British Journal of Pharmacology (2007) 152, 538–548
 0007–1188/07 $30.00
www.brjpharmacol.org

RESEARCH PAPER

Characterization of atypical antipsychotic drugs by a late decrease of striatal alpha1 spectral power in the electropharmacogram of freely moving rats

W Dimpfel

Justus-Liebig-University Giessen, Hessen, Germany

Background and purpose: Drug administration modifies the balance of neurotransmitter-controlled ion channel activity and consequently the firing pattern of local neuronal populations and intracerebral field potentials. Fast Fourier Transformation of these field potentials provides an electropharmacogram depicting drug-induced changes within defined frequency ranges. The present investigation was undertaken to investigate the difference between atypical and typical antipsychotic drugs.
Experimental approach: Adult Fisher rats were implanted with 4 bipolar concentric steel electrodes using a stereotactic surgical procedure. Field potentials from four selected brain areas in freely moving rats were used to analyse the frequency content of the electropharmacogram after administration of 4 clinically used atypical antipsychotic drugs.
Key results: Atypical antipsychotics exerted effects similar to those reported for typical antipsychotics, on the electropharmacogram during the first hour after administration, whereas clear differences emerged during the second and third hour after dosing. During the latter period, only atypical antipsychotic drugs produced a statistically significant decrease in alpha1 and beta1 spectral power, especially within the striatum, somewhat less in the cortex.
Conclusions and implications: Previous studies have attributed alpha1 frequency changes to the influence of 5-hydroxytryptamine (5-HT) and the present data are consistent with additional binding of atypical drugs to 5-HT receptors. This implies that a change in the balance between dopaminergic and 5-hydroxytryptaminergic neurotransmission (activation of both) is likely to underlie the relative lack of extrapyramidal side effects characteristic of atypical antipsychotics and also for their higher efficacy in the treatment of mood and cognition deficits in schizophrenics.
British Journal of Pharmacology (2007) **152,** 538–548; doi:10.1038/sj.bjp.0707427; published online 13 August 2007

Keywords: atypical antipsychotic drugs; Tele-Stereo-EEG; rat; electropharmacogram

Abbreviations: BPRS, brief psychatric rating scale; EEG, electroencephalogram; LSD, lysergic acid diethylamide; 8-OH-DPAT, (±)-8-hydroxy-2-dipropylaminotetralin; R-DOM, (−)-1-(2-5-dimethoxy-4-methylphenyl)-2-aminopropane

Introduction

Drugs commonly prescribed for the treatment of schizophrenia have an antipsychotic action. Classically, this action is accompanied by side effects with respect to the extrapyramidal motor system resulting in Parkinsonian symptomatology. However, historically there are two compounds—namely clozapine and thioridazine—which are devoid of such side effects. Since then a number of new antipsychotic drugs—among them ziprasidone (for review see Gunasekara *et al*., 2002)—have been developed aiming at the avoidance of these side effects but maintaining antipsychotic efficacy. Several hypotheses have been developed to explain the difference of the newer drugs in comparison to the typical ones developed earlier. One was proposed by Kapur and Seeman (2000) and involved different dopamine receptor kinetics, and another was based on the interaction of different antipsychotic drugs with the α-adrenoceptors (Svensson, 2003). The third hypothesis deals with the balance of dopaminergic and 5-hydroxytryptaminergic neurotransmitter activity based on the ability of the atypical drugs to interact more potently with the 5-HT_{2a} or possibly 5-HT_{1a} receptors than with the dopaminergic D_2 receptor (Meltzer *et al*., 2003).

There is an interaction between and integration of the action of different neurotransmitters within a given network of neurons. The net balance caused by changes in ion channel activity is reflected in the so-called field potential. As neurotransmitters at the molecular level act by interacting with receptors to switch conductances of a particular configuration of ion channels, the neuron integrates this bombardment of excitatory and inhibitory events leading

Correspondence: Professor W Dimpfel, Justus-Liebig-University Giessen, C/o NeuroCode AG, Sportparkstr 9, D-35578 Wetzlar, Hessen, Germany.
E-mail: w.dimpfel@neurocode-ag.com
Received 2 April 2007; revised 4 July 2007; accepted 6 July 2007; published online 13 August 2007

ultimately to activation or suppression of neuronal firing. Hence, the electrical activity of a neuronal network in the form of field potentials provides an intermediate level of information that is situated in between the biochemical molecular basis of communication and the level of behaviour. It is therefore meaningful to record field potentials to understand better the link between the effects of a drug at the molecular level and its effects in terms of behaviour. The local electrical network activity at a given locus within the brain in the presence of drugs is termed an electropharmacogram and corresponds to the electroencephalogram (EEG) recorded from the scalp in humans.

Analysis of brain field potentials recorded by the Tele-Stereo-EEG method has proven to be a very sensitive tool to characterize drug effects on the central nervous system. From the earliest use of this method, it became increasingly apparent that the electrical power within a single frequency range, as defined by Dimpfel *et al*. (1986), can change independently from each other depending on the particular behavioural or drug condition. After drug administration, the pattern of changes in the brain field potential with respect to defined frequency ranges is termed an 'electrical fingerprint' or an electropharmacogram of this drug. For example, drugs interacting with cholinergic transmission in an agonistic or antagonistic manner have been shown to induce changes mainly in spectral δ power (Dimpfel, 2005). Meanwhile electropharmacograms have been recorded from more than 150 compounds from a wide range of drug categories (for example, analgesics, antidepressants, neuroleptics, stimulants, tranquilizers, sedatives and narcotics). In general, electropharmacograms show prominent differences for drugs prescribed for different indications and are similar for drugs with similar clinical indications (Dimpfel, 2003).

The current experimental series was undertaken to learn more about the mechanism of action of atypical antipsychotic drugs. It was hypothesized that the electropharmacograms produced by newer, so-called 'atypical' antipsychotic drugs, would more likely resemble the results previously obtained with clozapine and that, in general, a difference might be observed from the pattern previously reported as characteristic of the classical antipsychotics (Dimpfel *et al*., 1992).

Materials and methods

Animal procedures

The principles of laboratory animal care were followed in all trials and the local authorities responsible for animal care approved the conduct of the studies according to German Health Guidelines. Adult Fisher rats (5–8 months of age and day–night converted (12/12 h)) were implanted with four concentric bipolar steel electrodes using a stereotactic surgical procedure. All four electrodes were placed 3 mm lateral within the left hemisphere. Anterior coordinates were 12.2, 5.7, 9.7 and 3.7 mm for frontal cortex, hippocampus, striatum and reticular formation, respectively (according to the atlas of Paxinos and Watson, 1982). A base plate carrying four bipolar stainless steel semi-micro electrodes (neurological electrodes 'SNF 100' from Rhodes Medical Instruments Inc., Summerland, CA, USA) and a five-pin plug was fixed to the skull by dental cement with three steel screws. The distal recording point of the electrode was the active electrode, whereas the proximal points of the four electrodes were connected to each other to provide a common reference. The base plate incorporated a plug for connection to a transmitter (weight: 5.2 g including battery; $26 \times 12 \times 6\,mm^3$).

Animals were allowed 2 weeks for recovery from the surgical procedure and thereafter the transmitter was connected for adaptation and control experiments with saline. During the recording, rats were unrestricted and could move freely. However, they were not permitted access to food during drug studies to avoid recording (chewing) artefacts.

EEG signals were recorded from frontal cortex, hippocampus, striatum and reticular formation of the animals kept inside a totally copper-shielded room. Signals were wirelessly transmitted by a radio-telemetric system (Rhema Labortechnik, Hofheim, Germany, using 40 MHz as carrier frequency) and were amplified and processed as described earlier to give power spectra of 0.25 Hz resolution (Dimpfel *et al*., 1986). After automatic artifact rejection, signals were collected in sweeps of 4 s duration and Fast Fourier transformed using a Hanning window. Sampling frequency was 512 Hz. Four values were averaged to give a final sampling frequency of 128 Hz, well above the Nyquist frequency. The resulting electrical power spectra were divided into six specially defined frequency ranges (δ: 0.8–4.5 Hz; θ: 4.75–6.75 Hz; $\alpha 1$: 7.00–9.50 Hz; $\alpha 2$: 9.75–12.50 Hz; $\beta 1$: 12.75–18.50 Hz; $\beta 2$: 18.75–35.00 Hz). These frequency ranges were recognized to change independently from each other in all earlier trials. Spectra were averaged in steps of 3 min each and displayed online. In the off-line procedure, spectra were averaged to give periods of 30 or 60 min for further analysis and data presentation, to average out short periods of sleep during the active waking period. Experiments were started always at the same time in the morning to exclude circadian influences.

We have now extended our database of drug characterization using drugs with a known primary antipsychotic action (see Tables 1–3). A group of rats were assigned to treatment with one of the newer so-called 'atypical' drugs and were crossed over to a control period with saline (NaCl, 0.9%; $1\,ml\,kg^{-1}$). Drugs were dissolved in saline. Comparisons were made with studies performed previously under identical conditions. Each drug, or saline, was administered as a single i.p. dose. After a pre-drug baseline recording period of 45 min (expressed as 100%), drug effects were monitored for a period of 180 min. Changes in the recorded electrical power ($\mu V^2/\Omega$) were documented as percent of the pre-drug value in hourly intervals. Values represent the mean of $n = 8$ animals. Essentially, no changes could be observed within the experimental period after administration of saline. Short periods of sleep averaged out due to the use of several animals. Changes within the four brain areas were documented separately. Animals were exposed to only one dose per week followed by a 7-day drug-free interval. At first, the experimental doses were selected on the basis of their clinical doses relative to each other in comparison to haloperidol (data for rats were available from an earlier experimental series) and then modified according to the results obtained.

Table 1 Significance of drug effects over the first hour (5–65 min) after dosing

	$mg\,kg^{-1}$	n	δ	θ	$\alpha1$	$\alpha2$	$\beta1$	$\beta2$
Frontal cortex								
Risperidone	0.10	7	0.17	3.19*	1.63	0.14	3.59*	2.58
	0.25	8	0.03	5.79***	7.79***	1.08	14.35***	15.23***
	0.50	7	0.63	7.49***	14.31***	2.73*	18.02***	27.61***
Quetiapine	1.00	8	0.07	6.76***	4.11**	0.31	5.09***	3.78*
	2.50	8	1.85	22.52***	7.21***	3.62*	12.05***	5.45***
	5.00	8	0.09	31.62***	22.26***	3.49*	33.49***	40.27***
Ziprasidone	1.00	8	0.01	19.17***	11.79***	0.16	20.64***	17.25***
	2.50	8	2.49	11.73***	17.35***	0.22	14.71***	13.62***
	5.00	8	0.39	61.00***	30.43***	0.88	26.34***	28.28***
Olanzapine	0.50	8	0.31	0.20	2.91*	3.78*	0.54	0.09
	3.00	8	0.75	3.74*	1.70	3.73*	2.91*	4.10**
	6.00	4	1.52	4.18**	0.75	0.10	1.50	3.77*
Hippocampus								
Risperidone	0.10	7	0.84	0.70	1.81	1.47	1.12	0.59
	0.25	8	11.21***	7.92***	2.45	13.28***	2.97*	0.37
	0.50	7	22.72***	3.43*	0.20	19.43***	7.28***	0.26
Quetiapine	1.00	8	0.93	0.15	0.17	0.09	0.19	0.46
	2.50	8	0.06	2.64	1.25	0.01	1.43	0.11
	5.00	8	5.68***	0.87	3.97**	1.66	0.46	0.44
Ziprasidone	1.00	8	12.95***	4.40**	3.13*	7.03***	3.29*	0.79
	2.50	8	13.43***	2.30	0.90	8.12***	0.90	0.13
	5.00	8	23.44***	0.91	0.99	16.55***	3.26*	4.66**
Olanzapine	0.50	8	3.29*	1.43	9.47***	4.02**	3.42*	4.00**
	3.00	8	1.10	1.19	23.95***	9.40***	13.94***	14.89***
	6.00	4	2.95*	0.67	0.36	0.10	0.17	3.37*
Striatum								
Risperidone	0.10	7	0.15	5.86***	5.28***	0.12	2.59	1.26
	0.25	8	0.04	12.43***	20.65***	0.05	14.53***	11.59***
	0.50	7	0.41	31.23***	34.25***	5.03***	14.23***	14.82***
Quetiapine	1.00	8	0.02	7.83***	2.72*	0.04	5.16***	1.26
	2.50	8	1.95	23.76***	5.49***	2.04	10.30***	2.36
	5.00	8	0.08	34.99***	21.24***	0.77	19.26***	8.46***
Ziprasidone	1.00	8	0.90	12.44***	4.26**	0.07	7.07***	1.48
	2.50	8	2.08	23.16***	13.90***	0.29	12.03***	7.65***
	5.00	8	1.56	58.80***	9.74***	0.86	7.08***	0.97
Olanzapine	0.50	8	0.11	0.79	3.23*	4.51**	1.28	1.07
	3.00	8	0.61	6.68***	1.29	2.79*	2.01	3.06*
	6.00	4	1.64	4.14**	0.98	0.37	1.82	2.58
Reticular formation								
Risperidone	0.10	7	1.50	0.33	0.96	1.47	0.00	0.09
	0.25	8	7.32***	0.98	0.17	6.61***	1.90	3.70*
	0.50	7	10.62***	0.02	0.42	10.05***	2.75*	14.80***
Quetiapine	1.00	8	0.93	0.39	0.48	0.00	0.90	0.43
	2.50	8	1.26	1.17	0.41	0.10	1.25	0.23
	5.00	8	4.95**	1.37	3.23*	0.58	4.74**	2.31
Ziprasidone	1.00	8	4.96**	0.05	1.38	1.80	3.04*	0.49
	2.50	8	9.52***	0.55	1.37	4.97**	0.56	0.47
	5.00	8	10.39***	4.82**	0.25	1.53	1.52	3.43*
Olanzapine	0.50	8	0.78	0.32	3.14*	0.58	0.23	0.12
	3.00	8	0.03	0.81	2.18	0.43	1.25	1.54
	6.00	4	0.10	0.09	0.59	0.13	0.94	0.82

Approximate F-statistics of drug effects on single frequency ranges is given in comparison to the corresponding saline experiment, after a single i.p. administration. Variance/co-variance was estimated on the basis of 39 groups from part of our database of reference drugs containing further dosages of these drugs with a total of 336 experiments carried out under identical conditions.
Variables: 1 (frequency range/brain region), *$F>2.70$ corresponds to $P<0.1$, **$F>3.84$ corresponds to $P<0.05$ and ***$F>5.02$ corresponds to $P<0.01$. df1 = 1; df2 = 279.

Statistics

Values were calculated as percent of the baseline values. These values were log transformed for approaching normal multivariate distribution to fulfill the preconditions of the parametrical statistical analysis. The first calculation consisted of comparing all 24 variables (four brain areas and six frequency bands) with respect to the effects of saline (placebo) and all other compounds. This analysis was performed to see if a drug was effective as such within this model at a particular dose, in analogy to human trials. The second calculation consisted of determining the statistical significance for each frequency band within each brain

Table 2 Significance of drug effects over the second hour (65–125 min) after dosing

	$mg\,kg^{-1}$	n	δ	θ	$\alpha1$	$\alpha2$	$\beta1$	$\beta2$
Frontal cortex								
Risperidone	0.10	7	0.00	1.29	0.01	0.17	0.04	0.14
	0.25	8	1.08	0.64	0.28	7.82***	0.22	1.81
	0.50	7	0.80	0.19	4.61**	8.67***	5.31***	15.14***
Quetiapine	1.00	8	2.45	0.69	0.53	1.35	0.36	0.44
	2.50	8	7.85***	5.00**	0.47	2.68	0.10	0.80
	5.00	8	0.65	3.22*	0.86	0.49	2.28	4.29**
Ziprasidone	1.00	8	2.02	3.15*	2.18	1.86	0.00	0.29
	2.50	8	1.45	0.01	0.40	4.61**	0.28	0.39
	5.00	8	10.45***	5.63***	1.08	2.50	1.51	2.25
Olanzapine	0.50	8	0.06	0.54	1.26	1.68	0.97	0.09
	3.00	8	0.21	3.08*	6.82***	3.64*	4.28**	3.00*
	6.00	4	0.08	6.26***	2.20	0.19	0.00	0.00
Hippocampus								
Risperidone	0.10	7	0.01	0.16	3.99**	1.42	2.24	0.87
	0.25	8	13.62***	10.96***	18.46***	24.92***	20.53***	4.37**
	0.50	7	18.27***	6.56***	3.85**	27.12***	16.91***	2.31
Quetiapine	1.00	8	0.76	0.00	1.84	0.05	0.01	0.02
	2.50	8	3.07*	1.15	0.93	0.72	0.27	0.02
	5.00	8	5.16***	0.37	1.50	5.90***	3.28*	0.62
Ziprasidone	1.00	8	11.27***	5.07***	18.40***	9.30***	9.36***	1.73
	2.50	8	6.87***	6.82***	4.59**	11.21***	8.28***	1.32
	5.00	8	24.82***	3.69*	12.24***	31.88***	27.44***	15.55***
Olanzapine	0.50	8	0.29	0.84	5.00**	2.52	2.48	1.49
	3.00	8	5.30***	4.27**	47.01***	19.93***	34.83***	21.06***
	6.00	4	0.35	0.42	5.44***	0.49	2.66	8.06***
Striatum								
Risperidone	0.10	7	0.69	0.71	0.00	2.65	0.14	0.07
	0.25	8	2.31	1.00	0.47	8.68***	0.00	0.46
	0.50	7	1.43	1.76	14.20***	18.43***	1.01	3.57*
Quetiapine	1.00	8	0.32	0.03	3.50*	0.55	1.39	1.54
	2.50	8	3.88**	2.23	1.47	0.16	0.03	1.20
	5.00	8	1.44	3.92**	1.01	2.11	0.63	0.28
Ziprasidone	1.00	8	4.27**	2.30	2.05	4.12**	0.54	0.74
	2.50	8	3.14*	0.19	0.18	6.57***	0.17	0.18
	5.00	8	6.98***	11.71***	0.45	14.06***	0.13	1.45
Olanzapine	0.50	8	0.04	0.07	3.43*	4.53**	1.32	0.57
	3.00	8	0.25	5.91***	7.13***	6.49***	6.27***	3.72*
	6.00	4	0.18	6.93***	4.32**	0.58	1.16	0.12
Reticular formation								
Risperidone	0.10	7	3.16*	0.19	6.29***	3.62*	2.63	2.43
	0.25	8	15.40***	7.11***	10.42***	21.50***	3.52*	1.12
	0.50	7	14.97***	4.74**	2.77*	25.58***	0.24	1.60
Quetiapine	1.00	8	0.13	0.01	1.32	0.05	1.02	1.69
	2.50	8	0.05	0.06	2.50	0.00	0.41	2.02
	5.00	8	9.34***	1.49	2.26	8.56***	1.14	0.74
Ziprasidone	1.00	8	9.24***	0.95	6.70***	7.26***	2.82*	1.67
	2.50	8	6.48***	4.17**	3.18*	9.20***	2.40	1.94
	5.00	8	26.62***	4.19**	15.21***	18.76***	5.57***	1.64
Olanzapine	0.50	8	0.54	0.01	2.63	1.30	0.68	0.53
	3.00	8	2.67	0.29	9.40***	2.84*	4.24**	2.46
	6.00	4	1.76	0.60	2.33	0.15	0.07	1.65

Approximate F-statistics of drug effects on single-frequency ranges is given in comparison to the corresponding saline experiment, after a single i.p. administration. Variance/co-variance was estimated on the basis of 39 groups from part of our database of reference drugs containing further dosages of these drugs with a total of 336 experiments carried out under identical conditions.
Variables: 1 (frequency range/brain region), *$F>2.70$ corresponds to $P<0.1$, **$F>3.84$ corresponds to $P<0.05$ and ***$F>5.02$ corresponds to $P<0.01$. df1 = 1; df2 = 279.

region, separately, to facilitate interpretation with respect to neurotransmission. Analysis always compared each time period against the identical time period of changes after saline administration (that is, 5–65 or 65–125 min). Overall the method of Ahrens and Läuter (1974) was followed.

Results

I.p. administration of saline in day–night (12/12 h)-converted rats did not show any prominent stable changes of electrical power over time in comparison to the pre-drug,

Table 3 Significance of drug effects over the third hour (125–185 min) after dosing

	$mg\,kg^{-1}$	n	δ	θ	$\alpha1$	$\alpha2$	$\beta1$	$\beta2$
Frontal cortex								
Risperidone	0.10	7	0.47	1.05	0.01	0.14	0.29	0.06
	0.25	8	0.36	0.04	0.62	7.84***	0.69	0.00
	0.50	7	1.86	0.12	0.05	11.41***	0.16	4.40**
Quetiapine	1.00	8	0.03	0.04	1.43	0.24	2.12	1.51
	2.50	8	7.27***	1.07	2.81*	1.28	2.00	4.81**
	5.00	8	0.90	2.17	0.00	0.03	0.03	0.23
Ziprasidone	1.00	8	0.43	0.47	3.06*	0.24	1.28	0.12
	2.50	8	0.01	0.04	0.74	3.42*	1.79	1.53
	5.00	8	2.41	0.57	0.02	1.41	0.00	0.04
Olanzapine	0.50	8	1.60	4.33**	0.18	0.49	0.11	0.17
	3.00	8	0.76	0.99	6.87***	6.06***	4.91**	2.65
	6.00	4	1.55	4.35**	6.33***	0.14	1.07	0.41
Hippocampus								
Risperidone	0.10	7	0.02	0.00	1.50	0.41	1.65	1.38
	0.25	8	4.13**	3.82**	10.50***	11.91***	10.82***	3.82**
	0.50	7	10.83***	4.76**	6.36***	19.15***	18.89***	5.48***
Quetiapine	1.00	8	0.23	0.00	0.76	0.27	0.20	1.03
	2.50	8	4.05**	0.80	1.24	1.28	0.40	0.23
	5.00	8	0.21	0.15	0.22	0.31	0.57	0.47
Ziprasidone	1.00	8	0.92	0.80	5.12***	1.09	2.34	1.22
	2.50	8	0.07	0.67	2.18	1.77	2.66	0.73
	5.00	8	6.03***	1.66	8.01***	14.08***	13.71***	8.73***
Olanzapine	0.50	8	1.55	0.50	0.10	0.16	0.16	0.79
	3.00	8	6.68***	5.98***	40.79***	21.55***	33.57***	19.82***
	6.00	4	0.97	0.21	15.75***	3.94**	9.86***	13.40***
Striatum								
Risperidone	0.10	7	0.05	0.11	0.28	1.60	0.56	0.58
	0.25	8	1.56	0.00	0.00	7.05***	0.75	0.12
	0.50	7	3.02*	0.00	2.75*	18.20***	0.27	0.14
Quetiapine	1.00	8	0.36	1.83	8.15***	2.40	4.80**	5.07***
	2.50	8	4.43**	0.19	4.91**	0.22	0.86	2.56
	5.00	8	0.00	0.36	0.92	1.40	1.14	1.41
Ziprasidone	1.00	8	0.19	0.01	3.86**	1.69	2.02	1.98
	2.50	8	0.14	0.35	0.31	2.91*	0.47	0.31
	5.00	8	1.57	0.30	0.64	15.14***	2.57	3.32*
Olanzapine	0.50	8	1.64	1.54	0.95	0.00	0.46	0.51
	3.00	8	0.99	2.43	7.18***	9.44***	6.45***	3.55*
	6.00	4	2.84*	2.82*	9.50***	3.17*	4.37**	2.46
Reticular formation								
Risperidone	0.10	7	0.51	0.20	0.64	0.23	0.21	0.25
	0.25	8	6.28***	3.06*	7.90***	15.90***	5.16***	3.09*
	0.50	7	17.52***	11.12***	15.15***	37.66***	8.87***	1.63
Quetiapine	1.00	8	0.87	0.09	1.10	0.18	0.85	0.67
	2.50	8	0.10	0.31	2.84*	0.00	2.30	4.76**
	5.00	8	1.37	0.72	2.84*	4.21**	3.40*	2.94*
Ziprasidone	1.00	8	1.75	0.10	1.93	1.53	0.88	0.51
	2.50	8	3.54*	2.70*	5.71***	6.91***	5.05***	3.24*
	5.00	8	12.12**	2.93*	11.55***	13.77***	5.54***	0.44
Olanzapine	0.50	8	0.77	1.79	0.06	0.62	0.00	0.24
	3.00	8	3.21*	1.70	12.01***	7.21***	6.37***	3.10*
	6.00	4	10.87***	4.27**	8.73***	1.88	3.36*	2.50

Approximate F-statistics of drug effects on single-frequency ranges is given in comparison to the corresponding saline experiment, after a single i.p. administration. Variance/co-variance was estimated on the basis of 39 groups from part of our database of reference drugs containing further dosages of these drugs with a total of 336 experiments carried out under identical conditions.
Variables: 1 (frequency range/brain region), *$F>2.70$ corresponds to $P<0.1$, **$F>3.84$ corresponds to $P<0.05$ and ***$F>5.02$ corresponds to $P<0.01$. df1 = 1; df2 = 279.

baseline values (Figure 1). Thus, this stable recording condition (rats were not sleeping for longer periods due to day–night conversion) allowed drug action to be observed continuously for 3 h after dosing. Data were averaged to give hourly values to average out short periods of sleep. Data recorded in the presence of drugs were compared statistically to the corresponding values obtained after saline injection (placebo), for each hour of observation.

Ziprasidone ($1\,mg\,kg^{-1}$) produced statistically highly significant increases in θ, $\alpha1$ and β spectral power within the cortex and less in the striatum, during the first hour after dosing. Statistically significant decreases in spectral δ and $\alpha2$

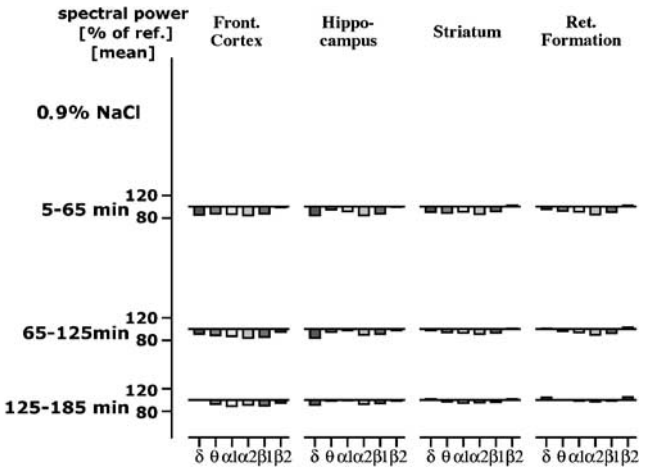

Figure 1 Time course of electrical frequency changes following treatment with saline (NaCl, 0.9%; 30 min periods). Frequency ranges (bar graphs) of δ, θ, $\alpha 1$, $\alpha 2$, $\beta 1$ and $\beta 2$ power (from left to right) are given in the Methods section. Drug-induced changes are shown as % of the pre-drug baseline value.

spectral power were observed in the hippocampus and somewhat less in the reticular formation (Figure 2). These changes were reproduced by administration of 2.5 and 5 mg kg^{-1} (Figure 2). However, this pattern changed completely over time and reversed into decreases of $\alpha 1$ ($P<0.01$) and, less evident, $\beta 1$ spectral power (Figures 6 and 7). Statistical comparison with experiments using saline is presented in Tables 1–3, over the 3 h of study (5–65, 65–125 and 125–185 min).

During the first hour, the effects of the low-dose quetiapine (1 mg kg^{-1}) were comparable to those of ziprasidone with prominent, statistically significant, θ, $\alpha 1$ and β increases in the frontal cortex and the striatum (Figure 3). The pattern over the third hour after administration of quetiapine showed a prominent, statistically significant, $\alpha 1$ decrease within the striatum (Figure 3; Table 3). At the same time a δ increase was observed, which was not seen anywhere else.

The effects of risperidone (0.1 mg kg^{-1}) were characterized by initial statistically significant increases in θ, $\alpha 1$ and β power in the frontal cortex and more pronounced within the striatum. θ power also increased in frontal cortex and the striatum. In the hippocampus and reticular formation, a decrease in δ and $\alpha 2$ spectral power was seen (statistically significant at the higher dosages) (Table 1). During the third hour, a statistically significant decrease in $\alpha 2$ power was documented for all brain areas at the higher dosage. No decrease in striatal $\alpha 1$ power could be observed (Figure 4).

The injection of olanzapine (3 mg kg^{-1}) did not show any change in $\alpha 1$ or β power during the first hour after administration in frontal cortex. Within the hippocampus, there was a statistically significant decrease in α and β power (Figure 5), whereas there was a statistically significant increase in θ power in the striatum (Table 1). Olanzapine showed θ increases in the striatum and at the higher dosage within the frontal cortex. Most prominent statistically highly significant changes were seen following olanzapine with respect to decreases in $\alpha 1$ power throughout all brain

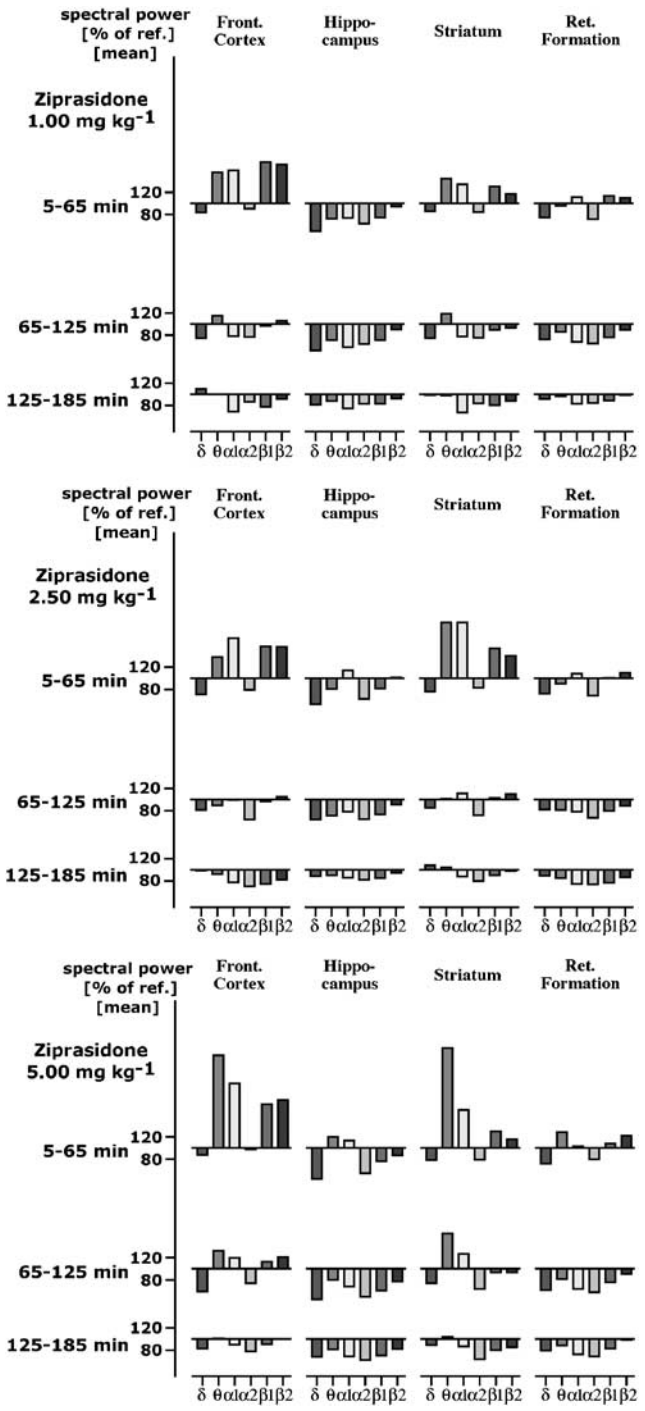

Figure 2 Electropharmacogram of electrical frequency changes of ziprasidone. Time-dependent results are shown for all three doses. Drug-induced changes are shown as % of the pre-drug baseline value.

areas (Tables 2 and 3). These changes were accompanied by somewhat less pronounced decreases in $\alpha 2$ and $\beta 1$ power, which were still highly significant in comparison to saline administration.

The common denominator of frequency changes during the first hour after antipsychotic drug administration (except for olanzapine) was an increase in $\alpha 1$ and β power in all brain

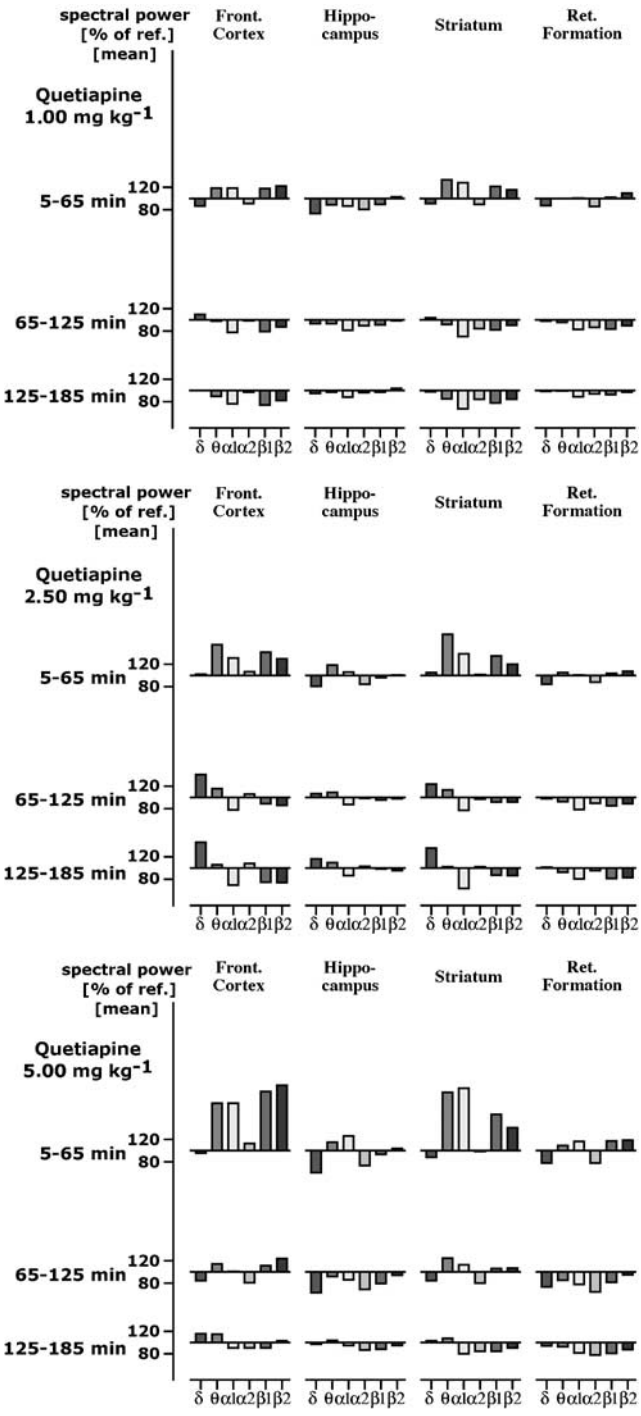

Figure 3 Electropharmacogram of electrical frequency changes of quetiapine. Time-dependent results are shown for all three doses. Drug-induced changes are shown as % of the pre-drug baseline value.

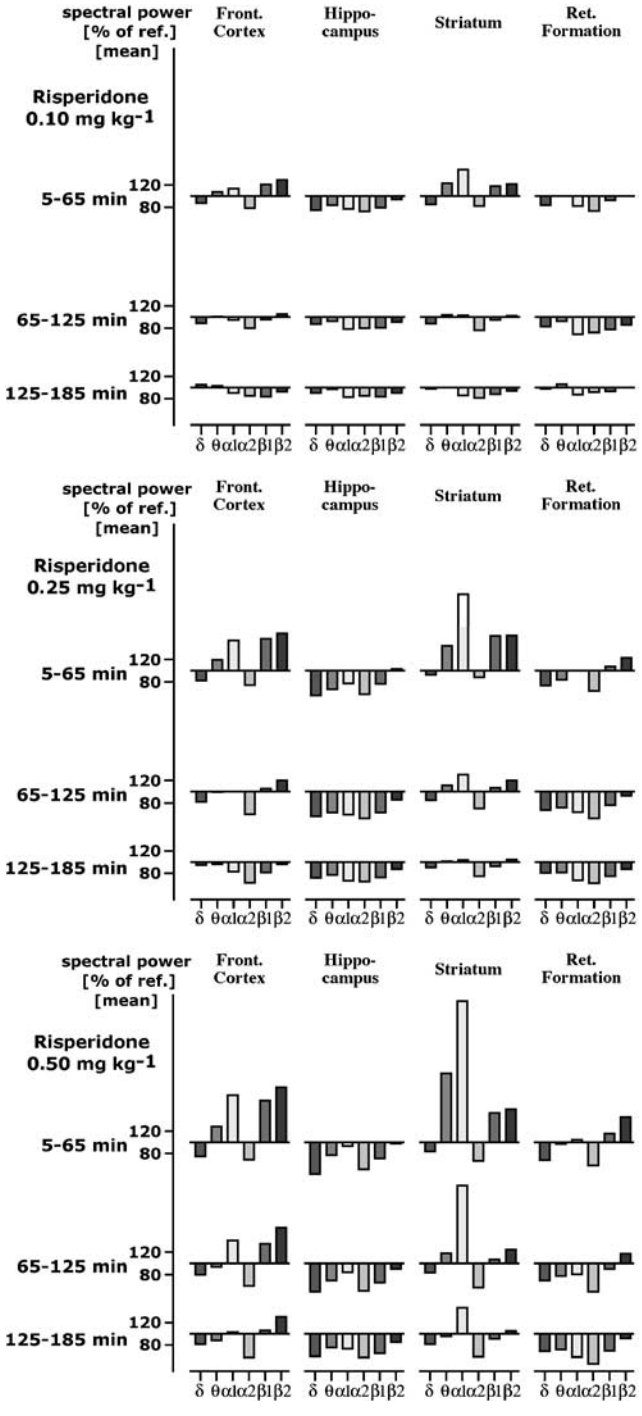

Figure 4 Electropharmacogram of electrical frequency changes of risperidone. Time-dependent results are shown for all three doses. Drug-induced changes are shown as % of the pre-drug baseline value.

areas, except for the hippocampus where a more or less pronounced decrease in δ and $\alpha 2$ power could be observed. A dose-dependent increase in θ power in the frontal cortex and striatum was also common to all antipsychotic drugs. However, the pattern of change becomes different during the subsequent hours, where atypical antipsychotics show a decrease in $\alpha 1$ and $\beta 1$ spectral power. The whole time course of $\alpha 1$ changes of typical antipsychotic drugs recorded under comparable conditions is shown in Figure 6 (values calculated from data published earlier) and the same time course for atypical ones of the present investigation in Figure 7. Decreases in $\beta 1$ are shown in Figures 8 and 9 for typical (calculated from data published earlier) and atypical drugs, respectively. All typical antipsychotic drugs lack the late

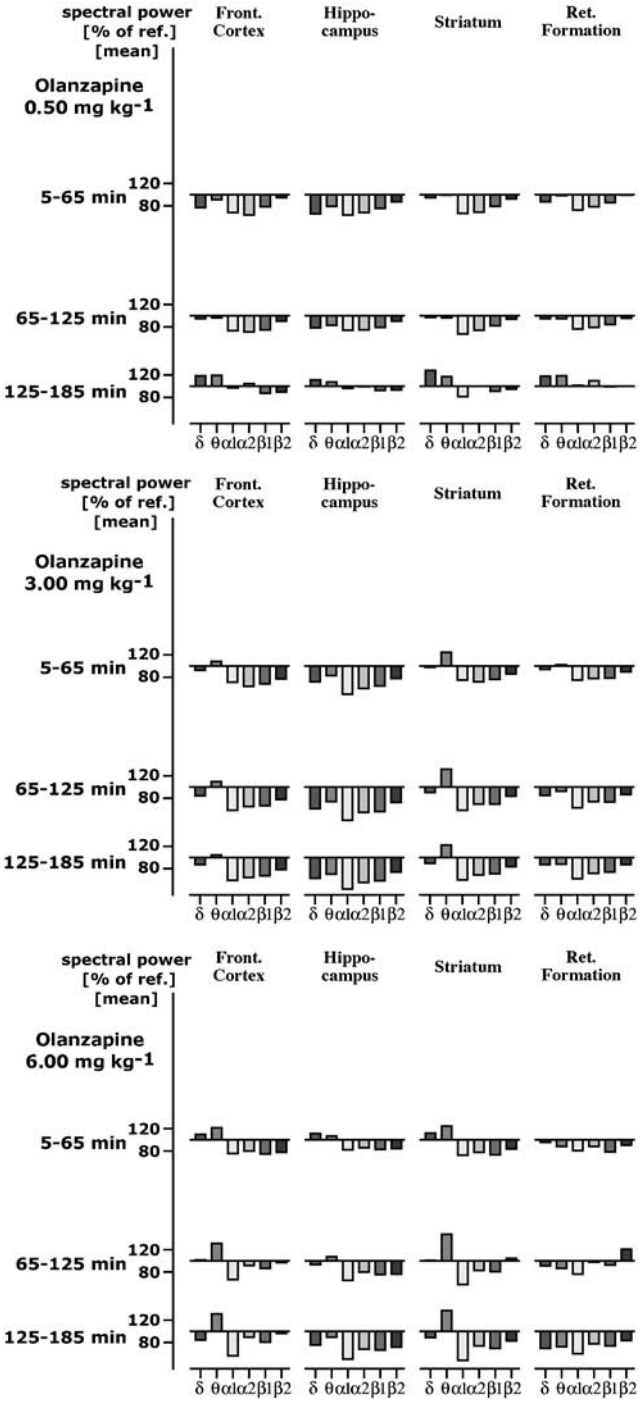

Figure 5 Electropharmacogram of electrical frequency changes of olanzapine. Time-dependent results are shown for all three doses. Drug-induced changes are shown as % of the pre-drug baseline value.

decreases in striatal $\alpha 1$ and $\beta 1$ power, whereas all so-called atypical drugs show this permanent decrease in the striatum mostly after an initial increase except in the case of olanzapine (which commences with a decrease already within the first hour). For statistical evaluation with respect to different frequencies and brain areas, see Tables 1–3. The statistical significance of the overall effects of the drugs in

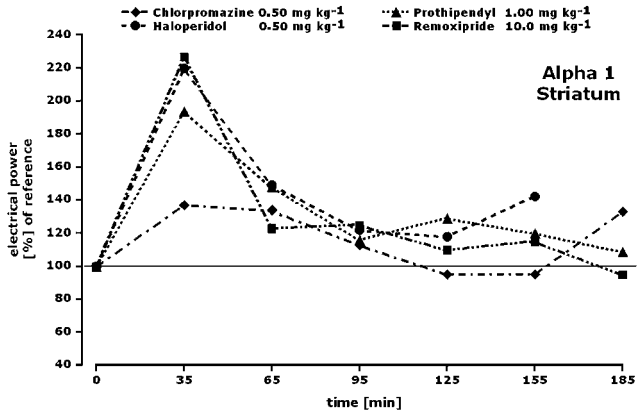

Figure 6 Time course of spectral power ($\alpha 1$) change of antipsychotic drugs with typical action. Drug-induced changes are shown as % of the pre-drug baseline value. Values transferred from data published earlier (Dimpfel *et al.*, 1992).

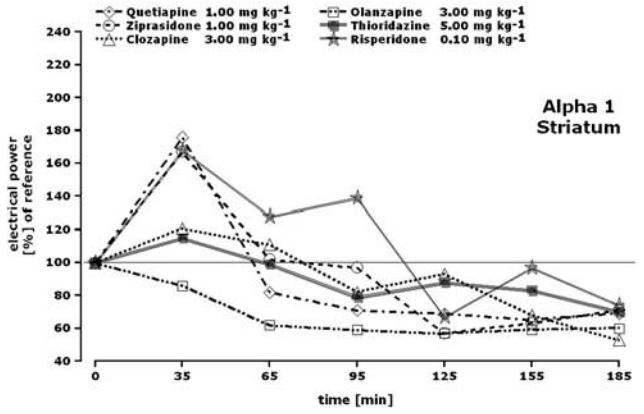

Figure 7 Time course of spectral power ($\alpha 1$) change of antipsychotic drugs with atypical action. Drug-induced changes are shown as % of the pre-drug baseline value.

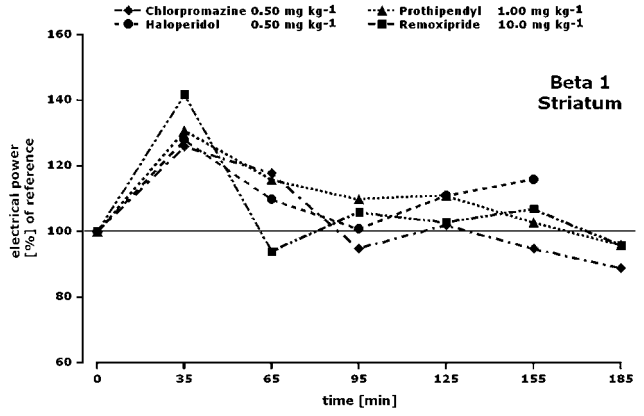

Figure 8 Time course of spectral power ($\beta 1$) change of antipsychotic drugs with typical action. Drug-induced changes are shown as % of the pre-drug baseline value. Values transferred from data published earlier (Dimpfel *et al.*, 1992).

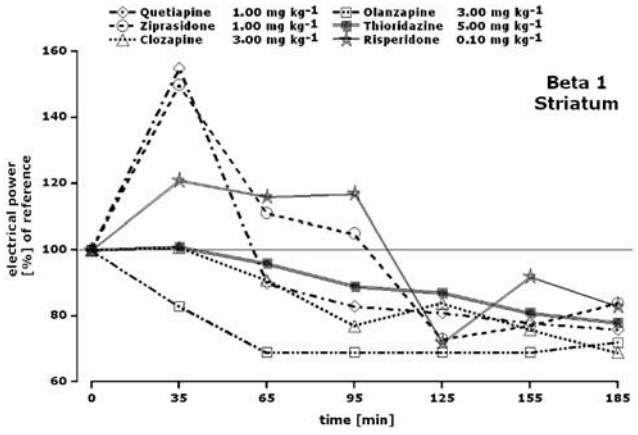

Figure 9 Time course of spectral power (β1) change of antipsychotic drugs with atypical action. Drug-induced changes are shown as % of the pre-drug baseline value.

comparison to saline with respect to all brain areas and six frequency ranges is documented in Table 4 using multivariate statistics. All drug effects could be differentiated from those of saline with high statistical significance.

Table 4 Multivariate F-statistics on 24 variables (6 frequencies × 4 brain areas) over the 3 h observation period for each atypical antipsychotic agent studied

24 variables	*mg kg^{-1}*	n	*5–65 min*	*65–125 min*	*125–185 min*
Risperidone	0.10	7	1.47*	1.70**	0.91
	0.25	8	4.15***	3.31***	1.67**
	0.50	7	5.83***	5.10***	3.71***
Quetiapine	1.00	8	1.49*	1.44*	1.62**
	2.50	8	2.78***	1.73**	1.63**
	5.00	8	4.29***	1.36*	0.90
Ziprasidone	1.00	8	4.66***	2.64***	1.22
	2.50	8	4.38***	2.07***	1.19
	5.00	8	10.36***	5.73***	3.37***
Olanzapine	0.50	8	2.92***	1.53**	1.02
	3.00	8	4.84***	6.25***	4.42***
	6.00	4	1.82***	3.63***	3.47***

Variance/co-variance was estimated on the basis of 39 groups from part of our database of reference drugs containing further doses of these drugs with a total of 336 experiments carried out under identical conditions.
Variables: 24 (6 frequency ranges × 4 brain areas), *$F>1.33$ corresponds to $P<0.1$, **$F>1.52$ corresponds to $P<0.05$ and ***$F>1.79$ corresponds to $P<0.01$. df1 = 24; df2 = 274.

Discussion and conclusions

The present investigation taken together with previously published data using the methodology of quantitative field potential analysis (electropharmacogram) revealed differences with respect to the action of the so-called typical and atypical antipsychotic (neuroleptic) drugs. The major difference in clinical use is seen in the fact that typical neuroleptics are prone to induce extrapyramidal side effects in schizophrenic patients, whereas atypical ones induce these effects significantly less or not at all. One of the major brain areas involved in these side effects is the striatum. The present results show a common decrease in α1 and β1 electrical power, especially within the striatum, only for the atypical drugs and are, therefore, consistent in terms of the brain area involved in regulation of extrapyramidal activity. However, it is also apparent that the initial increase in α1 and β1 power, which is observed for the typical drugs, is clearly less marked with atypical ones, with risperidone being on the boundary between typical and atypical drugs. This drug has been shown to induce extrapyramidal side effects only in higher doses in humans (Tarsy *et al*., 2002). With respect to changes of α1 electrical power, risperidone also occupies an intermediate position at the dose of 0.1 mg kg^{-1} body weight.

As far as possible from the available clinical reports, we have tried to present our results using three effective doses in this model. In addition, our objective has been to compare low doses with statistically proven effects on the electrical activity in rats. However, even higher dosages of typical antipsychotics (up to 2 mg kg^{-1} of haloperidol or up to 4 mg kg^{-1} of chlorpromazine) never exhibited a late decrease in striatal α1 power (Dimpfel *et al*., 1992). But higher dosages of ziprasidone (up to 10 mg kg^{-1}), quetiapine (up to 5 mg kg^{-1}) or olanzapine (up to 6 mg kg^{-1}) still showed a late decrease in striatal α1 power, which is in line with data after administration of 6 mg kg^{-1} of clozapine as reported earlier (Dimpfel *et al*., 1992).

The question arises how the difference of induced changes in α1 electrical power can be interpreted and possibly linked to the receptor specificity of antipsychotic drugs. From earlier studies with the administration of 5-HT$_{2a/2c}$ receptor agonists in the same model, it is known that LSD and R-DOM (a hallucinogenic amphetamine derivative) induce α1 power increases in the frontal cortex, hippocampus and striatum (Dimpfel *et al*., 1989), which is probably based on a presynaptic action of these compounds leading to attenuation of 5-hydroxytryptaminergic transmission. Since ziprasidone, quetiapine and olanzapine have been shown to possess antagonistic properties on this 5-HT receptor category, a postsynaptic effect probably underlies the increase in α1 power during the first hour. The late decrease in α1 power thus reflects an increase in 5-hydroxytryptaminergic transmission, possibly based on a low dosage of these compounds still available to the brain acting on presynaptic receptors. In addition, results on the effects of 5-HT$_{1a}$ receptor agonists in the same model reveal that in the presence of 8-OH-DPAT, or ipsapirone, α1 power in the frontal cortex and striatum initially increases, suggesting a presynaptic effect (unpublished experiments). Thus, interaction with the 5-HT$_1$ or 5-HT$_2$ receptor category could explain the changes observed. From this, it can be inferred that biphasic interaction of the newer antipsychotics with 5-hydroxytryptaminergic neurotransmission accounts for differences in the classification of these compounds using the current methodology. This technique can, therefore, be used to optimize further antipsychotic drugs with respect to potential development of extrapyramidal side effects, since an increase in 5-hydroxytryptaminergic transmission is obviously recommended for low extrapyramidal effects.

Another important question arises from the present findings: Is there any reflection of the possible antipsychotic

effects within these data? Since we are dealing with healthy animals, this question cannot be addressed directly. However, on the basis of published reports, one can assume that the clinical antipsychotic efficacy is due to interaction of these drugs with the dopaminergic receptor (Seeman *et al*., 1976; Gessa *et al*., 2000; but also see Jones and Pilowsky (2002) for a critical review). Drugs interacting with dopamine receptors have been characterized in the current experimental model earlier (Dimpfel *et al*., 1987). From these experiments, it became clear that drugs interacting with dopaminergic transmission, such as amphetamine or L-DOPA, lead to changes in $\alpha 2$ electrical power, whereby decreases of this frequency indicate enhancement of transmission. Accordingly, we can assume that the decreases in $\alpha 2$ power in the presence of antipsychotic drugs as observed to some degree in these experiments are in line with the interpretation of moderately increased dopaminergic transmission. This limited decrease in $\alpha 2$ power probably reflects a *presynaptic* action of antipsychotic drugs acting at the D_2 receptor. As in other catecholamine systems, blockade of the presynaptic receptor transiently leads to enhanced release of dopamine. In addition, the decreases or increases in electrical power within these frequency ranges represent the net effect of balanced neurotransmitter-mediated ion channel control. Considering the relationship between changes of late $\alpha 1$ and $\alpha 2$ frequencies, one observes stronger decreases in $\alpha 1$ than of $\alpha 2$ electrical power with the newer antipsychotics. This again is in concordance with the receptor affinity balance of the newer compounds, which have been especially optimized for stronger affinity to 5-HT receptors in comparison to dopamine D_2 receptors, founded on the hypothesis of Meltzer *et al*. (1989). This reasoning has been successfully extended to newer antipsychotics (Meltzer *et al*., 2003). Interestingly, single-unit *in vivo* recording from the A9 and A10 areas in rats has revealed two types of cells that responded differently to 3-weeks repetitive dosing with haloperidol or clozapine (Todorova and Dimpfel, 1994). The putative non-dopaminergic cells changing their activity in the presence of clozapine were speculated to be under the influence of 5-HT. In summary, the current results support the hypothesis of Meltzer *et al*. (1989).

With respect to the initial increase in $\alpha 1$ and β power, similar results have been obtained in humans for the administration of chlorpromazine (50 mg) and risperidone (2 mg), including increases in θ power (Hughes *et al*., 1999), on the basis of frequency ranges identical to those used in this study. Increases in $\alpha 1$ and $\beta 1$ power have likewise been reported by Yoshimura *et al*. (2007). The atypical drug quetiapine decreased $\alpha 1$ power during their experimental setting in humans. These data are in line with those reported in the present paper. For a lower dosage of risperidone, increases in absolute δ and θ activities have been reported by Lee *et al*. (1999). Data showing an increase in θ power and a decrease in $\alpha 2$ power in the presence of 5 mg of olanzapine were provided by Hubl *et al*. (2001) for volunteers. With respect to increases in $\alpha 1$ activity, Schellenberg *et al*. (1994) reported data suggesting a relationship between plasma levels and BPRS score after a single administration of haloperidol decanoate to schizophrenic patients monitored weekly for effects on the EEG with respect to temporal electrode T6. Increased α power after the administration of haloperidol and remoxipride in connection with clinical improvement has also been reported by Moore *et al*. (1997). From α power changes, Galderisi (2002) could predict a positive clinical response. Recently, an interaction between 5-hydroxytryptaminergic and dopaminergic transmission was proposed to explain the lack of induction of extrapyramidal side effects (Haleem, 2006). The relationship between clinically effective antipsychotic drug dosage and binding affinity to cloned dopamine and 5-HT receptor subtypes was analyzed by Richtand *et al*. (2007) in an effort to elucidate the contribution of individual receptor subtypes to medication response. According to these authors the ratio between dopamine D_2 and 5-HT receptors correlated best with the antipsychotic efficacy. Abnormalities in 5-hydroxytryptaminergic function have also causally been related to schizophrenia in terms of pathology and its effective antipsychotic treatment (Dean *et al*., 2006). Nevertheless, a safe predictor of antipsychotic efficacy has not yet been defined, but it has become clear that the electropharmacogram of drug action, as obtained in the rat, reflects the effects to be expected in humans and that these data can be used for preclinical classification of drugs with respect to different indications (for review see Dimpfel, 2003).

In the light of isolated huge θ power increases in the presence of medetomidine and other α_2 adrenoceptor agonists, such as clonidine, with their sedating properties (Dimpfel and Schober, 2001), the increases in θ power after the administration of antipsychotics most probably reflect the sedating properties of a drug and must as such be considered as a side effect. Finally, the interpretation of decreases in $\beta 1$ spectral frequencies remains uncertain. However, there is some evidence that they are under the control of glutamatergic transmission, since they change in a striking manner in the presence of compounds acting on glutamate receptors, such as memantine (Dimpfel *et al*., 1987).

In summary, the present findings provide evidence for a time-dependent, biphasic, action of atypical antipsychotic drugs. The reason for this could be detected in an enhancement of 5-hydroxytryptaminergic transmission reflected by decreases in $\alpha 1$ spectral power, in concordance with the different receptor profile of second-generation antipsychotic drugs, which involves also binding to 5-HT receptors.

Acknowledgements

We gratefully acknowledge the enthusiasm of Mrs Leoni Schombert in performing the experiments and helping in data management. I thank Dr Winfried Wedekind and Dr David Greenwood for reviewing the manuscript and giving useful suggestions.

Conflict of interest

Research was financially supported by Pfizer GmbH, Germany.

References

Ahrens H, Läuter J (1974). *Mehrdimensionale Varianzanalyse*. Akademie-Verlag: Berlin.

Dean G, Pavey G, Thomas D, Scarr E (2006). Cortical serotonin (7, 1D) and (1F) receptors: effects of schizophrenia, suicide and antipsychotic drug treatment. *Schizophr Res* **88**: 265–274.

Dimpfel W (2003). Preclinical data base of pharmaco-specific rat EEG fingerprints (Tele-Stereo-EEG). *Eur J Med Res* **8**: 199–207.

Dimpfel W (2005). Pharmacological modulation of cholinergic brain activity and its reflection in special EEG frequency ranges from various brain areas in the freely moving rat (Tele-Stereo-EEG). *Eur Neuropsychopharmacol* **15**: 673–682.

Dimpfel W, Schober F (2001). Norepinephrine, EEG theta waves and sedation. *Brain Pharmacol* **1**: 89–97.

Dimpfel W., Spüler M, Koch R, Schatton W (1987). Radioelectroencephalographic comparison of memantine with receptor specific drugs acting on dopaminergic transmission in freely moving rats. *Neuropsychobiology* **18**: 212–218.

Dimpfel W, Spüler M, Nichols DE (1989). Hallucinogenic and stimulatory amphetamine derivatives: fingerprinting DOM, DOI, DOB, MDMA and MBDB by spectral analysis of brain field potentials in the freely moving rat (Tele-Stereo-EEG). *Psychopharmacology* **98**: 297–303.

Dimpfel W, Spüler M, Nickel B (1986). Radioelectroencephalography (Tele-Stereo-EEG) in the rat as pharmacological model to differentiate the central action of flupirtine from that of opiates, diazepam and phenobarbital. *Neuropsychobiology* **16**: 163–168.

Dimpfel W, Spüler M, Wessel K (1992). Different neuroleptics show common dose and time dependent effects in quantitative field potential analysis in freely moving rats. *Psychopharmacology* **107**: 195–202.

Galderisi S (2002). Clinical applications of pharmaco-EEG in psychiatry: the prediction of response to treatment with antipsychotics. *Methods Find Exp Clin Pharmacol* **24** (Suppl): 85–89.

Gessa GL, Devoto P, Diana M, Flore G, Melis M, Pistis M (2000). Dissociation of haloperidol, clozapine, and olanzapine effects on electrical activity of mesocortical dopamine neurons and dopamine release in prefrontal cortex. *Neuropsychopharmacol* **22**: 642–649.

Gunasekara NS, Spencer CM, Keating GM (2002). A review of its use in schizophrenia and schizoaffective disorder. *Drugs* **62**: 1217–1251.

Haleem DJ (2006). Serotonergic modulation of dopamine neurotransmission: a mechanism for enhancing therapeutics in schizophrenia. *J Coll Physicians Surg Pak* **16**: 556–562.

Hubl D, Kleinlogel H, Frolich L, Weinandi T, Maurer K, Holstein W *et al*. (2001). Multilead quantitative electroencephalogram profile and cognitive evoked potentials (P300) in healthy subjects after a single dose of olanzapine. *Psychopharmacol* **158**: 281–288.

Hughes AM, Lynch P, Rhodes J, Ervine CM, Yates RA (1999). Electroencephalic and psychomotor effects of chlorpromazine and risperidone relative to placebo in normal healthy volunteers. *Br J Clin Pharmacol* **48**: 323–330.

Jones HM, Pilowsky LS (2002). Dopamine and antipsychotic drug action revisited. *Br J Psychiatr* **181**: 271–275.

Kapur S, Seeman P (2000). Antipsychotic agents differ in how fast they come off the dopamine D2 receptors. Implications for atypical antipsychotic action. *J Psychiatry Neurosci* **25**: 161–166.

Lee DY, Lee KU, Kwon JS, Jang IJ, Cho MJ, Shin SG *et al*. (1999). Pharmacokinetic–pharmacodynamic modeling of risperidone effects on electroencephalography in healthy volunteers. *Psychopharmacol* **144**: 272–278.

Meltzer HY, Li Z, Kaneda Y, Ichikawa J (2003). Serotonin receptors: their key role in drugs to treat schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **27**: 1159–1172.

Meltzer HY, Matsubara S, Lee JC (1989). Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin2 pKi values. *J Pharmacol Exp Ther* **252**: 238–246.

Moore NC, Tucker KA, Brin FB, Merai P, Shillcutt SD, Coburn KL (1997). Positive symptoms in schizophrenia: response to haloperidol and remoxipride is associated with increased alpha EEG activity. *Human Psychopharmacol* **12**: 75–80.

Paxinos G, Watson C (1982). *The Rat Brain in Stereotactic Coordinates*. Academic Press: New York.

Richtand NM, Welge JA, Logue AD, Keck PE, Strakowski SM, McNamara RK (2007). Dopamine and serotonin receptor binding and antipsychotic efficacy. *Neuropsychopharmacology* **32**: 1715–1726.

Schellenberg R, Milch W, Schwarz A, Schober F, Dimpfel W (1994). Quantitative EEG and BPRS data following Haldol-Decanoate® administration in schizophrenics. *Int Clin Psychopharmacol* **9**: 17–24.

Seeman P, Lee T, Chau-Wong M, Wong K (1976). Antipsychotic drug doses and neuroleptic/dopamine receptors. *Nature* **261**: 717–718.

Svensson TH (2003). Adrenoceptor modulation hypothesis of antipsychotic atypicality. *Prog Neuropsychopharmacol Biol Psychiatry* **27**: 1145–1158.

Tarsy D, Baldessarini RJ, Tarazi FI (2002). Effects of newer antipsychotics on extrapyramidal function. *CNS Drugs* **16**: 23–45.

Todorova A, Dimpfel W (1994). Multiunit activity from the A9 and A10 areas in rats following chronic treatment with different neuroleptic drugs. *Eur Neuropharmacol* **4**: 491–501.

Yoshimura M, Koenig T, Irisawa S, Isotani T, Yamada K, Kikuchi M *et al*. (2007). A pharmaco-EEG study on antipsychotic drugs in healthy volunteers. *Psychopharmacology* **191**: 995–1004.