

## Growth Hormone Response to Clonidine in Treatment-Resistant Schizophrenia†

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**=Abstract=**To examine whether there are abnormalities in growth hormone (GH) response to clonidine among treatment-resistant schizophrenics, the authors investigated the GH response to clonidine in 20 treatment-resistant male schizophrenics and in 16 normal controls. There was no statistically significant difference in the mean maximal  $\Delta$ GH, the level of GH at any observed time point, the mean duration required for the peak of GH response and the percentage of the blunted GH response between the treatment-resistant schizophrenics regardless of haloperidol administration and normal controls except for much wider variations of maximal  $\Delta$ GH values in the treatment-resistant schizophrenics. In the relationship between the clinical variables and GH responsiveness, under the haloperidol medication no clinical variables were related with maximal  $\Delta$ GH, but 2 weeks after discontinuation of haloperidol, withdrawal-retardation subscore of BPRS was negatively correlated with maximal  $\Delta$ GH. Similarly, in a comparison between the GH responsive and the blunted group, only at haloperidol withdrawal state, did the blunted group show a higher withdrawal-retardation subscore of BPRS.

**Key Words:** Treatment-resistant schizophrenia, Growth hormone, Clonidine, Blunted response, Withdrawal-retardation

### INTRODUCTION

It is well known that about 10-30% of schizophrenics show poor or no response to neuroleptic treatment and are categorized as

treatment-resistant schizophrenia (Kane *et al.* 1988). This group may be a homogenous subgroup at a certain dimension of pathophysiology. And there have been some reports that treatment-resistant schizophrenics have some abnormalities in their nor-adrenergic (NA) systems (Bowers 1990). Therefore, it is worthwhile to examine whether there are abnormalities of GH response to clonidine, an  $\alpha_2$ -adrenergic agonist, in treatment-resistant schizophrenia. If there are some abnormalities in GH response to clonidine, these may be served as a neuroendocrine mark-

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Received June 1993, and in final form August 1993.

† Supported by a grant from the Yong-In Psychiatric Research Institute and the Seoul National University Hospital Research Fund No. 02-93-148.

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er for treatment-resistance.

According to the results of previous studies, in schizophrenics as a whole, the GH responses to clonidine showed great variations. For example, increased GH responses in paranoid schizophrenics (Matussek *et al.* 1980) and blunted GH responses among the schizophrenics who had negative symptoms (Müller-Spahn *et al.* 1986) and who had been treated with neuroleptics for more than 5 years (Ackenheil *et al.* 1985) were reported. On the other hand, Lal *et al.* (1983) and our previous results (Shin *et al.* 1989) showed that there was no difference in GH response between chronic schizophrenics and the normal controls.

Clonidine stimulates GH secretion via growth hormone releasing factor (GHRH) by stimulating hypothalamic  $\alpha_2$ -adrenergic postsynaptic receptors (Lal 1987). Recently, it has been reported that there is no difference between normal controls and schizophrenics regarding GH secretion via GHRH. And this suggests that if there is any abnormality in GH secretion in schizophrenics it derives from suprapituitary dysfunction (Mayerhoff *et al.* 1990; Liberman and Koreen 1993). The secretion of GH is also regulated by dopaminergic, cholinergic, GABAergic, and serotonergic neurotransmitter systems along with many other variables that may involve hypothalamic pathways (Pearsall and Gold 1986; Lal 1987; Liberman and Koreen 1993). So it is a very important issue in the study of GH response to clonidine, to restrict these confounding variables including the effects of antipsychotics on the  $\alpha_2$ -adrenergic receptors.

We observed the GH response to clonidine in a relatively homogenous cohort of treatment-resistant schizophrenics, *i.e.*, we included only male subjects whose age, age of onset and weight ratio were within a narrow range, and we have restricted current antipsychotic medications to only haloperidol which has relatively low affinities for the  $\alpha_2$ -adrenergic and the cholinergic receptors in comparison with the other popular antipsychotics (Richelson and Nelson 1984; Blak and Richelson 1987), and we also moni-

tored the effects of haloperidol on dopaminergic (DA) neurons by measuring the level of plasma prolactin (Pearsall and Gold 1986).

## SUBJECTS AND METHODS

### Subjects

The subjects were 21 male schizophrenics who were admitted to Yong-In Mental Hospital ranging from 20 to 46 years in age. They were diagnosed with the diagnostic criteria of DSM-III-R (American Psychiatric Association 1990) and met the following criteria for the treatment-resistance adopted by Keefe *et al.* (1987) with some modifications. The criteria are the presence of persistent psychopathology showing some signs of personality deterioration and requiring admission for more than 5 years despite that the patients had been treated for at least 5 years with two different chemical classes of antipsychotics amounting to more than 1000mg of chlorpromazine (CPZ) equivalent.

None of the subjects had any history of head trauma, neurological diseases, endocrine disorders, and any abnormalities in routine laboratory examinations including electroencephalography. Consents were obtained from all subjects after an explanation of the purpose and process of this study had been given. The mean age of the subjects was  $33.9 \pm 5.3$  years and the mean weight ratio (ideal weight/current weight) of the subjects was  $1.00 \pm 0.12$ . The mean age of onset and the mean duration of the illness were  $21.9 \pm 4.8$  years and  $12.0 \pm 4.3$  years, respectively.

Normal controls were 19 healthy males who did not have any history of endocrine, neurological and psychiatric disorders within their second degree of relatives. They were also informed of the procedures of this study and gave their consent. The mean age of the normal controls was  $32.7 \pm 6.4$  years and the mean weight ratio of them was  $1.1 \pm 0.18$ .

We started giving all patients only haloperidol as antipsychotics two weeks before the challenge of clonidine. The dosage of haloperidol

was the equivalent of the antipsychotics that the patients had been receiving previously. No medication that affects GH response was allowed throughout the experiment.

#### Methods

Clonidine challenges were done twice. The first challenge was done two weeks after we changed all previously administered antipsychotics to haloperidol. Immediately after the first challenge, we withdrew haloperidol. The second challenge was done after haloperidol had been withdrawn for two weeks.

As clinical variables, we obtained the information on the age of onset, the duration of illness, the highest dose of antipsychotics during the hospitalization and the dosage of antipsychotics at the beginning of this study. The dosages of antipsychotics were converted to the CPZ equivalent dose (Baldessarini 1985).

For the evaluation of the psychopathology, the Brief Psychiatric Rating Scale (BPRS, Overall 1976) was applied. The BPRS scores were subgrouped as paranoid, thought, withdrawal-retardation and anxiety-depression clusters. The ratings were done the day before clonidine challenge.

All the patients and controls had fasted from 10 p.m. on the night before the test and had been restricted to lie in bed during the whole procedures. For the clonidine challenge, an intravenous indwelling catheter was inserted at 7:30 a.m. After one hour of stabilization, blood was drawn for the baseline and then 0.15mg of clonidine was introduced for 10 minutes. Blood samples were collected at 15, 30, 45, 60 and 120 minutes after the start of the infusion of clonidine. Blood pressure was also taken at the time of collecting blood samples. Plasma was separated and kept at  $-70^{\circ}\text{C}$  until analysis. The plasma levels of GH and prolactin were measured with a radioimmunoassay (RIA) kit (Diagnostic Products Corporation; Sensitivity = 0.9 ng/ml).

#### Data analysis

Before the analysis of data, we excluded one subject from the schizophrenics and three from the normal controls because their baseline levels of GH were above 5ng/ml (Murad and Hynes 1985). Finally, the data from 20 schizophrenics and 16 normal controls were analyzed. The levels of GH were measured as two ways,  $\Delta\text{GH}$  (the level of GH after the clonidine challenge minus the baseline level of GH) and AUC (area under the curve), the sum of the trapezoid areas. However, because these two values showed significant correlation ( $r = 0.90$ ,  $p < 0.01$  and  $r = 0.98$ ,  $p < 0.01$ , on and off-drug respectively), we analyzed only the  $\Delta\text{GH}$  of the result. The subjects were divided into the  $\Delta\text{GH}$  responsive and the blunted groups according to maximal  $\Delta\text{GH}$ . The responsive group included those who showed 5ng/ml or more in maximal  $\Delta\text{GH}$ , and the blunted group included those whose maximal  $\Delta\text{GH}$  were less than 5ng/ml according to Hunt *et al.*(1986). As statistical methods, multivariate analysis of variables (ANOVA), multivariate analysis of covariance (ANCOVA), Student's t-test, Pearson's product movement correlation coefficient, kappa value and  $\chi^2$ -test were used. All the statistical analyses were conducted using the Statistical Package for the Social Sciences for Personal Computer (SPSS/PC +). A P value of 0.05 was taken to be statistically significant.

## RESULTS

GH response after clonidine challenge in treatment-resistant schizophrenics and normal controls

There was no statistically significant difference in maximal  $\Delta\text{GH}$  between the treatment-resistant schizophrenics with ( $10.02 \pm 10.82\text{ng/ml}$ ) or without ( $8.07 \pm 7.89\text{ng/ml}$ ) haloperidol administration and normal controls ( $8.32 \pm 4.67\text{ng/ml}$ ) except for significantly wider variations of maximal  $\Delta\text{GH}$  values in the treatment-resistant schizophrenics ( $F = 5.36$ ,  $p < 0.05$  and  $F = 2.85$ ,  $p < 0.05$  normal control vs. on and off-haloperidol, respectively, Fig. 1). Also no signifi-

cant difference was observed in the levels of GH between treatment-resistant schizophrenics regardless of haloperidol administration and normal controls at any time point from the baseline to 2 hours after the clonidine challenge (Fig. 2). And the mean durations required for the peak of GH response were again not significantly different between the treatment-resistant schizophrenics with ( $40.6 \pm 10.3$  min) or without ( $43.1 \pm 16.3$  min) haloperidol administration and normal controls ( $42.0 \pm 16.2$  min, Fig.2).

There was no statistically significant difference regarding the percentage of blunted GH response between schizophrenics with or without haloperidol administration and normal controls (Table 1). Of the 7 schizophrenics who showed

blunted GH response under haloperidol, 5 patients (71.4%) showed blunted response without haloperidol. And of the 13 schizophrenics who were included in the responsive group under the medication, 8 patients (61.5%) maintained responsiveness in haloperidol withdrawn state. However, there was no statistically significant concordance in GH responsiveness between the on and off haloperidol state (Kappa = 0.15).

Clinical variables and the GH response to clonidine challenge

Under the haloperidol medication, there was no statistically significant correlation between the maximal  $\Delta$ GH and any clinical variables, *i.e.*, age, age of onset, duration of illness, dosage of haloperidol at the day of challenge, maximal dosage of neuroleptics, baseline serum level of prolactin, total and subscores of BPRS (paranoid, thought, withdrawal-retardation and anxiety- depression clusters). When we divided the patients into the GH responsive and the

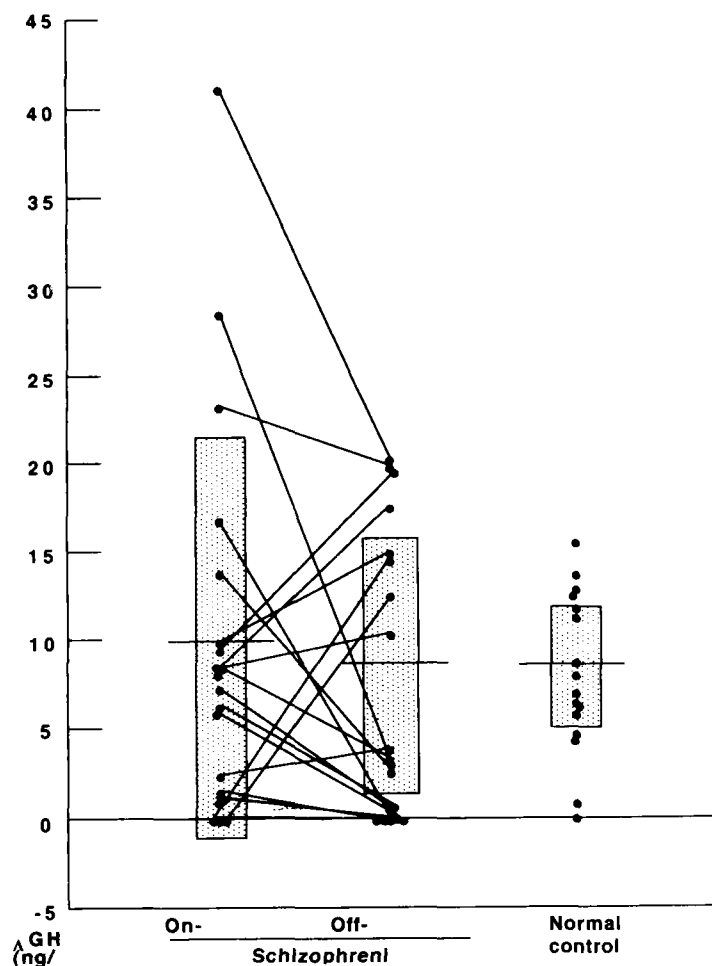


Fig.1. Maximal growth hormone increment ( $\Delta$ GH, ng/ml) in response to clonidine challenge (0.15mg i.v.). Each dot represents each subject. The interrupted lines and squares represent mean and SD respectively.

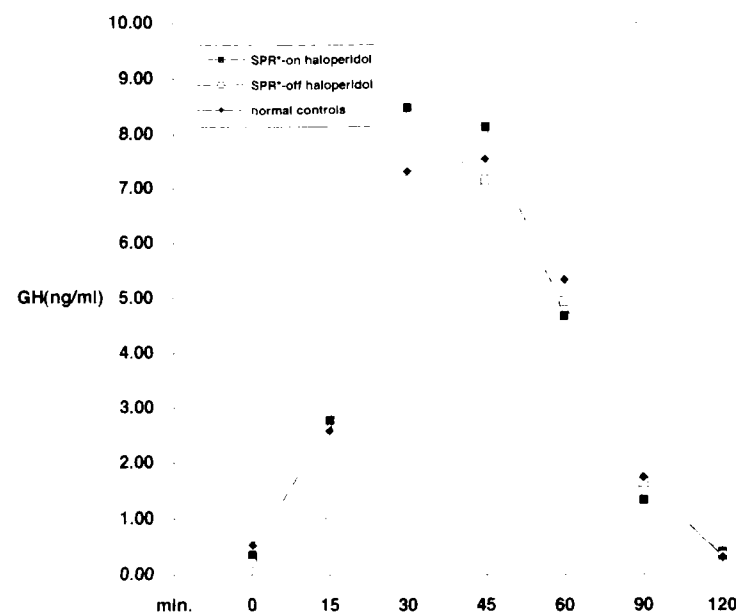


Fig.2. Time course of plasma growth hormone concentration after infusion of clonidine (0.15mg i.v.) in treatment-resistant schizophrenics on and off haloperidol medication (n = 20) and in normal controls (n = 16). \*SPR: schizophrenics.

No significant differences between the schizophrenics regardless of haloperidol medication and normal controls.

Table 1. Comparison of GH response between treatment-resistant schizophrenics on and off haloperidol and normal controls.

	Treatment resistant schizophrenics		Normal Controls (n = 16)
	On-haloperidol (n = 20)	Off-haloperidol (n = 20)	
Responsive group	13(65%)	10(50%)	12(75%)
Blunted group*	7(35%)	10(50%)	4(25%)

\*Blunted group: maximal GH increment after clonidine injection < 5ng/ml

$\chi^2 = 0.41$  d.f. = 1  $p = 0.522 > 0.05$ ; statistically not significant (on – off)

$\chi^2 = 0.08$  d.f. = 1  $p = 0.777 > 0.05$ ; statistically not significant (on – control)

$\chi^2 = 1.40$  d.f. = 1  $p = 0.236 > 0.05$ ; statistically not significant (off – control)

blunted groups during medication, comparison between the two showed no statistically significant difference in the clinical variables mentioned above (Table 2).

However, after 2 weeks of haloperidol withdrawal, age was positively correlated with maximal  $\Delta$ GH response ( $r = 0.44$ ,  $p < 0.05$ ), and withdrawal-retardation subscore of BPRS was negatively correlated with maximal  $\Delta$ GH ( $r = -0.44$ ,  $p < 0.05$ ). In comparison between the responsive and the blunted group, the blunted group showed significantly younger age ( $36.2 \pm 5.4$  years and  $31.6 \pm 4.1$  years, the responsive and the blunted group, respectively), significantly higher total score ( $48.9 \pm 9.5$  vs.  $58.7 \pm 10.1$ ) and withdrawal-retardation subscore ( $8.7 \pm 0.7$  vs.  $11.4 \pm 2.9$ ) of BPRS at  $p < 0.05$  (Table 2). However, according to ANCOVA with the age factor as covariate, the total scores of BPRS were not significantly different between the blunted and responsive groups (F value of main effects = 2.872,  $p = 0.108$ ) but the withdrawal-retardation subscore of BPRS was still significantly higher in the blunted group (F value of main effects = 5.243,  $p = 0.035$ ).

## DISCUSSION

We investigated whether there are abnormalities in GH response to clonidine among treatment-resistant schizophrenics. Because a lot of variables influence the secretion of GH, we

tried to construct a homogenous cohort with strict control of several variables, for example, sex of subject, range of age, age of onset and weight ratio, and we also adopted operational criteria for the treatment-resistance. Furthermore, during the experiment we restricted the antipsychotic medication to only haloperidol and monitored the extent of haloperidol induced DA antagonism by measuring the level of plasma prolactin.

From this we found that GH response to clonidine challenge in treatment-resistant schizophrenics is not different from normal controls regardless of haloperidol administration and that haloperidol medication does not affect the GH response in schizophrenics. These findings are consistent with the report of Lal (1983) and our previous observation (Shin *et al.* 1989), which showed no difference between chronic schizophrenics and normal control in the GH response to clonidine. These findings are also consistent with the report of Ackenheil *et al.* (1985), who argued that in chronic schizophrenics 5 and 10 days of neuroleptic-withdrawal do not affect the GH secretion response to clonidine stimulation. Therefore, it could be assumed that the treatment-resistant schizophrenics as a group may not differ from normal controls in  $\alpha_2$ -adrenergic responsiveness regardless of the dopaminergic antagonism. Nevertheless, there are some reservations in concluding that the treatment-resistant schizophrenics do not have

Table 2. Clinical characteristics of the GH responsive group and blunted group on and off haloperidol medication in treatment-resistant schizophrenics

	On-haloperidol		Off-haloperidol	
	Responsive G (n = 13)	Blunted G (n = 7)	Responsive G (n = 10)	Blunted G (n = 10)
Age	33.2 ± 6.0	35.1 ± 3.6	36.2 ± 5.4	31.6 ± 4.1*
Age of onset	24.1 ± 5.1	22.7 ± 4.5	23.7 ± 3.3	20.4 ± 5.3
Duration of illness	11.8 ± 5.2	12.3 ± 1.6	12.5 ± 4.2	11.1 ± 4.3
BPRS				
Total	51.5 ± 5.6	48.7 ± 5.6	48.9 ± 9.5	58.7 ± 10.1*
P-cluster	7.5 ± 1.5	7.7 ± 1.9	8.2 ± 1.9	9.6 ± 2.5
T-cluster	9.7 ± 4.7	8.3 ± 4.7	9.9 ± 4.3	9.5 ± 4.2
WR-cluster	9.7 ± 2.6	10.4 ± 2.4	8.7 ± 0.7	11.4 ± 2.9*
AD-cluster	7.7 ± 2.5	7.0 ± 1.4	7.0 ± 1.5	8.8 ± 2.7
Prolactin(ng/ml)	28.9 ± 37.9	26.2 ± 14.2	2.5 ± 1.1	6.1 ± 7.0

\* p < 0.05

Responsive G; responsive group, Blunted G; blunted group, P-cluster; paranoid cluster, T-cluster; thought cluster, WR-cluster; withdrawal-retardation cluster, AD-cluster; anxiety-depression cluster

any alterations in  $\alpha_2$ -adrenergic responsiveness. Because our present experiment, strictly controlled in a relative sense, showed wider variations of maximal  $\Delta$ GH values regardless of haloperidol medication, which is consistent with previous reports (Ackenheil *et al.* 1985; Shin *et al.* 1989).

In addition we observed that after the withdrawal of haloperidol, withdrawal-retardation subscore of BPRS was negatively correlated with maximal  $\Delta$ GH, whereas there is no correlation between the clinical variables and the GH responsiveness under haloperidol medication. Similarly, although there was no significant difference in any clinical variable between the responsive and blunted groups under the haloperidol medication, in haloperidol withdrawal state, the blunted GH responsive group showed higher withdrawal-retardation subscore of BPRS. These findings are partly compatible with Müller-Spahn *et al.* (1986), who reported reduced GH response to clonidine in negative schizophrenics after 12 days of drug withdrawal but no difference between schizophrenics and normal controls during medication.

It is interesting but difficult to interpret why

the withdrawal of haloperidol induces correlation between the degree of GH change and psychopathology, even though the mean maximal  $\Delta$ GH, the total score and other subscores of BPRS were not different between on and off states of haloperidol. A possible explanation may be that during the administration of haloperidol, various drug related variables might have blurring effects on the relationship between the clinical variables and the GH response, and after 2-weeks withdrawal of the medication, these blurring effects were removed. However, our previous study done with chronic but not all of them treatment-resistant schizophrenics (Shin *et al.* 1989) showed no correlation between clinical variables and the GH response after withdrawal of medication. So in drug withdrawal state, it is possible to assume that GH response to clonidine could be related with negative symptoms of not all but some schizophrenics. Of course, other interpretations are possible. One of them is that this might be an accidental finding because small number of the samples has low statistical power and our schizophrenics showed wider variations of maximal  $\Delta$ GH values and no concordance in terms of bluntedness between

on and off-drug state. So in further studies, clarifying the GH response to clonidine in various subgroups with a large number of patients at different dimensions of pathophysiology and psychopathology, and systematic evaluation of the effects of chronic antipsychotic medication and its withdrawal on the GH response may be needed.

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