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Research Article

# Kisspeptin-54 Ameliorates Electrocardiographic Abnormalities in an Experimental Parkinson's Rat Model

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## Abstract

**Aim:** Cardiac complications may arise in association with Parkinson's disease as age progresses. Kisspeptins are a group of peptides that mediate their physiological functions by binding to the GPR54 receptor. This study aimed to investigate whether KP-54 has an effect on the electrical activity of the heart in an animal model of Parkinson's disease.

**Material and Method:** Sprague-Dawley rats weighing between 290–310 g were used. An experimental hemiparkinsonian rat model was generated via stereotaxic injection of the neurotoxin 6-OHDA into the right medial forebrain bundle, effectively replicating unilateral dopaminergic neuronal loss. Rats received either control (aCSF, 5 µL, ICV) or KP-54 (3 nmol/kg, ICV) treatment once daily for seven consecutive days. At the end of the seventh day, behavioral tests were conducted on the rats. Following the behavioral tests, electrocardiographic (ECG) recordings were obtained.

**Results:** 6-OHDA significantly increased catalepsy time ($p<0.001$), which was effectively reduced by KP-54 ($p<0.05$). In the open field test (OFT), rats injected with 6-OHDA showed decreased distance traveled ($p<0.001$) and velocity ($p<0.01$) compared to controls, whereas KP-54 treatment partially improved these motor impairments ($p<0.01$). ECG data revealed that the heart rate (HR), impaired following 6-OHDA administration ($p<0.01$), returned to control levels in the 6-OHDA + KP-54 group ($p<0.01$). There were no notable differences between the groups regarding P duration, PR and QRS interval. However, the QT and QTc intervals were significantly increased ($p<0.01$) in the Parkinson's group and were normalized to control levels in the 6-OHDA + KP-54 group ($p<0.05$). These findings indicate that KP-54 corrected the QT prolongation induced by 6-OHDA.

**Conclusion:** In conclusion, the present findings suggest that alterations in HR and prolongation of the QT interval observed in Parkinson's disease could be prevented by the neuropeptide kisspeptin. Nevertheless, further research involving different administration routes is required to validate and expand upon these results.

**Keywords:** Electrocardiography, Kisspeptins, Parkinson's disease

## INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopamine-producing neurons in the substantia nigra. This neuronal loss leads to the development of motor symptoms, including tremors, rigidity, and bradykinesia (1,2). While current treatments (e.g., levodopa and dopamine agonists) alleviate symptoms, they do not halt disease progression and may cause side effects, including cardiovascular issues (3). Autonomic dysfunction, such as orthostatic hypotension and arrhythmias, is common and can be worsened by dopaminergic therapy, underscoring the need for treatments targeting both neurological and cardiovascular aspects of PD (4).

Kisspeptins are neuropeptides central to reproductive hormone regulation via activation of GnRH neurons in the hypothalamus (5). Encoded by the KISS1 gene, they are processed into active forms like kisspeptin-54 (KP-54), KP-14, KP-13, and KP-10, all acting through the GPR54 (KISS1R) receptor (6). KP-54 stands out for its longer half-life (~32 minutes vs. ~4 minutes for KP-10) and ability to cross the blood-brain barrier, allowing for more sustained central effects compared to shorter, rapidly cleared fragments (7).

Emerging evidence indicates that kisspeptins have significant effects beyond the reproductive axis, including

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roles in the cardiovascular system. GPR54 is expressed in cardiovascular tissues such as blood vessels and the heart (8). In the cardiovascular system, it is found in endothelial cells and cardiomyocytes, suggesting a direct role in modulating vascular tone, heart rhythm, and contractility (9). While its precise effects are still being studied, current evidence points to involvement in vasoconstriction and blood pressure regulation. Studies show that KP-10, KP-13, and KP-54 act as potent vasoconstrictors, similar to angiotensin II, and KP-10 enhances cardiac contractility in rodents and humans (9,10). These effects suggest kisspeptin modulates vascular tone, heart rate, and myocardial function. Notably, KP-54 can cross the blood-brain barrier, potentially influencing central cardiovascular regulation (7). While these findings highlight its therapeutic potential, further research is needed to clarify kisspeptin's role in cardiovascular physiology and disease.

PD patients often experience autonomic and cardiac issues, raising the question of whether kisspeptin affects cardiac function in this context. While kisspeptin's effects on blood pressure and heart rate have been studied, its influence on cardiac electrophysiology remains largely unknown, with no direct data on ECG parameters. Therefore, the present study was designed to investigate the effects of KP-54 on electrocardiographic parameters in a hemiparkinsonian rat model. We utilized 6-hydroxydopamine (6-OHDA) to create an experimental PD model and evaluated whether central administration of KP-54 could ameliorate ECG abnormalities. In particular, we focused on how KP-54 influences heart rate and various ECG intervals (P wave, PR, QRS, QT, and corrected QT) in 6-OHDA–lesionned rats. By addressing this gap, our study aims to shed light on the potential cardio-regulatory effects of KP-54 in a PD context.

## MATERIAL AND METHOD

### Animals

Adult male Sprague-Dawley rats (weighing 290–310 g) were used for all experiments. Rats were housed in transparent Plexiglas cages in a temperature-controlled room (22±2 °C) with a 12-hour light/dark cycle. They had free access to standard chow and water ad libitum. All experimental procedures were conducted in accordance with institutional and international guidelines for animal care and were approved by the Akdeniz University Faculty of Medicine Animal Ethics Committee (Approval No. 1689/2024.04.002, Decision date: 15.04.2024). Throughout the study, efforts were made to minimize animal stress and discomfort.

### Experimental Design

In the hemiparkinsonian rat model, 6-OHDA, a catecholaminergic neurotoxin, was administered into the right medial forebrain bundle using stereotaxic injection. The rats were administered either a vehicle (control) treatment or KP-54 (intracerebroventricular, ICV) once daily for seven consecutive days. The control treatment consisted of an injection of artificial cerebrospinal fluid (5 µL, ICV). The final dose of KP-54 was administered to the rats on the seventh day, 30 minutes before conducting the behavioral tests. Electrocardiographic (ECG) recordings were obtained one hour after the behavioral tests. Motor function in the 6-OHDA-induced PD model was objectively evaluated through the open field and catalepsy tests. Detailed experimental procedures are outlined in Figure 1.

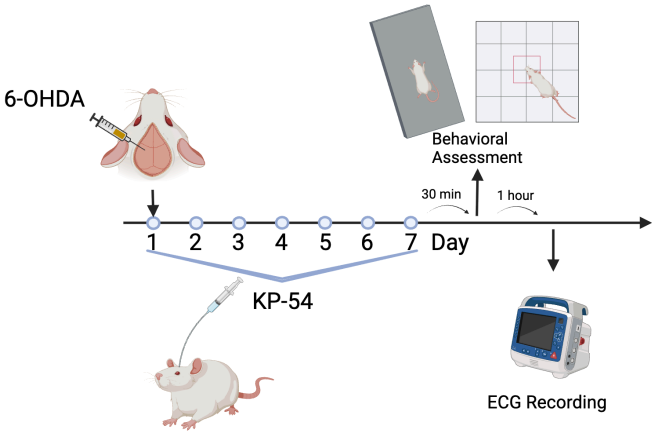


**Figure 1.** An overview of the experimental procedure timeline

### Surgery

Following intraperitoneal administration of ketamine (60 mg/kg) and xylazine (12 mg/kg), the animals were placed in a stereotaxic apparatus. The 6-OHDA (3×4 µg/µl) was injected stereotaxically into the right medial forebrain bundle using the following coordinates: 2.2 mm anteroposterior, 1.5 mm mediolateral (ml), and 8 mm dorsoventral relative to the bregma. The 6-OHDA solution prepared fresh in sterile saline with 0.2 mg/ml ascorbic acid, was administered in a 3 µl volume. In the sham surgery group, 0.1% ascorbic acid was used as a vehicle control. The syringe was kept in place for an additional 3 minutes to allow for optimal diffusion of the neurotoxin. To administer KP-54 (3 nmol/kg) via the ICV route, a cannula was surgically inserted into the lateral ventricle (11). After lesion induction, a 26G polyethylene cannula was placed stereotaxically into the right lateral ventricle using coordinates of 0.8 mm AP, 1.4 mm ML, and 4 mm DV from the bregma and skull surface, based on a rat brain atlas. To maintain stability, the cannula was firmly fixed in place using screws and dental cement. Central KP-54 ICV injections were administered every day for seven days.

### ECG Recordings

Electrocardiographic recordings were obtained on the final day of the experiment to evaluate cardiac electrical activity in each group. One hour after completion of the behavioral tests on the 7th day, rats were re-anesthetized with a light dose of ketamine (50 mg/kg i.p.) and xylazine (5 mg/kg i.p.) to minimize movement while preserving autonomic function as much as possible. Once anesthetized, each rat was placed in a supine position, and standard lead II ECG electrodes

were attached (subdermal needle electrodes). The ECG was continuously recorded for a period of 10 minutes using the data acquisition system (Biopac Systems, Inc., USA) at a sampling rate of 1 kHz. During recording, body temperature was maintained with a warming pad, and the depth of anesthesia was monitored to ensure the absence of pain reflexes while maintaining a relatively stable heart rate. The following ECG parameters were measured from the lead II recordings: heart rate (HR, beats per minute), P wave duration, PR interval, QRS complex duration, QT interval, and corrected QT (QTc) interval. Heart rate was determined by counting the number of R-wave peaks over the 10-minute recording period (and expressed as bpm). The QT interval was measured from the start of the QRS complex to the end of the T wave; QTc was calculated using Bazett's formula (QTc=QT/√(RR interval)) (12). For each rat, multiple cardiac cycles were analyzed to obtain representative values for intervals. ECG traces were analyzed offline using LabChart software (ADInstruments, NZ) by an investigator blinded to group assignments. Any ECG segments with movement artifacts were excluded from the analysis.

### Statistical Analysis

All data were analyzed using GraphPad Prism 8.0 (GraphPad Software, USA). Prior to statistical comparisons, datasets were checked for normality using the Shapiro-Wilk test. For normally distributed data, group comparisons were performed using one-way analysis of variance (ANOVA). This was followed by Tukey's post hoc test for multiple comparisons to identify differences between specific groups. Behavioral outcomes (catalepsy duration, open field distance, and velocity) and ECG parameters (HR, intervals) were each analyzed with one-way ANOVA across the three groups (Control, 6-OHDA, 6-OHDA+KP-54). All results are reported as the mean±standard error of the mean (SEM). A threshold of $p<0.05$ was considered statistically significant. In figures, statistically significant differences are indicated with asterisks or other annotations as described in the figure legends.

## RESULTS

### KP-54 Reduces the Motor Deficits Caused by 6-OHDA

In comparison to the control rats (1.24±0.09 s, n=7), 6-OHDA exhibited a marked increase in catalepsy duration (2.55±0.28 s, $p<0.001$, n=7). The elevation in catalepsy time induced by 6-OHDA was reduced by KP-54 (1.87±0.15 s, $p<0.05$ n=7), suggesting that KP-54 effectively mitigated the cataleptic effects of 6-OHDA (Figure 2A).

In the OFT, control rats traveled a typical distance. The 6-OHDA group (1982±175.9 cm, n=7) displayed a notable decrease in locomotor activity compared to the control rats (975.7±123.7 cm, $p<0.001$, n=7). On the other hand, the 6-OHDA + KP-54 group (1703±119.8 cm, $p<0.01$, n=7) showed a partial recovery in locomotor function (Figure 2B).

The control group (7.43±0.44 cm/s, n=7) exhibited the highest average velocity during the test. However, the 6-OHDA group (3.48±0.37 cm/s, $p<0.001$, n=7) showed a significant reduction in velocity, emphasizing the detrimental impact of 6-OHDA on movement velocity. Notably, administration of KP-54 (5.64±0.41 cm/s, $p<0.01$, n=7) led to a significant improvement in mean velocity, indicating a partial but meaningful recovery (Figure 2C).

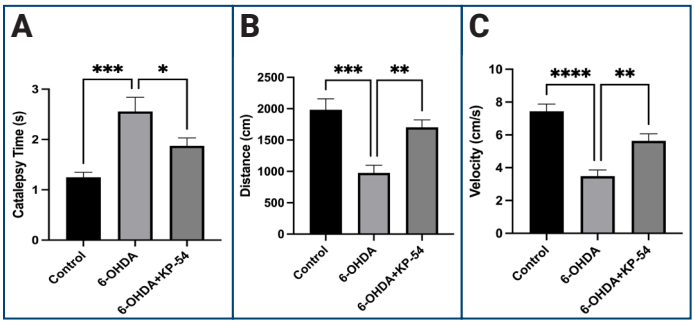


**Figure 2.** The impact of KP-54 administration on motor performance parameters (catalepsy duration, **A**; total distance traveled, **B**; and velocity, **C**) was evaluated in a hemiparkinsonian rat model. Statistical analysis was performed using one-way ANOVA followed by Tukey's post hoc test (n=7 rats per group); Levels of significance are indicated as follows: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001; All data are presented as mean ± S.E.M

As demonstrated in our previous study, the findings indicate that 6-OHDA causes motor impairments, evidenced by prolonged catalepsy duration and reductions in both distance traveled and movement speed (11). In contrast, ICV central administration of KP-54 helps reduce these motor impairments induced by 6-OHDA.

### KP-54 Restored the Increased QTc Interval to Its Baseline Following 6-OHDA Administration

Figure 3 illustrates the electrocardiographic parameters (including HR, P duration, QRS complex duration, PR, QT interval, and QTc) measured after 6-OHDA and KP-54 administration. HR refers to the number of heartbeats occurring within a 10-minute time period. In the group treated with 6-OHDA (250.7±8.03 bpm, n=7), heart rate (HR) was significantly reduced when compared to the control rats (293.3±7.41 bpm, $p<0.01$, n=7). This reduction was reversed to control levels following KP-54 administration (296.8±6.39 bpm, $p<0.01$, n=7, Figure 3A). The P wave duration, PR interval, and QRS duration did not exhibit any significant changes in either the 6-OHDA group or the 6-OHDA + KP-54 group (Figure 3B-C-D).

However, when examining the QT interval and QTc duration, a notable elevation was detected in the 6-OHDA group (71.44±3.24 ms and 159.6±12.53 ms, $p<0.01$, $p<0.05$, respectively; n=7) compared to the control rats (56.86±3.22 ms and 114.9±2.98 ms, respectively; n=7). In contrast, in the 6-OHDA + KP-54 group (58.4±1.8 ms and 111.2±2.92 ms, $p<0.05$, $p<0.05$, respectively; n=7), these values returned to control levels (Figure 3E–F).

The data show that in the 6-OHDA-induced hemiparkinsonian rat model, only the QT interval was significantly prolonged in the ECG waves, and this prolongation was reversed after the administration of KP-54.

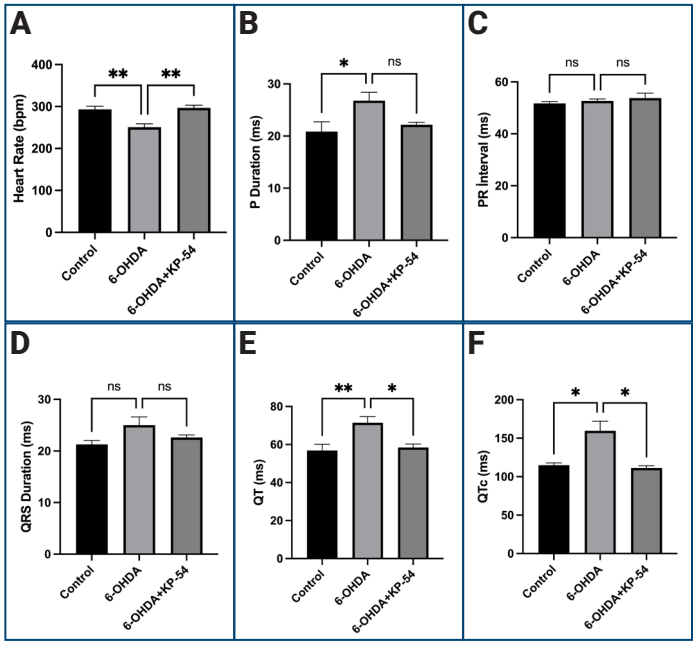


**Figure 3.** Electrocardiographic assessment of rats administered with 6-OHDA and 6-OHDA+KP-54; Each bar represents the alterations observed in ECG parameters; Statistical comparisons of group means were conducted using one-way ANOVA followed by Dunnett's test; Statistical significance levels are represented as follows: *p<0.05, **p<0.01, and ***p<0.001; All data are presented as mean±S.E.M; All values are expressed as the mean±S.E.M

## DISCUSSION

In this study, we investigated the effects of the neuropeptide KP-54 on cardiac electrical abnormalities in a rat model of PD. Our major findings can be summarized as the 6-OHDA lesion resulted in marked ECG changes, including a reduced heart rate and prolonged QT/QTc intervals relative to control groups. This suggests that the PD model produced bradycardia and a delay in cardiac repolarization, which are reminiscent of autonomic dysfunction-related cardiac effects. Notably, the KP-54 treatment normalized the heart rate and brought the abnormally prolonged QT and QTc intervals back to the control level. To our knowledge, this is the first direct evidence that KP-54 can modulate ECG parameters in an experimental Parkinsonian setting. The findings raise the possibility that kisspeptins have beneficial effects on the autonomic and cardiovascular dysfunction associated with PD.

The relationship between kisspeptin and PD is a novel area of investigation. However, our research team findings and other emerging evidence suggest that kisspeptin signaling may favorably influence PD-related pathology. One potential link is through neuroprotection: PD is characterized by the loss of specific neuronal populations (e.g., dopaminergic neurons and also some cholinergic and other brainstem neurons). Recent studies indicate that kisspeptin might have neuroprotective properties (11,13). Another aspect of the kisspeptin-PD relationship is the modulation of motor and mood circuits (14). Although kisspeptin has not traditionally been associated with CVS in the context of PD, our findings, together with supporting studies, suggest that kisspeptin may have a significant impact on PD symptoms (11, 13-15). In this regard, it emerges as a promising target for advancing our understanding of PD pathophysiology and developing novel therapeutic strategies.

In our study, a hemiparkinsonian model was induced using 6-OHDA, followed by a seven-day treatment with KP-54. Due to the lack of existing literature on the ICV administration of KP-54 in a rat model, our previous study established a dose-response curve based on motor performance outcomes and identified 3 nmol/kg as the effective dose, which was consistently administered over a period of seven days (11). The ICV route was selected for the administration of KP-54 to ensure effective delivery to brain regions associated with cardiovascular regulation, as oral or intravenous routes may reduce efficacy and such compounds often face challenges in crossing the blood-brain barrier.

Cardiovascular system involvement is a common but sometimes underappreciated aspect of PD. A substantial body of clinical evidence indicates that autonomic nervous system (ANS) dysfunction is a frequent non-motor feature of PD (16). Cardiovascular autonomic dysfunction can manifest as orthostatic hypotension, resting bradycardia, altered blood pressure variability, and even cardiac arrhythmias in PD patients (3). Epidemiological studies suggest that roughly 80% of PD patients have some form of cardiovascular abnormality related to autonomic failure (17).

In the context of cardiac electrophysiology, autonomic impairment in PD often leads to measurable ECG changes. One well-documented finding is a reduction in heart rate variability (HRV) in individuals with PD. HRV reflects the balance of sympathetic and parasympathetic inputs to the heart, and PD patients typically manifest reduced beat-to-beat variability, indicative of diminished parasympathetic (vagal) tone to the heart (18).

Given these autonomic changes, not surprisingly, various ECG abnormalities have been reported in PD patients. Beyond HRV changes, PD patients can exhibit subtle prolongation of conduction intervals or repolarization (19). Our findings suggest that as PD progresses, the cardiac conduction system may be increasingly affected (through autonomic or direct cardiac involvement). The QT interval and its heart-rate–corrected form (QTc) have also drawn attention in PD (18-21). Prolongation of the QT/QTc can predispose individuals to ventricular arrhythmias (like Torsades de Pointes), thus it is clinically relevant. Studies have noted that a significant subset of PD patients have an abnormally prolonged QTc. According to Malkiewicz et al. (2021), between 16% and 21% of PD patients in their study exhibited prolonged QTc intervals and they suggested that PD itself—regardless of medication use—could be a contributing risk factor (20). Older age and male sex were also associated with longer QTc in PD, and the authors could not exclude a specific predilection of PD for QTc prolongation. They recommended vigilant cardiac monitoring in PD patients, especially those on medications that affect QTc (20). Our 6-OHDA-lesioned rats showed QTc

prolongation (relative to controls), which is consistent with the notion that parkinsonian pathology (even in an animal model) can lead to repolarization changes. It is worth noting that the QTc prolongation in PD could stem from intrinsic cardiac sympathetic denervation (leading to electrical remodeling) or from side effects of PD drugs (many PD medications, such as some antidepressants used for PD depression or even domperidone used for nausea, can lengthen QT). In our experiment, drugs were not a confounding factor, so the QTc prolongation is more likely related to the 6-OHDA's effects on the autonomic network controlling the heart.

A key question arising from our work is whether kisspeptin's effects on heart rate and ECG are mediated centrally (via the brain) or peripherally (directly on the heart). Our experimental design, which used ICV KP-54, inherently targets central receptors first. The fact that KP-54 crossed out of the ventricular system to peripheral circulation is likely but not certain, however, given the small peptide size and one-hour gap between injection and ECG recording, some peripheral spillover is plausible. To tease apart the mechanism, one can consider prior studies: In healthy humans, intravenous infusion of KP-54 did not produce significant changes in heart rate or blood pressure (22). This implies that in a physiologically normal state, activating peripheral GPR54 (or even central GPR54 via a peptide that might reach the brain partially) has minimal effect on cardiovascular parameters.

In contrast, significant changes were observed following central administration of KP-54 in rats included in our PD model, suggesting that central effects may be the primary determinant. The peptide likely exerted its effects by modulating the already impaired autonomic network. In a study by Nijher et al., KP-54 was shown to have no effect on blood pressure or heart rate in healthy individuals (23). Considering this, KP-54 administration in healthy rats would not be expected to induce changes in the QT interval (note: in our study, a Control+KP-54 group was not established). Peripheral GPR54 activation is known to increase cardiac contractility (24). However, the study by Nijher et al. demonstrated that KP-54 had no impact on blood pressure or heart rate, indicating that its effects do not arise through peripheral pathways. However, our findings suggest that heart rate and QTc values may be similar between control rats and lesion-induced rats receiving KP-54. This finding supports the existence of a central compensatory mechanism: KP-54 likely exerted its effect only in the lesioned group, where an imbalance existed, thereby restoring homeostasis, while inducing no significant changes in the already balanced control group (23).

## CONCLUSION

In conclusion, our study lays the groundwork by showing that KP-54 has multi-faceted benefits in an experimental PD scenario. The findings encourage further research into kisspeptin's mechanisms and its potential as a novel therapeutic avenue. If future studies confirm these benefits in more chronic and translational models, kisspeptin or kisspeptin-based drugs could become a part of the repertoire to treat PD – not only addressing the classic motor symptoms but also the critical autonomic and cardiac manifestations that impact patient safety and quality of life.

**Limitation**

While our study provides important new data on the role of KP-54 in a PD model, several limitations should be acknowledged.

First, the 6-OHDA hemiparkinsonian model is a convenient and well-established platform for motor studies, but the autonomic effects of 6-OHDA lesions are relatively mild and acute. In idiopathic PD, cardiac sympathetic denervation and vagal impairment develop over years. Thus, it will be important to test whether KP-54 has similar beneficial effects in models that more closely mimic chronic PD, for example, an α-synuclein overexpression model or environmental toxin model that develops cardiac autonomic dysfunction over time.

Second, our ECG recordings were performed under anesthesia, which could influence the results. Anesthesia (especially the combination of ketamine/xylazine we used) tends to depress heart rate and alter autonomic tone. Although all groups were under the same anesthetic protocol, and we waited a standardized period before recording, the absolute heart rate values are on the low side for rats (even our control rats were ~293 bpm, whereas awake rats often have heart rates above 350 bpm). The anesthesia might have blunted the differences between groups or introduced its own effects on QT interval.

Third, we did not directly measure any autonomic or molecular endpoints to pinpoint mechanism. We infer mechanism from outcomes and existing literature. It would strengthen the conclusions to measure, for instance, plasma catecholamine levels, or tissue norepinephrine content in the heart, to see if KP-54 restored sympathetic neurotransmitter levels in 6-OHDA rats.

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***Ethical approval:*** *All experimental procedures were conducted in accordance with institutional and international guidelines for animal care and were approved by the Akdeniz University Faculty of Medicine Animal Ethics Committee (Approval No. 1689/2024.04.002, Decision date: 15.04.2024).*

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