Hormones and Behavior 145 (2022) 105235

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Sex difference in human olfactory sensitivity is associated with plasma adiponectin

Daniela M. Pfabigan [a,b], Cecilia Vezzani [a], Per Medbøe Thorsby [c], Uta Sailer [a,*]

[a] Dept. of Behavioural Medicine, Institute of Basic Medical Sciences, Faculty of Medicine, University of Oslo, Oslo, Norway
[b] Morbid Obesity Centre, Department of Medicine, Vestfold Hospital Trust, Tønsberg, Norway
[c] Hormone Laboratory, Dep of Medical Biochemistry and Biochemical Endocrinology and Metabolism Research Group, Oslo University Hospital, Aker, Oslo, Norway

ARTICLE INFO

Keywords:
Odour threshold
Ghrelin
Gut hormones
Food restriction
Fasting

ABSTRACT

Energy deprivation as well as hormones that regulate appetite and eating can influence olfactory function. This study investigated olfactory sensitivity for a food-related and a non-food odour prior to and after a meal, and its relationship to the energy-regulating hormones ghrelin and adiponectin.

The olfactory sensitivity for orange and rose (PEA) odour in healthy, normal-weight volunteers (19 women, 45 men, 1 undisclosed individual) was not affected by the consumption of a meal. Olfactory sensitivity was not associated with concentrations of circulating ghrelin. However, olfactory sensitivity was higher for women than for men, indicating better olfactory performance. This difference between women and men was related to concentrations of plasma adiponectin, an adipose-specific hormone.

Adiponectin may thus explain why sex differences in olfactory sensitivity emerge, and may also account for some of the inconsistencies in previous findings on sex differences. Our findings add to the limited literature on the impact of stomach and adipose tissue-derived hormones on olfactory sensitivity. Further studies are needed to establish a causal link between circulating adiponectin and a sex difference in olfactory sensitivity.

1. Introduction

The olfactory system plays a fundamental role in locating, identifying and enjoying food. The sense of smell can influence our food choices (Chambaron et al., 2015; Fedoroff et al., 1997; Gaillet-Torrent et al., 2014) and eating behaviour (e.g.; Sailer et al., 2016). Food odours perceived orthonasally appear to be predictive cues for the availability of nutrients (Small et al., 2005). In line with this, it has been shown that odours induce specific appetite for the same food (Boesveldt and de Graaf, 2017). For instance, individuals ate more pizza after they had been exposed to pizza odour compared to no odour (Fedoroff et al., 1997). Such odour-induced appetite can also generalize from one energy-dense food to other energy-dense foods (Zoon et al., 2016).

In addition to odours affecting appetite, it is likely that hunger or satiety in turn influence the way we perceive odours. Experiments testing this assumption date back as far as 1928 (Glaze, 1928). In this study, the sensitivity to various odours such as cedar wood and Russian leather increased during fasting for 5–10 days, a finding that was replicated in a subsequent experiment where the participants were tested before and after a meal. Since then, the finding of increased sensitivity to odours in a hungry state has been corroborated in rats (Aime et al., 2007) and humans (e.g., Goetzl and Stone, 1947; Hammer, 1951; Ramaekers et al., 2016); but see also (Janowitz and Grossman, 1949; Koelega, 1994) for conflicting findings in humans.

Despite the studies on the role of metabolic state on olfactory sensitivity, the underlying mechanisms remain poorly understood. To address this knowledge gap, the current study aimed to investigate the role of two appetite-regulating hormones on human olfactory sensitivity: ghrelin and adiponectin. Ghrelin is an appetite-stimulating hormone secreted mainly by the stomach (Kojima et al., 1999). Before meals, circulating ghrelin levels increase, whereas they decrease after meals (Cummings et al., 2001), affecting energy regulation in the short term. Ghrelin administration augments food intake in rats (Tschop et al., 2000) and in both healthy and obese humans (Druce et al., 2006, 2005). Ghrelin administration also enhanced food palatability in obese individuals (Druce et al., 2005), and increased brain activation in regions involved in encoding rewarding stimuli following the presentation of food pictures (Malik et al., 2008).

Ghrelin receptors have been identified in the rat brain's olfactory system (Cowley et al., 2003; Loch et al., 2015), and ghrelin binds to

* Corresponding author at: Dept. of Behavioural Medicine, Faculty of Medicine, Postboks 1111, Blindern, Oslo 0317, Norway.
E-mail address: uta.sailer@medisin.uio.no (U. Sailer).

https://doi.org/10.1016/j.yhbeh.2022.105235
Received 31 March 2022; Received in revised form 4 July 2022; Accepted 5 July 2022
Available online 20 July 2022

receptors in circuits of the olfactory pathway (Rhea et al., 2018; Tong et al., 2011). Similarly, ghrelin increases the reactivity of olfactory neurons in mice, and this effect can be abolished by treatment with a ghrelin receptor antagonist (Loch et al., 2015). Consistent with these findings, ghrelin administration increased sniffing behaviour and odour detection in rats, further strengthening the notion that ghrelin increases the responsivity to odours and modulates olfactory behaviour. For humans, the picture is less clear. Ghrelin was found to increase sniff (i.e., inhalation) magnitude for food- and non-food-related odours, but also for pure air (i.e. in the absence of an odour) in a sample of 9 humans (Tong et al., 2011). In one study, odour sensitivity was found to be unrelated to ghrelin concentrations (Trellakis et al., 2011). Recently, the sensitivity to a dairy odour – but not potato and vanilla odour - was found to increase with ghrelin concentrations in normal-weight and overweight men (Ginieis et al., 2022). A different study found serum ghrelin concentrations to be positively correlated with n-butanol odour sensitivity in women with obesity (Uygun et al., 2019). Altogether, the findings of ghrelin's role in human olfactory sensitivity are still inconclusive.

Whereas ghrelin is mainly secreted from the stomach, adiponectin is secreted from adipose tissue. Adiponectin facilitates the crosstalk between adipose tissue and other organs that control metabolism (Wang and Scherer, 2016). It enhances insulin sensitivity (Kim et al., 2010), regulates glucose uptake (Yamauchi et al., 2002), and lipid metabolism (Pandey et al., 2019). In contrast to ghrelin which increases food intake, adiponectin seems to influence weight change mainly by changing energy expenditure (Qi et al., 2004; Yamauchi et al., 2001). Adiponectin is correlated to body fat mass and higher in women than men (Bidulescu et al., 2013; Lubkowska et al., 2015; Song et al., 2014), but these effects seem to be partly independent (Christen et al., 2018; Cnop et al., 2003). There are to date only a few studies which investigated how adiponectin influences olfaction. In mice, it was found to enhance olfactory response amplitudes from the olfactory epithelium upon olfactory stimulation (Loch et al., 2013). One study in humans found no association between olfactory sensitivity and adiponectin concentrations (Trellakis et al., 2011). Thus, it is still unclear if and how adiponectin may influence olfactory detection ability in humans.

Therefore, the present pre-registered study investigated odour sensitivity in relation to plasma concentrations of ghrelin and adiponectin. Previous literature motivated the following pre-registered hypothesis: We expected that odour sensitivity would be higher for food odours when participants were fasted and had high ghrelin concentrations, than when they were satiated and had lower ghrelin concentrations. Since previous studies found sex differences in odour sensitivity (Brand and Millot, 2001; Doty and Cameron, 2009; Sorokowski et al., 2019), and in adiponectin concentrations (Bidulescu et al., 2013; Lubkowska et al., 2015), we also explored whether the two are related (analyses not pre-registered).

2. Methods

2.1. Participants

The pre-registered a priori sample size estimation was conducted with Pangea (Westfall, 2015) for linear mixed models. Assuming a medium-sized effect for a 2 × 2 within-subjects design with the factors metabolic state (fasting/food intake) and odour type (food/non-food), at least 67 participants were recommended to reach at least 80 % power (d = 0.45, replicants = 1, var(interaction) = 0.417; see Supplementary Materials). The original plan to recruit 80 participants to account for potential dropouts had to be altered due to the Covid-19 pandemic, so that only 68 volunteers were recruited.

Healthy volunteers (18–55 years) with a BMI in-between 18.0 and 29.9 were invited to the study via announcements on notice-boards around the university and on Facebook. To reduce the variance from sex hormone concentrations, only women not taking hormonal contraceptives were included, and their participation was scheduled so that it took place in the first week of their menstrual cycle (days 1–8). This specific time window was chosen to minimize variance in plasma ghrelin and olfactory performance due to variation in gonadal hormones (Doty, 1981; Hirschberg, 2012). Participants had no self-reported history of eating disorders, diabetes, gastrointestinal surgery, lactose intolerance, ongoing mental disorder, or current medication affecting gastrointestinal function.

From the 68 participants recruited, one dropped out due to circulatory problems, and two participants did not perform the odour sensitivity task due to time constraints, leaving us with 65 participants. 59 of these 65 attended both test sessions (see below), of which one person did not want to state their sex (chose the answer option “prefer not to answer”). Therefore, all following analyses which had sex as a factor were calculated without this person. Because each of the statistical analyses is based on a different number of participants, their demographical data are presented in the results of the respective analysis or in Supplementary Materials.

The study complies with the Declaration of Helsinki for Medical Research involving Human Subjects. The Regional Ethics Committee (REK South East B, project 26699) approved the protocol. Participants received universal gift cards (~EUR 150 for two visits of ~5 h each in which a range of other tasks was performed as well). The study was preregistered on the Open Science Forum (https://osf.io/f9rkq). A preregistration requires the specification of a study's research plan (hypothesis, sample size, experimental procedures, data analysis) in advance of the study and submitting it to a registry. The aim of a preregistration is to minimize questionable scientific practices and to increase transparency and replicability of conducted research.

2.2. Procedure

The study consisted of two sessions performed on different days following an at least 6-hour fast. To ensure compliance with the 6 h fasting requirement, participants were informed that we would verify whether they had fasted by measuring blood glucose. This was done via a pin prick test right after arrival. Participants also filled in a number of questions regarding their subjective hunger feeling and performed a range of other tasks which will be presented elsewhere.

In the second session, participants' body composition was measured with bioelectrical impedance analysis (seca mBCA 515, seca GmbH & Co. KG, Germany) to assess parameters such as fat mass and visceral adipose tissue.

Participants received a standardised liquid meal before testing in one session (“food intake condition”), and after testing in the other session (“fasting condition”). The order of conditions was randomised across participants. The meal consisted of 300 ml raspberry-flavored, probiotic fermented milk (Biola®, 50 kcal/100 g) and 300 ml chocolate milk (Sjokomelk, 58 kcal/100 g), both manufactured by TINE BA. Blood samples were taken at three different points in time to quantify plasma-acylated ghrelin and adiponectin: at arrival (baseline), following instructions for several tasks presented elsewhere and the meal in the food intake condition, and shortly before the odour sensitivity test. The time from arrival to the beginning of the third blood sample was ~3–3.5 h. Thus, for the data on odour sensitivity, only the third blood sample is of relevance.

Olfactory sensitivity were determined with a modified version (Croy et al., 2009) of the Sniffin' Sticks test (Burghart Instruments, Wedel, Germany) (Hummel et al., 1997). This modified version, consisting of 8 triplets instead of the standard 16 triplets used for the Sniffin' Stick test, has shown high correlation with the original version as well as significant test-retest reliability. In the present study, olfactory sensitivity was determined for one food odour, orange, and one non-food odour, phenylethyl alcohol (PEA), a rose-scented odour. A high score in the Sniffin' Sticks test corresponds to a higher olfactory sensitivity. Applying a pseudo-randomization, 30 participants started with the food odour,

while 30 started with the non-food odour in the fasted condition. Thirty-three participants started with the food odour and 30 with the non-food odour in the food intake condition. No significant difference was found in these distributions ($p = 0.787$). Each olfactory sensitivity test was performed as follows: The blindfolded participants were presented with three smelling pens at a time in front of their nose, two of which containing a solvent with neutral odour, and the third one containing the target odour. Eight such triplets for each odour were presented, each containing a different concentration (dilution) of the target odour. The order of the three pens was randomised across presentations. Participants had to identify the pen containing the target odour (3-alternative forced choice procedure, 3-AFC). One participant who was allergic against citrus fruits received cinnamon as food odour. Odour sensitivity was determined with a standard single-staircase procedure. The test started with the presentation of the triplet with the highest dilution (highest level of difficulty), and then moving on to the next lower dilution until a triplet was correctly identified twice in a row. This concentration represented the starting point for the actual test procedure. Beginning from this starting point, the next higher dilution was presented. Following an incorrect identification, the next lower dilution was presented, and following two consecutive correct identifications (i.e. on the same dilution level), the next higher dilution was presented. The task was considered concluded when five reversal points were passed, corresponding to five incorrect identifications along the task. Odour sensitivity was defined as the average among the dilution steps of the last four reversal points (Croy et al., 2009). Odour sensitivity thus varies between 1 and 8 in 0.25 increments. A score of 8 indicates the highest sensitivity, and a score of 1 lowest.

2.3. Hormone analyses

Blood samples for ghrelin assessment were collected in 2 ml EDTA tubes that were prepared with 100 µl protease inhibitor (Pefabloc® SC Plus, Merck KGaA, Germany). Immediately afterwards, the blood samples were centrifuged for 15 min at 4 °C and 3200*g*. The blood plasma was then aliquoted and stabilized with HCl. Ghrelin plasma was then frozen at −80 °C until analysis at the Hormone laboratory at Oslo University Hospital. Active (acylated) ghrelin concentrations were determined using the EZGRA-88 K kit (Merck, Germany) in duplicates (total analytical CV at 488 pg/ml 12 %).

Blood samples for adiponectin assessment were collected in 2 ml EDTA tubes that were centrifuged with the same parameters as the ghrelin samples. Afterwards, blood plasma was aliquoted and frozen at −80 °C until analysis at the Hormone Laboratory at Oslo University Hospital. Adiponectin was analysed with competitive radio immuno assay (Merck Millipore, Germany) in duplicates (total analytical CV at 1300 nmol/l 29 %).

2.4. Data analysis

2.4.1. Pre-registered analysis

Since plasma ghrelin concentrations in the fasting and the food intake condition did not differ, the values were averaged for all following analyses. Similarly, adiponectin values did not differ in the fasting and food intake condition (see Supplementary Materials), and were also averaged across these conditions.

A linear mixed model with odour (food/non-food) and metabolic state (fasting/food intake) as fixed factors and mean-centred plasma ghrelin concentrations as continuous predictors of olfactory sensitivity was calculated. Two-way interactions between odour and metabolic state, and odour and ghrelin were modelled. The random effects structure included a random intercept for participant and a random slope for metabolic state (model details in Supplementary Materials). We used the Satterthwaite method for approximation of degrees of freedom and applied a restricted maximum likelihood estimation for fixed effects. As effect size measures, semi-partial R^2 is reported (Edwards et al., 2008). Values of 0.02, 0.13, and 0.26 denote small, medium and large effects (Cohen, 1992).

2.4.2. Exploratory analyses

A linear mixed model with sex (women/men), odour (food/non-food), metabolic state (fasting/food intake) as fixed factors and mean-centred plasma adiponectin concentrations as continuous predictor for olfactory sensitivity was calculated. Two-and three-way interactions between odour, sex, metabolic state, and adiponectin were modelled. The random effects structure included a random intercept for participant and a random slope for metabolic state (model details in Supplementary Materials). All linear mixed model analyses were conducted with jamovi 1.6.23 (The jamovi project, 2021).

To obtain a more in-depth understanding of the relationships revealed in the linear mixed model, the results were followed up by a mediation analysis calculated with the PROCESS tool (Hayes, 2017) in SPSS v28. Mediation analysis allows to investigate if one variable X (here: sex) influences an outcome Y (here: olfactory sensitivity) through a single intervening variable M (here: plasma adiponectin). Accordingly, mediators are variables that partly explain the effect of the predictor on the outcome. Technically, this is realised by three different regressions, namely of X on Y, of M on Y, and of X+M on Y (Hayes, 2017). Because the preceding linear mixed model showed that olfactory sensitivity and plasma adiponectin did not differ significantly following fasting or food intake, these variables were averaged across metabolic states. Olfactory sensitivity was also averaged across the odour types because no significant differences were observed between sensitivity for orange and PEA. The ensuing (mean) olfactory sensitivity served as outcome, sex as predictor, and (mean) plasma adiponectin as mediator. Bootstrapping for indirect effects was performed with 5000 samples, the confidence interval level was 95 %. Of note, in the description of the mediation analysis results, we refer to associations as effects since this corresponds to the terminology typically used to describe results of this statistical method.

To further explore the observed associations of sex and plasma adiponectin with olfactory sensitivity, additional Welch's *t*-tests were computed to compare women and men on potential influencing variables (visceral adipose tissue, fat mass, and BMI). We then explored whether the results of the exploratory linear mixed model changed when adding fat mass and visceral adipose tissue as continuous predictors to this model. These results are presented in Supplementary Materials, Section 6.

3. Results

3.1. Results from pre-registered analyses

Blood glucose levels did not differ significantly from each other at the beginning of either the fasting or the food intake session ($t(58) = -1.84$, $p = 0.071$, $d = -0.24$). Age, sex and body composition of the participants are summarised in Table 1.

The data from these participants were submitted to a linear mixed model analysis to assess the effects of odour, metabolic state, and mean plasma ghrelin concentrations on olfactory sensitivity. This analysis revealed no significant main or interaction effects (all *p*-values >0.192;

Table 1
Age and body composition of the participants included in the pre-registered analyses, mean with SD in brackets.

	Women	Men	Non-disclosed
N (age)	19	45	1
Age	31.5(9.66)	27.9 (7.81)	30
BMI	22.607 (2.731)	24.250 (2.731)	24.400
Fat mass index	7.160 (2.131)	5.076 (2.085)	5.800
Visceral adipose tissue	0.534 (0.400)	1.420 (0.980)	1.500

see Fig. S1 and Table S1 in Supplementary Materials, Section 5).

3.2. Results from exploratory analyses

Mean olfactory sensitivity for men and women is shown in Table 2, mean plasma ghrelin and adiponectin concentrations for men and women are shown in Table S2 in Supplementary Materials (Section 5).

Women had significantly higher olfactory sensitivity than men, meaning that women correctly identified odours at lower concentrations than men, as evident from a main effect of sex (cf. Table 3). Olfactory sensitivity was also higher with higher compared to lower plasma adiponectin concentrations (main effect of adiponectin, cf. Table 3 and Fig. 1). Olfactory sensitivity was neither affected by the type of odour nor by metabolic state because no other main effects or interactions were significant (all p-values >0.072).

Since the previous analysis showed that olfactory sensitivity was higher in women who also had higher plasma adiponectin concentrations, this relationship was followed up by mediation analysis ($N = 62$, 18 women and 44 men). The aim of this analysis was to find out if and how adiponectin influences the relationship between sex and olfactory sensitivity. Adiponectin concentrations differed with sex (coefficient a = 6.802; $t = 4.127$; $p = 0.001$), where women had on average 6.802 mg/l higher plasma concentrations. Adiponectin influenced olfactory sensitivity (coefficient b = −0.081; $t = -3.225$; $p = 0.002$), so that women and men differing by 1 mg/l in adiponectin concentration were estimated to differ by an olfactory sensitivity of 0.081 (see Fig. 2).

Altogether, men tended to have an olfactory sensitivity that was on average 0.640 units lower than for women (total effect of sex on olfactory sensitivity of 0.640 ($t = 1.858$; $p = 0.068$)). However, this total effect (without considering adiponectin) only approached significance. Thus, sex only had a significant effect on olfactory sensitivity when plasma adiponectin concentrations were taken into account.

This total effect of sex on olfactory sensitivity can be partitioned into a direct effect (not mediated through adiponectin), and an indirect effect (i.e. the effect of sex on olfactory sensitivity via adiponectin concentrations, thus an effect mediated by adiponectin). Men compared to women with similar adiponectin concentrations had a lower olfactory sensitivity by 1.191 (c' = 1.191), (direct effect of sex with $t = 3.280$, $p = 0.002$). Relative to women, men were on average 0.550 units lower in olfactory sensitivity as a result of the effect of sex on adiponectin. This was evident from a statistically significant indirect effect ((6.802)* (−0.081) = −0.550; confidence interval from −1.087 to −0.121).

4. Discussion

Odour sensitivity for food and non-food odours did not vary with metabolic state or plasma ghrelin concentrations. However, concentrations of plasma adiponectin as a different hormone with metabolic properties were associated with sex differences in odour sensitivity. In particular, men had lower olfactory sensitivity (equivalent to worse odour detection), which was related to their lower adiponectin concentrations.

The finding that olfactory sensitivity was not affected by fasting is in contrast to findings of previous studies. For example, participants tested after 16 h of fasting and again 1 h after Ramadan supper (Ulusoy et al., 2017) showed higher olfactory sensitivity during fasting than after food intake. Also, fasting for 24 h improved odour sensitivity (Cameron et al., 2012). Making use of natural diurnal variations in hunger states prior to and following freely selected meals, olfactory sensitivity to food odours (coffee and citrus) was found to be higher prior to than following meals, and increased even more if a meal was skipped (Goetzl and Stone, 1947). These results were corroborated by other researchers in the 1950s (Guild, 1956; Hammer, 1951). However, other data with a similar before-and-after-lunch set-up and coffee odour did not provide evidence for hunger or satiety altering olfactory sensitivity (Janowitz and Grossman, 1949). More recently, the sensitivity for a neutral odour (n-butanol) was reported to be higher before than after food intake following a 24-hour fast. In contrast, the sensitivity for a food odour (food herbs) was higher before than after food intake, but only for participants with a high BMI (Stafford and Welbeck, 2011). The opposite effect was found in a study using banana (isoamyl acetate) as a food odour, where olfactory sensitivity was higher when satiated than hungry (Albrecht et al., 2009). There are a number of differences between all these studies and the present one, among which the duration of fasting

Table 2
Mean olfactory sensitivity with standard deviation (SD) for orange and PEA in different metabolic states for women and men.

Sex	Metabolic state	Odour	N	Mean	Std. DEVIATION
Women	Fasting	Orange	16	5.250	1.469
	Food-intake	Orange	18	5.028	1.805
	Fasting	PEA	16	4.625	1.777
	Food-intake	PEA	18	5.667	1.776
Men	Fasting	Orange	44	4.597	1.869
	Food-intake	Orange	44	4.943	1.863
	Fasting	PEA	44	4.455	1.825
	Food-intake	PEA	44	4.534	1.853

Table 3
Significant LMM parameters for olfactory sensitivity as a function of sex and adiponectin.

	Estimate	SE	*df*	*t*	*p*	Semi-partial R^2
Intercept	5.1389	0.1815	59.1	28.310	<0.001	
Sex	−1.1231	0.3630	59.1	−3.094	0.003	0.14
Adiponectin	−0.0698	0.0250	55.6	−2.789	0.007	0.12

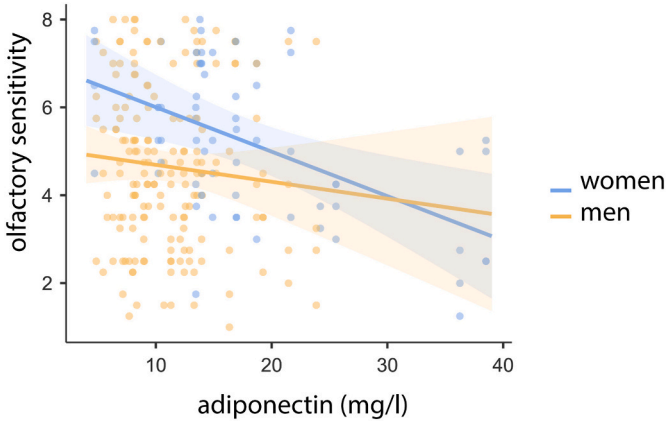

Fig. 1. Relationship between mean olfactory sensitivity, sex and plasma adiponectin concentrations with regression lines and 95 % confidence intervals. Olfactory sensitivity (Sniffin' sticks scores) can range from 1 (lowest score) to 8 (highest score) in 0.25 increments.

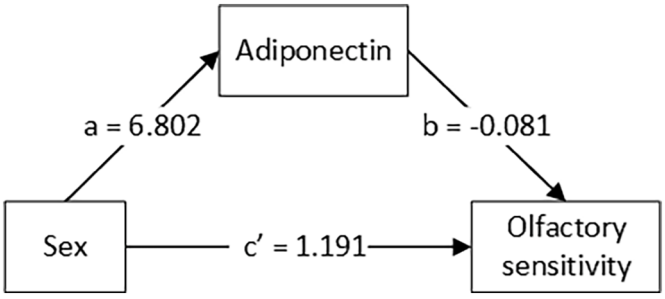

Fig. 2. Mediation model and results.

and the use of other odorants. In our participants, the time since the last meal was minimally around 9 h (6 h fasting and ~3 h until the Sniffin' Sticks test), thus a much shorter duration of fasting. This may not have induced large enough physiologic variations, also in the investigated hormones. In addition, sex hormones in women were kept constant, and participant's weight range in-between a BMI of 18.0 and 29.9 was rather narrow. Thus, circulating sex hormones may not have influenced odour sensitivity as much as in previous studies.

The exploratory analyses on sex differences substantiate the results of previous studies. Women are typically reported to have higher olfactory sensitivity than men (for overviews, see Brand and Millot, 2001; Doty and Cameron, 2009; Sorokowski et al., 2019). Effect sizes seem to be small (Sorokowski et al., 2019), but the effects are consistent. There are also several large studies which did not find sex differences in olfactory performance at all, for example (Sorokowska et al., 2015; Vennemann et al., 2008). In the present study, the sex difference in olfactory sensitivity could be explained with differing adiponectin concentrations. This raises the speculation that adiponectin may explain some of the previously observed inconsistencies in the findings on sex differences for odour sensitivity. For example, a large variation in adiponectin concentrations may make potential sex differences disappear, whereas a small variation could make them more evident. Because the amount of visceral adipose tissue and fat mass did not affect odour sensitivity (see additional analyses in Supplementary Materials), the sex differences do not appear to be due to differing amounts of adipose tissue.

The physiological role of adiponectin is not yet fully understood. It is considered a "starvation signal" (Ahima and Lazar, 2008; Henry and Clarke, 2008), and high concentrations stimulate food intake and reduce energy expenditure (Kubota et al., 2007). Thus, it is considered an important hormone in regulating energy homeostasis in the long run. Although adiponectin is secreted from adipose tissue (Nakano et al., 1996), it is negatively associated with obesity. Animal studies about the role of adiponectin on food intake show highly inconsistent results (Tang et al., 2021). Moreover, one animal study on adiponectin's role on olfaction reported that neural responses of olfactory sensory neurons increased after odour stimulation, which was interpreted as enhanced responsiveness of the olfactory system (Loch et al., 2013). This may be due to all mature olfactory sensory neurons in the mouse olfactory epithelium expressing one particular adiponectin receptor (adiponectin receptor 1, adipoR1 (Hass et al., 2008)). It was suggested that also human olfactory sensory neurons express this adipoR1 receptor (Guthoff et al., 2011). It is thus possible that higher concentrations of adiponectin are associated with enhanced reactivity of those olfactory neurons responding to a particular odour, or that higher adiponectin concentrations generally increase the sensitivity of all olfactory sensory neurons, i.e. recruiting also neurons that would usually not respond to the respective odour (Loch et al., 2013). This could contribute to the finding that women outperform men in terms of olfactory abilities on the group level (Sorokowski et al., 2019), because women also have higher adiponectin concentrations on the group level (Bidulescu et al., 2013; Lubkowska et al., 2015). However, the functions of adiponectin reach beyond metabolism and include immunity, cancer and bone formation (e.g., Parida et al., 2019). Therefore, the nature of the relationship between adiponectin and olfactory sensitivity remains unclear.

One limitation of the study is that the a priori power calculation was based on a medium-sized effect. Therefore, it was not possible to detect potential small effects of metabolic state, type of odour, and ghrelin concentrations on odour sensitivity. Another important limitation regards the choice of orange as a food odour. It is possible that administering a different odour associated with a more calorie-dense food could result in different effects. Finally, it is important to highlight that about two times as many men as women participated in our study, which implies lower statistical power in the female than the male sample.

Altogether, this study adds to the increasing body of research on the relationship between metabolic disorders, body weight, and olfaction, the results of which are often inconsistent. The present study suggests adiponectin – irrespective of the amount of body fat - as a further factor to influence olfactory sensitivity.

Open science information

The study was preregistered on the Open Science Forum (https://osf.io/f9rkq).

The manuscript has been uploaded to the preprint server OSF, doi: 10.31234/osf.io/59cuv.

Funding

This work was supported by the Norwegian Research Council [grant number 275316], ERA-NET NEURON JTC 2020/Norwegian Research Council [grant number 323047], and the South-Eastern Norway Regional Health Authority [grant number 2021046].

Data availability

The raw data on which this manuscript is based can be accessed on OSF: https://osf.io/qvcwf/

Acknowledgements

We are indebted to Thomas Hummel for providing the Sniffin' sticks and for helpful input on an early version of the manuscript. We thank TINE BA for providing us with Biola® and Sjokomelk for free. We also thank Aiste Gvildyte Næss, Pietro Aleksander Rocco Berger Lapolla, Aleksandra Pusica, Erik Rimestad Frogner, and Anbjørn Ree for their work with participant recruitment and data collection.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yhbeh.2022.105235.

References

Ahima, R.S., Lazar, M.A., 2008. Adipokines and the peripheral and neural control of energy balance. Mol. Endocrinol. 22, 1023–1031. https://doi.org/10.1210/me.2007-0529.

Aime, P., Duchamp-Viret, P., Chaput, M.A., Savigner, A., Mahfouz, M., Julliard, A.K., 2007. Fasting increases and satiation decreases olfactory detection for a neutral odor in rats. Behav. Brain Res. 179, 258–264. https://doi.org/10.1016/j.bbr.2007.02.012.

Albrecht, J., Schreder, T., Kleemann, A.M., Schöpf, V., Kopietz, R., Anzinger, A., Demmel, M., Linn, J., Kettenmann, B., Wiesmann, M., 2009. Olfactory detection thresholds and pleasantness of a food-related and a non-food odour in hunger and satiety. Rhinology 47, 160–165.

Bidulescu, A., Liu, J., Hickson, D.A., Hairston, K.G., Fox, E.R., Arnett, D.K., Sumner, A.E., Taylor, H.A., Gibbons, G.H., 2013. Gender differences in the association of visceral and subcutaneous adiposity with adiponectin in african americans: the Jackson heart study. BMC Cardiovasc. Disord. 13, 9. https://doi.org/10.1186/1471-2261-13-9.

Boesveldt, S., de Graaf, K., 2017. The differential role of smell and taste for eating behavior. Perception 46, 307–319. https://doi.org/10.1177/0301006616685576.

Brand, G., Millot, J.L., 2001. Sex differences in human olfaction: between evidence and enigma. Q. J. Exp. Psychol. B 54, 259–270. https://doi.org/10.1080/02724990143000045.

Cameron, J.D., Goldfield, G.S., Doucet, É., 2012. Fasting for 24h improves nasal chemosensory performance and food palatability in a related manner. Appetite 58, 978–981. https://doi.org/10.1016/j.appet.2012.02.050.

Chambaron, S., Chisin, Q., Chabanet, C., Issanchou, S., Brand, G., 2015. Impact of olfactory and auditory priming on the attraction to foods with high energy density. Appetite 95, 74–80. https://doi.org/10.1016/j.appet.2015.06.012.

Christen, T., Trompet, S., Noordam, R., van Klinken, J.B., van Dijk, K.W., Lamb, H.J., Cobbaert, C.M., den Heijer, M., Jazet, I.M., Jukema, J.W., Rosendaal, F.R., de Mutsert, R., 2018. Sex differences in body fat distribution are related to sex differences in serum leptin and adiponectin. Peptides 107, 25–31. https://doi.org/10.1016/j.peptides.2018.07.008.

Cnop, M., Havel, P.J., Utzschneider, K.M., Carr, D.B., Sinha, M.K., Boyko, E.J., Retzlaff, B.M., Knopp, R.H., Brunzell, J.D., Kahn, S.E., 2003. Relationship of adiponectin to body fat distribution, insulin sensitivity and plasma lipoproteins: evidence for independent roles of age and sex. Diabetologia 46, 459–469. https://doi.org/10.1007/s00125-003-1074-z.

Cohen, J., 1992. A power primer. Psychol. Bull. 112, 155–159. https://doi.org/10.1037//0033-2909.112.1.155.
Cowley, M.A., Smith, R.G., Diano, S., Tschop, M., Pronchuk, N., Grove, K.L., Strasburger, C.J., Bidlingmaier, M., Esterman, M., Heiman, M.L., Garcia-Segura, L. M., Nillni, E.A., Mendez, P., Low, M.J., Sotonyi, P., Friedman, J.M., Liu, H., Pinto, S., Colmers, W.F., Cone, R.D., Horvath, T.L., 2003. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 37, 649–661.
Croy, I., Lange, K., Krone, F., Negoias, S., Seo, H.-S., Hummel, T., 2009. Comparison between odor thresholds for phenyl ethyl alcohol and butanol. Chem. Senses 34, 523–527. https://doi.org/10.1093/chemse/bjp029.
Cummings, D.E., Purnell, J.Q., Frayo, R.S., Schmidova, K., Wisse, B.E., Weigle, D.S., 2001. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes 50, 1714–1719. https://doi.org/10.2337/diabetes.50.8.1714.
Doty, R.L., 1981. Olfactory communication in humans. Chem. Senses 6, 351–376. https://doi.org/10.1093/chemse/6.4.351.
Doty, R.L., Cameron, E.L., 2009. Sex differences and reproductive hormone influences on human odor perception. Physiol. Behav. 97, 213–228. https://doi.org/10.1016/j.physbeh.2009.02.032.
Druce, M.R., Neary, N.M., Small, C.J., Milton, J., Monteiro, M., Patterson, M., Ghatei, M. A., Bloom, S.R., 2006. Subcutaneous administration of ghrelin stimulates energy intake in healthy lean human volunteers. Int. J. Obes. 30, 293–296. https://doi.org/10.1038/sj.ijo.0803158.
Druce, M.R., Wren, A.M., Park, A.J., Milton, J.E., Patterson, M., Frost, G., Ghatei, M.A., Small, C., Bloom, S.R., 2005. Ghrelin increases food intake in obese as well as lean subjects. Int. J. Obes. 29, 1130–1136. https://doi.org/10.1038/sj.ijo.0803001.
Edwards, L.J., Muller, K.E., Wolfinger, R.D., Qaqish, B.F., Schabenberger, O., 2008. An R2 statistic for fixed effects in the linear mixed model. Stat. Med. 27, 6137–6157. https://doi.org/10.1002/sim.3429.
Fedoroff, I.C., Polivy, J., Herman, C.P., 1997. The effect of pre-exposure to food cues on the eating behavior of restrained and unrestrained eaters. Appetite 28, 33–47.
Gaillet-Torrent, M., Sulmont-Rosse, C., Issanchou, S., Chabanet, C., Chambaron, S., 2014. Impact of a non-attentively perceived odour on subsequent food choices. Appetite 76, 17–22. https://doi.org/10.1016/j.appet.2014.01.009.
Ginieis, R., Abeywickrema, S., Oey, I., Peng, M., 2022. Testing links of food-related olfactory perception to peripheral ghrelin and leptin concentrations. Front. Nutr. 9, 888608 https://doi.org/10.3389/fnut.2022.888608.
Glaze, J.A., 1928. Sensitivity to odors and other phenomena during a fast. Am. J. Psychol. 40, 569. https://doi.org/10.2307/1414335.
Goetzl, F.R., Stone, F., 1947. Diurnal variations in acuity of olfaction and food intake. Gastroenterology 9, 444–453.
Guild, A.A., 1956. Olfactory acuity in normal and obese human subjects: diurnal variations and the effect of D-amphetamine sulphate. J. Laryngol. Otol. 70, 408–414. https://doi.org/10.1017/S002221510005310X.
Guthoff, M., Tschritter, O., Berg, D., Liepelt, I., Schulte, C., Machicao, F., Breer, H., Haering, H.-U., Fritsche, A., 2011. A polymorphism in the gene encoding AdipoR1 affects olfactory recognition. Int. J. Obes. 35, 873–876. https://doi.org/10.1038/ijo.2010.211.
Hammer, F.J., 1951. The relation of odor, taste, and flicker-fusion thresholds to food intake. J. Comp. Physiol. Psychol. 44, 403–411. https://doi.org/10.1037/h0062712.
Hass, N., Haub, H., Stevens, R., Breer, H., Schwarzenbacher, K., 2008. Expression of adiponectin receptor 1 in olfactory mucosa of mice. Cell Tissue Res. 334, 187–197. https://doi.org/10.1007/s00441-008-0677-6.
Hayes, A., 2017. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach, 2. Guildford Publications.
Henry, B.A., Clarke, I.J., 2008. Adipose tissue hormones and the regulation of food intake. J. Neuroendocrinol. 20, 842–849. https://doi.org/10.1111/j.1365-2826.2008.1730.x.
Hirschberg, A.L., 2012. Sex hormones, appetite and eating behaviour in women. Maturitas 71, 248–256. https://doi.org/10.1016/j.maturitas.2011.12.016.
Hummel, T., Sekinger, B., Wolf, S.R., Pauli, E., Kobal, G., 1997. "Sniffin" sticks': olfactory performance assessed by the combined testing of odor identification, odor discrimination and olfactory threshold. Chem. Senses 22, 39–52.
Janowitz, H.D., Grossman, M.I., 1949. Gustoolfactory thresholds in relation to appetite and hunger sensations. J. Appl. Physiol. 2, 217–222. https://doi.org/10.1152/jappl.1949.2.4.217.
Kim, D.H., Vanella, L., Inoue, K., Burgess, A., Gotlinger, K., Manthati, V.L., Koduru, S.R., Zeldin, D.C., Falck, J.R., Schwartzman, M.L., Abraham, N.G., 2010. Epoxyeicosatrienoic acid agonist regulates human mesenchymal stem cell-derived adipocytes through activation of HO-1-pAKT signaling and a decrease in PPARγ. Stem Cells Dev. 19, 1863–1873. https://doi.org/10.1089/scd.2010.0098.
Koelega, H.S., 1994. Diurnal variations in olfactory sensitivity and the relationship to food intake. Percept. Mot. Skills 78, 215–226. https://doi.org/10.2466/pms.1994.78.1.215.
Kojima, M., Hosoda, H., Date, Y., Nakazato, M., Matsuo, H., Kangawa, K., 1999. Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402, 656–660. https://doi.org/10.1038/45230.
Kubota, N., Yano, W., Kubota, T., Yamauchi, T., Itoh, S., Kumagai, H., Kozono, H., Takamoto, I., Okamoto, S., Shiuchi, T., Suzuki, R., Satoh, H., Tsuchida, A., Moroi, M., Sugi, K., Noda, T., Ebinuma, H., Ueta, Y., Kondo, T., Araki, E., Ezaki, O., Nagai, R., Tobe, K., Terauchi, Y., Ueki, K., Minokoshi, Y., Kadowaki, T., 2007. Adiponectin stimulates AMP-activated protein kinase in the hypothalamus and increases food intake. Cell Metab. 6, 55–68. https://doi.org/10.1016/j.cmet.2007.06.003.
Loch, D., Breer, H., Strotmann, J., 2015. Endocrine modulation of olfactory responsiveness: effects of the orexigenic hormone ghrelin. Chem. Senses 40, 469–479. https://doi.org/10.1093/chemse/bjv028.
Loch, D., Heidel, C., Breer, H., Strotmann, J., 2013. Adiponectin enhances the responsiveness of the olfactory system. PLoS ONE 8, e75716. https://doi.org/10.1371/journal.pone.0075716.
Lubkowska, A., Radecka, A., Bryczkowska, I., Rotter, I., Laszczyńska, M., Dudzińska, W., 2015. Serum adiponectin and leptin concentrations in relation to body fat distribution, hematological indices and lipid profile in humans. Int. J. Environ. Res. Public Health 12, 11528–11548. https://doi.org/10.3390/ijerph120911528.
Malik, S., McGlone, F., Bedrossian, D., Dagher, A., 2008. Ghrelin modulates brain activity in areas that control appetitive behavior. Cell Metab. 7, 400–409. https://doi.org/10.1016/j.cmet.2008.03.007.
Nakano, Y., Tobe, T., Choi-Miura, N.H., Mazda, T., Tomita, M., 1996. Isolation and characterization of GBP28, a novel gelatin-binding protein purified from human plasma. J. Biochem. (Tokyo) 120, 803–812. https://doi.org/10.1093/oxfordjournals.jbchem.a021483.
Pandey, G.K., Vadivel, S., Raghavan, S., Mohan, V., Balasubramanyam, M., Gokulakrishnan, K., 2019. High molecular weight adiponectin reduces glucolipotoxicity-induced inflammation and improves lipid metabolism and insulin sensitivity via APPL1-AMPK-GLUT4 regulation in 3T3-L1 adipocytes. Atherosclerosis 288, 67–75. https://doi.org/10.1016/j.atherosclerosis.2019.07.011.
Parida, S., Siddharth, S., Sharma, D., 2019. Adiponectin, obesity, and cancer: clash of the bigwigs in health and disease. Int. J. Mol. Sci. 20, 2519. https://doi.org/10.3390/ijms20102519.
Qi, Y., Takahashi, N., Hileman, S.M., Patel, H.R., Berg, A.H., Pajvani, U.B., Scherer, P.E., Ahima, R.S., 2004. Adiponectin acts in the brain to decrease body weight. Nat. Med. 10, 524–529. https://doi.org/10.1038/nm1029.
Ramaekers, M.G., Verhoef, A., Gort, G., Luning, P.A., Boesveldt, S., 2016. Metabolic and sensory influences on odor sensitivity in humans. Chem. Senses 41, 163–168. https://doi.org/10.1093/chemse/bjv068.
Rhea, E.M., Salameh, T.S., Gray, S., Niu, J., Banks, W.A., Tong, J., 2018. Ghrelin transport across the blood-brain barrier can occur independently of the growth hormone secretagogue receptor. Mol. Metab. 18, 88–96. https://doi.org/10.1016/j.molmet.2018.09.007.
Sailer, U., Triscoli, C., Croy, I., 2016. Still eating despite decreased olfactory pleasure-the influence of odor liking and wanting on food intake. Chem. Senses 41, 497–504. https://doi.org/10.1093/chemse/bjw052.
Small, D.M., Gerber, J.C., Mak, Y.E., Hummel, T., 2005. Differential neural responses evoked by orthonasal versus retronasal odorant perception in humans. Neuron 47, 593–605. https://doi.org/10.1016/j.neuron.2005.07.022.
Song, H.J., Oh, S., Quan, S., Ryu, O.-H., Jeong, J.-Y., Hong, K.-S., Kim, D.-H., 2014. Gender differences in adiponectin levels and body composition in older adults: Hallym aging study. BMC Geriatr. 14 https://doi.org/10.1186/1471-2318-14-8, 8-8.
Sorokowska, A., Schriever, V.A., Gudziol, V., Hummel, C., Hähner, A., Iannilli, E., Sinding, C., Aziz, M., Seo, H.S., Negoias, S., Hummel, T., 2015. Changes of olfactory abilities in relation to age: odor identification in more than 1400 people aged 4 to 80 years. Eur. Arch. Oto-Rhino-Laryngol. Off. J. Eur. Fed. Oto-Rhino-Laryngol. Soc. EUFOS Affil. Ger. Soc. Oto-Rhino-Laryngol. - Head Neck Surg. 272, 1937–1944. https://doi.org/10.1007/s00405-014-3263-4.
Sorokowski, P., Karwowski, M., Misiak, M., Marczak, M.K., Dziekan, M., Hummel, T., Sorokowska, A., 2019. Sex differences in human olfaction: a meta-analysis. Front. Psychol. 10 https://doi.org/10.3389/fpsyg.2019.00242, 242-242.
Stafford, L.D., Welbeck, K., 2011. High hunger state increases olfactory sensitivity to neutral but not food odors. Chem. Senses 36, 189–198. https://doi.org/10.1093/chemse/bjq114.
Tang, N., Zhang, X., Chen, D., Li, Z., 2021. The controversial role of adiponectin in appetite regulation of animals. Nutrients 13, 3387. https://doi.org/10.3390/nu13103387.
The jamovi project, 2021. jamovi (Version 1.6).
Tong, J., Mannea, E., Aime, P., Pfluger, P.T., Yi, C.-X., Castaneda, T.R., Davis, H.W., Ren, X., Pixley, S., Benoit, S., Julliard, K., Woods, S.C., Horvath, T.L., Sleeman, M.M., D'Alessio, D., Obici, S., Frank, R., Tschop, M.H., 2011. Ghrelin enhances olfactory sensitivity and exploratory sniffing in rodents and humans. J. Neurosci. 31, 5841–5846. https://doi.org/10.1523/JNEUROSCI.5680-10.2011.
Trellakis, S., Tagay, S., Fischer, C., Rydleuskaya, A., Scherag, A., Bruderek, K., Schlegl, S., Greve, J., Canbay, A.E., Lang, S., Brandau, S., 2011. Ghrelin, leptin and adiponectin as possible predictors of the hedonic value of odors. Regul. Pept. 167, 112–117. https://doi.org/10.1016/j.regpep.2010.12.005.
Tschop, M., Smiley, D.L., Heiman, M.L., 2000. Ghrelin induces adiposity in rodents. Nature 407, 908–913. https://doi.org/10.1038/35038090.
Ulusoy, S., Dinc, M.E., Dalgic, A., Topak, M., Dizdar, D., İs, A., 2017. Are people who have a better smell sense, more affected from satiation? Braz. J. Otorhinolaryngol. 83, 640–645. https://doi.org/10.1016/j.bjorl.2016.08.011.
Uygun, B., Kiyici, S., Ozmen, S., Gul, Z., Sigirli, D., Cavun, S., 2019. The association between olfaction and taste functions with serum ghrelin and leptin levels in obese women. Metab. Syndr. Relat. Disord. 17, 452–457. https://doi.org/10.1089/met.2019.0037.
Vennemann, M.M., Hummel, T., Berger, K., 2008. The association between smoking and smell and taste impairment in the general population. J. Neurol. 255, 1121–1126. https://doi.org/10.1007/s00415-008-0807-9.
Wang, Z.V., Scherer, P.E., 2016. Adiponectin, the past two decades. J. Mol. Cell Biol. 8, 93–100. https://doi.org/10.1093/jmcb/mjw011.
Westfall, J., 2015. PANGEA : Power ANalysis for GEneral Anova Designs.
Yamauchi, T., Kamon, J., Minokoshi, Y., Ito, Y., Waki, H., Uchida, S., Yamashita, S., Noda, M., Kita, S., Ueki, K., Eto, K., Akanuma, Y., Froguel, P., Foufelle, F., Ferre, P., Carling, D., Kimura, S., Nagai, R., Kahn, B.B., Kadowaki, T., 2002. Adiponectin

stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. Nat. Med. 8, 1288–1295. https://doi.org/10.1038/nm788.
Yamauchi, T., Kamon, J., Waki, H., Terauchi, Y., Kubota, N., Hara, K., Mori, Y., Ide, T., Murakami, K., Tsuboyama-Kasaoka, N., Ezaki, O., Akanuma, Y., Gavrilova, O., Vinson, C., Reitman, M.L., Kagechika, H., Shudo, K., Yoda, M., Nakano, Y., Tobe, K., Nagai, R., Kimura, S., Tomita, M., Froguel, P., Kadowaki, T., 2001. The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nat. Med. 7, 941–946. https://doi.org/10.1038/90984.
Zoon, H.F., de Graaf, C., Boesveldt, S., 2016. Food odours direct specific appetite. Foods 5. https://doi.org/10.3390/foods5010012.