The Mini-TRH Test

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ABSTRACT

Thyrotropin-releasing hormone (TRH), at doses lower than those needed to stimulate prolactin secretion directly, can almost completely antagonize dopamine inhibition of prolactin release. In normal men, prolactin increases 15 min following an i. v. bolus of 12.5 µg TRH (the mini-TRH test), but not the maximal prolactin response to TRH or basal prolactin, positively correlated with prolactin response to haloperidol and negatively with 24-h urinary excretion of homovanillic acid (HVA). These results suggest that the mini-TRH test is a better estimate of dopamine inhibition of prolactin release than the maximal prolactin response or basal prolactin level. A recent neuroimaging study suggested that in schizophrenia, there is a widely distributed defect in extrastriatal dopamine release, but the patients were not in the most acute phase of psychosis. The evidence is reviewed that this defect extends to tuberoinfundibular dopamine (TIDA) and which symptoms are associated with the test. In patients with acute nonaffective psychosis, the mini-TRH test positively correlated with nonparanoid delusions and memory dysfunction, indicating decreased dopamine transmission in association with these symptoms. In patients with acute drug-naïve first-episode schizophrenia, the mini-TRH test negatively correlated with negative disorganization symptoms and with basal prolactin. The latter correlation suggests the contribution of factors related to maximal prolactin stimulation by TRH; therefore, an alternative dose of 6.25 µg TRH could be used for the mini-TRH test in first-episode patients, allowed by increased sensitivity of the present prolactin tests. Future studies are needed to investigate whether the mini-TRH test could help in finding the optimal antipsychotic medication.

Introduction

Tuberoinfundibular dopamine (TIDA) is the major prolactin-inhibiting factor in both the rat and in man; it is secreted in the medial basal hypothalamus via the pituitary stalk circulation to stimulate dopamine-2-receptors on pituitary lactotrophs [1]. It was estimated that 40–70 % of the total prolactin-inhibiting activity in the pituitary stalk plasma in the rat could be directly attributed to dopamine [2]. Prolactin short feedback, i. e., prolactin-induced increase in TIDA turnover, started to increase TIDA release after 1 to 3 h to reach significant levels thereafter [3]. In normal men, peak prolactin levels were reported to occur within 15 min after the i. v. administration of thyrotropin-releasing hormone (TRH) and maximal prolactin levels were produced by 25 to 100 µg i. v. as reviewed earlier [4]. A mutual antagonism was reported between TRH and dopamine on prolactin secretion in men [5]. In stalk-sectioned monkeys, an increased prolactin response to submaximal stimulation by TRH was demonstrated [6], suggesting a role of decreased dopamine in the response. TRH, at doses lower than that needed to stimulate prolactin secretion directly, can almost completely antagonize the inhibitory effect of dopamine on pituitary prolactin release in vitro [7]. This finding is the rationale for determining the prolactin increase 15 min following an i. v. bolus of 12.5 µg TRH (the mini-TRH test) to estimate endogenous dopamine transmission avoiding direct effects of non-dopamine prolactin inhibiting or releasing factors. The mini-TRH test was extended to include prolactin response to 200 µg TRH (max-TRH test) 15 min after the mini-TRH test pro-

lactin response [4]. TRH passes the blood-brain barrier poorly [8], and this enables the mini-TRH test to estimate predominantly or entirely hypophyseal effects of TRH on prolactin secretion. In small doses, TRH antagonizes dopamine signal transduction downstream of the membrane site of dopamine receptor at the guanine nucleotide-binding protein level [9]. Therefore, an integrated effect of the level of TIDA and dopamine-2 receptor sensitivity contributes to the mini-TRH test. As far as I know, utilizing a neuroimaging technique or some other hormonal test fails to assess this kind of integrated dopamine transmission, although two tests were recently integrated in an attempt to achieve this [10].

In addition to small doses of TRH, neuroleptics antagonize the effect of dopamine on prolactin release. Because i. v. haloperidol was not approved by the United States Food and Drug Administration, we used intramuscular (i.m.) responses to haloperidol as a safety measure, although the individual release of the drug into the circulation was expected to increase the variability of the response. For a near-maximal prolactin response to haloperidol, i.m. doses of 1 or 1.5 mg were required in normal men [11]. However, these doses consistently produced various degrees of sedation and/or restlessness; 0.5 mg of haloperidol i.m. caused no side effects and produced a prolactin increase of at least 50 % (mean 60 %) of the maximal prolactin increase in 90 min [11]. At that time point, prolactin feedback loops are only starting to become operative. Low dopamine levels reaching the hypophysis would be expected to result in a relative preponderance of haloperidol over endogenous dopamine and produce an enhanced prolactin response to the drug. To avoid the apprehension-stress-induced increases in prolactin release [12] provoked by side effects, prolactin response to 0.5 mg i.m. haloperidol at 90 min (hal-test) was used as a reference estimate of dopamine inhibition of prolactin release. The combined mini-TRH test/max TRH test was done at least one week before or after the hal-test. These tests were done in normal men after 1 h of rest in a quiet laboratory, during weekends, and with no interruptions [13]. We used standard blood extraction between 11 a.m. and 1 p.m. to avoid circadian variability of basal [14] and of TRH-induced prolactin release [15]. The nocturnal rise in pulsatory prolactin is stabilized in about 2 h after awakening [16].

The activity of brain dopaminergic structures may be reflected in urinary dopamine metabolites [17]. In normal women, dexamethasone-induced inhibition of prolactin secretion was not accompanied by blunting of maximal prolactin response to TRH [18], but submaximal stimulation by TRH was not studied. There is a lack of studies investigating the association of endogenous glucocorticoids and dopamine inhibition of prolactin release in normal men. Our cohort of healthy men collected their 24-h urinary samples of 17-ketogenic steroids (u-17-KGS) and homovanillic acid (u-HVA) during weekends under relaxed conditions. Urinary excretions were correlated with prolactin tests. Blood and urine specimens were (with one exception) obtained on separate days to minimize the potentially blurring effects of stress reactions on correlations between prolactin tests and urinary excretions.

We were the first to study submaximal prolactin responses to TRH and correlate mini-TRH test results with key psychotic symptoms, including memory dysfunction in inpatients hospitalized for acute psychosis [19–21]. Only one study examined physical distress-induced prolactin increase in schizophrenia and found it to be significantly greater than, but of the same duration as in control subjects [22]. Having a protein-rich lunch stimulates prolactin release, which occasionally results in mild, short-lasting hyperprolactinemia [23]. We took much care to avoid confounding factors, especially stress. My coworker (P-E B) applied an anesthetic cream on an antebrachial vein on the morning of the mini-TRH test and secured a rest period with no interruption, even by lunch. Immediately thereafter, he performed mini-TRH tests between 10:00 and 11:30. In our study with nonaffective psychosis, the rest period was 90 to 120 min [19]. As prolactin levels in schizophrenia returned from acute stress-induced levels to pretest levels in 30 min [22], we shortened the rest period in our study with drug-naïve first episode schizophrenia to 30 min [20]. In addition to painless blood extraction, rest periods were used for the general calming down of psychotic patients. Because the distribution of prolactin response and basal prolactin were skewed, the obtained data were log-transformed before statistical calculations.

Studies in healthy subjects

The subjects were 28 normal men [4], of whom two refused to participate in the hal-test, and in one, max-TRH was not obtained. Any correlations of ≤ .18 are reported as no correlation. There was a positive correlation between the mini-TRH test and the hal-test, $rp(23) = +0.57$, $p = 0.003$ [4], and a negative correlation between the mini-TRH test and u-HVA, $rp(26) = -0.48$, $p = 0.010$ even after controlling for 24-h urinary vanillylmandelic acid excretion to decrease the effect of HVA derived from the sympathetic nervous system, $rp(25) = -0.44$, $p = 0.022$ [13]. On the other hand, the max-TRH test did not significantly correlate with the hal-test $rp(23) = +0.29$, $p = 0.16$. [4] and there was no correlation between the max-TRH test and u-HVA [21]. The results suggest that a dose of 12.5 µg TRH was small enough to antagonize TIDA in normal man and that the mini-TRH test is positively associated with dopamine receptor-mediated inhibition of prolactin secretion as well as negatively associated with widespread dopamine turnover/release, which could extend to TIDA as well.

As opposed to the mini-TRH test, basal prolactin did not correlate with the hal-test [4], confirming previous findings [11]. Neither did basal prolactin correlate with u-HVA [13]. The results suggest that the mini-TRH test may be a better estimate than basal prolactin of dopamine inhibition of prolactin release. No correlations were found between the mini-TRH test and basal prolactin obtained either in the TRH test or in the hal-test [24], further emphasizing the difference in these tests.

A significant negative correlation was detected of u-17-KGS with the mini-TRH test, $rp(23) = -0.64$, $p < 0.001$, but with the hal-test it was marginal, $rp(23) = -0.39$, $p = 0.054$ [24]. There were no correlations of u-17KGS with the max-TRH test or with basal prolactin [24]. The absence of any correlation between endogenous cortisol levels and basal prolactin was also reported in women [25]. Glucocorticoids may amplify various dopamine-mediated processes [24]. Indeed, in 26 men with both the mini-TRH test and hal-test performed, controlling for u-17-KGS reduced the correlation between the mini-TRH test and u-HVA from − 0.53 to − 0.16 and between the hal-test and u-HVA from − 0.25 to + 0.04 [26]. Preincubation with glucocorticoids decreased prolactin response to submaximal stimulation by TRH in the rat hypophysis [27], in line with our re-

sults. The widespread origin of urinary HVA raises the possibility that glucocorticoids might integrate TIDA release and dopamine release in other dopamine structures sensitive to them [26].

The max-TRH test significantly correlated with basal prolactin rp(23) = + 0.52, p = 0.008 [24]; an association also found in depressive women [28]. However, no correlation was detected between the max-TRH test with basal prolactin obtained in the hal-test [24], suggesting that the max-TRH test may be associated with fluctuations in basal prolactin. These fluctuations may be induced by non-dopamine factors because the results of the hal-test and u-HVA did not significantly correlate with the max-TRH test or with basal prolactin. Absent of correlation was also reported between cerebrospinal fluid (CSF) HVA and basal prolactin level [29].

Prolactin secretory bursts occur every 42 to 65 min. Their duration is about 24 min, independent of prolactin levels and sex [30]. The prolactin level is determined at least as much by secretory pulses as by the time-invariant mode of prolactin secretion [16]. We determined in 26 normal men under unstressed conditions; two basal prolactin levels were drawn with an interval of at least one week. The correlation between the two prolactin determinations was only + 0.21, although the mean prolactin level was almost exactly the same in the two prolactin tests [4]. In a strictly controlled study in normal women, a straightforward correlation between the logarithm of two prolactin levels one year apart was + 0.40 in 60 premenopausal and + 0.18 in 47 postmenopausal subjects [31]. In the former 13 samples and in the latter 40 samples, the reliability of a single prolactin determination was required to be raised to a target level near 0.90 [31]. These studies suggest that the widely held view that basal prolactin could be used as a trait variable to estimate dopamine-mediated tonic inhibition of prolactin release, even in unstressed subjects, is surprisingly poorly grounded.

Studies in schizophrenia disorders

CSF HVA is an estimate of widespread dopamine release/turnover. In one meta-analysis, it was found to decrease in schizophrenia [32]. In post-mortem samples of psychiatric patients and controls, CSF HVA correlated with prefrontal HVA content but not with striatal HVA [33]. A widespread defect in amphetamine-induced dopamine release, indicating a reduced capacity for dopamine release, was discovered in the prefrontal cortex and most extrastriatal regions in 20 drug-free patients with schizophrenia [34]. The positive symptom mean score was 15.1 on the Positive and Negative Symptom Scale (PANSS) [34], which is very similar to a score of 14.9 reported in 1538 patients with schizophrenia stabilized with drugs [35], suggesting that the defect in extrastriatal dopamine release was not studied in the most acute phase of the disease. Even in the acute phase of psychosis, scores on the mini-TRH test were about two times higher in two populations of acutely psychotic men than in normal men [20]. In schizophrenic exacerbation and in control subjects, no difference was found in dopamine-agonist-induced decrease in serum prolactin [36]. These results suggest that decreased TIDA release could not be fully compensated by increased sensitivity of dopamine receptors [26], suggesting a predominant role for TIDA release in determining the mini-TRH test. In 20 patients with nonaffective psychoses after controlling for sex, age, and drug use, the mini-TRH test significantly correlated with the total rating for the Comprehensive Psychiatric Rating Scale (CPRS) psychosis subscale rp(15) = + 0.71, p = 0.001 [19]. Because the mini-TRH test reflects widespread dopamine release, the above result is consistent with a negative correlation between CSF HVA and key positive symptoms in schizophrenia [37, 38]. In every psychotic patient studied by us, the basal prolactin level was below the hyperprolactinemic level [19, 20], indicating that local anesthesia (applied by the same investigator who performed the mini-TRH test) protected from the most stress-induced increase of prolactin. I suggest that this routine is followed in future studies.

The correlation between the mini-TRH test and the CPRS psychosis subscale score was mostly driven by the correlation between the test and the score for other delusions, rp(15) = + 0.73, p < 0.001 [19]. This item excludes paranoid delusions and many other delusional states not specific to schizophrenia [19]. Negative correlations were reported between nonparanoid delusions and 24-h urinary excretion of dopamine and its metabolites in chronic schizophrenia [17]. Because the mini-TRH test reflects urinary excretion of HVA, our results may extend the association of decreased dopamine release and nonparanoid delusions to newly admitted patients in the acute phase of psychosis [19]. The mini-TRH test marginally correlated with non-hallucinatory first-rank symptoms, rp(15) = + 0.51, p = 0.036 [19]. Although such symptoms are heterogenous in nature [39], a negative correlation was reported between the number of first-rank symptoms and CSF HVA in acute schizophrenia [40], which is consistent with our results. As far as I know, there are no studies reporting positive correlations between urinary or CSF HVA and nonparanoid delusions or first-rank symptoms.

We found no significant correlation between the mini-TRH test and scores for ideas of persecution rp(15) = + 0.05 [19] or hallucinations rp(15) = + 0.36, p = 0.15 [19]. In an independent sample of acutely psychotic patients with first-episode schizophrenia, there was no correlation between the test and PANSS hallucinatory behavior, rp(11) = − 0.12 [26]. Hallucinations and persecutory delusions have been suspected to represent unspecific [41] and emotional [42] reactions in psychosis. In the setting of decreased prefrontal activity, these symptoms have been associated with increased mesotemporal and ventral striatal activity in response to threatening or even seemingly neutral stimuli in schizophrenia [43]. The lack of correlations between these symptoms and the mini-TRH test suggests that the test may not be sensitive in reflecting the activity of the above structures. In the acute phase of schizophrenic psychosis, amphetamine-induced striatal dopamine release was increased, and it was suspected that activation of preexisting dysfunctional circuits was involved [44]. On the other hand, reduced activation of several frontal and parietal areas in schizophrenia was found during probabilistic reasoning [45], which might not only trigger but create new delusions. Future studies are required to find out if probabilistic reasoning is reflected in the mini-TRH test. We discovered no significant associations between basal prolactin and positive symptoms. Mixed results in associating basal prolactin and individual positive symptoms may be explained by differences in patient populations and the measures used to assess symptoms [46] but also by heterogeneous variables that affect prolactin levels in addition to tonic dopamine inhibition [1].

Poor performance on everyday memory was reported in schizophrenia [47]. Among our patients with nonaffective psychosis [19], 8/20 scored memory dysfunction on an estimate of everyday memory dysfunction, the CPRS item failing memory [21]. After controlling for age, sex, and drug use, the score for failing memory correlated with the mini-TRH test, rp(15) = + 0.67, p = 0.003 [21], associating increasing memory dysfunction with decreasing hypothalamic-pituitary dopamine transmission. There was no correlation between basal prolactin level and score for failing memory [21].

In 19 patients with acutely psychotic drug-naïve first-episode schizophrenia, negative correlations were detected between the mini-TRH test and the disorganization symptoms in the Scale for the Assessment of Negative Symptoms (SANS) poverty of content of speech rp(17) = − 0.55, p = 0.014, and objective inattention rp(17) = − 0.52, p = 0.022 [20]. There were no significant correlations between the rest of the SANS symptoms (actual negative symptoms) and the mini-TRH test, suggesting that they are not reflected in TIDA during the acute stage of psychosis. No significant correlations were detected between basal prolactin and any SANS symptoms [20]. Differences in correlations of the mini-TRH test with CPRS subscale score and the test with PANSS disorganization symptoms in 13 available patients with first-episode schizophrenia utilizing the Wallwork model [48] showed significant separation of CPRS psychotic subscale from the difficulty of abstract thinking, z = 2.89, p = 0.004, and poor attention, z = 2.97, p = 0.003, but no significant separation from conceptual disorganization, z = 1.68, p = 0.093 [49]. The latter is the only PANSS disorganization symptom that rates positive formal thought disorder [50].

In patients with first-episode schizophrenia, the mini-TRH test significantly correlated with basal prolactin level, rp(17) = + 0.61, p = 0.006 [20]. No such correlation was present in patients with nonaffective psychosis [19]. In normal subjects, the max-TRH test significantly correlated with basal prolactin. These findings suggest a shift of the TRH-induced prolactin dose-response curve to the left in patients with first-episode schizophrenia. The same kind of shift was observed in pituitary stalk-sectioned monkeys with a smaller dose of TRH than in normal monkeys needed to induce a prolactin response [6]. To reduce the effects of maximal prolactin responses, a 6.25 µg dose could be used in the TRH test, especially in first-episode patients. This is allowed by the increased sensitivity of the present prolactin tests.

It is unlikely that TIDA is responsible for symptoms of schizophrenia. A more plausible explanation for our findings is a synchronized action of dopamine-mediated inhibition of prolactin release and the activity of cortical dopamine structures involved in psychotic symptoms. The thalamus is able to mediate communication between various cortical areas [51]. In schizophrenia, reduced thalamic connections with frontal regions were associated with PANSS delusions [52], and increased connections with parietal regions in association with PANSS difficulty in abstract thinking [52] were found. Cerebellum-thalamic-cortical hyperconnectivity was associated with state-independent disorganized thought and speech [53]. In line with the above findings, the mini-TRH test revealed decreased dopamine transmission in association with PANSS delusions and increased dopamine transmission with SANS and PANSS negative disorganization symptoms. As far as I know, the association between nonparanoid delusions and functional thalamic connections has not been investigated as yet.

A hypoactive extrastriatal dopaminergic state may not be confined to schizophrenia-related disorders. In unipolar depression, significantly blunted amphetamine-induced activation in prefrontal and frontal regions was reported [54]. A recent meta-analysis revealed that only CSF HVA levels but not CSF 5-HIAA or MHPG levels were decreased in depressive disorder [55]. The mini-TRH test results suggest that a hypodopaminergic state in depression extends to the hypothalamic-pituitary dopamine system [20]. Antipsychotic drugs increase prefrontal cortical and striatal dopamine and noradrenaline release [56]. In an animal model depression, the mildly stressed rats, acute repeated quetiapine at antidepressant doses increased ventral tegmental area dopamine neuron population activity to normal levels [57]. In future studies, the mini-TRH test could be correlated with antidepressant responses to antipsychotic medications.

Conclusion

Studies in acutely psychotic subjects suggest that the mini-TRH test reflects extrastriatal rather than striatal dopamine transmission and decreased dopamine release, which cannot be fully compensated by increased dopamine receptor sensitivity. As opposed to patients with paranoid delusions or hallucinations, in patients with memory dysfunction or nonparanoid delusional symptoms more specific to schizophrenia, the mini-TRH test results showed the lowest dopamine transmission. Such patients may not fully benefit from drugs with strong dopamine antagonism, and future studies are needed to find out whether the mini-TRH test could help in choosing the optimal antipsychotic medication. In patients with negative disorganization symptoms, the mini-TRH test results approached the level found in normal subjects, but even these symptoms might not respond well to antipsychotic drugs because they may be more or less state-independent.

Conflict of Interest

The authors declare that they have no conflict of interest.

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