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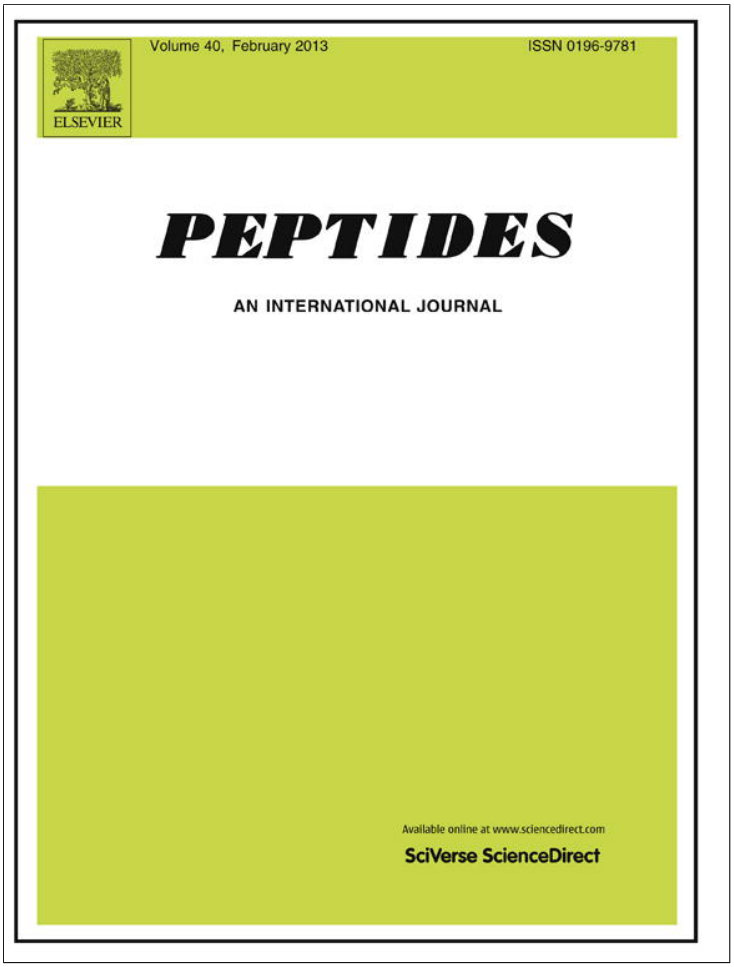

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Short communication

Salivary vasopressin increases following intranasal oxytocin administration

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ABSTRACT

Extant research has documented the effects of intranasal administration of oxytocin (OT), and to a lesser degree Arginine Vasopressin (AVP) – two structurally-related neuropeptides – on brain and behaviour, yet the effects of exogenous manipulation of one on circulating levels of the other remain unknown. Studies have shown that OT administration impacts the peripheral levels of numerous hormones; however, whether OT administration also increases AVP concentrations has not been explored. Utilizing a double-blind placebo-controlled within-subject design, ten male and female subjects provided ten saliva samples over four consecutive hours: at baseline and nine times following OT administration. Results indicate that salivary AVP increased in the first hour following OT manipulation (OT condition: mean AVP = 2.17 pg/ml, *SE* = 28, placebo condition: mean AVP = 1.42 pg/ml, *SE* = .18) but returned to baseline levels at the next assessment (80 min) and remained low for the remaining period. Similar to OT, AVP showed high degree of individual stability and baseline levels of AVP correlated with AVP concentrations at the first and second post-administration hours regardless of drug condition (Pearson $r = .85–.93$). Validity of salivary AVP ELISA measurement was verified by demonstrating individual stability of salivary AVP over a six-month period ($r = .70$, $p < .000$) as well correlation with plasma levels over the same period ($r = .32$, $p = .037$) in a sample of 45 young adults who did not participate in the current study. Overall, findings suggest a potential crosstalk between OT and AVP and indicate that baseline levels of the two neuropeptides may shape the degree to which these systems respond to exogenous manipulation.

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1. Introduction

Arginine Vasopressin (AVP) is a nine amino-acid peptide that is structurally related to oxytocin (OT) and the two neuropeptides differ in only two amino acids. AVP and OT are part of a family of nonapeptides that can be traced phylogenetically to invertebrates [12] but are unique in that they are found exclusively in mammals. The two neuropeptides likely evolved from the same ancestral peptide – arginine vasotocin – and differ from it in a single amino acid [1]. Both central AVP and OT are synthesized in magnocellular neurons in the supraoptic (SON) and paraventricular (PVN) nuclei of the hypothalamus and are stored in the posterior pituitary gland for release into circulation. Additionally, there is a dendritic release of OT and AVP from magnocellular neurons into the extracellular space, resulting not only in local action but also in diffusion throughout the brain which reaches distant targets. Furthermore, smaller parvocellular neurons in the PVN also produce OT and AVP and project directly to other regions in the brain [13].

AVP, an antidiuretic hormone, is secreted primarily under circumstances of dehydration [4]. A rise in extracellular solute concentration is one of the most effective stimuli for AVP release, with as little as 2% elevation in plasma osmolality causing a two-to three-fold increase in peripheral AVP levels. The kidneys are exquisitely sensitive to AVP, thereby affording adaptive renal water conservation during dehydration. AVP also is a vasoconstrictor agent and is secreted in relatively large amounts during hypovolemia and hypotension in the absence of changes in plasma osmolality. Only such large amounts of AVP produce vasoconstriction; approximately 40 times more AVP is needed for a pressor response compared to antidiuresis [e.g., 19]. The physiological function of OT, named for "quick birth", has generally been linked with uterine contraction and lactation. Similarities between AVP and OT are typically manifested in the domain of social neuroscience and both peptides have shown to play a key role in the modulation of complex social cognitions and social behaviours, such as attachment, social exploration, recognition and aggression, fear conditioning, and fear extinction [3,21]. However, unlike the anxiolytic and social-enhancement effects of OT, AVP is thought to facilitate anxiogenic and even aggression-related expressions in the context of bonding, particularly in males [21].

Abbreviations: AVP, arginine vasopressin; OT, oxytocin; SON, supraoptic nuclei; PVN, paraventricular nuclei; IU, international units; CSF, cerebrospinal fluid; CV, coefficient variance; IU, international units; ELISA, enzyme immunoassay; SEM, standard error mean.

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Since the discovery that intranasal administration of neuropeptides can cross the blood–brain-barrier and reach the cerebrospinal fluid (CSF), a growing number of studies have used intranasal administration of OT, and to a lesser extent AVP, to demonstrate the effects of these neuropeptides on human social cognition, motivation, and behaviour [20]. For example, intranasal OT was found to enhance social functioning, including trust, empathy, and "theory-of-mind" [2], and is currently examined as a therapeutic agent in conditions associated with severe social dysfunction [21]. Intranasal studies that manipulated OT and AVP within the same experimental paradigm showed some similar effects as well as different outcomes for the two neuropeptides. Israel and colleagues reported that OT, but not AVP, increased both in-group and universal altruism in a lab-manipulated social dilemma [18]. In a functional neuroimaging study, OT increased activations in reward pathways whereas AVP increased activations in brain regions implicated in affiliative behaviour. Administration of both OT and AVP increased functional connectivity between the amygdala and anterior insula, suggesting that the two peptides mediate the effects of emotional processing on decision making [22].

Despite the fact that the large body of research on OT administration was initiated by discovering the effects of intra-nasal administration of AVP on the brain [5], it is still unclear whether the influence of OT and AVP administration on peripheral levels of these two hormones is unique or interchangeable. One way to address this issue is by testing the effects of intranasal administration of one hormone on the peripheral expression of the other. In general, research has shown that OT administration has an effect on the peripheral levels of numerous hormones. Intranasal OT was found to markedly increase levels of plasma and salivary OT [14,17,25], reduce levels of salivary cortisol [e.g., 8], and alter levels of plasma testosterone [14]. Recently, we showed that OT administration induced substantial increases in salivary OT among ten healthy male and female subjects over a period of 4 h [24]. Under the OT condition, salivary OT levels rose dramatically already 15 min after administration, reached plateau at 45–120 min, and did not return to baseline by 4 h. Although the mechanisms underlying these dynamic changes are not fully understood, it has been suggested that the OT system employs feed-forward mechanisms, as seen, for instance, in human lactation. However, whether OT manipulation also increases AVP levels across this period remains unknown and this is the goal of the present study.

In the current investigation we used the saliva samples collected in the aforementioned Weisman et al. study [24] and analysed the same samples for salivary AVP. Utilizing a double-blind placebo-controlled design, individuals provided ten saliva samples, at baseline and nine times over four consecutive hours. This experimental paradigm enabled us to assess changes in AVP concentrations following OT administration in an attempt to test for the first time the dynamic interchange in levels of these two neuropeptide following manipulation (intranasal administration of 24 IU) to one. To validate our assessment of salivary AVP, we compared salivary and plasma concentration of AVP measured on a different sample of young adults assessed twice across a six-month period. Such assessment enabled to test both the long-term stability of our salivary AVP analysis and its correlations with plasma concentrations.

2. Materials and methods

2.1. Participants

Ten individuals (5 men, and 5 women) participated in a randomised double-blind, placebo-controlled within-subject design. Participants' age averaged 28.25 years ($SD = 4$, range = 20.5–33.0) and all reported being healthy with no history of chronic mental or physical illness, medication intake, or smoking. One female participant gave insufficient saliva for hormonal analysis and was therefore drawn from the study, resulting in nine subjects. Participants were instructed to abstain from food, caffeine, or beverage other than water 2 h prior to experiment. Since no behavioural measures or other factors were assessed in this study apart from salivary AVP, we did not control for women's menstrual cycle or hormonal contraception. Our working hypothesis was that intranasal administration of OT creates an ad-hoc robust effect on salivary AVP independent of the menstrual cycle. However, pregnant women or those trying to get pregnant were excluded. The study was approved by the Institutional Review Board, and all participants signed an informed consent. Participants received gift vouchers for their participation.

2.2. Salivary vasopressin collection and analysis

Saliva samples were collected using a Salivette (Sarstedt, Rommelsdorft, Germany). Ten samples at each session were collected: at baseline, and 15, 30, 45, 60, 80, 100, 120, 180, and 240 min following administration. Sessions were held between 12:30 h and 17:30 h. Time window for the experiment was chosen in order to minimize diurnal variation in OT. We are not familiar with research on diurnal variation in AVP.

Salivettes were immediately stored at −20 °C to be centrifuged twice at 4 °C at 1500 × *g* for 15 min within two weeks. All samples were lyophilized overnight to concentrate them by four times and kept at −20 °C until assayed. Determination of salivary AVP was performed using a 96-plate commercial ELISA kit (ENZO, NY, USA), according to kit's instructions. These ELISA is highly sensitive (minimal detection levels = 3.39 pg/ml vasopressin) with very little antibody cross-reactivity for other neuropeptides.

For the AVP ELISA kit, the cross-reactivity between OT and AVP was <0.001%. In fact, in order to eliminate the possibility that we are measuring OT rather than AVP, the seven standards of the OT kit (OT 15.6, 31.2, 62.5, 125, 250, 500, 1000 pg/ml) were constructed in the AVP kit. The kit failed to detect OT even in the highest concentration (1000 pg/ml). Of the entire sample, forty-two samples were run in duplicates. The intra-assay coefficients of variation were 21.2% for the assay. This relatively high coefficient variance (CV) resulted from the many low level values. Inter-assay was not calculated as all samples were assayed at the same day, time, and batch. Sample concentrations were calculated by MatLab-7 according to relevant standard curve. Since samples were concentrated by four, raw values were now divided by four. Twenty values lower than the kit's detection limits were given the minimal value of 0.8 pg/ml. Importantly, the pattern of results remained the same even when these minimal scores receive the actual values measured or when zeroed. However, since some amount of AVP was indeed measured, we believe these assessments should receive a minimal value and not disregarded. The kit's observed lowest detection limit is 2.4 pg/ml, as calculated by us using five samples. These samples were measured twice: diluted and undiluted, and yielded CV less than 15% for the lowest range. Both assay and AVP calculation were conducted by experienced biochemist (O.ZS.) blind to drug condition.

2.3. Procedure

Following arrival, participants signed informed consent and provided the first (baseline) saliva sample. Immediately after, participants self-administered either drug – a single dose of intranasal OT including 24 international units (IU), 3 puffs per nostril, each puff containing 4 IU (Syntocinon Spray, Novartis, Basel, Switzerland) – or placebo. Each participant visited the lab twice, a week apart.

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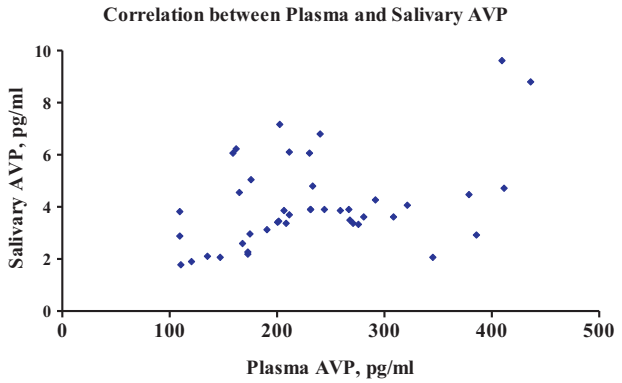
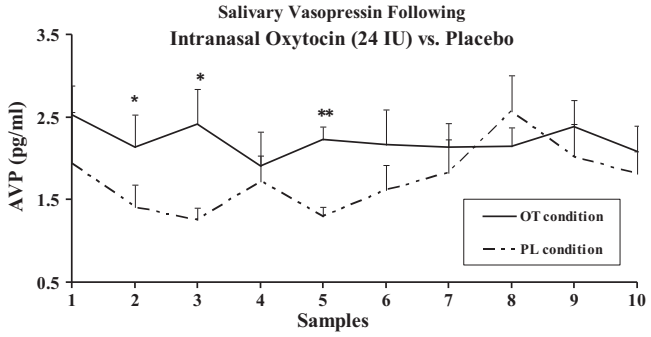


Fig. 1. Scatter plot of plasma (*x* axis) and salivary (*y* axis) AVP levels. Samples collected from 45 healthy young adults across a six-month period. Correlation between these two peripheral markers further validates the use of ELISA method for AVP determination.



* p=.01
** p<.01

Fig. 2. Salivary AVP concentrations before and 4 h following administration: in the OT (full line) vs. the PL condition (dotted line). Error bars indicated standard error of means (SEM).

Participants were encouraged to drink water between samples to produce sufficient saliva, and to eat a small meal just after the eighth sample (2 h) to prevent fatigue.

2.4. Statistical analysis

Missing values due to insufficient saliva volume necessary for hormonal analysis (15% of 180 samples) were replaced with their predicted values using 'linear trend at point' estimation method, in which the existing series is regressed on an index variable scaled 1 to *n*. The missing values were distributed across the entire matrix: in 7 out of the 9 subjects, at both drug conditions, and at baseline sample as well as the ones to follow. Repeated-measures ANOVA was conducted with drug (OT, PL) and time (10 samples) as within-subjects factors and gender as between-subjects factor. Paired *t*-tests were computed to compare levels at each time-point across conditions. In addition, mean levels of AVP during the first, second, and third-to-fourth hours were averaged into three composites in each condition and were compared. Finally, Pearson correlations between OT and AVP levels were conducted.

3. Results

First, in order to validate our measure of salivary AVP using ELISA we collected both plasma and salivary AVP at the same time from 45 young adults who did not participate in the current study at two time-points six months apart. Both plasma and salivary AVP showed high individual stability across the six-month period. Correlations between plasma AVP at time 1 and time 2 was r = .80, p < .000, and correlations between salivary AVP at the two time-points was r = .70, p < .000. The averaged plasma and averaged salivary scores were inter-related, r = 32, p = .037, and this correlation increased following the exclusion of one outlier plasma score (above 2.5 *SD*), r = 42, p < .01. These data highlight the individual stability of AVP as measured in both plasma and saliva and the associations between these two peripheral markers of AVP and are consistent with our findings for plasma OT both in terms of individual stability and plasma-saliva correlations [11] (Figs. 1 and 2).

Repeated-measures ANOVA yielded a significant main effect for condition, F (1,9) = 20.80, p = .003, Eta^2 = .75. Salivary AVP levels were significantly higher (mean = 2.20, *SE* = .27) in the OT condition compared to placebo (mean = 1.78, *SE* = .25). No main effect was found for time, F (9,63) = 1.83, p > .05, but a condition-by-time interaction emerged, F (9,63) = 2.36, p = .022, Eta^2 = .25. Paired *t*-tests revealed no difference at baseline but significant differences at the second, third and fifth time points (15, 30 and 60 min following administration, respectively) (Table 1). No main effect for gender emerged, F (1,7) = .36, p > .05, and due to the small sample size analysis was conducted across gender.

Table 1
Salivary AVP levels at baseline and in multiple assessments following the administration of OT vs. placebo.

Time\minutes	Mean salivary vasopressin, pg/ml (*SE*) *T*		
	OT condition	PL condition	
0 (baseline)	2.52 (.35)	1.93 (.62)	NS
15 min	2.13 (.39)	1.40 (.27)	3.36*
30 min	2.41 (.42)	1.25 (.14)	3.23*
45 min	1.91 (.40)	1.72 (.30)	NS
60 min (1 h)	2.22 (.15)	1.29 (.11)	3.64**
80 min	2.16 (.42)	1.61 (.30)	NS
100 min	2.13 (.29)	1.82 (.40)	NS
120 min (2 h)	2.14 (.23)	2.56 (.44)	NS
180 min (3 h)	2.38 (.32)	2.01 (.39)	NS
240 min (4 h)	2.07 (.31)	1.81 (.27)	NS

* p = .01
** p < .01

Following, AVP levels at first hour (assessments 2, 3, 4, 5), second hour (assessments 6, 7, 8), and third-to-fourth hours (assessments 9, 10) were averaged into three new variables for each condition. A significant difference between conditions (OT vs. PL) emerged at the first hour following administration, with AVP concentrations being higher after OT treatment (mean = 2.17, *SE* = .28 and mean = 1.42, *SE* = .18, respectively), t(8) = 4.72, p = .001. AVP concentrations at baseline, second hour, and third-to-fourth hours did not differ between drug conditions.

As baseline levels of AVP did not differ between the OT and PL conditions, mean baseline AVP was calculated by averaging the two values. Baseline AVP showed high degree of individual stability and correlated with AVP at the first and second post-administration hours regardless of condition (OT condition – first hour: r = .89, p = .001; second hour: r = .85, p = .003. PL condition – first hour: r = .93, p < .001; second hour: r = .85, p = .004). In the third-to-fourth hours, correlation was found only in the PL condition (r = .82, p = .007).

Few correlations emerged between levels of OT and AVP at both individual assessment or for the three composites. OT during the third-to-fourth hours in the PL condition correlated with AVP in the OT condition at both the second, r = .66, p = .05, and third-to-fourth hours, r = .77, p = .01.

4. Discussion

The current findings are the first to demonstrate that intranasal administration of OT alters circulating levels of AVP and that this

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effect is traceable in human saliva. Results indicate that, relative to placebo, salivary AVP increases in the first hour following OT treatment and that AVP returns to baseline level already at the next assessment (80 min) and stays at this level for the remains of the sampling period. Although much less research has focused on the role, functions, and peripheral expression of AVP as compared to OT, our findings demonstrate that manipulating CNS levels of one hormone has an impact on peripheral levels of the other. These findings lend support to research suggesting a crosstalk between these two neuropeptides [7] and to models indicating that high concentrations of OT bind to AVP receptors and further promote AVP synthesis.

In addition to showing AVP increases for an entire hour following OT administration, our findings demonstrate for the first time that plasma and salivary AVP concentrations are inter-related. Similar to the findings for OT [11,26], we show here that salivary AVP is highly stable between individuals over a lengthy period in both saliva and plasma and that the two peripheral markers show medium-level correlations. The findings also suggest that endogenous levels of the hormone shape the individual's response to administration and that higher baseline AVP results in higher levels of the hormone in response to manipulation.

Most studies to date on circulating AVP measured concentrations in plasma and showed associations with aspects of social functioning. For example, higher plasma AVP was associated with self-reported marital distress [23]. Others, however, found links between plasma AVP and lower frequencies of negative communication during marital discussion [15]. Plasma AVP levels have similarly been linked with larger social networks, fewer negative marital interactions, less attachment avoidance, more attachment security, and greater spousal social support [16]. The current study is among the first to measure peripheral AVP in saliva and the first to assess salivary AVP following intranasal administration of OT. The assessment of OT in human saliva using ELISA technique has already been conducted across several laboratories [9,17,27], and salivary OT is considered a reliable biomarker of circulating levels of the hormone [6]. Moreover, research has shown that salivary OT correlates with plasma OT and with a range of attachment-related and social processes [10,11], as we demonstrate here for plasma and salivary AVP. Measuring AVP in human saliva may similarly advance research on this hormone and its correlates by making it more accessible for collection in various populations.

Given the preliminary nature of the current study, further research is clearly needed. Specifically, future research should assess the associations between salivary AVP and a range of social factors and uncover the unique and shared effects of OT and AVP on social cognitions and affiliation-related processes in humans.

In conclusion, salivary AVP increased in the first hour following intranasal OT administration, but returned to baseline level already at the next assessment. AVP demonstrated high degree of individual stability. Findings also suggest that endogenous levels of the hormone shape the individual's response to intranasal administration.

Conflict of interest

Drs. Weisman, Schneiderman, Zagoory-Sharon, and Feldman have no conflict of interest to disclose.

Contributors

Authors RF, OW and OZS designed the study. OW ran the experiment. OZS conducted hormonal analyses. RF and OW conducted statistical analyses and wrote the manuscript. All authors contributed to and have approved the final manuscript. IS conducted the validation study.

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