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ORIGINAL PAPER

Dual-isotope SPECT imaging of striatal dopamine: a comparative study between never-treated and haloperidol-treated first-episode schizophrenic patients

G. J. E. Schmitt · S. Dresel · T. Frodl · C. la Fougère · R. Boerner · K. Hahn · H.-J. Möller · E. M. Meisenzahl

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Abstract The aim of this dual-isotope SPECT imaging study was to evaluate striatal dopamine transporter (DAT) and D2 receptor availability in first-episode never-treated and haloperidol-treated schizophrenic patients and whether the availability is associated with psychopathology. Twenty-four inpatients with a first acute schizophrenic episode were enrolled in the study; 12 of these patients were treated with haloperidol for 2 weeks before dual-isotope SPECT was performed, whereas the other 12 patients underwent the SPECT evaluation directly after enrollment. Twelve healthy control persons were also recruited and evaluated with the dual-isotope SPECT protocol. Psychopathology was assessed by the Positive and Negative Syndrome Scale and other scales. D2-radioligand binding did not differ between drug-naïve patients and the control group but was significantly lower in the haloperidol-treated group. DAT availability was also significantly lower in the haloperidol patients than in the other two groups and differed significantly between drug-naïve, positive-syndrome-type patients and healthy controls. The data obtained with the new dual-isotope SPECT technique reveal a direct effect of haloperidol at the D2 and DAT receptor level.

Keywords Striatal D2 receptor binding · Striatal dopamine autoreceptor (DAT) binding · SPET imaging · Schizophrenia · Haloperidol

G. J. E. Schmitt · T. Frodl · R. Boerner · H.-J. Möller · E. M. Meisenzahl (✉)
Department of Psychiatry and Psychotherapy, Ludwig Maximilians University, Nussbaumstrasse 7, 80336 Munich, Germany
e-mail: Eva.Meisenzahl@med.uni-muenchen.de

S. Dresel · C. la Fougère · K. Hahn
Department of Nuclear Medicine, Ludwig Maximilians University, Munich, Germany

Introduction

To some extent, research in schizophrenia has evolved in parallel to the development of in vivo imaging techniques. For example, in vivo imaging results strengthened the hypothesis about illness-phase-dependent changes in striatal dopamine metabolism [6, 7, 24]. Additionally, imaging can support efforts to identify neurobiological correlates of psychopathological symptoms. Different groups have succeeded in identifying correlations between "hallucinatory behaviour" and other relevant symptoms of the acute psychotic syndrome and changes in brain activity, especially in the striatum [8, 34, 35, 40]. In this context, the large number of striatal D_2 receptor imaging studies assessing receptor occupancy by antipsychotics is also noteworthy. In a very concise paper, Marc Laruelle argued that SPECT and PET receptor imaging can be understood as competition experiments between the endogenous ligand and the radioligand or—in antipsychotic-treated patients—the antipsychotic [23]. In other words, radioligand binding to the dopamine transporter (DAT) or dopamine D_2 receptors reflects the occupancy of these structures by endogenous dopamine or the antipsychotics themselves. In this model, differences in radioligand binding between patient and healthy control groups are a result of changes in endogenous dopamine levels or in density or function of the binding structures or a combination of both.

The striatal dopaminergic synapse is one of the key structures associated with a supposed hyperdopaminergic state accompanying the acute psychotic syndrome in schizophrenia [6]. Until recently, only one side of the synapse could be assessed at a time. Dual-isotope imaging of the pre- and postsynaptic sides with specific radioligands opens a new methodological approach to addressing these questions in humans in vivo. It depends on the ability to

use two different radioisotopes with similar but not identical decay characteristics. The cocaine analogues of the tropane family are presynaptic dopamine transporter ligand candidates that can be labelled with technetium-99 m for use in SPECT. Kung and colleagues developed the radiopharmaceutical [99 mTc]TRODAT-1 [18, 20] which, when applied simultaneously with the well-known dopamine D_2 receptor ligand [123I]IBZM, represents a new methodological approach to assessing striatal dopamine pre- and postsynaptic structures.

Dual-isotope SPECT studies of the DAT (with [99 mTc]TRODAT-1) and dopamine D_2 receptor (with [123 I]IBZM) simultaneously have been performed not only in animals—in baboons [13] and monkeys [25]—but also in first-episode, drug-naïve schizophrenic patients. We reported preliminary analyses of a dual-isotope SPECT study in such patients, which demonstrated the feasibility of the approach [33]. The study found no significant differences in specific binding of TRODAT-1 or IBZM between the patients ($n = 9$) and the control group. Our findings were confirmed by Yang and colleagues, who performed a dual-isotope study in eleven first-episode schizophrenic patients and twelve healthy controls [43]. Both our study [33] and that of Yang [43] found a positive correlation between DAT and D_2 availability and the specific radioligands in patients but not in controls. Additionally, in a larger sample of drug-naïve, first-episode schizophrenic patients, we could demonstrate that a subgroup of patients with a predominantly positive syndrome has a significantly higher availability of the presynaptic DAT [35]. In this patient group, we also found an inverse correlation between the symptoms "delusions," "conceptual disorganization" and "hallucinatory behaviour" on the one hand and DAT and D_2 receptor availability on the other.

The correlations between the presynaptic DAT and postsynaptic D_2 receptor in schizophrenic patients, and between striatal dopamine and psychopathology, can be interpreted as a cause or a consequence of the illness or a compensatory reaction to it [3]. To help understand these results, it is of great interest to assess the effect of treatment with neuroleptic medication on the dopaminergic synapse, and this is the first study to use a dual-isotope approach to do so.

Aim of the study

A dual-isotope SPECT technique that simultaneously assessed the pre- and postsynaptic part of the striatal dopaminergic synapse was used to analyse DAT availability—through binding of [99 m Tc]TRODAT-1—and D_2 receptor availability—through binding of [123 I]IBZM—in patients with a first episode of schizophrenia and in healthy controls. To evaluate differences in the striatal dopamine synapse in the untreated and antipsychotic-treated state, a group of drug-naïve patients ($n = 12$) was compared with a group ($n = 12$) receiving haloperidol in monotherapy. The psychopharmacological agent haloperidol was chosen because it is a well-known antipsychotic known to have effects at the striatal dopamine D_2 receptor. On the day of SPECT, psychopathology was assessed with the Clinical Global Impression (CGI), Global Assessment of Functioning (GAF) and Positive and Negative Syndrome Scale (PANSS) [17]. Scores were examined for a possible correlation between the extent of symptoms and DAT and D_2 receptor availability.

Experimental procedures

The study was approved by the ethics committee of the Ludwig Maximilian University of Munich, Germany, and the local radiation protection authorities and performed in accordance with the Declaration of Helsinki (revised version from 2000). Written informed consent was obtained from all subjects.

Patient and healthy groups

Twenty-four inpatients with a first acute exacerbation of paranoid schizophrenia diagnosed according to DSM-IV/ICD-10 criteria and twelve age- and gender-matched healthy controls (HC) were included in the study [35].

The patients were divided into two groups: a drug-naïve group (NT-SZ; $n = 12$), who underwent dual-isotope SPECT immediately after study entry, and a treatment group (T-SZ, $n = 12$), who received haloperidol for a 14-day steady-state period before dual-isotope SPECT was performed. The haloperidol dose regimen was adapted to clinical needs within the recommended dose range up to 20 mg/day. Patients in the two groups were matched with respect to age, gender, socioeconomic state, illness duration and intensity of psychopathological symptoms. Concomitant medication was restricted to lorazepam, zopiclon and biperiden and given only when necessary.

Assessment of psychopathology

In the T-SZ group, baseline ratings were performed at study entry; the CGI and GAF were assessed in all patients ($n = 12$), but the PANSS in only eight. On the morning of the dual-isotope SPECT, two psychiatrists assessed psychopathology in all patients of all three groups with the GAF, CGI and PANSS.

To define the predominant psychopathological syndrome type, we calculated the composite score, as described by Kay and colleagues [17], for each patient, i.e. the

difference between the PANSS positive and negative subscale sum scores. Patients with a difference greater than zero were defined as being of the positive syndrome type and the others as being of the negative syndrome type.

SPECT procedure

[99 m Tc]TRODAT-1 was prepared as described elsewhere [20, 21, 26, 27], and [123 I]IBZM [19] was purchased commercially. The kinetics of TRODAT-1 binding had been analysed in earlier experiments [13, 21]. The SPECT protocol had been established previously [13, 21, 33] and was performed as follows: because of the kinetics of the two radiotracers, 740 MBq [99 m Tc]TRODAT-1 was administered first as a slow intravenous bolus1 injection; 60 min later, 185 MBq [123 I]IBZM were administered also as a slow bolus intravenous injection. After the injections, patients were kept in a quiet environment. The acquisition of SPECT data commenced 3 h after administration of TRODAT-1 (and thus 2 h after IBZM administration). SPECT was performed on a triple-headed gamma camera (Picker, Cleveland, Ohio) equipped with high-resolution fan beam collimators. The acquisition parameters included a 15% energy window centred on 140 keV for registration of 99 m-technetium decay, a 10% energy window centred on 159 keV for 123-iodine decay and a rotational radius of 13 cm or less. For each energy window, 10 scans of 5-min duration were recorded simultaneously. The acquisition lasted 50 min in total.

After data acquisition, all raw data frames were checked manually for movement artefacts. If head rotation was detectable in a frame, the frame was not used for further data processing. The projection images were reconstructed by filtered back projection and filtered by a low pass filter. Chang's first-order method was used for uniform attenuation correction. Images were uniformly resliced by drawing a line connecting the anterior-most aspect of the frontal pole to the posterior-most aspect of the occipital pole, which approximates the line connecting anterior and posterior commissures (AC-PC line).

To assess specific tracer uptake in the striatum, the region of interest (ROI) technique was used for both radioligands: mean specific activity in the basal ganglia regions was calculated by subtracting the mean counts per pixel in the background region (BKG) from the basal ganglia region (STR) and dividing the results by the mean counts per pixel in the background [(STR-BKG)/BKG]. In accordance with our established protocol for each of the ligands [10–12, 21, 28, 29, 32–38], the frontal cortex was defined as the background region for specific IBZM binding and the cerebellar cortex as the background region for specific TRODAT-1 binding. Each patient's data were evaluated in the two consecutive transverse slices showing the highest tracer accumulation in the basal ganglia, and the arithmetic mean of these two slices was calculated. Templates were used to define the striatal ROIs. The size and shape of the templates were established and optimized using the data from the control group. Simultaneous data acquisition allowed identical ROIs to be used to assess the specific binding of the two radioligands. The predefined templates were adjusted to fit individuals by using each individual's MRI data, so that only minor corrections for the individual shape and size were necessary. This procedure enhanced intraobserver reliability. The operator was blind to the clinical data.

Measurements in controls ($n = 12$) were used to ensure that the approach yielded comparable data. Mean binding in the control group was defined as normal binding. The 100% value for 123I-IBZM specific binding was 0.82; for [99 m Tc]TRODAT-1, 1.08.

Statistics

SPSS version 14.0 was used for statistical analysis of the SPECT and sociodemographic data. Student's t test was used to compare two independent groups, i.e. patients versus controls. Equality of variances was tested with Levene's test of equality of variances. ANOVA was used to compare the mean values of the three groups, i.e. drug-naïve patients, haloperidol-treated patients and healthy controls. Continuous values were correlated by using Pearson correlation coefficients, and Spearman's rho was calculated for categorical data. Differences were considered to be significant when $P < 0.05$.

Results

Sociodemographic data

Patients and HC were comparable with respect to age and gender (ANOVA for age: df 2, $F = 1.351$, $P = 0.273$). The HC group ($n = 12$) consisted of nine men and three women. Each of the patient groups (NT-SZ and T-SZ) consisted of 12 patients—ten men and two women. The patient groups were also comparable with respect to the assessed socioeconomic variables, i.e. height, weight, daily nicotine and alcohol consumption, consumption of illegal drugs, education level, family history of psychiatric disorders, and duration of illness (see Table 1).

Psychopathology

At baseline, psychopathology—as assessed by the GAF, CGI and PANSS—was similar in the NT-SZ and T-SZ groups.

Table 1 Sociodemographic variables of the drug-naïve (NT-SZ) and treated (T-SZ) patients

Socioeconomic variables	NT-SZ ($n = 12$)	T-SZ ($n = 12$)	Student's t test T, P value
Age (year)	27.57 ± 5.34	26.41 ± 5.29	0.533; 0.599
Gender (m/f)	10/2	10/2	nd
Handedness	12 Right handed	12 Right handed	nd
Weight (kg)	71.93 ± 11.75	76.16 ± 9.55	−0.738; 0.468
Schooling			
Grammer school students	0	2	nd
2nd School	4	0	nd
2nd School certificate	4	4	nd
GQ University	4	6	nd
Duration of illness (month)	23.75 ± 26.42		0.377; 0.710
Cigarette consumption (cig/d)	9.17 ± 13.29		0.166: 0.629
Alcohol consumption (g alcohol/d)	13.15 ± 19.62		0.489; 0.629
Use of illegal drugs	8 Never; 2 occasionally, 2 regularly cannabis	8 Never; 2 occasionally, 2 regularly cannabis	Nd

nd Not done

Table 2 Psychopathology of the drug-naïve (NT-SZ) and treated (T-SZ) patients at baseline

Psychopathological ratings at baseline	NT-SZ ($n = 12$)	T-SZ ($n = 12$)	Student's t test, T, P value
GAF	77.08 ± 10.97	74.58 ± 10.78	0.564; 0.579
CGI	6.29 ± 0.62	6.64 ± 0.55	−1.403; 0.175
PANSS positive symptoms	30.92 ± 7.75	28.75 ± 8.01 ($n = 8$)	0.604; 0.553
PANSS negative symptoms	25.58 ± 5.04	27.13 ± 7.53 ($n = 8$)	−0.551; 0.588
PANSS global score	56.75 ± 12.54	56.75 ± 20.44 ($n = 8$)	0.000; 1.000
Positive syndrome type	8	4	nd
Negative syndrome type	4	4	nd

nd Not done

Table 3 Psychopathology of the drug-naïve (NT-SZ) and treated (T-SZ) patients on the day of SPECT

Psychopathological ratings at the day of SPECT	NT-SZ ($n = 12$)	T-SZ ($n = 12$)	Student's t test, T, P value
CGI	6.29 ± 0.62	5.46 ± 0.81	2.828, 0.010
PANSS positive symptoms	30.92 ± 7.75	23.08 ± 7.34	2.542, 0.019
PANSS negative symptoms	25.58 ± 5.04	27.25 ± 5.10	−0.805, 0.429
PANSS global score	58.75 ± 12.54	54.00 ± 12.92	0.529, 0.602
Positive syndrome type	8	3	Nd
Negative syndrome type	4	9	Nd
pp1 Delusions	5.50 ± 1.31	4.08 ± 1.78	2.217, 0.037
pp2 Conceptual disorganization	4.75 ± 1.22	3.83 ± 0.94	2.069, 0.051
pp3 Hallucinatory behaviour	3.75 ± 2.18	2.42 ± 1.73	1.660, 0.111

nd Not done

PANSS baseline ratings were missing for four patients in the T-SZ group, so that the syndrome type of these patients could not be determined. Eight of the NT-SZ and four of the T-SZ patients were of the positive syndrome type, while the remaining four patients in each group were of the negative syndrome type (see Table 2). At the time of dual-isotope SPECT, the T-SZ patients had significantly lower scores than the NT-SZ patients for the CGI, PANSS positive symptoms and the acute syndrome core symptoms such as delusions, conceptual disorganization and hallucinatory behaviour. In the NT-SZ group, eight patients were rated as being of the positive syndrome type and four of the negative syndrome type; in the T-SZ group, three patients were of the positive syndrome type and nine of the negative syndrome type (see Table 3).

Haloperidol treatment

Haloperidol treatment was given for a mean of 14.83 days (14.83 ± 2.86, range 11–20). The mean daily dose was 12.63 mg (12.63 ± 5.30, range 4–20), and the mean dose per kg body weight (BW) was 0.17 mg/kg (0.17 ± 0.075, range 0.04–0.27). Haloperidol blood levels at the time of SPECT were available for seven patients: the mean blood level was 5.37 ng/ml (5.37 ± 4.346, range 0–11.00).

Table 4 Specific radioligand binding values and between-group comparison

Radioligand	NT-SZ ($n = 12$)		T-SZ ($n = 12$)		HC ($n = 12$)		ANOVA F	P value	Bonferroni-corrected P value
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range			
spB TRODAT-1	1.09 ± 0.13	0.86–1.31	0.82 ± 0.16	0.48–1.12	1.08 ± 0.09	1.00–1.30	17.184	0.000	0.000
spB IBZM	0.78 ± 0.17	0.51–1.00	0.13 ± 0.09	0.01–0.32	0.82 ± 0.08	0.70–0.98	130.385	0.000	0.000

Dopamine D_2 receptor availability

The whole-group comparisons of mean specific striatal IBZM binding found significant differences between the T-SZ patients, NT-SZ patients and HC. Specific IBZM binding was significantly lower in the T-SZ group, while binding was very similar in the NT-SZ and HC groups (Table 4). An inverse correlation was found between the haloperidol dose in mg/kg BW and postsynaptic D_2 receptor availability, although results only showed a trend towards significance (Fig. 1). An inverse correlation was also found between daily dosage in mg and D_2 availability, although again only a trend towards significance was found (Spearman's Rho $= -0.222$, $P = 0.488$). Analysis of the effect of biperiden comedication showed no difference in DAT or D_2 receptor availability between biperiden-treated ($n = 6$) and biperiden-free ($n = 6$) T-SZ patients (see Table 4).

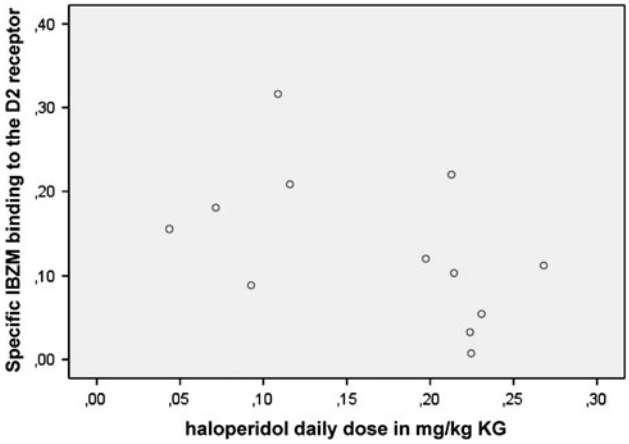

Fig. 1 Correlation between haloperidol dose in mg per kg KG and specific IBZM binding to the striatal dopamine D2 receptor ($n = 12$ T-SZ); Pearson's $r = -0.501$, $P = 0.097$

Dopamine transporter availability

TRODAT-1 bound significantly less in the T-SZ group than in the NT-SZ and HC groups, which showed no difference (see Table 4). There was a significant, positive correlation between the haloperidol dose in mg/kg BW and the availability of the presynaptic DAT for specific TRODAT-1 binding (Fig. 2) and between the daily dosage and TRODAT-1 binding (Spearman's Rho $= 0.659$, $P = 0.020$). Biperiden comedication had no effect on DAT availability (see Table 5).

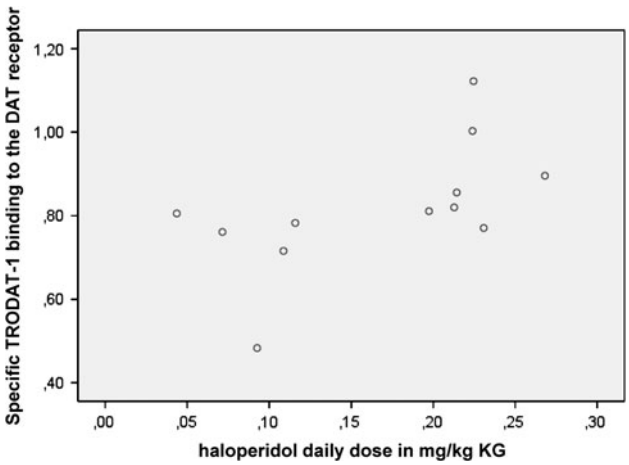

Fig. 2 Correlation between haloperidol dose in mg per kg KG and specific TRODAT-1 binding to the striatal DAT receptor ($n = 12$ T-SZ); Pearson's $r = 0.580$, $P = 0.048$

Correlation between D_2 receptor and DAT availability

Pearson's correlation coefficient was calculated for specific radioligand binding. Specific binding of TRODAT-1 correlated positively with IBZM binding in the NT-SZ patients (Pearson's $r = 0.229$, $P = 0.475$), although the correlation did not reach significance. The correlation was higher in positive-syndrome-type NT-SZ patients ($n = 8$) (Pearson's $r = 0.530$, $P = 0.176$); there was no such correlation in the control group (Pearson's $r = 0.054$, $P = 0.868$). The T-SZ patients showed an inverse but non-significant correlation between pre- and postsynaptic specific binding (Pearson's $r = -0.434$, $P = 0.158$). At the time of SPECT, three of the patients in this group were of the positive syndrome type. The nine negative-syndrome-type patients did not differ from the whole T-SZ group (Pearson's r 0–0.472, $P = 0.20$).

Table 5 Comparison of specific radioligand binding values and D_2 occupancy by haloperidol in patients treated or not treated with biperiden

	T-SZ without biperiden ($n = 6$)	T-SZ with biperiden ($n = 6$)	Student's t test T, P value
spB TRODAT-1 to the DAT	0.81 ± 0.26	0.83 ± 0.04	−0.161, 0.875
spB IBZM to the D_2 receptor	0.14 ± 0.12	0.13 ± 0.06	0.214, 0.835
D_2 occupancy %	85.37 ± 12.38	86.57 ± 5.87	−0.214, 0.835

D_2 receptor and DAT availability and psychopathology

The correlation between psychopathology at the time of SPECT and striatal dopamine metabolism revealed clear differences between NT-SZ and T-SZ patients. The NT-SZ group showed a negative correlation between D_2 receptor binding and the PANSS items "delusions," "conceptual disorganization" and "hallucinatory behaviour"; this correlation was strongly significant for "conceptual disorganization" and "hallucinatory behaviour" in the eight positive-syndrome-type patients. No such correlation was found in the T-SZ patients. The correlation between psychopathology and DAT availability also showed clear differences between NT-SZ and T-SZ patients: the eight positive-syndrome-type NT-SZ patients showed an overall negative correlation between DAT availability and psychopathology at the time of SPECT, which reached significance for the PANSS positive subscale and showed a trend towards significance for "hallucinatory behaviour." Again, no such correlation was found in the T-SZ patients. Table 6 shows Spearman's Rho and P values.

Table 6 Correlation between psychopathology and specific radioligand binding (SpB)

	SpB IBZM	spB TRODAT-1
NT-SZ ($n = 12$)	Spearman's Rho, P	Spearman's Rho, P
Delusions	−0.407, 0.189	0.252, 0.429
Conceptual disorganization	−0.598, 0.04*	0.251, 0.432
Hallucinatory behaviour	−0.559, 0.05*	−0.200, 0.534
T-SZ ($n = 12$)		
Delusions	0.079, 0.808	0.000, 1.000
Conceptual disorganization	−0.038, 0.907	0.098, 0.762
Hallucinatory behaviour	0.209, 0.513	0.164, 0.611
NT-SZ ps ($n = 8$)		
Delusions	0.617, 0.103	−0.463, 0.248
Conceptual disorganization	0.805, 0.016*	−0.268, 0.521
Hallucinatory behaviour	0.843, 0.009*	−0.651, 0.081
T-SZ ns ($n = 9$)		
Delusions	0.228, 0.555	0.152, 0.696
Conceptual disorganization	−0.310, 0.416	−0.037, 0.926
Hallucinatory behaviour	−0.027, 0.944	0.393, 0.296
NT-SZ ns ($n = 4$)	nd	nd
T-SZ ps ($n = 3$)	nd	nd

PS Positive syndrome type, *ns* negative syndrome type, *nd* not done
Significant correlations are marked with a *

Discussion

We investigated the striatal dopaminergic synapse in haloperidol-treated and untreated first-episode schizophrenic patients and in healthy controls. The two patient groups were matched with regard to age, gender, socioeconomic status, illness duration and intensity of psychopathological symptoms; the healthy controls were matched with regard to age and gender. The dual-isotope SPECT findings differed significantly between the two groups.

D_2 receptor availability

Postsynaptic D_2 availability did not differ between untreated patients and healthy controls. This result confirms findings of earlier studies that used dopamine stimulation protocols to obtain baseline radioligand binding data from mostly mixed samples of drug-naïve and neuroleptic-free, acute and chronic schizophrenic patients and also found no significant differences in baseline D_2 receptor availability [1, 4, 24, 35]. However, in a later study, Abi-Dargham and colleagues demonstrated in a group of 18 schizophrenic patients that occupancy of the postsynaptic striatal dopamine D_2 receptor by endogenous dopamine was significantly higher in patients than in healthy controls [2].

The mean haloperidol occupancy of about 90%, with a mean daily dose of 12.6 mg, is in line with the results of many other dopamine D_2 receptor PET or SPECT studies that analysed the effects of different haloperidol treatment regimes on D_2 occupancy [9, 15, 16, 30, 31, 41, 44]. The dose correlates with D_2 receptor availability, although the correlation is not strong. The IBZM SPECT study in 10 haloperidol-treated schizophrenic patients performed by Tauscher and colleagues, the most similar study to ours, found a quite similar D_2 receptor availability (mean specific binding of the radioligand = 0.11) after treatment with a similar haloperidol dose (mean daily dose: 12.9 mg) [41].

DAT availability

It is difficult to interpret the finding that the availability of DAT for the specific radioligand TRODAT-1 is significantly lower after 14 days of haloperidol treatment than in the untreated state. This finding is supported by that made some years ago by different groups in DNA transfection, cell culture and animal brain slice experiments [5, 39, 42] that haloperidol and its metabolites block the DAT directly. Even if the amount of DAT blockade by haloperidol and its metabolites differs markedly between the different experimental conditions—a finding that cannot be explained by the authors [5]—there is no doubt that the blockade happens.

The only PET study to examine the effect of antipsychotic treatment on DAT availability was performed in chronically ill, stabilized patients with different pharmacological regimens [22]. Laakso and colleagues showed in this study that the availability of DAT was significantly lower than in age-matched healthy volunteers. In conclusion, he assumed this reduction could be due to a disease-related loss of "striatal dopaminergic nerve terminals and/or decreased expression of DAT in a subset of chronic schizophrenic patients, although the role of medication cannot be ruled out at this point" [22]. Our data from first-episode, haloperidol-treated patients support a role of medication in this patient group: we found a positive, significant correlation between DAT availability to TRODAT-1 and the haloperidol dose in mg per kg BW. This result is not self-explanatory, because one would rather have expected to find an inverse correlation, as found in previous in vitro experiments [5, 39] and for the D_2 receptor in our study. This positive correlation may perhaps occur only after steady-state treatment: the in vitro cell culture and brain slice experiments tested a single haloperidol treatment condition [5, 39]. Another explanation could be that a high dose of haloperidol results in a high occupancy of the postsynaptic D_2 receptor. As a consequence, more intrasynaptic endogenous dopamine would be available that could be bound to the DAT and therefore become displaced by the radioligand. Alternatively, haloperidol itself may be displaced by the radioligand. The fact that TRODAT-1 differs in binding characteristics from other radioligands like ß-CIT, FP-CIT or CFT was demonstrated in animal competition experiments evaluating the kinetics and binding affinities of this new ligand [14].

Interaction between DAT and D_2 receptor availability

The interaction between dopamine D_2 receptors and DAT has not yet been analysed in vivo or even in cell culture or animal experiments. Two studies found a positive correlation between DAT and D_2 receptor radioligand binding in drug-naïve patients with schizophrenia but not in the control groups [35, 43]. Our earlier study showed that the correlation is driven by patients with a predominantly positive syndrome type [35]. In the present study, we found a negative correlation between the availability of both the DAT and D_2 receptors in the treated group, although the correlation did not reach significance. The fact that the majority of the haloperidol patients showed a negative syndrome type after a 14-day treatment period supports the hypothesis of a "hyperdopaminergic state" in acute psychotic, untreated patients [6].

Correlation with psychopathology

The above concept is further supported by the findings about the relationship between dopamine and psychopathological symptoms for the three acute psychotic core symptoms in the drug-naïve positive-syndrome-type patients: the more pronounced the symptoms are, the lower the availability of DAT and D_2 receptor for specific radioligand binding seems to be [35]. On the basis of the sophisticated discussion about what receptor-ligand imaging studies actually assess [23], one can interpret our data as follows: the more pronounced the psychopathological symptoms are, the more endogenous dopamine is available to occupy presynaptic DAT and postsynaptic D_2 receptors. The finding of a significant negative correlation between the productive psychotic core symptoms and D_2 receptor availability supports this interpretation. Even though the correlation between psychopathology and dopamine metabolism does not reach the strength that we found in a larger patient sample only recently [35], the trend is clear.

Limitations of the data

The groups are quite small, particularly those used to study psychopathological correlations. This was the first study to evaluate dual-isotope SPECT in two differently treated patient groups, an untreated and a haloperidol-treated group. Sample sizes should be increased to allow better examination of correlations with psychopathology. The question of an interrelationship between negative syndrome characteristics and striatal dopamine metabolism is interesting with regard to the interaction between striatal dopamine and other relevant brain regions, for example the prefrontal cortex. Further research in different patient groups is needed in this area.

Another shortcoming of our data is the fact that five of the haloperidol blood levels are missing. The data are missing for different reasons: three patients refused to allow haloperidol blood level analysis and two of the samples were not suitable for laboratory testing. The latter problem could not be solved by resampling because of

study protocol timelines. As a result, we cannot provide correlations between haloperidol blood levels and specific radioligand binding, which would have allowed a more accurate interpretation of the action of haloperidol at the DAT, for example whether the correlation is stronger or perhaps weaker than with the dosage. Finally, unfortunately four PANSS baseline ratings are missing in the haloperidol-treated patients. However, the correlative analysis regarding psychopathology and SPECT measurements focussed on the psychopathology measurements at the time of the SPECT evaluation, and therefore, the missing data do not interfere with the performed analysis.

Conclusion

To summarize, our data show in vivo in first-episode schizophrenic patients a significant effect of haloperidol on the availability of the postsynaptic D_2 receptor and the presynaptic DAT for specific radioligand binding. With respect to mechanisms underlying the findings, animal models need to be established to analyse the observed effects in detail. In humans, different antipsychotic regimens should be assessed by the dual-isotope technique to expand on the haloperidol data. Dual-isotope SPECT imaging has opened a new field of research on the striatal dopaminergic synapse in schizophrenic patients. Additional investigations are needed to confirm potential alterations of DAT availability in subgroups of patients and to elucidate the underpinnings and functional consequences of these potential abnormalities.

The use of dual-isotope SPECT imaging may significantly advance the understanding of potential mechanisms of action of the broad range of antipsychotics and could help us understand the different effects of psychopharmacological treatment strategies in our patients.

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