Pharmacological Modulation of Dopaminergic Brain Activity and Its Reflection in Spectral Frequencies of the Rat Electropharmacogram

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Key Words
Dopamine receptors · Electropharmacogram · Field potential · Tele-Stereo-EEG · L-DOPA

Abstract
Background: Particular frequencies of electropharmacograms have been attributed to cholinergic, noradrenergic or dopaminergic mediated neurotransmission. This investigation deals with changes induced by L-DOPA or dopamine D2 receptor agonists. Method: Adult rats (day-night converted) were instrumented with four bipolar concentric semi-microelectrodes into the frontal cortex, hippocampus, striatum and reticular formation. Field potentials were recorded during a pre-drug reference period followed by 4 h of recording thereafter. Data were transmitted wirelessly for spectral frequency analysis. Results: At low doses of L-DOPA (1–5 mg kg⁻¹) and of the D2 agonists talipexole and quinpirole (0.1 mg kg⁻¹), a delayed increase of delta and theta power was observed. Higher doses led to immediate stable decreases of alpha1, alpha2 and beta1 power as reported for dopamine D1 receptor agonists. Administration of the D2 blocker sulpiride (10–20 mg kg⁻¹) resulted in increases of alpha2 power. Conclusion: A common denominator for changes of dopaminergic transmission could be seen in immediate changes of spectral alpha2 power. Delayed increases of delta and theta activity after low dosages of the medication are considered to originate from heterosynaptic, presynaptic D2 receptors sitting on cholinergic neurons. This pattern could explain daytime tiredness or sudden sleep attacks in Parkinson patients.

Introduction

Dopamine seems to play a key role in the modulation of the electrochemical communication structure of the brain. Focal excitability depends on the availability of one or more of the five dopamine receptors commonly designated as D1-D5. Chemical interaction of drugs with these receptors leads to massive consequences which can be followed on ion channel activity, electrical activity of cellular networks or on the behavioral level. Pharmacological assessment of drugs interacting with neurotransmitter receptors is usually achieved by the measurement of biochemical or behavioral parameters. But there is often a problem with respect to relating an interaction of more or less specific drugs with one of the neurotransmitter receptors (like for acetylcholine or dopamine) to behavioral consequences. Obviously, behavior results from the changing balance of all transmitter activities throughout the complete network of active brain regions which have a mutual influence on each other. The matter becomes more complicated by the fact that interaction with presynaptic and/or postsynaptic receptors sometimes leads to opposite effects. Striatal release of acetylcholine in vivo might be regarded as an example where interaction of compounds with dopamine D1 and D2 receptors has been shown to result in increase or decrease of acetylcholine, respectively [1]. In addition, dosage plays a significant role as seen with the dopamine D2 receptor. For example, low dosage of the D2 dopamine receptor agonist pramipexole leads to sedative-like effects, whereas a higher dose produces stimulant-like effects [2].

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general, there is an intimate relationship between frequency changes and behaviour: for example, increases of delta and theta spectral power have been regularly observed during decreased vigilance, tiredness, sedation and sleep [6, 7], whereas decreases of delta and theta power relate to behavioral activation.

The question therefore arose if local field potentials recorded from focal brain regions reflect the balance of transmitter activities, thereby providing the net effect of drug-brain interaction. In other words: Does chemical interaction with particular neurotransmitter receptors relate to special frequency changes of local field potentials? A possible approach to test this hypothesis is to administer chemical compounds to rats which interact with known neurotransmitter receptors followed by recording of the changes of local field potentials in particular target areas in comparison to pre-drug baseline values. First results following this reasoning were obtained at the end of the eighties following the administration of dopamine D1 receptor agonists and memantine [3]. Administration of compounds acting on the dopamine D1 receptor resulted mainly in changes of alpha2 spectral frequencies. But shortly later a report appeared relating alpha1 frequencies to action of dopaminergic compounds using a comparable telemetric technology [4]. Thus, a relation between dopaminergic transmission and a particular field potential frequency remained a matter of debate. A possible reason could be seen by a different activation of D1 or D2 receptors [5]. After thorough exploration of dopamine D1 receptor induced changes using this methodology in an earlier publication [3], the present investigation deals with dose and time dependence of spectral changes following the administration of several doses of L-DOPA (used to increase the availability of brain dopamine), quinpirole, talipexole (dopamine D2 receptor agonists) and sulpiride (dopamine D2 receptor antagonist). The limited number of compounds was chosen because they are freely available and no conflict of interest could emerge.

Material and Methods

Implantation of Electrodes

Fourteen adult Fisher rats (6–8 months of age and day – night converted for at least 2 months: 12/12 beginning at 6 a.m.) were implanted during 2 series of experiments (8 and 6 rats) with 4 bipolar concentric steel electrodes within a stereotactic surgical procedure usingatraumatic fixation by a device from David Kopf Instruments, Tujunga, Calif., USA. All 4 electrodes were placed 3 mm lateral within the left hemisphere. Dorsolateral coordinates were 4, 6, 4.2 and 8 mm and anterior coordinates (bregma: 9.0) were 12.2, 9.7, 5.7 and 3.7 mm for frontal cortex, striatum, hippocampus, and reticular formation, respectively [8]. A pre-constructed base plate carrying 4 bipolar stainless steel semi-micro electrodes (neurological electrodes ‘SNF 100’ with a diameter of 0.25 mm from Rhodes Medical Instruments, Inc., Summerland, Calif., USA) and a 5-pin plug was fixed to the skull by dental cement interacting with 3 steel screws placed on distance into the bone. This surgical procedure has now been repeated more than 700 times during the last 20 years and no behavioral abnormality has been observed. Implants could be used on average for 5 months without any problems. The distant recording spot of the electrode was the active electrode, whereas the proximal circular spots of the 4 electrodes were connected to each other as reference. The base plate was carrying a plug to receive later on the transmitter during the experimental phase (weight: 5.2 g including battery, 26 × 12 × 6 mm of size).

Recording and Parametrization

EEG signals were recorded from frontal cortex, hippocampus, striatum and midbrain reticular formation from inside a totally copper shielded room. Signals were wirelessly transmitted by a radio-telemetric system as used by Gottesmann [9] (Rhema Laborteknik, 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 [10]. In short, after automatic artefact 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 6 specially defined frequency ranges (delta: 0.8–4.5 Hz; theta: 4.75–6.75 Hz; alpha1: 7.00–9.50 Hz; alpha2: 9.75–12.50 Hz; beta1: 12.75–18.50 Hz; beta2: 18.75–35.00 Hz). These frequency ranges were recognized to change independently from each other in all earlier trials and have been used in rats [4] and in humans [11, 12]. Spectra were averaged in steps of 3 min each and displayed online. In an off-line procedure, spectra were averaged to give 30 min or longer periods for further analysis and data presentation. With these longer periods, short-term fluctuations of changes were averaged out in order to emphasize pharmacological effects. This type of field potential changes in the presence of drugs compared to baseline has been called an electropharmacogram.

Experimental Design

Animals were given 2 weeks for recovery from this procedure. After this, the transmitter was plugged in for adaptation (1 complete experimental day), and thereafter control experiments with saline were performed. During the recording rats were not restricted and could move freely but did not have food available (chewing would have produced too many artefacts). Experiments began at 6.30 a.m. during lights off. The principles of laboratory animal care were followed in all trials, and the local authorities responsible for animal welfare allowed the performance according to German Guidelines. We now extend our data base of electropharmacograms with further drugs of a known primary action on the dopaminergic system. Groups of rats were assigned to receive several doses of L-DOPA, quinpirole, talipexole, sulpiride or as a control experiment saline (1 ml kg⁻¹) in a random manner using a crossover design within the 2 groups of rats (8 and 6). Each drug or saline was applied as a single dose intraperitoneally. After
a pre-drug period of 45 min for baseline recording (result set to 100%), drug effects were observed for 125 or 245 min after administration of the particular compound. Changes of the recorded electrical power (μV²/Hz) are documented in percent of the predrug value at hourly intervals. Values represent the mean of n = 5–14 animals from 2 groups (injections with saline were pooled from the 2 groups to give n = 14 for control, 25 mg kg⁻¹ of L-DOPA was tested within both groups). Changes within the 4 brain areas are documented in separate. Animals were exposed to 1 dosage of a drug per week (leading to a 6-days drug-free interval).

**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 calculation consisted in determining the statistical significance for each frequency band within each brain region separately under drug conditions in comparison to control experiments (pooled from both series to give n = 14), in order to facilitate interpretation with respect to neurotransmission. Statistical analysis always compared each time period against the identical time period of changes after saline administration (control). Statistics were calculated according to Ahrens and Läuter [13].

**Results**

The intraperitoneal administration of saline (n = 14 rats) did not show any significant changes of electrical power (see for example fig. 4 for the second hour of recording). The administration of L-DOPA led to dose and time dependent biphasic changes of electrical power. The lowest dosage of L-DOPA (1 mg kg⁻¹) resulted in a small decrease of delta, theta and alpha2 power during the first hour (statistically significant from control for alpha2 in the striatum and reticular formation) followed by an increase of all frequencies (except for beta2) starting 90 min after administration predominantly in the frontal cortex and including beta2 in the hippocampus. Increases of delta, theta and alpha2 were statistically significant different from control (fig. 1). Increase of the dosage of L-DOPA to 2.5 mg kg⁻¹ led to a similar pattern of early decreases of power followed by later increases of power mainly in the frontal cortex starting at 2 h after administration. This pattern was restricted to frontal cortex. The initial general decrease of spectral power (highly significant from control during the first hour) could be observed with respect to all brain areas (fig. 1). After administration of 25 mg kg⁻¹ only time dependent decreases of spectral power were observed. Dose dependent massive decreases in spectral alpha2 and delta power but also in theta and alpha1 power during the first hour after administration are shown in table 1 for dosages up to 100 mg kg⁻¹. It could be shown that high dosages attenuated spectral alpha2 power only somewhat more, but changes lasted longer.

A compound activating the dopamine D2 receptor is talipexole. Administration of the lowest dosage of 0.05 mg kg⁻¹ resulted in increases of delta power starting after 30 min (fig. 2). The increase of delta was statistically significant from saline for the second hour after administration. Doubling of the dosage reproduced this increase during the second hour within the frontal cortex and striatum but led to statistically significant decreases of spectral power within the hippocampus and the reticular formation. The highest dosage of 0.2 mg kg⁻¹ of talipexole resulted in a general decrease of spectral power, mainly

<table>
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<th>Time</th>
<th>1.0 mg kg⁻¹ (n = 6)</th>
<th>2.5 mg kg⁻¹ (n = 6)</th>
<th>5.0 mg kg⁻¹ (n = 7)</th>
<th>12.5 mg kg⁻¹ (n = 11)</th>
<th>25 mg kg⁻¹ (n = 12)</th>
<th>100 mg kg⁻¹ (n = 5)</th>
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<tr>
<td>5–35 min</td>
<td>76 ± 5</td>
<td>57 ± 5**</td>
<td>58 ± 8**</td>
<td>67 ± 10**</td>
<td>56 ± 5**</td>
<td>62 ± 9**</td>
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<td>35–65 min</td>
<td>76 ± 4</td>
<td>68 ± 11**</td>
<td>74 ± 13**</td>
<td>64 ± 11**</td>
<td>61 ± 8**</td>
<td>56 ± 8**</td>
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<tr>
<td>65–95 min</td>
<td>92 ± 7</td>
<td>83 ± 17</td>
<td>89 ± 19</td>
<td>65 ± 10**</td>
<td>64 ± 6**</td>
<td>53 ± 7**</td>
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<td>95–125 min</td>
<td>94 ± 9</td>
<td>83 ± 11</td>
<td>93 ± 14</td>
<td>60 ± 6**</td>
<td>71 ± 6</td>
<td>50 ± 4**</td>
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<td>125–155 min</td>
<td>106 ± 18</td>
<td>106 ± 10</td>
<td>90 ± 18</td>
<td>72 ± 10*</td>
<td>78 ± 8</td>
<td>52 ± 5**</td>
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<tr>
<td>155–185 min</td>
<td>131 ± 21**</td>
<td>108 ± 15</td>
<td>92 ± 12</td>
<td>73 ± 8</td>
<td>90 ± 7</td>
<td>59 ± 6*</td>
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<tr>
<td>185–215 min</td>
<td>133 ± 25*</td>
<td>105 ± 14</td>
<td>97 ± 15</td>
<td>78 ± 12</td>
<td>81 ± 6</td>
<td>64 ± 8**</td>
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<tr>
<td>215–245 min</td>
<td>149 ± 25**</td>
<td>129 ± 17**</td>
<td>89 ± 11</td>
<td>67 ± 6**</td>
<td>80 ± 5</td>
<td>76 ± 9</td>
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</table>

Values are given in % of the preadministration values ± SEM. Statistical significance to control values is indicated by * p < 0.05 and ** p < 0.025. Please note increases of spectral power only at the two lowest dosages. Higher dosages lead to longer duration of effects.
**Fig. 1.** Time course of frequency changes after intraperitoneal administration of 3 dosages of L-DOPA. Data are depicted as % of predrug baseline values (ordinate). For definition of frequency ranges from delta through beta2 (abscissa), see ‘Materials and Methods’. Statistical analysis was performed according to Ahrens and Läuter [13] against identical time periods from control data. * p < 5%, ** p < 2.5% error probability.
within the hippocampus and reticular formation (fig. 2), where mainly alpha1 and alpha2 power decreased followed by delta and beta1. Within the frontal cortex and striatum only alpha2 decreases were statistically significant from saline.

Another compound activating the dopamine D2 receptor is quinpirole. In general, effects as seen with talipexole could be observed. Similar to the action of L-DOPA slight decreases of delta, alpha2 and beta1 power were observed during the first hour at the lowest dosage of 0.1 mg kg⁻¹, which were statistically significant different from saline except for the reticular formation. Increases of delta, theta and to a lesser degree of alpha2 power were seen starting 60 min after administration of the low dosage of 0.1 mg kg⁻¹ of quinpirole mainly within the frontal cortex and striatum only alpha2 decreases were statistically significant different from saline except for the reticular formation. Increases of delta, theta and to a lesser degree of alpha2 power were seen starting 60 min after administration of the low dosage of 0.1 mg kg⁻¹ of quinpirole mainly within the frontal cortex (fig. 2). Opposite to this, further increase of the dosage to 0.5 mg kg⁻¹ led to pronounced decreases of alpha1, alpha2, beta1 and also beta2 frequencies within all brain areas. This pattern was stable over the whole recording period of 2 h. Further increase of the dosage to 1 mg kg⁻¹ again provided a different pattern of electrical changes. Delta power again increased, but alpha2, beta1 and beta2 power decreased at the same time. A peculiar finding was that only within the reticular formation alpha1 power showed a time-dependent strong increase also paralleled by time-dependent increases in delta power.

Attenuation of dopaminergic neurotransmission was thought to result in an increase of alpha2 power as seen in earlier trials with a dopamine D1 antagonist. This could now be confirmed by administration of higher dosages of a D2 receptor antagonist. Data are documented for the action of sulphiride in figure 3. At low dosage, a decrease in delta, theta and alpha2 power is observed confined mainly to frontal cortex and hippocampus. Upon increase of the dosage to 10 or 20 mg kg⁻¹, enhancement of alpha2, less delta and even less theta activity is observed mainly within the frontal cortex in a time dependent manner with a maximum during the third hour after administration of the highest dosage. At this dosage increases of alpha2 power are also observed in the striatum and reticular formation (fig. 3). An overview of statistical significances according to multivariate analysis of all brain areas and frequency changes (24 variables) is given in table 2. Statistically significant changes with respect to single frequencies as documented in the figures are regarded as descriptive.

Summarizing the results of the experimental series, three main findings emerge: firstly, low dosages of dopamine D2 receptor agonists lead to a delayed increase of delta and theta activity; secondly, high dosages of dopamine D2 receptor agonists induce power decreases in alpha and beta1 frequencies, and, thirdly, administration of a dopamine D2 receptor antagonist evokes profound increases of alpha2 activity. An overview is given in figure 4. A similar dose-dependent feature is observed after administration of L-DOPA.

**Fig. 2.** Effects of the dopamine D2 receptor agonists talipexole and quinpirole. Data are depicted as % of predrug baseline values (ordinate). For definition of frequency ranges from delta through beta2 (abscissa), see ‘Materials and Methods’. Statistical analysis was performed according to Ahrens and Läuter [13] against identical time periods from control data. * p < 5%, ** p < 2.5% error probability.
Discussion and Conclusions

Quantitative analysis of field potentials recorded by the Tele-Stereo-EEG method has been proven to be a very sensitive tool to characterize drug effects on the central nervous system. Since the start of this method it became more and more clear, that the electrical power of single frequency ranges, as defined, change independently from each other depending on the particular behavioural or drug condition. After drug administration, the pattern of changes of the brain field potential with respect to these specially defined frequency ranges was called an 'electrical fingerprint' of this drug or an electropharmacogram. For example, an interaction of drugs with a norepinephrine alpha2 receptor like clonidine or medetomidine was reported to lead to major increases of spectral theta power [14] coinciding with increased tiredness. Based on numerous experiments with compounds interacting with defined transmitter receptors, one must hypothesize that the fingerprints obtained from several brain areas are reflecting the net effects or balance of neurotransmission. Meanwhile, the electropharmacograms of more than 150 compounds have been obtained including more than 50...
standard drugs (e.g. 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 indication [15]. Since human EEG data obtained with some of these compounds [unpubl.] show a very similar fingerprint, extrapolation of the rat data to human use seems to be justified.

The effects of L-DOPA (which increases the availability of dopamine in the brain) can be separated into a low dose and a high dose pattern and early effects followed by late effects coming up during the second or third hour after administration. At the two lowest dosages main changes in comparison to baseline consisted in early decreases in delta and alpha2 power followed by delayed increases of spectral delta, theta and alpha2 power, predominantly within the frontal cortex. Desynchronisation of the EEG (decrease of spectral power) after administration of D1 agonist SKF 38393 and increases of spectral power in the rat EEG after activation of putative dopamine autoreceptors by a small dose of apomorphine, accompanied by hypokinesia and sedation have been reported earlier [16]. The same feature was also shown in this experimental series by administration of low dosages of talipexole and quinpirole, two dopamine D2 receptor agonists. The increase of delta and theta activity obviously indicates increased tiredness [6]. The delayed pattern is also somewhat reminiscent to the action of higher doses of the dopamine D2 antagonist sulpiride. However, sulpiride leads to more increases of alpha2 power than of delta power. This is probably due to a postsynaptic blockade of D2 receptors and signalizes attenuation of dopaminergic transmission. Increases of alpha2 spectral power have been observed after injection of the dopamine D1 blocker SCH 23390 [1] and also – using the same frequency definitions by telemetric recording in freely moving rats – by other authors [17]. Thus, increase of alpha2 power is in line with the view that dopaminergic transmission is attenuated under these conditions.

Higher doses of dopamine D2 agonists seem to act on the postsynaptic site and mimic stronger dopaminergic activity which can be recognized as attenuation of alpha2 power. This biphasic behavior of dopamine agonists has also been observed [18] using a similar telemetric technology, but recording from the surface of the brain. These authors observed increases of power after low dosages of D2 agonists accompanied by sedation as observed in the present study. Highest increases were also observed within the delta range by these authors. Decreases of spectral power were accompanied by stereotypes after higher dosages of apomorphine, quinpirole and talipexole. Thus, these results could be confirmed in the present study with respect to quinpirole and talipexole. There are also other reports in the literature on the effects of low-dose quinpirole: ‘Low quinpirole doses impaired performance of the prefrontal cortex and fine motor tasks, while higher doses improved memory performance and induced dyskinesias and ‘hallucinatory-like’ behavior’ in young adult monkeys [19]. In our series, the D2 agonist quinpirole predominantly decreased power only at the high dosage of 0.5 or 1 mg kg\(^{-1}\). These data are also in line with the observation that low doses of dopaminergic D2 agonists increase EEG power, whereas higher doses decrease EEG power [20].
From recent reports in the literature there is an alternative explanation for this time dependent biphasic behavior in dopaminergic neurotransmission. Investigations have shown that, apart from the canonical actions on G-protein mediated signaling and the regulation of the cAMP-PKS pathway, dopamine receptors exert their effects in vivo through cAMP-independent mechanisms. This newly recognized mode of dopamine receptor signaling involves proteins that have classically been implicated in G-protein-coupled receptor desensitization. Interestingly, the regulation of this β-arrestin-2-mediated pathway of dopamine action – confined to D2 receptors – shows particular kinetics (starting after 30 min and reaching maximum during the second hour after initiation), which corresponds to the delta increasing effects of dopaminergic drugs seen now within the same time line. Therefore, the pattern of changes as observed during this time course with increases of delta activity might be attributed to this signaling cascade caused by dopamine D2 receptor modulation.

Interesting in this respect is the fact that there are presynaptic D2 receptors sitting on cholinergic neurons. Consequently, low doses of dopamine D2 agonists or L-DOPA (which leads to dopamine acting also via D2 receptors) could induce an anticholinergic effect by interaction with heterosynaptic, presynaptic receptors. This means that the delayed increase of delta activity – as observed with the low dosages – presumably reflects attenuation of the cholinergic system as can be derived by comparison of this pattern to earlier results with anticholinergic drugs.

In general, the dopaminergic regulation of acetylcholine release has been known for a long time and was confirmed recently. A D2-like dopamine receptor activation inhibiting Ach-mediated inhibitory postsynaptic potential through a presynaptic mechanism was reported for the striatum. An explanation could be seen in the β-arrestin signaling pathway as mentioned above, which has also been described for muscarinic acetylcholine receptor signaling. Therefore, the similarity of spectral changes between the delayed effects of low dose antiparkinson medication and the spectral delta increasing effects of anticholinergic drugs like scopolamine and biperiden might be due to this β-arrestin signaling in cholinergic cells.

Furthermore, memory impairment induced by intraperitoneal administration of scopolamine could be counterbalanced by direct injection of quinpirole into the hippocampus of rats mimicking and corresponding to a high dose of quinpirole. Vice versa memory impairment induced by administration of the dopamine D2 receptor blocker sulpiride could be antagonized by nicotine. In addition, administration of nicotine in this model led to decrease of alpha 2 waves reflecting activation of the dopaminergic system which is in accordance with a report showing modulation of dopamine release by nicotine. Since electropharmacograms reflect the net balance of neurotransmitter action, delta and alpha 2 frequency changes obviously reflect this well known cholinergic-dopaminergic functional link on an intermediate anatomical level of the communication structure of the brain. Thus, low doses of D2 agonists probably activate presynaptic receptors sitting on cholinergic neurons resulting in a cAMP-independent inhibition of β-arrestin-2-mediated cholinergic transmission. Higher doses of L-DOPA seem to result in the activation of several transmission systems as reflected in decreases of delta (cholinergic system) and theta (noradrenergic system), in addition to the dopaminergic system (alpha2 frequency).

In conclusion, the results of this study support the hypothesis that dopaminergic activity is reflected mainly in alpha 2 frequencies of the electropharmacogram, recorded as field potential from 4 different brain areas in freely moving rats. The present study supports and extends earlier studies involving the action of amphetamine and dopamine D1 agonists like SKF 38393 and dihydrexidine, all of which predominantly attenuated spectral alpha2 frequency more or less accompanied by decreases in delta activity or general decrease of power in the case of cocaine, SKF 38393 or amphetamine. However, activation of a presynaptic dopamine D2 receptor (e.g. by increase of dopamine induced by a low dose of L-DOPA) seems to result in attenuation of cholinergic transmission as reflected in transient increases of delta activity, an effect time related to the recently described Akt-GSK-3 signaling cascade (β-arrestin-2-mediated signaling). It could well be that this effect relates to day-time tiredness and/or sleep attacks, which seem to occur in up to 30% of Parkinson patients. Among the Parkinson medications tested in this model up to now only dopamine D1 agonists, amantadine (not published) and rasagiline did not produce such delayed delta increases. Possibly, these drugs should be preferred or at least added when day time sleepiness or sleep attacks are reported by the patients.

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References


