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BRIEF COMMUNICATION

Growth hormone response to clonidine in male patients with panic disorder untreated by antidepressants

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SYNOPSIS We report a non-significantly higher growth hormone (GH) response to intravenous clonidine administration (150 μg) in 10 male patients with panic disorder who had never received antidepressant therapy than in 10 matched controls. These results are consistent with data suggesting a normal or increased adrenergic receptor sensitivity in panic disorder patients.

INTRODUCTION

A large body of evidence suggests alterations in noradrenergic function in patients with panic disorders (Redmond & Huang, 1979; Ko *et al.* 1983). One experimental strategy that has been used to study the noradrenergic system is the acute challenge with the pharmacological agent clonidine (Matussek *et al.* 1980). It is recognized that clonidine, by stimulating hypothalamic alpha-2 adrenergic receptors, induces a discrete pulse of growth hormone (GH) release over the usual low baseline levels in humans (Ghigo *et al.* 1990). The GH response to clonidine may thus provide an indirect index of central adreno-receptor function.

Three groups have reported independently that patients with panic disorder manifest a blunted GH response to clonidine in comparison with control subjects (Uhde *et al.* 1986; Charney & Heninger, 1986; Nutt, 1989). In a previous study, however, we found no difference among panic and control subjects in their GH response to i.v. clonidine administration (Schittecatte *et al.* 1988). Eriksson (1989) also mentions a similar lack of difference when comparing 26 panic disorder patients with matched controls.

These discrepancies could be related to the influence of several variables which themselves may alter GH response. First, data in normal subjects (Corn *et al.* 1984), in one patient with panic disorder (Schittecatte *et al.* 1991) and in depressed patients (Schittecatte *et al.* 1989*a*) have demonstrated that studies on the GH response to clonidine have to take into account the confouding and long-lasting effects of tricyclics. In the studies of Uhde *et al.* (1986) and Charney & Heninger (1986) patients had a drug-free period of, respectively, two or three weeks before the clonidine challenge. The patients studied by Nutt (1989) were more carefully controlled with regard to the exposure to tricyclics. Two out of 13 patients had received tricyclic treatment a number of years previously for episodes of depression, but had been off drugs for over a year before entering his study (personal communication).

Secondly, Nutt (1989) used a fixed dose of 1·5 μg/kg which was demonstrated as being inadequate to differentiate clearly GH responders and non-responders in normal male volunteers (Hoehe *et al.* 1988).

Thirdly, previous investigations included mainly females among patients and controls and did not mention their hormonal status. Studies in animals show that 'GH responses to clonidine may be drastically modulated by steroidal hormones, probably acting at multiple levels of the alpha-2-receptor /GHRH/GH axis (Ericksson *et al.* 1988)'.

We have previously shown (Schittecatte *et al.* 1989*b*) the problems raised by these variables when the GH response to clonidine is studied in

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depressed patients. We suggested that studies designed to evaluate disease-related changes in alpha-2 adrenergic receptors by the GH response to clonidine should preferentially use untreated male patients. This study was therefore designed to replicate previous studies on the GH response to clonidine in untreated male patients suffering from panic disorder.

METHOD

Subjects

In a prospective study, we carefully selected 10 male patients with panic disorder who had never received antidepressant therapy. They were seen as out-patients at the Psychiatric Unit of the University Hospital of Liège (7 patients) or at the Department of Psychiatry of the Vincent Van Gogh Hospital, Charleroi (3 patients). They were assessed by means of the French version of the Schedule for Affective Disorders and Schizophrenia (SADS) (Spitzer & Endicott, 1978; Charles & Ansseau, 1987) and met RDC criteria (Spitzer *et al.* 1977; Ansseau, 1985) for panic disorder with agoraphobia. They all had presented three panic attacks during the preceding three weeks in the absence of current or past primary affective disorders. All patients had been drug-free of benzodiazepines for at least 5 days. None had any medical disorder or was overweight.

Ten male controls (7 from Liège and 3 from Charleroi) volunteered to participate in this study. They were free of any medical and psychiatric illness.

Analysis of variance (ANOVA) did not reveal any significant age difference between the two groups of patients and controls ($30{\cdot}2 \pm 7$ *v.* $36{\cdot}8 \pm 9{\cdot}4$; $F = 3{\cdot}4$; P = NS). Patients and controls participated in this study after giving their informed consent. The investigation was approved by the two hospital ethical committees.

Procedure

At 8 a.m., after an overnight fast, an intravenous catheter was inserted into a forearm of the reclining patients. Blood samples (5 ml) for hormone determination were taken 20 min (Liège) or 30 min (Charleroi) before clonidine infusion ($t-1$) and immediately prior to the infusion ($t-0$) at 9 a.m.

Clonidine was administered intravenously at a fixed dose of 150 μg dissolved in 9 ml saline over a 10 min period. Subsequent blood samples ($t+1$; $t+2$; $t+3$) were collected +20, +30 and +60 min (Liège) or +30, +45 and +60 min (Charleroi) after the infusion.

Blood samples were centrifuged within 2 h and the serum was stored at −40 °C. GH determinations were performed in each town using a radioimmunoassay according to a methodology previously described (Ansseau *et al.* 1984, 1988; Schittecatte *et al.* 1988). GH dosages previously performed on the same 48 blood samples at Liège and Charleroi had shown that the two dosage methods were highly correlated ($N = 48$; Pearson's $r = 0{\cdot}93$; $P < 0{\cdot}0001$).

We calculated a mean GH value which was the mean of the ($t-1$) and the ($t-0$) value and a Δ_{max} GH value – the difference between the highest value following the injection and the mean baseline value. GH response was also measured as the 'area under the response curve' following the injection of the drug (Area).

Statistics

The two groups were compared using the SPSS computer package (Hull & Nie, 1981) by a two-way ANOVA with groups and time as independent dimensions and GH values as repeated measures. All P values were two-tailed. The Areas and the mean GH and Δ_{max} values were compared using a Kruskall–Wallis one-way ANOVA (Theodorsson-Norheim, 1986).

RESULTS

ANOVA showed a highly significant time effect ($F = 16{\cdot}94$; $P < 0{\cdot}0001$) of clonidine on plasma GH values but no Group effect ($F = 1{\cdot}4$; P = NS) and no effect for Group × Time interaction ($F = 0{\cdot}69$; P = NS). Weights, lengths of current episode, mean baseline GH values, Δ_{max} GH values and 'Areas' of patients and controls are shown in Table 1.

The patients did not differ from controls for mean (±S.D.) baseline GH values ($0{\cdot}9 \pm 0{\cdot}9$ *v.* $0{\cdot}6 \pm 0{\cdot}4$; $F = 0{\cdot}84$; P = NS), Δ_{max} GH values ($18{\cdot}7 \pm 11{\cdot}4$ *v.* $14{\cdot}3 \pm 11{\cdot}2$; $F = 0{\cdot}76$; P = NS) and 'Areas' (43 ± 34 *v.* $27{\cdot}7 \pm 16{\cdot}5$; $F = 1{\cdot}6$; P = NS) (see Fig. 1). All patients had a GH response to clonidine in the normal range. The confidence

Table 1. *Effect of clonidine* (150 μg *i.v.*) *on plasma growth hormone response concentrations in male untreated panic patients* (*P.*) *and healthy controls* (*C.*)

Patient No.	Weight (kg)	Length of current episode (months)	Mean BL GH value (ng/ml)	Δ_{max} GH value (ng/ml)	Area	Control No.	Weight (kg)	Mean BL GH value (ng/ml)	Δ_{max} GH value (ng/ml)	Area
P. 1	68	8	0·26	18·54	49·44	C. 1	68	0·43	11·07	27·51
P. 2	71	12	0·25	10·65	22·79	C. 2	73	0·26	10·24	24·92
P. 3	76	18	0·36	9·84	27·42	C. 3	75	0·27	6·60	14
P. 4	78	72	0·65	14·95	24·1	C. 4	70	0·25	7·54	19·33
P. 5	72	8	1·05	8·55	12·4	C. 5	64	1·25	10·15	23·25
P. 6	68	6	0·75	27·25	40·2	C. 6	72	1·45	16·05	34·05
P. 7	83	24	0·5	9·9	21·95	C. 7	63	0·4	12·06	22·30
P. 8	70	12	0·7	14·7	29·7	C. 8	69	0·6	32·1	48·7
P. 9	64	8	0·75	44·05	123·7	C. 9	68	0·5	36·2	59·9
P. 10	76	18	3·45	28·55	78·85	C. 10	76	0·3	0·7	2·8
Mean	72·6	18·6	0·9	18·7	43		69·8	0·6	14·3	27·7
±S.D.	5·6	19·6	0·9	11·4	34		4·3	0·4	11·2	16·5

BL = Baseline.

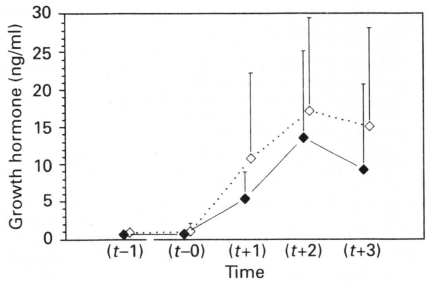

FIG. 1. Effect of clonidine (150 μg i.v.) on plasma growth hormone (GH) response concentrations in male untreated panic patients (◇---◇, $N = 10$) and controls (◆—◆, $N = 10$). Clonidine was administered immediately after ($t-0$). For the timing of blood samples for GH determination: ($t-1$); ($t-0$); ($t+1$); ($t+2$); and ($t+3$), see text. No significant difference between patients and controls.

intervals of the patients and controls were respectively for the baseline GH values (0·25–3·45 *v.* 0·25–1·45), for the Δ_{max} GH values (9·84–44·05 *v.* 0·7–36·2) and for the 'Areas' (12·4–123·7 *v.* 2·8–59·9).

DISCUSSION

The results of the present study indicate that male patients with panic disorder, who had never received tricyclic therapy, present a normal or even slightly higher GH response to clonidine than matched controls. These findings, therefore, do not support the hypothesis of a down-regulation of alpha-2 adrenoceptors in such patients, in contrast to three previous reports showing a blunted GH response.

Some methodological problems mentioned in the introduction might explain these discrepancies. Moreover, it is of interest to note that the data of Nutt (1989) suggest two different subgroups: six of his 13 patients had a normal or even slightly higher GH response to clonidine than controls.

Those results were observed in a small sample of panic patients, who had recently received benzodiazepines because of the difficulty in finding strictly 'untreated' panic patients. However, there are preliminary data (Eriksson *et al.* 1986) suggesting that benzodiazepines, in contrast to antidepressants, do not activate the brain alpha-2-adrenoceptors involved in GH regulation.

Two observations are consistent with our results. First, the number of alpha-2-adrenergic receptor binding sites on platelet membranes of patients with panic anxiety, as measured with tritiated clonidine, was the same as in normal subjects and lower than in depressed patients (Cameron *et al.* 1984). Secondly, the infusion of clonidine produces a greater decrease in serum concentrations of the noradrenaline metabolite MHPG and a more pronounced hypotension in patients with panic disorder than in matched controls, suggesting an increased alpha-2-adrenoceptor sensitivity in those patients (Charney *et al.* 1986; Nutt, 1986).

Finally, recent observations in patients with panic disorder of a blunted GH release after

GHRH infusion (Rapaport, 1989) are intriguing and could reflect a change in function at the pituitary level. Further studies using experimental strategies other than clonidine and GHRH–GH release are needed to understand the role of noradrenergic function in anxiety states associated with panic.

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