Schizophrenia Research 215 (2020) 449–450

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Letter to the Editor

Separation of positive and disorganization symptoms by prolactin response to 12.5 μg intravenous TRH

Keywords:
Prolactin
TRH
Dopamine
Schizophrenia
Positive symptoms
Disorganization

Dear Editor

TRH, at doses lower than those needed to stimulate prolactin release directly, can almost completely antagonize the inhibitory effect of dopamine on prolactin release in vitro (Hill-Samli and McLeod, 1974). In addition to being influenced by dopamine receptor sensitivity, stimulation of prolactin release by TRH is determined by dopamine release in the pituitary (Kineman et al., 1996). In man plasma prolactin increase at 15 minutes following administration of 12.5 μg intravenous (i.v.) TRH (Δprol) has been reported to negatively correlate with 24-h urinary excretion of homovanillic acid (HVA) (Spoov and Karonen, 1987). Serum prolactin response to apomorhine, a dopamine agonist, has been reported to be unrelated to ratings of psychosis in schizophrenia (Meltzer et al., 1984). The finding of associations between psychotic symptoms and Δprolactin may be related to dopamine release rather than to dopamine D2 receptor sensitivity. In 20 patients with non-affective psychosis, after the linear effects of age, sex and drug use were removed from the correlations, a positive correlation ($r = +0.71$) has been reported between Δprol and ratings for the Comprehensive Psychopathological Rating Scale (CPRS) psychosis subscale (Spoov et al., 1991). Of the items on the subscale only ratings for other delusions (representing non-paranoid, non-grandiose delusions) and disrupted thoughts (comprised of thought blocking, insertion or withdrawal or listened to or broadcast) significantly correlated with Δprol. On the other hand, negative correlations between Δprol and ratings for inattention ($r = -0.52$) and poverty of content of speech ($r = -0.55$) on the Scale for the Assessment of Negative Symptoms (SANS) have been reported in 19 acute drug-naïve patients with first episode schizophrenia (Spoov et al., 2010). These symptoms have been associated with disorganization symptoms of schizophrenia. Separation by TIDA activity of positive symptoms from other aspects of disorganization has not been studied. Wallwork et al., (2012) studied how many times each Positive and Negative Symptom Scale (PANSS) symptom loaded on each of five factors in non-affective psychosis. Their final model, requiring a strongest loading in at least 24 out of 29 study samples, resulted in a dimension with three disorganization symptoms: poor attention, difficulty in abstract thinking and conceptual disorganization.

We compared differences in correlations of the rating for the CPRS psychosis subscale and Δprol in 20 subjects with nonaffective psychosis (Spoov et al., 1991) and of the ratings for PANSS disorganization symptoms and Δprol in a subgroup of 13 patients with first episode schizophrenia from our previous study (Spoov et al., 2010). In these patients PANSS was rated before treatment by a psychiatrist trained on the scale (P-E B). In both populations of patients on the morning of the prolactin test, an anesthetic cream was applied on an antebrachial vein and after at least 30 min rest the rise in plasma prolactin was determined after a bolus of 12.5 μg TRH. Spearman's rank correlation was used to calculate correlations of Δprol with the ratings for the PANSS disorganization symptoms, see Table 1.

The probability for the differences between the correlations of Δprol and the CPRS rating (+0.71) and of Δprol and difficulty in abstract thinking (−0.30) and poor attention (−0.33) reached statistical significance ($p < 0.005$), but the corresponding probability with conceptual disorganization (+0.19) did not ($p > 0.05$).

As far as we know the present study is the first to investigate separation of positive symptoms and PANSS disorganization symptoms by dopamine. Negative correlations have been reported between first rank symptoms and cerebrospinal fluid HVA in acute schizophrenia (Post et al., 1975) and between nonparanoid delusions and urinary excretion of dopamine and its metabolites in chronic schizophrenia (Karoum et al., 1987). We are not aware of studies reporting positive correlations between the above HVA measures and the above symptoms. On the other hand, positive correlations between disorganized but no other schizotypal traits and dopamine release in several cortical and subcortical regions have been reported in healthy volunteers (Woodward et al., 2011). Our results suggest that conceptual disorganization may not contribute to the separation by Δprol of the CPRS positive psychosis subscale and PANSS disorganization symptoms. It has been maintained to be the only PANSS disorganization symptom that rates positive formal thought disorder (White et al., 1997).

In other studies, TIDA has been estimated by an i.v. haloperidol test, in which immediately after the baseline prolactin sample, haloperidol 0.5mg is injected i.v. and five more samples of blood are taken at 45 min intervals. The haloperidol response is defined as the area under the curve corrected for baseline prolactin (Keks et al., 1995). Blunted prolactin responses to haloperidol have been reported in Kraepelinian, but not in Schneiderian patients (Keks et al., 1992), suggesting that also the haloperidol test separates Schneiderian symptoms from the disorganization (and negative)

https://doi.org/10.1016/j.schres.2019.09.017

Table 1
Spearman's rank correlations between plasma prolactin response to 12.5 μg intravenous TRH (Δprol, μg/l) and the PANSS disorganization symptoms as presented by Wallwork et al. (2012).

patient	Δprol	P2	N5	G11
1	20.6	4	3	1
2	45.5	4	6	4
3	16.8	6	6	6
4	5.4	5	6	5
5	28.5	5	5	4
6[m]	7.2	4	6	4
7	20.0	5	6	5
8	31.8	5	6	3
9	15.1	4	6	4
10	27.1	6	3	4
11	20.5	5	6	4
12	31.4	5	1	4
13[m]	16.2	1	3	2
r		+0.19	−0.30	−0.33

Rating of no symptom = 1, maximal rating = 7.
P2 = conceptual disorganization, N5 = difficulty in abstract thinking, G11 = poor attention.
[m] = male.
r = Spearman's rank correlation between Δprol and symptoms.

symptoms described by Kraepelin. The lack of correlation between the haloperidol test response and conceptual disorganization (Keks et al., 1995) is consistent with our results. However, blunted responses in the haloperidol test in male subjects are in contrast with the finding of the mean Δprol being about twice as high in male patients with schizophrenia as compared to the mean Δprol in normal male subjects (Spoov et al., 2010). An increase in TIDA release has been reported to begin after one to 3 h of increase in prolactin levels and to increase significantly thereupon (Hentschel et al., 2000). The discrepancy between the tests might be explained by an enhanced activation in schizophrenia of prolactin induced TIDA release in the time frame of the haloperidol test on top of reduced basal TIDA. As opposed to the evidence of excessive dopamine release in the associative striatum, a widespread defect in dopamine release involving most extra-striatal regions (cortical and midbrain) has been reported in drug-free schizophrenia (Slifstein et al., 2015). In five male patients with newly diagnosed untreated Parkinson's disease the mean Δprol did not exceed the mean in 25 normal male subjects (Spoov and Laaksovirta, unpublished observations) suggesting that Δprol may not reflect the striatal defect in dopamine in that disorder and it may not reflect overall striatal activity.

Acknowledgement

The expert advice of Prof. S Sarna in helping with the statistics is kindly acknowledged.

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Johan Spoov*
Department of Clinical Chemistry, University of Helsinki, Haartmaninkatu 8, P.O. Box 63, 00014, Helsinki, Finland

Per-Erik Bredbacka
Päijät-Häme Central Hospital, Keskussairaalakatu 7, 15850, Lahti, Finland
E-mail address: bredbacka@doctors.org.uk.

Ulf-Håkan Stenman
Department of Clinical Chemistry, University of Helsinki, Haartmaninkatu 8, P.O. Box 63, 00014, Helsinki, Finland
E-mail address: ulf-hakan.stenman@helsinki.fi.

* Corresponding author.
E-mail address: jspoov@gmail.com (J. Spoov).

5 September 2019
Available online 26 October 2019