Schneider, C.A., Rasband, W.S., Eliceiri, K.W., 2012. NIH Image to ImageJ: 25 years of image analysis. Nat. Methods. https://doi.org/10.1038/nmeth.2089.
Sharma, S., Fulton, S., 2013. Diet-induced obesity promotes depressive-like behaviour that is associated with neural adaptations in brain reward circuitry. Int. J. Obes. 37, 382–389. https://doi.org/10.1038/ijo.2012.48.
Soriguer, F., Rojo-Martínez, G., Goday, A., Bosch-Comas, A., Bordiú, E., Caballero-Díaz, F., Calle-Pascual, A., Carmena, R., Casamitjana, R., Castaño, L., Castell, C., Catalá, M., Delgado, E., Franch, J., Gaztambide, S., Girbés, J., Gomis, R., Gutiérrez, G., López-Alba, A., Teresa Martínez-Larrad, M., Menéndez, E., Mora-Peces, I., Ortega, E., Pascual-Manich, G., Serrano-Rios, M., Urrutia, I., Valdés, S., Antonio Vázquez, J., Vendrell, J., 2013. Olive oil has a beneficial effect on impaired glucose regulation and other cardiometabolic risk factors. Di@bet.es study. Eur. J. Clin. Nutr. 67, 911–916. https://doi.org/10.1038/ejcn.2013.130.
Spence, R.D., Hamby, M.E., Umeda, E., Itoh, N., Du, S., Wisdom, A.J., Cao, Y., Bondar, G., Lam, J., Ao, Y., Sandoval, F., Suriany, S., Sofroniew, M.V., Voskuhl, R.R., 2011. Neuroprotection mediated through estrogen receptor- in astrocytes. Proc. Natl. Acad. Sci. Unit. States Am. 108, 8867–8872. https://doi.org/10.1073/pnas.1103833108.
Stamou, M., Wu, X., Kania-Korwel, I., Lehmler, H.J., Lein, P.J., 2014. Cytochrome P450 mRNA expression in the rodent brain: species-, sex-, and region-dependent differences. Drug Metab. Dispos. 42, 239–244. https://doi.org/10.1124/dmd.113.054239.
Straub, R.H., 2007. The complex role of estrogens in inflammation. Endocr. Rev. https://doi.org/10.1210/er.2007-0001.
Strawbridge, R., Arnone, D., Danese, A., Papadopoulos, A., Herane Vives, A., Cleare, A.J., 2015. Inflammation and clinical response to treatment in depression: a meta-analysis. Eur. Neuropsychopharmacol. https://doi.org/10.1016/j.euroneuro.2015.06.007.
Tayefi, M., Shafiee, M., Kazemi-Bajestani, S.M.R., Esmaeili, H., Darroudi, S., Khakpouri, S., Mohammadi, M., Ghaneifar, Z., Azarpajouh, M.R., Moohebati, M., Heidari-Bakavoli, A., Parizadeh, M.R., Nematy, M., Safarian, M., Ebrahimi, M., Ferns, G.A., Mokhber, N., Ghayour-Mobarhan, M., 2017. Depression and anxiety both associate with serum level of hs-CRP: a gender-stratified analysis in a population-based study. Psychoneuroendocrinology 81, 63–69. https://doi.org/10.1016/j.psyneuen.2017.02.035.
Teres, S., Barcelo-Coblijn, G., Benet, M., Alvarez, R., Bressani, R., Halver, J.E., Escriba, P.V., 2008. Oleic acid content is responsible for the reduction in blood pressure induced by olive oil. Proc. Natl. Acad. Sci. U. S. A. 105, 13811–13816. https://doi.org/10.1073/pnas.0807500105.
Thaler, J.P., Yi, C.X., Schur, E.A., Guyenet, S.J., Hwang, B.H., Dietrich, M.O., Zhao, X., Sarruf, D.A., Izgur, V., Maravilla, K.R., Nguyen, H.T., Fischer, J.D., Matsen, M.E., Wisse, B.E., Morton, G.J., Horvath, T.L., Baskin, D.G., Tschop, M.H., Schwartz, M.W., 2012. Obesity is associated with hypothalamic injury in rodents and humans. J. Clin. Invest. 122, 153–162. https://doi.org/10.1172/JCI59660.
Tonn Eisinger, K.R., Gross, K.S., Head, B.P., Mermelstein, P.G., 2018a. Interactions between estrogen receptors and metabotropic glutamate receptors and their impact on drug addiction in females. Horm. Behav. https://doi.org/10.1016/j.yhbeh.2018.03.001.
Tonn Eisinger, K.R., Larson, E.B., Boulware, M.I., Thomas, M.J., Mermelstein, P.G., 2018b. Membrane estrogen receptor signaling impacts the reward circuitry of the female brain to influence motivated behaviors. Steroids 133, 53–59. https://doi.org/10.1016/j.steroids.2017.11.013.
Ul-Haq, Z., Smith, D.J., Nicholl, B.I., Cullen, B., Martin, D., Gill, J.M.R., Evans, J., Roberts, B., Deary, I.J., Gallacher, J., Hotopf, M., Craddock, N., Mackay, D.F., Pell, J.P., 2014. Gender differences in the association between adiposity and probable major depression: a cross-sectional study of 140,564 UK Biobank participants. BMC Psychiatr. 14, 153. https://doi.org/10.1186/1471-244X-14-153.
Vetter, M.L., Wadden, T.A., Vinnard, C., Moore, R.H., Khan, Z., Volger, S., Sarwer, D.B., Faulconbridge, L.F., 2013. Gender differences in the relationship between symptoms of depression and high-sensitivity CRP. Int. J. Obes. 37, S38–S43. https://doi.org/10.1038/ijo.2013.95.
Walf, Alicia A., Koonce, C., Manley, K., Frye, C.A., 2009. Proestrous compared to diestrous wildtype, but not estrogen receptor beta knockout, mice have better performance in the spontaneous alternation and object recognition tasks and reduced anxiety-like behavior in the elevated plus and mirror maze. Behav. Brain Res. 196, 254–260. https://doi.org/10.1016/j.bbr.2008.09.016.
Walf, A.A., Koonce, C.J., Frye, C.A., 2009. Adult female wildtype, but not oestrogen receptor β knockout, mice have decreased depression-like behaviour during pro-oestrus and following administration of oestradiol or diarylpropionitrile. J. Psychopharmacol. 23, 442–450. https://doi.org/10.1177/0269881108089598.
Wang, J., Yu, R., Han, Q.Q., Huang, H.J., Wang, Y.L., Li, H.Y., Wang, H.M., Chen, X.R., Ma, S.L., Yu, J., 2019. G-1 exhibit antidepressant effect, increase of hippocampal ERs expression and improve hippocampal redox status in aged female rats. Behav. Brain Res. 359, 845–852. https://doi.org/10.1016/j.bbr.2018.07.017.
Zhong, Y.H., Dhawan, J., Kovoor, J.A., Sullivan, J., Zhang, W.X., Choi, D., Biegon, A., 2017. Aromatase and neuroinflammation in rat focal brain ischemia. J. Steroid Biochem. Mol. Biol. 174, 225–233. https://doi.org/10.1016/j.jsbmb.2017.09.019.



Léa Décarie-Spain. Léa obtained an Honors bachelor's degree in Nutritional Sciences from the University of Ottawa in 2013. All the while completing her academic and clinical dietetic training, she gained experience in various research fields ranging from international infant malnutrition to nutrigenomics and metabolism. Early on, her interests revolved around eating behaviors and their modulation by the central nervous system. She joined the research groups of Stephanie Fulton and Thierry Alquier as a candidate to the Master's degree in Neurological Sciences at the University of Montreal and transferred early to the doctorate program in 2015. Over the course of her graduate studies, Léa obtained numerous training, travel and presentation awards at the provincial, national and international level, in addition to collaborating with well-established researchers at the University of Copenhagen and the University of Bordeaux. She served as a student member for her research centre's animal ethics committee and has integrated optimized animal handling practices into her studies. In 2020, she successfully defended her PhD thesis on the neural mechanisms mediating the relationship between dietary fatty acids and mood and motivational deficits in mice. Léa is currently a postdoctoral scholar in the laboratory of Scott Kanoski at the University of Southern California, where she investigates the higher order control of eating with a specific emphasis on the contribution of vagal afferences and hippocampal function. Throughout this postdoctoral training, she aims to integrate the cognitive aspect into her understanding of the modulation of eating behaviors in order to become a well-rounded independent researcher in the field of obesity and disordered eating.