

## The role of oropharyngeal receptors in thirst perception after dehydration and rehydration

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**Summary:** This study examined the effect of drinking and gargling on thirst perception (TP) in 33 young dehydrated female subjects (18-25yrs), using the visual analogue scale (VAS). Group A subjects drank, while group B gargled the fluid provided - 0.0%, 0.9% and 1.8% NaCl (7.0 ml/kg body weight of fluid). The procedure was alternated two weeks later. All subjects dehydrated for 18 hours prior to the study, and the last 12-hour urine was collected and volume recorded. Subject who provided a 12hr urine volume greater than 400ml was excluded from the study. After recording the baseline TP, and voiding the bladder, drinking/gargling was done within 5 minutes, and the subsequent TPs were recorded at 5 minutes interval for 25 minutes. Blood samples were collected before and at the end of the 30 minutes, when urine volumes were recorded. Drinking (0.0% and 1.8% NaCl) resulted in an initial decrease in thirst perception, which was statistically significant ( $p < 0.05$ ) only up to 10 minutes. Water intake ad libitum (mean  $\pm$  SEM) at the end of the 30 minutes was statistically significantly lower ( $p < 0.05$ ) only in the group that drank 0.0% NaCl. Gargling on the other hand did not affect TP and water intake throughout the period of study. It can be concluded that drinking, but not gargling reduces thirst perception irrespective of the tonicity of the fluid as earlier reported (Obika et. al., 2009; Salata et. al., 1987). This study suggests that the oropharyngeal receptors for TP are activated by recurrent stimulation by the act of drinking rather than gargling.

**Keywords:** Dehydration, Rehydration, Oropharyngeal Receptors, Thirst perception, Drinking, Gargling.

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Manuscript Accepted: April, 2014

### INTRODUCTION

Thirst is a conscious sensation of a need for water (Robertson, 1991). It is important for maintaining body fluid homeostasis and may arise from deficits in either intracellular or extracellular fluid volume (Micheal et al., 2004). The stimuli for thirst includes increase in plasma osmolality, decrease in blood volume, decrease in blood pressure, increase in angiotensin II, dryness of mouth and throat (Adolph et al., 1954). Among the above listed stimuli, evaluation of changes in the concentration of blood extracellular fluid, measured as the osmolality of blood plasma appears to be the primary regulator of thirst.

Water deprivation results in increased plasma osmolality, thirst and increased secretion of arginine vasopressin, AVP (Bayliss and Robertson, 1980; Stricker and Verbalis, 2002). Plasma osmolality has been linked inextricably to determine the sensation of thirst (Baylis and Robertson, 1980). In humans, thirst and AVP are controlled by similar sensitive osmoregulatory mechanisms such that above a certain osmotic threshold of 280 – 288

mOsm/kg H<sub>2</sub>O, there is a linear relationship between the increase in plasma osmolality ( $P_{osm}$ ) and the increase in AVP and thirst (Bayliss and Robertson, 1980). Robertson (1991) determined the osmotic threshold for the onset of thirst to be about 294 mOsm/kg H<sub>2</sub>O while that of vasopressin release threshold to be about 284 mOsm/kg H<sub>2</sub>O in healthy humans.

Geelen et al., (1984) reported that the close relationship between  $P_{osm}$  and  $P_{AVP}$  is lost during the act of drinking which causes rapid suppression of vasopressin secretion before changes in  $P_{osm}$  occurs. It has also been documented in dogs and humans (Bruner, 1993; Haung et al., 2000; Obika et al., 2009) that when dehydrated animals drink, vasopressin secretion and thirst is rapidly inhibited before systemic rehydration is evident. Because absorption of ingested water must take time, and systemic factors do not change rapidly enough to account for the termination of drinking in many species, some other rapid, perhaps preabsorptive factor or factors must be important. One of such possible mechanism could arise from the oropharyngeal stimulation which occurs while water is being ingested. Simply tasting

the water and swallowing it could be sufficient to induce satiety and therefore terminate drinking (Obika et al., 2009).

The early signal that inhibits thirst has been widely related to oropharyngeal receptors signals originating from the oropharyngeal region (Figora and Mack, 1997). Oropharyngeal receptors not only contribute to the sensation of thirst but also to the control of vasopressin secretion (Geelen et al., 1984). Although oropharyngeal factors acting alone may not be sufficient to account for the normal termination of drinking in most species, it has however been suggested to play a role in the initiation and maintenance of drinking as well as to contribute to the termination of drinking (Holmes, 1964; Rolls et al., 1980; Applegreen et al., 1991; Ajayi and Obika, 2000).

Research is still on going to fully determine the definitive role of oropharyngeal receptors. Obika et al. (2009) reported a reduction in thirst during sham-drinking experiments involving the stimulation of the oropharyngeal receptors by repeated gargling in man. Since drinking involves "repeated gargling", the purpose of this work is to determine the effect of drinking and "single gargling" on thirst perception in young dehydrated female subjects.

## MATERIALS AND METHODS

### Subjects

The subjects were thirty-three (33) apparently healthy female undergraduate volunteers, between the ages of 18 and 25 years, who gave their consent. Two Groups of studies A and B were carried out and each subject participated in the two studies, separated by a two (2) week interval. The subjects in Group A drank while those in Group B did not drink (i.e., gargled) the 0.0%, 0.9% and 1.8% NaCl solutions. For this study the subjects were further divided into three subgroups which they maintained for both studies. Subgroup 1 of either Group A or B drank or gargled distilled water (0.0% NaCl solution) respectively. Similarly, subgroups 2 and 3 drank or gargled 0.9% or 1.8% NaCl solution respectively.

### Procedure for dehydration

All subjects abstained from drinking water or any other fluid for 18hours (3pm-9am). Their last 12hours urine (9pm-9am) was collected in a container and the volume recorded. Subjects with urine volume greater than 400ml were considered not to have adhered to the dehydration procedure and were therefore excluded from the study.

Each of the subjects were dehydrated and arrived at the laboratory on the day of the experiment prior to the end of the dehydration period. Resting blood pressure was measured after 15 minutes of rest in the laboratory with the subject seated and the right hand supported at heart level. Two (2) basal readings were

obtained on each subject at 3 minutes interval and the mean was recorded as the normal blood pressure.

The subject's anthropometric data were taken and body mass index was calculated from-

$$BMI = \frac{Weight (kg)}{height (cm)}$$

At the end of the dehydration period (9am) final urine sample was collected to make up the 12hours urine volume (9pm - 9am). Aliquots of the urine were analyzed for Na<sup>+</sup>, K<sup>+</sup>, Cr and Urea concentrations. Blood samples were collected from each of the subjects and kept in appropriate anticoagulant bottles which were properly labeled. After centrifugation, the plasma concentrations of Na<sup>+</sup>, K<sup>+</sup>, Cr and Urea were determined. Baseline thirst ratings were estimated by the subjects, using the Visual Analogue Scale (VAS) as modified by Thompson et al., (1991). The Visual Analogue Scale (VAS) is a 10cm marked vertical but uncalibrated line which is labeled "Very thirsty" at the top mark and "Not thirsty" at the bottom mark. The measurement from the bottom mark, to the mark made on the VAS by the subject in response to the question "How thirsty are you NOW?" gives a subjective rating of the thirst perception (TP) at that point in time.

### Group A Study: Effect of drinking distilled water and NaCl solutions on thirst perception

Thereafter, the subjects drank the respective solutions provided (7.0ml/kg body weight of 0.0%, 0.9%, or 1.8% NaCl) within 5mins. TP was again measured using the VAS after drinking and at five (5) minutes interval for the next thirty (30) minutes. At the 30<sup>th</sup> minute, urine samples were collected in separate bottles which made up 30 minutes urine volume, blood samples were once again collected.

Finally the subjects were provided with bottles of distilled water with volumes unknown to them. They were asked to drink freely till satiety and the volume of water drunk by each subject was calculated by subtracting the final volume of fluid in the container from the initial volume.

The subjects from group A study returned to the laboratory after a 2 weeks interval for the group B study, both studies were carried out on the same individuals to avoid large error margins.

### Group B study: Effect of gargling distilled water and NaCl solutions on thirst perception

As in Group A study, subjects again went through an 18 hour dehydration period. The subjects then gargled the respective solutions (7.0ml/kg body weight of 0.0%, 0.9% or 1.8 % NaCl). They gargled the entire volume comfortably within 5 minutes, and returned the already gargled fluid continuously into a container provided. Thereafter, and at 5 minutes interval and for 30 minutes, TP was measured using the VAS. Blood samples were again collected as well as 30 mins urine samples from each subject.

Finally, subjects drank ad-libitum the distilled water provided and the volume drunk was calculated as earlier stated. The gargled fluid returned to the containers were measured and subjects who returned volumes significantly lower than the initial volume given to them were excluded from the experiment.

**Calculations:**

1. Fractional excretion of water, (FE<sub>H2O</sub>) was calculated using the formula:

$$FE_{H2O} = \frac{P_{cr} \left(\frac{mg}{dl}\right)}{U_{cr} (mg/dl)}$$

Where Pcr =Plasma creatinine concentration

Ucr =Concentration of creatinine in urine.

2. Fractional excretion of sodium, FENa<sup>+</sup> was calculated using the formula:

$$FENa^+ = \frac{UNa (mol/l) \times PCr(mg/dl)}{PNa (mol/l) \times UCr (mg/dl)}$$

Where UNa = Urinary sodium concentration

PNa = Plasma sodium concentration

PCr = Plasma creatinine concentration

UCr = Concentration of creatinine in Urine.

**Statistical analysis:**

Data were presented as mean ± standard error of mean (SEM). Intra group and inter group comparisons were made using the one way analysis of variance (ANOVA). The Students't-test was used for comparisons between the experimental and control values. Confidence limit was set at 95% and a P value less than 0.05 was considered statistically significant.

**RESULTS**

Table 1 shows the anthropometric data and baseline readings after dehydration in groups A and B subjects. There was no significant difference in these values measured two weeks apart in the subjects. Table 2 shows the mean values of some urine characteristics, which were not statistically significant between the two groups of subjects

**Group A: Effect of drinking 0.0%, 0.9% and 1.8% NaCl solution on thirst perception.**

The baseline thirst rating in group A study and their thirst ratings after drinking are as shown figure 1. The

control TP value (Baseline TP) was not significantly different within the subgroups. There was a decrease (p<0.05) in TP in all the subgroups within five minutes after drinking, irrespective of the solution drank, although this decrease was only significant in subjects that drank 0.0% and 1.8% NaCl solution. The gradual decrease in mean TP continued significantly up to the 15 minutes in the subjects that drank 0.0%. These decreases in TP were followed by a gradual rise to the baseline values at the end of the experiment. On the other hand, in the 1.8% NaCl subgroup, the significant fall in TP was followed by a significant rise in the 10<sup>th</sup> minute after drinking. The TP continued to rise till the termination of the experiment.

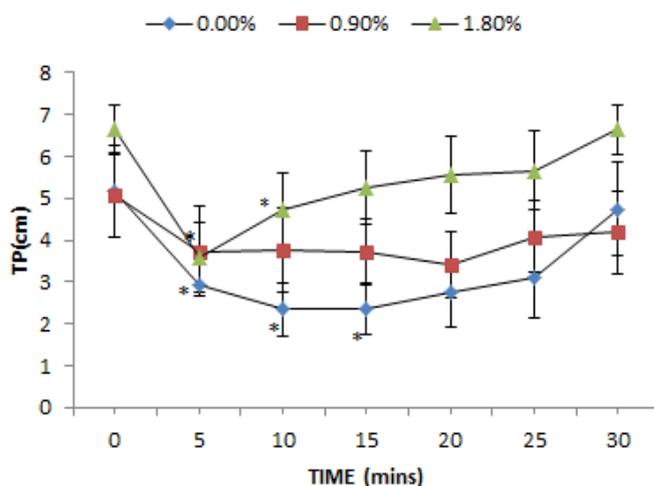


Figure 1: shows the mean basal TP (cm) in the dehydrated female subjects (TP at 0), and the changes in the mean TP at 5mins interval for 30mins, after drinking 0.0%, 0.90% or 1.8% NaCl within the first 5mins. \* =p<0.05.

**Group B: Effect of gargling 0.0%, 0.9% and 1.8% NaCl solution on thirst perception.**

TP was recorded in these subjects at 0mins (baseline TP) and at 5 minutes interval for 30 minutes after gargling. The control TP (baseline) was not significantly different within the subgroup, and there was no significant change in TP within 30 minute after gargling with 0.0%, 0.9% and 1.8% NaCL. This is in marked contrast to the observation in the group that drank the fluids.

Table 1: Anthropometric data, Blood pressure indices and serum Na, K, Cr and Urea level collected from the subjects on arrival at the laboratory (expressed as mean ± SEM).

Group	Age (yr)	SBP(mmHg)	DBP(mmHg)	Wt (Kg)	Ht (cm)	BMI(Kg/m <sup>2</sup> )	Na <sup>+</sup> (mmol/L)	K <sup>+</sup> (mmol/L)	Cr (mmol/L)	Urea (mmol/L)
A (n=33)	20.94±0.35	111.5±0.5	63.94±0.39	59.94±0.64	162.7±0.4	23.04±0.26	135.0±0.2	3.65±0.04	0.67±0.01	10.71 ±0.22
B (n=33)	20.94±0.35	112.1±1.04	64.55 ±0.88	60.24±1.83	162.7±1.03	23.15±0.73	134.9±0.71	3.62±0.12	0.69±0.04	10.90±1.63

Table 2: Mean baseline characteristics of 12hr urine samples collected during the dehydration period from the subjects studied (expressed as mean ± SEM).

Group	Volume (ml)	flow rate (ml/min)	Na <sup>+</sup> (mmol/L)	K <sup>+</sup> (mmol/L)	Cr (mmol/L)	Urea (mmol/L)	FE Na <sup>+</sup>	FE H <sub>2</sub> O
A (n=33)	353.12 ±22.29	0.49±0.03	201.86 ±9.46	48.20 ±4.91	16.16 ±0.73	396.36 ±12.67	4.16 ±0.29	3.55 ±0.77
B (n=33)	345.52±24.54	0.49±0.03	197.86 ±6.02	45.88 ±7.64	14.68 ±0.23	399.19 ±9.84	4.99 ±0.22	3.80 ±0.10

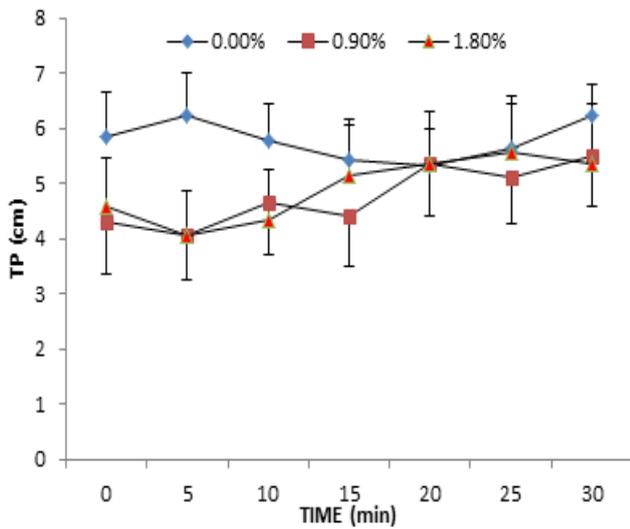


Figure 2: Shows the mean basal TP (cm) in the dehydrated female subjects (TP at 0), and the changes in the mean TP at 5mins interval for 30mins, after gargling with 0.0%, 0.90% or 1.8% NaCl within the first 5mins.

**Effect of drinking/gargling the same concentration of NaCl solution on TP**

The graph shows the effect of drinking and gargling the same volume of 0.0% (Fig. 3), 0.9% (Fig. 4) and 1.8% (Fig. 5) NaCl solution on thirst perception in the same dehydrated subjects at two weeks interval. As shown in Fig. 3, TP was statistically significantly lower in DW in group A than GW in group B, from the 5th minute to the 25th minute after drinking/gargling the same volume of distilled water. There was however no statistical significant change in TP with gargling and/or drinking of the same volume of 0.9% NaCl (Fig.4) and 1.8% NaCl (Fig. 5) in the dehydrated subjects as shown in the graphs.

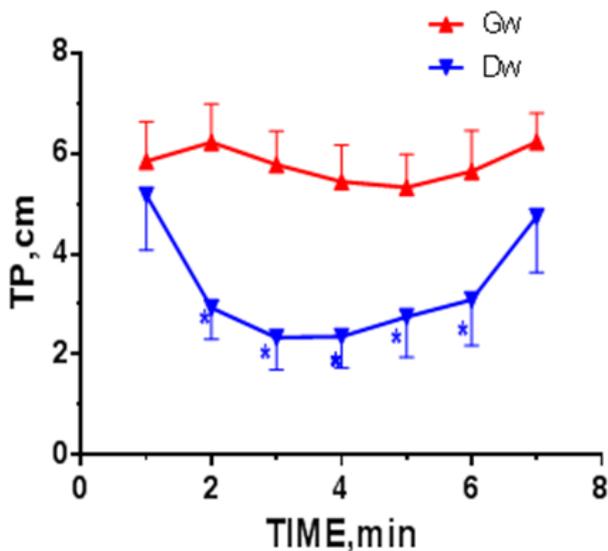


Figure 3: Effect of drinking/gargling of 0.0% NaCl solution on TP. \* =p<0.05

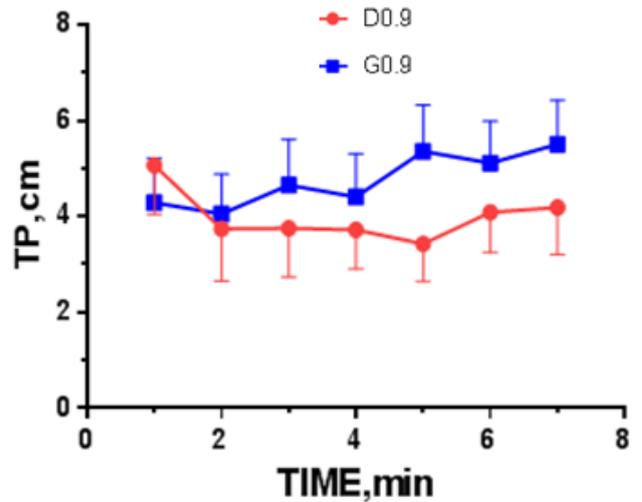


Figure 4: Effect of drinking/gargling of 0.9% NaCl solution on TP.

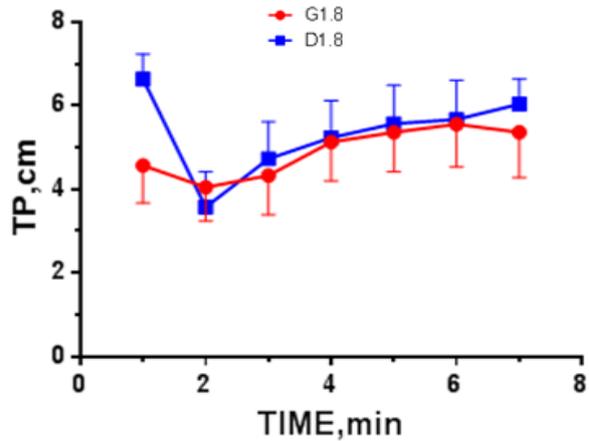


Figure 5: Effect of drinking/gargling of 1.8% NaCl solution on TP. \* =p<0.05

**Other parameters**

Other parameters including those calculated from results of urine and blood sample analysis are as shown in tables 3 and 4. All the parameters measured in this Group A were similar within the subgroups, except the *ad libitum* water intake, which was significantly (p<0.05) lower in the subgroup that drank water.

The volumes gargled and that recovered were similar in Group B (Table 4), indicating that the subjects in this group did not drink the solution. There was no significant difference between the subgroups in all the other parameters measured in Group B.

When Groups A and B were compared, there was no difference in the *ad libitum* water intakes (except in those that drank 0.0% NaCl solution: 63.6±35.9 vs 263.2±45.4ml, p<0.05). The volume of 12hr urine output and the fractional excretion of water were generally lower in Group B, though not statistically significant.

**Table 3: Shows the volume of fluids drunk, 12 hour urine volume, fluid intake ad-libitum, and 30 mins urine volume, fractional excretion of water and fractional excretion of sodium after drinking in Group A.**

	Vol. of fluid intake (7.0ml/kg)	Regurgitated Vol. (ml)	Volume Of fluid Intake <i>ad libitum</i> (ml)	30 mins Urine Vol. (ml)	12hr Urine Vol.	FE <sub>H2O</sub>	FE <sub>Na+</sub>
D.WATER (N=11)	434.36±29.14	0	*63.63±35.93	52.85±7.87	307.36±52.95	6.14±1.90	5.80±0.29
0.9% NaCl (N=10)	408.10±18.69	0	243.45±70.22	48.50±17.02	326.5±30.90	5.94±1.77	6.09±0.36
1.8% NaCl (N=12)	417.25±18.82	0	279.17±40.04	47.12±12.18	396.33±36.44	5.09±1.13	6.46±0.27

(\* =  $P \leq 0.05$ ), vs Euhydrate and Dehydrate

**Table 4: Shows the volume of fluids gargled, 12 hour urine volume, fluid intake ad-libitum and 30mins urine volume, fractional excretion of water and fractional excretion of sodium after gargling in Group B.**

	Vol. of fluid intake (7.0ml/kg)	Regurgitated Vol. (ml)	Volume Of fluid Intake <i>ad libitum</i> (ml)	30 mins Urine Vol. (ml)	12hr Urine Vol.	FE <sub>H2O</sub>	FE <sub>Na+</sub>
D.WATER (N=11)	438.45±28.37	438.27±27.90	263.18±45.40	28.08±17.71	322.09±32.41	4.16±0.29	5.80±0.29
0.9% NaCl (N=10)	411.3±18.94	405.30±21.15	291.0±64.85	22.80±4.35	359.80±37.51	4.15±0.23	6.09±0.36
1.8% NaCl (N=12)	416.50±19.35	413.25±19.46	264.08±38.59	24.58±4.01	291.58±28.98	4.23±0.18	6.46±0.27

## DISCUSSION

The visual analogue scale has been widely used with success as an indirect tool in measuring thirst perception in individuals (Seckl et al, 1986; Obika et al., 2009). The thirst ratings obtained from the scale has been shown to be highly reproducible within individuals on repeated testing (Thompson *et al.*, 1991). In this study the VAS was also employed in assessing thirst perception in dehydration and rehydration. The baseline thirst perception immediately before drinking or gargling the same volume of the solutions remained similar in the two groups of study.

From this study a gradual fall in the mean thirst rating was observed in all the dehydrated subjects that drank the solutions. This decrease was statistically significant with 0.0% and 1.8% NaCl solution. This decrease occurred right from the 5<sup>th</sup> minute after drinking irrespective of the tonicity of the fluid drunk. The time duration within which these changes were observed is obviously not sufficient for substantial changes in plasma osmolality to have occurred through absorptive route (Obika et al., 2009). Since this decrease in TP occurred immediately after drinking in these subjects, the presence of fluid in the mouth and the act of swallowing may have actually stimulated the oropharyngeal receptors to cause the decrease in thirst perception (Holmes 1964; Applegreen et al., 1991; Igbokwe and Obika, 2008).

As observed above, drinking brought about a decrease in thirst perception irrespective of the tonicity of fluid drunk. In previous works by Obika and Mowoe (1997), and Rolls et al., (1980) the authors reported a fall TP in normal euhydrate subjects when hypertonic, and/or hypotonic fluid loads were administered. Geelen et al. (1984) also reported a decrease in thirst after drinking hypertonic

saline. Salata et al. (1987) reported no changes in vasopressin level in subjects who held concentrated solutions in their mouths for 30mins and thus concluded that oropharyngeal receptors are not responsive to local changes in osmolality. This is in line with our findings that the tonicity of fluid is irrelevant with respect to the response of oropharyngeal receptors to thirst perception. In addition, Crammer (1991) concluded from his study that drinking is an activity determined partly by oropharyngeal stimulation, and that thirst need not be involved.

In the contrast, thirst ratings taken after “single gargling” in this experiment showed no significant change from the control throughout the duration. However, Obika et al. (2009), recorded a significant decrease in thirst perception upon “repeated gargling” at 10 minutes interval for 60 minutes with 0.0%, 0.9% and 1.8% NaCl solution, gargling was done for the first 5minutes within the 10 minutes interval, and thirst perception was rated 5minutes later, and thus they reported that the reduction in thirst perception by the oropharyngeal receptors was unrelated to drinking. Although single gargling showed no significant change throughout the duration of the experiment, from the above it can be suggested that the receptors present in the mouth require some form of agitations such as repeated gargling as was carried out by Obika et al. in 2009, or continuous intake of bouts of fluid as occurs in drinking, to produce a response, since acute stimulation (“single gargling”) as carried out in this study did not bring about a significant change in thirst perception. These results suggest that the oropharyngeal receptors may be rapidly adapting.

Furthermore, the initial decrease in thirst perception after drinking was followed by a gradual rise in mean thirst rating towards the control TP by the 30<sup>th</sup> minutes. Accordingly, the volume of fluid

drunk *ad-libitum* by the subjects at the end of the experiment was not significantly different after drinking or gargling of the fluids, but was only significantly lower in the subjects that drank 0.0% NaCl solution. This suggests that oropharyngeal stimulations results in the initial decrease in thirst, but does not abolish thirst.

It can be concluded from this study, that drinking but not “single gargling” reduces thirst perception irrespective of the tonicity of the fluid. This study further suggests that the oropharyngeal receptors are activated by recurrent stimulation by the act of drinking and may be rapidly adapting.

*Part of this work has been presented at the 33<sup>rd</sup> Annual Scientific Conference of the Nigeria Physiological Society, held at the Department of Physiology of the University of Ibadan, Nigeria, 12-15<sup>th</sup> February, 2014.*

## REFERENCES

- Ajayi, OI and Obika, LFO. (2000): Role of oropharyngeal receptors in thirst perception: Abstract No 54 of the 22<sup>nd</sup> Scientific Conference of the Physiological Society of Nigeria.
- Appelgren, BH., Thrasher, TN., Keil, LC and Ramsay, DJ. (1991): Mechanism of drinking induced inhibition of Vasopressin secretion in dehydrated dogs. *Am. J. Physiol. Regulatory, Integrative Comp. Physiol.*, 261: R1226-R1233.
- Bayliss, PH and Robertson, GL. (1980): Plasma vasopressin response to hypertonic saline infusion to assess posterior pituitary function. *J. Roy. Med.*, 73: 255-260.
- Bruner, FP. (1993): Pathophysiology of dehydration. *Schweiz Rundsch. Med. Prax.* 82(29-30): 784-787.
- Crammer, JL. (191): Drinking, thirst and water intoxication. *Br. J. Psychiatry.* 159: 83-89.
- Figora, MK and Mack, GW. (1997): Regulation of fluid intake in dehydrated humans: role of oropharyngeal stimulation. *Am. J Physiol.*, 272: 1740-1746.
- Fitzsimons, JT. (1979): *The Physiology of Thirst and Sodium Appetite*. Cambridge, UK: Cambridge University Press. 129-222.
- Geelen, GL., Keil, LC., Kravik, SE., Wade, CE., Thrasher, TN and Barnes, PR. (1984). Inhibition of plasma Vasopressin by drinking in healthy humans. *Am. J. Physiol.*, 247: R247-R971.
- Haug, W., Sved, AF and Striker, EM. (2000): Water injection provides an early signal inhibiting osmotically stimulated vasopressin secretion in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 279(3): R756-R760.
- Holmes, JH. (1964): Thirst and fluid intake problems in clinical medicine in thirst. Ed: MJ. Waymer, NY. Macmillian. 345-364.
- Igbokwe, VU and Obika, LFO. (2008): Thirst perception and dryness of mouth in healthy young adult Nigerians. *Afri. Biomed. Res.*, II 39-46.
- Obika, LFO, Idu, FK., George, GO., Ajayi, OI and Mowoe, R.S. (2009): Thirst perception and drinking in euhydrate and dehydrate human subjects. *Nig. J. Physiol. Sci.*, 24(1): 25-32.
- Obika, LFO and Mowoe, RS. (1997): Thirst perception in young adult males before and after an oral fluid load and after dehydration. *International Union of Physiological Society Congress*. Abstract No. 101.01.16.
- Robertson, GL. (1991): Disorders of thirst in Man. *In: Thirst, physiological and psychological aspects*. (eds: DJ. Ramsay and DA. Booth), Springer Verlag, London. Pp. 453-477.
- Rolls, BJ., Wood, RJ., Rolls, ET., Lind, HM., Lind, RW and Ledingham, JGG. (1980): Thirst following water deprivation in humans. *Am. J. Physiol.*, 239: R476-R482.
- Salata, R.A., Verbalis, JG., Robinson AG. (1987): Cold water stimulation of oropharyngeal receptors in man inhibits release of vasopressin. *J. Clin. Endocrinol. Metab.*, 65(3): 561-7.
- Seckl, JR., Williams, DM and Lightman, SL. (1986): Oral hypertonic saline causes transient fall in vasopressin in humans. *Am. J. Physiol.*, 251: R214-R217.
- Stricker, EM and Verbalis, JG. (2002): Fluid intake and homeostasis. *In: Fundamental Neuroscience* (2<sup>nd</sup> ed.), edited by Squire, LR., Bloom, FE., McConnell, SK., Roberts, JL., Spitzer, NC and Zigmond MJ. Academic Press, San Diego, CA. Pp. 1011-1029.
- Thompson, C.J., Selby, P and Bayliss, P.H. (1991): Reproducibility of osmotic and non-osmotic tests on vasopressin secretion in men. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, 260: 533-539
- Zerbe, RL and Robertson, GL. (1983): Osmoregulation of thirst and vasopressin secretion in human subjects: effect of various solutes. *Am. J. Physiol. Endocrinol. Metab.*, 244: E607-E614.