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## Effects of acute metabolic stress on the peripheral vasopressinergic system in schizophrenia

Igor Elman<sup>1</sup>, Scott Lukas<sup>1</sup>, Susan E. Shoaf<sup>2</sup>, David Rott<sup>3</sup>, Caleb Adler<sup>4</sup> and Alan Breier<sup>5</sup>

<sup>1</sup>Behavioral Psychopharmacology Research Laboratory, McLean Hospital, Harvard Medical School, Belmont, MA, <sup>2</sup>Otsuka Maryland Research Institute, Rockville, MD, <sup>3</sup>Medstar Cardiovascular Research Institute, Washington, DC, <sup>4</sup>Department of Psychiatry, University of Cincinnati College of Medicine Cincinnati, OH, and <sup>5</sup>Lilly Research Laboratories, and, Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, USA.

Although both vasopressin and stress have been implicated in the course of schizophrenia, it is unknown whether schizophrenic patients have altered stress-induced function of the vasopressinergic system. We examined the effects of acute metabolic stress induced by pharmacological doses (40 mg/kg) of 2-deoxyglucose (2DG) on plasma concentrations of vasopressin in 13 patients with schizophrenia (with no history of polydipsia and hyponatremia) and 12 healthy control subjects. Baseline vasopressin levels were lower in the schizophrenic patients and progressively increased in both groups throughout the 60 min following 2DG administration to a similar absolute amount, thus remaining lower in the schizophrenic group. Concomitantly, patients with schizophrenia had significantly higher 2DG-induced plasma homovanillic acid (HVA) and 5-hydroxyindoleacetic acid levels. Vasopressin responses correlated positively and significantly with the HVA responses in schizophrenics and with the pituitary–adrenal axis responses in controls. These results suggest two different patterns of neuroendocrine alterations in schizophrenia, namely a relatively normal vasopressin response to 2DG despite significantly decreased baseline levels and exaggerated responses of the peripheral dopaminergic and serotonergic systems in the face of normal baseline concentrations.

**Key words:** 2-DG, dopamine, glucoprivation, 5-HIAA, HVA, serotonin

### Introduction

Vasopressin is a neurohypophyseal nonapeptide that plays a critical role in both maintenance of total body water content and homeostatic response to physical and psychological stress (Axelrod and Reisine, 1984; de Goeij *et al.*, 1991; de Goeij *et al.*, 1992), including regulation of pituitary–adrenocortical (PA) axis activity (de Goeij *et al.*, 1991; de Goeij *et al.*, 1992; Aguilera, 1994; Romero *et al.*, 1994; Romero and Sapolsky, 1996; Scott and Dinan, 1998; Aguilera and Rabadan-Diehl, 2000). In addition, this neurohormone has been implicated in the pathophysiology of various stress-related neuropsychiatric syndromes, such as depression, mania, anxiety and schizophrenia (Legros, 1992; Legros *et al.*, 1993; Purba *et al.*, 1996; Scott and Dinan, 1998; Marx and Lieberman, 1998).

There are several lines of evidence that link vasopressin to schizophrenia. From a neuroanatomical perspective, limbic structures (Riggs *et al.*, 1991), including the hypothalamus and hippocampus (Umbricht, 1994; Goldman and Nettles, 1996; Luchins *et al.*, 1997; Nettles *et al.*, 2000; Onaka and Yagi, 2001), that synthesize and/or regulate vasopressin secretion have been reported to be abnormal in schizophrenia (Stevens, 1982; Luchins,

1990; Luchins *et al.*, 1997). At the neurochemical level, vasopressin secretion is directly regulated by both dopamine and serotonin (Moos and Richard, 1982; Brownfield *et al.*, 1988; Riggs *et al.*, 1991; Legros *et al.*, 1992; Umbricht *et al.*, 1993; Spigset and Hedenmalm, 1996), two of the most extensively investigated neurotransmitters in schizophrenia. Hence, vasopressin may be used to probe the functional status of major neuroanatomical and neurotransmitter systems implicated in this illness.

The association between vasopressin and schizophrenia is further supported by extensive clinical literature on disorders of water homeostasis (Illovsy and Kirch, 1988; Riggs *et al.*, 1991; McKenna and Thompson, 1998) including altered hormonal levels (Raskind *et al.*, 1978; Linkowski *et al.*, 1984; Raskind *et al.*, 1987; Emsley *et al.*, 1989; Kishimoto *et al.*, 1989; Sarai and Matsunaga, 1989; Legros *et al.*, 1992) and schizophrenic symptoms amelioration with vasopressin hormone therapy (Forisz, 1952; Korsgaard *et al.*, 1981; Iager *et al.*, 1986; Brambilla *et al.*, 1988) in up to 70% of patients, clinically significant polydipsia in 20–40% and life-threatening water intoxication in 5–10% (Vieweg *et al.*, 1985, 1988; de Leone *et al.*, 1994; Mercier-Guidez and Loas, 2000). While physiological mechanisms underlying vasopressinergic alterations in schizophrenia remain unclear, Goldman *et al.* (1997)

reported that pharmacologically induced psychotic exacerbation was associated with more elevated vasopressin levels in hyponatremic patients than in their non-hyponatremic counterparts. Thus, regulatory deficits in vasopressinergic function may be uncovered using experimental paradigms perturbing both vasopressin- and schizophrenia-related neurocircuitries.

Glucose deprivation may be a useful experimental paradigm to investigate the vasopressinergic system in schizophrenia because: (i) it provides central (i.e. independent of peripheral osmotic and/or haemodynamic changes) hypothalamic stimulus for vasopressin secretion (Baylis and Robertson, 1980a,b; Baylis *et al.*, 1981; Thompson *et al.*, 1981; Chiodera *et al.*, 1992) and (ii) unlike cognitive stressors, it is not associated with performance bias, so that equal 'amounts' of perturbation are induced in both cognitively impaired patients with schizophrenia and healthy control subjects. Although this kind of metabolic stress may be distinct from the environmental stress implicated in exacerbation of psychosis (Jansen and Gispen-de Wied, 2000), it may provide unique information pertaining to general stress and limbic responsiveness.

The effects of glucose deprivation on plasma vasopressin have been mostly investigated during insulin-induced hypoglycaemia (Baylis and Robertson, 1980a; Baylis *et al.*, 1981; Ellis *et al.*, 1990; de Goeij *et al.*, 1991; de Goeij *et al.*, 1992; Chiodera *et al.*, 1992). In pharmacological doses, the glucose analog, 2-deoxyglucose (2DG), is another glucoprivic agent that is transported across the blood-brain barrier into brain tissue where it inhibits intracellular glucose metabolism and produces a clinical state similar to hypoglycaemia (Breier, 1989). The value of using 2DG is that it eliminates confounds of the direct effects of insulin and produces a centrally generated stimulus, which is not derived from peripheral glucose uptake.

Our previous work suggested that 2DG robustly activates the pituitary-adrenal (PA) axis and that patients with schizophrenia had significantly greater 2DG-induced plasma adrenocorticotropic hormone (ACTH) levels compared to healthy controls (Elman *et al.*, 1998). In the present study, we attempted to extend our previous work by examining 2DG vasopressin effects in schizophrenia. In addition, we measured plasma concentrations of dopamine and serotonin metabolites, homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA), which purportedly reflect central activity of these neurotransmitters (Meek and Neff, 1973; Sternberg *et al.*, 1983; Pietraszek *et al.*, 1992; Breier *et al.*, 1993) and may potentially influence vasopressin findings. Finally, the association between 2DG-induced plasma vasopressin levels and other neuroendocrine indices, including HVA, 5HIAA, ACTH and cortisol, was also explored.

## Materials and methods

### Subjects

Thirteen patients with schizophrenia and 12 healthy control subjects participated in this study during a protocol involving positron emission tomography (PET). The neuroimaging and the PA axis results from these subjects are reported elsewhere (Elman *et al.*, 1998, 1999). The PA axis data are included in this report to allow for correlational analyses with the vasopressin effects.

All subjects provided their written informed consent to a

National Institute of Mental Health Institutional Review Board approved protocol. The patients were diagnosed by a research psychiatrist using a best estimate format that utilizes all available sources of information, including clinical history, interview and the Structured Clinical Interview for DSM-III-R (SCID). The patients were all stable outpatients with a chronic course of illness (mean age at appearance of DSM-IV criterion A symptoms of schizophrenia  $\pm$  SD = 22.5  $\pm$  3.5 years; mean duration of the illness = 15.7  $\pm$  9.3 years) and were tested during treatment with a stable dose of a typical antipsychotic drug (APD) for a minimum of 2 weeks (except one patient, who was treated for 8 days; mean duration of treatment = 245  $\pm$  242 days). Drug and dose (chlorpromazine equivalent mean = 748.5  $\pm$  501.3 mg/day, range 333–2000) were varied to achieve a stable clinical condition. The patients were not treated with drugs that are known to alter vasopressin activity (i.e. diuretics, lithium, carbamazepine or chlorpropamide). The baseline Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) total symptom score (24-item scale; items rated 1–7) on the study day was 33.2  $\pm$  4.9, which is indicative of low to moderate symptom levels.

Healthy control subjects were recruited through the NIH normal volunteer program and had no psychiatric history as determined by SCID. None of the subjects displayed polydipsia, orthostatic hypotension or signs of endocrine, renal, hepatic or cardiac disease. Their good physical health was ascertained by physical examination, electrocardiogram, screening blood work-up and urinalysis.

### Clinical protocol

On the morning of the procedure, subjects were admitted to the 4E Unit of the Clinical Center, NIH after having fasted and refrained from alcohol, tobacco, caffeine, or physical activity for at least 10 h. While in the supine position, an arterial catheter was inserted percutaneously after local anaesthesia of the overlying skin. Arterial sampling was employed because it was essential for the PET data analysis. An intravenous catheter (for 2DG infusion) was placed into the antecubital fossa of the contralateral arm and was kept patent with a slow isotonic (0.9% w/v) saline drip. After a 90-min rest period, 2DG (40 mg/kg, maximal dose 4 g) in 50 ml of isotonic saline solution was administered as an intravenous bolus. Continuous cardiac monitoring was performed throughout the course of the study. Blood pressure and heart rate along with BPRS scores were collected immediately before (0 min) and at 20, 40 and 60 min after the challenge. Both total BPRS scores and factor scores for positive symptoms, thought disturbance, withdrawal/retardation, anxiety/depression and hostility were used.

### Biochemical variables

Arterial blood samples were collected in heparinized tubes at 30 min before (–30), immediately before bolus (0) and at +20, +40 and +60 min following the bolus and were placed on wet ice. After separation by refrigerated centrifugation, the plasma was stored at –80 °C. Vasopressin was measured with radioimmunoassay (the intra- and interassay coefficient of variation 5.5% and 9.5%, respectively; Miller and Moses, 1972). Plasma concentrations of HVA (the intra- and interassay coefficient of variation was 5.0% and 7.0%, respectively) and 5-HIAA (the intra- and interassay coefficient of variation was 3.0% and 5.0%, respectively) were determined by liquid chromatographic method with electro-

chemical detection using an internal standard, 3-ethoxy-4-hydroxyphenylglycol (Scheinin *et al.*, 1983). Kinetic UV assay (Tietz, 1995), was used to measure plasma blood urea nitrogen (BUN, the intra- and interassay coefficient of variation was 2% and 3.3%, respectively).

### Statistical analysis

Data were analysed using the statistical package Statistica (StatSoft, Inc., Tulsa, OK, USA). Hormonal plasma concentrations at -30 min and 0-min time points were averaged to constitute a single baseline value. To determine effects of glucoprivation on plasma indices (vasopressin, HVA, 5-HIAA and BUN) along with behavioural (BPRS scores) and physiological (heart rate and blood pressure) variables, a one-way analysis of variance (ANOVA) with repeated measures design was conducted. Diagnosis was the grouping factor, and time was the within subjects factor. Baseline vasopressin, HVA and 5-HIAA were covariates in the neurochemical data analyses. When group-by-time interactions were significant, post-hoc Newman-Keuls *t*-tests were performed to determine if and at what times the changes from the pre-2DG administration baseline were significant.

Areas under the concentration-time course curve (AUC) were computed using trapezoidal integration. The non-parametric Spearman correlation coefficient was used for correlation analyses. Group data were summarized as mean  $\pm$  SD. All analyses were two-tailed with  $\alpha < 0.05$  set as the threshold for statistical significance. Plasma concentrations of HVA and 5-HIAA data were not available for one patient subject.

## Results

### Demographic characteristics

There were no significant differences between schizophrenic patients and control subjects in age ( $37.7 \pm 8.7$  and  $32.7 \pm 6.5$  years;  $t = 1.70$ ; d.f. = 23;  $p = 0.10$ ), gender (10 men and three women and 10 men and two women; chi squared = 0.16; d.f. =

1;  $p = 0.69$ ), education ( $14 \pm 1.4$  and  $13.5 \pm 1.0$  years;  $t = 1.0$ ; d.f. = 23;  $p = 0.31$ ) and weight ( $81.5 \pm 13.5$  and  $78.5 \pm 16.5$  kg;  $t = 0.63$ ; d.f. = 23;  $p = 0.53$ ).

### 2DG effects on plasma indices

The *t*-tests for independent samples revealed significant differences at baseline between schizophrenic and control groups in plasma vasopressin ( $P < 0.01$ ), but not in HVA and 5HIAA concentrations (Table 1).

In both groups, vasopressin plasma levels progressively increased throughout the 60 min following 2DG administration (time effect:  $F = 32.5$ ; d.f. = 3,23;  $p < 0.01$ ) (Table 1) to a similar absolute amount ( $2.3 \pm 1.4$  and  $2.4 \pm 1.9$ ; group-by-time interaction:  $F = 0.09$ ; d.f. = 3,23;  $p = 0.94$ ), but the percentage increase at 60 min was actually greater ( $t = 2.06$ ; d.f. = 23;  $p < 0.05$ ) in patients ( $286 \pm 227\%$ ) than in control subjects ( $136 \pm 97\%$ ).

As shown in Table 1, bolus administration of 2DG resulted in significantly higher increases in HVA (group-by-time interaction:  $F = 2.99$ ; d.f. = 3,22;  $p = 0.04$ ) and 5-HIAA (group-by-time interaction:  $F = 3.85$ ; d.f. = 3,22;  $p = 0.01$ ) in patients with schizophrenia than in control subjects. Post-hoc Newman-Keuls *t*-tests revealed significantly higher HVA levels for patients at 20 ( $p = 0.02$ ), 40 ( $p < 0.01$ ) and 60 ( $p < 0.01$ ) min and significantly higher 5-HIAA levels at 40 ( $p = 0.02$ ) and 60 ( $p = 0.003$ ) min.

BUN was used as a general measure of hydration, and no significant group ( $F = 0.43$ ; d.f. = 1,23;  $p = 0.52$ ) or time ( $F = 1.43$ ; d.f. = 3,23;  $p = 0.24$ ) effects, or group by time interaction ( $F = 0.36$ ; d.f. = 3,23;  $p = 0.78$ ) were observed for this variable (Table 1).

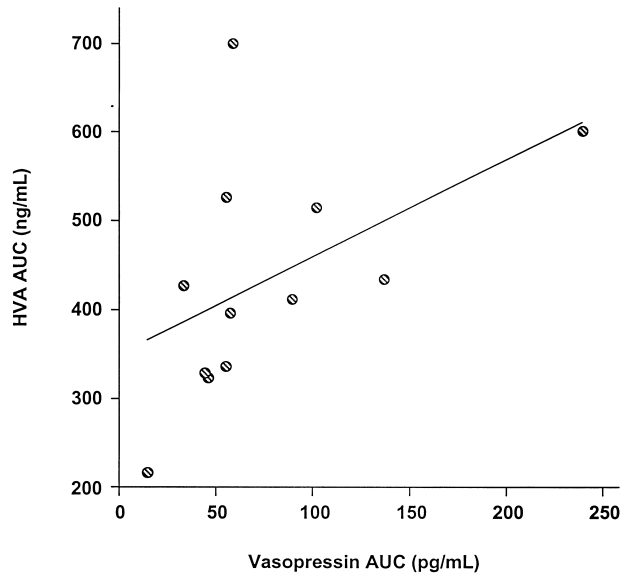
### Physiological and behavioural variables

Overall, no group differences or group by time interactions were observed in the haemodynamic responses to 2DG (Table 1). However, diastolic blood pressure did decrease over time, producing a compensatory increase in heart rate (Goldstein *et al.*,

**Table 1** The effects of 2-deoxyglucose on neuroendocrine, physiological and behavioural variables in patients with schizophrenia ( $n = 13$ ) and healthy controls ( $n = 12$ )

Group	Baseline		20 min		40 min		60 min	
	Schizophrenia	Control	Schizophrenia	Control	Schizophrenia	Control	Schizophrenia	Control
Vasopressin (pg/ml) <sup>a</sup>	1.0 $\pm$ 0.3	2.1 $\pm$ 1.0	1.8 $\pm$ 0.4	2.74 $\pm$ 1.0	2.4 $\pm$ 0.9	3.3 $\pm$ 1.3	3.3 $\pm$ 1.4	4.4 $\pm$ 1.8
HVA (ng/ml) <sup>b</sup>	6.0 $\pm$ 2.3	6.9 $\pm$ 3.3	6.8 $\pm$ 2.1	7.5 $\pm$ 3.2	7.6 $\pm$ 2.4	7.5 $\pm$ 3.2	8.8 $\pm$ 2.6	8.3 $\pm$ 3.3
5HIAA (ng/ml) <sup>c</sup>	4.9 $\pm$ 1.6	3.9 $\pm$ 1.4	5.3 $\pm$ 1.5	4.0 $\pm$ 0.6	5.5 $\pm$ 1.8	4.0 $\pm$ 0.6	5.8 $\pm$ 1.9	4.0 $\pm$ 0.5
BUN (mg/dl) <sup>d</sup>	12.2 $\pm$ 2.5	12.6 $\pm$ 3.8	11.5 $\pm$ 3.2	12.5 $\pm$ 3.8	11.5 $\pm$ 3.5	12.3 $\pm$ 3.6	11.1 $\pm$ 3.7	12.3 $\pm$ 4.1
Blood pressure								
Systolic (mmHg) <sup>d</sup>	123.3 $\pm$ 15.5	115.8 $\pm$ 13.6	116.8 $\pm$ 18.7	114.5 $\pm$ 13.1	115.7 $\pm$ 14.9	114.5 $\pm$ 14.7	115.9 $\pm$ 14.8	116.1 $\pm$ 15.8
Diastolic (mmHg) <sup>e</sup>	68.2 $\pm$ 13.7	70.3 $\pm$ 14.4	59.9 $\pm$ 7.4	57.1 $\pm$ 12.1	62.2 $\pm$ 12.4	58.3 $\pm$ 12.7	60.7 $\pm$ 9.6	57.3 $\pm$ 10.3
Heart rate (beats/min) <sup>e</sup>	62.8 $\pm$ 10.9	65.2 $\pm$ 9.4	71.7 $\pm$ 14.5	70.0 $\pm$ 11.1	72.3 $\pm$ 16.8	68.3 $\pm$ 9.7	73.8 $\pm$ 14.1	71.5 $\pm$ 10.6
Total BPRS score <sup>f</sup>	33.2 $\pm$ 4.9	24 $\pm$ 0.7	34.8 $\pm$ 7.5	24.1 $\pm$ 0.0	35.9 $\pm$ 6.3	24.4 $\pm$ 0.3	37.5 $\pm$ 6.0	24.3 $\pm$ 1.0
Positive symptoms <sup>f</sup>	4.0 $\pm$ 1.2	3.0 $\pm$ 0.0	4.5 $\pm$ 1.5	3.0 $\pm$ 0.0	4.3 $\pm$ 1.8	3.0 $\pm$ 0.0	4.7 $\pm$ 1.5	3.0 $\pm$ 0.0
Thought disturbance <sup>f</sup>	4.1 $\pm$ 1.6	3.0 $\pm$ 0.0	4.2 $\pm$ 1.7	3.0 $\pm$ 0.0	4.2 $\pm$ 1.5	3.0 $\pm$ 0.0	4.2 $\pm$ 1.4	3.1 $\pm$ 0.3
Withdrawal <sup>f</sup>	4.6 $\pm$ 1.7	3.0 $\pm$ 0.0	5.1 $\pm$ 1.8	3.0 $\pm$ 0.0	5.0 $\pm$ 2.1	3.0 $\pm$ 0.0	5.8 $\pm$ 2.5	3.0 $\pm$ 0.0
Anxiety <sup>f</sup>	5.5 $\pm$ 1.9	3.0 $\pm$ 0.4	5.4 $\pm$ 1.3	3.0 $\pm$ 0.0	6.0 $\pm$ 1.6	3.1 $\pm$ 0.3	5.8 $\pm$ 2.0	3.2 $\pm$ 0.6
Hostility <sup>d</sup>	3.7 $\pm$ 2.0	3.0 $\pm$ 0.0	3.8 $\pm$ 1.5	3.0 $\pm$ 0.0	3.8 $\pm$ 1.3	3.0 $\pm$ 0.0	3.5 $\pm$ 1.1	3.0 $\pm$ 0.0

Data are means  $\pm$  SD. <sup>a</sup> Significant time and group effect, no significant group by time interaction. <sup>b</sup> Significant time effect and group by time interaction, no significant group effect. <sup>c</sup> Significant time and group effect, significant group by time interaction. <sup>d</sup> No significant group and time effects or group by time interaction. <sup>e</sup> Significant time effect, no significant group effect or group by time interaction. <sup>f</sup> Significant group effect, no significant time effect or group by time interaction. HVA, homovanillic acid; 5HIAA, 5-hydroxyindoleacetic acid; BUN, blood urea nitrogen.



**Figure 1** Scatterplot relating individual vasopressin and HVA AUC values in patients with schizophrenia using Spearman coefficient ( $r_s = 0.70$ ; d.f. = 10;  $p < 0.05$ )

1992) and resulting in a significant time effect for these two variables ( $p < 0.01$ ). Taken alone, patients displayed no changes in total BPRS and its factors scores in response to 2DG (Table 1). No subject spontaneously reported nausea, which may be a potent stimulus for vasopressin secretion (Rowe *et al.*, 1979).

#### Correlation analyses

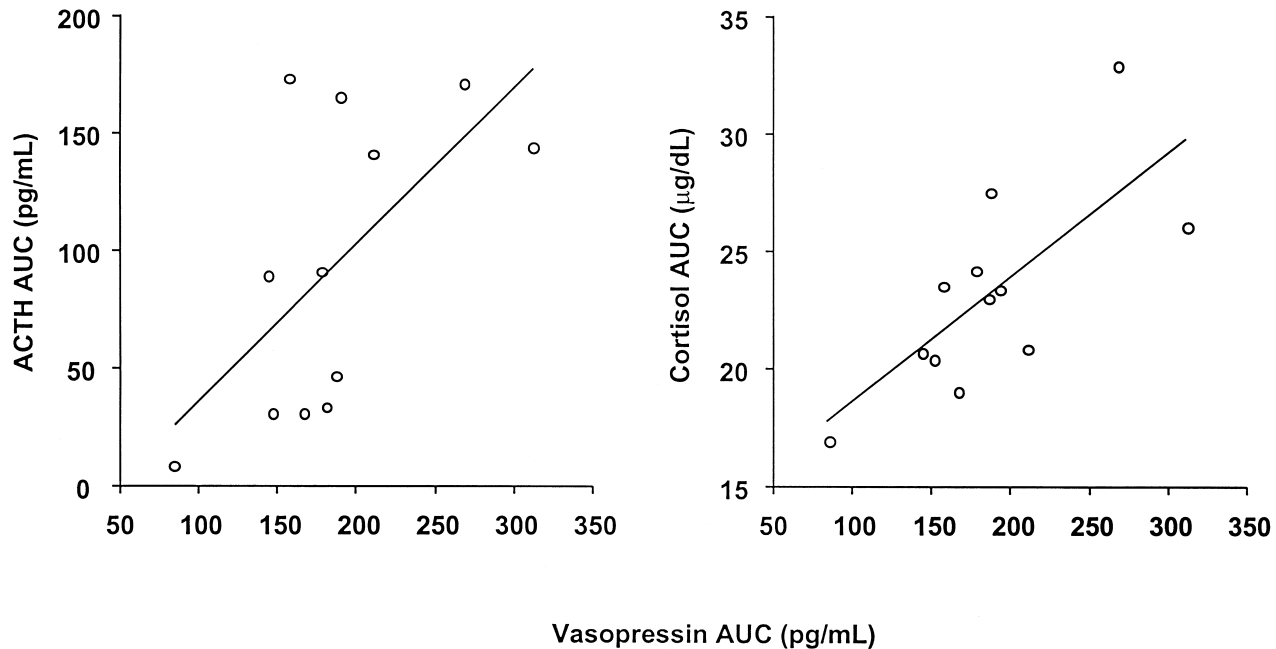
AUC vasopressin and HVA values were correlated across schizophrenic ( $r_s = 0.70$ ; d.f. = 10;  $p < 0.05$ ) (Fig. 1), but not

healthy ( $r_s = 0.17$ ; d.f. = 10;  $p = 0.59$ ; data not shown) individuals. Exclusion of one schizophrenic subject with a high vasopressin response (239 pg/ml) produced no significant differences in our results ( $r_s = 0.65$ ;  $p < 0.05$ ). No correlation between AUC vasopressin and 5-HIAA values was detected in both groups ( $p > 0.37$ ). There was a significant relationship between 2DG-induced AUC values for vasopressin and ACTH ( $r_s = 0.58$ ; d.f. = 10;  $p < 0.05$ ) and cortisol ( $r_s = 0.71$ ; d.f. = 10;  $p < 0.01$ ) values in healthy controls (Fig. 2), but not in the schizophrenic group ( $p < 0.52$ ). Finally, no significant correlations were detected between duration of APD treatment and basal vasopressin and HVA levels and between APD doses and basal HVA levels ( $p > 0.7$ ).

#### Discussion

Vasopressin directly reflects the neuroendocrine events occurring in the hypothalamus as it is synthesized in the hypothalamic paraventricular and supraoptic nuclei and stored/released into the peripheral circulation from the neurohypophysis. In this study, metabolic stress produced significant increases in plasma vasopressin levels in both groups. Patients with schizophrenia displayed normal absolute vasopressin response, and their percentage change increases were probably determined by lower baseline levels. Concomitantly patients had significantly higher 2DG-induced plasma HVA and 5-HIAA levels. In addition, the vasopressin responses correlated positively and significantly with the HVA responses in schizophrenics and the PA axis responses in controls.

The vasopressin data are consistent with previous preclinical (Baylis and Robertson, 1980b) and clinical (Thompson *et al.*, 1981) studies demonstrating significant increases in vasopressin



**Figure 2** Scatterplot relating individual vasopressin with ACTH ( $r_s = 0.58$ ; d.f. = 10;  $p < 0.05$ ) and cortisol ( $r_s = 0.71$ ; d.f. = 10;  $P < 0.01$ ) AUC values in healthy controls using Spearman coefficient

secretion following 2DG administration. The lack of a significantly greater absolute vasopressin response in schizophrenic patients and its dissociation from the response of the exaggerated PA axis (Elman *et al.*, 1998) may be related to patients in this study presenting no symptoms of polydipsia and hyponatremia, suggesting that they may not have abnormalities in the stress-related vasopressinergic function. However, the finding that vasopressin and HVA elevations accounted for 49% of each others variance in schizophrenics versus 28.9% in controls suggests possible differences in vasopressin regulation, and indicates the need for further studies to examine the complex interactions between the peripheral vasopressinergic and dopaminergic systems that appear to exist in patients with schizophrenia.

Serotonin is another neurotransmitter implicated in the regulation of vasopressin secretion (Spigset and Hedenmalm, 1996). A metabolite of serotonin, 5-HIAA, was differentially affected by 2DG, which evoked significant increases in patients and no changes in controls. Although our results suggest that vasopressin and 5-HIAA effects were unrelated, this finding also requires further validation because of the questionable validity of the peripheral 5-HIAA as a marker of central activity (Meek and Neff, 1973; Pietraszek *et al.*, 1992).

It is of interest that baseline vasopressin levels in schizophrenic patients were significantly lower compared to controls. While it is tempting to suggest that this finding reflects the impact of schizophrenia neuropathology on the neural circuitry mediating basal vasopressin secretion (Raskind *et al.*, 1978; Raskind *et al.*, 1987; Illowsky and Kirch, 1988; Emsley *et al.*, 1989; Spigset and Hedenmalm, 1996; Goldman *et al.*, 1997), other explanations are also possible.

First, baseline vasopressin differences may have been caused by variations in plasma osmolality, which was not measured in this study. If this were the case, overhydration or hypovolemia would have, respectively, blunted or enhanced osmoregulated vasopressin levels. BUN and haemodynamic data render this option unlikely and suggest similar hydration status in both groups. Nonetheless, potential osmolality effect is an important consideration for future research regarding vasopressin response to various stressors. Second, there is a considerable amount of preclinical and clinical data supporting the attribution of decreased baseline vasopressin levels to the pharmacotherapy with APD (Raskind *et al.*, 1987; Illowsky and Kirch, 1988; Yamaguchi and Hama, 1989; Sarai and Matsunaga, 1989; Marx and Lieberman, 1998), but other reports suggest the opposite (i.e. stimulatory effects of APD on vasopressin release) (Peck and Shenkman, 1979; Spigset and Hedenmalm, 1996; Marx and Lieberman, 1998; Aguilera and Rabadan-Diehl, 2000). Even though there was no significant relationship between baseline vasopressin level and APD doses or treatment duration in our subjects, the question regarding the precise role of APD in modulation of vasopressin secretion still remains open, and more research adjusting for the APD status is warranted to fully address the effects of APD on plasma vasopressin levels.

Our data contrast with a previous report of vasopressin response in schizophrenia by Kudoh *et al.* (1998), who found absolute vasopressin increases during abdominal surgery in 18 chronic schizophrenic patients compared to healthy controls. We found normal absolute response and only percentage increase following exposure to a different kind of stress. These contrasting data might be accounted for by differences between the two respective studies,

including patients' selection criteria, surgery itself and anaesthetic agents used by Kudoh *et al.* (1998).

Additional caveats that should be considered in interpreting our data pertain to the type of stress, duration of the study and the number of participants. Metabolic stress in this study was qualitatively different from environmental stressors that have been implicated in exacerbation of the schizophrenic disease process (Jansen and Gispen-de Wied, 2000). Even though our paradigm involved a psychological stress component (confinement to the novel environment of the PET scanner) that may, in part, account for the differences in HVA and 5-HIAA changes, the BPRS ratings of anxiety, mood and psychosis were not significantly affected, even in the presence of this potentially stressogenic condition. Because various stressors may have unique effects on hormonal regulation (Breier, 1989), future studies employing distinctly metabolic, psychosocial and physical stressors will be needed to further clarify this issue. Moreover, this study assessed only acute stress response and longer study periods may have yielded different results. Finally, these findings should be considered as preliminary pending replication with a larger sample.

In conclusion, our data shed light on the function of the peripheral vasopressinergic, dopaminergic and serotonergic systems in patients with schizophrenia, and suggest that pharmacological doses of 2DG may be a useful paradigm for illuminating the neurobiological correlates to impaired stress response in these patients.

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## Address for correspondence

Igor Elman  
Behavioral Psychopharmacology Research Laboratory  
McLean Hospital/Harvard Medical School  
115 Mill Street  
Belmont, MA 02478  
USA  
Email: ielman@partners.org

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