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Brief report

Basal norepinephrine in depersonalization disorder

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Abstract

In contrast to the noradrenergic dysregulation described in PTSD, little is known regarding noradrenergic function in dissociative disorders. The purpose of this preliminary study was to investigate basal norepinephrine in depersonalization disorder (DPD). Nine subjects with DSM-IV DPD, without lifetime PTSD, were compared to nine healthy comparison (HC) subjects. Norepinephrine was measured via 24-h urine collection and three serial plasma determinations. Groups did not differ significantly in plasma norepinephrine levels. Compared to the HC group, the DPD group demonstrated significantly higher urinary norepinephrine, only prior to covarying for anxiety. The DPD group also demonstrated a highly significant inverse correlation between urinary norepinephrine and depersonalization severity ($r = -0.88$). Norepinephrine and cortisol levels (reported in a prior study) were not intercorrelated. We concluded that although dissociation accompanied by anxiety was associated with heightened noradrenergic tone, there was a marked basal norepinephrine decline with increasing severity of dissociation. The findings are in concordance with the few reports on autonomic blunting in dissociation and merit further investigation.

Keywords: Dissociation; Catecholamines; Autonomic system; Sympathetic system

1. Introduction

A strong association to traumatic stress has been compellingly shown for various dissociative conditions (van Ijzendoorn and Schuengel, 1996), including depersonalization disorder (Simeon et al., 2001a). Therefore, study of the major systems mediating stress adaptation, such as the hypothalamic–pituitary–adrenal (HPA) and the noradrenergic axes, is of particular interest in these conditions. Relatively little is known about the biological correlates of dissociation, particularly when occurring in the absence of PTSD. Norepinephrine plays a central role in arousal, attention and emotional memory. In PTSD, basal catecholamine, noradrenergic challenge and receptor binding studies have revealed heightened noradrenergic tone, consistent with the hyperarousal and intrusive symptomatology characteristic of the disorder (Southwick et al., 1999).

In contrast, given the 'shut-down' symptomatology typically characteristic of dissociative states, one might predict autonomic hyporesponsivity. There is limited support for this hypothesis in the literature. After rape, women scoring high in dis-

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sociation showed diminished heart rate and galvanic skin responses (Griffin et al., 1997). Sierra et al. (2002) showed that, compared to anxiety disorder and healthy control subjects, those with depersonalization disorder exhibited reduced magnitude and increased latency of skin conductance response to unpleasant stimuli, but not to nonspecific stimuli, suggesting a selective inhibition of emotional processing.

To our knowledge, norepinephrine has not been investigated in dissociative disorders. One study has examined peritraumatic dissociation and norepinephrine (Delahanty et al., 2003), and reported that in motor vehicle accident victims, peritraumatic dissociation was negatively associated with norepinephrine and epinephrine in a 15-h urine sample collected in the emergency room. In the current pilot study, we assessed basal norepinephrine in the plasma and urine of subjects with a primary dissociative disorder, depersonalization disorder (Simeon et al., 1997, 2003). We hypothesized that depersonalization would be characterized by noradrenergic blunting. Specifically, we predicted that lower urine and plasma norepinephrine would be associated with depersonalization disorder and with severity of dissociation.

2. Methods

2.1. Subjects

Nine subjects with DSM-IV depersonalization disorder (DPD) and nine healthy comparison (HC) subjects free of lifetime Axis I and Axis II disorders were recruited for the study. The same subjects participated in the HPA axis protocol reported elsewhere (Simeon et al., 2001b). After a complete description of the study, written informed consent was obtained. Subjects were evaluated by structured interviews for DSM-IV dissociative disorders (Steinberg, 1994) and other Axis I disorders (First et al., 1995). They completed the Dissociative Experiences Scale (DES) (Bernstein-Carlson and Putnam, 1993), which yields a depersonalization score 'DES-DPS' (Simeon et al., 1998). Anxiety was rated by the Hamilton Rating Scale for Anxiety (HRSA) (Hamilton, 1959).

Subjects had to be medically healthy with normal physical examination, normal routine laboratory testing and negative urine toxicology. DPD subjects were excluded from the study if they met criteria for lifetime PTSD, lifetime psychotic disorder, current major depression, current eating disorder, or current substance use disorder. We excluded comorbid PTSD in order to eliminate confounding effects of posttraumatic stress on dissociation-related findings; other anxiety disorders were not excluded. All subjects were required not to have taken any psychotropic or other medications for at least 5 weeks before the study.

2.2. Procedures

Subjects were admitted to the Mount Sinai General Clinical Research Center for a 2-night stay. They fasted from 20.00 to 08.00 h, ate meals at fixed times after 08.00 h, and were limited to bedrest overnight and low-level monitored activity during the day, largely supine. On day 1 at 22.00 h, the 24-h urine collection began. On day 2, three serial blood samples (08.00, 15.00 and 23.00 h) were drawn via an indwelling catheter for measurement of plasma norepinephrine and the mean value was used. Blood samples were immediately spun and serum was stored in aliquots and frozen at -80 °C until analyzed. Urine collection bottles were refrigerated, measured for volume, divided into aliquots and frozen at -80 °C until analyzed. Norepinephrine concentrations were measured by high-pressure liquid chromatography (Yang et al., 1988), with intra-assay coefficients of variation (CV) of 7.7% and 7.0%, and inter-assay CV of 11.6% and 9.0%, for plasma and urine, respectively.

3. Results

3.1. Group comparisons

The two groups did not differ in age (DPD 30.8 ± 10.0 years, HC 31.4 ± 13.6 years, $t = 0.12$, d.f. $= 16$, NS) or gender (five men and four women per group). Age of onset of DPD was 15.2 ± 5.3 years, with a duration of 11.1 ± 13.4 years. As expected, the two groups differed significantly in

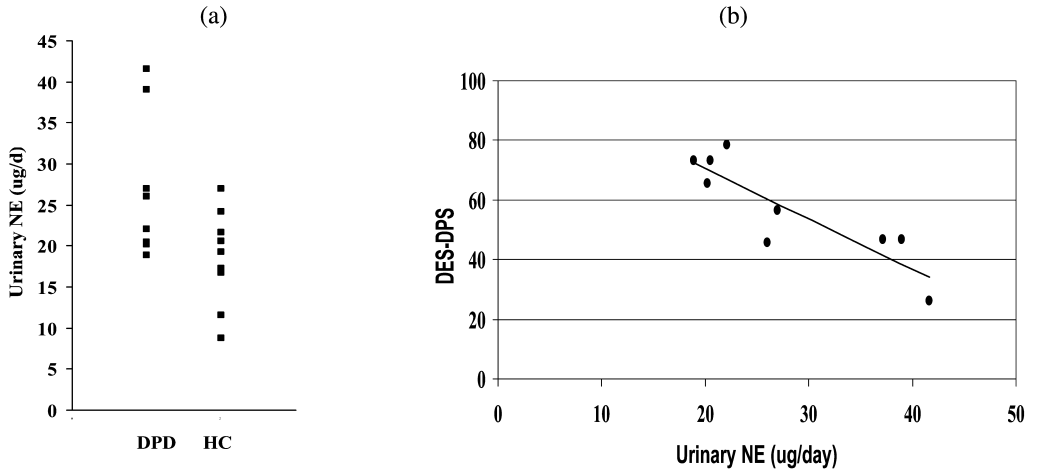

Fig. 1. (a) Individual urinary norepinephrine levels in the depersonalization disorder and healthy comparison groups. (b) Relationship between depersonalization severity and urinary norepinephrine in the depersonalization disorder group.

depersonalization scores (DES-DPS: DPD 56.9 ± 17.1, HC 1.7 ± 1.7, $t = 9.65$, d.f. $= 16$, $P < 0.001$). They also differed in anxiety scores (HRSA: DPD 9.2 ± 6.1, HC 1.7 ± 1.4, $t = 3.62$, d.f. $= 16$, $P < 0.01$). Of the nine DPD subjects, two had current Axis I comorbidity, one with generalized anxiety disorder and panic disorder and one with social phobia.

Urinary norepinephrine was significantly elevated in the DPD compared to the HC group (DPD 28.1 ± 8.9 μg/day, HC 18.5 ± 5.7 μg/day, $t = 2.70$, d.f. $= 16$, $P = 0.016$). However, this group difference did not reach statistical significance when anxiety was controlled by analysis of covariance ($F = 2.93$, d.f. $= 1,15$, $P = 0.11$). Fig. 1a displays the distribution of urinary norepinephrine in individuals of the two groups.

Mean plasma norepinephrine did not significantly differ between the two groups (DPD 193.4 ± 76.6 pg/ml, HC 172.6 ± 75.7 pg/ml, $t = 0.58$, d.f. $= 16$, $P = 0.57$), although it was higher in the DPD group, consistent with the urinary finding. The intraclass correlation coefficient for the three plasma norepinephrine samples was $\alpha = 0.74$, reflecting adequate assay reliability as a measure of individual differences.

3.2. DPD group

Fig. 1b demonstrates that within the DPD group there was a highly significant inverse correlation between urinary norepinephrine and DES-DPS depersonalization severity ($r = -0.88$, d.f. $= 7$, $P = 0.002$). The association was strengthened when anxiety was controlled for by partial correlation ($r = -0.94$, d.f. $= 6$, $P < 0.001$). Depersonalization and anxiety scores were not significantly correlated ($r = 0.24$, d.f. $= 7$, $P = 0.53$).

Although the detailed cortisol data in this sample were the subject of a prior report and are not presented here (Simeon et al., 2001b), there were no significant relationships between urinary or mean plasma basal cortisol measures, as well as cortisol suppression in response to low-dose dexamethasone, and urinary or mean plasma basal norepinephrine values. The correlation between the 24-h urinary cortisol and the 24-h urinary norepinephrine values was $r = -0.38$, d.f. $= 7$, $P = 0.31$.

4. Discussion

This is, to our knowledge, the first pilot study investigating noradrenergic function in a primary

dissociative disorder. The current study suggests that dissociation may be associated with noradrenergic dysregulation under basal conditions. The elevated urinary norephinephrine in DPD appears mostly attributable to co-occurring anxiety, given the diminution of this finding when anxiety was controlled by analysis of covariance. Three sources of coexisting anxiety are plausible, and not mutually exclusive. Firstly, of the three DPD subjects who had urinary norepinephrine values above the group mean, two had comorbid anxiety disorder on Axis I. Secondly, anxiety may have been differentially heightened in the dissociative compared to the control subjects by the stress of the new testing environment. Thirdly, anxiety may be part-and-parcel of the phenomenology of depersonalization in at least a subgroup of subjects. Phenomenologically, some individuals with DPD describe themselves as being in a chronic state of very high arousal and anxiety, while others describe a converse state of hypoarousal and stupor.

Within the dissociative group there was a very strong association between increasing dissociation severity and declining norepinephrine, independent of anxiety; indeed dissociation and anxiety were not intercorrelated. We speculate that this noradrenergic blunting might partly explain the hypoarousal, attentional difficulties and short-term memory deficits characteristic of depersonalization (Guralnik et al., 2000). Our finding is in good accordance with other reports describing autonomic physiologic blunting in dissociation (Griffin et al., 1997; Sierra et al., 2002). The present finding is also very similar to the single published study, to our knowledge, which has examined norepinephrine and dissociation (Delahanty et al., 2003). This study found that in the immediate aftermath of motor vehicle accidents, 15-h urinary norepinephrine was inversely correlated to the severity of peritraumatic dissociation.

On first examination, the findings of the study may appear paradoxical, in terms of higher baseline norepinephrine in DPD that was inversely related to depersonalization severity. However, variable degrees and origins of anxiety in the DPD group, as described above, could explain this seeming inconsistency and better future research controlling for anxiety-related variance could prove helpful in this regard. The finding of a relationship between dissociation and urinary, but not plasma, norepinephrine levels may reflect that plasma values are more subject to moment-to-moment fluctuations whereas urinary values provide a better integrated measure over time.

Peripheral norepinephrine has been investigated in relation to various stress, anxiety and personality-related measures. Panic disorder (Wilkinson et al., 1998) and OCD patients (Benkelfat et al., 1991) have shown comparable plasma norepinephrine levels to healthy controls. Elevated plasma norepinephrine has been associated with dysfunctional, depression-prone attitudes (Gruen et al., 2000) and with novelty-seeking temperament (Gerra et al., 1999), but not with general personality disorder comorbidity (Ekeberg et al., 2003). With respect to trauma-related disorders, posttraumatic stress has been most consistently associated with peripheral catecholamine elevations (Southwick et al., 1999).

Strengths of this pilot study include use of a dissociative group without complicating PTSD, well-controlled testing conditions, well-validated measures of dissociation and anxiety, and use of 24-h urine norepinephrine as a more integrated measure than plasma sampling alone.

Limitations include the small sample size and the peripheral measurement of a single catecholamine. Urinary MHPG would have better reflected CNS noradrenergic activity, while urinary norepinephrine is a better measure of peripheral catecholamine metabolism or of total peripheral and central norepinephrine release. Thus, the findings may be more reflective of peripheral, as opposed to central, catecholamine alterations in dissociation.

In summary, autonomic blunting may in part underlie the hypoaroused, shut-down state that characterizes dissociation, in contrast to the heightened arousal and re-experiencing characteristic of PTSD. The finding merits further exploration in larger samples, with various dissociative disorder diagnoses, under basal and stress-induction conditions, using multiple autonomic measures.

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References

Benkelfat, C., Mefford, J.N., Masters, C.F., Nordahl, T.E., King, A.C., Cohen, R.M., Murphy, D.L., 1991. Plasma catecholamines and their metabolites in obsessive–compulsive disorder. Psychiatry Research 37, 321–331.

Bernstein-Carlson, E., Putnam, F.W., 1993. An update on the Dissociative Experiences Scale. Dissociation 6, 16–27.

Delahanty, D.L., Royer, D.K., Raimonde, A.J., Spoonster, E., 2003. Peritraumatic dissociation is inversely related to catecholamine levels in initial urine samples of motor vehicle accident victims. Journal of Trauma and Dissociation 4, 65–79.

Ekeberg, O., Hedley, L., Einvik, G., Rostrup, M., Hoffart, A., 2003. Sympathetic reactivity in agoraphobic patients with and without personality disorders. Journal of Psychosomatic Research 54, 457–463.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Version 2. New York State Psychiatric Institute, Biometrics Research, New York.

Gerra, G., Avanzini, P., Zaimovic, A., Sartori, R., Bocchi, C., Timpano, M., Zambelli, U., Delsignore, R., Gardini, F., Talarico, E., Brambilla, F., 1999. Neurotransmitters, neuroendocrine correlates of sensation-seeking temperament in normal humans. Neuropsychobiology 39, 207–213.

Griffin, M.G., Resick, P.A., Mechnic, M.B., 1997. Objective assessment of peritraumatic dissociation: psychophysiological indicators. American Journal of Psychiatry 154, 1081–1088.

Gruen, R.J., Ehrlich, J., Silva, R., Schweitzer, J.W., Friedhoff, A.J., 2000. Cognitive factors and stress-induced changes in catecholamine biochemistry. Psychiatry Research 93, 55–61.

Guralnik, O., Schmeidler, J., Simeon, D., 2000. Feeling unreal: cognitive processes in depersonalization. American Journal of Psychiatry 157, 103–109.

Hamilton, M., 1959. The assessment of anxiety states by rating. British Journal of Medical Psychology 32, 50–55.

Sierra, M., Senior, C., Dalton, J., McDonough, M., Bond, A., Phillips, M.L., O'Dwyer, A.M., David, A.S., 2002. Autonomic response in depersonalization disorder. Archives of General Psychiatry 59, 833–838.

Simeon, D., Gross, B.A., Guralnik, O., Stein, D.J., Schmeidler, J., Hollander, E., 1997. Feeling unreal: 30 cases of DSM-III-R depersonalization disorder. American Journal of Psychiatry 154, 1107–1113.

Simeon, D., Guralnik, O., Gross, S., Stein, D.J., Schmeidler, J., Hollander, E., 1998. The detection and measurement of depersonalization disorder. Journal of Nervous and Mental Disease 186, 536–542.

Simeon, D., Guralnik, O., Schmeidler, J., Sirof, B., Knutelska, M., 2001a. The role of childhood interpersonal trauma in depersonalization disorder. American Journal of Psychiatry 158, 1027–1033.

Simeon, D., Guralnik, O., Knutelska, M., Hollander, E., Schmeidler, J., 2001b. Hypothalamic–pituitary–adrenal axis dysregulation in depersonalization disorder. Neuropsychopharmacology 25, 793–795.

Simeon, D., Knutelska, M., Nelson, D., Guralnik, O., 2003. Feeling unreal: a depersonalization disorder update of 117 cases. Journal of Clinical Psychiatry 64, 990–997.

Southwick, S.M., Bremner, J.D., Rasmusson, A., Morgan III, C.A., Arnsten, A., Charney, D.S., 1999. Role of norepinephrine in the pathophysiology and treatment of posttraumatic stress disorder. Biological Psychiatry 46, 1192–1204.

Steinberg, M., 1994. Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D), Revised. American Psychiatric Press, Washington, DC.

van Ijzendoorn, M.H., Schuengel, C., 1996. The measurement of dissociation in normal and clinical populations: meta-analytic validation of the Dissociative Experiences Scale (DES). Clinical Psychology Review 16, 365–382.

Wilkinson, D.J., Thompson, J.M., Lambert, G.W., Jennings, G.L., Schwartz, R.G., Jefferys, D., Turner, A.G., Esler, M.D., 1998. Sympathetic activity in patients with panic disorder at rest, under laboratory mental stress, and during panic attacks. Archives of General Psychiatry 55, 511–520.

Yang, R.K., Campbell, G., Cheng, H., Tsuboyama, G.K., Davis, K.L., 1988. High-performance liquid chromatographic determination of free 3-methoxy-4-hydroxyphenylethyleneglycol in plasma using a rapid Sep-Pak alumina B cartidge extraction. Journal of Liquid Chromatography 11, 3223–3231.