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The gonadal axis in men with schizophrenia

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Abstract

The typical onset of schizophrenia during late adolescence and early adulthood has stimulated interest in the potential contribution of hypothalamo-pituitary-gonadal (HPG) axis abnormalities to this disorder. Previous investigations of reproductive hormone function in men with schizophrenia suggest diminished activity of the HPG axis. These studies have been hampered, however, by methodologic limitations. We have attempted to address these limitations by rigorous determination of gonadotropin and gonadal hormone levels, and attention to demographic and diagnostic variables. In contrast to prior studies, our results indicate that schizophrenic patients do not show statistically significant differences from healthy volunteers with respect to luteinizing hormone pulsatility, response to gonadotropin-releasing hormone challenge, and testosterone secretion. Due to the small number of subjects, however, these findings must be regarded as preliminary and warrant further study.

Keywords: Gonadotropin; Luteinizing hormone; Testosterone; Gonadotropin-releasing hormone

1. Introduction

The typical onset of schizophrenia during late adolescence and early adulthood has led to considerable speculation that the pubertal hormone surge plays a role in triggering the onset of this disorder. Three critical brain events occur at this life stage, each of which are proposed to be important in the pathogenesis of schizophrenia (Weinberger, 1987): the functional maturation of the dorsolateral prefrontal cortex (Goldman and Alexander, 1977; Goldman-Rakic et al., 1983), myelination of the subiculum (Benes, 1989; Gray et al., 1991), and full development of the dopaminergic system (McGeer and McGeer, 1981; Goldman-Rakic and Brown, 1982). Weinberger (1987) and others (Seeman and Lang, 1990; Benes, 1989) have suggested that the normal pubertal hormone surge may interact with a fixed early brain lesion or genetic predisposition to precipitate the onset of illness. It is also conceivable, however, that a

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dysfunctional gonadal axis, either alone or in combination with an early neurodevelopmental lesion, could be responsible for alterations in the programmed synaptic pruning that is believed to occur during this period (Feinberg, 1983; Feinberg et al., 1990), contributing to the onset of at least some cases of schizophrenia. There is evidence from the preclinical literature supporting the plausibility of these hypotheses (Meyer et al., 1978; Mitchell and Stewart, 1989; Goudsmit et al., 1990; Gould et al., 1991).

Evidence from studies of reproductive hormone disorders indicates that measurement of gonadotropin and gonadal hormone function reflects hormonal disturbances apparent as early as puberty (Crowley et al., 1985). Thus, it is likely that hormonal abnormalities detected in young, otherwise physically healthy adult men with schizophrenia were present during adolescence, a time during which hormonal abnormalities could have an impact on the development of disorder. In several studies of gonadotropin and gonadal function in schizophrenia, abnormalities of hypothalamo-pituitary-gonadal (HPG) axis function in unmedicated male patients with chronic schizophrenia have been reported. Lower levels of basal luteinizing hormone (LH), follicle-stimulating hormone (FSH) (Brambilla et al., 1974, 1976, 1977; Brambilla, 1980; Ferrier et al., 1982, 1983), and testosterone (Brambilla et al., 1974, 1977; Brambilla, 1980), as well as reduced spontaneous fluctuations in LH secretion (Ferrier et al., 1982, 1983), have been demonstrated in men with schizophrenia compared with normal comparison subjects. Studies using gonadotropin-releasing hormone (GnRH) challenges have also revealed that men with schizophrenia have blunted LH and FSH responses (Brambilla et al., 1976; Brambilla, 1980; Ferrier et al., 1983; Cantalamessa et al., 1984). The results of these studies suggest that dysfunction of the gonadal axis occurs in schizophrenia. A careful analysis of these investigations, however, reveals methodologic problems.

The most significant limitation is that the vast majority of studies made infrequent measurements of gonadotropins. Since gonadotropins are released in a pulsatile manner, their levels fluctuate markedly throughout the day. In some studies, baseline levels of gonadotropins were assessed over two consecutive mornings at the same time of day. While this method yields some information on baseline HPG axis function, the best indicator of GnRH pulse generator activity is LH pulsatility, which cannot be quantitated by this approach. Second, some of these studies included patients over the age of 50, potentially confounding the results because of the effects of chronic institutionalization and age-related alterations in reproductive hormone secretion (Urban et al., 1988; Veldhuis, 1988). Third, several studies did not specify the diagnostic criteria used in the selection of patients and comparison subjects.

Therefore, we examined specific aspects of gonadal axis function in patients with chronic schizophrenia using: (1) more frequent gonadotropin measures, drawn over longer time periods; (2) chronically ill patients from the community instead of from long-term institutional settings; (3) characterization of patients by *DSM-III-R* criteria; (4) careful screening of comparison subjects; and (5) exclusion of subjects over age 45. Because of the fluctuations in ovarian steroid secretion throughout the menstrual cycle, and the consequent difficulties in measurement of gonadotropins and gonadal hormones in women, we elected to study male patients only. We measured the pulse frequency (number of pulses/8 h) and the mean pulse amplitude of LH as these measures have been shown to be reliable peripheral indicators of the function of the hypothalamic GnRH pulse generator, which regulates the secretion of LH and FSH from the pituitary (Veldhuis, 1988). We also measured the LH response to GnRH challenge in an attempt to detect potentially more subtle abnormalities of the gonadal axis, analogous to studies of thyrotropin-releasing hormone challenge, which have revealed thyroid dysfunction despite normal levels of thyroid hormones and thyroid-stimulating hormone (TSH) (Prange et al., 1987). We hypothesized that men with schizophrenia would show evidence of deficient HPG axis functioning: specifically, diminished LH pulse frequency and mean LH pulse

amplitude, and a blunted LH response to GnRH challenge. In addition, we measured several other reproductive hormone indices for which we had no specific hypotheses but that were regarded as sources of additional information on the integrity of the gonadal axis.

2. Methods

2.1. Subjects

The patient group consisted of 8 male inpatients, aged 28–40, with a *DSM-III-R* diagnosis of chronic schizophrenia (American Psychiatric Association, 1987) who were hospitalized on the Schizophrenia Research Unit (SRU) of the New York State Psychiatric Institute (NYSPI). Of these patients, only one had been hospitalized for a continuous period >1 year; the remainder were recruited from the community. Diagnoses were made with the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger et al., 1994), a semistructured instrument that allows for systematic and comprehensive evaluation of psychiatric symptomatology, and detailed collection of medical and substance abuse history. Intrasite and intersite reliability studies of the DIGS have reported a κ coefficient of 0.90 for schizophrenia. Patients had been withdrawn from neuroleptic medication and were free of all other medications for ≥2 weeks (mean = 20 days; range = 14–29 days). The subjects had normally developed secondary sexual characteristics, and they had no significant medical (including endocrinologic) illnesses or abnormalities as determined by physical examination and routine laboratory testing. All patients were administered the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) after ≥2 weeks of neuroleptic withdrawal, as part of the standard SRU protocol. The group of comparison subjects consisted of eight age-matched male volunteers who were recruited from the Normal Controls Unit of the Mental Health Clinical Research Center at NYSPI. The volunteers had been administered the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS-L; Endicott and Spitzer, 1978; Spitzer et al., 1978) and were diagnosed as "never mentally ill." The male volunteers had not taken any medications (other than occasional over-the-counter remedies) for at least 3 months before the study, and they had no history of neuroleptic exposure. Initial testing did not reveal any significant medical (including endocrinologic) illnesses. They had normal physical examinations, no abnormalities on routine laboratory tests, and normal secondary sexual characteristics.

At the time of screening, all subjects had single serum measurements of thyroxine, triiodothyronine resin uptake (T_3RU), free thyroxine index (FTI), and TSH. On day 1 of the gonadal hormone studies, all subjects had blood drawn for measurement of serum prolactin.

2.2. Hormone studies

The studies were performed over 2 days: on day 1, baseline measures of LH and testosterone were obtained; on day 2, the LH response to GnRH challenge was quantitated. Subjects were at bedrest for at least 8 h before and during the studies, which began at 08:00 h on both days. A light breakfast was served on days 1 and 2, before the procedure, and subjects received lunch on day 1 at 12:00 h.

Baseline hormone study (day 1). A No. 18 intravenous (i.v.) catheter was inserted into an antecubital vein and kept patent with a slow (1000 ml/24 h) i.v. drip of dilute heparinized saline. A double stock was used; 4 ml of blood were drawn into a draining syringe to ensure comparability of samples. Twenty minutes elapsed between the catheter insertion and blood drawing. Sequential 5-ml blood samples were drawn from the i.v. line at 10-min intervals over an 8-h period. Sera were obtained by centrifugation at 2000 r/min for 15 min, transferred by micropipette into labeled polypropylene tubes, and frozen and stored at -20°C.

GnRH challenge study (day 2). The same technique for catheter insertion and blood drawing was used as on day 1. For the first hour, sequential 5-ml blood samples were drawn at 10-min intervals. An i.v. bolus of 100 μg GnRH (Factrel, Wyeth/Ayerst) was then administered over 60 s.

Blood samples (5 ml) were then drawn from the i.v. line at 20, 40, 60, 90, and 120 min after the injection. Sera were obtained as described in the baseline study.

2.3. Hormone assays

The LH and testosterone assays were performed in the Sloane Andrology Laboratory of Columbia-Presbyterian Medical Center. LH was assayed with a double antibody radioimmunoassay (RIA). The reagents were provided in a kit by Diagnostic Products Corporation (DPC). The kit was modified for these assays to obtain a sensitivity of 1.0 mIU/ml. The intra-assay and interassay coefficients of variation (CVs) for serum samples containing 1–3 mIU/ml are 9% and 12%, respectively, and for samples containing 1–30 mIU/ml, 6% and 10%, respectively. Samples containing >30 mIU/ml have CVs of 11% and 15%, respectively. Two hundred microliters of serum were micropipetted into each assay tube; each assay was run in duplicate and repeated if the average difference between duplicates was >10%. Accuracy of the assay was determined by paired assays between the DPC kit as modified, an in-house RIA consisting of five overnight incubations at 0–6°C, using NIH reagents first antibody: rabbit anti-human LH no. 2; tracer: iodinated ^{125}I-hLH-I-3 (Amersham Corp.), iodinated not more than 3 weeks before use and prepurified on a Biogel P-60 column; standard: LER-907 in 0.1% PBS-gel, *p*H +7.0; second antibody: sheep anti-rabbit γ-globulin (Bioscience), and a nonradiometric assay (*Stratus LH*). The correlation coefficients for these two methods with the DPC method are 0.92 ($P < 0.003$) and 0.86 ($P < 0.015$), respectively.

Sera were pooled over each hour for measurement of total testosterone. Testosterone assays were carried out using a solid phase RIA in which anti-testosterone antibody-coated tubes were prepared by DPC and ^{125}I-testosterone was used as tracer. The sensitivity of the assay was 20 ng/dl of serum, with 50 μl of serum required for each assay tube. Thus, the minimum sensitivity of the assay was 10 pg/assay tube, with intra-assay and interassay CVs of 7% and 12%, respectively. Precision for serum processed (values range between 100 and 1000 ng/dl) was 5% and 8%, respectively. Recovery experiments demonstrated 96–112% recovery of added testosterone to steroid-free serum.

2.4. Data analysis

Baseline study. The LH data for each subject were analyzed on a microcomputer with the Pulsar program (Merriam and Wachter, 1982), a standard pulse-identification algorithm that calculated pulse number (per 8 h), mean pulse amplitude, mean LH concentration, CV of LH pulses, and interpulse interval. Area under the LH baseline curve was calculated by trapezoidal analysis. Mean testosterone levels were calculated by averaging the values obtained from each hourly pool.

GnRH challenge study. The baseline (prechallenge) mean LH concentration was calculated by averaging the three readings immediately preceding the GnRH injection. The LH peak increment was derived by subtracting the baseline LH value from the peak LH value following GnRH administration. The area under the LH response curve was also calculated by trapezoidal analysis. Each of the baseline and GnRH challenge parameters was compared between schizophrenia and control groups with Student's *t* tests for independent samples.

3. Results

Table 1 presents characteristics of the patient group. The mean ages of the schizophrenia (32.8, SD = 4.2) and comparison (29.6, SD = 2.1) groups did not differ significantly ($t = 1.5$, $df = 13$, $P = 0.16$). The mean age of onset of schizophrenia was 21.4 years (SD = 4.1). The mean duration of illness was 10.8 years (SD = 3.5). PANSS scores were obtained for seven of the eight patients studied. During neuroleptic withdrawal, patients had a mean total PANSS score of 69.3 (SD = 11.6), with a mean positive subscale score of 16.9 (SD = 7.7) and a mean negative subscale score of 21.6 (SD = 5.2). After a 6-week trial of haloperidol, 10–15 mg/day, medication response was assessed based on at least a 20% improvement in the total PANSS score, as was used in the defini-

Table 1
Characteristics of the patient sample

Patient no.	Age	Age of onset	Duration of illness (years)	PANSS Score						Haloperidol response
				Neuroleptic withdrawal			Haloperidol treatment			
				Positive	Negative	Total	Positive	Negative	Total	
1	34	24	10	—	—	—	—	—	—	—
2	29	22	7	13	19	55	11	21	52	No
3	36	20	16	11	26	61	9	25	57	No
4	30	25	5	16	25	72	12	30	65	No
5	29	18	11	20	15	61	22	20	68	No
6	28	17	11	13	24	69	9	18	54	Yes
7	31	17	14	12	27	78	15	26	73	No
8	40	28	12	33	15	89	28	14	85	No
Mean	32.1	21.4	10.8	16.9	21.6	69.3	15.1	22.0	64.9	
SD	4.2	4.1	3.5	7.7	5.2	11.6	7.2	5.4	11.7	

Note. The total PANSS (Positive and Negative Syndrome Scale) score is the sum of scores on the positive syndrome, the negative syndrome, and general psychopathology scales. PANSS data are not available for patient no. 1. Patient no. 5 completed the baseline study only. Haloperidol response was defined as a 20% decrease from baseline in the total PANSS.

tion of haloperidol treatment response by Kane et al. (1988). Only one of the seven patients with PANSS assessments was rated as a haloperidol responder.

There was a trend for increased prolactin levels in the patients (mean = 9.2 ng/ml, SD = 3.4) compared with the normal volunteers (mean = 6.4 ng/ml, SD = 2.0; $t = 1.9$, $df = 13$, $P = 0.07$). None of the thyroid hormone measures differed significantly between the two groups (results available on request).

Gonadotropin and gonadal hormone testing revealed that one control subject had evidence of significant gonadal dysfunction. The results for this subject were thus excluded from the analyses.

In the baseline study, all of the patients with schizophrenia had evidence of LH pulses, as did the volunteers (range = 7–12 pulses/8 h in both groups). There were no significant differences between the patients and the comparison subjects with respect to LH pulse number per 8 h and mean LH pulse amplitude. In addition, no significant differences were observed in the exploratory analyses, including testosterone concentration, mean LH concentration, CV, interpulse interval, and area under the curve (see Table 2).

Table 2
Parameters of baseline luteinizing hormone (LH) pulses and testosterone secretion

	Chronic schizophrenia ($n = 8$)		Normal comparison group ($n = 7$)			
	Mean	SD	Mean	SD	t	P
Pulses/8 h	8.9	1.5	9.0	1.6	0.15	0.88
Mean pulse amplitude	1.8	0.47	1.5	0.44	1.08	0.30
Mean LH concentration	4.6	2.7	3.5	1.5	1.02	0.33
Coefficient of variation	0.44	0.21	0.45	0.22	0.10	0.92
Interpulse interval	21.0	3.5	20.8	4.5	0.08	0.94
Area under curve	2154.9	1320.2	1615.0	756.4	0.99	0.35
Mean testosterone concentration	410.5	112.1	468.4	162.7	0.79	0.45

Table 3
Luteinizing hormone (LH) response after gonadotropin-releasing hormone (GnRH) challenge

	Chronic schizophrenia ($n = 7$)		Normal comparison group ($n = 7$)			
	Mean	SD	Mean	SD	t	P
Baseline LH concentration	4.8[a]	2.4	3.3[a]	1.9	1.31	0.22
LH peak increment	33.4[b]	19.2	36.1[b]	14.5	0.30	0.77
Area under curve	2130.7	1153.8	2443.9	996.6	0.54	0.60

[a]Based on average of three readings immediately preceding GnRH injection; [b]peak LH value following GnRH injection minus baseline LH value.

In the GnRH study, the LH peak increment, baseline (prechallenge) LH (based on the mean of three serial LH values), and area under the LH response curve did not differ significantly between the two groups (see Table 3 and Fig. 1). In both the baseline and GnRH studies, the results for our control subjects were closely comparable to values reported in the literature for healthy men (Urban et al., 1988; Veldhuis, 1988).

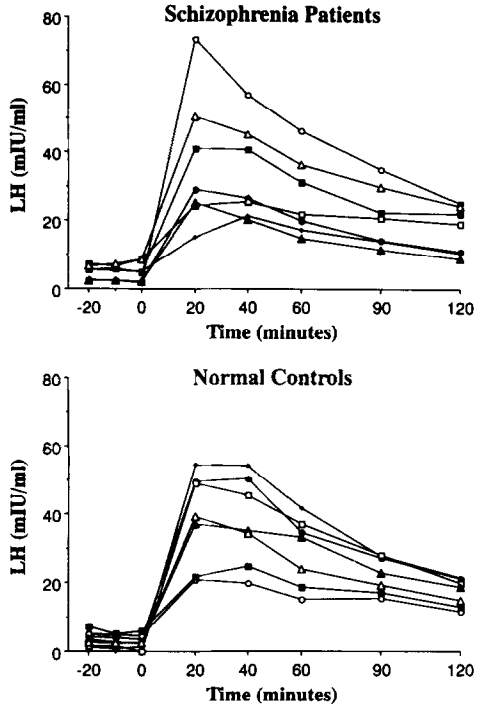

Fig. 1. Luteinizing hormone (LH) response to gonadotropin-releasing hormone challenge in 7 schizophrenic patients and 7 normal volunteers (each symbol denotes an individual subject).

4. Discussion

Our data suggest that LH pulse frequency, mean LH pulse amplitude, and LH response to GnRH challenge do not show statistically significant differences between male patients with chronic schizophrenia and healthy male volunteers. In addition, we did not demonstrate any significant differences with respect to several indices of pulsatile LH release and response to GnRH challenge, and testosterone levels. These results are contrary to the findings of most reproductive hormone investigations of schizophrenic men.

We propose three major reasons for these differences. First, some studies quantitated baseline LH levels only twice over a 48-h period during each phase of testing (Brambilla et al., 1974, 1975). Given the marked fluctuations of LH levels, it is likely that valid inferences cannot be drawn about mean LH secretion based only on an average of two values. Although Ferrier et al. (1982) attempted to improve on the design by quantitating LH pulse secretion from measures performed at 15- to 20-min intervals over 2.5–4 h, Crowley et al. (1985) have demonstrated that unless blood samples are obtained at intervals ≤ 10 min, a significant number of LH pulses are missed. Ferrier et al. (1982) reported that only 35% of men with chronic schizophrenia exhibited any evidence of episodic LH secretion. In contrast, the more rigorous sam-

pling method used here revealed that LH pulses occurred in all of the schizophrenic men. To our knowledge, this is the first such report in the literature.

Second, there were problems in the characterization of patients with schizophrenia and comparison subjects in previous gonadal studies. Brambilla et al. (1974, 1975) selected patients with "hebephrenia" and "chronic schizophrenia," but they did not specify the criteria used. Similarly, comparison subjects were reported to have "sociofamilial mental deficiency" (Brambilla et al., 1976) and "reactive depression" (Ferrier et al., 1982) or were identified as "normal" in the absence of assessment details.

Finally, differences in patient characteristics between the present study group and those of previous studies should be considered. A number of prior studies included subjects over 50 years of age (Brambilla et al., 1975; Brambilla, 1980; Ferrier et al., 1982), a period marked by significant changes in LH and testosterone secretion (Urban et al., 1988; Veldhuis, 1988). In addition, some of these studies included inpatients hospitalized on a long-term basis (Ferrier et al., 1982, 1983). As a result, the reproductive hormone abnormalities observed might be more reflective of differences in the aging process between patients and comparison subjects, or the effects of chronic institutionalization. Differences between the results of our study and those of prior studies may also be explained by differences in illness characteristics between patient groups. The chronically hospitalized patients in the studies by Brambilla et al. (1974, 1976, 1977) and Ferrier et al. (1982, 1983) are likely to have been more severely ill than our patients with respect to symptomatology and level of function. However, the degree of symptomatology in our patients was comparable to the PANSS scores required for participation in a recent pharmacologic study of inpatients with schizophrenia (Marder and Meibach, 1994). In addition, although our patients were not chronically institutionalized, most had been chronically ill for at least several years. Furthermore, seven of eight patients did not respond to a 6-week trial of haloperidol at therapeutic doses (see Table 1). Given the possibility that differences in illness characteristics could explain discrepant findings between studies (one could also argue that our patients represented a unique group with respect to medication response), a study relating HPG axis function to specific domains of psychopathology and medication response could prove fruitful.

There are three major limitations to our study. First, it could be argued that our results did not reach statistical significance because of insufficient power resulting from the small number of subjects. We therefore calculated, for each of the measures, the number of subjects that would be required for the group differences that we found to become statistically significant (Cohen, 1977). With an α of 0.05 and power of 0.80, the requisite number of subjects is 1571 for LH pulse frequency, 35 for LH mean pulse amplitude, and 400–500 for LH peak increment after GnRH challenge. With the exception of mean LH concentration and area under the curve (n = 35 and 32 subjects, respectively) the exploratory measures would require an n of at least 135 subjects to detect significant differences between groups. It should be noted that although there appear to be group differences in the baseline LH concentration before GnRH challenge (albeit nonsignificant differences), these values were based on an average of only three readings (see Table 3). Thus, for two of the three most important measures, and most of the exploratory measures, our failure to demonstrate statistically significant differences between groups may not be related to a small number of subjects since the group differences found in this study would require an unusually large n to achieve statistical significance. Although it is feasible to obtain a sufficient n to demonstrate significant group differences in mean LH pulse amplitude, one cannot conclude that there are differences in GnRH pulse generator function based solely on this one measure. In addition, our results for the mean LH pulse amplitude were opposite to the hypothesized direction: this value was slightly elevated in patients with schizophrenia compared with volunteers.

Given the heterogeneity of biological measures in schizophrenia (Carpenter et al., 1993), however, it is possible that gonadal dysfunction is present in a subgroup of patients. Thus, future studies with

larger numbers of subjects are necessary to demonstrate that there are no statistically significant differences between the groups.

Second, the results of the baseline LH study could possibly be explained by continuing effects of antipsychotic medication on the neuroendocrine system (evidenced by the trend for higher prolactin levels in patients), since the patients with schizophrenia had been withdrawn from neuroleptic medication for an average of only 3 weeks. The effects of antipsychotic medications on pulsatile LH secretion have not been studied. However, elevated prolactin levels result in suppression of gonadotropin secretion (Glasier et al., 1984; McNeilly, 1988); since previous studies with longer medication-free intervals demonstrated diminished LH function in schizophrenia, it is unlikely that increased prolactin secondary to recent neuroleptic treatment could account for our finding of similar LH parameters between groups. In addition, the results of the GnRH challenge study are unlikely to be a result of prior antipsychotic treatment since these medications either dampen (Apter et al., 1983) or do not affect (Brambilla et al., 1976) the LH response to GnRH. However, an alternative explanation for our findings is that patients with schizophrenia have increased LH pulsatility and enhanced response to GnRH challenge that are masked by neuroleptic treatment. Although there are no published data to support this possibility, limitations of previous investigations could have concealed an increased sensitivity of the HPG axis in at least a subgroup of patients.

Third, the fact that we did not demonstrate an abnormality of HPG axis function during the third or fourth decade of life does not exclude a disturbance of gonadotropin or gonadal hormone function at the time of puberty. A study of patients during the first episode of schizophrenia could shed further light on this question.

In conclusion, in a study comparing male patients with schizophrenia and healthy age-matched male volunteers, we found: (1) evidence of LH pulsatility in each patient studied; and (2) baseline LH pulsatile function, testosterone levels, and LH responses to GnRH challenge that did not differ significantly from comparison values. These findings contrast with the results of earlier studies and may be explained, at least in part, by the more rigorous methodology used here. Due to the small number of subjects, however, these findings must be viewed as preliminary. Further investigations in an expanded number of subjects are warranted in the study of HPG axis function and schizophrenia.

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