

# Fatty taste variability in obese subjects: the oral microbiota hypothesis<sup>☆</sup>

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**Abstract** – Origin of the great inter-individual variability of the fatty taste perception found in obese subjects is challenging. The fact that recent studies suggest interrelations between taste perception and oral microbiota composition, prompt us to explore the putative impact of such a connection in the context of obesity. To check this hypothesis, the oro-sensory perception thresholds of linoleic acid and the composition of oral microbiota surrounding the gustatory circumvallate papillae (CVPs) were analyzed in obese adult men (BMI  $\geq 30$  kg/m<sup>2</sup>,  $n=42$ ). A specific microbial signature (higher diversity, pro-inflammatory bacterial profile, lower methanogenesis activity) discriminated subjects with a degraded fatty taste sensitivity (perception threshold  $\geq 0.05\%$  LA = Low-LA tasters,  $n=22$ ) from high-LA tasters ( $n=20$ ). Collectively, these data substantiate the association between the microbial microenvironment surrounding CVPs and the fatty taste sensitivity and provide a plausible explanation about the variability of the fatty taste sensitivity in obesity.

**Keywords:** Circumvallate papillae / oral microbiota / taste sensitivity / lipids / obesity

**Résumé – Variabilité du goût du gras chez les sujets obèses: l'hypothèse du microbiote oral.** L'origine de la grande variabilité inter-individuelle de la perception gustative des lipides alimentaires chez les sujets obèses est énigmatique. Le fait que des études récentes suggèrent que la composition du microbiote oral pourrait jouer un rôle dans la sensibilité gustative, nous a incité à explorer cette piste dans le cadre d'une obésité. Pour tester cette hypothèse, les seuils de perception oro-sensorielle d'un lipide modèle (acide linoléique – LA) ainsi que la composition du microbiote oral présent au niveau des papilles gustatives calciformes (CVPs) ont été analysés chez des hommes adultes obèses (IMC  $\geq 30$  kg/m<sup>2</sup>,  $n=42$ ). Cette approche nous a permis de montrer que les sujets hyposensibles dont la perception lipidique est dégradée (Low-Lipid tasters ou LLT, seuil  $\geq 0,05\%$  LA,  $n=22$ ) se distinguent des sujets hypersensibles (High-lipid tasters HLT,  $n=20$ ) par une signature microbienne spécifique caractérisée par une plus grande diversité, un profil pro-inflammatoire et une activité méthanogénique réduite. Ces résultats inédits confirment l'existence d'un lien fonctionnel entre le micro-environnement microbien des CVPs et la perception gustative et fournissent une explication plausible à la variabilité inter-individuelle de la perception orosensorielle des lipides alimentaires observée chez les sujets obèses.

**Mots clés :** Papilles gustatives calciformes / microbiote oral / sensibilité gustative / lipides / obésité

## 1 Introduction

Increasing prevalence of obesity constitutes a major public health challenge worldwide due to associated comorbidities (e.g. type-2 diabetes, hypertension or cardiovascular disease).

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Obesogenic behaviors notably the over-consumption of high palatable (*i.e.* pleasant) energy dense foods and a sedentary lifestyle are undoubtedly major contributors to this phenomenon by generating a chronic imbalance between calories consumed and expended. Conversely, studies indicate that obesity can also be associated with a preferential consumption of fat-rich foods (Mela and Sacchetti, 1991; White *et al.*, 2002; Drewnowski 2003). However, origin of this obesogenic food selection remains poorly understood. Among the sensory systems, taste plays a significant role in the food choice and, thereby, their intake. Taste sensation is detected by the interaction of

a chemosensory stimulus (*e.g.* long-chain fatty acids) with a specific receptor (*e.g.* CD36) located in the taste bud cells, found mainly upon the tongue dorsum. Resulting taste signal is integrated at the brain levels to other sensory and metabolic information contributing to the decision to eat. Interestingly, neuroimaging studies have highlighted in obese subjects the existence of functional alterations in brain areas (*i.e.* cortico-mesolimbic system) involved in the food sensations, including taste, and in the reward processing (Carnell *et al.*, 2012; Besnard, 2016). This “obese brain” phenotype (de Lima-Junior *et al.*, 2015) might contribute to the susceptibility to overeat lipid-rich foods (Berridge *et al.*, 2010; Berthoud, 2011, Volkow *et al.*, 2013). Paradoxically, involvement of alterations of the oral taste circuitry in this unhealthy food choice remains poorly investigated in human.

Relationship between intestinal dysbiosis and obesity is well documented (Turnbaugh *et al.*, 2006). Oral dysbiosis has also been reported in obese subjects (Goodson *et al.*, 2009). In the oral cavity, the main reservoir of bacteria is located upon the dorsal part of the tongue and displays a complex spatially structured microbial community (Wilbert *et al.*, 2020). In contrast to other lingual papillae, the circumvallate papillae (CVPs) exhibit a dome-shape structure with a circular cleft potentially favorable to the development of specific multispecies bacterial communities. The fact that CVPs also house the most of oral taste buds renders these papillae attractive for studying the relationships between microbiota and taste sensitivity. Therefore, to test this hypothesis, oro-sensory detection thresholds of a model lipid (linoleic acid, LA) were determined in combination with oral microbiota composition surrounding the CVPs of obese volunteers.

## 2 Materials and Methods

### 2.1 Subjects

Forty-two male subjects, 26–74 years of age and BMI > 30 kg/m<sup>2</sup>, participating to the HumanFATaste program, were included in this study. All subjects received detailed information about the study and gave written consent (ANSM n° B90706-40). HumanFATaste was approved by the local ethics committee (Comité de Protection des Personnes—CPP Est1, n° 2009/18) and registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02028975) (#NCT02028975).

### 2.2 Oral lipid perception

The determination of orosensory perception threshold of lipids was performed using the three-alternative forced-choice test (Chale-Rush *et al.*, 2007), with linoleic acid (LA) as lipid model (Chevrot *et al.*, 2014). To limit ingestive and post-ingestive interferences on oral lipid perception, tests were performed in the morning in fasted subjects. The protocol used is fully detailed elsewhere (Chevrot *et al.*, 2014). In brief, to minimize textural cues between control and experimental solutions (from 0.00028% to 5% LA wt/wt, spaced by 0.25 log units), 5% acacia gum and 5% mineral oil (wt/wt) were added in mineral water. Subjects had to identify the LA solution among 3 samples. Each sample (5 ml) was kept in the mouth for 7 s then spit out, before tasting the next sample 20 s later. The use of alimentary dyes demonstrated that this protocol allows the contact of the solutions with the whole dorsal

tongue including the CVPs. Sets were offered in an ascending concentration of LA with a break of 60–120 s between 2 sets, allowing a mouth rinsing with water. The procedure was stopped when a LA sample was correctly identified 3 times, consecutively. This concentration constitutes the LA perception-threshold of the subject. Testing was conducted under red lighting and with participants wearing a nose clip to limit visual and olfactory inputs, respectively.

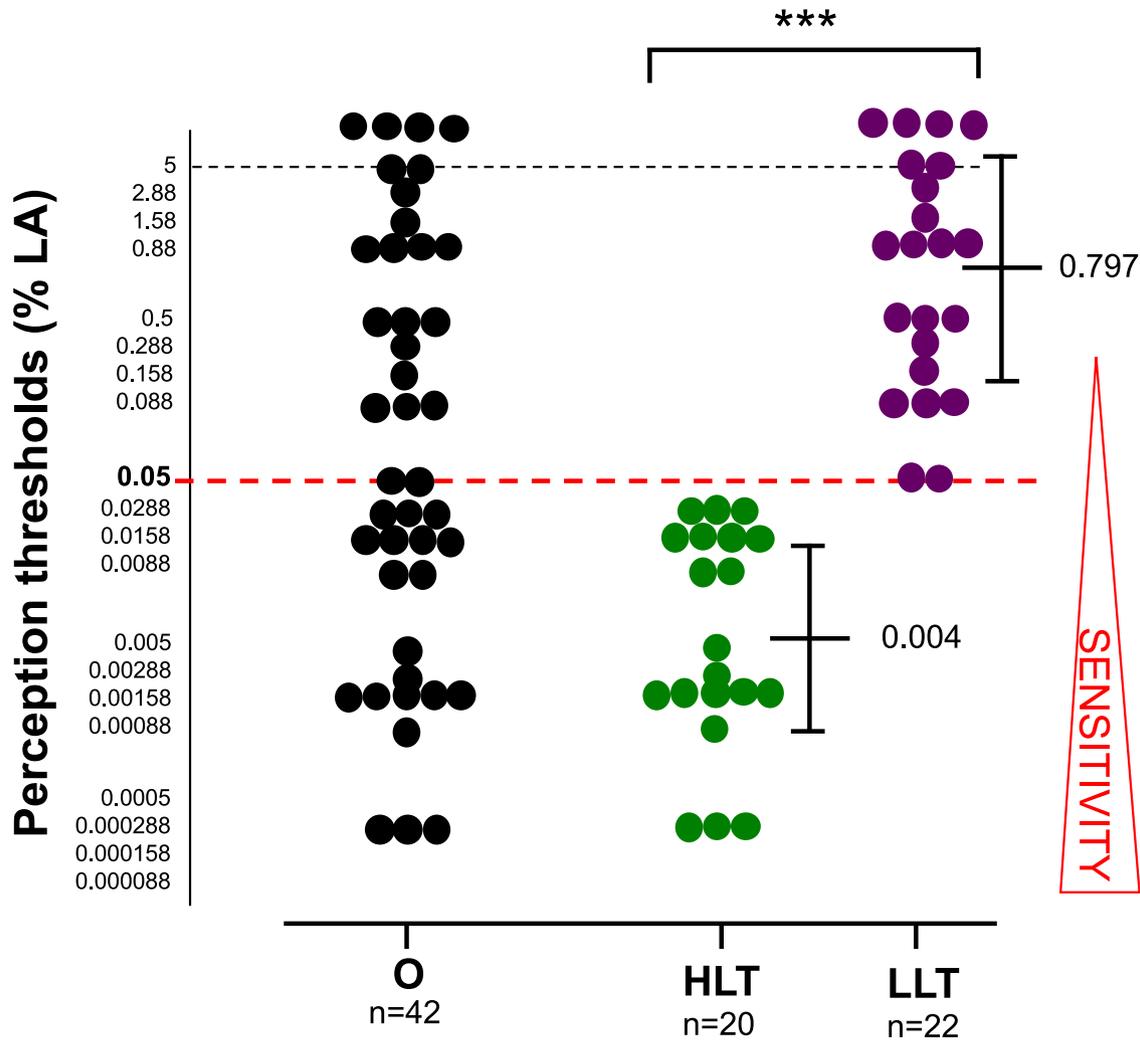
### 2.3 Oral microbiota samples and analysis

Swab samples were taken directly from the V-shaped row formed by the dozen CVPs found at the posterior part of the tongue dorsum to collect associated microbiota. These gustatory papillae were preferred to fungiform and foliate papillae because the CVPs house the most of the taste buds found in lingual epithelium. Moreover in contrast to other gustatory papillae, the CVPs display a dome-shape structure with a circular cleft favorable to the development of specific bacterial communities. Consistent with this assumption, a recent analysis of microbiota distribution across the human dorsal tongue highlighted a complex spatial organization with multiple microbial consortia (Wilbert *et al.*, 2020).

### 2.4 Oral microbiota analysis

Total bacterial DNA was extracted as previously described (Paisse *et al.*, 2016). The bacterial population present in the samples has been determined using next generation high throughput sequencing of variable regions of the 16S rRNA bacterial gene (Paisse *et al.*, 2016). V3-V4 hyper-variable regions of the 16S rDNA gene were amplified from the DNA extracts during a first PCR step using universal 16S primers V2, as described (Paisse *et al.*, 2016). The targeted metagenomic sequences from microbiota were analyzed using an established bioinformatics pipeline (Paisse *et al.*, 2016). Specifically after demultiplexing of the barcoded Illumina paired reads, single read sequences were cleaned and paired for each sample independently into longer fragments. To obtain optimal results, the last 80 bases of the R2 reads were trimmed due to low base quality score. After alignment against a 16S reference database, sequences were clustered into operational taxonomic units (OTU) with a 97% identity threshold. Remaining sequencing errors were filtered out by eliminating the OTU with less than 3 sequences, and a taxonomic assignment was performed in order to determine community taxonomic profiles against the RDP database using the RDP Classifier tool. An average of 61 842 raw pairs (123 684 raw reads) per sample were obtained by sequencing and 59 369 pairs (118 737 reads) were conserved after QC filters. To estimate individual CVP microbial alpha diversity, rarefaction curves were generated based on metrics and the number of OTUs present in the samples was determined (Shannon diversity index). The taxonomic output matrix containing the count data for OTUs per sample was processed with the online Galaxy interface for LEfSe (linear discriminant analysis effect size) (Segata *et al.*, 2011) algorithm using sample normalization, an alpha parameter significance threshold for the Kruskal-Wallis (KW) test among classes set to 0.05, and the logarithmic LDA score cut-off set to 2.0.

The functional metagenome was inferred from the clustered 16S sequences using the PICRUSt software (version 1.0.0) as per



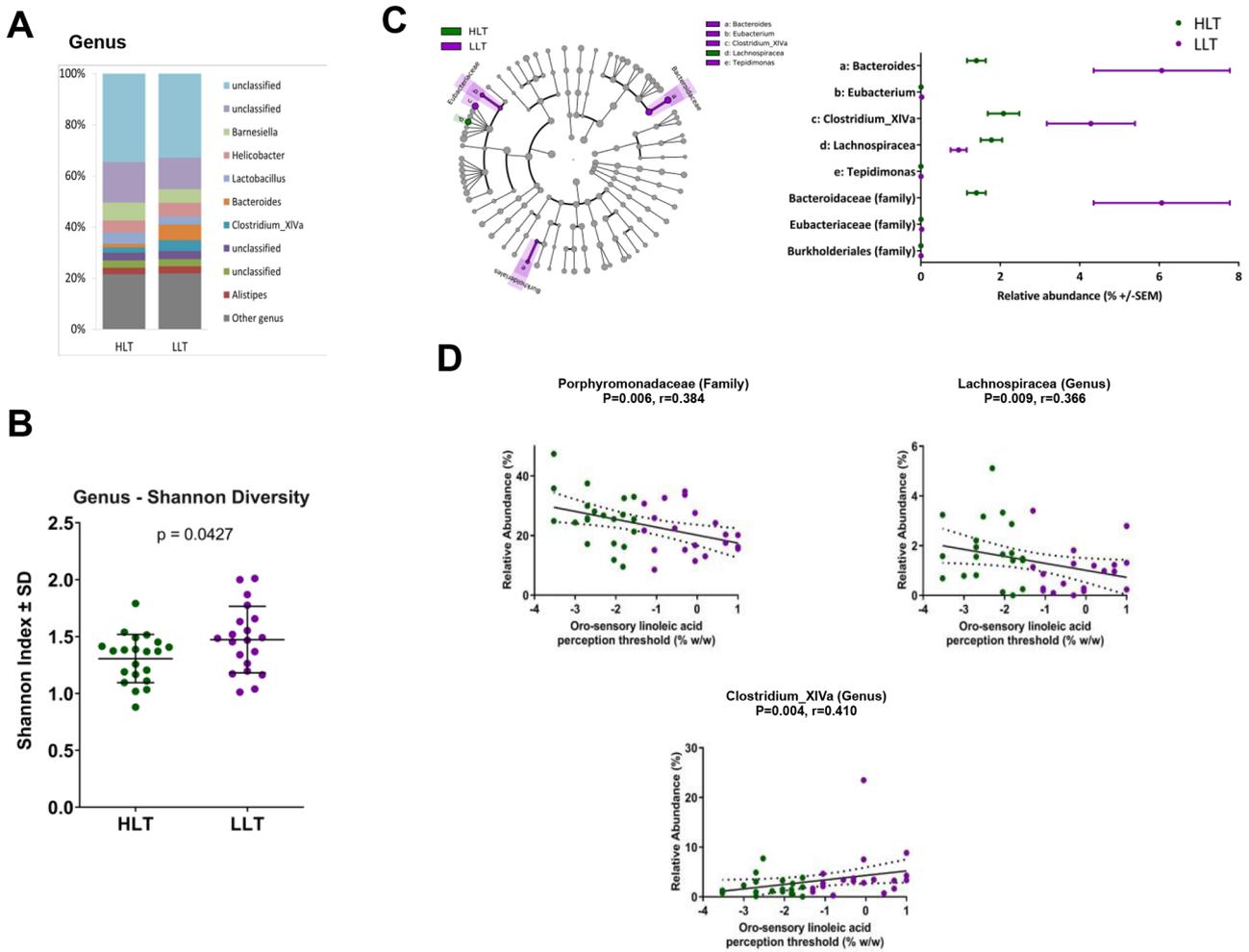
**Fig. 1.** Orosensory variability of lipid perception in adult obese subjects. Lipid perception thresholds performed using the three-alternative forced-choice tests with linoleic acid (LA) as lipid model. To explore the putative links between orosensory perception of LA and oral microbiota composition, and to overcome limitation due to the great variability of lipid perception, it was postulated that all the subjects displaying a threshold value  $\leq 0.05\%$  LA (*i.e.* LA median value) were high-LA tasters (HLT), others being low-LA tasters (LLT) Mean  $\pm$  SEM,  $p < 0.001$ . O, obese subjects.

the instructions provided for the Genome Prediction Tutorial for PICRUSt (<http://picrust.github.io/picrust/tutorials>) with recommended scripts and default settings (Langille *et al.*, 2013). As described in the PICRUSt tutorial, the sequences previously grouped into OTU were processed through the QIIME closed reference OTU picking tool with a 97% similarity threshold to obtain a set of OTU IDs from the Greengenes reference collection (gg\_otus\_13\_5.tar.gz) as input for prediction of corresponding metagenomes by PICRUSt. Through this inference process, the abundance values of each OTU were normalized to their respective predicted 16S rRNA copy numbers and then multiplied by the respective gene counts for metagenome prediction. PICRUSt was also used to calculate the nearest sequenced taxon index (NSTI) to quantify dissimilarity between reference genomes and the predicted metagenomes. The resulting core output was a list of Kyoto Encyclopedia of Genes and Genomes (KEGG) orthologues and predicted gene count data for each sample. We used in house scripts to parse the output into KEGG module categories for functional pathways and structural complex hierarchies using the KEGG database

(<http://www.genome.jp/kegg/module.html>). The output matrix containing the relative abundance of KEGG orthologous groups (KO) per sample was processed with the online Galaxy interface for LEfSe using an alpha parameter significance threshold for the Kruskal-Wallis (KW) test among classes set to 0.05 and the logarithmic LDA score cut-off set to 2.0. Respective cladograms were generated with modules at the lowest level. Quantitative plots of differential features were generated from normalized module level predicted gene data showing means with standard deviation using GraphPad Prism 7.05 software (GraphPad Software, La Jolla, CA, USA). Pathway KO differential enrichment images were generated using KEGG Mapper (v2.8) (Kanehisa *et al.*, 2012). Functional hierarchies of differentially enriched KO were generate using the KEGG BRITE database.

## 2.5 Statistical analysis

For the peri-papillae microbiota, the output matrix containing the relative abundance of OTUs per sample was



**Fig. 2.** Microbiota composition surrounding the gustatory circumvallate papillae (CVP) in high-lipid tasters (HLT) and low-lipid tasters (LLT). A. Distribution of the most abundant resolved taxa at the genus level. B. Microbiota alpha diversity (Shannon index). C. LefSe cladogram of 16S sequences from CVP and histogram showing the taxonomic groups from phylum to genus and relative abundance plots for significant genera and family differential features. The cladogram shows the taxonomic levels represented by rings with phyla at the innermost ring and genera at the outermost ring, and each circle is a member within that level. Taxa at each level are shaded according to the group in which it is most abundant ( $P < 0.05$ ; LDA score 2.0). D. Selected regression plots for significant Spearman rank correlations between LA perception and relative abundance of identified target bacteria.

processed with the LefSe (linear discriminant analysis effect size) algorithm using an alpha cut-off of 0.05 and an effect size cut-off of 2.0. Statistical analyses (non-parametric Mann-Whitney's tests and non-parametric Kruskal-Wallis tests followed by Dunn's multiple comparison tests and Spearman's correlations) were conducted using the software PRISM (v6.05 for Windows, GraphPad Software, La Jolla California USA) and the software environment R version (v3.3.1; The R Foundation, Vienna, Austria).

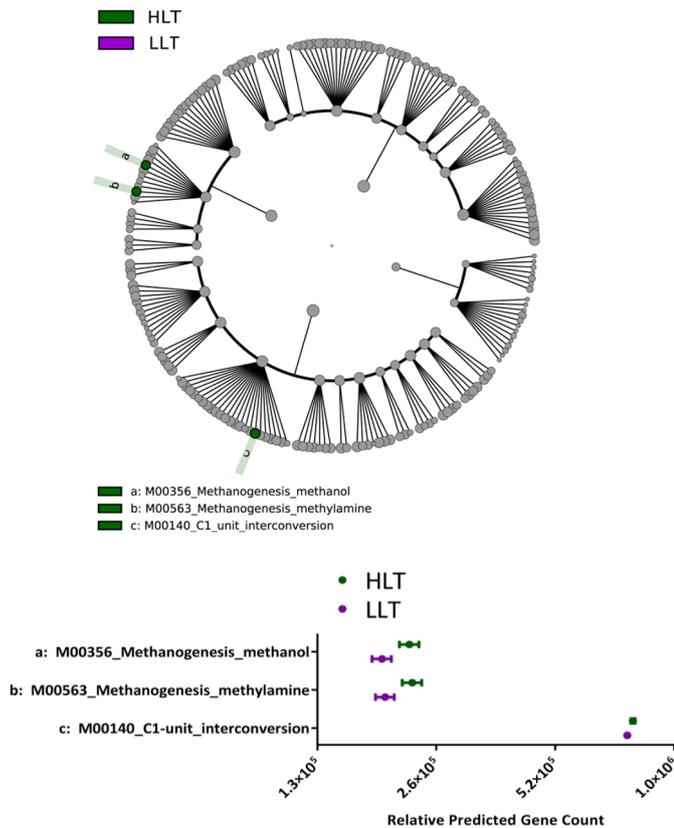
### 3 Results

#### 3.1 Differences in the microbiota surrounding circumvallate papillae were found between low- and high-LA obese tasters

Consistent with previous studies (Chale-Rush *et al.*, 2007; Chevrot *et al.*, 2014), a large interindividual variability of LA

perception was found in obese (O) subjects (Fig. 1A). This phenomenon was independent of adiposity since HLT and LLT displayed similar BMI ( $36.08 \pm 1.06$  vs.  $35.04 \pm 1.19$  kg/m<sup>2</sup>,  $p=0.28$ ) and abdominal waist ( $1.18 \pm 0.02$  vs.  $1.16 \pm 0.02$  m,  $p=0.55$ ). To further explore the putative links between orosensory perception of lipids and CVPs microbiota composition, we postulated that all the subjects displaying a threshold value  $\leq 0.05\%$  LA (*i.e.* median LA concentration value) were high-LA tasters (HLT), others being low-LA tasters (Fig. 1). This new analysis led to two groups of similar size ( $n=20$  and  $22$  in HLT and LLT, respectively).

In LLT patients, an increase in the abundance of *Bacteroidaceae* family (notably *Bacteroides* genus) and *Clostridium\_XIV* was associated with a decrease in *Lactobacillus* (Fig. 2A). A significant increase in alpha diversity was also found in this group as compared to HLT, but only at the genus level (Fig. 2B). The LefSe analysis identified five discriminating genera (Fig. 2C). This difference was mainly



**Fig. 3.** Putative microbial molecular pathways differentially abundant in high-lipid tasters (HLT) and low-lipid tasters (LLT) in the direct vicinity of gustatory circumvallate papillae (CVPs). The LefSe cladogram shows the KEGG metabolic pathway hierarchy represented by rings with the consolidated pathway modules (identified in the legend) at the outermost ring, and each circle is a member within that level. KEGG modules are shaded in color according to the group in which it is most abundant ( $P < 0.05$ ; LDA score 2.0).

due to the higher frequency of *Bacteroides* and *Clostridium\_XIV* in the LLT group. Spearman rank correlation coefficients ( $\rho$ ) were computed for all levels of the microbiome taxonomic abundance in combination with LA perception thresholds (Fig. 2D). It was found a significant positive correlation between LA perception and the *Bacteroides* and *Clostridium\_XIV*, and a negative one for *Lachnospiraceae* (Fig. 2D).

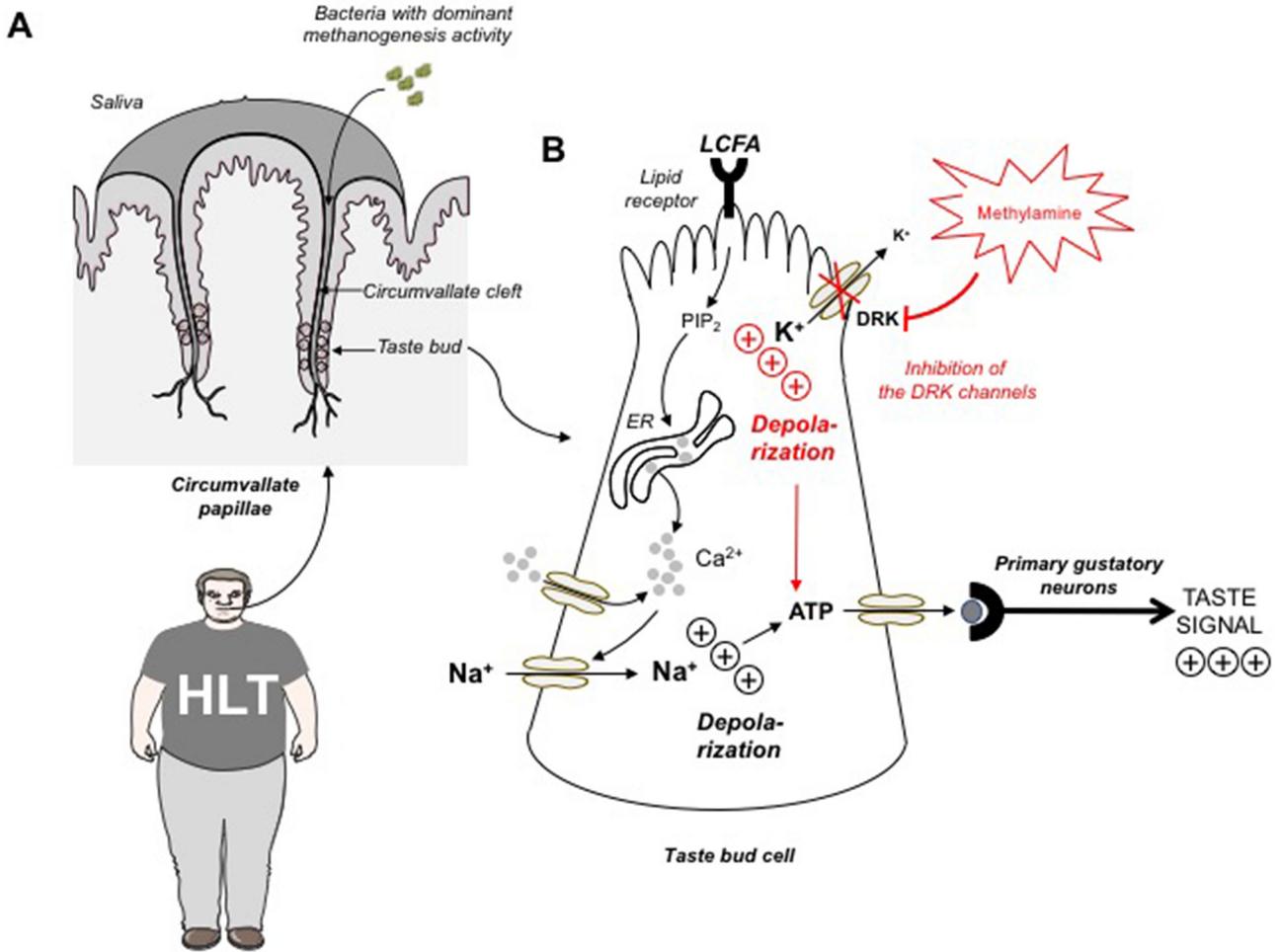
To generate hypotheses regarding the putative microbial molecular pathways involved we performed a predicted metagenomics analysis using PICRUSt to identify the relative abundance of KEGG modules for metabolic pathways and structural complex features. A LefSe analysis identified 3 KEGG modules with differential metabolic pathway features between LLT and HLT, with a high proportion of this difference due to a module related to counts for the methanogenesis pathway (*i.e.* methanol and methylamine), which was less prevalent in the LLT group (Fig. 3).

## 4 Discussion

Some obese subjects overeat lipid-rich foods (Drewnowski *et al.*, 1985; Mela and Sacchetti, 1991; White *et al.*, 2002).

Origin of this obesogenic eating behavior is poorly understood despite its long-term negative impacts on the quality of life. A body of evidence, mainly obtained in rodents (Berthoud *et al.*, 2011; Besnard 2016), strongly suggests that obesity may compromise the orosensory sensitivity to food stimuli, but the underlying mechanisms remains elusive. Recent studies suggest the existence of an association between taste sensitivity and lingual microbiota composition in humans (Besnard *et al.*, 2018; Cattaneo *et al.*, 2019; Mameli *et al.*, 2019). Using the bitter tastant propylthiouracil to segregate tasters from non-tasters in healthy volunteers, it was shown that the microbial composition of tongue dorsum was different between two groups, this change being correlated with the efficiency of orosensory perception to bitter, sweet, salty and sour stimuli (Cattaneo *et al.*, 2019). A relationship between specific microbiota signatures and fatty taste sensitivity was also reported by comparing obese lipid-tasters ( $n=9$ ) and lipid-non tasters ( $n=8$ ), (Besnard *et al.*, 2018). Nevertheless, the significance of this last result is limited by the small sample size. The aim of the present study was to further explore this issue.

Overall, current data strengthen our previous results (Chevrot *et al.*, 2014; Besnard *et al.*, 2018) and provide additive new information. Firstly, they show that fatty taste variability in obese subjects is independent of adiposity, in contrast to what is found in mice (Chevrot *et al.*, 2013). Indeed, HLT and LLT displayed similar BMI, and circumference waist. This observation is significant given the controversy about the impact of BMI, as variable in the oral lipid sensitivity in humans, some studies report a negative correlation while no association is found in others (for a review, see Tucker *et al.*, 2017). Secondly, they substantiate the fact that LLT subjects are characterized by a greater microbiota diversity and a pro-inflammatory signature due to a high *Bacteroides/Lactobacillus* ratio as compared to HLT subjects. Such a bacterial environment, in the direct vicinity of CVP, might interfere with the fatty taste perception since obesity-induced inflammation reduces the taste bud density and turnover in the mouse (Kaufman *et al.*, 2018), an event known to specifically reduce the fatty taste sensitivity in humans (Jilani *et al.*, 2017). Consistent with this assumption, the oral *Bacteroides* abundance and the LA perception thresholds were found positively correlated in obese subjects (Fig. 2D). Therefore, it is tempting to speculate that the high *Bacteroides* frequency found in LLT might participate to their inability to detect properly low lipid stimuli. Thirdly by using a predicted metagenomic approach, the present data highlighted a predominant microbial metabolic pathway discriminating LLT from HLT subjects. Identified genes were involved in the methanogenesis with methanol and methylamine, as end-products. Methylamine is a bioactive molecule implicated in eating behavior by inhibiting shaker-like KV1 potassium channels (Pirisino *et al.*, 2001). Such a blocking activity might also play a role at the gustatory papillae level according to the following working model. In HLT patients, bacteria lining the CVP with a dominant methanogenesis activity release methylamine in the CVP cleft, where taste buds are located (Fig. 4A). During the prandial period, activation of taste bud cells expressing lipid receptors (*e.g.* CD36) by long-chain fatty acids (*e.g.* LA) triggers a signaling cascade leading the cell depolarization required to generate a lipid signal (Fig. 4B).



**Fig. 4.** Fatty taste variability in obese subjects: the oral microbiota hypothesis. A. Schematic structure of circumvallate papillae. B. Simplified LCFA-mediated signaling in taste bud cells (modified from (Besnard *et al.*, 2016)). HLT: High-lipid taster; LCFA: Long-chain fatty acid; ER: Endoplasmic reticulum; DRK: Delayed rectifying K<sup>+</sup> channel; PIP<sub>2</sub>: Phosphatidyl-inisitol diphosphate.

By inhibiting the KV1 potassium channels located in plasma membrane of the taste receptor cells (Liu *et al.*, 2005), methylamine amplifies the cell depolarization, and thereby the intensity of the fatty taste signal (Fig. 4B). Methanogenesis being prevalent in HLT subjects as compared to LLT subjects (Fig. 3), this scenario provides an original regulatory mechanism linking the bacterial metabolism and fatty taste sensitivity. Further investigations are needed to validate this hypothesis. Altogether these data strengthen our previous investigation suggesting the existence of functional links between microbiota surrounding CVP and fatty taste sensitivity.

In conclusion, a variation in the oral microbiota composition might affect the orosensory perception of food in an obesity context. Since we have previously found that obese patients unable to detect LA preferentially consumed energy-dense foods (Chevrot *et al.*, 2014), the composition of oral microbiota in direct vicinity of gustatory papillae might be predictive of unhealthy food habits. Identification of microbial biomarkers might provide a useful tool for identifying these patients at risk and offer them appropriate nutritional care.

## Supplementary Material

**Supplementary Table S1:** KEGG Module Path P and Q values. The Supplementary Material is available at <http://www.ocl-journal.org/10.1051/oc/2020033/olm>.

## Abbreviations

CVP	Circumvallate papillae
HLT	High linoleic acid tasters
KEGG	Kyoto encyclopedia of genes and genomes
LA	Linoleic acid
LLT	Low linoleic acid tasters

## Disclosures

PB, JEC, AB, IRS, XC and BV have nothing to disclose. RB is a founder and has shares of Vaiomer S.A.S., which is providing the microbiota sequencing data.

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