European Neuropsychopharmacology, 4 (1994) 513–516

NEUPSY 00218

Prolactin and TSH responses to TRH and to haloreridol in schizophrenic patients before and after treatment

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(Received 20 September 1993)
(Accepted 14 June 1994)

Key words: Schizophrenia; Haloperidol; TRH; Prolactin; TSH

Summary

The prolactin (PRL) and the TSH responses to thyrotropin releasing hormone (TRH, 0.4 mg i.v.) and to haloperidol (5 mg i.m.) were studied in 11 male schizophrenic patients in a drug-free state and after treatment with haloperidol, 60 mg daily. The PRL responses observed after i.m. haloperidol in the drug-free state, on average 35.4 ng/ml, were abolished after treatment, indicating complete receptor blockade, while the PRL responses to TRH were preserved, although moderately reduced (from 19.4 to 14.8 ng/ml on average). The TSH responses to TRH were unaltered by the treatment (means 8.25 and 7.74 mIU/l). The results show that the TSH and partially the PRL releasing actions of TRH are not mediated via receptors that are effectively blocked by haloperidol.

Introduction

The prolactin (PRL) releasing action of neuroleptics can be satisfactorily explained by the blockade of dopamine receptors localized in both hypothalamus and pituitary (Besses et al., 1975; Meltzer et al., 1981), while thyrotropin releasing hormone (TRH) seems to release PRL mainly by acting directly on the pituitary, through binding with receptors located on the membrane of the lactotroph cells (Diefenbach et al., 1976; Labrie et al., 1976). Less clarity exists regarding the thyrotropin (TSH) releasing property of TRH, which is influenced by a variety of factors, among which dopamine seems to exert an inhibitory effect (Burrow et al., 1977; Delitala et al., 1981; Connell et al., 1985). The dopamine antagonist metoclopramide increases TSH (Healy et al., 1977), but another (peripheral) antagonist, domperidone, does not influence TSH release (Wenzel et al., 1982). After low-dose haloperidol administration for 7 days in borderline patients (Garbutt et al., 1987), and after treatment with neuroleptics of schizophrenic patients (Naber et al., 1980), no changes in the TSH response to TRH were observed. The neuroleptic doses used in the last two studies, though, were rather low to allow assumption of complete receptor blockade.

The complete blockade of dopamine receptors in the pituitary during treatment with neuroleptics in man can be verified by the lack of increases in plasma PRL after administration of an additional 5 mg haloperidol i.m. (Markianos et al., 1991). In this study, we searched for possible changes in the PRL and TSH responses to TRH before and after treatment of schizophrenic patients with relatively high doses of haloperidol, and using the PRL release by i.m. haloperidol as a test for the

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SSDI 0924-977X(94)00098-O

blockade of dopamine receptors in the pituitary.

Patients and methods

Eleven male patients (mean age 38.0, SD = 11.2) were studied. They suffered from schizophrenia according to DSM-IIIR criteria, with a mean duration of illness of 12.5 (SD = 8.2) years. Eight of them were categorized as paranoid, two as undifferentiated, and one as disorganized. They were hospitalized in the Athens University Psychiatric Clinic, Eginition Hospital, during an exacerbation of their illness after discontinuation of their medication. In the hospital, they were kept drug-free for 2 weeks before the testing. The TRH test was first performed by i.v. administration of 0.4 mg TRH, and blood samples were taken at times 0, 20, 30, 40, and 60 min for hormone estimation.

After 2 days, the haloperidol challenge test was performed by administering 5 mg haloperidol i.m., and blood sampling at times 0, 60, 90, and 120 min. The patients were then treated with increasing doses of haloperidol, which reached 60 mg/day within a week. They were kept on that dose for another week, and the tests were repeated in the same manner. Plasma was separated by centrifugation and kept frozen until estimations. PRL was assessed using the radioimmunoassay kits of Serono Diagnostics, Italy (coefficients of variation 2–6%), and TSH using the kits of Medgenix, Belgium (sensitivity 0.025 mIU/l, CV less than 5%).

For the statistical evaluation of the data we used repeated measures analysis of variance (ANOVAR), with state (drug-free and treated) and time as dependent variables, followed by post-hoc (Tukey test) and planned comparisons.

Results

The mean values of the PRL and TSH plasma levels measured during the haloperidol test and the TRH test, in the drug-free state and after 2 weeks treatment with haloperidol, are shown in Table 1. In the drug-free state, the baseline PRL levels were within the normal range (3.1–11.7 ng/ml, mean 7.2, SD = 2.9), indicating an efficient wash-out from previous neuroleptic treatment. Administration of 5 mg haloperidol i.m. caused increases in plasma PRL, ranging from 21.1 to 60.0 ng/ml (mean 35.4, SD = 12.2) (Fig. 1). After 2 weeks treatment with haloperidol, the baseline PRL levels increased to 44.6 on average (SD = 14.7), and additional administration of 5 mg haloperidol i.m. did not cause any further increase in PRL plasma levels, indicating a complete receptor blockade. The difference in the patterns of the PRL release during the haloperidol test between the drug-free state and the state under neuroleptics is expressed by the significance of the interaction state versus time in the repeated measures ANOVA ($F = 67.73$, $P = 0.000$).

The patterns of PRL release by TRH did not show this difference (Fig. 2). In both states, TRH caused substantial increases in the PRL plasma

TABLE 1

PROLACTIN AND TSH PLASMA LEVELS DURING THE HALOPERIDOL TEST (HAL TEST) AND THE TRH TEST IN 11 SCHIZOPHRENIC PATIENTS IN THE DRUG-FREE STATE AND AFTER TREATMENT WITH HALOPERIDOL

Time	HAL test				Time	TRH test			
	PRL		TSH			PRL		TSH	
	drug-free	treated	drug-free	treated		drug-free	treated	drug-free	treated
0	7.18 (2.8)	44.6 (14.7)	1.00 (1.10)	0.67 (0.37)	0	8.6 (5.3)	46.1 (14.2)	1.81 (1.33)	1.74 (1.32)
60	42.1 (13.1)	44.6 (14.4)	0.93 (0.85)	0.56 (0.45)	20	28.0 (11.1)	60.9 (18.9)	9.39 (5.92)	8.96 (4.88)
90	37.8 (9.9)	44.4 (13.7)	0.93 (0.96)	0.53 (0.36)	30	24.3 (9.0)	58.4 (17.2)	9.78 (6.10)	9.39 (5.15)
120	34.2 (9.0)	42.9 (13.9)	0.89 (0.89)	0.52 (0.37)	40	(19.7 (5.7)	52.9 (15.1)	9.15 (6.03)	8.83 (4.95)
					60	15.0 (4.6)	49.1 (13.4)	7.92 (5.57)	7.35 (4.20)
Effect	*F*	*P*	*F*	*P*		*F*	*P*	*F*	*P*
state	8.11	0.01	1.47	0.24		45.13	0.001	0.03	0.85
time	65.32	0.001	2.30	0.09		75.72	0.001	58.41	0.001
state vs time	67.73	0.001	0.10	0.96		1.35	0.26	0.05	0.99

Results are means and SD. Statistical evaluation by two-way ANOVA with repeated measures.

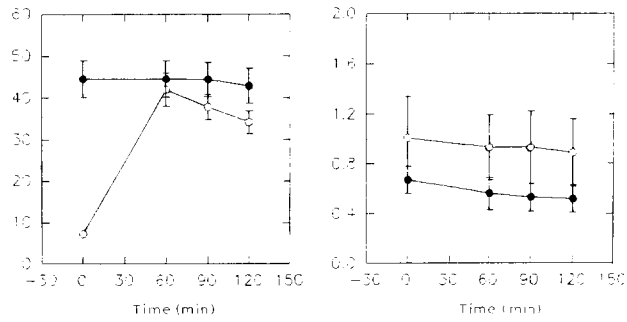

Fig. 1. Prolactin (ng/ml, left) and TSH (mIU/ml, right) plasma levels during the administration of 5 mg haloperidol i.m. in 11 schizophrenic patients, in drug-free state (open circles), and after 2 weeks treatment with haloperidol 60 mg daily. Mean values and SEM.

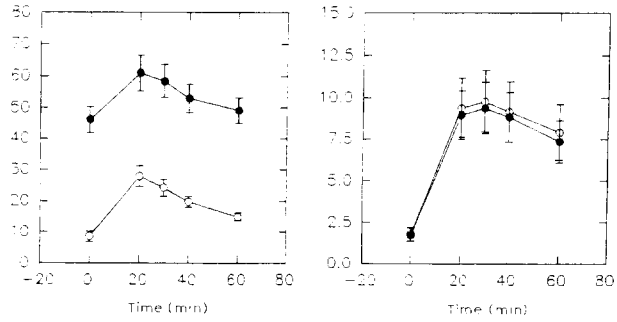

Fig. 2. Prolactin (left) and TSH (right) plasma levels during the TRH test (0.4 mg i.v.). Conditions and symbols as in Fig. 1.

levels, and there was no significant interaction state versus time ($F=1.35$, $P=0.26$). This also proves that the lack of PRL release during the haloperidol test under neuroleptics is not due to a ceiling effect, since the pituitary can release more prolactin by another stimulation.

There were no differences in the patterns of plasma TSH during the haloperidol test in the two states (state versus time $F=0.10$, $P=0.96$). A marginal time effect ($F=2.30$, $P=0.09$) was observed, which will be discussed below.

The TSH patterns during the TRH test in the drug-free state and after treatment were almost identical, and no state or state versus time effect was observed (Table 1). The TSH increases in the drug-free state are preserved after neuroleptic treatment.

The baseline plasma levels of TSH were not significantly influenced by the treatment ($F=0.93$, $P=0.35$). In the drug-free state, the maximal PRL responses to haloperidol (35.4 ng/ml on average) were higher than the maximal PRL responses to TRH (Wilcoxon matched pairs test, $z=2.934$, $P=0.003$). The reduction in PRL response to TRH from an average of 19.4 in the drug-free state to an average of 14.8 ng/ml after treatment does not reach statistical significance.

Discussion

The PRL and TSH responses to TRH were assessed in our patient group in a drug-free state, and after treatment with relatively high doses of haloperidol. The blockade of the receptors that induce release of prolactin by haloperidol was verified after treatment, by the absence of further PRL increases to additional i.m. haloperidol. The main finding of the study is that the PRL responses to TRH are preserved in patients treated with high doses of haloperidol (60 mg/day), and only a moderate, non-significant reduction is observed. This indicates that TRH releases PRL by mechanisms that are independent of actions on receptors that are blocked by haloperidol, such as dopamine receptors in the hypothalamus-pituitary axis. It can be assumed that TRH releases prolactin by a direct action on pituitary receptors, and these receptors are not influenced by neuroleptic treatment.

Blockade of dopamine receptors by haloperidol did not influence the TSH response to TRH. This lack of influence has been reported previously (Naber et al., 1980; Garbutt et al., 1987; Paunovic et al., 1991). In this study, the lack of effect was observed after complete blockade of receptors that participate in the PRL release, as verified by the absence of PRL increases after i.m. haloperidol.

During the haloperidol test, there was a tendency for reduction in TSH, which did not reach significance (Fig. 1 and Table 1, $F=2.30$, $P=0.09$). However, the small changes deserve consideration, since the measurements were done using a highly sensitive assay with low coefficients of variation (sensitivity 0.025 mIU/l, CV below 5%). Since we have observed such reductions in TSH during placebo trials in healthy volunteers (Markianos et al., 1994), we think that the small reduction in TSH observed during the test in both states should not be attributed to the haloperidol treatment.

In summary, we showed that the TSH responses to TRH are unaltered under conditions that i.m. haloperidol does not release PRL, while the PRL responses to TRH are preserved. Other receptors, not blocked by haloperidol, seem to be important for the hormonal releasing mechanisms of TRH,

and they could be, in addition to the direct action of TRH in the pituitary, receptors to which haloperidol shows a low binding affinity, such as D3 dopamine (Sokoloff et al., 1990), or serotonin receptors.

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