

Suppression of exaggerated neuronal oscillations by oxytocin in a rat model of Parkinson's disease

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Abstract. Increased oscillatory activity has been demonstrated in the basal ganglia of Parkinson's disease (PD) patients. The aim of the present study was to evaluate the effects of oxytocin (OT) on local field potentials (LFPs) in a rotenone-induced rat model of PD. Adult male Sprague-Dawley rats were unilaterally injected with rotenone (3 µg/µl in DMSO) into the left substantia nigra pars compacta whereas vehicle group was received only DMSO. PD-developed rats were then administered either OT (160 µg/kg/day, *i.p.*) or saline for three weeks. Following treatment period, LFPs were recorded from the left striatum of freely moving rats and neuronal cell loss was evaluated by Nissl staining. We found significant increase in all frequency bands except delta in saline group when compared with vehicle ($p < 0.0005$), while treatment of OT prevented these alterations in electroencephalography (EEG) recordings. Besides, histopathological evaluation of the striatal sections revealed a significant cell loss ($p < 0.005$), whereas administration of rats with OT significantly lessened the neuronal death. These findings suggest that injury of dopaminergic neurons triggers exaggerated neuronal oscillations in the striatum and oxytocin may have some inhibitory effects on neuronal activity in PD.

Key words: Parkinson's disease — Rotenone — EEG — Oxytocin

Abbreviations: DA, dopamine; DBS, deep brain stimulation; EEG, electroencephalography; EMG, electromyography; GA, glutamate decarboxylase; LFPs, local field potentials; 6-OHDA, 6-hydroxy-dopamine; OT, oxytocin; PD, Parkinson's disease; ROS, reactive oxygen species; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; TH, tyrosine hydroxylase.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative disorders that produce muscular rigidity, bradykinesia, resting tremor and loss of postural balance. The principle pathology of PD includes selective and progressive loss of dopaminergic neurons in the substantia nigra and depletion of striatal dopamine. Although the etiopathogenesis of PD is still not fully understood, mounting evidence suggests that combination of factors including excitotoxic cell damage, environmental and genetic factors may have roles in the development of disease (Dauer and Przedborski 2003; Greenamyre et al. 2003; Cannon and Greenamyre 2011).

Rotenone, a well-known pesticide, rapidly crosses cell membrane due to its lipophilic structure and causes selective degeneration of the nigrostriatal dopaminergic pathway by inhibiting mitochondrial complex I. The rotenone-induced PD model appears to be an exact model in that complex I inhibition results in specific histological and behavioral symptoms similar to that observed in PD patients (Alam and Schmidt 2002; Cannon et al. 2009).

Several studies have indicated the importance of neuronal oscillations in physiological processes such as diurnal rhythms of the sleep-wake cycle, perception, memory and motor functions (Buzsaki 2002; Vandecasteele et al. 2007; Rutishauser et al. 2010). On the other hand, exaggerated oscillatory activity has been recorded in the external and internal segments of the globus pallidus and subthalamic nucleus in PD patients (Brown 2003, 2006). Recent clinical reports have demonstrated that dopaminergic drugs signifi-

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cantly reduce oscillatory activity in nigrostriatal pathway, suggesting a role of oscillations in the pathophysiology of PD. Furthermore, the degree of reduction in oscillatory activity following treatment correlates with the clinical improvement of motor symptoms (Brown 2006; Kühn et al. 2006).

Oxytocin (OT), a neurohypophyseal nanopeptide, exerts several important physiological functions, including regulation of uterus contraction during parturition and milk ejection reflex during lactation (Gimpl and Fahrenholz 2011). OT and its receptor are expressed extensively throughout the body suggesting the various paracrine and endocrine activities of OT (Gutkowska and Jankowski 2009; Gimpl and Fahrenholz 2011). Oxytocin has a wide spectrum of central and peripheral roles both in males and females including sexual and maternal behavior, social recognition, aggression, neuromodulation, cognition and tolerance (Gutkowska and Jankowski 2009; Gimpl and Fahrenholz 2011). Besides, it elicits anti-inflammatory and anti-oxidant effects in ischemia-reperfusion injury and sepsis-induced multiple organ damage *via* maintaining a balance of anti-inflammatory and pro-inflammatory cytokines (Iseri et al. 2005; Alizadeh et al. 2012). Recently, *in vitro* and *in vivo* studies have suggested the stimulatory effect of OT on cell viability against neuronal cell death (Bakos et al. 2012; Leuner et al. 2012).

In the present study, we aimed to explore the alterations in electrophysiological activity in a rat model of PD by recording local field potentials (LFPs) and whether OT has any influence on the electrophysiological activity of PD rats.

Materials and Methods

Animals

Twenty-one adult male Sprague-Dawley rats (200–240 g) were included in the study. All animals were kept on a 12 h light/dark cycle with lights on (8:00 a.m.) and lights off (8:00 p.m.) at room temperature ($22 \pm 2^\circ\text{C}$). They were fed by standard pellet diet and tap water *ad libitum* through the

study. The experimental procedures employed in the study were approved by the Institutional Animal Care and Ethical Committee of Ege University.

Chemicals

All chemicals were purchased from Sigma Chemicals (St. Louis, MO, USA) unless otherwise indicated.

Stereotaxic surgery

Animals were divided randomly into two groups: 1) rotenone group ($n = 14$), and 2) vehicle (DMSO, $n = 7$). Rotenone-induced PD model was performed stereotaxically, as described previously (Xiong et al. 2009). Briefly, rats were deeply anesthetized by the combination of ketamine hydrochloride (40 mg/kg, Alfamine®, Alfasan International B.V. Holland) and xylazine hydrochloric (4 mg/kg, Alfazyme®, Alfasan International B.V. Holland) *i.p.* and placed in a stereotaxic frame. Stereotaxic coordinates were calculated according to the rat brain atlas of Paxinos and Watson (Paxinos and Watson, 1998). Rotenone ($3 \mu\text{g}/\mu\text{l}$ in DMSO) was injected into the left substantia nigra pars compacta (SNc, AP: 5.0 mm, L: 2.0 mm, DV: 8 mm) with a 28-gauge Hamilton syringe. Sham-operated rats received only vehicle ($1 \mu\text{l}$ DMSO) instead of rotenone. The needle was left at the target site for an additional five minutes for complete diffusion of the drugs. All animals were injected penicillin (*i.m.*) to prevent postsurgical infection. One rat from DMSO group died during the first 24 hours of drug administration and was excluded from the study. After surgery, rats were monitored daily for behavior and health conditions. All rotenone-treated rats were developed PD-like symptoms such as hypokinesia, freezing and flexed posture within the 7–10 days following stereotaxical surgery. A summary of the study design is presented in Figure 1.

Apomorphine-induced rotation test

The extent of the rotenone lesion was assessed behaviorally 10 days after rotenone injection by challenge with apomor-

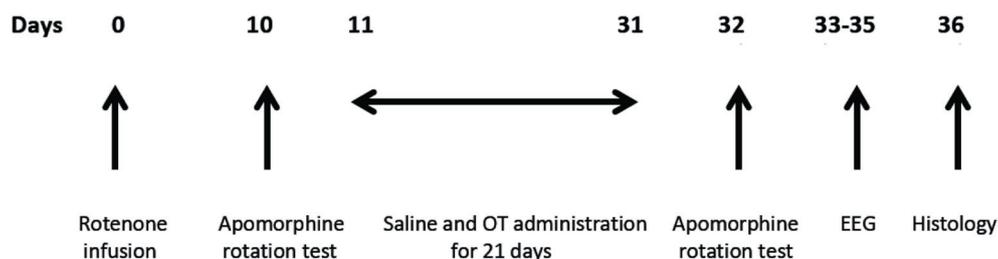


Figure 1. Schematic diagram of study design.

phine (2 mg/kg, *i.p.* dissolved in saline contains 0.01% ascorbic acid). After apomorphine injection, the rats were placed on a platform (1 × 1 meter) and full 360 degrees unilaterally turns in a 10 min period were recorded. The model was considered successful in those animals that made ≥ 70 full unilaterally rotations in 10 min (Jin et al. 2008). Rotation test was repeated at the end of treatment protocol to evaluate the effect of OT on rotenone toxicity.

Oxytocin treatment

Following rotation test, the valid PD rats were randomly divided into two groups of seven animals each. Group 1 ($n = 7$) was administered saline (1 ml/kg/day, *i.p.*) and Group 2 ($n = 7$) was administered Oxytocin (Pituisan®, Alfasan International B.V. Holland) 160 μ g/kg/day (*i.p.*) through three weeks.

Electrophysiological recordings

Electroencephalography (EEG) recordings were performed following saline and OT treatments. LFPs were recorded from the left striatum of awake and freely moving rats in a plastic box. Briefly, on the day of experimentation, rats were deeply anesthetized by mixture of ketamine (40 mg/kg, *i.p.*) and xylazine (4 mg/kg, *i.p.*) and bipolar semi-microelectrodes (Polyamide-coated stainless steel wires, 0.1 mm diameter and electrical resistance $< 1 \Omega/10$ mm) were implanted into the left striatum (AP: 0 mm, L: 3.4, DV: 5.2 mm) under stereotaxic conditions. A reference electrode was placed in the skull above the ipsilateral cerebellar hemisphere. The implanted electrodes were linked to a microconnector and fixed to the skull with dental cement. When rats became active 1–2 h after the surgery, there were allowed to return to their cages. Animals were allowed at least 48 h to recover from the surgery (Erbas et

al. 2012a). All registrations were made from 9:00 to 12:00 h in the morning. After the initial baseline session, striatal LFPs were registered for 30 min in the range of 1–60 Hz *via* Biopac MP30 system and converted to power spectral density algorithm with a frequency resolution of ~ 1 Hz. LFPs were amplified (10 000 \times) and band pass filtered (0.3–1500 Hz). The raw EEG spectra of striatum were averaged for 30 minutes and same procedure was employed for each of the five frequency bands: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), low beta (12–20 Hz) and high beta (20–30 Hz). Figure 2 validates the histological position of the electrode in the striatum.

Histopathological evaluation

The extent of the rotenone lesion was examined quantitatively in the striatum by Nissl staining. Briefly, following electrophysiological recordings, all animals were anesthetized and perfused with 200 ml of 4% formaldehyde in 0.1 M phosphate-buffer saline (PBS). After the brains were removed, they were moved into 30% sucrose and stored at 4°C until infiltration was complete. The brains were cut coronally on a frozen sliding microtome at 40 μ m and mounted on gelatinized glass slides. The striatal sections were stained with cresyl violet for visualising general morphology and total cell count. All sections were examined and photographed with Olympus C-5050 digital camera at Olympus BX51 microscope. Total neuron counts were performed in six sections *per* studied group by an image analysis system (Image-Pro Express 1.4.5, Media Cybernetics, Inc. USA).

Tyrosine hydroxylase immunostaining

For immunohistochemistry, sections were incubated with H₂O₂ (10%) for 30 min to eliminate endogenous peroxidase

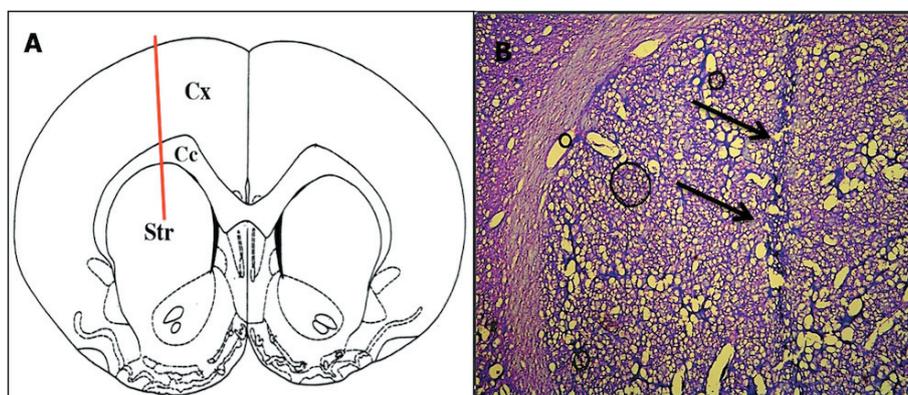


Figure 2. A. Schematic diagram illustrating recording site in the striatum (according to Paxinos and Watson 1998). B. Histological verification of the position of the EEG electrode in a striatal section (arrows indicate the electrode placement).

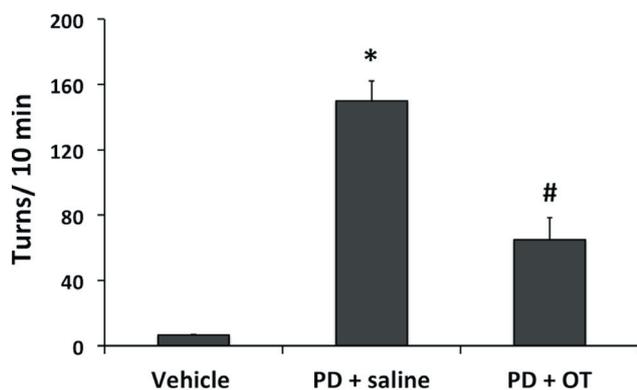


Figure 3. Results of apomorphine-induced rotational test following saline and OT treatments in PD rats. The number of rotations was significantly higher in saline-treated group compared to vehicle (DMSO) group. OT-treated rats showed a significant decline in apomorphine-induced rotations compared to saline group. Data are the mean \pm S.E.M. * $p < 0.0005$ vs. vehicle; # $p < 0.005$ vs. saline-treated group. OT, oxytocin; PD, Parkinson's disease.

activity and then blocked with 10% normal goat serum (Invitrogen) for 1 h at room temperature. The sections were then incubated in primary antibodies (tyrosine hydroxylase, Chemicon; 1/100) for 24 h at 4°C. Antibody detection was carried out with the Histostain-Plus Bulk kit (Invitrogen) against rabbit IgG and 3,3' diaminobenzidine (DAB) was used to visualize the final product (Xiong et al. 2009). All sections were washed in PBS and photographed with Olympus C-5050 digital camera mounted on Olympus BX51 microscope. Tyrosine hydroxylase (TH) immunostaining in the striatal sections was quantified by determining intensity *per area* using Image J software (National Institutes of Health, Bethesda, MD). The intensity measurements were performed in three striatal sections of each brain and 8–10 microscopic fields in each section.

Statistical analysis

All quantitative data were analyzed by one-way ANOVA, followed by Tukey's HSD post-hoc tests. The p -value of <0.05 was considered to indicate a significant difference between two groups. All data were presented as the mean \pm S.E.M.

Results

Apomorphine-induced rotation test

Apomorphine-induced rotational behavior was evaluated prior to OT treatment to confirm rotenone-induced PD

model. All rotenone injected rats made ≥ 70 full unilaterally rotations in 10 min and accepted as PD. Following treatment period, rotation test was repeated to assess the effect of OT treatment. Saline-treated PD rats showed significantly higher rotational numbers compared to vehicle group ($p < 0.0005$). However, OT treatment significantly diminished the rotational behavior compared to rats receiving saline (65 ± 14.42 and 150 ± 12.25 turns/10 min, respectively) ($p < 0.005$, Fig. 3).

Evaluation of cell injury in the striatum

Dopaminergic cell loss in the striatal sections was further confirmed by Nissl staining and TH immunostaining. As shown in Fig. 4, total count of Nissl-stained striatal neurons confirmed a significant cell loss in saline-treated group, while DMSO group revealed a regular morphology in the striatum ($p < 0.0005$). However, striatal cell loss was significantly reduced by OT treatment compared to saline-treated group ($p < 0.005$). Similarly, there was a considerable decrease in TH immunoreactivity of saline group compared to vehicle ($p < 0.05$) whereas OT treatment significantly lessened the loss of TH+ neurons in the striatum ($p < 0.05$, Fig. 5).

EEG analysis

In the present study, power spectral analysis technique was utilized to quantify changes in striatal LFPs obtained from rats, as mentioned earlier in the methods. One-way ANOVA revealed a significant difference between the groups for all bands ($p < 0.0005$). Fig. 6 demonstrates the striatal EEG recordings in all groups and Fig. 7 describes the alterations in frequency bands as delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz) and beta (12–30 Hz). Post-hoc Tukey HSD test revealed a marked decrease in delta band in saline-treated rats when compared with vehicle-treated rats ($p < 0.0005$). However, treatment with OT completely reversed the PD-induced changes in delta power. On the other hand, a significant elevation in theta, alpha and beta band power was observed in saline-treated group in comparison with vehicle group ($p < 0.005$, $p < 0.0005$ and $p < 0.05$, respectively). Similarly, OT treatment significantly reversed all PD-induced alterations in EEG (Fig. 7).

We also evaluated the alterations in low beta (12–20 Hz) and high beta (20–30 Hz) bands following rotenone treatment. There was no statistically significant difference in low beta and high beta bands between vehicle-treated and saline-treated groups. Interestingly, OT administration significantly enhanced low beta power compare to saline treatment (79.6% vs. 73.4 , $p < 0.05$) whereas no significant change was found in high beta power (Fig. 8).

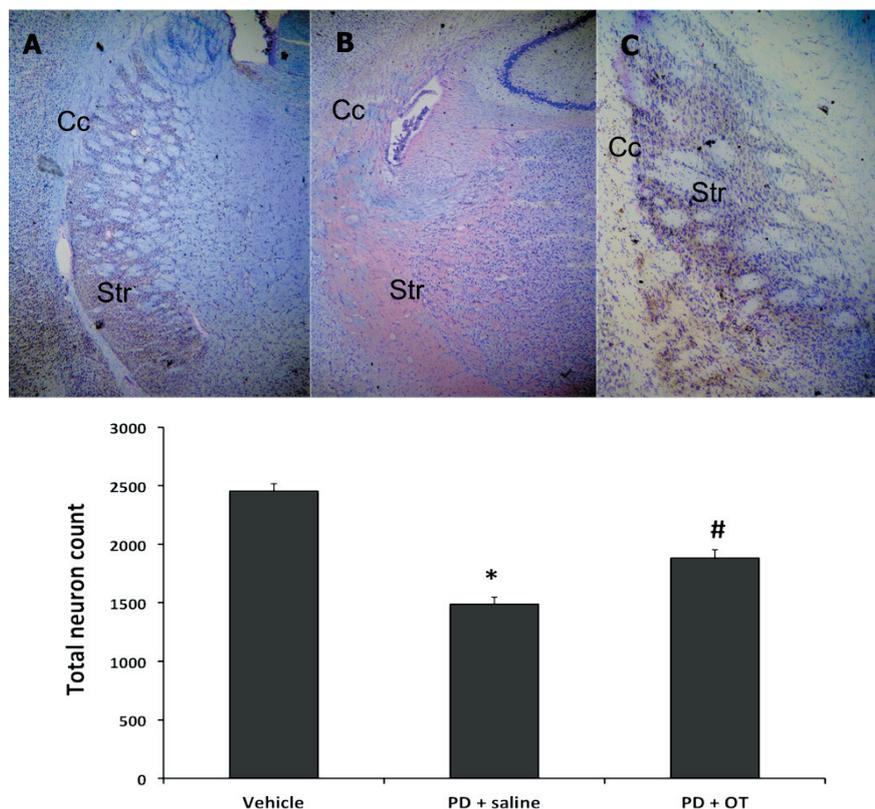


Figure 4. Evaluation of cell loss in the striatum. **A.** Vehicle (DMSO group). **B.** Saline-treated PD group. **C.** OT-treated PD group. Total neuron counts were performed in six sections *per* studied group by an image analysis system. * $p < 0.0005$ vs. vehicle and # $p < 0.005$ vs. saline-treated group. Bars represent means \pm S.E.M. Scale bars represent 125 μ m. Cc, Corpus callosum; OT, oxytocin; PD, Parkinson's disease; Str, striatum.

Discussion

The primary findings of the present study were that unilateral lesion of the dopaminergic neurons significantly caused an increase in the striatal LFPs and systemic injection of OT could successfully suppress the exaggerated oscillations in rotenone-lesioned rats. These results were accompanied by the improvement of behavioral and histological changes.

Rotenone, as an environmental toxin, specifically affects electron transport chain in mitochondria and causes reactive oxygen species (ROS) overproduction within the cells (Greenamyre et al. 2003; Cannon and Greenamyre 2011). As confirmed by previous studies, dopaminergic neurons are more vulnerable to the prolonged exposure of rotenone than the other neurons including GABAergic, cholinergic or serotonergic (Heikkila et al. 1985; Marey-Semper et al. 1995; Sherer et al. 2003; Saravanan et al. 2005). Intracerebral administration of rotenone can lead progressive neuropathological changes in the nigrostriatal pathway mimicking idiopathic PD (Saravanan et al. 2005). Systemic administrations of rotenone also cause severe depletion of striatal dopamine levels in rats, however, these models have some limitations due to its peripheral toxicity and high mortality in animals. In the present study,

rotenone-treated animals developed motor and postural deficits characteristic of PD, such as hypokinesia, freezing and flexed posture, at the end of the first week following stereotaxic surgery. Furthermore, both Nissl staining and TH immunohistochemistry confirmed a marked decrease of nigrostriatal dopaminergic neurons in rotenone-treated rats. Despite the fact that the current study suggests a highly reproducible procedure in terms of the behavioral and pathological features of PD, the variability observed in toxin-induced PD models range from none to nearly complete dopaminergic lesions is interesting (Ferrante et al. 1997; Betarbet et al. 2000; Sherer et al. 2003b; Zhu et al. 2004). This variability is most likely due to differences in the injection site (injection of toxin into the SNc vs. medial forebrain bundle), dosage of toxin (single vs. repeated) or species examined (rat vs. mouse).

Previous studies have revealed that some of the striatal TH+ neurons also express the enzyme glutamate decarboxylase (GAD) and therefore, these neurons appear to represent a particular subtype of GABA-ergic striatal interneurons capable of producing both GABA and dopamine (DA). Furthermore, the quantity of these neurons was reported to increase significantly in parkinsonian rodents and monkeys compared with controls (Tashiro et al. 1989; Betarbet et al. 1997; Tandé et al. 2006). Tandé et al. have indicated that

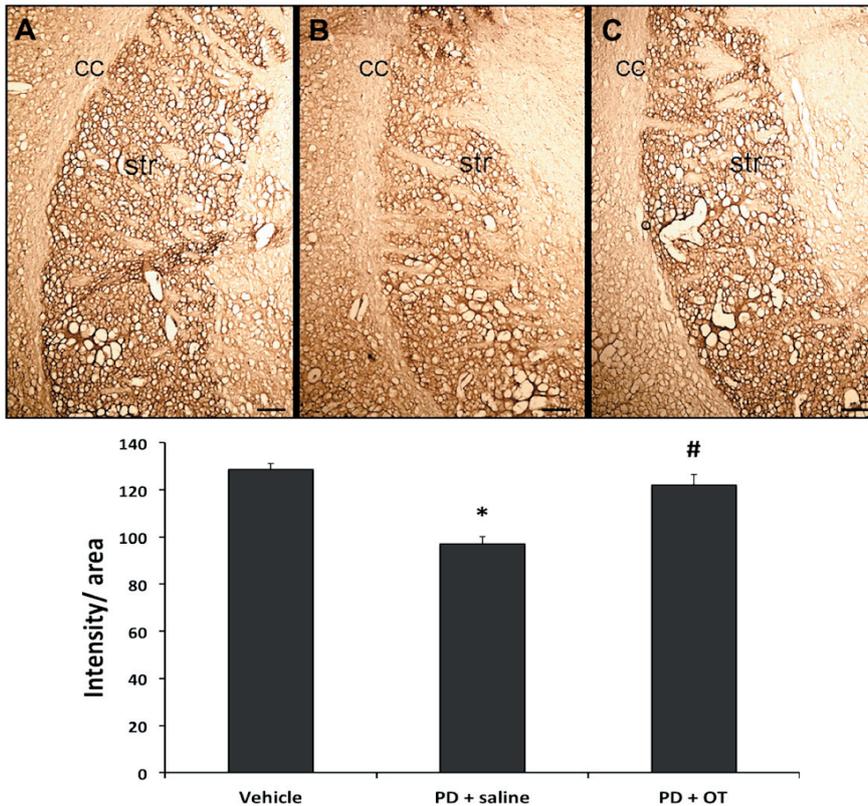


Figure 5. Tyrosine hydroxylase immunohistochemistry. **A.** Vehicle (DMSO group). **B.** Saline-treated PD group. **C.** OT-treated PD group. Quantification of the optical density of tyrosine hydroxylase immunostaining in the striatum revealed significant difference between the groups. * $p < 0.0005$ vs. vehicle and # $p < 0.005$ vs. saline-treated group. Bars represent means \pm S.E.M. Scale bars represent 125 μ m. For abbreviations, see Fig. 4.

TH+ neurons that appear after dopamine depletion in the striatum of aged macaques do not result from neurogenesis but rather from a phenotypic shift of pre-existing neurons (Tandé et al. 2006). On the other hand, in a recent study, it has been demonstrated that these neurons appear in the striatum as early as 3 days after a 6-OHDA lesion but by 1 week after the lesion, the number of TH+ neurones starts to decline and this decline lasts significantly over time (Darmopil et al. 2008).

In recent years, oscillatory activity in the basal ganglia has attracted a great deal of interest because it is thought to be essential for both normal physiological processing of voluntary movement and pathophysiology of PD. Two distinct methods, measuring of single-/multiunit activity and LFPs, are often used to evaluate the frequency of synchronized and/or oscillatory activity in networks of neurons. Single-/multiunit activity represents the action potential discharges of one cell or a small group of neurons, whereas LFPs are dominated by synchronized, subthreshold and, to a smaller degree, suprathreshold events in much larger populations of neurons (Berke et al. 2004). Electrophysiological studies have shown that dopamine depletion has significant effects on synchronization and oscillatory activity in the nigrostriatal pathway (Brown 2003, 2006; Hammond et al. 2007; Moran et al. 2010). LFPs recorded from the subthalamic nucleus (STN) in human with PD have revealed increased

power in the beta oscillations supporting an abnormal synchrony among basal ganglia and cortical circuits (Brown 2003; Kühn et al. 2004, 2006). Similar to the human studies, experimental animal models of PD have demonstrated that loss of dopamine neurons significantly increased beta frequency band recorded from the STN and cortex (Sharott et al. 2005). Furthermore, it has been reported that high beta LFPs (25–40 Hz) recorded from substantia nigra was selectively increased in the dopamine-depleted hemisphere than in non-lesioned and control hemisphere during motor activity (Avila et al. 2010).

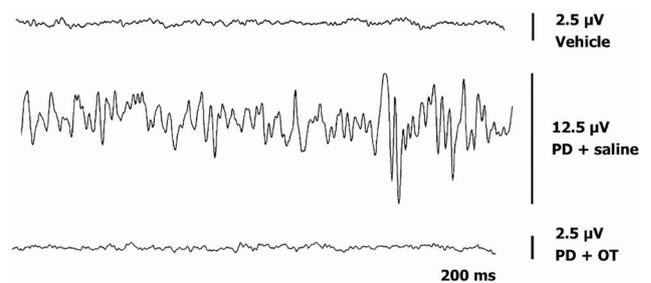


Figure 6. Examples of EEG recordings from the striatum of vehicle, saline-treated and OT-treated PD rats. For abbreviations, see Fig. 4.

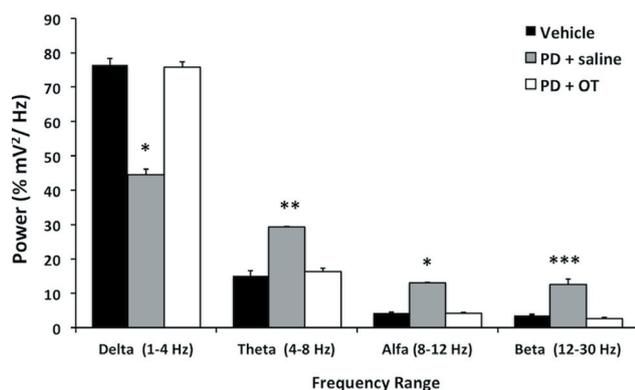


Figure 7. Striatal EEG and its frequency bands (percent of total power). Data are shown as mean \pm S.E.M. Statistical evaluation was performed by one-way ANOVA followed by Tukey's HSD post-hoc test ($n = 6-7$); * $p < 0.0005$, ** $p < 0.005$ and *** $p < 0.05$ vs. vehicle and OT-treated group. For abbreviations, see Fig. 4.

Electrical activity of striatal neurons is modulated by dopamine and degeneration of nigrostriatal pathway causes long-lasting changes on spontaneous activity of striatal neurons. Dopamine tonically prevents striatal acetylcholine release under physiological conditions by stimulating D2 receptors, and inhibition of D2 receptors or depletion of striatal dopamine can cause increased levels of acetylcholine in the striatum (DeBoer et al. 1996; Ikarashi et al. 1997). In addition, corticostriatal glutamatergic pathways can enhance their activities following nigrostriatal lesion (Meshul et al. 1999). Although there are controversial results regarding the striatal activity in PD, our findings confirmed the association between dopamine depletion and increased oscillatory activity in the striatum. In addition, we observed a non-significant decrease in low beta and elevation in high beta band power in rotenone-lesioned rats. These results are in agreement with previous observations. Vorobyov et al. (2003) have reported a decrease in low beta (12.6–17.5 Hz) and an increase in high beta band (17.6–27.5 Hz) power in the striatum of 6-OHDA lesioned rats, which are modified by apomorphine and MK-801, a NMDA receptor blocker. More recently, based on experimental and computational models, it has been suggested that dopamine depletion and increased striatal cholinergic activity can lead to enhanced beta frequency oscillations in the striatum (McCarthy et al. 2011).

Although the functional physiological importance of both normal and pathological beta rhythms remains to be clarified, recent observations have indicated a considerable correlation between the abnormal rhythms and movement impairments in PD patients. Moreover, many chemicals including anti-parkinsonian drugs and deep brain stimulation (DBS) can modify oscillatory activity in human and animals (Wichmann et al. 1994; Brown 2003; Lehmkuhle et

al. 2009). Therefore, any therapy, which can lessen the exaggerated neuronal activity, would attenuate clinical symptoms in PD patients.

In the current study, treatment of rats with 160 $\mu\text{g}/\text{kg}/\text{day}$ OT for 3 weeks successfully reduced the rotenone-induced neurotoxicity and suppressed the increased activity in EEG. To our knowledge, there is no use of oxytocin in a similar protocol and therefore we cannot compare the dosage regime used in the present study with others. However, previous experimental studies have recommended that pharmacological doses of OT between 100–1000 $\mu\text{g}/\text{kg}$ are more effective in preventing and/or lessening tissue damage (Pettersson et al. 2001; Iseri et al. 2005; Leuner et al. 2012; Erbas et al. 2013). Moreover, in a recent study, we found that both 80 $\mu\text{g}/\text{kg}$ OT and 160 $\mu\text{g}/\text{kg}$ OT could inhibit pentylentetrazol-induced seizures and significantly improve EEG abnormalities in rats (Erbas et al. 2012a).

According to results of our study, we propose that OT can act as a neuroprotective agent and reduce cell death in the injured striatum because of its anti-inflammatory, anti-apoptotic, anti-oxidant and trophic effects. Indeed, many studies, both *in vitro* and *in vivo*, have suggested the cytoprotective and trophic potential of oxytocin using various experimental models (Iseri et al. 2005; Ceanga et al. 2010; Alizadeh et al. 2012; Bakos et al. 2012; Erbas et al. 2012b; Leuner et al. 2012). For instance, preincubation of cells with OT reduces toxicity and induce cell viability in neuronal cell cultures exposed to 6-OHDA (Bakos et al. 2012). Recently, we have demonstrated the beneficial effect of OT against sepsis-induced polyneuropathy by evaluating electromyography (EMG) changes and biochemical parameters including plasma TNF- α , malondialdehyde and total anti-oxidant capacity in critical illness (Erbas et al. 2013).

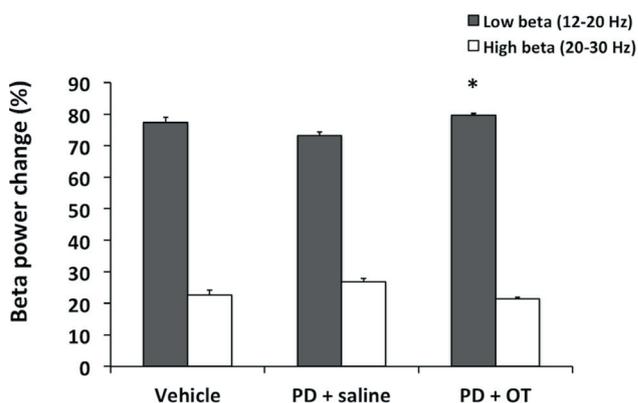


Figure 8. The effects of oxytocin on the striatal beta oscillations in experimentally induced- PD rats. Data are expressed as mean values \pm S.E.M. Statistical evaluation was performed by one-way ANOVA followed by Tukey's HSD post-hoc test ($n = 6-7$); * $p < 0.005$ vs. saline-treated group. For abbreviations, see Fig. 4.

Taken together, our findings support that injury of dopaminergic neurons generate exaggerated neuronal oscillations in the striatum and oxytocin may have some inhibitory effects on neuronal activity in PD. Investigating how striatal activity is altered by oxytocin may disclose new alternative therapeutic approaches for Parkinson's disease.

Conflict of interest: The authors report no declarations of interest.

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Received: December 11, 2012

Final version accepted: April 19, 2013