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Rapid Communication

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Proposed Motor Scoring System in a Porcine Model of Parkinson's Disease induced by Chronic Subcutaneous Injection of MPTP

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Destruction of dopaminergic neurons in the substantia nigra pars compacta (SNpc) is a common pathophysiology of Parkinson's disease (PD). Characteristics of PD patients include bradykinesia, muscle rigidity, tremor at rest and disturbances in balance. For about four decades, PD animal models have been produced by toxin-induced or gene-modified techniques. However, in mice, none of the gene-modified models showed all 4 major criteria of PD. Moreover, distinguishing between PD model pigs and normal pigs has not been well established. Therefore, we planned to produce a pig model for PD by chronic subcutaneous administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), neurotoxin. Changes in behavioral patterns of pigs were thoroughly evaluated and a new motor scoring system was established for this porcine model that was based on the Unified Parkinson's Disease Rating Scale (UPDRS) in human PD patients. In summary, this motor scoring system could be helpful to analyze the porcine PD model and to confirm the pathology prior to further examinations, such as positron emission tomography-computed tomography (PET-CT), which is expensive, and invasive immunohistochemistry (IHC) of the brain.

Key words: Parkinson's disease, pig, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), scoring analysis

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INTRODUCTION

Parkinson's disease (PD), which may affect 1% of the human population over 60 years old, is the second most common neurodegenerative disorder in humans after Alzheimer's disease [1, 2]. Destruction of dopaminergic neurons projected to the

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substantia nigra pars compacta (SNpc) causes movement disorders that are designated the four major symptoms of PD: bradykinesia, muscle rigidity, tremor at rest and disturbances in balance [3-5]. However, to date, the exact pathophysiology of PD is not clearly understood [6]. It is important to develop animal models for PD to clarify the causative factors [7, 8]. Two common methods, toxin-induction and gene-modification, have been used to produce invaluable model animals for PD over many years [7, 9]. Several toxins were discovered, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [10, 11], rotenone [12] and paraquat [13], that can be administered systemically, and 6-hydroxydopamine (6-OHDA) [14] and lipopolysaccharide (LPS) [15] that can be locally applied. Genes of interest related to PD are α-synuclein [16], leucine-rich repeat serine/threonine

Table 1. Proposed motor scoring system for a porcine PD model based on the Unified Parkinson's disease rating scale (UPDRS) in human PD patients

No.	Categories	Score 0 (Normal)	Score 1 (Mild)	Score 2 (Moderate)	Score 3 (Severe)
Tremor					
1	Tremor at rest	None	Mild	Moderate	Severe
2	Tremor in moving	None	Mild	Moderate	Severe
Loss of automatic movements					
3	Drooling	Never	Sometimes	Frequent	Always
4	Amount of food intake	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
5	Amount of water intake	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
6	Number or speed of nictation	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
7	Movement	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
8	Response to pungent odor	Moves immediately	Sometimes	Rarely	No response
Slowed motion (bradykinesia)					
9	Contact response	React	Sometimes	Rarely	No reaction
10	Speed of walking	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
Impaired posture and balance					
11	Balance of body in walking	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
12	Reaction velocity for threat	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
13	Balance of body in normal status	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
Impaired response to external stimuli					
14	Curiosity for new object	Curious and play	Sometimes	Rarely	No reaction
15	Escaping	None	1 time per week	2~6 times per week	Everyday
16	Change in grunting sound	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
17	Response to spotlight	Moves immediately	Sometimes	Rarely	No response
18	Response to loud sound	React	Sometimes	Rarely	No response
19	Crying sound before eating	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
20	Foot retrieval from holding devices	Normal	Decreased to 70% of normal	Decreased to 40~70% of normal	Decreased to below 40% of normal
21	Response to attachable materials	React	Sometimes	Rarely	No response

kinase 2 (LRRK2) [17], autosomal dominant PD, PTEN-induced putative kinase 1 (PINK1) [18], Parkin [19] and DJ-1 [20], autosomal recessive PD.

Numerous animal models have been produced by toxin-induced or gene-modified methods, but nevertheless, none of these models showed exactly the progression as human PD. Toxin-induced models showed an acute progression of PD that could gradually recover, which made it hard to evaluate appropriate cures for PD. Moreover, numerous gene-modified models did not show all of the symptoms of PD, especially in transgenic mice [9].

MPTP is metabolized into 1-methyl-4-phenylpyridinium ion (MPP^+) that destroys dopaminergic neurons in the SNpc. In this study, we attempted to generate a toxin-induced miniature pig PD model, using MPTP chronically administered by subcutaneous injection. Furthermore, the MPTP-induced PD model pig was evaluated by a scoring analysis table that was based on the Unified Parkinson's Disease Rating Scale (UPDRS). Confirmation of dopaminergic neuron destruction was evaluated by positron emission tomography-computed tomography (PET-CT) and immunohistochemistry (IHC).

MATERIAL AND METHODS

All chemicals were obtained from Sigma-Aldrich Co. LLC. (St. Louis, Missouri, USA) unless otherwise stated.

Animals

All miniature pigs were conditioned by keeping them in 45~55% humidity, 23~25°C temperature, a 12 hour photoperiod, and limited feeding twice daily each with 500 g and water ad libitum. Three 60 kg male miniature pigs were used for MPTP administration.

MPTP injection site and concentration

MPTP was injected into the miniature pig subcutaneously, at the center of the first tits under the umbilicus, 25 times with a total amount of 18.5 mg/kg. Daily injection amounts were 0.5 mg/kg of MPTP (10 times), 0.7 mg/kg (5 times) and 1.0 mg/kg (10 times), all at 2~3 day intervals.

Motor Scoring System for MPTP induced PD model

The scoring analysis table for pigs was based on UPDRS. This newly constructed scoring analysis table has 21 categories each with a score from 0 to 3, representing none to severe, respectively (Table 1). Thus, the sum total of scores ranged from 0 to 63.

PET-CT imaging and analysis

Nine months after firstly subcutaneous administration of MPTP to drug induced PD model and the similar aged control minipig were anesthetized using 1.25 mg/kg of zoletil (Virbac, Carros, France). The PET scan was done using Biograph TruePoint40 with a TrueV (Siemens, Munich, Germany). The [^{18}F]N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane (FP-CIT) was purchased from Asan Medical Center, Seoul, Korea, and was injected (185 MBq/pig) *via* the ear vein. Static images of the brain for 15 min were acquired 2 h after injection. The next day, ^{18}F fluorodeoxy-D-glucose positron emission tomography (^{18}F-FDG PET) images of the brain were obtained for 15 min, 45 min after injection of 5 MBq/kg. All animals were fasted for 8 h before imaging. Computed tomography (CT) was performed in the same location of the brain.

PET images were reconstructed using a TrueX 3D iterative algorithm (6 iterations, 21 subsets) with an image matrix size of 256×256. Attenuation correction was done using CT images. Brain PET images were manually co-registered to a volume of interest template of the pig brain using the PMOD program (PMOD Technologies Ltd., Zurich, Switzerland). In [^{18}F]FP-CIT images, the binding potential (BPnd) of bilateral putamens was calculated

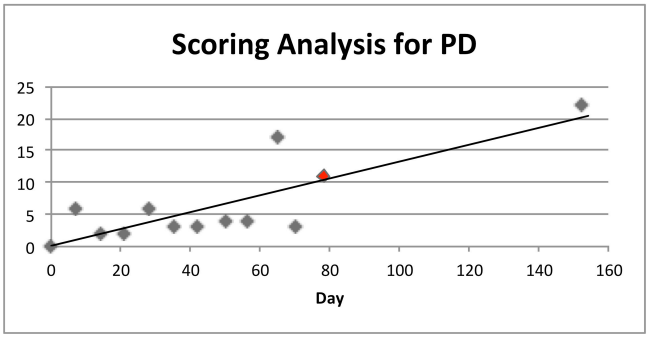

Fig. 1. Chronic changes of motor scores in a miniature pig with MPTP administered chronically by subcutaneous injection. According to the scoring analysis for pigs that was based on the Unified Parkinson's Disease Rating Scale (UPDRS), scores were increased in a time-dependent manner after subcutaneous MPTP administration. MPTP was injected into the miniature pig subcutaneously, at the center of the first tits under the umbilicus, 25 times with a total amount of 18.5 mg/kg. Daily injection amounts were 0.5 mg/kg of MPTP (10 times), 0.7 mg/kg (5 times) and 1.0 mg/kg (10 times), all at 2~3 day intervals. Of several MPTP-induced pigs, only one was subjected to scoring analysis because the other MPTP-induced miniature pigs died before completing scoring analysis. This made it difficult to interpret the scoring data. When MPTP-treated pigs were compared to normal miniature pigs up to 78 days after MPTP injection, no abnormal behaviors were observed. However, from that day when the total accumulated amount of MPTP injected exceeded 14 mg/kg and scoring numbers exceeded '11', the MPTP-induced pig gradually started to exhibit abnormal behaviors, including collapse, circling behavior, drooling, seizure and hind limb paralysis.

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using the occipital cortex as a reference tissue.

Immunohistochemistry (IHC)

Brain samples were obtained from a euthanized MPTP-induced PD model miniature pig and a normal pig. Those were fixed by immersion in 10% neutral buffered formalin. Midrain was sliced with similar intervals (3~4 sections) from mammillary body to pons. After routine tissue processing for histopathology, the sections were embedded in paraffin wax and cut into 5 μm thick sections using a microtome. Tissue sections were mounted onto silane coated slide glasses (MUTO Pure Chemicals, Tokyo, Japan). After deparaffinization and hydration, sections were incubated in 3% hydrogen peroxide in PBS to quench endogenous peroxidase activity. Heat-mediated antigen retrieval was accomplished with a citrate buffered solution (pH 6.0). The first antibody, rabbit anti-tyrosine hydroxylase (1:1,000; Abcam, Cambridge, UK), was applied at 37°C for 1 hour, then a second antibody, Dako REAL™ EnVision™ Detection System, Peroxidase/DAB+, Rabbit/Mouse (Dako, Glostrup, Denmark) was used at 37°C for 40 min. Diaminobenzidine (DAB) solution was used for visualization of TH-positive cells. A formalin-fixed brain sample from a normal pig was used as a negative control. Among overall midbrain tissue slides, those with uniformly distributed dopaminergic neurons in substantia nigra were chosen for further analysis.

Statistical analysis

All data were analyzed by paired t-test using GraphPad Prism version 5.01 to determine differences among experimental groups.

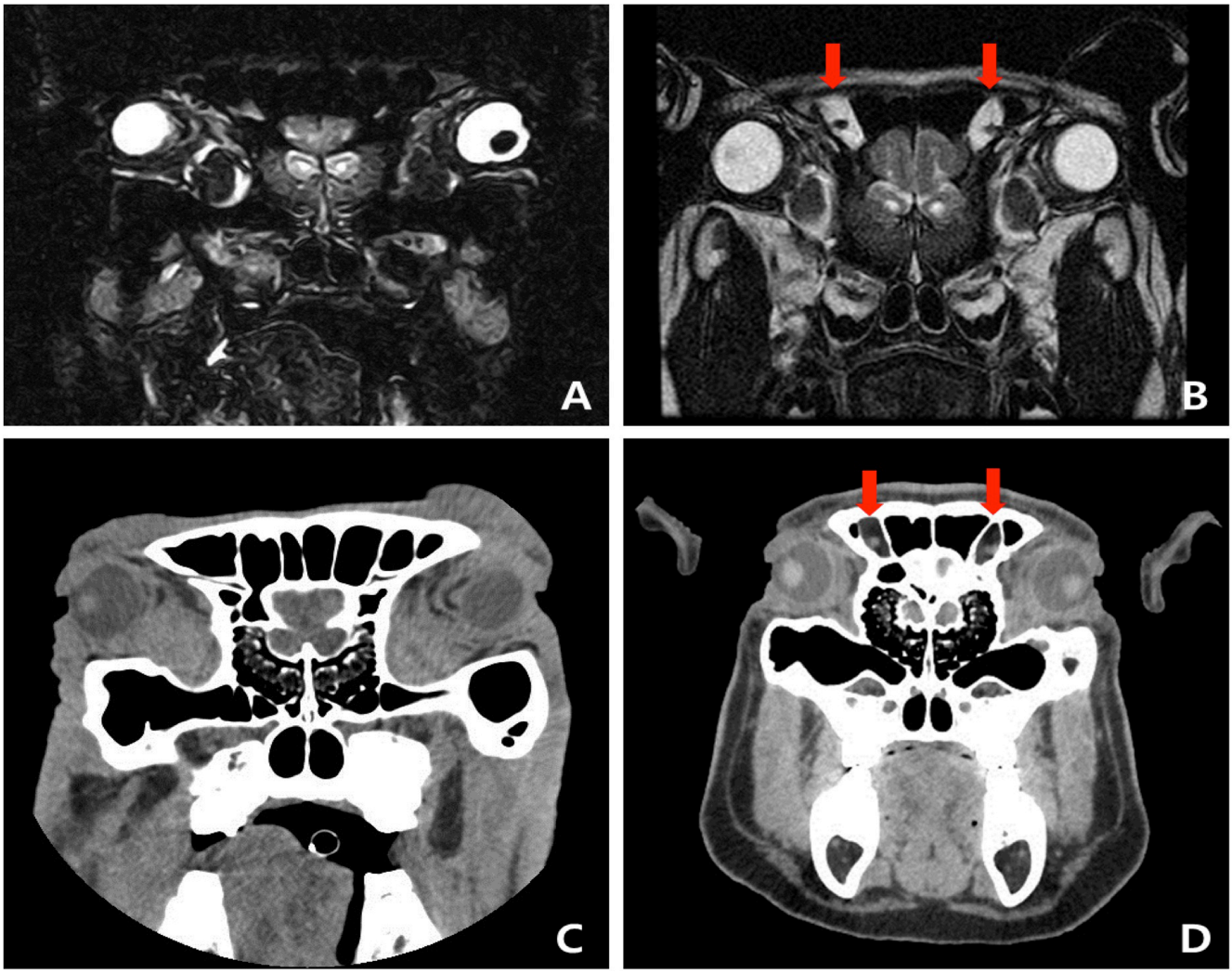

Fig. 2. MRI and CT images. (A) and (B) are MRI images and (C) and (D) are CT images. Brain images of an MPTP-treated PD model pig are (A) and (C), control images are (B) and (D). In both MRI and CT images, no evidence of differences was found in brain regions. However, frontal sinus mucoceles were observed in the control pig which are indicated by red arrows.

Statistical significance was determined when the p-value was less than 0.05.

RESULTS

Scoring analysis

According to the scoring analysis based on UPDRS, the score was increased in a time-dependent manner with subcutaneous MPTP administration (Fig. 1). Among several MPTP-treated miniature pigs, only one pig was available for the scoring analysis because all the other treated pigs died before scoring analysis could be completed. This was a setback to interpretation of the scoring data. When we compared the MPTP-treated pig to normal miniature pigs up to 78 days after the final MPTP injection, no abnormal behaviors were observed in this treated pig. However, from that day, when the total amount of MPTP injected exceeded 14 mg/kg and the scoring number was greater than 11, the MPTP treated pig gradually started to exhibit abnormal behaviors, including collapse, circling movements, drooling, seizures and hind limb paralysis.

MRI, CT and PET-CT imaging and analysis

In both MRI and CT images, no evidence of differences was found in the brain regions of MPTP-treated and normal pigs (Fig. 2). However, [^{18}F]FP-CIT uptake was markedly decreased in the bilateral putamen of the MPTP-treated pig compared to normal pigs. Moreover, [^{18}F]FP-CIT uptake in the MPTP-treated pig was asymmetrical while it was symmetrical in normal pigs. The BPnd values of both putamens of the MPTP-treated pig were 0.49 (right) and 0.63 (left). On the other hand, BPnd values of both putamens of a normal pig were 1.25 (right) and 1.10 (left). Regional brain metabolism was also assessed and compared

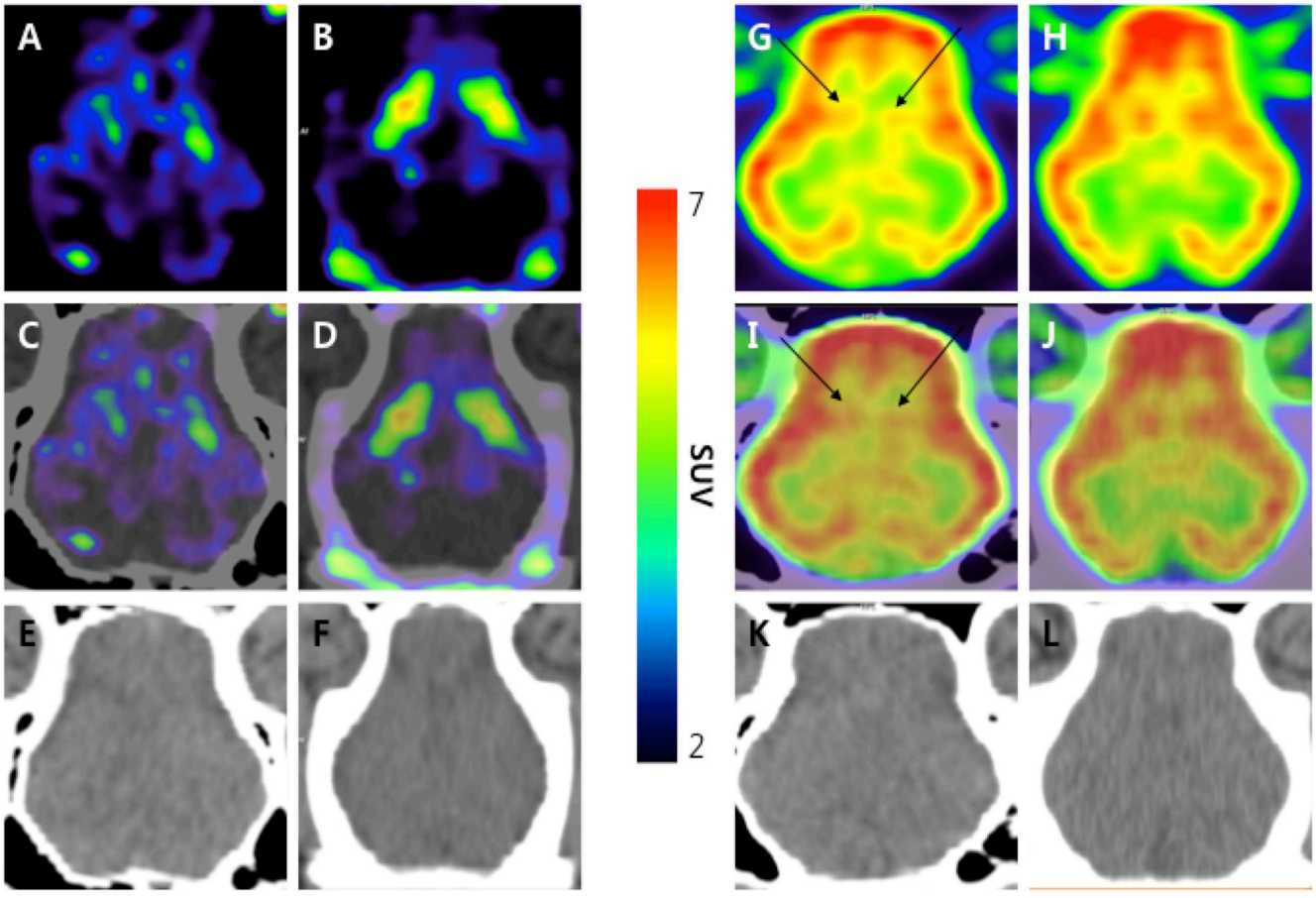

Fig. 3. [^{18}F]FP-CIT (images A to F) and ^{18}F-FDG PET (G to L). [^{18}F]FP-CIT uptake was markedly decreased at the bilateral putamen of the MPTP-treated pig (A, C and E, PET, fusion PET/CT and CT image, respectively). However, [^{18}F]FP-CIT uptake was symmetrically visualized in the same area of a normal pig (B, D and F, PET, fusion PET/CT and CT image, respectively). The BPnd of both putamens of the MPTP-treated pig were 0.49 (right) and 0.63 (left). In contrast, BPnd of both putamens of a normal pig were 1.25 (right) and 1.10 (left). Regional brain metabolism was assessed and compared visually between the MPTP-induced PD pig model (G, I and K) and a normal pig (H, J and L) by ^{18}F-FDG PET images. There was no significant difference in cortical metabolism but slight hypometabolism was noted in the bilateral putaminal area in the MPTP-induced PD pig model (arrow).

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visually in the MPTP-treated pig and a normal pig by ^{18}F-FDG PET administration. There was no significant difference in cortical metabolism but a slight hypometabolism was noted in bilateral putaminal area in the MPTP-treated pig (Fig. 3).

IHC

The distribution of dopaminergic neurons in the MPTP-treated pig and a control pig were determined by IHC (Fig. 4). Three pictures were analyzed to calculate cell numbers in the SNpc of the brain. The numbers of antibody-positive cells in SNpc were significantly decreased in the MPTP-treated pig compared to a negative control pig; 65.3±6.2 and 161.0±7.9, respectively (Fig. 4).

DISCUSSION

Different from genetically modified PD animal models, produ-

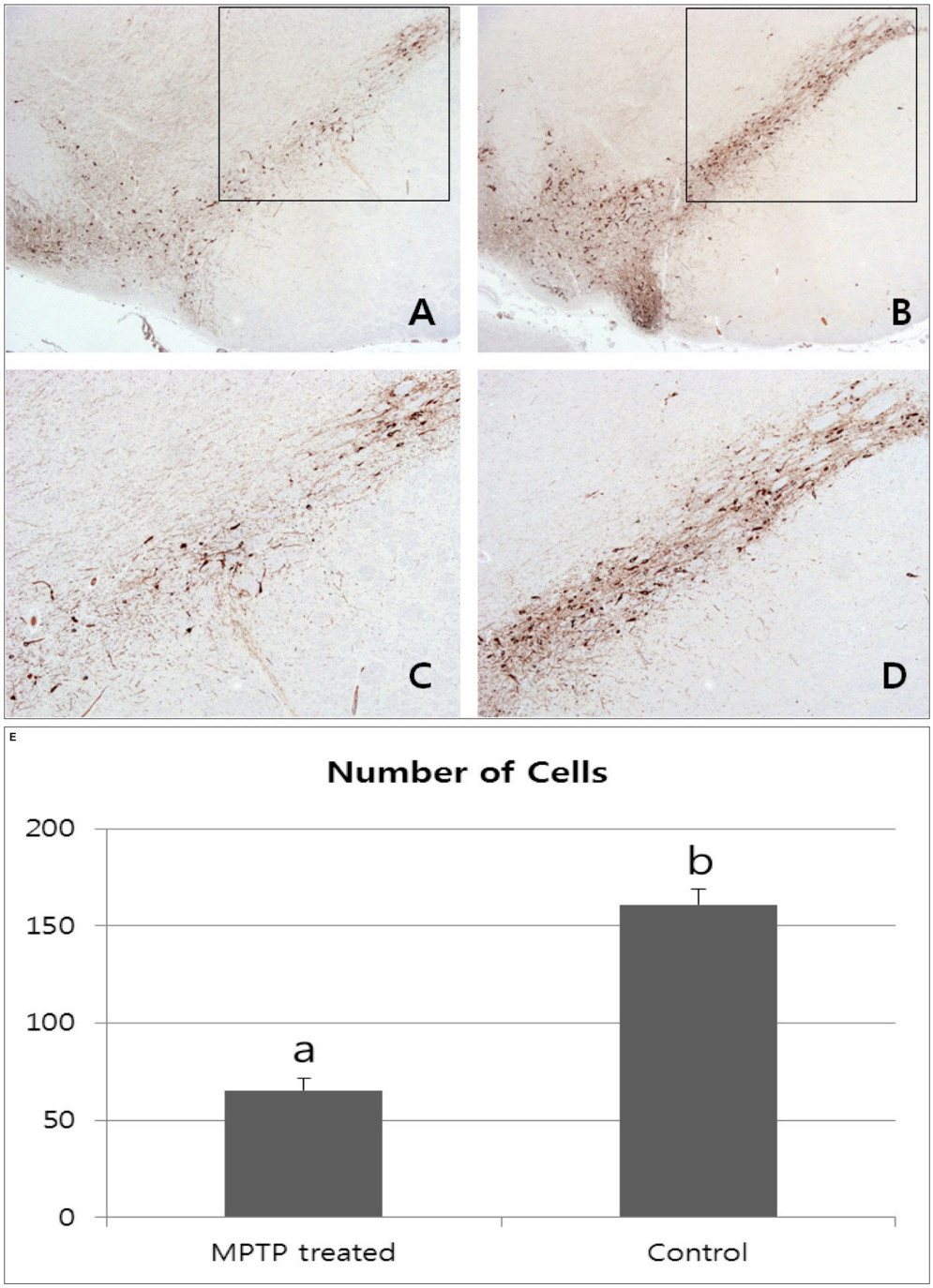

Fig. 4. Results of IHC. Brain images of an MPTP-induced PD model pig are shown in (A and C); (C) is a magnified picture from the rectangled area in figure (A). (B and D) are brain images from a negative control pig. (D) is a magnified picture from the rectangled area in figure (B). Numbers of positive cells in SNpc were significantly decreased in the MPTP-treated pig compared to a negative control pig. IHC. (A and B): ×20; (C and D): ×40.

cing a toxin-induced PD model has tremendous difficulties. The toxin MPTP has the same destructive effect on human dopaminergic neurons that cause rapid onset of PD in researchers [21]. For this reason, the number of experimental miniature pigs available for the present work was very low, which limited the study. Despite this limitation, a beneficial aspect of the approach is the reproducibility of the neuropathology outcomes of MPTP-induced PD model pigs [22]. Thus, we found that long-term administration of the neurotoxin by subcutaneous injection was a good method for creating PD model pig that will help further PD model pig production. Similar to other studies [23], destruction of dopaminergic neurons was verified by PET-CT and IHC in our MPTP-induced PD model pig.

In the MPTP-induced PD model pig, [^{18}F]FP-CIT uptake was significantly decreased in the bilateral putamen than in normal pigs. The [^{18}F]FP-CIT is a well-established dopamine transporter imaging probe [24] and has been used for imaging dopaminergic neuron degeneration in mouse, rat and monkey PD models induced by MPTP [25-28]. To the best of our knowledge, this is the first report to show decreased dopaminergic neuron density using [^{18}F]FP-CIT imaging in a MPTP-induced pig model. Moreover, the decreased uptake and calculated BPnd in our MPTP-induced pig PD model were well correlated with the IHC results. The FDG images revealed slight hypometabolism in the bilateral putamen in the MPTP-induced pig model, which is in accordance with the results of a report using a MPTP-induced primate PD model [29].

To date, validations of MPTP-induced PD model animals were made using PET-CT [30] or IHC [23], which are respectively expensive or invasive. Prior to euthanizing PD model pigs, as well as toxin-induced or gene-modified pig models, we proposed a new way to validate PD model pigs compared with control pigs by scoring analysis. Our scoring analysis table for pigs that was based on UPDRS has 21 categories (Table 1) while UPDRS has 42 categories.

Further, combining PET-CT and IHC results ascertained that scoring analysis could be applied to detection of PD in the pig at an early stage of abnormalities. More replications are necessary to confirm the score ranges for normal and abnormal pigs. However, our study suggested that exceeding score number '11' was one of the landmarks for distinguishing PD model pigs from normal pigs.

CONCLUSIONS

In conclusion, destruction of dopaminergic neurons in a pig's brain was effectively induced by injecting MPTP by the subcutaneous route. Dopaminergic neuronal destruction in MPTP-induced model pigs was confirmed by PET-CT and IHC. Moreover, clinical staging of PD model pigs could also be possible using our newly proposed motor scoring system for porcine PD models that was based on the Unified Parkinson's Disease Rating Scale (UPDRS) in human PD patients.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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