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To cite this version:

Arnaud Bernard, Déborah Ancel, Patricia Passilly-Degrace, Jean-François Landrier, Laurent Lagrost, et al.. A chronic LPS-induced low-grade inflammation fails to reproduce in lean mice the impairment of preference for oily solution found in diet-induced obese mice. Biochimie, Elsevier, 2019, 159, pp.112-121. https://www.sciencedirect.com/science/article/pii/S0300908418302414?via%3Dihub . 10.1016/j.biochi.2018.08.004 . hal-01998523

HAL Id: hal-01998523
https://hal-amu.archives-ouvertes.fr/hal-01998523
Submitted on 29 Jan 2019

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1. Introduction

Recent literature highlighted that food-induced obesity is associated with a dysfunction of the gustatory pathway promoting harmful food choices for health both in human and rodents [1–3].

**Abbreviations:** CVP, circumvallate papillae; DIO, diet-induced obesity; HFD, high fat diet; IPA, Ingenuity Pathway Analysis; LPS, lipopolysaccharides; NAc, nucleus accumbens; TBC, taste bud cells; TLR, Toll-like receptor.

During the prandial period, integration of peripheral taste signals occurs in a set of brain areas responsible for emotional representation of foods (i.e., corticomesolimbic system) [4]. In humans, neuroimaging studies have highlighted an abnormal pattern of activation of this neural network in some obese subjects. For instance, presentation of high palatable food pictures triggers a greater neural activation in regions responsible for motivation/reward (i.e. ventral tegmental area, accumbens nucleus - NAc) and emotion/memory (i.e. amygdala, hippocampus) in obese women than in normal weight controls [5]. It was postulated that this central obesity-mediated neuro-vulnerability might play a role in the preferential consumption of high palatable energy-dense foods (rich in fat and sugar), usually observed in these obese individuals [6]. In rodents, an orosensory stimulation with corn oil leads to a
rise in the dopaminergic activity in brain areas responsible for the reward pathway (e.g. NAc), independently of any ingestion [7]. Mice chronically fed a diet high in saturated fat develop NFκB-mediated inflammatory responses in the NAc [8]. This phenomenon might lead to eating behavior impairments since diet-induced obesity (DIO) rats display a progressively worsening deficit of neural reward responses consecutively to a down-regulation of striatal dopamine D2 receptors [9].

Consumption of an obesogenic diet also seems to disturb the taste system in periphery. In rodents, DIO shifts the preference for oily solutions towards higher concentrations, as compared to lean controls, both in rats and mice subjected to brief-access licking paradigm (i.e. a few sec) [2,3], used to analyze taste-guided drinking behavior. An impairment of the lipid–mediated signaling in taste bud cells (TBC) might explain this blunted gustatory detection. Indeed, the intracellular calcium response to a linoleic acid stimulation and the subsequent release of serotonin are lower in TBC from DIO mice than in those from lean controls [3,10]. However, mechanism(s) by which an obesogenic diet can affect the orosensory fat detection remains elusive.

A nutritional obesity is associated with a chronic low-grade metabolic inflammation. Diets rich in saturated fatty acid lead to a glyc dysbiosis [11]. This microbiome alteration affects the intestinal permeability increasing the systemic release of lipopolysaccharides (LPS) from the outer membrane of Gram–negative bacteria [12]. By activating members of the Toll-like receptors (TLR) family, these endotoxins promote the synthesis of pro-inflammatory cytokines in various tissues. Interestingly, mouse TBC express the TLR-4 signaling cascade [13]. Therefore, it is not surprising that an acute administration of LPS (5 mg/kg body weight by intra-peritoneal injection) induces the expression of inflammatory cytokines (TNFα, INFγ and IL6) in mouse CVP and shortens the life span of TBC [13,14]. LPS eliciting apoptosis in different cell-types [15]. Unfortunately, the outcome of such a drastic LPS treatment on food choice was not studied. Similarly, we don’t know whether an inflammation of the gustatory tissue takes place in DIO mice and whether the low-grade systemic endotoxemia induced by a chronic consumption of obesogenic diets interferes with the preference for fat. The purpose of the present study was to explore these issues.

2. Materials and methods

2.1. Animals

This study was carried out in the strict accordance with European guidelines for the care and use of laboratory animals and protocol approved by the French National Animal Ethic Committee (CNEA 105, n° APAFiS#6090–2016060916268600 v3). Six-week-old C57Bl/6 male mice were purchased from Charles River Laboratories (France). Animals were individually housed in a controlled environment (constant temperature and humidity, dark period from 7 p.m. to 7 a.m.) and had free access to tap water and chow. Experiments took place after a one-week acclimatization period (Fig. 1).

In a first experiment (Fig. 1-A), impact of chronic high fat diet consumption on the orosensory perception of dietary lipids was analyzed using the two bottle preference test on a large cohort of mice (n = 19–20), then the transcriptomic profile of CVP was analyzed in a sub-group of these mice (n = 7–8). Control mice were fed ad libitum for 4 weeks a standard laboratory chow (4RF21, Mucedola, Italy, containing 3% fat, w/w), whereas experimental mice were subjected to a saturated fatty acids-rich diet (Table 1). Evolution of the body composition (i.e. fat mass and lean mass) was determined by molecular resonance imaging (EchoMRI - Echo Medical Systems, Houston, Texas, USA).

In a second experiment (Fig. 1-B), to mimic the chronic low-grade inflammation induced by the chronic consumption of the saturated fatty acids-rich diet, mice fed the standard chow (n = 20) were equipped for 4 weeks with an mini-osmotic pump (Alzet pump, model 2004; Alza, Palo Alto, CA) filled with apyrogen saline (0.9% NaCl, control mice) or LPS (Escherichia coli, serotype 055:B5, Sigma Chemicals) in saline.

2.2. Surgery procedures

Isoflurane anesthetized mice were laparotomized (1 cm incision) for introducing a filled mini-pump in the peritoneal cavity. Once the pump inserted, the muscle layer was sutured using an absorbable surgery wire, then the skin incision was closed with 2 wound clips. The experiment was designed to infuse 300 μL/kg/day for 4 weeks. Animals were intraperitoneally injected with an analgesic (0.3 mg/kg body weight buprenorphine) in post-surgery. At the end of experiments, isoflurane anesthesized animals were sacrificed by cervical dislocation.

2.3. Tissues and blood samples

In the lingual epithelium, taste buds are present in three specialized gustatory papillae (i.e. fungiform, foliate and circumvallate) displaying different spatial distribution. We have chosen to perform the transcriptomic analysis of gustatory tissue in the single CVP found in the mouse because i) it displays the highest density of taste buds of the tongue, ii) it is connected with the von Ebner’s glands known to produce a triglyceride lipase essential to generate a lipid signal by specialized taste buds cells, iii) it can be isolated without major contamination with other cells adjacent to the CV unit (e.g. muscle cells) and iv) it is the most studied gustatory papillae in this species (for a review see [16]). CVP from control and DIO mice were isolated according to a previous published procedure [17]. In brief, lingual epithelium and sub-epithelial stromal tissue were enzymatically dissociated (elastase and dispase mixture, 2 mg/ml each in a Tyrode buffer, pH 7.4), then CVP was properly isolated from subjacent tissue under a binocular microscope before to be snap-frozen in liquid nitrogen and stored at −80 °C until transcriptomic analysis. After a blood collection, plasma was obtained by centrifugation (5000 g for 10 min, 4 °C) and stored at −20 °C until the LPS assay.

2.4. Two-bottle preference test

To analyze the impact of DIO or LPS on the ingestive behavior, individually housed mice were subjected to two bottle preference tests at the beginning of the dark period for 12 h. Animals were food restricted during the duration of the test [18]. This protocol provides behavioral data combining orosensory sensations (i.e. oral detection and central perception) and post-ingestive cues. Mice were subjected to a choice between a control (water) or an oily solution containing 2.0% rapeseed oil (w/v, Fleur de Colza, Lesieur, France) in water. Xanthan gum (0.3% w/v, Sigma-Aldrich, France) was added to control and oily solution in order to minimize textural cues between control and experimental solutions and enhance the stability of oily emulsion. At the end of the test, fluid intake was measured for each bottle and the preference for the oily solution (i.e. ratio between oily solution intake and total intake) was determined.

2.5. LPS assay

Plasma LPS levels were determined according to [19]. In brief, LPS-derived 3-hydroxyxymristate was extracted from plasma
samples with an organic solvent, separated by reversed phase HPLC, then quantitated by MS/MS.

2.6. Transcriptomic analysis

Total RNA in CVP from lean controls (n = 8) and DIO mice (n = 8) were extracted using a total RNA purification kit (Norgen Biotek, Canada) according to the manufacturer’s instructions. Briefly, the nitrogen-frozen CVP were homogenized in the lysing buffer with a RNase free piston pellet, then RNA were selected using purification columns and treated with an amplification grade DNase (RNase-free DNase I kit, Norgen Biotek, Canada) to ensure genomic DNA removal. Purified RNA was assayed using a nanodrop spectrometer (Thermo Fischer Scientific). Transcriptomic analysis was performed by the Get-TRIX platform (INRA, Toulouse, France) using Agilent Sureprint G3 Mouse microarrays (8 x 60 K, design 028005). For each sample, Cyanine-3 (Cy3) labeled RNA was prepared from 25 ng of total RNA using the One-Color Quick Amp Labeling kit (Agilent), followed by Agencourt RNAclean XP (Agencourt Bioscience Corporation, Beverly, MA). Cy3-labeled RNA (600 ng) was hybridized on a microarray slide. After washing, the slides were scanned on Agilent G2505C Microarray Scanner using Agilent Scan control A.8.5.1 software and the fluorescence signal was extracted using Agilent Feature (extraction software v10.10.1.1 with default parameters). One sample from lean controls didn’t pass the quality check and was excluded from the analysis. Microarray data and experimental details are available in the Gene Expression Omnibus (NCBI-GEO) database (accession GSE111719).

2.7. Statistics

Results are expressed as Means ± SEM. The significance of differences between groups was evaluated with Graph-Pad Prism (GraphPad Software). We first checked that the data for each group were normally distributed and that variances were equal. We then carried out two-tailed Student’s t-test, Two-way ANOVA with Sidak’s post-hoc test or Pearson’s correlation.
3. Results

3.1. Mice fed a high fat diet display a lower preference for oily solutions

HFD for 4 weeks renders mice obese as assessed by the significant increase of their body mass (Fig. 2-A, P < 0.001, t = 4.173; df = 37) and the two-fold rise in their fat mass (Fig. 2-B, P < 0.001, t = 6.234, df = 37). Consistent with our previous published data [3], DIO mice subjected to a long-term (12 h) two-bottle preference test showed a lower intake and preference for 2.0% oily solution than controls (Fig. 2-C & D, P < 0.001, t = 6.232, df = 37). Therefore, this data confirms that the chronic consumption of a saturated fat-rich diet decreases the spontaneous consumption of lipids.

3.2. DIO promotes the expression of inflammatory genes in circumvallate papillae

To determine whether the lower lipid preference observed in the high fat diet (HFD) fed mice could be partly explained by a functional impairment of the gustatory peripheral system, comparison of the transcriptional activities of CVP freshly isolated from lean and DIO mice were undertaken using micro-arrays. Among the genes differentially expressed, 10 were directly related to inflammation (Fig. 3-A), 8 encoding for pro-inflammatory proteins (Aif1, P < 0.001, t = 6.397, df = 13; Tlr12, P < 0.001, t = 5.091, df = 13; Slamf9, P < 0.001, t = 6.131, df = 13; Ptger1, P < 0.001, t = 4.681, df = 13; Ccl3, P < 0.01, t = 3.492, df = 13; C2cd4b, P < 0.05, t = 2.587, df = 13; Cxcl5, P < 0.01, t = 3.208, df = 13; Hif3a, [P < 0.05, t = 2.862, df = 13] [20–27, and 2] for molecules with anti-inflammatory properties (Nfil3, P = 0.08, t = 1.889, df = 13; ppp2Ca, P < 0.001, t = 4.921, df = 13) [28,29] (Fig. 3-A). The most of identified genes were tightly related to immune cells (Table 2) and encode for cytokines, receptors, transcription factors or enzymes (Fig. 3-B). As shown in Fig. 3-C, CVP from DIO mice displayed a pro-inflammatory transcriptomic pattern as compared to what was found in lean controls. To further gain insight into the identified genes, a transcriptomic network analysis was undertaken using the Ingenuity Pathway Analysis (IPA) software which combines a molecule interaction database (i.e. ingenuity knowledge base) and a network generation algorithm. This bioinformatics analysis generates the optimal gene network

Fig. 2. Typical phenotyping characteristics of controls (C) and diet-induced obese (DIO) mice. A- Body mass. B- Relative fat mass. C- Intake and preference for oily solution during two bottle preference tests. Means ± SEM, n = 19–20. *, P < 0.05; ***, P < 0.001.

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for a given set of transcriptomic data. It clearly highlighted that identified inflammatory genes were interconnected inside a gene network in which NFkB, IL2 and AKT genes appeared as major central nodes (Fig. 4). Interestingly, the proteins encoded by these transcripts are known to be key players in the inflammatory process. It is important to underline that the very low quantity of gustatory tissue available (a single CVP/mouse with a mass <0.5 mg) does not allow multiple assays on the same animal (e.g.

Table 2
Inflammatory-related genes differentially expressed in the circumvallate papillae from lean controls and DIO mice.

| Genes          | Names                               | Transcript Function                                                                 | References |
|----------------|-------------------------------------|-------------------------------------------------------------------------------------|------------|
| Aif1 (IBA1)    | Allograph inflammatory factor 1     | Cytokine. Chronic inflammation process. Activation of macrophages.                  | [20]       |
| Tlr12          | Toll-like receptor 12               | Receptor. Host resistance. Promote macrophage activation.                            | [21]       |
| Slamf9         | Signaling lymphotic activation molecule | Receptor. Increase the production of inflammatory cytokines by macrophages.           | [22]       |
| Ptger1         | Prostaglandin E2 receptor           | Receptor. Local inflammation mediated by PgE2. Activation of Th17.                   | [23]       |
| Ccl3 (MIP1a)   | Cytokine macrophage inflammatory protein | Chemokine. Induce the chemotaxis of monocytes.                                      | [24]       |
| C2cd4b (Nif2)  | C2 calcium-dependent domain containing 4B | Pro-inflammatory cytokine induced by IL1                                             | [25]       |
| Hif3a          | Hypoxia-inducible factor 3A         | Transcription factor. Pro-inflammatory cell signaling.                               | [26]       |
| Cxcl5          | Chemokine C-X-C motif ligand 5      | Chemokine. Chemotaxis of neutrophils. Increased during inflammation by IL1.          | [27]       |
| Nfii3 (E4BP4)  | Nuclear factor interleukin 3-regulated | Nuclear receptor. Inhibit IL12 produced by macrophages. Decrease inflammation.       | [28]       |
| ppp2Ca         | Ser-Thr protein phosphatase A2      | Enzyme. Disrupt the signal promoting TLR4-MyD88 association.                        | [29]       |

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transcriptomic and qPCR analyses) and thus constitutes significant experimental limitation.

3.3. Plasma LPS levels are inversely correlated with the preference for the oily solution

LPS are known to be inflammatory endotoxins released from the gram-negative bacteria cell wall. Since HFD-induced obesity and metabolic endotoxemia-mediated inflammation are tightly linked [30], and mouse TBC are able to release pro-inflammatory cytokines through TLR signaling pathways [31], the putative influence of blood LPS on the preference for dietary lipids was compared in lean and DIO mice. As expected, a higher plasma LPS levels was found in DIO mice as compared to lean controls suggesting a chronic low-grade inflammatory state in our DIO mouse model (Fig. 5-A, $P < 0.05$, $t = 2.669$, df = 34). This LPS-mediated endotoxemia was found to be positively correlated with fat mass (Fig. 5-B, $P < 0.05$, $r = 0.33$, $F = 4.904$). By contrast, plasma LPS levels and preference for oily solutions was negatively associated (Fig. 5-C, $P < 0.05$, $r = -0.496$, $F = 7.843$).

3.4. Induction of a chronic low-grade endotoxemia is not sufficient to alter the preference for oily solution in lean mice

To determine whether behavioral alterations observed in DIO animals leading to a decrease of lipid preference might be explained by this low-grade metabolic endotoxemia, a cohort of lean mice were subjected to a chronic LPS load by using intraperitoneal osmotic mini-pumps. As shown in Fig. 6-A, this protocol induced a chronic endotoxemia resulting in a rise of plasma LPS levels ($P < 0.001$, $t = 4.253/4.385/7.261/8.006$, df = 92) similar to those previously found in DIO mice (Fig. 5-A). The efficiency of the treatment was supported by the concomitant enlargement of liver ($P < 0.01$, $t = 3.373$, df = 23) [32] and spleen ($P < 0.05$, $t = 2.661$, df = 23) [33] observed in mice receiving the LPS (Fig. 6-B). LPS mice had a similar body mass growth than controls, suggesting that this LPS treatment did not elicit a change in their energy balance. Unexpectedly, LPS-treated mice displayed a similar preference for the oily solution than controls subjected to the vehicle alone, despite a two-fold rise in plasma LPS levels (Fig. 6-C).
4. Discussion

The hypothesis of a putative functional link between nutritional obesity, fatty taste detection/perception and motivational eating behavior is gradually substantiated in rodent models. However, origin of this relationship remains unknown. Using a whole transcriptomic gene profiling and bioinformatics analysis, we found that the chronic saturated high-fat feeding triggers a pro-inflammatory transcriptomic pattern in the CVP, as recently reported in the NAc, a brain area also involved in the food sensation [8]. This finding corroborates the conclusion of a recent study showing that the decreased number of taste buds found in CVP from DIO mice was lacking in TNFα-null mice fed a high-fat diet suggesting that taste dysfunction in obesity might result of systemic inflammation [34]. The most of identified genes being related with inflammatory cells (i.e. monocytes/macrophages, lymphocytes, neutrophils), it is likely that our obesogenic diet promotes a cell remodeling in the direct vicinity of TBC. IPA analysis reveals that the identified inflammatory genes belong to a network in which NFkB, a transcription factor driving gene expression of pro-inflammatory cytokines [35], appears to be one of the central nodes. Interestingly, a diet high in saturated fat also induces a NFkB-mediated neuroinflammation response in the NAc, heightened food cravings in the mouse [8]. It is noteworthy that the NFkB gene expression is known to be LPS sensitive [36]. Since i) an excessive high fat feeding is associated with a low-grade systemic endotoxemia by promoting intestinal dysbiosis and permeation [30], ii) LPS induce the gene expression of key players of the inflammatory response (e.g. NFkB, TLR) identified in the CVP from DIO mice, iii) TBC express the TLR-4 signaling cascade [13] (Fig. 5-D), iv) a LPS overload decreases the TBC life span and renewal [14] and v) an inverse correlation between plasma LPS levels and preference for fat was found in DIO mice (Fig. 5-C), it was tempting to speculate that the low-grade LPS-mediated inflammation found in DIO mice might contribute to the impairment of their orosensory perception of lipids.

Exploration of this assumption was carried out in lean mice fed a standard laboratory chow by using mini-osmotic pumps filled with LPS. Surprisingly, a chronic LPS-induced low-grade inflammation failed to reproduce in lean mice the impairment of the preference for oily solution found in obese mice. Variation of the LPS structure constitutes a specific bacterial signature playing a significant role in the innate immune recognition [37]. Therefore, all LPS are not endotoxins. It is noteworthy that the LPS-type used herein (i.e. E. coli, serotype 055/B5) displays an endotoxemic activity. Indeed, an acute load of this LPS-type triggers typical behavioral changes (prostration, shivering, eyes closed, reduced respiration, anorexia [38]) associated with a septic shock in the mouse (observational data).
and its chronic infusion promotes significant spleen and liver mass gain (Fig. 6-B), as expected [32,33]. Moreover, continuous infusion of this LPS through mini-osmotic pumps designed to deliver the same quantity than that used in the present study is able to induce the glucose-stimulated insulin secretion [39], demonstrating its biological efficiency.

This unexpected result demonstrates that a chronic moderate systemic LPS-mediated endotoxemia cannot explain alone the eating behavioral change observed in DIO mice. The fact that their TLR-4 mRNA level in CVP was unchanged as compared to lean controls (Fig. 5-D) is consistent with this assumption. Indeed, the preference for fat is positively correlated to the expression of this LPS receptor in this tissue [40]. Therefore, origin of the behavioral change observed in mice fed this obesogenic diet is probably more complex than initially expected [41]. The following integrative scenario may be proposed (Fig. 7). The chronic consumption of an obesogenic diet elicits a shift in the gut microbiota composition and a progressive body fat accumulation. Collectively, these changes might promote a new inflammatory and endocrine environment affecting both the oral lipid detection (taste bud level) and the central treatment of the peripheral lipid signal by the brain areas responsible for the taste perception and food reward (i.e. cortico-mesolimbic system). These sensory alterations might create an obesogenic detrimental circle promoting energy-dense foods seeking and consumption in order to make up the sensory and hedonic deficits (For details see [41]). To date, this working model is likely incomplete and somewhat speculative.

In conclusion, the present data corroborate the lowering of the preference for oily solutions in DIO mice and bring the demonstration that the chronic consumption of an obesogenic diet rich in saturated fatty acids induces a pro-inflammatory gene profile in the mouse CVP. Despite the role played by LPS in the promotion of inflammatory response, no causal relationship between the induction of a chronic low-grade systemic endotoxemia and the fat preference was found suggesting that origin of taste dysfunction in obesity results of a complex systemic dysfunction.

Understanding the molecular mechanisms by which the nutrient composition of diet may affect orosensory fat perception might lead to new food formulations favoring a healthier eating behavior and contributing to limit the progression of the obesity epidemic.

Disclosures

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.
Fig. 7. Putative mechanisms that could explain the change in the preference for fat in DIO mice: Working model. Chronic consumption of an obesogenic diet (e.g. saturated high fat diet) leads to a shift in the gut microbiota composition and a progressive body fat accumulation. These changes might promote a chronic low-grade inflammation (e.g. endotoxin release and production of pro-inflammatory cytokines) and a new endocrine balance (e.g. drop of GLP-1 and rise of leptin) decreasing the oral lipid acuity (taste bud level) and related reward response (corticoemolimbic level). Taken together these alterations might promote an over-consumption of energy-dense foods to compensate the sensory deficit.

Acknowledgements

This study was supported by grants from the French National Research Agency: SensoFAT-2 project (ANR-12-BSV1-0027-01 to P.B.) and ANR-11-LABX-0021-LipSTIC (to L.L.). AB was a post-doctoral fellow from ANR-11-LABX-0021-LipSTIC. The authors thank Jean-Christophe Blanchard for the animal management, Guillaume Maquart and Jean-François Merlin for the technical assistance and Jean-Paul Pais de Barros from the Lipidomic platform (Univ Bourgogne-Franche Comté) for LPS assays.

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