Eur Arch Psychiatry Clin Neurosci (2007) 257:135–139 DOI 10.1007/s00406-006-0686-y

ORIGINAL PAPER

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Gonadal axis hormones in psychiatric male patients after a suicide attempt

Received: 19 July 2006 / Accepted: 24 July 2006 / Published online: 25 November 2006

Abstract Epidemiological and clinical studies support the view that aggressive acts like suicidal and violent behaviors share a common substrate. Certain aspects of violence in males have been related to high testosterone levels, but the relation of testosterone to attempted suicide has not been studied until now. We estimated plasma levels of testosterone (T), LH, and FSH in 80 male subjects after a suicide attempt and in whom a psychiatric assessment was done during their hospitalization. Suicide intent was evaluated in 72 subjects. A group of 56 healthy males in the same age range served as control. As a group, attempters showed significantly lower T levels, marginally higher LH, and normal FSH compared to controls. The attempters who used violent methods (26 subjects) had T levels even lower than the non-violent (drug overdose) subgroup. Comparisons of T levels of subgroups according to the (main) drug ingested (analgesics, benzodiazepines, antidepressants, neuroleptics, or other drugs) did not reveal any significant drug effect. In relation to diagnosis, the lowest T levels were found in the subgroup with schizophrenia (29 subjects). The T levels of this subgroup were also significantly lower compared to those of a group of 31 male schizophrenic patients, hospitalized and treated with neuroleptics. If the influence of post-attempt stress and medical condition on plasma T could be ruled out, low plasma T may prove to be a biological predictor of attempt, at least in male schizophrenic patients. Nevertheless, the findings differentiate suicidal behavior from other aggressive/violent behaviors and do not support the notion that suicidal and aggressive behaviors are manifestations of the same impulse.

Key words attempted suicide · psychiatric diagnosis · testosterone · LH · FSH

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Introduction

It has been postulated that suicidal and violent behaviors are manifestations of the same aggressive impulse turned towards self (suicide) or towards others (violence) [1, 2] and some clinical and epidemiological studies supported this view. Male and female adolescents who reported suicidal feelings had significantly higher scores in the Aggression Questionnaire than did those who denied suicidal ideation in an Italian study [3]. Significant correlations have been found between measures of suicidal behavior, aggressive behavior, and impulsivity in adolescent psychiatric inpatients [4], while the co-occurrence of personality disorders of more than one cluster contributes to the risk for completed suicide [5]. Significant temperamental similarities by means of the Karolinska Scales of Personality between suicide attempters and violent offenders have been reported [6].

Aggression is one of the aspects of behavior that has been linked to testosterone (T) levels. Kalin [7] has studied the biological mechanisms that underlie aggression in rhesus monkeys and has established two different categories of aggression, defensive and offensive, with different biological substrates. Defen-

sive- or fear-motivated aggression is related to extreme asymmetric right frontal activity in the brain and high plasma cortisol concentrations, while offensive or impulsive aggression to low serotonergic activity in the central nervous system, high levels of testosterone and lower levels of cortisol. In male prisoners with a history of high levels of aggressiveness, testosterone levels have often been found to be linked with violent behavior [8–10].

Few studies have attempted to assess simultaneously the possible differential contributions of serotonin and T in the expression and inhibition of aggressive behavior. Higley et al. [11] found in nonhuman primates that high CSF free T concentrations are associated with competitive aggression, while low CSF 5-HIAA concentrations are associated with severe aggression which results from impaired impulse control. Simon et al. [12] support the view that T and its metabolites modulate 5HT1A and 5HT1B agonist effects on intermale aggression (see their extensive review of the literature on the subject). Although the association between suicidal—aggressive—impulsive behavior and serotonergic activity seems to hold true, no differences were found in the frequencies of the serotonin receptor Cys23Ser polymorphism between suicide victims and controls [13], a polymorphism which has been shown to be connected to impulsiveness [14].

And while suicidal behavior is held to be a form of inward directed aggression, very few studies have been performed investigating androgens in attempted suicide. In veterans with posttraumatic stress disorder (PTSD), significantly higher median dehydroepiandrosterone (DHEA) levels were found in those who had attempted suicide compared to those who had not [15]. In 8 cases of suicide in young men, 5 were making use of anabolic androgenic steroids at the time they killed themselves and 2 had stopped the use 2 and 6 months earlier [16]. Testosterone levels in CSF have been reported lower in suicide attempters compared to aggressive violent offenders [17].

The purpose of the present study was to investigate the plasma levels of T, luteinizing hormone (LH), and follicle stimulating hormone (FSH) in a group of male subjects after a suicide attempt, and to compare them with those of normal controls. Data on plasma T levels after a suicide attempt are lacking, although the association of androgen levels to aggressive and violent acts, mentioned above, justify such studies. It is clear that there are many factors that can influence the hormonal levels of the study subjects and have to be considered in the evaluation of the data. The stress of the attempt, the stress of the hospitalization in a serious physical condition, the acute effect of drug overdose ingested during the attempt, and the long term effect of the medication in attempters who were on drug therapy, are some of the issues that have to be faced.

Subjects and methods

Eighty (80) male subjects, admitted after a suicide attempt to the medical wards of Evangelismos General Hospital and of Asclepeion Hospital in Athens, were included in the study. They were all assessed and followed during hospitalization by the psychiatric liaison team of the two hospitals. The psychiatric diagnosis was made according to the DSM-IV criteria and the severity of the suicidal intent was estimated with the Suicidal Intent Scale (SIS) [18].

For each patient the following parameters were recorded: Age, mode of attempt, drugs ingested in those who took an overdose, previous attempts, medication, diagnosis, and the score in Beck's Scale. Sixteen patients received the diagnosis of adjustment disorder, 18 of personality disorder, 17 of major depressive disorder, and 29 of schizophrenia. Twenty-six patients employed a violent method and 54 had taken a drug overdose. Twenty-eight subjects (35%) had at least one previous attempt.

A control group was established from 56 male normal volunteers who had no psychiatric history or history of suicide attempt. Their ages matched the ages of the attempters. In addition, and since the subgroup of attempters with schizophrenia was large enough (29 subjects), we compared the hormone levels of this subgroup to those of 31 male schizophrenic patients from a previous study of ours [19]. These two comparison groups are thus matched according to sex, age, diagnosis, treatment, and hospitalization.

From each subject a single blood sample was drawn between 8:00 AM and 9:00 AM during the first days of hospitalization. EDTA was used as anticoagulant and the plasma was separated by centrifugation and stored at −30°C until determination. For the estimation of T, LH, and FSH plasma levels, we used commercially available radioimmunoassay kits (Adaltis, Casalecchio di Reno, Italy). The inter- and intra-assay coefficients of variation were close to 5%.

For the statistical evaluation of the data, we employed multiple regression analysis, analysis of variance using age as covariate with planned comparisons when appropriate. We also used linear regression analysis and the Spearman rank order correlation test in searching for correlations between variables.

Results

In Table 1 are shown the mean values and SD of age and the plasma levels of T, LH, and FSH of the healthy control group and the group of attempters, as well as the results of the comparisons (ANCOVA, age as covariate) between the groups. The group of attempters showed significantly lower plasma testosterone levels compared to healthy controls (df = 1,133, $F = 9.81$, $P = 0.002$), a trend towards higher LH levels in the patients ($F = 3.69$, $P = 0.057$), and no significant differences concerning the levels of FSH ($F = 0.66$, $P = 0.42$).

To evaluate the overall influence of various factors on T levels of the attempters' group ($n = 80$), we first performed three multiple regression analyses, each with dependent variable plasma T, LH, or FSH levels and independent variables age, diagnosis, mode of attempt (drug used, other mode), and violence of attempt. For T we obtained a multiple R value of 0.4288, with $P = 0.004$ (df = 4,75, $F = 4.22$). Beta-weights were significant for diagnosis ($\beta = 0.3521$, $P = 0.003$), and non-significant for age ($\beta = -0.1697$, $P = 0.11$), mode of attempt ($\beta = 0.0219$, $P = 0.87$), or violence

Table 1 Mean values (±SD) of age, plasma testosterone (ng/ml), LH and FSH (mIU/ml) in the groups of male controls and males after a suicide attempt

Group	*N*	Age	T	LH	FSH
Control	56	35.3 ± 8.7	4.82 ± 2.02	2.28 ± 1.35	3.26 ± 2.16
Attempt	80	34.4 ± 12.6	3.48 ± 2.92	2.82 ± 1.82	3.52 ± 2.55
ANCOVA, cov. = age :		*F* 1,133	9.81	3.69	0.66
		P	0.002	0.057	0.42
Controls	56	35.3 ± 8.7	4.82 ± 2.02	2.28 ± 1.35	3.26 ± 2.16
Non-violent	54	34.6 ± 13.3	3.94 ± 2.90	2.90 ± 1.94	3.41 ± 2.07
Violent	26	34.0 ± 11.2	2.53 ± 2.78	2.66 ± 1.58	3.75 ± 3.38
ANCOVA, cov. = age :		F 2,132	8.04	1.99	0.57
		P	0.0005	0.14	0.57
Planned comparisons					
Control versus non-violent, *F*(1,107)			3.72	3.92	
		P	0.066	0.049	
Control versus violent, *F*(1,79)			15.95	1.04	
		P	0.0001	0.31	
Non-violent versus violent, *F*(1,77)			5.92	0.32	
		P	0.016	0.57	
SCH-controls	31	30.4 ± 8.4	4.76 ± 2.25	2.54 ± 1.00	2.82 ± 1.68
SCH-attempters	29	33.9 ± 11.6	2.13 ± 1.93	2.41 ± 1.56	3.21 ± 2.46
F(1,57)			21.01	0.28	0.06
P			0.0001	0.60	0.80

The data of the subgroups of subjects who used violent or non-violent methods are also given and evaluated separately. Attempters with schizophrenia are also compared to a group of hospitalized schizophrenic patients under neuroleptic treatment (SCH-controls)

(β = 0.1251, P = 0.33). The multiple regression was not significant for LH (R = 0.2080, P = 0.50), while for FSH was significant (R = 0.3884, P = 0.014), with only age to contribute significantly to the hormone levels (β = 0.338, P = 0.002).

We then undertook a more detailed elaboration of the data regarding the drugs ingested, the mode of attempt (violent versus nonviolent), psychiatric diagnosis and previous attempts.

For the evaluation of possible influences of the drugs ingested on the hormone levels, we formed 5 subgroups according to the main drug ingested, i.e. analgesics (14 subjects), benzodiazepines (15 subjects), antidepressants (5 subjects), neuroleptics (8 subjects), and other drugs (7 subjects). The individual T levels of the patients in each of these subgroups are shown in Fig. 1.

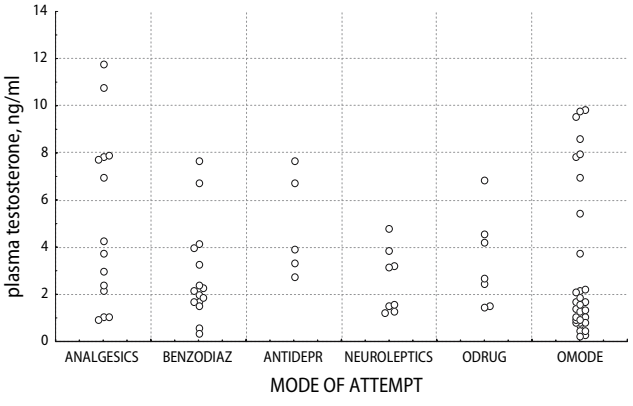

Fig. 1 Individual plasma testosterone levels in male suicide attempters. Subgroups according to the (main) drug used for attempt. ODRUG: other drug(s); OMODE: other, non-pharmacologic mode, in most cases violent

An analysis of covariance (ANCOVA) in which we compared the T levels of the 5 drug subgroups using age as covariate, gave an F value of 2.34, with df = 4,43, and p = 0.07. Consequent post hoc comparisons (Tukey-test) did not reveal any significant differences among the subgroups (the strongest difference was between analgesics and benzodiazepine subgroups, with a P = 0.11, n.s.) It seems thus, that the low plasma T levels of the attempters cannot be attributed to the drug ingested.

In the subgroup OMODE (other mode) of Fig. 1, we included the subjects who ingested substances not intended for human consumption (8 subjects) and 23 subjects who used a violent method (fall, shooting, stabbing). A second ANCOVA including this subgroup (6 subgroups of Fig. 1), with 5,73 degrees of freedom, gave an F = 1.55, and P = 0.19. We conclude that subjects with low plasma T levels are equally found in all subgroups, i.e. it is not the mode of attempt that determines the hormone levels.

We investigated further possible differences in plasma T levels among subgroups according to the psychiatric diagnosis, by performing an ANCOVA with age as covariate for the four diagnostic subgroups (adjustment disorder, personality disorder, major depression, schizophrenia) and controls. With df = 4,130, we obtained an F value of 7.75, with P = 0.001. Planned comparisons revealed significant differences from controls for schizophrenia (P = 0.0001), marginally for major depression (P = 0.077), and non-significant for adjustment disorder (P = 0.48) or personality disorder (P = 0.12). Figure 2 shows the individual T levels of the subjects in these subgroups.

Twenty-six subjects had applied violent attempt methods that included digestion of corrosive liquids,

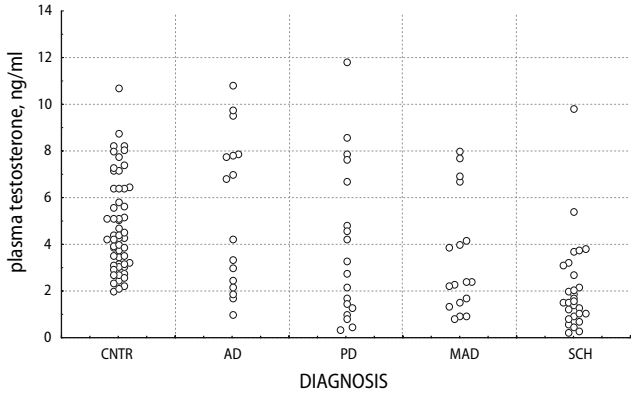

Fig. 2 Individual values of plasma testosterone in male suicide attempters. Subgroups according to psychiatric diagnosis. AD: adjustment disorder; PD: personality disorder; MAD: major affective disorder; SCH: schizophrenia

stabbing, shooting, or fall from heights, while the rest 54 subjects used non-violent methods (drug overdose). The data for these subgroups, as well as the results of the comparisons to the control group (ANCOVA with age as covariate) are shown in Table 1. Violent attempters had lower T levels than controls ($P = 0.0001$). In addition, LH levels were marginally higher than controls only in the non-violent attempt group. Figure 3 shows the individual T values of controls, non-violent, and violent attempters.

Furthermore, the hormone data of the subgroup of attempters with schizophrenia (29 subjects) were compared to those of 31 age-matched hospitalized schizophrenic patients under neuroleptic treatment (Table 1). Attempters had highly significant lower plasma T levels (2.13 ± 1.93 vs. 4.76 ± 2.25 ng/ml, $P < 0.0001$), while there were no differences in LH or FSH levels.

In relation to previous attempts we had reliable data for 75 cases. Twenty-eight subjects had a previous attempt in the past (about 50% of the subjects

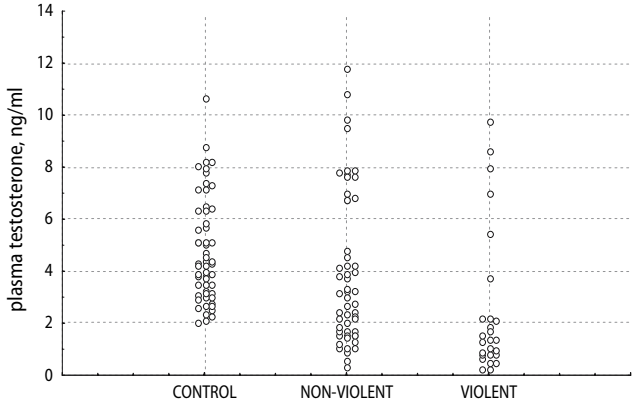

Fig. 3 Total plasma testosterone of healthy control males and males after a non-violent (drug overdose) or a violent suicide attempt. Both attempter groups have significantly lower than normal testosterone levels

who received the diagnoses of schizophrenia and personality disorder and 20% of the subjects who received the diagnoses of major depression and adjustment disorder). Testosterone levels were 3.12 + 3.08 ng/ml in those with a previous attempt and 3.65 + 2.81 ng/ml in the first attempters, the difference being non significant (ANOVA with age as covariate, df = 1, 75, $F = 0.21$, $P = 0.65$). The expected negative correlations of age to T, present in our control group ($r = -0.4255$, $n = 56$, $P = 0.001$), was not significant in the schizophrenia subgroup of attempters ($r = -0.2043$, $n = 29$, n.s.), but T was positively correlated to LH ($r = 0.4493$, $P = 0.014$).

Since it has been postulated that high T levels may be related to intended violent acts, it was of interest to search for possible correlation between plasma T levels and the score in Suicidal Intent Scale, which was assessed in 72 subjects. The correlation was not significant (Spearman correlation coefficient $R_s = -0.1490$, $P = 0.21$).

Discussion

The idea that suicidal and violent behaviors are manifestations of the same aggressive impulse is supported by numerous epidemiological and clinical studies. In addition, several studies in animals and humans find an association between aggression and high testosterone levels. In this respect one would expect that neuroendocrine characteristics would possibly reflect a regulatory mechanism that determines the direction of the aggression either outward or inward.

The findings of the present study do not support this idea. We found that our group of attempters had significantly lower plasma T levels compared to the group of healthy controls and this difference was more pronounced in the subgroup of attempters who used violent methods. In the subgroup of nonviolent attempters there were lower plasma T levels and a trend towards higher LH levels, which is indicative of a normal function of the HPG axis. In the subgroup of violent attempters though, the lower compared to controls plasma T levels without a concomitant LH increase is indicative of a dysfunction of the axis.

Before though we rush into a conclusion for a dysfunction of the hypothalamic-pituitary-gonadal (HPG) axis in our group of attempters, it is necessary to discuss certain crucial points.

Plasma T levels are expected to be influenced by stress. Both mental stress [20] and acute metabolic stress [21] have a lowering effect on plasma T levels. It is possible that the subjects in the violent subgroup experienced more stress either from the attempt itself and/or the hospitalization in a serious medical condition. Reproductive axis suppression in acute medical conditions has been reported to be related to disease severity [22]. Some of our patients and

particularly those who attempted by jumping from heights underwent orthopaedic surgery and remained in the hospital for several weeks.

We found that plasma T levels were significantly lower in the subgroup of attempters with the diagnosis of schizophrenia compared either to healthy controls or to hospitalized schizophrenic patients. Studies of the pituitary-gonadal axis in male schizophrenic patients rather indicate a normal functioning. No differences from healthy volunteers in the levels of gonadotropin and gonadal hormones have been reported [23]. The positive correlation between T and LH in the schizophrenia subgroup of the present study signifies a functional HPG-axis, so that the cause of hypogonadism does not seem to be a result of a decreased hypothalamo-pituitary input in this group. Possible influence of long-term neuroleptic use cannot be ruled out, although there are indications against such a possibility. Schizophrenic patients under treatment with classical neuroleptics have normal T plasma levels and they remain so after switch to treatment with clozapine [19] or other atypical antipsychotic drugs [24], although prolactin levels were substantially decreased after the switch in both mentioned studies. In the group of 29 schizophrenic patients of the present study, T levels did not correlate to age, duration of illness, or years of neuroleptic therapy, so that other reasons should be searched to explain the low T levels in suicide attempters.

In a recent study, Mann et al. [25] used two biological tests, the dexamethasone suppression test and cerebrospinal fluid 5-hydroxyindoleacetic acid levels, and calculated their specificity and sensitivity to predict suicide. The results of the present study suggest total plasma testosterone levels to be another candidate as a biological predictor of suicidal behavior, at least in male schizophrenic patients, where 18 of the 29 attempters (62%) had levels lower than 2 ng/ml plasma. This percentage was lower, but still considerably large, in attempters with major affective disorder (35%), personality disorder (39%), or adjustment disorder (19%). Prospective studies with assessment of suicidal ideation and behavior with measurements of plasma T levels are needed to elucidate this hypothesis.

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