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Vasopressin needs an audience: Neuropeptide elicited stress responses are contingent upon perceived social evaluative threats

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ABSTRACT

The nonapeptide arginine vasopressin (AVP) plays an important role in hypothalamus–pituitary–adrenal axis regulation and also functions as a social hormone in a wide variety of species, from voles to humans. In the current report we use a variety of stress inducing tasks, including the Trier Social Stress Test (TSST) and intranasal administration of AVP to show that intranasal administration of this neuropeptide leads to a significant increase in salivary cortisol and pulse rate, specifically in conditions where subjects perform tasks in the presence of a social evaluative threat (task performance could be negatively judged by others). In contrast, in conditions without a social evaluative threat (no task condition, modified TSST without audience and bike ergometry), subjects receiving AVP did not differ from subjects receiving placebo. Thus exogenous AVP's influence is contingent upon a circumscribed set of initial conditions that constitute a direct threat to the maintenance of our social selves. Stress evoked by social threat is an integral part of social life and is related to self-esteem and in extreme forms, to poor mental health (e.g., social phobia). Our findings suggest that AVP is a key component in the circuit that interlaces stress and social threat and findings offer inroads to our understanding of individual differences in sociability and in stress response elicited in threatening social situations.

Introduction

Social behavior requires the drive to approach others and the diminution of stress and fear that is naturally elicited by proximity to others. The nonapeptide arginine vasopressin (AVP), which has been related to social behavior and hypothalamus–pituitary–adrenal (HPA) axis regulation, seems to be a prime candidate for modulating stress in social situations (Goodson, 2008).

To begin with, AVP is an important chemical messenger mediating stress since it is secreted by hypothalamic neurons along with corticotrophin releasing hormone (CRH) (Aguilera and Rabadan-Diehl, 2000). Both hormones act synergistically on the pituitary to finally release corticotrophin (adrenocorticotrophic hormone, ACTH) and other peptides. Additionally, AVP is a neuromodulator within the brain and its dual function both peripherally and centrally have deep evolutionary roots (Goodson, 2008). AVP, by modulating regions of the limbic system such as the amygdala, nucleus accumbens and subgenual cingulate (Caldwell et al., 2008; Zink et al., 2010), has an influential role in regulating affiliative and aggressive tendencies (Ferris et al., 1994; Carter et al., 2008; Ferris et al., 2008; Young et al., 2008; Ebstein et al., 2009). Concomitantly with the important role of AVP in stress regulation, chronic over-secretion of this peptide is accompanied by untoward side effects including depression and anxiety (Keck, 2006). Moreover, there is a growing consensus that stress, hostility and social isolation confer vulnerability to some diseases (Miller et al., 2009).

Several studies have shown that neuropeptides bypass the blood–brain barrier after intranasal (IN) administration, providing a useful method for studying central nervous system effects of AVP in humans (Born et al., 2002; Thompson et al., 2006). Evidence suggests that IN-AVP stimulates agonistic facial motor patterns in response to the faces of unfamiliar men in men (Thompson et al., 2006), suggesting that AVP may lead to aggressive behavior in response to threat in men. IN-AVP also substantially increased the electrophysiological response to an event related potential (ERP) (Pietrowsky et al., 1996), showing the effect on central processes in the brain. In a recent fMRI study (Zink et al., 2010) IN-AVP also mediated the activity in limbic regions in the brain during a negative emotional task.

To shed light on the neurobiological substrate of AVP in modulating social behavior in the context of social stress, we employed the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993b), a paradigm that has proven particularly effective in

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evaluating psychosocial stress under controlled laboratory conditions. Gender (Kirschbaum et al., 1995; Uhart et al., 2006), genetics (Kumsta et al., 2007; Shalev et al., 2009), and environmental stressors (Macmillan et al., 2009) among other factors (Kudielka et al., 2009) influence individual's responses during the TSST. In this context, HPA axis reactivity is indexed by measuring salivary cortisol while central nervous system reactivity is measured by monitoring blood pressure and pulse rate. Given AVPs established dual roles in modulating both the HPA axis and social signaling, we hypothesized that IN-AVP prior to the TSST would lead to an interaction with the stress response and heightened cortisol reactivity when compared to placebo. Furthermore, given the long evolutionary history of AVP as a social hormone (Goodson, 2008), we hypothesized that the effects of AVP on the stress response could be specifically attributed to the social evaluative elements of the TSST. We therefore designed a set of studies to investigate the influence of AVP on HPA reactivity under a set of conditions varying in social evaluation and exposure to stress. We began by investigating the effect of IN-AVP on HPA axis reactivity in the full TSST and hypothesized that IN-AVP would enhance salivary cortisol output.

Despite indirect evidence for its contribution to social signaling (Goodson, 2008), little is known regarding the role of AVP in the context of human social stress. For example, it could be the case that IN-AVP, even in the absence of stressful cues, would directly activate the HPA axis, resulting in increased cortisol levels. Furthermore, it may also be the case that stressors in general, even those absent the social evaluative threat produced in the TSST, may interact with AVP to trigger a rise in cortisol. Hence, we tested the hypothesis that the effect of IN-AVP on the salivary cortisol response is contingent upon social contexts. To address this issue, we implemented three additional experimental conditions.

The first experiment was entitled the “no task” group and controlled for direct physiological influences of AVP administration on HPA reactivity under a no stress condition. In this experiment, subjects were simply administered IN-AVP or placebo while sitting by themselves in a controlled environment, absent stressful stimuli. The second experiment was entitled the “no audience,” in which participants engaged in a modified TSST, absent audience and cameras, and consequently absent social evaluative threats yet still retaining enough stressors to trigger a cortisol response. The third experiment employed an exercise bike (“bike ergometry”), also absent audience and cameras, which was designed to evoke physiological stress (cortisol, blood pressure and heart rate) but not a social stress response. The purpose of these three additional experiments was to isolate the social evaluative threat and determine the specificity of AVP effect on this component of the TSST procedure.

If IN-AVP resulted in a direct physiological response then we would expect to observe increases in cortisol levels in the AVP group in all four conditions. Alternatively, if IN-AVP was sensitive to stress responses in general, then we would expect to observe AVP's effects on cortisol reactivity for the full TSST, the “no audience” and the “bike ergometry” conditions. However, if AVP's effects were specific to contexts which contained social evaluative threats, then we would expect to observe an effect of AVP on cortisol response in the full TSST condition only.

Materials and methods

Subjects

Participants were primarily college students at Israeli institutions of tertiary education, recruited by word of mouth and advertisements on campus notice boards for a study on the neurobiological substrates of personality. Selection criteria stipulated that subjects were <35 years old, had no history of psychiatric or endocrine illness (by self-report and standardized questionnaires), were non-smokers, and were not using medication on a regular basis. Individuals with any medical condition were excluded from further study, as were individuals taking any prescription medications that might interact with AVP or with the HPA axis.

Prior to administering AVP or saline control, participants were debriefed about the physiological effects of AVP and informed consent was obtained from each subject. Altogether, 152 male subjects (mean age = 25.11, SD = 2.80) participated in the experiment; 62 participated in the full TSST ($n = 31$ AVP; $n = 31$ placebo), 30 in the “no task” condition ($n = 15$ AVP; $n = 15$ placebo), 30 in the modified TSST “no audience” ($n = 15$ AVP; $n = 15$ placebo), and additional 30 in the “bike ergometry” condition ($n = 15$ AVP; $n = 15$ placebo). The project was approved by the S. Herzog Hospital IRB committee and the Israeli Ministry of Health. All subjects were reimbursed for participating in the experiment. Demographics of the samples are presented in Table 1.

General procedure

Testing was carried out in a laboratory at the Hebrew University Department of Psychology. Subjects were scheduled for testing within a fixed time-window (between 15:00 and 18:00 h) to counter effects of circadian changes in cortisol. To limit variance, subjects were given explicit instructions to refrain from excessive physical activity for 2 h prior to the experiment and from brushing their teeth, eating, and drinking (besides water) for the 90 min prior to the testing session. The full TSST session was carried out as described in previous studies (Kirschbaum et al., 1993b; Shalev et al., 2009). Briefly, the TSST consists of a free speech and a mental arithmetic task of 10 min duration performed in front of a panel of two women with a camera and microphone situated between the interviewers. The modified TSST, “no audience” control protocol, was designed to follow as closely as possible the full TSST, replicating the instructions and time points, however absent the social evaluative component. After IN administration subjects were told that they would play the role of an interviewee for a job and had 5 min to make an argument for their candidacy. Subjects entered the interview room 15 min after IN administration and rather than standing up and speaking in front of a committee for a 5-min interview, were told instead to sit behind a table and write on a piece of paper their suitability for a particular job. The experiment room was absent of committee members, however a timer counting backwards from 5 min was placed on the table and subjects were instructed to sit and write for 4 min. When the timer counted down to 1 min, subjects then had to stand in an upright posture and speak out loud to a virtual committee to create similar motor and physiological response as in the full TSST since an orthostatic response may influence sympathetic nervous system parameters (Januszewicz et al., 1982; Goldstein, 1987; Carnethon et al., 2002).

After 5 min, the second task emphasizing the cognitive load of the TSST commenced. Subjects were instructed to do the second phase for which no details were provided on a computerized program similar to the mental arithmetic task as in the full TSST counting backwards from 1687 in jumps of 13.

The “no audience” task was performed in the same room as the full TSST but all social context elements of the TSST (committee, video camera and microphone) were removed prior to the start of the session. Further to this, to ensure the absence of social evaluative threats, subjects were notified beforehand that they would be alone in the room, and that they would not be observed. In order to ascertain the compliance of the subjects to the task the experimenter (I.S.) watched all subjects behind a one-sided mirror. All subjects complied with the task. After the mental arithmetic task, subjects returned to the waiting room for further sampling, questionnaires and debriefing.

In the “no task” control group subjects were instructed to sit and read National Geographic magazines for 80 min following IN