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CLINICAL REPORT

Effects of tandospirone, a serotonin-1A agonist, on the hypothalamo-pituitary-gonadal axis of male patients

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Abstract

BACKGROUNDS: Serotonin (5-HT) agonists are reported to affect prolactin (PRL) and gonadotropin secretion. A small study was conducted on male patients with generalized anxiety disorders to investigate the clinical and neuroendocrinological effects of the 5-HT_{1A} receptor agonist tandospirone (TDS) on the hypothalamo-pituitary-gonadal (HPG) axis.
METHODS: The subjects for the present study included 11 male outpatients. Informed consent was obtained from all subjects involved in this study. The endocrine studies were done before and during TDS administration. Psychiatric ratings were done using the Japanese version of the Spielberger's State-Trait Anxiety Inventory.
RESULTS: We found that (1) both state- and trait-anxiety scores were significantly reduced by TDS treatment; (2) there was no significant difference in PRL, gonadotropins or testosterone (T) between the patients and normal controls; (3) TDS administration showed significant stimulatory effects on PRL and T; and (4) PRL change between baseline and TDS steady state (ΔPRL) did not show a significant correlation with improvement in state or trait-anxiety scores.
CONCLUSIONS: Our results indicate that (1) PRL response may not provide a clinical predictor; (2) PRL level may not reflect the level of anxiety, and (3) 5-HT_{1A} may have stimulatory effects on PRL. However, further, double-blind evaluation with a larger sample would be needed for clarification of effects of 5-HT_{1A} on the HPG axis.

Introduction

We reported a case of unilateral gynecomastia without galactorrhea in a man during the serotonin (5-HT)-$_{1A}$ receptor agonist tandospirone (TDS) treatment [1], and his laboratory data during TDS showed an increased testosterone (T) level. Although there is extensive evidence that 5-HT is implicated in the neuroendocrine control regulating the secretion of several anterior pituitary hormones, i.e., 5-HT agonists are reported to increase the blood prolactin (PRL) [2, 3], the involvement of specific 5-HT receptor subtypes in this action is not yet fully elucidated. Moreover, there have been few reports of human studies. In the present work, we attempted to determine the clinical and neuroendocrine role of the 5-HT$_{1A}$ receptor subtype, using TDS. Furthermore, we examined the hypothesis that 5-HTergic system status, as measured by the PRL response to TDS, may predict outcome for a group of patients treated with TDS, since serum PRL levels in humans is suggested to represent a useful tool to evaluate the activity of drugs possessing putative 5-HTergic properties [3].

Patients and methods

The original sample of this study consisted of 11 male outpatients with generalized anxiety disorder (GAD) meeting the DSM (Diagnostic and Statistical Manual of the American Psychiatric Association)-IV [4] diagnostic criteria. Eleven age-matched normal subjects were obtained as a control sample. Table 1 shows the demographic characteristics of the subjects. We chose to examine only male subjects in order to avoid the problem of menstruation-related hormonal fluctuations. No subjects had any significant physical abnormalities as determined by physical examinations and routine laboratory testing. Subjects had no ongoing medication. The study was approved by the relevant ethics committees and was performed in accordance with the Declaration of Helsinki II. Informed consent was obtained from all subjects for the research involved in this study.

Psychiatric ratings were done using the Japanese version [5] of the Spielberger's State-Trait Anxiety Inventory (STAI) [6]. The STAI is composed of two separate 20-item scales constructed to measure "state" and "trait" anxiety, using 4-point scales. The STAI scores were calculated for the complete 40-item measure.

The neuroendocrine studies were done on two occasions (1) prior to TDS and (2) after a mean period of 28.6 days (SD = 22.2, range 7–85) treatment.

The time when blood samples were drawn was different among subjects, but the same in each subject for the consecutive sampling. Sera were prepared and stored at –20 centigrade until the time of analysis. Prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and T were assayed by a radioimmunoassay [7–9].

Statistical analyses were done using the nonparametric tests (e.g. Mann Whitney's U-test, Wilcoxon signed rank test, Spearman's rank correlations), because of the small sample size. The time effect for each of the psychological and biochemical variables was examined by analysis of variance with repeated measures (ANOVA).

Results

1. Subjective measures of anxiety

The mean state-anxiety score in the patients was significantly higher than that in the normal subjects (U-test, $p < .05$), and there was a trend for patients to have high trait-anxiety scores (Fig. 1).

Both state- and trait-anxiety scores were significantly reduced by TDS treatment (Wilcoxon signed rank test, $p < .01$ and $p < .05$, respectively) (Fig. 1).

Table 1. Demographic characteristics of subjects

	Normals Mean (SD)	Patients Mean (SD)
N	11	11
Age (yrs)	44.3 (17.7)	42.8 (1.62)
Body weight (kg)	59.2 (1.3)	58.5 (8.6)
Dose (mg/day)	-	30.0 (11.6)
Administration periods (days)	-	28.6 (22.2)
Luteinizing hormone (mIU/mL)	8.51 (5.81)	7.35 (4.72)
Follicular-stimulating hormone (mIU/mL)	10.98 (6.95)	9.49 (4.62)
Prolactin (ng/mL)	8.38 (4.37)	5.90 (3.40)
Testosterone (ng/dL)	676.6 (166.8)	594.7 (166.4)
State-Trait Anxiety Inventory		
State-anxiety	42.1 (8.8)	52.1 (10.1)*
Trait-anxiety	41.7 (10.2)	51.2 (10.4)

*$p < .05$ versus normals by the Mann Whitney's U-test.

2. Biochemical Measures

By the Mann Whitney's U-test, there was no significant difference in baseline PRL, gonadotropins or T between the patients and normal subjects (Fig. 1).

The Wilcoxon signed rank test showed significant increase in PRL ($p < .05$), but not in gonadotropins and T by TDS treatment (Fig. 1).

Significantly greater PRL and T responses in patients with TDS than in drug-free normal subjects were shown by ANOVA [group x time interaction for PRL: $F = 4.57$, $p < .05$; for T: $F = 8.74$, $p < .01$] (Fig. 1).

However, PRL change between baseline and TDS steady state (ΔPRL) did not show a significant correlation with improvement in state- or trait-anxiety scores.

Discussion

Our results show that repeated treatment of male patients with a clinically-effective dose of TDS produces an increase in basal blood PRL and T levels.

Tandospirone is an azapirone drug that has high affinity for 5-HT_{1A} receptors and preclinical effects predictive of antidepressant and/or anxiolytic efficacy [10]. Serotonergic neurons are involved in the PRL release [3]. Also, they are involved in the gonadotropin release, and their effects on gonadotropins are different according to areas [11].

In humans, 5-HT agonists are known to increase the serum PRL levels [2; 3]. Tandospirone is reported to increase the plasma PRL concentration in rats [12], as well as another 5-HT_{1A} receptor agonist, such as ipsapirone [13]. Our findings suggest that a partial 5-HT_{1A} agonist administration has stimulatory effects on PRL also in humans, and the findings are consistent with previous reports that showed a significant increase in PRL levels was noted after administration of another 5-HT_{1A} partial agonist buspirone [14; 15] or ipsapirone [16]. Tandospirone is not a full but partial agonist, i.e., TDS has the potency to induce the "5-HT behavioral syndrome" [17]; on the other hand it blocks elicitation of the "5-HT behavioral syndrome" [18]. Thus, from our findings in the patients, TDS is indicated to act as a 5-HT stimulator, not an inhibitor in the pituitary and hypothalamus. However, we cannot deny the possibility that the prolactogenic effect of TDS may occur directly via the dopaminergic (DArgic) system, since TDS exhibits DA antagonistic action, though the potency of TDS as an DA agonist is less than one fourth that of buspirone [10].

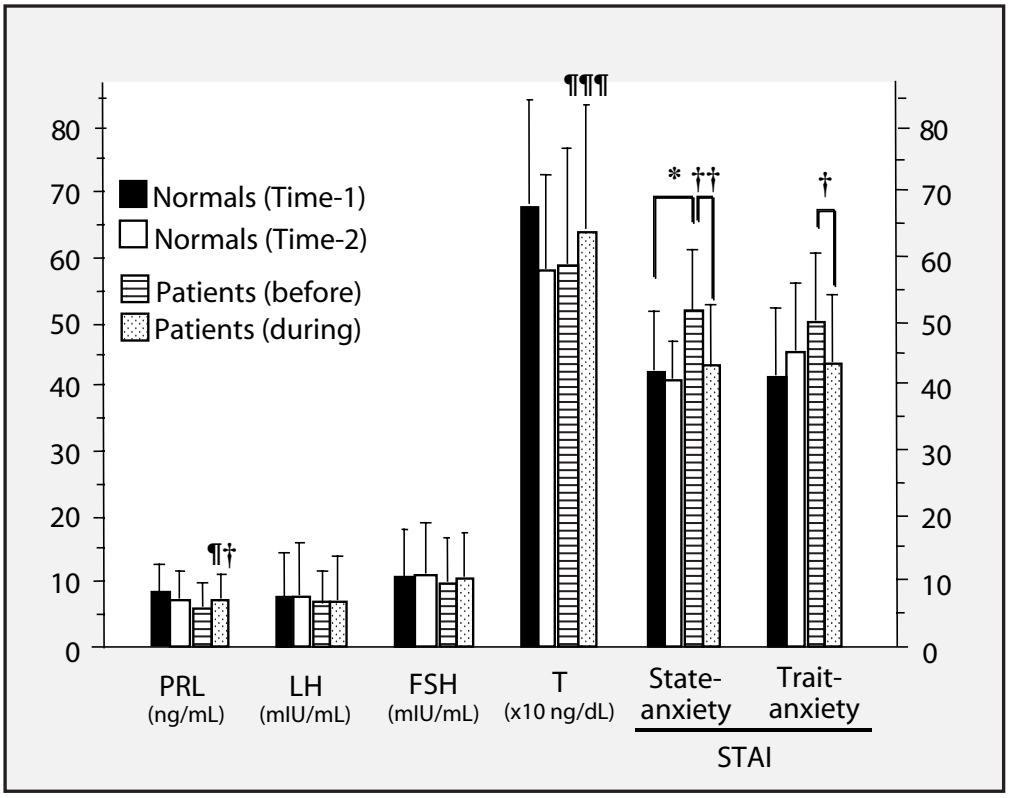

Fig. 1. Effects of Tandospirone on Hypothalamo-Pituitary-Gonadal (HPG) Axis and State-Trait Anxiety Inventory (STAI) Scores. FSH = follicular-stimulating hormone; LH = luteinizing hormone; PRL = prolactin; T = testosterone. *$p < .05$ versus normals by the Mann Whitney's U-test.

†$p < .05$ and ††$p < .01$ versus patients before tandospirone therapy by the Wilcoxon signed rank test. ¶ $p < .05$ and ¶¶¶ $p < .001$ versus normals by analysis of variance with repeated measures (ANOVA).

Serotonergic neurons are also involved in the gonadotropin release, and their effects on gonadotropins are different according to areas [11]. However, the identity of the subtype of 5-HT receptor that mediates the effects is unclear. In rats, 5-HT_{1A} agonist has been reported not to affect plasma LH [13]. Meanwhile, several lines of evidence suggest that 5-HT is involved in the regulation of the development of the testis. In adult rats, 5-HT injection resulted in a significant decrease in basal testosterone, and the effect of 5-HT is thought to be mediated through 5-HT_2 receptors [19]. We, however, cannot prepare clear-cut explanation for our findings of increased T during TDS treatment without increased gonadotropins. The findings could be interpreted as a result of a stimulatory effect of 5-HT_{1A} on T secretion, or peripheral antagonism of T action. Therefore, to clarify the effects of this specific 5-HT receptor subtype on the hypothalamo-pituitary-gonadal (HPG) axis, further evaluation with a larger sample would be needed.

Although anxiety is thought to be related to hyper-5-HTergic activity [20], there was no significant difference in baseline PRL between the patients and normal controls in this study. These results suggest that baseline PRL may not reflect the level of anxiety. Serum PRL levels in humans is suggested to represent a useful tool to evaluate the activity of drugs possessing putative 5-HTergic properties [3]. We hypothesized that the PRL response to TDS may predict outcome for a group of patients treated with TDS. Although the present study has demonstrated efficacy of TDS in the treatment of GAD as it was expected [21], PRL response to TDS seems not to predict clinical response.

A few caveats should be considered in interpreting the findings of this study. We did not study a group of subjects taking placebo, and it is possible that our data might have occurred simply from one blood sampling occasion to another. However, studies with other anxiolytic agents do not reveal a general tendency for PRL, LH, FSH or T levels to increase [22–24].

Conclusions

Our results indicate that (i) PRL response may not provide a clinical predictor; (ii) PRL level may not reflect the level of anxiety, and (iii) 5-HT_{1A} may have stimulatory effects on PRL. However, further, double-blind evaluation with a larger sample would be needed for clarification of effects of 5-HT_{1A} on the HPG axis.

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REFERENCES

1 Kaneda Y, Morimoto T, Fujii A. Gynecomastia induced by treatment with a serotonin-1A agonist, tandospirone. J Psychiatry Neurosci 2001; **26**:152–3.
2 Lowy MT, Meltzer HY. Stimulation of serum cortisol and prolactin secretion in humans by MK-212, a centrally active serotonin agonist. Biol Psychiatry 1988; **23**:818–28.
3 Quattrone A, Tedeschi G, Aguglia U, Scopacasa F, Direnzo GF, Annunziato L. Prolactin secretion in man: a useful tool to evaluate the activity of drugs on central 5-hydroxytryptaminergic neurons. Studies with fenfluramine. Br J Clin Pharmacol 1983; **16**:471–5.
4 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Washington, D.C.: American Psychiatric Association; 1994.
5 Nakazato K, Mizuguchi T. Development and validation of Japanese version of State-Trait Anxiety Inventory: a study with female subjects (in Japanese). Shinshin-Igaku (Japanese Journal of Psychosomatic Medicine) 1982; **22**:107–12.
6 Spielberger CD, Gorsuch RL, Lushene RE. STAI manual. California: Consulting Psychologists Press; 1970.
7 Aono T, Matsumoto S, Kumamoto Y, Sasaki Y, Tamada T, Mizuno M, et al. Multicentric clinical studies on immunoradiometric assays (SPAC-S LH, SPAC-S FSH) for measurement of serum LH & FSH using the pituitary gonadotropin standards (in Japanese). Horumon To Rinsho (Clinical Endocrinology) 1988; **36**:1087–97.
8 Aono T, Kumamoto Y, Sasaki Y, Tamada T, Mizuno M, Takakura K, et al. Multicentric Basic and clinical studies on immunoradiometric assay (SPAC-S Prolactin Kit) for measurement of serum prolactin using WHO standard sample (in Japanese). Horumon To Rinsho (Clinical Endocrinology) 1989; **37**:441–55.
9 Tanaka T, Furuta I, Aihara T, Tanaka S, Sato H, Mizumoto M et al. Determination of total blood testosterone concentration by coated tube method (Coat-A-Count TOTAL TESTOSTERONE), and basic examinations on specificity of anti-testosterone antibody of the kit (in Japanese). Horumon To Rinsho (Clinical Endocrinology) 1989; **37**:961–4.
10 Shimizu H, Hirose A, Tatsuno T, Nakamura M, Katsube J. Pharmacological properties of SM-3997: a new anxioselective anxiolytic candidate. Jpn J Pharmacol 1987; **45**:493–500.
11 Johnson MD, Crowley WR. Acute effects of estradiol on circulating luteinizing hormone and prolactin concentrations and on serotonin turnover in individual brain nuclei. Endocrinol 1983; **113**:1935–41.
12 Mulroney SE, Skudlarek C, Shemer A, Lumpkin MD, Kellar KJ. Tandospirone stimulates prolactin secretion in the rat by an action at serotonin-1A receptors. J Pharmacol Exp Ther 1994; **268**:862–7.
13 Di Sciullo A, Bluet-Pajot MT, Mounier F, Oliver C, Schmidt B, Kordon C. Changes in anterior pituitary hormone levels after serotonin 1A receptor stimulation. Endocrinol 1990; **127**:567–72.

14 Dinan TG, Barry S, Yatham LN, Mobayed M, O'Hanlon M. The reproducibility of the prolactin response to buspirone: relationship to the menstrual cycle. Int Clin Psychopharmacol 1990; **5**:119–23.
15 Meltzer HY, Flemming R, Robertson A. The effect of buspirone on prolactin and growth hormone secretion in man. Arch Gen Psychiatry 1983; **40**:1099–102.
16 Cleare AJ, Forsling M, Bond AJ. Neuroendocrine and hypothermic effects of 5-HT_{1A} receptor stimulation with ipsapirone in healthy men: a placebo-controlled study. Int Clin Psychopharmacol 1998; **13**:23–32.
17 Shimizu H, Tatsuno T, Tanaka H, Hirose A, Araki Y, Nakamura M. Serotonergic mechanisms in anxiolytic effect of tandospirone in the Vogel conflict test. Jpn J Pharmacol 1992; **59**:105–12.
18 Wieland S, Fischette CT, Lucki I. Effect of chronic treatments with tandospirone and imipramine on serotonin-mediated behavioral responses and monoamine receptors. Neuropharmacology 1993; **32**:561–73.
19 Csaba Z, Csernus V, Gerendai I. Intratesticular serotonin affects steroidogenesis in the rat testis. J Neuroendocrinol 1998; **10**:371–6.
20 Iversen SD. 5-HT and anxiety. Neuropharmacology 1984; **23**:1553–60.
21 Feighner JP, Boyer WF. Serotonin-1A anxiolytics: an overview. Psychopathology 1989; **22** Suppl. 1:21–6.
22 D'Armiento M, Bisignani G, Reda G. Effect of bromazepam on growth hormone and prolactin secretion in normal subjects. Horm Res 1981; **15**:224–7.
23 Grandison L. Actions of benzodiazepines on the neuroendocrine system. Neuropharmacology 1983; **22**:1505–10.
24 Cook PS, Notelovitz M, Kalra PS, Kalra SP. Effect of diazepam on serum testosterone and the ventral prostate gland in male rats. Arch Androl 1979; **3**:31–5.