科技部補助專題研究計畫成果報告
期末報告

調節麩胺酸神經系統活性與神經新生作用對巴金森氏症失智之效果：從動物實驗建立治療潛力

計 畫 類 別 ：個別型計畫
計 畫 編 號 ：MOST 102-2410-H-040-004-
執 行 期 間 ：102 年 08 月 01 日至 103 年 10 月 31 日
執 行 單 位 ：中山醫學大學心理學系（所）（臨床組）

計 畫 主 持 人：何應瑞

計畫參與人員：碩士班研究生-兼任助理人員：何詩君

報 告 附 件 ：出席國際會議研究心得報告及發表論文

處 理 方 式 ：
1.公開資訊：本計畫涉及專利或其他智慧財產權，2 年後可公開查詢
2.「本研究」是否已有嚴重損及公共利益之發現：否
3.「本報告」是否建議提供政府單位施政參考：否

中 華 民 國 104 年 01 月 28 日

中 文 摘 要 ： 麩胺酸神經系統過度活化與其所產生的興奮毒性參與巴金森氏症（Parkinson’s disease； PD）之神經退化，使用藥物調節麩胺酸神經系統之活性可能有利於治療 PD。目前已知頭孢曲松（ceftriaxone）可以增加麩胺酸轉運蛋白的表現，進而增加麩胺酸的再回收。本研究的目的是要探討在 MPTP 誘導的 PD 大鼠模型下，ceftriaxone 對工作記憶、物件辨識能力與神經退化的效果。MPTP 透過立體定位手術注射到雄性 Wistar 大鼠的黑質緻密部（substantia nigra pars compacta）以誘發 PD 大鼠模式，隔天（第 1 天）起，大鼠每日接受腹腔注射頭孢曲松（200 mg/kg）或是注射生理食鹽水（1 ml/kg），連續 14 天。然後在第 8-10 天時，施予大鼠 T-型迷宮測試（T-maze test）；在第 12-14 天施予物件辨識測試（object recognition test）。PD 之大鼠在 T-型迷宮測試中出現工作記憶缺陷，在物件辨識測試中出現辨識功能受損。施予大鼠頭孢曲松治療，可以減少上述 MPTP 所誘發的認知缺陷。此外，這項研究提供的證據顯示頭孢曲松能抑制 MPTP 所誘發的黑質紋狀體多巴胺神經系統退化之現象、減少黑質紋狀體裡微膠細胞的活化現象，並且回覆海馬迴 CA1 區的細胞密度。上述研究結果顯示：麩胺酸神經系統過度活化參與 PD 的病理生理學變化，並推論頭孢曲松可能可以發展為治療 PD 患者之失智症狀的藥物。

中文關鍵詞： 巴金森氏症、麩胺酸神經系統過度活化、頭孢曲松、失智症、神經保護作用、認知功能

英 文 摘 要 ： Hyperactivity of the glutamatergic system is involved in excitotoxicity and neurodegeneration in Parkinson’s disease (PD) and treatment with drugs modulating glutamatergic activity may have beneficial effects. Ceftriaxone has been reported to increase glutamate uptake by increasing glutamate transporter expression. The aim of this study was to determine the effects of ceftriaxone on working memory, object recognition, and neurodegeneration in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD rat model. MPTP was stereotaxically injected into the substantia nigra pars compacta (SNc) of male Wistar rats. Then, starting the next day (day 1), the rats were injected daily with either ceftriaxone (200 mg/kg/day, i.p.) or saline for 14 days and underwent a T-maze test on days 8-10 and an object recognition test on days 12-14. MPTP-lesioned rats showed

impairments of working memory in the T-maze test and of recognition function in the object recognition test. The treatment of ceftriaxone decreased the above MPTP-induced cognitive deficits. Furthermore, this study provides evidence that ceftriaxone inhibits MPTP lesion-induced dopaminergic degeneration in the nigrostriatal system, microglial activation in the SNc, and cell loss in the hippocampal CA1 area. In conclusion, these data support the idea that hyperactivity of the glutamatergic system is involved in the pathophysiology of PD and suggest that ceftriaxone may be a promising pharmacological tool for the development of new treatments for the dementia associated with PD.

英文關鍵詞： Parkinson’s disease, glutamatergic hyperactivity, ceftriaxone, dementia, neuroprotection, cognition

科技部補助專題研究計畫成果報告

（□期中進度報告/■期末報告）

調節麩胺酸神經系統活性與神經新生作用對巴金森氏症失智之效果：從動物實驗建立臨床應用之潛力

Effects of modulating glutamatergic activity and neurogenesis on Parkinson's disease dementia: establishing clinical potential based on animal study

計畫類別：■個別型計畫　□整合型計畫

計畫編號：NSC 102-2410-H-040-004

執行期間：102 年 08 月 01 日至 103 年 07 月 31 日

執行機構及系所：中山醫學大學 心理學系

計畫主持人：何應瑞

共同主持人：

計畫參與人員：何詩君

本計畫除繳交成果報告外，另含下列出國報告，共 1 份：

□執行國際合作與移地研究心得報告

■出席國際學術會議心得報告

期末報告處理方式：

1. 公開方式：

□非列管計畫亦不具下列情形，立即公開查詢

■涉及專利或其他智慧財產權，□一年■二年後可公開查詢

2.「本研究」是否已有嚴重損及公共利益之發現：■否 □是

3.「本報告」是否建議提供政府單位施政參考 ■否 □是，（請列舉提供之單位；本部不經審議，依勾選逕予轉送）

中華民國 104 年 01 月 22 日

目錄

研究計畫執行成果

一、摘要

中文摘要

麩胺酸神經系統過度活化與其所產生的興奮毒性參與巴金森氏症（Parkinson's disease; PD）之神經退化，使用藥物調節麩胺酸神經系統之活性可能有利於治療 PD。目前已知頭孢曲松（ceftriaxone）可以增加麩胺酸轉運蛋白的表現，進而增加麩胺酸的再回收。本研究的目的是要探討在 MPTP 誘導的 PD 大鼠模型下，ceftriaxone 對工作記憶、物件辨識能力與神經退化的效果。MPTP 透過立體定位手術注射到雄性 Wistar 大鼠的黑質緻密部（substantia nigra pars compacta）以誘發 PD 大鼠模式，隔天（第 1 天）起，大鼠每日接受腹腔注射頭孢曲松（200 mg/kg）或是注射生理食鹽水（1 ml/kg），連續 14 天。然後在第 8-10 天時，施予大鼠 T-型迷宮測試（T-maze test）；在第 12-14 天施予物件辨識測試（object recognition test）。PD 之大鼠在 T-型迷宮測試中出現工作記憶缺陷，在物件辨識測試中出現辨識功能受損。施予大鼠頭孢曲松治療，可以減少上述 MPTP 所誘發的認知缺陷。此外，這項研究提供的證據顯示頭孢曲松能抑制 MPTP 所誘發的黑質紋狀體多巴胺神經系統退化之現象、減少黑質紋狀體裡微膠細胞的活化現象，並且回覆海馬迴 CA1 區的細胞密度。上述研究結果顯示：麩胺酸神經系統過度活化參與 PD 的病理生理學變化，並推論頭孢曲松可能可以發展為治療 PD 患者之失智症狀的藥物。

關鍵詞：巴金森氏症、麩胺酸神經系統過度活化、頭孢曲松、失智症、神經保護作用、認知功能

英文摘要

Hyperactivity of the glutamatergic system is involved in excitotoxicity and neurodegeneration in Parkinson's disease (PD) and treatment with drugs modulating glutamatergic activity may have beneficial effects. Ceftriaxone has been reported to increase glutamate uptake by increasing glutamate transporter expression. The aim of this study was to determine the effects of ceftriaxone on working memory, object recognition, and neurodegeneration in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD rat model. MPTP was stereotaxically injected into the substantia nigra pars compacta (SNc) of male Wistar rats. Then, starting the next day (day 1), the rats were injected daily with either ceftriaxone (200 mg/kg/day, i.p.) or saline for 14 days and underwent a T-maze test on days 8-10 and an object recognition test on days 12-14. MPTP-lesioned rats showed impairments of working memory in the T-maze test and of recognition function in the object recognition test. The treatment of ceftriaxone decreased the above MPTP-induced cognitive deficits. Furthermore, this study provides evidence that ceftriaxone inhibits MPTP lesion-induced dopaminergic degeneration in the nigrostriatal system, microglial activation in the SNc, and cell loss in the hippocampal CA1 area. In conclusion, these data support the idea that hyperactivity of the glutamatergic system is involved in the pathophysiology of PD and suggest that ceftriaxone may be a promising pharmacological tool for the development of new treatments for the dementia associated with PD.

Keywords: Parkinson's disease, glutamatergic hyperactivity, ceftriaxone, dementia, neuroprotection, cognition

二、報告內容

（一）前言、文獻探討與研究目的

Glutamate, an excitatory neurotransmitter in the mammalian central nervous system, plays a role in excitotoxicity in oxidative stress and neurodegeneration [1]. Excessive synthesis and release of glutamate can overstimulate N-methyl-D-aspartate (NMDA) receptors, causing calcium overload in neurons and triggering apoptotic cell death [2-4]. A recent study using magnetic resonance spectroscopy found dysregulation of glutamatergic neurotransmission in several brain regions of patients with Parkinson's disease (PD) [5]. Nigrostriatal dopaminergic (DAergic) depletion causes overactivity of the glutamatergic projections from the subthalamic nucleus to the basal ganglia output nuclei [6]. Moreover, DAergic degeneration in PD leads to hyperactivity of the corticostriatal glutamatergic pathway [7, 8]. Thus, in addition to DAergic degeneration, hyperactivity of the glutamatergic system also plays a role in the pathophysiology of PD.

Functional interaction between the DAergic and glutamatergic systems in the brain has been shown to regulate motor function, positive reinforcement, attention, and working memory [9]. Degeneration of the nigrostriatal DAergic system results in increased striatal release of glutamate [10] and blockade of glutamatergic activity therefore attenuates parkinsonian motor symptoms and improves DAergic therapy [11]. Several studies in the last decade have demonstrated beneficial effects of NMDA receptor antagonists in animal models of PD [12-14]. Furthermore, the NMDA receptor antagonists amantadine and memantine [15] have been found to produce antiparkinsonian effects in monoamine-depleted rodents [16] and are currently used clinically for the treatment of PD. Although antagonism of the glutamatergic system is effective in treating motor dysfunction in PD patients, NMDA receptors are critical for cognitive function [17] and agents blocking NMDA receptors are not well tolerated in primates due to a high number of unwanted side effects [18].

Glutamate released at the synapse is taken up by glial cells via glutamate transporter-1 (GLT-1) and is then converted to glutamine, terminating glutamate function at the synapse [19]. Since glutamatergic hyperactivity contributes to excitotoxicity, neurodegeneration, and memory loss, increasing glutamate uptake from the synapse could be effective in preventing excitotoxic cell death. Ceftriaxone, a β–lactam antibiotic, is an FDA-approved antibiotic for treating respiratory tract infection, urinary tract infection, bacterial septicemia, and meningitis [20]. In 2005, Rothstein et al. [21] reported that ceftriaxone upregulated expression of GLT-1, and several subsequent studies demonstrated the antiexcitotoxic potential of this compound [22]. Neurohistological and molecular changes have been demonstrated following 5 days of pretreatment with ceftriaxone (200 mg/kg/day) in ischemia and stroke [23]. Treatment with ceftriaxone (200 mg/kg/day) for 7 or 14 days during hypoxic exposure was found to increase GLT-1 expression, resulting in sequestration of excess glutamate into glial cells, protection of neurons from excitotoxicity, and improved spatial memory retrieval [24]. However, nothing is known about the effects of ceftriaxone on cognitive behavior and neurodegeneration in PD.

Since it increases GLT-1expression and reuptake of released glutamate and may thus

reduce excitotoxicity, ceftriaxone may be useful for treating PD symptoms. In addition to motor dysfunction, dementia is seen in 25-30% of patients with PD and is referred to as PD dementia (PDD) [25, 26], the symptoms of which include deficits of working memory and object recognition [27-29]. The effects of increasing GLT-1 expression on cognitive function in PDD have not yet been examined. Our previous studies demonstrated that MPTP-lesioned rats show cognition deficits accompanied by neurodegeneration in the nigrostriatal system and hippocampus and thereby can act as a model for the symptoms and pathophysiology of PDD [30-34]. The aim of the present study was to elucidate the effects of ceftriaxone on working memory, object recognition, and neuroprotection in the MPTP-induced PD rat model.

（二）研究方法

2.1. Animals

Male Wistar rats (430 ± 6.0 g; National Laboratory Animal Center, ROC) were housed in groups of four in acrylic cages (35 cm × 56 cm × 19 cm) in an animal room on a 12 h light-dark cycle (lights on at 07:00 h) with food and water available *ad libitum*. Each animal was handled for 5 min/day on 3 consecutive days, starting one day after arrival, before being used in the study. All experimental procedures were performed according to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care Committee of Chung Shan Medical University (IACUC approval No. 1001). All efforts were made to minimize animal suffering, to reduce the number of animals used, and to utilize alternatives to in vivo techniques, if available.

2.2. General procedure

All animals underwent stereotaxic surgery on day 0. Brain surgery was performed as described in our previous reports [31-35]. Briefly, the rats were anesthetized by intraperitoneal injection (i.p.) of tiletamine/zolazepam (20 mg/kg, in total; Virbac, Carros, France), then two groups underwent bilateral infusion of MPTP-HCl (1 μmol in 2 μl of saline; Rocephine, USA) into the SNc using the following coordinates adapted from the rat brain atlas [36]: AP: -5.0 mm, ML: ±2.0 mm, DV: -7.7 mm from the bregma, midline, and skull surface, respectively, while a third group was infused with 2 μl of saline (sham-operated group). Immediately after surgery, the rats were injected intramuscularly with penicillin-G procaine (0.2 ml, 20,000 IU), then housed individually in acrylic cages for a week before being returned to their initial home cages (rats from the same home cage underwent the same treatment). During the first 5 post-operative days, 10% sucrose solution was provided *ad libitum* to prevent weight loss after surgery and reduce mortality [37, 38].

Starting on the day after surgery (day 1), the MPTP-treated rats received 14 daily injections (1 ml/kg, i.p.) at 15:00 h of either ceftriaxone (200 mg/kg/day; Hoffmann La Roche, Switzerland) (MPTP+ceftriaxone group, n = 11) or saline (MPTP+saline group; n = 14), while the sham-operated rats received saline injections (1 ml/kg) (sham+saline group; n = 12). This dosage of ceftriaxone was chosen because of a previous report that treatment with ceftriaxone (200 mg/kg/day i.p.) for 5 days increases GLT-1 expression in the forebrain and has protective effects on hippocampal CA1 neurons in an ischemia animal model [39]. In addition, ceftriaxone injection (200 mg/kg/day i.p.) for 7 or 14 days during exposure to

hypobaric hypoxia was shown to improve the spatial memory of rats in the water maze and enhance neuronal survival [24].

The rats were then subjected to a battery of behavioral tests performed as in our previous studies [31-35], namely a bar test on days 1 and 7, a T-maze test on days 8-10, and an object recognition test on days 12-14. All behavioral tests were started at least 2 h after the beginning of the light phase (7:00 h) and were performed in a dim observation room (28 lx red light) with sound isolation reinforced by a masking white noise of 70 db. The test equipment and objects used in this study were cleaned using 20% ethanol and thoroughly dried before each trial. On day 15 after MPTP lesioning, the rats were euthanized by exposure to CO_2, transcardially perfused with phosphate-buffered saline (PBS), and the brain immediately removed for histological examination.

2.3. Behavioral tests

Bar test: The bar test was performed on days 1 and 7 after MPTP lesioning. Catalepsy was evaluated by measuring the mean time taken for a rat to climb over a 9 cm high bar after being laid across it with its hind limbs on the floor [31-35]. Based on our previous study, changes of motor function after MPTP lesioning were well documented [31-35], therefore randomly selected animals (n = 7-10) from each group were tested in 3 consecutive trials on each trial day.

T-maze test: The construction of the T-maze and the test procedures were identical to those described in our previous studies [31-35]. Briefly, in the training sessions performed on 2 consecutive days (days 8 and 9), the rats learned to find food rewards (chocolate pellets; Kellogg's, Taiwan) in the T-maze using their working memory, then, on day 10, a test session was performed and the percentage of correct responses recorded. Each training session consisted of 9 trials, each composed of two parts, a forced run and a choice run. In the forced run, one of the arms (left or right in a random order) was closed by a sliding door and the reward was located at the end of the open arm. In the choice run, which was carried out 30 sec after the forced run, both arms were open and the correct response for obtaining a reward was to choose the newly opened arm, the opposite to that used in the forced run. On the test day, 3 forced-choice-choice run trials were carried out, in which the rats made 2 choices following a single forced run, and correct responses in the 6 choice runs were recorded. On the day before T-maze training, the rats were partially food restricted, the diet only being provided for 1 h, while, on the 2 training days, the diet was provided for only 1 h after the behavioral observation on that day and, on the test day, food was not provided before testing, but was freely available afterwards.

Object recognition test: The apparatus, an open box (60 cm long × 60 cm wide × 60 cm high), and the test procedure for the object recognition test were identical to those in our previous reports [31-35]. Each rat was subjected to 3 exposure sessions at 24 h intervals (days 12-14), then, 5 min after the last exposure session on day 14, a test session was performed. Four different objects that were unfamiliar to the rats before the experiment were used for each rat. Three of the objects ("A", "B", and "C") were fixed to the floor 27 cm from three corners of the arena. Starting on day 12 after MPTP lesioning, the rat was allowed to explore the objects in the open box for 5 min on 3 consecutive days, then, 5 min after the last exposure session, object "B" was replaced by a novel object, "D", and the animal was returned to the open box for a 5 min test session. The time spent exploring the objects during the exposure sessions and test session was recorded, exploration of an object being defined as the rat approaching it and making physical contact with it with its snout and/or forepaws. The difference in the percentage of time spent exploring object "B" in exposure session 3 and the

novel object “D” in the test session served as a measure of recognition memory for the familiar object. In addition, rearing number in the test was also recorded; rearing was recorded when the rat stood on its hind legs, raised both forepaws off the ground, and stretched its back, and was considered to end when at least one forepaw had been returned to the floor.

2.4. Histological assessment and image analysis

For histological assessment, 4 randomly selected rats per group were perfused intracardially with 4% paraformaldehyde in PBS, then the brains were rapidly removed and post-fixed in PBS containing 30% sucrose and 4% paraformaldehyde at 4°C until use. To detect DAergic degeneration and microglial activation, frozen coronal brain sections (30 μm) were cut and immunostained overnight at 4°C with mouse monoclonal antibodies against rat tyrosine hydroxylase (TH) (1:2000; Zymade, USA) or rat MHC class II (OX-6; 1:200; BD Biosciences Pharmingen, CA, USA), as in our previous reports [31-35]. In sections containing the hippocampus, Nissl staining was used to identify neurons.

The stained brain sections were used to measure histological changes as described previously[31-35] using a microscope (ZEISS AXioskop2, Germany) coupled to a CCD (Optronics, USA) and Image Pro Plus Software 6.0 (Media Cybernetics, CA, USA). In this study, we created three square areas of interest, one of 32,037 μm^2 in the striatum to determine the background-corrected optical density of TH immunoreactivity, and one of 2,817,932 μm^2 in the SNc and another of 147,410 μm^2 in the hippocampal CA1 area to determine neuronal density in these regions. In the striatum, we measured the density of DAergic projections by converting the TH-stained images to gray-scale, then measuring the gray level of the area of interest and subtracting background staining measured in the non-immunoreactive corpus callosum, giving the background-corrected optical density of the TH-reactive tissue. In the SNc, we measured the density of DAergic neurons and activated microglia by capturing images, overlaying an area of interest in this region, and counting the somas of TH-immunoreactive neurons and activated microglia in these areas. In the hippocampal CA1 area, as the neurons are tightly packed, it is difficult to directly count the number of pyramidal neurons from a 30 μm thick brain section, so we measured the density of pyramidal neurons by estimating neuronal density using a semi-quantitative method involving calculating the percentage of an area of interest in the CA1 area occupied by Nissl-stained neurons. Although a stereological approach involving the counting of cells in a complete series of sections would provide additional data [38], calculating the cell number in representative brain sections yielded similar histological results to those reported in the literature [37].

2.5. Data analysis

Analysis of variance (ANOVA), followed by the least-significant difference (LSD) post hoc test, was used to analyze the bar test, T-maze test, and histological results, while the paired-samples *t*-test and ANOVA were used to analyze the object recognition test data. All results are expressed as the mean ± SEM. The level of significance was defined as $P < 0.05$ (two-tailed).

（三）結果

Fig. 1 shows changes in motor function after MPTP lesioning. ANOVA followed by the LSD test showed that, at one day after MPTP lesioning, the crossing latency in the bar test was significantly longer in rats that had undergone MPTP lesioning (the MPTP+saline and MPTP+ceftriaxone groups) ($F(2,24) = 5.94$, both P values < 0.05) than in the sham-operated group, indicating that MPTP lesioning induced motor impairment. However, on day 7 after MPTP lesioning, no difference was observed between the groups, indicating spontaneous recovery of motor function, as in our previous reports [31-35].

As shown in Fig. 2, MPTP lesioning significantly decreased the percentage of correct responses in the T-maze test performed on day 10 compared to the sham-operated group ($F(2, 36) = 7.88$, $P < 0.001$), indicating a deficit of working memory, and this was prevented by ceftriaxone treatment.

The procedure used in the object recognition test is shown in Fig. 3A. ANOVA revealed that there were no differences between the groups in total exploration time or the percentage of time exploring object “B” in the exposure session 3. As shown in Fig. 3B, ANOVA followed by the LSD post hoc test showed that MPTP+saline group spent a smaller percentage of time exploring object “D” than sham+saline group ($F(2,36) = 4.60$, $P < 0.01$). Analysis using the paired-samples t-test showed that rats in the sham-operated group (df = 11, $t = 4.26$, $P < 0.001$) and the MPTP+ceftriaxone group (df = 10, $t = 3.30$, $P < 0.01$), but not the MPTP+saline group, spent a higher percentage of time exploring object “D” than exploring object “B”.

Representative photomicrographs of immunostained and Nissl-stained brain sections are shown in Figs. 4-7. TH immunoreactivity was observed in the cell bodies of DAergic neurons in the SNc and in DAergic processes in the striatum.

ANOVA showed that rats in the MPTP+saline group exhibited a decreased density of DAergic neurons in the SNc ($F(2,11) = 15.58$, $P < 0.001$) (Fig. 4B and E) and a lower background-corrected TH immunoreactivity optical density in the striatum ($F(2,11) = 70.97$, $P < 0.001$) (Fig. 5B and E) compared to the sham-operated group. The MPTP-induced decrease in the density of DAergic neurons in the SNc was totally prevented by ceftriaxone treatment (Fig. 4C and E), while the MPTP-induced decrease in TH immunoreactivity in the striatum was ameliorated by ceftriaxone treatment ($P < 0.05$) (Fig. 5C and E).

An increase in the number of activated microglia was indicated by an increase in OX-6-positive cells. In the SNc, the density of activated microglia in the MPTP+saline group was much higher than that in the sham-operated control ($F(2,11) = 100.18$, $P < 0.001$) (Fig. 6B and E) and this effect was ameliorated by ceftriaxone treatment ($P < 0.001$ compared to the MPTP+saline group) (Fig. 6C and E).

Figure 7D shows a schematic drawing of the hippocampal area. Neuronal density in the pyramidal cell layer in the hippocampal CA1 area was decreased in the MPTP+saline group compared to the sham-operated group ($F(2,11) = 14.77$, $P < 0.001$) (Fig. 7B and E) and this effect was prevented by ceftriaxone treatment (Fig. 7C and E).

（四）討論

In the present study, MPTP lesioning caused behavioral deficits in working memory and object recognition which were prevented or ameliorated by two weeks of treatment with ceftriaxone at a dosage of 200 mg/kg/day. MPTP lesioning also decreased the density of DAergic neurons in the SNc and of pyramidal neurons in the hippocampal CA1 area and induced microglia activation in the SNc and all of these neurohistological and neuroinflammatory changes were partially inhibited by ceftriaxone treatment. To our knowledge, this is the first evidence that ceftriaxone can prevent hippocampal cell loss and improve cognitive function in a PD rat model. These results suggest that treatment with ceftriaxone may have beneficial effects on neuronal and behavioral impairments in PDD. The present study had limitations on the small number of brain examined, which temper our conclusions and should be addressed in future investigations.

In glutamatergic hyperactivity, glutamate acts as an excitotoxic agent and is involved in the degeneration of DAergic neurons seen in PD [40]. DAergic degeneration induced by MPTP lesioning in the SNc results in disturbances of motor function and cognitive behavior, for example, learning [38, 41], working memory [30, 42, 43], episodic-like memory [31], and object recognition [32, 35]. Blockade of NMDA receptors has been found to be effective in the treatment of PD. Administration of NMDA antagonists, for example, ketamine [44] and MK-801 [33, 45], both by systematic injection and brain infusion, have antiparkinsonian activity in MPTP-induced and 6-OHDA-induced PD rat models. Clinically, NMDA receptor antagonists, for example, amantadine and memantine, have been used for decades in the treatment of motor dysfunction in PD [46]. In agreement with a previous report [47, 48], our recent studies demonstrated that suppressing hyperactivity of the glutamatergic system using either MK-801 [33] or 2-methyl-6-(phenylethylnyl)-pyridine [34], a metabotropic glutamate receptor antagonist, reduces DAergic degeneration in the SNc and improves cognitive behaviors in an MPTP-induced PD rat model, suggesting that excessive glutamatergic activity is involved in the neuronal and behavioral deficits in PD. Reduction of glutamatergic hyperactivity has therefore been suggested as an effective therapeutic intervention for neurodegeneration and cognitive deficits in PD [49].

Removal of synaptically released glutamate ameliorates glutamate excitotoxic cell death. GLT-1, which is present in the membrane of glial cells, is one of the main glutamate transporters and is essential for recycling glutamate from the synaptic space and maintaining functional levels of glutamate in the synapse [50]. The glutamate that is taken up is then converted to glutamine and shuttled back to the neurons for synthesis of glutamate [51]. Increased clearance of glutamate from the synapse helps prevent glutamate excitotoxicity [52-54] and could be an alternative strategy for protecting neurons from excitotoxic cell death.

The neurological symptoms of patients suffering from neurodegenerative diseases, such as PD, often worsen during infection [55]. Interestingly, Ebert et al. [56] reported that the onset and course of PD in an α-synuclein transgenic PD mice model were not influenced by repeated systematic infections with *Streptococcus pneumonia* and that no signs of microglial activation were observed in the mouse brain; however, the *Streptococcus pneumonia* was co-administered with ceftriaxone (100 mg/kg, twice per day for 3 days) which may have had not only antibiotic activity, but also other effects, for example, a direct neuroprotective effect. Ceftriaxone can pass freely through the blood brain barrier [23] and can be found in the

cerebrospinal fluid [57]. In an animal model of cerebral ischemia, i.p. injection of ceftriaxone (200 mg/kg/day for 5 days) was reported to reduce brain damage [22]. Systemic injection of ceftriaxone (200 mg/kg/day for 7 days) increased the expression and function of GLT-1 on glia and neurons, potentiated glutamate uptake, and acted as a neuroprotection agent in a mouse model of amyotrophic lateral sclerosis [21] and in neurological disorders associated with glutamate excitotoxicity [58]. A ceftriaxone-induced decrease in glutamatergic hyperactivity might explain the neuroprotective effects of ceftriaxone in the striatum, SNc, and hippocampus seen in the present study.

A previous study demonstrated the presence of activated microglia in PD brains and suggested that these cells are involved in the neurodegenerative process [59]. Animal studies showed that activated microglia are also seen in the SNc after MPTP lesioning [30, 31, 35], indicating that neurodegeneration leads to microglia activation. In addition, activated microglia release inflammatory cytokines [60], which may lead to cell death [61] and aggravate neuroinflammation, and thus play an important role in the pathophysiology of PD [62]. In the present study, MPTP lesioning-induced microglial activation in the SNc was prevented by ceftriaxone treatment. In parallel, the MPTP-induced DAergic degeneration in the SNc and striatum was also abolished by ceftriaxone treatment. This result provides support for a correlation between microglial activation and neurodegeneration, as suggested previously [62].

The hippocampus is involved in many processes, such as working memory, long-term memory, memory retrieval, declarative memory, and spatial navigation. Excessive release of glutamate and excitotoxicity-induced neurodegeneration in the hippocampus may be responsible for the memory impairment observed in neurodegenerative animal models. Intraperitoneal injection of ceftriaxone (200 mg/kg/day for 7 or 14 days) increases GLT-1 expression and ameliorates hypoxia-induced memory impairment and cell loss in the hippocampus [24], indicating reduced glutamate-induced excitotoxicity in the hippocampus. The hippocampal CA1 area is rich in glutamatergic synapses and is particularly vulnerable to excitotoxic damage. Brain areas adjacent to the hippocampus are also involved in object recognition, while, hippocampal CA1 neurons play a crucial role in memory consolidation and retrieval. Thus, excitotoxic damage to these neurons could contribute to the impairments of working memory and recognition seen in PD. It needs further study whether increasing GLT-1 expression plays a role in our present findings that ceftriaxone protects neurons in the hippocampal CA1 area and improves cognitive behaviors in the MPTP-induced rat PD model.

Since the upregulation of GLT-1 expression by ceftriaxone is short-lived [21], long-term administration has been suggested so as to potentiate and prolong its beneficial effects. In clinical application, the dosage of ceftriaxone used to treat bacterial infections and meningitis in a human adult has been reported to be 2 g/day for 2 months, with no side-effects being reported [63]. Based on dose translation from animal to human studies [64], a daily dose of ceftriaxone of 200 mg/kg was used in the present study and no adverse side-effects were observed. Similarly, no side-effects were reported when ceftriaxone at the dose of 200 mg/kg per day was tested in a Huntington's disease mouse model [65].

In summary, the present study shows that sub-chronic administration of ceftriaxone inhibits MPTP-induced deficits in working memory and object recognition and partially suppresses neuroinflammation and neurodegeneration in the DAergic system and hippocampal CA1 area. These data suggest that ceftriaxone is a promising pharmacological tool for the development of new treatments for PDD.

Acknowledgements

This work was supported by grants from the National Science Council of the ROC (**NSC 102-2410-H-040-004**, NSC 101-2410-H-040-003, and NSC 100-2923-H-040-009-MY3), and was partially supported by budget from project No. 053 of the State Research Institute of Physiology and Fundamental Medicine SB RAMS and from the Molecular and Cell Biology Program of the Russian Academy of Sciences (grant no. 6.7). Conflicts of interest: The authors declare no conflicts of interest for the material in the manuscript.

（五）參考文獻

[1] Johnston MV. Excitotoxicity in neonatal hypoxia, Ment Retard Dev Disabil Res Rev 2001;7:229-234.

[2] Luetjens CM, NT Bui, B Sengpiel, G Munstermann, M Poppe, AJ Krohn, et al. Delayed mitochondrial dysfunction in excitotoxic neuron death: cytochrome c release and a secondary increase in superoxide production, J Neurosci 2000;20:5715-5723.

[3] Perez Velazquez JL, MV Frantseva, PL Carlen. In vitro ischemia promotes glutamate-mediated free radical generation and intracellular calcium accumulation in hippocampal pyramidal neurons, J Neurosci 1997;17:9085-9094.

[4] Chihab R, J Oillet, C Bossenmeyer, JL Daval. Glutamate triggers cell death specifically in mature central neurons through a necrotic process, Mol Genet Metab 1998;63:142-147.

[5] Martin WR. MR spectroscopy in neurodegenerative disease, Mol Imaging Biol 2007;9:196-203.

[6] Marino MJ, O Valenti, PJ Conn. Glutamate receptors and Parkinson's disease: opportunities for intervention, Drugs Aging 2003;20:377-397.

[7] Centonze D, P Gubellini, S Rossi, B Picconi, A Pisani, G Bernardi, et al. Subthalamic nucleus lesion reverses motor abnormalities and striatal glutamatergic overactivity in experimental parkinsonism, Neuroscience 2005;133:831-840.

[8] Blandini F, RH Porter, JT Greenamyre. Glutamate and Parkinson's disease, Mol Neurobiol 1996;12:73-94.

[9] Cepeda C, MS Levine. Dopamine and N-methyl-D-aspartate receptor interactions in the neostriatum, Dev Neurosci 1998;20:1-18.

[10] Meshul CK, N Emre, CM Nakamura, C Allen, MK Donohue, JF Buckman. Time-dependent changes in striatal glutamate synapses following a 6-hydroxydopamine lesion, Neuroscience 1999;88:1-16.

[11] Hill MP, P Ravenscroft, E Bezard, AR Crossman, JM Brotchie, A Michel, et al. Levetiracetam potentiates the antidyskinetic action of amantadine in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned primate model of Parkinson's disease, The Journal of pharmacology and experimental therapeutics 2004;310:386-394.

[12] Loschmann PA, C De Groote, L Smith, U Wullner, G Fischer, JA Kemp, et al. Antiparkinsonian activity of Ro 25-6981, a NR2B subunit specific NMDA receptor antagonist, in animal models of Parkinson's disease, Exp Neurol 2004;187:86-93.

[13] Nash JE, SH Fox, B Henry, MP Hill, D Peggs, S McGuire, et al. Antiparkinsonian actions of ifenprodil in the MPTP-lesioned marmoset model of Parkinson's disease, Exp Neurol 2000;165:136-142.

[14] St-Pierre JA, PJ Bedard. Systemic administration of the NMDA receptor antagonist MK-801 potentiates circling induced by intrastriatal microinjection of dopamine, Eur J Pharmacol 1995;272:123-129.

[15] Kornhuber J, M Weller, K Schoppmeyer, P Riederer. Amantadine and memantine are NMDA receptor antagonists with neuroprotective properties, J Neural Transm Suppl 1994;43:91-104.

[16] Skuza G, Z Rogoz, G Quack, W Danysz. Memantine, amantadine, and L-deprenyl potentiate the action of L-dopa in monoamine-depleted rats, J Neural Transm Gen Sect 1994;98:57-67.

[17] Santini E, RU Muller, GJ Quirk. Consolidation of extinction learning involves transfer from NMDA-independent to NMDA-dependent memory, Journal of Neuroscience 2001;21:9009-9017.

[18] Kornhuber J, M Weller. Psychotogenicity and N-methyl-D-aspartate receptor antagonism: implications for neuroprotective pharmacotherapy, Biol Psychiatry 1997;41:135-144.

[19] Nicholls D, D Attwell. The release and uptake of excitatory amino acids, Trends Pharmacol Sci 1990;11:462-468.

[20] Congeni BL. Comparison of ceftriaxone and traditional therapy of bacterial meningitis, Antimicrob Agents Chemother 1984;25:40-44.

[21] Rothstein JD, S Patel, MR Regan, C Haenggeli, YH Huang, DE Bergles, et al. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression, Nature 2005;433:73-77.

[22] Chu K, ST Lee, DI Sinn, SY Ko, EH Kim, JM Kim, et al. Pharmacological induction of ischemic tolerance by glutamate transporter-1 (EAAT2) upregulation, Stroke 2007;38:177-182.

[23] Lipski J, CK Wan, JZ Bai, R Pi, D Li, D Donnelly. Neuroprotective potential of ceftriaxone in in vitro models of stroke, Neuroscience 2007;146:617-629.

[24] Hota SK, K Barhwal, K Ray, SB Singh, G Ilavazhagan. Ceftriaxone rescues hippocampal neurons from excitotoxicity and enhances memory retrieval in chronic hypobaric hypoxia, Neurobiol Learn Mem 2008;89:522-532.

[25] Brown RG, CD Marsden. How common is dementia in Parkinson's disease?, Lancet 1984;2:1262-1265.

[26] Aarsland D, K Andersen, JP Larsen, A Lolk, H Nielsen, P Kragh-Sorensen. Risk of dementia in Parkinson's disease: a community-based, prospective study, Neurology 2001;56:730-736.

[27] Barnes J, L Boubert, J Harris, A Lee, AS David. Reality monitoring and visual hallucinations in Parkinson's disease, Neuropsychologia 2003;41:565-574.

[28] Laatu S, A Revonsuo, L Pihko, R Portin, JO Rinne. Visual object recognition deficits in early Parkinson's disease, Parkinsonism Relat Disord 2004;10:227-233.

[29] Ramirez-Ruiz B, C Junque, MJ Marti, F Valldeoriola, E Tolosa. Neuropsychological deficits in Parkinson's disease patients with visual hallucinations, Mov Disord 2006;21:1483-1487.

[30] Ho YJ, SC Ho, CR Pawlak, KY Yeh. Effects of D-cycloserine on MPTP-induced behavioral and neurological changes: potential for treatment of Parkinson's disease dementia, Behav Brain Res 2011;219:280-290.

[31] Wang AL, YM Liou, CR Pawlak, YJ Ho. Involvement of NMDA receptors in both MPTP-induced neuroinflammation and deficits in episodic-like memory in Wistar rats, Behav Brain Res 2010;208:38-46.

[32] Wang WF, SL Wu, YM Liou, AL Wang, CR Pawlak, YJ Ho. MPTP lesion causes neuroinflammation and deficits in object recognition in Wistar rats, Behav Neurosci 2009;123:1261-1270.

[33] Hsieh MH, SL Gu, SC Ho, CR Pawlak, CL Lin, YJ Ho, et al. Effects of MK-801 on recognition and neurodegeneration in an MPTP-induced Parkinson's rat model, Behav Brain Res 2012;229:41-47.

[34] Hsieh MH, SC Ho, KY Yeh, CR Pawlak, HM Chang, YJ Ho, et al. Blockade of metabotropic glutamate receptors inhibits cognition and neurodegeneration in an MPTP-induced Parkinson's disease rat model, Pharmacol Biochem Behav 2012;102:64-71.

[35] Sy HN, SL Wu, WF Wang, CH Chen, YT Huang, YM Liou, et al. MPTP-induced dopaminergic degeneration and deficits in object recognition in rats are accompanied by neuroinflammation in the

hippocampus, Pharmacol Biochem Behav 2010;95:158-165.

[36] Paxinos G WC, The rat brain in stereotaxic coordinates., Academic Press, London, 1986.

[37] Da Cunha C, MS Gevaerd, MA Vital, E Miyoshi, R Andreatini, R Silveira, et al. Memory disruption in rats with nigral lesions induced by MPTP: a model for early Parkinson's disease amnesia, Behav Brain Res 2001;124:9-18.

[38] Ferro MM, MI Bellissimo, JA Anselmo-Franci, ME Angellucci, NS Canteras, C Da Cunha. Comparison of bilaterally 6-OHDA- and MPTP-lesioned rats as models of the early phase of Parkinson's disease: histological, neurochemical, motor and memory alterations, J Neurosci Methods 2005;148:78-87.

[39] Ouyang YB, LA Voloboueva, LJ Xu, RG Giffard. Selective dysfunction of hippocampal CA1 astrocytes contributes to delayed neuronal damage after transient forebrain ischemia, J Neurosci 2007;27:4253-4260.

[40] Albin RL, JT Greenamyre. Alternative excitotoxic hypotheses, Neurology 1992;42:733-738.

[41] Gevaerd MS, RN Takahashi, R Silveira, C Da Cunha. Caffeine reverses the memory disruption induced by intra-nigral MPTP-injection in rats, Brain Res Bull 2001;55:101-106.

[42] Braga R, I Kouzmine, NS Canteras, C Da Cunha. Lesion of the substantia nigra, pars compacta impairs delayed alternation in a Y-maze in rats, Exp Neurol 2005;192:134-141.

[43] Bellissimo MI, I Kouzmine, MM Ferro, BH de Oliveira, NS Canteras, C Da Cunha. Is the unilateral lesion of the left substantia nigra pars compacta sufficient to induce working memory impairment in rats?, Neurobiol Learn Mem 2004;82:150-158.

[44] Ferro MM, ME Angelucci, JA Anselmo-Franci, NS Canteras, C Da Cunha. Neuroprotective effect of ketamine/xylazine on two rat models of Parkinson's disease, Braz J Med Biol Res 2007;40:89-96.

[45] Graham WC, RG Robertson, MA Sambrook, AR Crossman. Injection of excitatory amino acid antagonists into the medial pallidal segment of a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) treated primate reverses motor symptoms of parkinsonism, Life Sci 1990;47:PL91-97.

[46] Goetz CG. New lessons from old drugs: amantadine and Parkinson's disease, Neurology 1998;50:1211-1212.

[47] Turski L, K Bressler, KJ Rettig, PA Loschmann, H Wachtel. Protection of substantia nigra from MPP+ neurotoxicity by N-methyl-D-aspartate antagonists, Nature 1991;349:414-418.

[48] Zuddas A, G Oberto, F Vaglini, F Fascetti, F Fornai, GU Corsini. MK-801 prevents 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in primates, Journal of neurochemistry 1992;59:733-739.

[49] Pittenger C, JH Krystal, V Coric. Glutamate-modulating drugs as novel pharmacotherapeutic agents in the treatment of obsessive-compulsive disorder, NeuroRx 2006;3:69-81.

[50] Mao J. Glutamate transporter: an unexpected target for some antibiotics, Mol Pain 2005;1:5.

[51] Beart PM, RD O'Shea. Transporters for L-glutamate: an update on their molecular pharmacology and pathological involvement, Br J Pharmacol 2007;150:5-17.

[52] Rothstein JD, M Dykes-Hoberg, CA Pardo, LA Bristol, L Jin, RW Kuncl, et al. Knockout of glutamate transporters reveals a major role for astroglial transport in excitotoxicity and clearance of glutamate, Neuron 1996;16:675-686.

[53] Kanai Y, MA Hediger. The glutamate and neutral amino acid transporter family: physiological and pharmacological implications, Eur J Pharmacol 2003;479:237-247.

[54] Huang SS, J He, DM Zhao, XY Xu, HP Tan, H Li. Effects of mutant huntingtin on mGluR5-mediated dual signaling pathways: implications for therapeutic interventions, Cell Mol Neurobiol 2010;30:1107-1115.

[55] Perry VH, C Cunningham, C Holmes. Systemic infections and inflammation affect chronic

neurodegeneration, Nat Rev Immunol 2007;7:161-167.

[56] Ebert S, M Goos, L Rollwagen, D Baake, WD Zech, H Esselmann, et al. Recurrent systemic infections with Streptococcus pneumoniae do not aggravate the course of experimental neurodegenerative diseases, J Neurosci Res 2010;88:1124-1136.

[57] Nau R, HW Prange, P Muth, G Mahr, S Menck, H Kolenda, et al. Passage of cefotaxime and ceftriaxone into cerebrospinal fluid of patients with uninflamed meninges, Antimicrob Agents Chemother 1993;37:1518-1524.

[58] Verma R, V Mishra, D Sasmal, R Raghubir. Pharmacological evaluation of glutamate transporter 1 (GLT-1) mediated neuroprotection following cerebral ischemia/reperfusion injury, Eur J Pharmacol 2010;638:65-71.

[59] McGeer PL, S Itagaki, BE Boyes, EG McGeer. Reactive microglia are positive for HLA-DR in the substantia nigra of Parkinson's and Alzheimer's disease brains, Neurology 1988;38:1285-1291.

[60] Yasuda Y, T Shimoda, K Uno, N Tateishi, S Furuya, K Yagi, et al. The effects of MPTP on the activation of microglia/astrocytes and cytokine/chemokine levels in different mice strains, J Neuroimmunol 2008;204:43-51.

[61] Nakajima K, S Kohsaka. Microglia: neuroprotective and neurotrophic cells in the central nervous system, Curr Drug Targets Cardiovasc Haematol Disord 2004;4:65-84.

[62] McGeer PL, EG McGeer. Inflammation and neurodegeneration in Parkinson's disease, Parkinsonism Relat Disord 2004;10 Suppl 1:S3-7.

[63] Roelcke U, W Barnett, E Wilder-Smith, D Sigmund, W Hacke. Untreated neuroborreliosis: Bannwarth's syndrome evolving into acute schizophrenia-like psychosis. A case report, J Neurol 1992;239:129-131.

[64] Reagan-Shaw S, M Nihal, N Ahmad. Dose translation from animal to human studies revisited, FASEB J 2007;22:659-661.

[65] Miller BR, JL Dorner, M Shou, Y Sari, SJ Barton, DR Sengelaub, et al. Up-regulation of GLT1 expression increases glutamate uptake and attenuates the Huntington's disease phenotype in the R6/2 mouse, Neuroscience 2008;153:329-337..

（六）圖表與說明

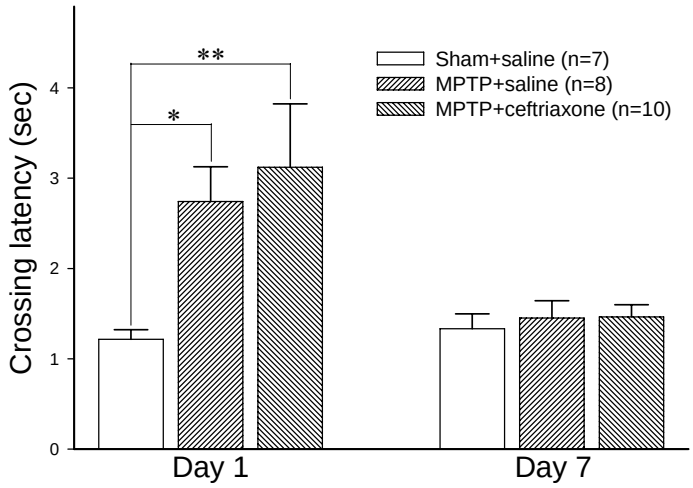

Fig. 1. Effect of ceftriaxone on the catalepsy of MPTP-lesioned rats in the bar test. MPTP (1 μmol) was bilaterally infused into the substantia nigra pars compacta, then ceftriaxone (200 mg/kg/day, i.p.) or saline (1 ml/kg/day, i.p.) was administered from day 1 after MPTP lesioning for 14 days. The bar test was performed on days 1 and 7 after MPTP lesioning. The data are expressed as the mean ± SEM for the indicated number of rats. * $P < 0.05$, ** $P < 0.001$ compared to the sham+saline group.

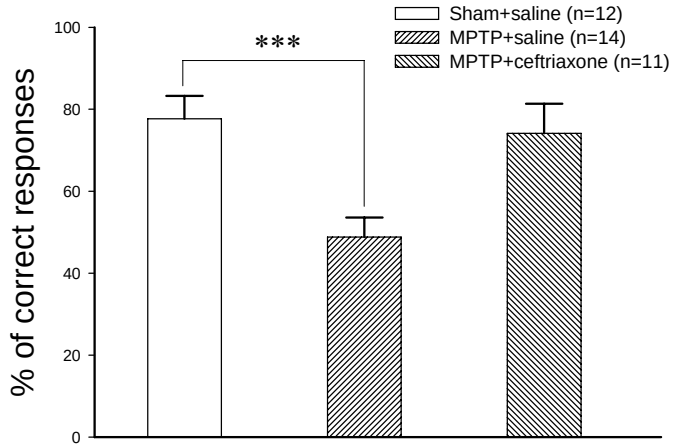

Fig. 2. Effect of ceftriaxone on the behavior of MPTP-lesioned rats in the T-maze test. Animals were treated as in Fig. 1, then the T-maze test was performed on day 10. The data are expressed as the mean ± SEM. *** $P < 0.001$ compared to the sham+saline group.

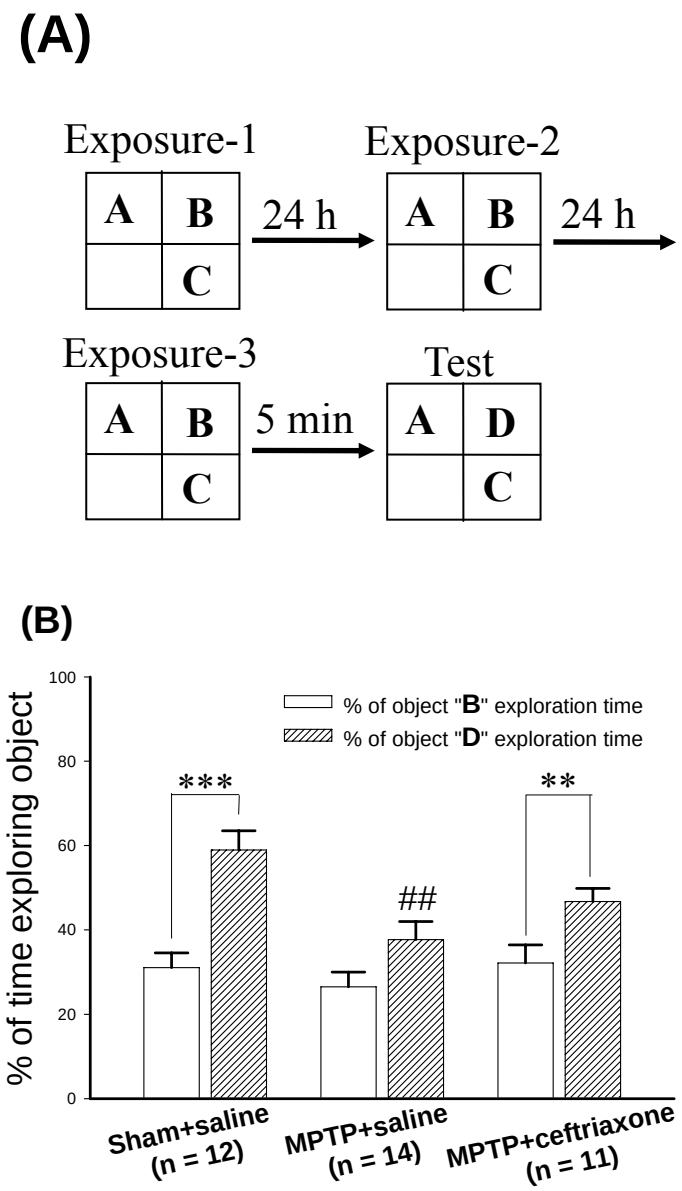

Fig. 3. Effect of ceftriaxone on object recognition in MPTP-lesioned rats. Animals were treated as in Fig. 1 and the object recognition test was performed on days 12–14. (A) Schematic diagram of the arrangement of the objects in the test. The rats underwent 3 exposure sessions (5 min each) at 24 h intervals, then were tested for 5 min starting 5 min after the end of exposure session 3. In the test session, object "B" was replaced by a novel object "D". (B) Percentage of time spent exploring object "B" or "D". The data are expressed as the mean ± SEM. ## $P < 0.01$ compared to percentage of time exploring object "D" in sham+saline group. ** $P < 0.01$, *** $P < 0.001$ compared to the percentage of time spent exploring object "B" (paired *t*-test).

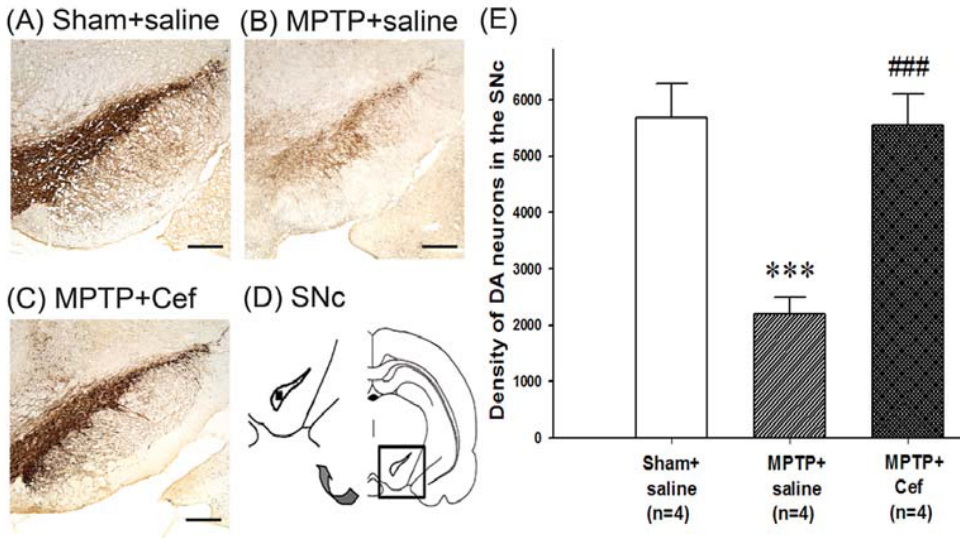

Fig. 4. Effect of ceftriaxone (Cef) on the MPTP-induced change in the density of dopaminergic neurons in the SNc on day 15 after MPTP lesioning. Animals were treated as in Fig. 1. (A-C) Dopaminergic neurons stained for tyrosine hydroxylase are shown in representative coronal sections. Magnification, 50×; bar, 200 μm. The rectangle in D indicates the area shown in A-C, and the small black square inside the rectangle indicates the area used for measuring the density of dopaminergic neurons. (E). Quantitative results. *** $P < 0.001$ compared to the sham+saline group. ### $P < 0.001$ compared to the MPTP+saline group.

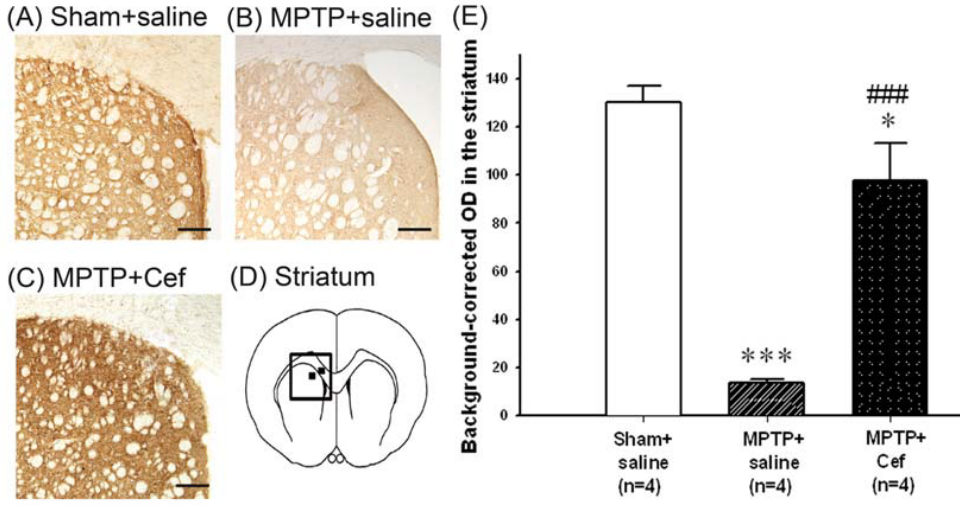

Fig. 5. Effect of ceftriaxone (Cef) on the MPTP-induced change in tyrosine hydroxylase immunoreactivity in the striatum on day 15 after MPTP lesioning. Animals were treated as in Fig. 1. (A-C) Tyrosine hydroxylase immunoreactivity in representative coronal sections. Magnification, 50×; bar, 200 μm. The rectangle in D indicates the area shown in A-C, and the two small black squares inside the rectangle indicate the areas used for measuring the optical density (OD). (E). Quantitative results. *** $P < 0.001$, * $P < 0.05$ compared to the sham+saline group. ### $P < 0.001$ compared to the MPTP+saline group.

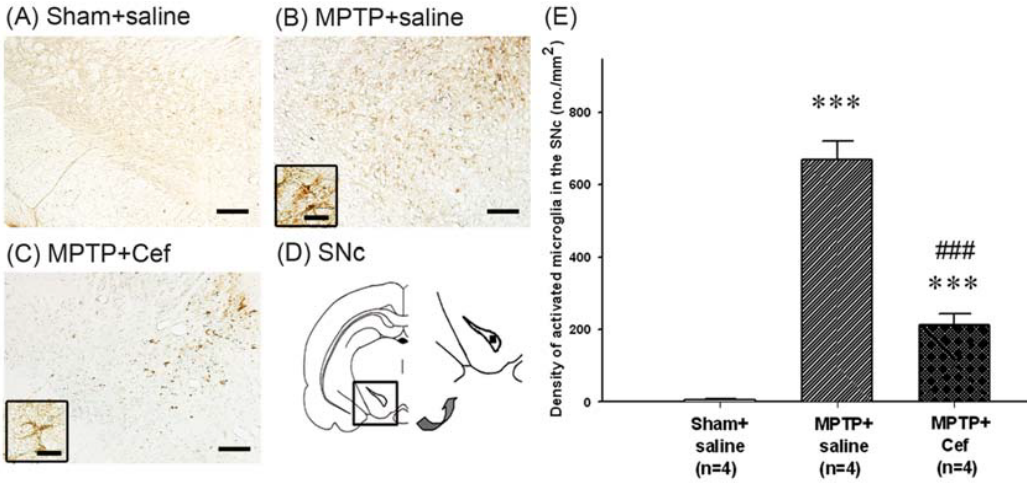

Fig. 6. Effect of ceftriaxone (Cef) on the MPTP-induced density of activated microglia in the SNc on day 15 after MPTP lesioning. Animals were treated as in Fig. 1. (A-C) Staining for activated microglia (anti-OX-6 antibody) in representative coronal sections. Magnification, 50×; bar, 200 μm. A high magnification image (200×, bar, 20 μm) of the activated microglia is shown in the insets. The rectangle in D indicates the area shown in A-C, and the small black square inside the rectangle indicates the area used for measuring the density (no./mm^2) of activated microglia in the SNc. (E). Quantitative results. *** $P < 0.001$ compared to the sham+saline group. ### $P < 0.001$ compared to the MPTP+saline group.

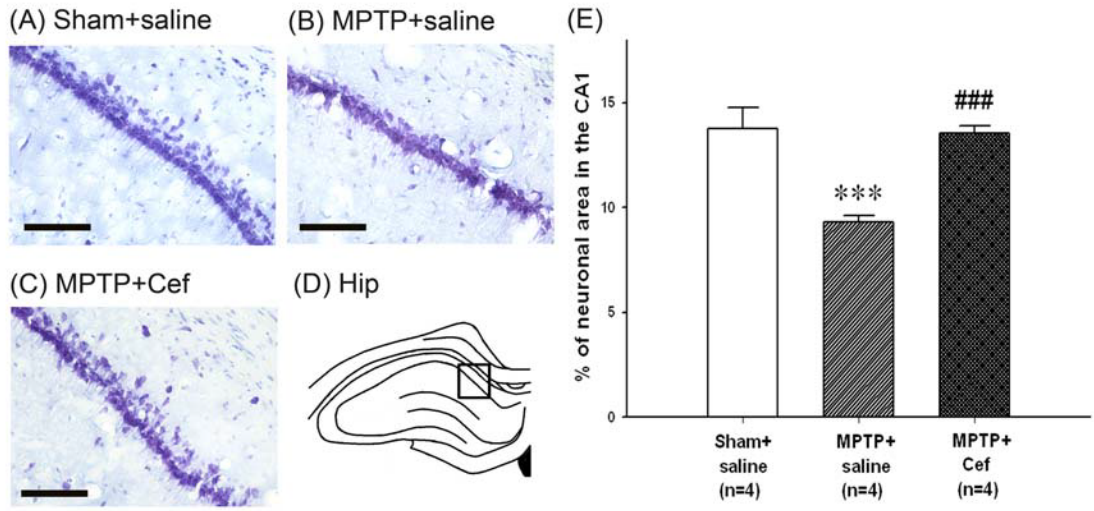

Fig. 7. Effects of ceftriaxone (Cef) on the MPTP-induced pyramidal cell loss in the hippocampal CA1 area on day 15 after MPTP lesioning. Animals were treated as in Fig. 1. The images show Nissl-stained pyramidal neurons in the CA1 area of the hippocampus, as indicated in the square in the schematic drawing. Magnification, 200×; bar, 100 μm. The rectangle in D indicates the area shown in A-C for measuring the density of pyramidal neurons in the hippocampal CA1 area. *** $P < 0.001$ compared to the sham+saline group. ### $P < 0.001$ compared to the MPTP+saline group.

三、 科技部補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現（簡要敘述成果是否有嚴重損及公共利益之發現）或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■ 達成目標

□ 未達成目標（請說明，以 100 字為限）

□ 實驗失敗

□ 因故實驗中斷

□ 其他原因

說明：經由本研究計畫相關經費及資源之協助，計畫主持人得以致力於研究工作，順利發表研究論文，文中均明確致謝本研究計畫之支持。

2. 研究成果在學術期刊發表或申請專利等情形：

論文：■已發表 □未發表之文稿 □撰寫中 □無

專利：■已獲得 □申請中 □無

技轉：□已技轉 □洽談中 ■無

已經發表之論文：

1. Tikhonova MA, CH Ting, NG Kolosova, CY Hsu, JH Chen, CW Huang, GT Tseng), CS Hung, PFu Kao, TG Amstislavskaya, **YJ Ho***. Improving bone microarchitecture in aging with diosgenin treatment: a study in senescence-accelerated OXYS rats. ***Chin J Physiol*** (2015, in press). (**國科會優良期刊**) [NSC 102-2410-H-040-004] **(SCI)**.

2. CY Hsu, CS Hung, HM Chang, WC Liao, SC Ho, **YJ Ho***. Cetriaxone prevents and reverses behavioral and neuronal deficits in an MPTP-induced animal model of Parkinson's disease dementia. ***Neuropharmacology*** 91:43-56, 2015. **(SCI)** [NSC 102-2410-H-040-004]

3. Ho SC, CC Hsu, CR Pawlak, MA Tikhonova, TJ Lai, TG Amstislavskaya, **YJ Ho***. Effects of ceftriaxone on the behavioral and neuronal changes in an MPTP-induced Parkinson's disease rat model. ***Behav Brain Res*** 268: 177-84, May 05, 2014. **(SCI)** [(NSC 102-2410-H-040-004]

4. Ho SC, CC Hsu, CH Yu, WN Huang, MA Tikhonova, MC Ho, CS Hung, TG Amstislavskaya, **YJ Ho***. Measuring Attention in a Parkinson's disease Rat Model using the 5-arm Maze Test. ***Physiology & Behavior*** 130: 176-81, May 05, 2014. **DOI:** 10.1016/j.physbeh.2014.03.017. **(SCI)** [(NSC 102-2410-H-040-004]

已獲得專利：

使用頭孢曲松來治療和/或預防巴金森氏症失智。**中國專利**。核准發文序號：20141119003202 90

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性），如已有嚴重損及公共利益之發現，請簡述可能損及之相關程度

本專利為應用頭孢曲松於治療巴金森氏症失智，具有臨床價值。由於頭孢曲松原先已經獲得核准可以使用於治療人類疾病，具有高度安全性，再經過臨床試驗測試使用劑量，即可用於治巴金森氏症失智，對於患者具有助益。

目前持續進行技術移轉，以便盡快進入臨床實用階段。

四、科技部補助計畫衍生研發成果推廣資料表

日期：104 年 01 月 26 日

<table>
<tr><td>科技部補助計畫</td><td colspan="3">計畫名稱：調節麩胺酸神經系統活性與神經新生作用對巴金森氏症失智之效果：從動物實驗建立臨床應用之潛力
計畫主持人：何應瑞
計畫編號：NSC 102-2410-H-040-004
領域：生物醫學</td></tr>
<tr><td rowspan="2">研發成果名稱</td><td colspan="3">（中文）使用頭孢曲松來治療和/或預防巴金森氏症失智。中國專利</td></tr>
<tr><td colspan="3">（英文）TREATMENT AND/OR PREVENTION OF PARKINSON’S DISEASE DEMENTIA WITH CEFTRIAXONE</td></tr>
<tr><td>成果歸屬機構</td><td>中山醫學大學、何應瑞、晉亞化工廠</td><td>發明人
(創作人)</td><td><u>何應瑞</u></td></tr>
<tr><td rowspan="2">技術說明</td><td colspan="3">（中文）本發明揭示頭孢曲松(ceftriaxone)可被用來治療和/或預防巴金森氏症失智(Parkinson’s disease dementia, PDD)。</td></tr>
<tr><td colspan="3">（英文）This invention discloses that ceftriaxone can be used in the treatment and/or prevention of Parkinson’s disease dementia (PDD).</td></tr>
<tr><td>產業別</td><td colspan="3">生物醫藥業</td></tr>
<tr><td>技術/產品應用範圍</td><td colspan="3">醫藥製品</td></tr>
<tr><td>技術移轉可行性及預期效益</td><td colspan="3">本技術及專利具有實施之可行性、具有醫藥價值，並且有商業利益。</td></tr>
</table>

註：本項研發成果若尚未申請專利，請勿揭露可申請專利之主要內容。

科技部補助專題研究計畫項下出席國際學術會議心得報告

日期：104 年 01 月 24 日

計畫編號	NSC 102-2410-H-040-004		
計畫名稱	調節麩胺酸神經系統活性與神經新生作用對巴金森氏症失智之效果：從動物實驗建立治療潛力		
出國人員姓名	何應瑞	服務機構及職稱	中山醫學大學 心理學系
會議時間	103 年 06 月 22 日 至 06 月 24 日	會議地點	**美國紐澳良**
會議名稱	(中文)第四屆國際區域（北美）壓力與行為會議 (英文) The 4th International Regional (North America) Stress and Behavior Conference		
發表論文題目	**Ho YJ***, SC Ho, CS Hung. Ceftriaxone prevents and reverses behavioral and neuronal deficits in MPTP-induced animal model of Parkinson's disease dementia. The 4th Regional International "Stress and Behavior" 2014 Conference, Jun 22-24, 2014, **New Orleans, LA, USA**		

一、參加會議經過

於 103 年 6 月 22 日至 24 日出席於美國紐澳良所舉行之「第四屆國際區域（北美）壓力與行為會議」。

二、與會心得

會議中以演講發表一篇論文（如下），並且與其他國家學者共同討論最新之神經行為病理學發現。會議中特別留意到今年亞洲國家之研究團隊出席相當踴躍，並且著重發表生物醫學、生物神經科學及行為科學之研究成果。

本人發表一篇研究成果，題目為：Ceftriaxone prevents and reverses behavioral and neuronal deficits in MPTP-induced animal model of Parkinson's disease dementia。

會議中，有許多來自紐西蘭及中東等國之學者，是因為看到大會公告

之發表主題，特地前來聽我的演講。演講後與會者討論踴躍。因此更肯定研究之價值。

三、建議

建議爾後多鼓勵國內相同領域之學者多共同出席國際會議，可以形成一種學術氛圍並吸引注意。

四、攜回資料名稱及內容　（與會手冊封面、論文暨海報發表時程等影本）會議手冊等

議程與摘要集

Program and Abstracts

4th International Regional (North America) ISBS Neuroscience and Biological Psychiatry "Stress and Behavior" Conference

New Orleans, LA, USA
June 22-24, 2014

Final Program

Day 1. Sun, June 22, 2014

Ballroom, 8th floor, Holiday Inn - Downtown Superdome, 330 Loyola Avenue, New Orleans, LA

09.30-05.00 Conference registration

Morning session

10.00-10.40 **OPENING AND WELCOMING ADDRESS.** AV Kalueff (Conference Chair and ISBS President)

PRESENTATION OF THE INTERNATIONAL STRESS AND BEHAVIOR SOCIETY INDUCTION OF 2014 ISBS FELLOWS

10.40-11.25 **ISBS FELLOW LECTURE: UTILIZING BRAIN AWARENESS WEEK TO PROMOTE ACTIVE LEARNING AND CIVIC ENGAGEMENT.** JE Warnick (ISBS Fellow) and M Varner, Department of Behavioral Sciences, Arkansas Tech University, Russellville, AR, USA

11.25-12.00 **MULTIVARIATE ANALYSIS OF ENVIRONMENT-LIFE FOR PSYCHIATRY.** M Koshiba (ISBS Fellow), G Karino, K Mimura, K Ikegami, H Tokuno, S Usui, I Tanaka, Y Honda, T Kodama, K Sato, W Tsugawa, K Sode, H Kishino, M Shukuya, T Kunikata, S Nakamura (ISBS Fellow) and H Yamanouchi, Tokyo University of Agriculture and Technology, Tokyo, Saitama Medical University, Saitama, TMIM, NCNP, University of Tokyo, Tokyo City University, Tokyo, Japan

12.00-01.00 **Lunch break (free time)**

Afternoon session

01.00-02.30 **SYMPOSIUM I: BIOLOGICAL PSYCHIATRY OF STRESS**
Chairs: JE Warnick, D Echevarria (USA)

Presentations 15 min

OCCUPATIONAL STRESS, PSYCHIATRIC ILLNESS AND THE LAW. G Mendelson, D Mendelson, School of Clinical Sciences, Faculty of Medicine, Nursing and Health Sciences, Monash University, School of Law, Faculty of Business and Law, Deakin University, Melbourne, Victoria, Australia

DIURNAL FLUCTUATIONS IN HPA AND NEUROPEPTIDE Y (NPY)-ERGIC SYSTEMS UNDERLIE DIFFERENCES IN VULNERABILITY TO TRAUMATIC STRESS RESPONSES AT DIFFERENT CIRCADIAN PHASES. S Cohen, E Vainer, N Kozlovsky, Z Kaplan, J Zohar, AA Mathe and H Cohen, Department of Psychology, Beer-Sheva Mental Health Center, Ben-Gurion University, Beer-Sheva, The Chaim Sheba Medical Center, Tel-Aviv, Israel; Clinical Neuroscience Department, Karolinska University Hospital, Stockholm, Sweden

PERINATAL DEPRESSION AND OMEGA-3 FATTY ACIDS: A MENDELIAN RANDOMISATION STUDY. H Sallis, C Steer, L Paternoster, G Davey Smith and J Evans, MRC Integrative Epidemiology Unit, Centre for Academic Mental Health, Centre for Child and Adolescent Health, School of Social and Community Medicine, University of Bristol, Bristol, UK

SODIUM VALPROATE TREATMENT FOR PSEUDOBULBAR AFFECT WITH PERSEVERATION: A CASE REPORT. S Cyriac and A Jain, St. Mary Mercy Hospital, Livonia, MI, USA

PSYCHO-NEUROIMMUNOLOGICAL IMPLICATIONS OF MEANING-MAKING IN ADVANCED CANCER. E Lau, SB Miller and B Gagnon, Department of Clinical Psychology, Columbia University, New York, NY, USA; Department of Clinical Psychology, Concordia University, Montreal, QC; Faculty of Medicine, McGill University, Royal Victoria Hospital, Montreal, QC, Candada

- **DISCUSSION**

02.30-03.00 **Coffee Break**

03.00-03.20 **"PROJECT L/EARN" PROGRAM PRESENTATION.** D Davis, Institute for Health, Health Care Policy and Aging Research, Rutgers, the State University of New Jersey, New Brunswick, NJ, USA

03.20-05.00 **SYMPOSIUM II: LAPIN SYMPOSIUM ON TRANSLATIONAL PSYCHIATRY**
Chairs: AV Kalueff (USA), JE Warnick (USA)

Presentations 20 min

INTRODUCTION: PROF. IZYASLAV P. LAPIN. This regular ISBS symposium is dedicated to Professor Izyaslav (Slava) P. Lapin (1930-2012), one of the true pioneers of experimental neuropsychopharmacology.

THE EFFECT OF SOCIAL AND THERMAL ENVIRONMENT ON THE DEVELOPMENT OF INFANT COMMON MARMOSET PHYSIOLOGY AND BEHAVIOR. G Karino, W Tsugawa, K Sode, T Murakoshi, T Kunikata, H Yamanouchi, S Nakamura (ISBS Fellow) and M Koshiba (ISBS Fellow), Tokyo University of Agriculture and Technology, Tokyo, Saitama Medical University, Saitama, Japan

BENEFICIAL EFFECTS OF CRHR1 SIGNALING ON ISCHEMIA-INDUCED MEMORY DEFICITS AND NEURONAL LOSS IN THE CA1 OF THE HIPPOCAMPUS BUT NOT IN THE BLA. PB de la Tremblaye, M Bonneville and H Plamondon, Behavioral Neuroscience Program, School of Psychology, University of Ottawa, Ottawa, Canada

ESTRADIOL AND PROGESTERONE CAN PREVENT DEPRESSIVE-LIKE BEHAVIOR IN AN EXPERIMENTAL MODEL OF PERIMENOPAUSE. KV Weissheimer and JA Anselmo-Franci, Department of Morphology, Physiology and Basic Pathology, Dental School of Ribeirao Preto, University of Sao Paulo, Ribeirao Preto, Sao Paulo, Brazil

CEFTRIAXONE PREVENTS AND REVERSES BEHAVIORAL AND NEURONAL DEFICITS IN MPTP-INDUCED ANIMAL MODEL OF PARKINSON'S DISEASE DEMENTIA. Y-J Ho, S-C Ho and C-S Hung, School of Psychology, Chung Shan Medical University Hospital, Chung Shan Medical University, Department of Education and Research, Taipei City Hospital, Taipei, Taiwan, ROC

- **DISCUSSION**

05.00-06.00 **CAREER DEVELOPMENT IN NEUROSCIENCE, BIOLOGICAL PSYCHIATRY AND BIOPSYCHOLOGY:** ROUND TABLE (moderators: AV Kalueff, JE Warnick)

Social event:
7.45 pm City Night 2-h walking tour (admissions)

Day 2. Mon, June 23, 2014

Ballroom, 8th floor, Holiday Inn - Downtown Superdome, 330 Loyola Avenue, New Orleans, LA

09.30-05.00 Conference registration

Morning session

10.00-01.00 **SYMPOSIUM III: ZUKOWSKA SYMPOSIUM ON STRESS RESEARCH**
Chairs: AV Kalueff (USA), JE Warnick (USA)

INTRODUCTION: PROF. ZOFIA M. ZUKOWSKA. This regular ISBS symposium is dedicated to Professor Zofia Zukowska (1949-2012).

10.10-10.50 **ISBS Lecture: SAFETY AND THE SWEET SCIENCE: USING EMPIRICAL EVIDENCE TO GUIDE CHANGES TO PROFESSIONAL BOXING RULES AND REGULATIONS.** JE Warnick (ISBS Fellow), Department of Behavioral Sciences, Arkansas Tech University, Russellville, AR, USA

10.50-11.30 **NEURAL AND BEHAVIORAL CORRELATES OF STRESS VULNERABILITY IN CHILDREN AT HIGH RISK FOR ADULT PSYCHOPATHOLOGY.** EA Beaton, Department of Psychology, University of New Orleans, New Orleans, LA, USA

11.30-11.50 **Coffee break**

11.50-12.25 **VITAMIN D, ANXIETY AND EXCESSIVE SWEATING.** KK Abdul-Razzak and NM Ayoub, Jordan University of Science and Technology, Irbid, Jordan

12.25-01.00 **STRESS AND ITS INTERACTION WITH DRUG CUE IN THE REINSTATEMENT OF NICOTINE-SEEKING BEHAVIOR IN A RAT MODEL OF RELAPSE.** X Liu, Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson, MS, USA

01.00-02.20 **Lunch break (free time)**

Afternoon session

02.20-02.35 **TAKOTSUBO CARDIOMYOPATHY, ALSO KNOWN AS STRESS CARDIOMYOPATHY, PRESENTING AS CARDIAC EMERGENCY SECONDARY TO ACUTE AND CHRONIC STRESS: A CASE SERIES.** A Rai, FE George, ST Cyriac and S Zampani, St Mary Mercy Hospital, Livonia, MI, USA

02.35-02.50 **PSYCHOLOGICAL STRAIN AND ITS OUTCOMES AMONG LECTURERS IN EASTERN SAUDI ARABIA.** AA Motawa, M Jdaitawi, F Talafha and AM Awwad, University of Dammam, Dammam, Saudi Arabia

02.50-05.30 **SYMPOSIUM IV: INTERACTIVE GUIDED POSTER SESSION**

ANTIPSYCHOTIC USE IN THE TREATMENT OF ANXIETY DISORDERS. SR Weber and AM Duchemin, Ohio State University Wexner Medical Center, Columbus, OH, USA

TELEPSYCHIATRY: SOLVING CLINICAL CHALLENGES AND IMPROVING PATIENT CARE. SD Yoho and A Savageau, Ohio State Wexner Medical Center, Columbus, OH, USA

Day 3. Tue, June 24, 2014

Ballroom, 8th floor, Holiday Inn - Downtown Superdome, 330 Loyola Avenue, New Orleans, LA

Morning session

10.00-10.10 **INTRODUCTION: THE INTERNATIONAL ZEBRAFISH NEUROSCIENCE RESEARCH CONSORTIUM (ZNRC)**

10.10-10.40 **ISBS PRESIDENTIAL LECTURE: ZEBRAFISH MODELS IN TRANSLATIONAL NEUROSCIENCE RESEARCH – FROM TANK TO BEDSIDE.** AV Kalueff (ISBS Fellow) and AM Stewart, ZENEREI Institute and the International Zebrafish neuroscience Research Consortium (ZNRC), New Orleans, LA, University of Pittsburgh, Pittsburgh, PA, USA

10.40-11.20 **ZNRC Lecture: EXPLORING INDIVIDUAL DIFFERENCES IN ZEBRAFISH (DANIO RERIO) BEHAVIOR.** DJ Echevarria (ISBS Fellow), Department of Psychology, Behavioral Neuroscience Lab, University of Southern Mississippi, Hattiesburg, MS, USA

11.20-12.00 **ZEBRAFISH AND CONDITIONED PLACE PREFERENCE: A TRANSLATIONAL MODEL OF DRUG REWARD.** AD Collier, KM Khan, EM Caramillo and DJ Echevarria (ISBS Fellow), Department of Psychology, University of Southern Mississippi, Hattiesburg, MS, USA

12.00-12.20 **CLOSING CEREMONY. ANNOUNCING THE 2015-2016 ISBS CONFERENCES**

12.20-12.50 **Coffee break**

POST-CONFERENCE SATELLITE EVENT

02.00-05.00 **SATELLITE ISBS/ZNRC SYMPOSIUM V: 6th INTERNATIONAL ZEBRAFISH NEUROBEHAVIORAL AND NEUROPHENOTYPING WORKSHOP ZB2N-2014** (registration is required; Board Meeting room)

This workshop consists of a series of presentations covering major neurobehavioral domains and advanced phenotyping techniques for probing normal and pathological behaviors in zebrafish.

Social event:
5.30 pm - Cafe du Monde and Carriage city tour (admissions)

Day 3. Tue, June 24, 2014

Ballroom, 8th floor, Holiday Inn - Downtown Superdome, 330 Loyola Avenue, New Orleans, LA

Morning session

10.00-10.10 **INTRODUCTION: THE INTERNATIONAL ZEBRAFISH NEUROSCIENCE RESEARCH CONSORTIUM (ZNRC)**

10.10-10.40 **ISBS PRESIDENTIAL LECTURE: ZEBRAFISH MODELS IN TRANSLATIONAL NEUROSCIENCE RESEARCH – FROM TANK TO BEDSIDE.** AV Kalueff (ISBS Fellow) and AM Stewart, ZENEREI Institute and the International Zebrafish neuroscience Research Consortium (ZNRC), New Orleans, LA, University of Pittsburgh, Pittsburgh, PA, USA

10.40-11.20 **ZNRC Lecture: EXPLORING INDIVIDUAL DIFFERENCES IN ZEBRAFISH (DANIO RERIO) BEHAVIOR.** DJ Echevarria (ISBS Fellow), Department of Psychology, Behavioral Neuroscience Lab, University of Southern Mississippi, Hattiesburg, MS, USA

11.20-12.00 **ZEBRAFISH AND CONDITIONED PLACE PREFERENCE: A TRANSLATIONAL MODEL OF DRUG REWARD.** AD Collier, KM Khan, EM Caramillo and DJ Echevarria (ISBS Fellow), Department of Psychology, University of Southern Mississippi, Hattiesburg, MS, USA

12.00-12.20 **CLOSING CEREMONY. ANNOUNCING THE 2015-2016 ISBS CONFERENCES**

12.20-12.50 **Coffee break**

POST-CONFERENCE SATELLITE EVENT

02.00-05.00 **SATELLITE ISBS/ZNRC SYMPOSIUM V: 6th INTERNATIONAL ZEBRAFISH NEUROBEHAVIORAL AND NEUROPHENOTYPING WORKSHOP ZB2N-2014** (registration is required; Board Meeting room)

This workshop consists of a series of presentations covering major neurobehavioral domains and advanced phenotyping techniques for probing normal and pathological behaviors in zebrafish.

Social event:
5.30 pm - Cafe du Monde and Carriage city tour (admissions)

7

Acceptance Letter

邀請演講函

----- Original Message -----

From: Ho

To: International Stress and Behavior Society ISBS

Sent: Sunday, May 11, 2014 9:12 PM

Subject: Re: Preliminary Program - 4th Regional International "Stress and Behavior" 2014 Conference in New Orleans, LA, USA (June 22-24, 2014)

----- Original Message -----

From: International Stress and Behavior Society ISBS

To: International Stress and Behavior Society ISBS

Sent: Sunday, May 11, 2014 1:37 PM

Subject: Preliminary Program - 4th Regional International "Stress and Behavior" 2014 Conference in New Orleans, LA, USA (June 22-24, 2014)

Dear Colleagues,

Please find attached Preliminary Program of the 4th Regional International "Stress and Behavior" 2014 Conference in New Orleans, LA, USA (June 22-24, 2014).

We kindly ask you to identify and review your presentations, including all authors' names, presentation titles, and shortened affiliations - for accuracy. Please contact us by May 20, 2014, if you have any corrections to make. We ask speakers to confirm attendance by May 25, 2014.

Final program will be sent to all delegates by June 10, 2014.

We look forward to meeting you all soon in New Orleans!

Cordially,

Allan V Kalueff PhD

Conference Chair

2014-2015 CONFERENCE SECRETARIAT

E-mail: isbs.congress@gmail.com

http://www.stressandbehavior.com

Please visit our ISBS Booth during the Society for Neuroscience SfN2014 conference in Washington DC (Nov 15-19, 2014)

Connect to us via FB https://www.facebook.com/isbs.conf

Connect to us via Twitter https://twitter.com/ISBSConference

Connect to us via LinkedIn http://www.linkedin.com/profile/view?id=282700913

發表研究成果摘要

Ceftriaxone Prevents and Reverses Behavioral and Neuronal Deficits in MPTP-induced Animal Model of Parkinson's Disease Dementia

Ying-Jui Ho[1]*, Shih-Chun Ho[1], Ching-Sui Hung[2]

[1] School of Psychology, Chung Shan Medical University Hospital, Chung Shan Medical University, Taiwan, ROC; [2] Department of Education and Research, Taipei City Hospital, Taipei 10341, ROC

Abstract

Glutamatergic hyperactivity plays an important role in pathophysiology of Parkinson's disease (PD). Ceftriaxone increases expression of glutamate transporter 1 (GLT-1) and shows neuroprotection. This study was aimed at clarifying whether ceftriaxone prevents or reverses behavioral and neuronal deficits in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD rat model.

Male Wistar rats were used in this study. A set of animals received ceftriaxone (100 and 200 mg/kg/day, i.p.) treatment, starting from either 5 days before or 3 days after the MPTP lesioning. Starting on the next day (day 1) of MPTP lesioning, the rats underwent a bar-test on days 1-7, a T-maze test on days 8-10, and an object recognition test on days 12-14. On the next day of behavioral test the brains were taken for histological evaluation. Another set of animals was sacrificed on the 3rd or 15th day after the brain surgery, without receiving behavioral test, for histological analysis.

Dopaminergic degeneration in the SNc and striatum was observed on the 3rd day after the MPTP lesioning and was not recovered till the 15th day. Behaviorally, one day after the MPTP lesioning, motor dysfunctions in bar test were observed. Such impairments were spontaneously recovered to control level in a week. In addition, MPTP lesioning resulted in deficits in working memory and object recognition in the T-maze test and object recognition task, respectively. These cognitive deficits were not observed in rats both receiving pre- and post-treatment with ceftriaxone. MPTP lesioning also caused neurodegeneration in the hippocampal CA1 area and induced glutamatergic hyperactivity in the subthalamic nucleus, these changes were suppressed by ceftriaxone treatment. Moreover, increase of GLT-1 expression and its colocalization with astrocyte were observed in the striatum and hippocampus. These results suggest that, by increasing GLT-1 expression, ceftriaxone prevents and reverses PD-related neurodegeneration and cognitive dysfunctions. Thus, ceftriaxone may have clinical potential for prevention and treatment of dementia associated with PD.

Keywords: Parkinson's disease, glutamatergic hyperactivity, glutamate transporter 1, ceftriaxone, dementia, neuroprotection, cognition

科技部補助計畫衍生研發成果推廣資料表

日期:2015/01/23

科技部補助計畫	計畫名稱: 調節麩胺酸神經系統活性與神經新生作用對巴金森氏症失智之效果：從動物實驗建立治療潛力
	計畫主持人: 何應瑞
	計畫編號: 102-2410-H-040-004- 學門領域: 生物心理學

無研發成果推廣資料

102 年度專題研究計畫研究成果彙整表

計畫主持人：何應瑞	計畫編號：102-2410-H-040-004-
計畫名稱：調節麩胺酸神經系統活性與神經新生作用對巴金森氏症失智之效果：從動物實驗建立治療潛力	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	1	1	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	8	8	100%		
		專書	0	0	100%		
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	1	1	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
國外	論文著作	期刊論文	5	2	250%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	1	1	100%		
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	1	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（外國籍）	碩士生	1	1	100%	人次	
		博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		

其他成果 (無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。)	無

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

科技部補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□未達成目標（請說明，以 100 字為限）

□實驗失敗

□因故實驗中斷

□其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：■已發表 □未發表之文稿 □撰寫中 □無

專利：■已獲得 □申請中 □無

技轉：□已技轉 ■洽談中 □無

其他：（以 100 字為限）

已經獲得中國發明專利（專利名稱：使用頭孢曲松來治療和/或預防巴金森氏症失智），正在進行領證（中國知識產權局，發文序號：2014111900320290）。

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）（以 500 字為限）

運用本計畫之經費進行研究，除了發表 4 篇 SCI 論文，部分研究成果具有醫藥實用價值，已經獲得中國發明專利，正在進行領證。