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CHEMOSENSORY STIMULATION DURING SLEEP – AROUSAL RESPONSES TO GUSTATORY STIMULATION

B. A. STUCK, [a,b*†] **T. T. MOUTSIS,** [b†] **U. BINGEL** [c] **AND J. U. SOMMER** [b]

[a] *Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Essen, Germany*

[b] *Sleep Disorders Centre, Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Mannheim, Germany*

[c] *Department of Neurology, University Duisburg-Essen, Germany*

Abstract—The processing of nociceptive, visual, vibrotactile, thermal and acoustic stimuli during sleep has been extensively investigated in the past. Recently, interest has focused on the impact of olfactory stimulation on sleep. In contrast to all other sensory systems, olfactory stimulation does not lead to an increased arousal frequency, regardless of hedonicity and concentration. The impact of the second chemosensory system, gustation, on sleep however has not been investigated to date. Twenty-one normosmic and normogeusic volunteers of both genders, aged 19–33 years, participated in the trial. Stimulation was performed with a gustometer using the following aqueous solutions: saccharose 20% (sweet), sodium chloride (NaCl) 7.5% (salty), citrate 5% (sour), and quinine 0.02% (bitter). A tasteless solution was used as negative control. Capsaicin, a strong trigeminal stimulus, served as positive control. Primary outcome was arousal frequency per stimulus in each sleep stage, as assessed with polysomnography. The frequency of arousals decreased in deeper sleep stages (N1: 211 arousals of 333 stimuli = 63%, N2: 676/2728 = 25%, N3: 43/1378 = 3%, REM: 57/1010 = 6%). Statistically significant differences in terms of arousal frequency were found in N2 between the negative control and NaCl 100 μl ($p < 0.001$), saccharose 100 μl, citrate 50 μl & 100 μl, and quinine 100 μl ($p < 0.05$). Capsaicin led to complete awakenings in 94% of stimuli (30/32). These results demonstrate that gustatory stimulation during sleep induces arousals depending on stimulus intensity and sleep stage, which is different to olfactory stimulation and may be related to differences in central processing of the two chemosensory systems.

Key words: gustation, chemosensation, arousals, taste, sleep, olfaction.

*Correspondence to: B. A. Stuck, Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital Essen, Hufelandstr. 55, 45147 Essen, Germany. Tel: +49-201-723-2964; fax: +49-201-723-5903.

E-mail address: boris.stuck@uk-essen.de (B. A. Stuck).

† The first two authors contributed equally to the publication.

Abbreviations: NaCl, sodium chloride; SAS, Statistical Analysis Software; TDI, threshold, discrimination, identification; NRS, numeric rating scale.

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INTRODUCTION

Sleep is a state of reduced responsiveness to internal and external stimuli; nevertheless, sensory information is generally processed also during sleep. The processing of sensory stimuli has extensively been studied especially for auditory stimuli, but also for visual and somatosensory stimulation. The processing of chemosensory stimuli during sleep however has only recently been addressed.

The processing of sensory stimuli during sleep can be studied in multiple ways, e.g. by assessing changes in cortical activation as measured by surface electroencephalogram, effects on memory consolidation and learning, as well as behavioral changes and modification of dream content and dream emotions as a result of stimulation. For the chemosensory system several of these strategies were used in the past to assess whether or not chemosensory stimuli are processed during sleep. With the help of olfactory event-related potentials it was possible to demonstrate that olfactory stimuli are processed on a cortical level during sleep (Stuck et al., 2006). Following olfactory stimulation, respiratory patterns change during sleep (Arzi et al., 2010). In addition, Rasch et al. were able to show that olfactory stimulation during sleep can enhance memory consolidation when odor cues that are presented during the learning period are presented again during sleep (Rasch et al., 2007). Arzi et al. were able to document that aversive olfactory conditioning can reduce cigarette-smoking behavior when both aversive olfactory stimuli and cigarette smoke are presented during sleep (Arzi et al., 2014). Moreover, Schredl et al. were able to demonstrate that dream emotions and dream content can be influenced by nocturnal olfactory stimulation (Schredl et al., 2009, 2014).

A unique feature of the olfactory system is the fact that in contrast to all other sensory systems studied, olfactory stimulation does not lead to arousal or awakening during sleep (Stuck et al., 2007; Arzi et al., 2010). This is not only the case for relatively neutral substances such as phenylethyl alcohol or hydrogen sulfide but also for relevant stimuli such as smoke (Heiser et al., 2012). Arousal reactions however occur reliably with nasal trigeminal stimulation (Stuck et al., 2008). Nocturnal olfactory stimuli can increase the responsiveness to these trigeminal stimuli (Stuck et al., 2011). This unique feature of the olfactory system has been attributed to the fact that olfactory processing largely bypasses the thalamus (Neville and Haberly, 2004; Landis et al., 2005; Gottfried, 2006), which

typically gates information from other sensory systems during sleep (Steriade et al., 1997).

If and to what extent gustatory stimulation during sleep is processed and may induce arousal reactions has not been studied to date, which may be related to the technical difficulties in nocturnal gustatory stimulation. Based on the results on olfactory stimulation however, it can be hypothesized that gustatory stimuli are also processed on a cortical level during sleep. Supposing that the lack of arousal in olfactory stimulation is due to its specific central processing however, different results might be expected for gustatory stimulation.

The aim of the study was to assess whether gustatory stimulation during sleep leads to an increase in arousal reactions compared to a tasteless control to gain first insights in gustatory processing during sleep. Based on the differences in central processing of gustatory compared to olfactory information, particularly regarding the connection of afferent input with the thalamus and brainstem nuclei, we hypothesized that gustatory stimulation during sleep would induce arousals as all other sensory stimuli except smell. We also aimed at exploring potential differences between the different basic qualities of taste sweet, sour, salty and bitter as well as dose-related aspects.

EXPERIMENTAL PROCEDURES

The study was performed at the Sleep Disorders Center at the Department of Otorhinolaryngology, Head and Neck Surgery Mannheim, Germany. The study protocol was approved by the local ethics board of the Medical Faculty Mannheim of the University of Heidelberg (2013-625N-MA). The study was performed according the Declaration of Helsinki; written informed consent was obtained from all participants.

Participants

Twenty one adult healthy volunteers of both genders between the age of 19 and 33 were recruited for the trial with the help of bulletins placed at the campus of the Medical Faculty Mannheim. Exclusion criteria were as follows: history of smell or taste disorders in medical history, regular intake of any medication that potentially affects chemosensory function (Ackerman and Kasbekar, 1997), known sleep disorders such as insomnia or sleep-disordered breathing, relevant intraoral pathology and smell or taste dysfunction assessed with psychophysical measures. All participants had normal gustatory and olfactory function as assessed by the Taste Strips and the Sniffin' Sticks test kit (see below).

Study protocol

After informed consent, in- and exclusion criteria were reviewed and psychophysical testing was performed during a screening visit. During this visit the subjects were exposed to the taste solutions used for the experiment during wakefulness to ensure that they were sensitive to all substances used.

Subjects were scheduled for two nights of testing. The individual number of stimuli varied depending on the individual sleep profile and the length of sleep stages. Primary outcome measure was the appearance of arousals following gustatory stimulation in terms of arousal frequency (number of arousals/number of stimuli) by stimulus and sleep stage.

Psychophysical chemosensory testing

To assess subjective gustatory functions, the Taste Strips test kit (Burghart Messtechnik GmbH, Wedel, Germany) was used (Mueller et al., 2003; Landis et al., 2009). Filter papers impregnated with four different taste qualities (sweet, sour, bitter and salty) are placed on the anterior third of the tongue, centrally. Similar strips without impregnation are used as controls. Contrary to standard procedure, the left and right halves of the tongue were not evaluated separately, because our test setup targeted the center of the tongue. For each taste quality, four different concentrations are used and the sum of the correctly identified tastes is scored. The maximum achievable score is 16; normogeusia was defined as a score of 10.

Subjective olfactory function was assessed with the help of the Sniffin' Sticks test kit (Burghart Messtechnik GmbH, Wedel, Germany) (Hummel et al., 1997; Kobal et al., 2000). Testing involves assessment of n-butanol odor threshold (T), odor discrimination (D), and odor identification (I). From the sum of these 3 scores, a composite TDI score is compiled to quantify olfactory function (Wolfensberger et al., 2000). The maximum achievable score is 46 points; normosmia was defined as a TDI score of 30 according to the 10th percentile of the corresponding age group (Kobal et al., 2000).

Chemosensory stimulation

Gustatory stimulation was performed using a gustometer, the Multistimulator OG001 (Burghart Messtechnik GmbH, Wedel, Germany). It allows controlled stimulation with defined quantities of aqueous taste solutions in programmable order at defined intervals. An individually adjusted intraoral device (SomnoGuard AP, Tomed Dr. Toussaint GmbH, Bensheim, Germany) was adapted to host four flexible tubes (Fig. 1), three of which were connected to the gustometer. The tubes were adjusted to target the center of the tongue.

For stimulation with the four basic gustatory qualities, the following solutions were used: saccharose 20% (sweet), sodium chloride (NaCl) 7.5% (salty), citrate 5% (sour), and quinine 0.02% (bitter). Concentrations of taste solutions were adapted from literature (Rollin, 1975; Bartoshuk et al., 1983; Smith, 1988; Pingel et al., 2010). As test conditions limited the number of solutions, a pilot study was conducted to optimize the intensity of each stimulus. To this end, six of the twenty-one participants were asked to subjectively assess the intensity of a set of different concentrations of each substance using a numeric rating scale (NRS) ranging von 1 (no perception) to 10 (very intense perception) for each type of taste. This was done for each test substance used. A concentration that produced a stimulus of middle to higher intensity