Original Paper

Psychopharm

Journal of Psychopharmacology
27(3) 265–275

DOI: 10.1177/0269881112472567
jop.sagepub.com
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Opiate agonists and antagonists modulate taste perception in opiate-maintained and recently detoxified subjects

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Abstract

Heroin addicts consume large quantities of refined sugars. This study investigated the effect of opiate use and antagonism on sweet taste in opiate-maintained drug users and detoxified former chronic opiate users, using a within-subject design.

Seven opiate users received methadone and seven buprenorphine maintenance. Six detoxified subjects received naltrexone. Sucrose recognition thresholds and measurements of pleasantness and intensity were determined before and four hours after 1) a single dose of methadone or buprenorphine or 2) naltrexone. Control data were taken from a cohort of healthy volunteers including smokers.

All measures of sweet and salt taste perception were significantly greater in opiate users and recently detoxified subjects compared to control subjects, with the exception of sweet pleasantness, which returned to control level after detoxification. Acute methadone administration reduced salt thresholds and unpleasantness to control levels. Increased sweet thresholds and salt unpleasantness in detoxified subjects were reversed by acute opioid antagonism, returning to control levels. These results suggest that opiate use and antagonism alters taste perception. Some of the alterations reverse on detoxification (sweet pleasantness), and others can be reversed by opioid antagonism (sweet threshold, salt unpleasantness). Changes in taste perception may underlie altered consumption of refined sugars in opiate users.

Keywords

Human, methadone, naltrexone, taste

Introduction

Chronic opiate addicts, either when maintained on opiate agonists or when abstinent (Weiss, 1982), have increased craving, preference for, and intake of sugary foodstuffs (Kolarzyk et al., 2005a; Morabia et al., 1989; Nolan and Scagnelli, 2007; Zador et al., 1996), with added sugar contributing ~30% of total calorific intake (Saeland et al., 2011). These preference and dietary effects are known to be linked to opiate intake (Titsas and Ferguson, 2002), and are also seen in experimental animals (Bodnar, 2004; Kelley et al., 2002). The increased intake of processed sugars in opiate addicts may be linked to the reward associated with sucrose (Langleben et al., 2012), rather than other factors, as there are no clear relationships between, for example, socioeconomic status and diet in these individuals (Morabia et al., 1989; Zador et al., 1996). The majority of studies find that this dietary change does not significantly affect body mass index (BMI), as this is in the normal range (Forrester et al., 2005; Kolarzyk et al., 2005b; Morabia et al., 1989) (but see also (Nolan and Scagnelli, 2007)). The principal result of this increased sugar intake in opiate addicts, and also in those on opiate-substitution therapy, such as methadone or buprenorphine, is that they typically have poor oral and dental health, compared to non-intravenous drug users, or non-addicts (Reece, 2007; Robinson et al., 2005; Titsas and Ferguson, 2002).

In non-drug-using populations, opiates are well recognised to exert potent effects on appetite and eating behaviour (Yeomans and Gray, 1997); similar effects are seen in experimental animals (Yeomans and Gray, 2002). Opiate antagonists generally decrease food intake (Bertino et al., 1991), sweet preference (Fantino et al., 1986) and measures of food palatability in humans (Yeomans and Gray, 2002), although this is not a universal finding (Hetherington et al., 1991).

The consistent effects of opiate antagonists on palatability in healthy humans do not, however, extend to other aspects of taste perception, such as intensity (strength of perceived taste) or threshold measurements. Perceived intensity (ratings of "saltiness" or "sweetness") is unaffected by opiate antagonists (Bertino et al., 1991; Hetherington et al., 1991; Scinska et al., 2000; Yeomans and Gray, 1996). The cortical area associated with taste intensity is the insular cortex (Grabenhorst and Rolls, 2008).

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Table 1. Participant characteristics.

Study group (*n*)	Drug	Male:Female	Age range	Smoking status	% Sweet liker	% Salt disliker
Drug users (14)	methadone	6:1	30 (21–38)	5/13	83	75
	buprenophine	4:3			86	100
Detox (6)	naltrexone	4:2	35 (27–43)	4/6	67	83
Naloxone (10)	naloxone	4:6	32 (23–40	0/10	60	90
Controls (65)	—	25:40	30 (19–63)	24/65	70[a]	85[a]

[a]One participant rated 1 M sucrose as exactly zero (neutral) on first exposure to sweet, and two participants rated 1 M NaCl as zero on first exposure to salt, and therefore could not be classified as either 'liker' or 'disliker'. Note that there is a significantly higher proportion of women in the control group than in the experimental groups. Median and range are shown for ages in each group.

There is little published evidence that insular cortex function is changed by chronic opiate use in humans, although there is greater neuronal activation of this area immediately following opiate detoxification in rats, and on acute morphine challenge (Taracha et al., 2008). Taste thresholds are similarly unaffected by opiate antagonists in healthy individuals (Arbisi et al., 1999).

Opioid peptides have not been detected in taste cells or associated nerve fibres in humans (Astback et al., 1995; Astback et al., 1997; Kusakabe et al., 1998), but encephalin has been localised to rodent taste cells (Yoshie et al., 1993). In rodents, opioid peptides and mu (Ding et al., 1998; Mansour et al., 1995) and delta receptors (Ichikawa et al., 2005) are found throughout the ascending gustatory pathways, particularly in the nucleus tractus solitarius (NTS), and opiates in the NTS reduce gustatory input in approximately 25% of gustatory neurons (Li et al., 2003). This inhibition is not related to any taste modality. Thus, there are other potential central nervous system (CNS) sites where exogenous opioids could directly modulate aspects of taste perception such as threshold and intensity.

Areas of the brain involved in mediating opiate effects on eating behaviour and hedonic measures of rewarding taste (for example, sweet (Rolls and Grabenhorst, 2008)), such as orbitofrontal cortex, are known to be dysfunctional in opiate, cocaine and alcohol users (Ma et al., 2010; Volkow and Fowler, 2000). We hypothesised that ratings for a pleasant taste (sweet), but not an unpleasant taste (salt) would be altered in participants on opiate-maintenance therapy (OMT). As these neuronal changes are also known to be maintained for some time following detoxification from alcohol addiction (Volkow and Fowler, 2000), we also hypothesised that acutely detoxified opiate users would show similar changes in taste pleasantness perception, i.e. that any changes seen in opiate users would be similar to those seen in acutely detoxified ex-opiate users.

This study therefore addressed the following hypotheses: that opiate maintenance therapy would be associated with a change in sweet, but not salt taste threshold, intensity and pleasantness; that opiate detoxification would not, in the short term, affect the opiate-related change in sweet taste observed in opiate users; that acute administration of an opiate antagonist would reverse these changes, and that acute administration of an opiate antagonist in healthy controls would alter taste pleasantness, but not intensity or thresholds.

Materials and methods

Four participant groups were recruited to address the study aims.

1) Opiate addicts (drug-user group) receiving maintenance-opiate treatment with either methadone or buprenorphine,
2) recently detoxified former opiate addicts (detox group),
3) healthy volunteers given intravenous (i.v.) naloxone (naloxone control group),
4) a control group of healthy individuals, including some smokers.

Local research ethics committees (National Health Service (NHS) Local Research Ethics Committee, Groups 1 and 2, and University of Bristol Faculty Research Ethics Committee, Groups 3 and 4) approved all procedures and protocols. After full explanation of the study aims and procedures, all participants gave written informed consent. Participants in Groups 1, 2 and 4 were given a £10 voucher for a local supermarket in recompense for their time.

The general characteristics of the participants are summarised in Table 1.

Different protocols were used for each part of the study, as detailed below.

Within-subject studies on the effect of chronic opiate use on taste threshold, intensity and pleasantness perception (in drug-user group)

Recruitment and selection. Participants were recruited from patients attending Bristol Specialist Drug and Alcohol Service (BSDAS), the NHS substance misuse service in Bristol. Participants were selected based on a diagnosis of opiate dependence, and attended the service for heroin substitution with either methadone or buprenorphine (see Table 1 for details).

Inclusion/exclusion criteria. All patients attending for maintenance therapy were approached with a view to recruitment. Participants were excluded on initial screening on the following criteria: abnormal findings of clinical significance on medical or psychiatric history (excluding opiate dependence); high caffeine intake (greater than six cups of coffee/day); illicit drug use (except prescribed opiates); excessive alcohol intake (greater than 30 units/week); heavy smoking (greater than 20 cigarettes/day); pregnancy; current prescribed psychotropic drugs; high scores for anxiety and/or depression (measured by Speilberger's Anxiety Inventory and Beck's Depression Inventory (Beck et al., 1961; Spielberger et al., 1983)). A laboratory urine sample was collected from each participant, and those who had evidence of heroin,

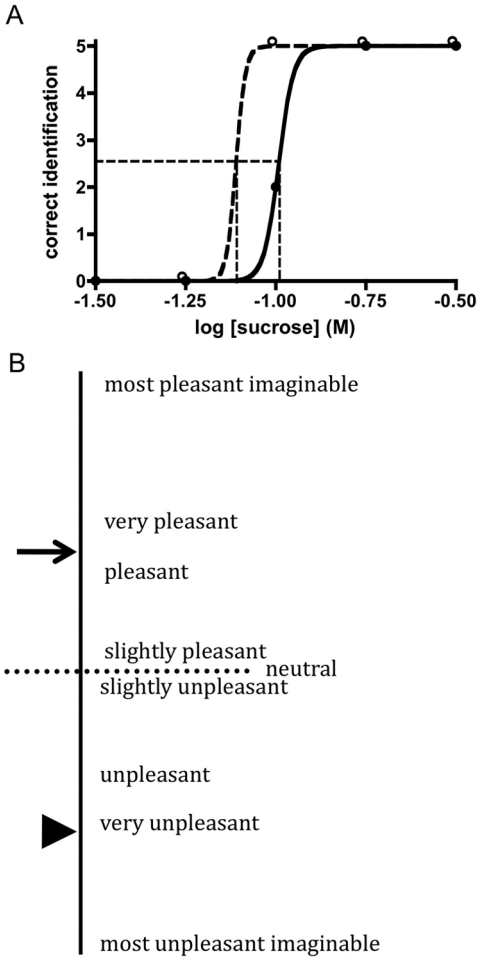

Figure 1. A. Psychophysical taste functions for a participant in the detox group. The curves shown are before (filled circles) and after naltrexone (open circles, dotted line). The horizontal and vertical dotted lines show the values determined for threshold (i.e. correct identification of the stimulus as sweet in 2.5 of five presentations). Note that the symbols for the values after naltrexone have been shifted slightly upward to prevent overlap with the filled symbols. Note also that the *x*-axis is reversed, i.e. lowered threshold is indicated by a *leftward* shift of the function.
B. The positive/negative generalised Labeled Magnitude Scale used to assess pleasantness. The central dotted line represents the 'neutral' point, neither pleasant nor unpleasant. Solutions were rated according to the anchors shown and expressed as a positive (arrow) or negative (arrowhead) distance on the line, and then converted to a 100-point scale as detailed in the methods.

cocaine, benzodiazepines or cannabis use in the preceding seven days were also excluded from analysis. During the period of the study (January–December 2007) several researchers were present on the clinic (AG, ES, AK, JO'S), for one day per week. When researchers were present on the clinic, all patients attending for OMT were approached for recruitment to the study. Twenty patients agreed to take part in the study in the recruitment period and attended for both taste-testing sessions. Of these 20, six participants were later excluded, largely as a result of other drug or alcohol use in the time between the baseline and subsequent taste tests. All included subjects refrained from alcohol intake for at least 12 hours prior to testing and refrained from caffeine consumption on the day of the test.

Taste recognition threshold was determined in all participants before and four hours after maintenance-opiate administration, at a dose commensurate with each participant's usual maintenance requirements.

Taste threshold was determined at each test by construction of taste psychophysical functions for sweet and salt taste recognition (Heath et al., 2006; Prutkin et al., 1999) (Figure 1). Participants were informed as to the taste modality they would receive at each point in the procedure (Pilková et al., 1991). Sucrose and sodium chloride (NaCl) tastes were tested separately and the order of testing was counterbalanced across participants. A range of concentrations was made by serial dilution from 1 M stock of either sucrose or NaCl. Solutions, in an overall concentration range from 1 M to 1 mM, separated by one-quarter log concentration steps, were applied to the tip of the tongue using a saturated cotton bud for each application. The different concentrations were presented in a pseudorandom order; if a participant easily recognised a concentration, the following concentration presented would be a lower concentration; if the taste was not recognised then a higher concentration would be presented. Once concentrations were determined at which recognition occurred at every presentation (100% recognition, five of five presentations) or did not occur (0% recognition), concentrations between these two were presented. Each concentration was presented five times. Participants rinsed the mouth between each presentation, and the inter-stimulus interval was approximately 30 seconds. The participant responses were then used to generate a psychophysical taste function using a sigmoidal curve fit of the stimulus-response curves constrained at 0 and 5 (Figure 1A). Recognition threshold was determined as the concentration at which the participant could detect the taste 50% of the time (Figure 1) (Heath et al., 2006; Mullings et al., 2009).

Taste pleasantness and intensity were determined using generalised Labeled Magnitude Scales (gLMS) (Bartoshuk et al., 2004; Mullings et al., 2009). For pleasantness/unpleasantness, a quasi-logarithmic 170 mm positive/negative scale (85 mm positive, 85 mm negative) was used, anchored at "most pleasant imaginable" and "least pleasant imaginable", with "neutral" as a midpoint (Figure 1B). Unpleasant taste is indicated by a negative score on this scale. For intensity a 150 mm scale was used, anchored at "barely detectable" and "strongest imaginable sensation". The descriptors on both scales were placed at the same relative intervals as those originally reported for a 100-unit gLMS (Bartoshuk et al., 2004), so descriptors on figures are comparable to those from other studies using a similar gLMS. The values presented are converted to a 100 mm scale (0–100 for intensity, and −50 to +50 for pleasantness, so a positive point 70 mm on the pleasantness scale would be represented as 70/85*100 = 82) to allow comparison to literature values.

Use of the gLMS was carefully explained to participants, but they received no prior training session in its use because of time constraints. Participants were asked to swill 5 mL of a suprathreshold salt or sweet (1 M) solution around their mouth for 10 seconds and then rate pleasantness and intensities on the scales. Sweet and salt "likers" and "dislikers" in each group were classified by a positive or negative score on first exposure to 1 M sucrose or salt solution (Looy and Weingarten, 1992).

Sweet taste was hypothesised to be the taste that would be modulated by opioidergic systems, and salt was used as a control taste modality, as it is transduced by a separate population of taste cells (Type III cells as opposed to Type II cells (Roper, 2007)). Only two taste modalities were tested in all participants because of time constraints for testing, particularly in participants prior to their maintenance-opiate administration.

Within-subject studies on the effect of opiate antagonism in recently detoxified ex-opiate user on taste perception (detox group)

Recruitment and selection. All participants were in-patients from the dedicated NHS substance misuse inpatient unit in Bristol (Table 1). They were selected for recruitment interview on the basis of a diagnosis of opiate dependence and were inpatients for opiate detoxification and possible naltrexone treatment. Participants were completely abstinent from all opiates for at least one week (confirmed by urine analysis), and were abstinent from alcohol intake for greater than one week prior to the test day. The inpatient service admits ~two to three people per week for detoxification. During the period of the study (July–December 2007) a researcher (AG) was present on the ward and interviewed all admitted patients with an appropriate diagnosis about recruitment to the trial. During that time, only eight patients were willing to be recruited to the trial, despite a larger number of patients approached. Two of these participants were subsequently excluded as a result of incomplete data sets. The number of patients going through the detoxification programme who are subsequently prescribed naltrexone as outpatients are a very small number of the total number going through detoxification, hence the relatively low numbers recruited to this arm of the study. This is primarily because of patient resistance to being prescribed any medications following detoxification.

Exclusion/inclusion criteria. The criteria for exclusion from the study are as detailed for Group 1. One data set was incomplete for a participant who developed acute symptoms of naltrexone treatment (nausea and vomiting) in whom taste testing was not possible.

None of the detox participants had been previously treated with naltrexone. A single oral dose of 25 mg naltrexone is routine clinical practice on the ward for patients opting to move onto naltrexone therapy after detoxification, so this intervention conformed to the usual clinical treatment in this unit. None of the patients went into acute withdrawal after naltrexone administration.

Taste threshold, pleasantness and intensity were determined in these participants before and four hours after a single 25 mg dose of naltrexone using the same methods as described for Group 1.

Within-subjects placebo-controlled crossover study on the effect of endogenous opiates on taste perception (naloxone group)

Healthy volunteers were recruited from within the University of Bristol (Table 1). Subjects were all non-smokers who met the overall inclusion criteria detailed for Group 1 (other than opiate dependence).

In the naloxone group, taste threshold, intensity and pleasantness were determined before and 10, 25 and 45 minutes after an intravenous (i.v.) injection of 13 μg/kg naloxone (made up to 5 mL in saline) or 5 mL saline (both administered to each participant at a single visit), through an indwelling Venflon (20G) inserted into the antecubital fossa. The drugs were delivered double blind, and the order of saline/naloxone delivery counter-balanced for the participants. This concentration of naloxone has been demonstrated to occupy 50% of CNS opioid receptors in healthy individuals (Melichar et al., 2003).

Control group

Taste perception was also measured using the same techniques in the same time period in a group of healthy controls. These included some non-abstinent smoking participants (all ≥ five cigarettes per day, smoking first cigarette within one hour of waking), and the proportion of smokers in the control group was equivalent to those in the drug-user and detox groups (Table 1). Despite a larger age range in the control group, the age distribution was not different between control and experimental groups. The data collected from smokers were derived from a different previously published study (Mullings et al., 2009). Data from otherwise healthy normal weight (BMI 18–25), smoking and non-smoking participants were derived from our anonymised database of taste thresholds, liking and intensity, some of which have been included in previous studies (Donaldson et al., 2009; Heath et al., 2006; Mullings et al., 2009). Some of the data from drug-user and detox groups have been published in abstract form (Green et al., 2008; Kaul et al., 2008).

Methodological consideration of taste recognition determination. This method was chosen over more widely used two- or three-way forced-choice methods as it permits very rapid testing and generation of full psychometric functions. The method is based on physiological definition of sensory threshold, as being the stimulus intensity that evokes a response at 50% of presentations (Kandel et al., 2000). Rapid testing is required when working with opiate addicts prior to administration of their maintenance dose of either buprenorphine or methadone. Full psychometric functions (Figure 1) can yield information not found with methods that determine only threshold, such as taste acuity (slope of the function). In a direct comparison between this method and a two-way forced choice regional threshold determination (McMahon et al., 2001), we found no differences in threshold values (Bennett and Donaldson, 2008, unpublished observations). In addition, this method of regional threshold determination has the advantage that it reduces the possibility of potential confounds arising from spatial differences in taste thresholds in the mouth. The tip of the tongue also displays the smallest differences in salt and sweet thresholds between men and women, as previously demonstrated (Sato et al., 2002).

Data analysis

Data were analysed using GraphPad Prism version 4.00 for Macintosh (GraphPad Software, San Diego, CA, USA, www.graphpad.com). Group comparisons were made using analysis of variance (ANOVA), and post-hoc Bonferroni tests were used, as all data sets were Gaussian. Paired two-group comparisons were made

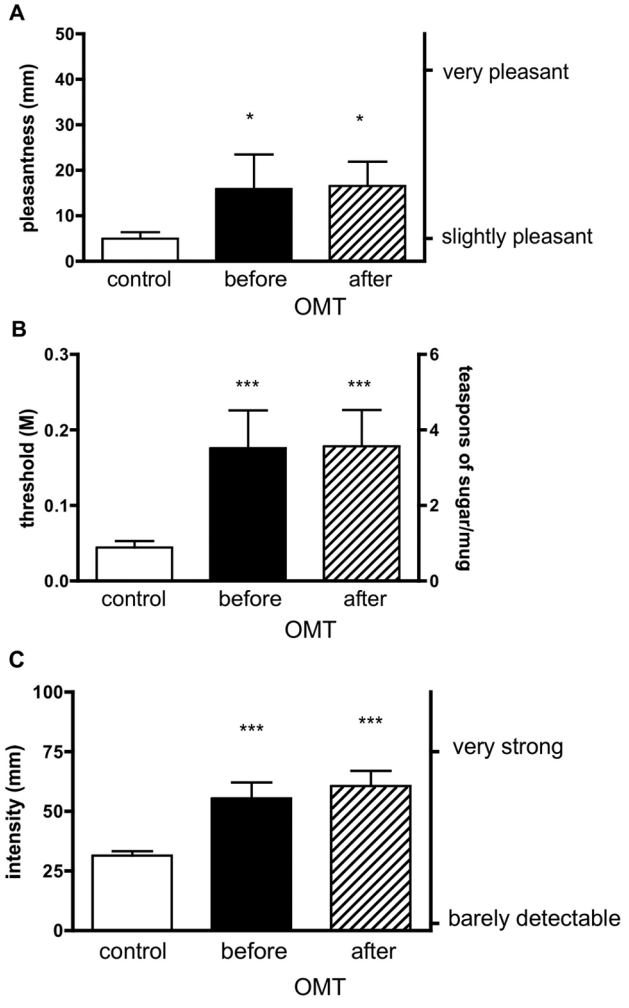

Figure 2. Effect of opiate maintenance and opiate-maintenance therapy (OMT) on sweet taste perception in opiate users.

A. Opiate-maintained drug users rated 1 M sucrose as significantly more pleasant than controls. Before and after refer to ratings taken before and four hours after OMT.

B. Opiate-maintained drug users had significantly higher sweet recognition thresholds than controls, and OMT had no effect on threshold. Note that the right-hand *y* axis shows the concentration of sucrose represented as approximate teaspoons of sugar/mug, i.e. 0.3 M is equivalent to ~ six teaspoons in a 200 mL mug, for comparison.

C. Opiate-maintained drug users rated 1 M sucrose as significantly stronger than controls. OMT had no effect on intensity. Data are mean + SEM, $*p<0.05$; $***p<0.001$.

(paired *t* tests) to compare means before and after an intervention, i.e. within the drug-user and detox groups. Repeated-measures ANOVA was used for comparison of data from participants given i.v. naloxone/saline. Two-tailed Spearman rank order correlations were used to determine relationships between variables.

Results

Alteration in taste threshold, intensity and pleasantness in participants on OMT and relationship to opiate dose

The overall pattern of taste changes in opiate addicts under treatment was not significantly different for participants receiving methadone or buprenorphine. The findings for these two groups are therefore presented together.

Based on previously published data on the dietary shift toward processed sugars in opiate users (Saeland et al., 2011; Zador et al., 1996) and opiate involvement in palatability and pleasantness of food in opiate users (Kolarzyk et al., 2005b; Morabia et al., 1989; Titsas and Ferguson, 2002), we hypothesised that the pleasantness of sucrose would be higher in the drug-user group, and our findings supported this hypothesis (Figure 2A). There was no difference in the absolute numbers of sweet "likers" versus "dislikers" in the control group compared to drug users before opiate administration (Table 1; Fisher's exact test $p=0.33$). In addition, both sweet taste recognition thresholds (Figure 2B) and intensity of the 1 M sucrose solution were significantly raised in drug users compared to controls (Figure 2C). There were no differences in these measures between the methadone- and buprenorphine-maintained participants. The administration of maintenance opiate had no effect on any measure of sweet taste perception.

The effect of opiate maintenance on salt taste measures was different from the effect on sweet taste. Control participants generally perceived the salt solution tested as being "slightly" to "moderately" unpleasant (Figure 3A), and participants on OMT rated the salt solution as being significantly more unpleasant ("very unpleasant") than the control group before their maintenance dose. As with sweet liking, there was no difference in the proportions of salt dislikers (before opiate) between groups (Table 1; $p=1$). The administration of opiate resulted in a small, non-significant decrease in the perceived unpleasantness of salt in these participants (Figure 3A) (this was largely attributable to one participant in whom pleasantness shifted from −77 mm to +77 mm). The recognition threshold for salt was also significantly raised in these participants, and, in contrast to the observations for sucrose taste, administration of opiate resulted in a significant reduction in threshold, effectively returning recognition threshold to control levels in these participants (Figure 3B).

The intensity of the 1 M salt solution was significantly raised in opiate-maintained participants, and this was also unaffected by opiate administration (Figure 3C).

The maintenance dose of methadone reflects the degree of opiate tolerance of a patient, inasmuch as this is the opiate dose required to evoke an effect, i.e. to prevent withdrawal. To address the possible relationships between different aspects of taste perception, and this readout of opiate tolerance, we examined the correlation between different taste measures (pleasantness, recognition threshold and intensity) before and after the acute methadone administration, and methadone-maintenance dose. Buprenorphine doses used for maintenance are all supramaximal, as this drug is a partial rather than a full μ opiate receptor agonist. Data were therefore available only for the seven participants who were maintained on methadone.

There was no significant correlation between sweet taste intensity and dose of methadone either before (Spearman $r = -0.75$, $p=0.053$; Figure 4A) or after methadone administration (Spearman $r = -0.02$, $p=0.97$; Figure 4B), although intensity before methadone and dose bordered on significance. Sweet taste threshold before methadone was also not correlated with methadone dose ($r=0.15$, $p=0.75$; Figure 4C), whereas after methadone, when receptor occupancy would be increased, the sweet taste thresholds were significantly correlated with the methadone dose (Spearman $r = 0.81$, $p=0.027$; Figure 4D). There were no significant correlations between sweet taste pleasantness, nor between any measure of salt taste and methadone dose (not shown).

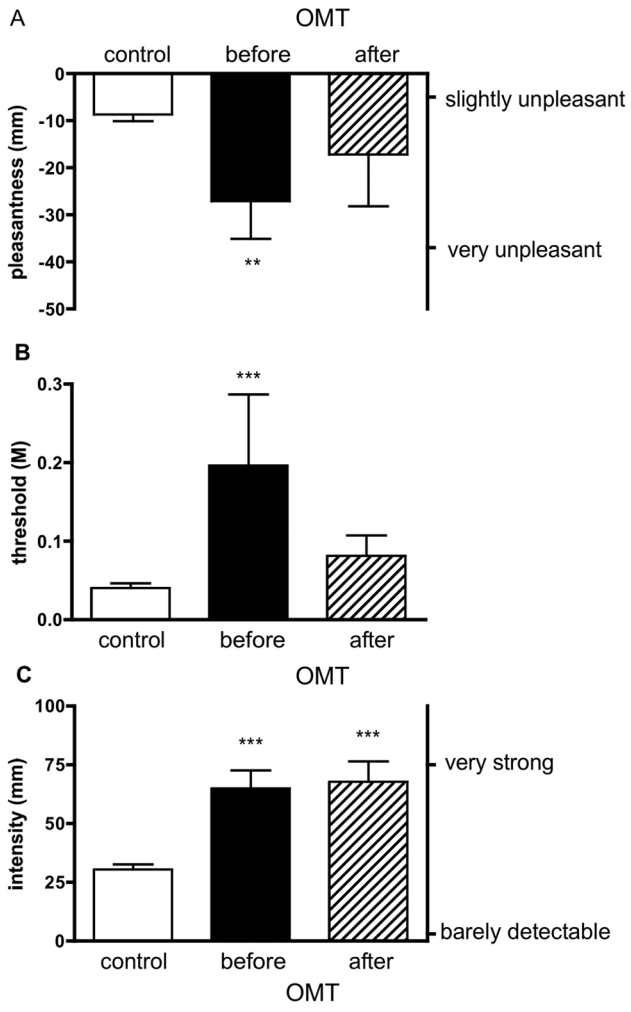

Figure 3. Effect of opiate maintenance and opiate maintenance therapy (OMT) on salt taste perception in opiate users.
A. Opiate-maintained drug users rated 1 M NaCl as significantly more unpleasant than controls and OMT returned unpleasantness toward control values (NS).
B. Opiate-maintained drug users had significantly higher salt recognition thresholds, and OMT lowered thresholds to the same level as controls.
C. Opiate-maintained drug users rated 1 M NaCl as significantly stronger than controls, and OMT had no effect on the intensity ratings.
Data are mean + SEM, $**p<0.01$; $***p<0.0001$; NS: not significant.

Alteration of taste perception after detoxification, and the effect of acute opiate antagonist administration

There were no differences in sweet pleasantness ratings in detoxified participants, either before or after acute naltrexone administration (Figure 5A), or compared to the control group, indicating that detoxification had reversed the changes in pleasantness seen in opiate users. As with the drug-user group, there was no difference in the proportion of sweet likers between the two groups (Table 1; $p=1$). Variability of pleasantness increased after naltrexone as a result of one participant whose pleasantness ratings increased from −50 to +78 mm. In comparison to drug users, detoxified participants had lower pleasantness ratings, but equivalent intensities and recognition thresholds to those seen in drug users (Figure 5B and 5C). Sucrose recognition thresholds were higher in detoxified participants than in controls (Figure 5B), and acute administration of naltrexone reversed these to the same level as in the control group. Naltrexone administration had no effect on sucrose intensity ratings (Figure 5C).

In contrast, the pattern for salt taste unpleasantness ratings in detox participants, immediately after detoxification, was similar to that seen in drug users (Figure 6A) in that salt continued to be rated as being significantly more unpleasant, and more intense after detoxification, compared to control groups. Thresholds were also still raised after detoxification. There was no difference in the proportion of salt dislikers between the two groups (Table 1; $p=0.57$). No measure of salt taste was affected by naltrexone administration (Figures 6A–6C), although unpleasantness was non-significantly reduced.

Acute administration of opiate antagonist in healthy individuals

Naloxone had no effect on taste perception, either on threshold, intensity or pleasantness in healthy non-smoking controls (Table 2).

Discussion

These findings demonstrate that people on opiate maintenance for the treatment of addiction have disrupted measures of taste perception that are in part reversed in recently detoxified former opiate users, when compared to controls.

Opiate users perceive sucrose as being more pleasant than controls, whereas in detoxified ex-users pleasantness ratings are no different from controls, indicating that detoxification can reverse the changes in sweet pleasantness seen in opiate users. Neither OMT nor naltrexone administration themselves had an effect on sweet pleasantness. These findings indicate that altered pleasantness for sucrose, which may underpin the altered processed carbohydrate intake in opiate users, is rapidly changed after a short period of detoxification.

Previous observations of sweet taste pleasantness in heroin-using addicts have shown an increase in perceived pleasantness (Perl et al., 1997). Detoxified addicts or those maintained on methadone did not have altered pleasantness ratings compared to controls (Bogucka-Bonikowska et al., 2002; Perl et al., 1997). In both these previous studies, the values obtained for the control group pleasantness ratings using the linear visual analogue scale (VAS) were higher than those in our study. Our use of the positive/negative gLMS may therefore have served to discriminate more effectively between the different groups, who are very likely to have different sensory perceptual experiences. This is a strength of this scale compared to linear VAS (Bartoshuk et al., 2004).

Our data suggest that one week of detoxification might begin to reset enhanced pleasantness perception in drug users, but it would be important to determine the long-term effect of detoxification on taste pleasantness in order to define whether the reversal in sweet taste perception is maintained, whether it is sufficient to influence dietary carbohydrate content, or if changes in threshold, intensity or salt taste are also needed to affect dietary choice, and, finally, whether these changes could be attributable to altered cortical function.

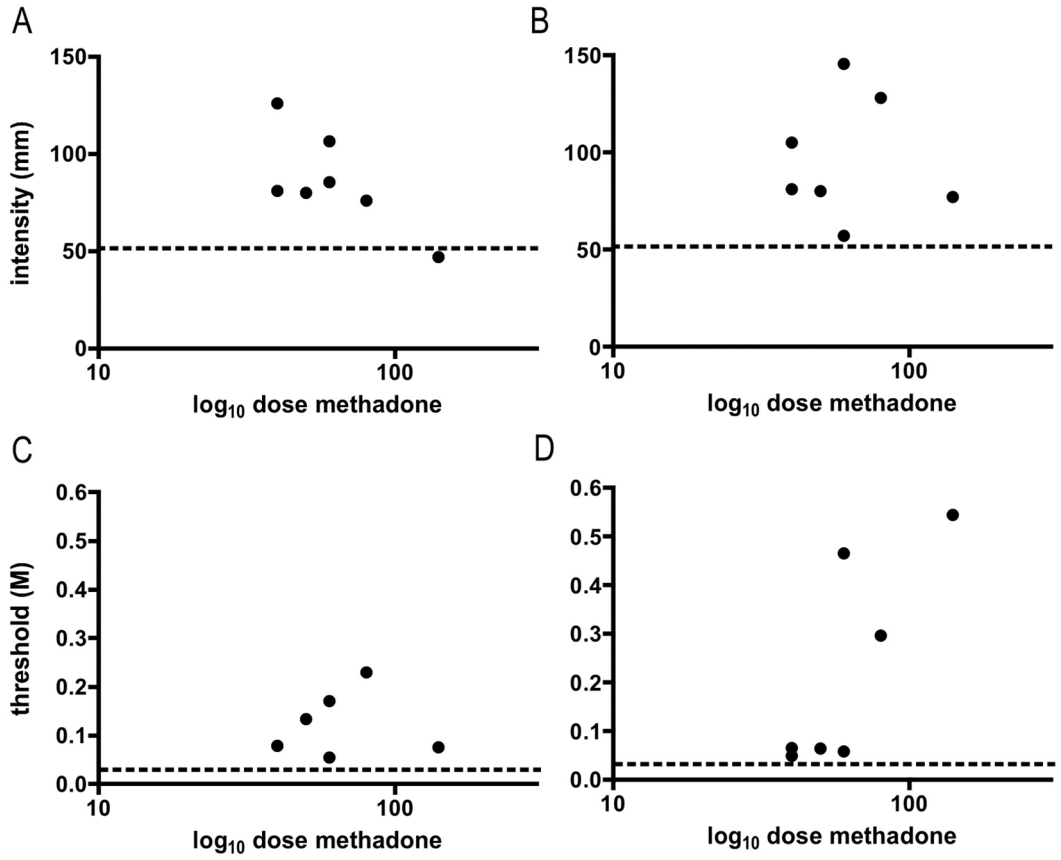

Figure 4. Relationships between different measures of taste perception and opiate tolerance.
A. The intensity of 1 M sucrose was inversely related to the opiate tolerance, as estimated by the required dose of methadone. This relationship did not quite reach significance (Spearman $r = -0.75$, $p=0.053$).
B. The intensity of 1 M sucrose was not related to opiate tolerance after methadone administration ($r = -0.02$, $p=0.97$).
C. Sucrose recognition threshold was not correlated with opiate tolerance before opiate administration ($r=0.15$, $p=0.75$).
D. After opiate administration, when opiate receptors are occupied, the sucrose recognition threshold was significantly correlated with methadone dose ($r = 0.81$, $p=0.027$). Dotted lines show mean intensities (A and B) and thresholds (C and D) in the controls for comparison.

The observations in both the experimental groups, particularly in comparison to each other, should be treated with some caution because of low numbers, particularly in the detox group. Recruitment in this group was particularly problematic as a result of the wish amongst detoxified addicts as well as their support workers to avoid any drug treatment, leading to an avoidance of opting for naltrexone treatment in inpatients.

There were other limitations to this study that also should be acknowledged, such as failure of drug users to commit to two test visits, or illicit drug use between taste tests. We acknowledge that the drug treatments cannot be compared to a placebo control, nor blinded, as for ethical reasons we could not alter the planned clinical treatment of these patients. The control group was taken from our previous studies as being representative of smoking status and age, and is large, and as such may confound the data. There are also proportionally more women than men in this group compared to the experimental groups.

Contrary to our original hypothesis, and in contrast to the effects on sweet taste, changes were also observed for salt taste, in that both experimental groups perceived salt as being more unpleasant than controls, prior to any acute drug administration.

Naltrexone administration had no significant effect on sweet pleasantness or salt unpleasantness in the small group of detoxified addicts in this study; the slight tendency for this to change is attributable to one participant in whom, for example, sweet ratings increased from −50 to +78 mm. This is in contrast to a large number of studies in *healthy* volunteers where naltrexone reduced food palatability, intake and sweet pleasantness ratings (see introduction and references in (Yeomans and Gray, 2002) but also (Hetherington et al., 1991; Scinska et al., 2000)). Depot naltrexone also reduced both 'liking' and a measure of sweet intensity in abstinent opiate addicts (Langleben et al., 2012). This latter finding suggests that longer-term, or higher dose, naltrexone therapy may be required to see any effect on taste perception, or that opiate antagonist effects are different in detoxified former drug users than in other populations. The test dose of naltrexone used in this study is 25 mg, as opposed to the 50 mg used in most other studies, as a result of the need to adhere to usual clinical practice in our clinic.

Finally, naloxone had no effect on pleasantness of sweet taste in healthy participants, despite published reports that naloxone has similar effects on taste hedonics and food palatability to naltrexone

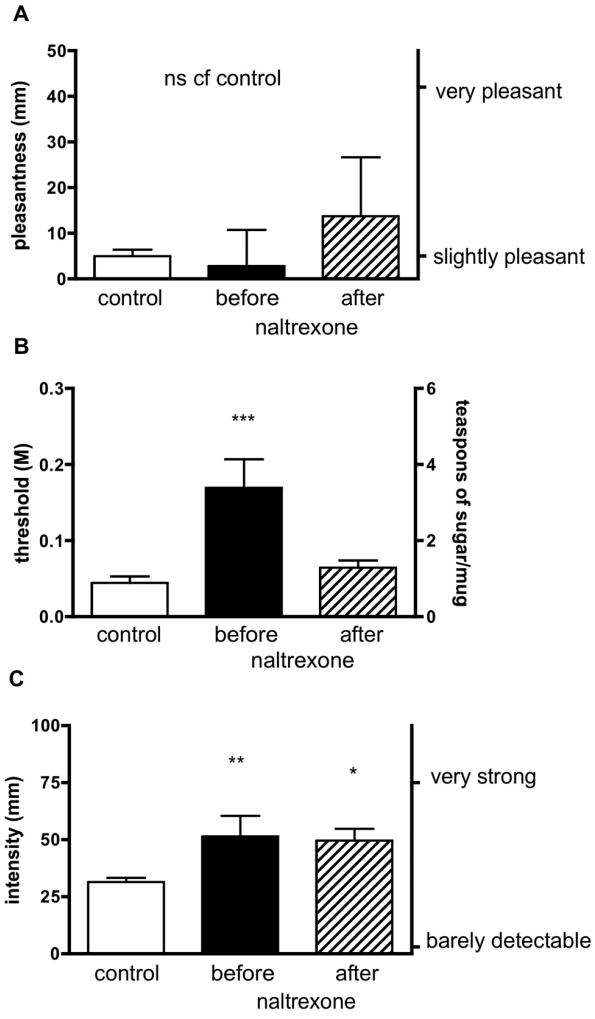

Figure 5. Effect of opiate antagonist on sweet taste in detoxified opiate users.
A. Detoxified opiate users rated 1 M sucrose as being only as pleasant as control participants did, and the acute administration of opiate had a slight but non-significant effect on this. Before and after refer to ratings taken before and four hours after administration of naltrexone.
B. Sweet taste thresholds were higher in detoxified opiate users than in controls, and were acutely lowered by naltrexone administration.
C. Detoxified opiate users rated 1 M sucrose as significantly more intense than controls, and the acute administration of naltrexone had no effect on intensity ratings. Data are mean + SEM; *p<0.05; **p<0.01; ***p<0.001.

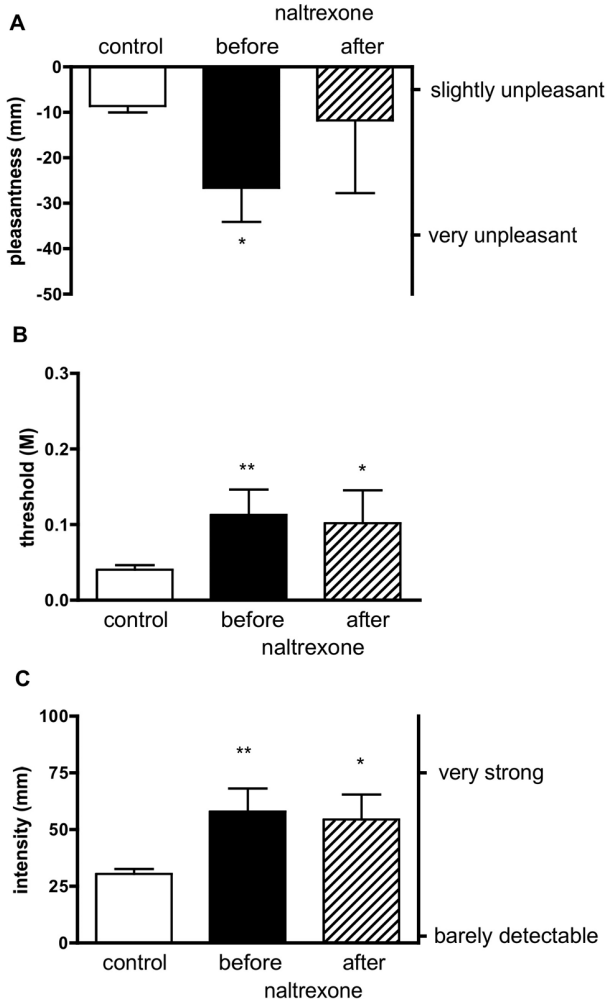

Figure 6. Effect of opiate antagonist on salt taste in detoxified opiate users.
A. Detoxified opiate users rated 1 M NaCl as being more unpleasant than the controls. Although acute administration of naltrexone reduced unpleasantness, this was not significantly different from either before naltrexone, or control.
B. Salt taste recognition thresholds were higher in detoxified opiate users than in controls, and were unaffected by naltrexone administration.
C. Detoxified opiate users rated 1 M NaCl as significantly more intense than controls, and the acute administration of naltrexone had no effect on intensity ratings. Data are mean + SEM; *p<0.05; **p<0.01; ***p<0.001.

Table 2. Taste measures in healthy participants before and after i.v. naloxone.

Time	Pleasantness (mm)				Threshold (mM)				Intensity (mm)			
	Sweet		Salty		Sweet		Salty		Sweet		Salty	
	saline	naloxone	saline	naloxone	saline	naloxone	saline	naloxone	saline	naloxone	saline	naloxone
before	9±14	5±16	−22±9	−19±10	30±24	36±30	52±73	44±36	43±9	39±16	53±15	40±19
10 minutes	9±17	6±17	−26±12	−20±7	36±32	33±29	38±38	51±52	41±17	39±16	57±14	48±13
25 minutes	8±19	6±15	−25±8	−21±10	46±43	36±22	42±41	36±33	41±16	37±16	53±14	49±19
45 minutes	9±17	6±15	−25±6	−24±11	36±31	34±24	36±36	37±31	41±13	36±17	53±13	51±16

i.v.: intravenous. Data shown are means ±SD in mM (thresholds), and mm (intensity and pleasantness). Negative pleasantness values indicate unpleasant taste. The ratings for intensity and pleasantness are given in mm as determined from the generalised Labeled Magnitude Scales (gLMS). For reference the following mm measurements relate to the given descriptors on the scales: intensity (100 mm scale: moderate = 17mm, strong = 35 mm), pleasantness/unpleasantness (positive/negative 100 mm scale, midpoint neutral (0 mm), moderately pleasant/unpleasant = ±8 mm, pleasant/unpleasant = ±17 mm, very pleasant/unpleasant = 26 mm).

(Drewnowski et al., 1995; Komorowski and Komorowska, 1986; Trenchard and Silverstone, 1983). Thus, although naltrexone and naloxone may not be directly comparable as a result of different routes of administration and dose, our data disagree with the majority of literature data on the effects of opiate antagonism on sweet taste pleasantness. Like naltrexone, the dose of naloxone, while being a concentration that results in occupation of 50% of opiate receptors (Melichar et al., 2003), is at the lower end of literature values, and the lack of effect seen here may be a combination of lower dose and shorter time scale of study (< one hour).

No study has previously reported taste threshold data in opiate users or detoxified addicts. We found that sucrose thresholds were significantly increased in opiate users to a level equivalent to approximately three to four teaspoons of sugar in a mug — interestingly, this is the minimum level of sweetness reported by recovering drug users to be preferred in their drinks (Robinson et al., 2005). This might suggest that the raised threshold in this group contributes to the increase in sucrose added to beverages, as it may necessary to add sugar to drinks to achieve a suprathreshold level of sweetness. Opiate administration had no effect on sucrose thresholds. In contrast, the acute administration of opiate reduced the higher salt recognition threshold seen in drug users to control levels. We suggest that a reduced threshold after opiate administration would, at the least, enable recognition of lower levels of salt in food, and the combination of these shifts in threshold may contribute to a move away from salty and toward sweet foodstuffs in these individuals, to reach a concentration of sugar that is detectable in the diet.

Surprisingly, in the detox group naltrexone did reduce the increased sweet threshold back to control levels. The significant effect of naltrexone on sucrose recognition thresholds in recently detoxified users may indicate that the opioidergic receptor systems involved in sweet taste recognition are not initially affected by detoxification, but may be acutely "reset" by naltrexone. This could be interpreted as indicating that opiate receptors in brain areas involved in sweet taste recognition threshold might behave differently from those elsewhere in the brain, as most altered opioidergic systems in chronic drug users are not thought to be acutely reset by antagonist treatment. This suggests that naltrexone treatment after detoxification might have an adjunct effect of helping reverse some of the gustatory changes that might contribute to altered eating behaviour in opiate addicts. The blunted thresholds might be attributable to altered processing in other gustatory areas, for example, gustatory inputs into the nucleus of the solitary tract, which are known to be modulated by opiates in experimental rodents (Li et al., 2003).

Intensity of both sweet and salt taste was increased in drug users as well as detox groups and was unaffected by either opiate or naltrexone. This is in contrast to previous studies where intensity was not different in methadone-maintained men (Bogucka-Bonikowska et al., 2002), and after depot naltrexone, when "sweetness" was reduced, albeit at only two sucrose concentrations (Langleben et al., 2012).

There are two areas of interest that should be highlighted in the findings — firstly that OMT did not increase the pleasantness of *all* tastes, but only sucrose and not salt, in which pleasantness decreased, and secondly, that increased pleasantness of sucrose in opiate users is also associated with increased thresholds and intensities. While it may seem counterintuitive that these very different measures of taste perception are all altered in opiate users, it is known that these different aspects of taste are not directly related (Keast and Roper, 2007), and indeed are encoded in different areas of the brain. For example, umami (the taste of glutamate) thresholds are raised, but suprathreshold intensity measures were unaltered in obese women (Pepino et al., 2010). Alterations in pleasantness and intensity suggest that there is altered central processing of taste in opiate users, and that some of this might be acutely reversed on detoxification. Pleasantness is represented in the orbitofrontal and insular cortices (Rolls and Grabenhorst, 2008; Small et al., 2003), whereas intensity is represented in insular cortex and amygdala (Grigson, 2002; Small et al., 2003). This is consistent with the known disruption seen in these areas in opiate users (Daglish et al., 2003; Volkow and Fowler, 2000).

The observations of relationships between methadone dose and taste threshold and intensity are possibly suggestive of a contribution of the opiate receptor state in these participants to these sensory measures, although interpretation is, of course, limited by low participant numbers. However, we could speculate that the more tolerant users are to methadone (as indicated by their higher dose of methadone), the more blunted their sweet taste threshold, and the less intense they find a highly concentrated sucrose solution. In more general terms relating to addictions, alcoholics show altered sweet taste perception, particularly in relation to sweet preference, a measure that may indicate the efficacy of naltrexone for the treatment of alcoholism (Garbutt et al., 2009; Laaksonen et al., 2011). Accumulating evidence therefore suggests that sweet taste hedonic measures and, as we have shown, possibly other perceptual measures such as intensity and thresholds may represent indicators of opiate tolerance and appropriate methadone-maintenance regimens.

Acknowledgements

We would like to thank all our participants, and the staff of BSDAS, Bristol. We acknowledge the University of Bristol for financial support for incidental expenses associated with the study.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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