科技部補助專題研究計畫成果報告
期末報告

評估併用頭孢曲松與紅血球生成素對巴金森氏症失智之療效：腦部影像與神經行為科學之研究(第2年)

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中 華 民 國 106 年 03 月 08 日

中 文 摘 要 ： 人口老化在可以預見的未來將會造成嚴重的醫藥負擔。使用合適的老化動物模式以評估新藥的抗老化效果是有其必要的。OXYS大鼠是常被用來作為快速老化的動物品系。頭孢曲松(eftriaxone; CEF)具有降低興奮性毒性與活化抗氧化系統之功能，被報導具有神經保護之效果。本研究探討CEF(50 or 100 mg/kg/day, i.p., 36 天)在5個月大之OXYS大鼠的認知效果與神經保護之功能。長期投與CEF(100 mg/kg/day)可以部份減輕OXYS大鼠的運動障礙並改善其物件辨識缺陷。就神經型態學而言，與Wistar大鼠對照組比起來，OXYS大鼠海馬迴CA1區域內之神經密度比較低，其黑直至密區(SNc)內之神經細胞密度也較低。CEF(50 or 100 mg/kg/day)可以增加OXYS大鼠海馬迴CA1區域內錐狀細胞之密度，OXYS大鼠之紋狀體內酪胺酸酵素(tyrosine hydroxylase; TH))較低，但是CEF(50 mg/kg)治療可以增加TH的濃度。OXYS大鼠海馬迴齒狀回的顆粒下層中的神經新生現象(neurogenesis)較對照組為高，此現象暗示代償作用可能抑制了CEF對神經新生作用之效果。CEF恢復認知功能並且改善CA1裡的神經密度脂機轉，可能包括促進新生細胞之存活。本研究之結果推論，CEF可能具有抑制老化時出現認知缺陷的功能。

中 文 關 鍵 詞 ： 頭孢曲松、神經保護、老化、認知缺陷、海馬迴、神經新生、多巴胺神經系統

英 文 摘 要 ： Population aging will cause heavy medical burden in the foreseeable future. Using a suitable animal model to evaluate anti-aging property of new drug is needed. Rats of OXYS strain are characterized by genetically defined accelerated senescence. Ceftriaxone (CEF) exerts neuroprotective effects by decreasing the excitotoxicity and activation of antioxidant system. Here, we studied the effects of CEF (50 or 100 mg/kg/day, i.p., 36 days) on cognitive and neuronal deficits in 5-month-old OXYS rats. Chronic CEF administration in a dose of 100 mg/kg partially inhibited impairments of movement and restored the deficit in the novel object recognition in OXYS rats. Neuromorphologically, control OXYS rats exhibited a lowered neuronal density in the hippocampal CA1 area and there was a tendency to decrease in the substantia nigra pars compacta compared to Wistar controls. Both doses of CEF increased the density of pyramidal neurons in the CA1 area in OXYS rats. Control OXYS rats demonstrated a tendency to lower tyrosine hydroxylase (TH) immunoreactivity in the striatum compared with Wistar rats, while CEF treatment at a dose of 50 mg/kg significantly augmented this parameter. In control OXYS rats, the levels of neurogenesis in the subgranular zone of the dentate gyrus of the hippocampus were significantly higher than in Wistar rats indicating compensatory processes that probably prevented the further induction of neurogenesis by CEF. Restoration of the recognition function and neuronal density in the CA1 area

in OXYS rats after CEF treatment might be related to activation of the mechanisms that provide survival of newborn neurons. The data suggested CEF as a promising pharmacological tool for the prevention of cognitive decline at accelerated aging.

英文關鍵詞：ceftriaxone, neuroprotection, aging, cognitive deficit, hippocampus, neurogenesis, dopaminergic nigrostriatal system

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）

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計畫主持人：何應瑞
共同主持人：翁駿程
計畫參與人員：蒙婉筠、沈枚萱、張詩涵、陳奕如

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
□出國參訪及考察心得報告

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中華民國 106 年 3 月 8 日

內容

報告內容

Neuroprotective Effects of Ceftriaxone Treatment on Cognitive and Neuronal Deficits in a Rat Model of Accelerated Senescence

中文摘要

人口老化在可以預見的未來將會造成嚴重的醫藥負擔。使用合適的老化動物模式以評估新藥的抗老化效果是有其必要的。OXYS 大鼠是常被用來作為快速老化的動物品系。頭孢曲松(eftriaxone; CEF) 具有降低興奮性毒性與活化抗氧化系統之功能，被報導具有神經保護之效果。本研究探討 CEF(50 or 100 mg/kg/day, i.p., 36 天)在 5 個月大之 OXYS 大鼠的認知效果與神經保護之功能。長期投與 CEF(100 mg/kg/day)可以部份減輕 OXYS 大鼠的運動障礙並改善其物件辨識缺陷。就神經型態學而言，與 Wistar 大鼠對照組比起來，OXYS 大鼠海馬迴 CA1 區域內之神經密度比較低，其黑直至密區(SNc)內之神經細胞密度也較低。CEF(50 or 100 mg/kg/day)可以增加 OXYS 大鼠海馬迴 CA1 區域內錐狀細胞之密度，OXYS 大鼠之紋狀體內酪胺酸酵素(tyrosine hydroxylase; TH))較低，但是 CEF(50 mg/kg)治療可以增加 TH 的濃度。OXYS 大鼠海馬迴齒狀回的顆粒下層中的神經新生現象(neurogenesis)較對照組為高，此現象暗示代償作用可能抑制了 CEF 對神經新生作用之效果。CEF 恢復認知功能並且改善 CA1 裡的神經密度脂機轉，可能包括促進新生細胞之存活。本研究之結果推論，CEF 可能具有抑制老化時出現認知缺陷的功能。

關鍵字： 頭孢曲松、神經保護、老化、認知缺陷、海馬迴、神經新生、多巴胺神經系統

Abstract

Population aging will cause heavy medical burden in the foreseeable future. Using a suitable animal model to evaluate anti-aging property of new drug is needed. Rats of OXYS strain are characterized by genetically defined accelerated senescence. Ceftriaxone (CEF) exerts neuroprotective effects by decreasing the excitotoxicity and activation of antioxidant system. Here, we studied the effects of CEF (50 or 100 mg/kg/day, i.p., 36 days) on cognitive and neuronal deficits in 5-month-old OXYS rats. Chronic CEF administration in a dose of 100 mg/kg partially inhibited impairments of movement and restored the deficit in the novel object recognition in OXYS rats. Neuromorphologically, control OXYS rats exhibited a lowered neuronal density in the hippocampal CA1 area and there was a tendency to decrease in the substantia nigra pars compacta compared to Wistar controls. Both doses of CEF increased the density of pyramidal neurons in the CA1 area in OXYS rats. Control OXYS rats demonstrated a tendency to lower tyrosine hydroxylase (TH) immunoreactivity in the striatum compared with Wistar rats, while CEF treatment at a dose of 50 mg/kg significantly augmented this parameter. In control OXYS rats, the levels of neurogenesis in the subgranular zone of the dentate gyrus of the hippocampus were significantly higher than in Wistar rats indicating compensatory processes that probably prevented the further induction of neurogenesis by CEF. Restoration of the recognition function and neuronal density in the CA1 area in OXYS rats after CEF treatment might be related to activation of the mechanisms that provide survival of newborn neurons. The data suggested CEF as a promising pharmacological tool for the prevention of cognitive decline at accelerated aging.

Keywords: ceftriaxone, neuroprotection, aging, cognitive deficit, hippocampus, neurogenesis, dopaminergic nigrostriatal system

1. Introduction

Due to global population aging, dementia caused by neurodegeneration has received increasing attention. It is estimated that the United States alone has over five million patients with dementia.

Over the last few years, a large amount of experimental data has demonstrated that accelerated senescent OXYS rats are a suitable model of aging. OXYS rats were produced in the Institute of Cytology and Genetics of Siberian Branch of the Russian Academy of Sciences (Novosibirsk, Russia) by selective breeding of Wistar rats that were highly sensitive to the cataractogenic effect of D-galactose [1]. OXYS rats have a shortened lifespan and show early development of age-related pathological phenotypes similar to geriatric disorders observed in humans, including senile osteoporosis [2], cataract [3], retinopathy [4, 5], and signs of accelerated aging [6, 7]. They also demonstrate cognitive deficit, reproductive dysfunction and neurodegeneration as early as 3 months of age [8, 9], and have high levels of free radicals [10] and oxidative damage to DNA and proteins in liver mitochondria and cytosol [11-13]. Our recent study showed increased bone loss [14] and decreased sperm motility [15] in OXYS rats compared with Wistar rats of the same age. These features make it possible to use OXYS rats to evaluate the efficacy of treatments for functional impairments in aging.

Glutamate, an excitatory neurotransmitter, plays a role in excitotoxicity and aging-related neurodegeneration [16]. Excessive release of glutamate can overstimulate N-methyl-D-aspartate (NMDA) receptors, causing calcium overload in neurons and triggering apoptotic cell death [17-19]. Thus, glutamatergic hyperactivity and oxidative stress contribute to neurodegeneration and cognitive deficits in aging. A recent study showed dysregulation of glutamatergic neurotransmission in several brain regions in patients with neurodegenerative disorders, for example, in Parkinson's disease (PD) [20]. Nigrostriatal DAergic depletion causes overactivity of glutamatergic projections to the basal ganglia output nuclei from the corticostriatal pathway [21, 22] and the subthalamic nucleus (STN) [23], and increases striatal release of glutamate [24]. Moreover, blockade of glutamatergic activity may attenuate neuronal and cognitive deficits in aging [25]. Glutamate released at the synaptic cleft is taken up by glial cells via glutamate transporter-1 (GLT-1), thus terminating glutamate function at the synapse [26]. Since glutamatergic hyperactivity contributes to excitotoxicity, neurodegeneration, and memory loss, the ability to increase glutamate uptake from the synapse might prevent excitotoxic cell death.

Ceftriaxone (CEF), a beta-lactam antibiotic, increases GLT-1 expression and removal of released glutamate and ameliorates glutamate excitotoxicity [27]. Several studies have demonstrated the antiexcitotoxic potential of this compound [28, 29]. In animal models, pretreatment with CEF (200 mg/kg/day) prevented ischemia and stroke-induced neurohistological and molecular changes in Wistar rats [30, 31]. Treatment of rats with the same dose of ceftriaxone for 7 or 14 days during hypoxic exposure was found to increase GLT-1 expression, resulting in sequestration of excess glutamate in glial cells, protection of hippocampal neurons from excitotoxicity, and improved spatial memory retrieval [32]. Therapeutic effects of ceftriaxone have also been observed in animal models of amyotrophic lateral sclerosis [27], Huntington's disease [27,

33, 34], and spinal muscular atrophy [35, 36]. Previous studies demonstrated that ceftriaxone rescues the impairment of hippocampal synaptic plasticity and memory formation in AQP4 knockout mice [37] and reduces DAergic degeneration and motor dysfunction in a 6-hydroxydopamine (6-OHDA)-induced PD model [38]. Our recent studies demonstrated that treatment with CEF at dosages of 100 and 200 mg/kg/day inhibits neurodegeneration in the hippocampus and nigrostriatal dopaminergic (DAergic) system and improves cognitive function in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced PD rat model [39-41].

Movement and cognitive impairments are associated with aging, and these deficits are found to be correlated with DAergic and hippocampal neurodegeneration. This study therefore measured behavioral and neuronal effects of ceftriaxone in OXYS rats.

2. Materials and Methods

2.1. Experimental animals

14-week-old male Wistar rats weighing 440.1 ± 17.0 g and OXYS male rats of the same age weighing 304.9 ± 6.0 g from The Federal Research Center "Institute of Cytology and Genetics", Siberian Branch of the Russian Academy of Sciences (Novosibirsk, Russia) were used. Rats were housed in groups of five in acrylic cages (40 × 60 × 20 cm) in an animal room under standard conditions (a natural light-dark cycle (16 h light and 8 h dark), temperature: 18-22^{o}C, relative humidity: 50-60%, standard food and water *ad libitum*). Each animal was handled for 5 min/day on three consecutive days, before taking into experiment. Rats were divided into four experimental groups: Control (Saline-treated) Wistar males ("Wistar+saline" group, *n*=10), Control (Saline-treated) OXYS males ("OXYS+saline" group, *n*=10), Ceftriaxone-treated at a dose of 50 mg/kg OXYS males ("OXYS+Cef50" group, *n*=10), and Ceftriaxone-treated at a dose of 100 mg/kg OXYS males ("OXYS+Cef100" group, *n*=10).

All experimental procedures were performed according to the NIH Guide for the Care and Use of Laboratory Animals and approved by the Animal Care Committee of Chung Shan Medical University (IACUC approval No.: 1018). All efforts were made to minimize the number of animals used and their suffering.

2.2. General procedures

Starting from the age of 14-week old (day 1), Wistar rats received 36 daily intraperitoneal (i.p.) injections of saline while the respective groups of OXYS rats received 36 daily i.p. injections of saline or ceftriaxone (50 or 100 mg/kg/day). Rats were weighed weekly during the experiment to correct drug dosages.

In the last week of treatment, i.e. at the age of 19-week old, all animals were subjected to tests for behavioral phenotyping: the test for locomotor and exploratory activity on the day 33 of the treatment and the novel object recognition test on the days 34-36 as in our previous studies [42-46]. All behavioral observations were performed during the light phase between 12:00 and 18:00 h. For behavioral testing, the animals were placed individually in a clean cage (25 × 41 × 19 cm), and

transported to a dim observation room (28 lx of the red light) with sound isolation reinforced by a masking white noise of 70 dB. Performance in the behavioral tests was monitored using a video camera (Sony, China) positioned above the apparatus and processed with original EthoVision XT software (Noldus, Netherlands). The test equipment and objects used in this study were cleaned using 20% ethanol and thoroughly dried before each test trial. On the day 37 the rats were sacrificed by exposure to CO_2, transcardially perfused with phosphate-buffered saline (PBS) and followed by 4% paraformaldehyde in PBS, then their brains were taken for further neuromorphological study.

2.3. Drug Administration

Ceftriaxone was purchased from Roche (Switzerland). The rats were injected daily with either saline (1 ml/kg; Wistar+saline and OXYS+saline groups) or ceftriaxone at the dose of 50 (OXYS+Cef50 group) or 100 mg/kg/day (OXYS+Cef100 group) for 36 days. The rationale behind the ceftriaxone dosages (50, 100 mg/kg/day) adopted in the current study was based on our recent study showing neuroprotective effects of ceftriaxone in the subthalamic nucleus and hippocampal CA1 at the dosage of 200 and 100 mg/kg/day [14]. In this study, we also examined the effectiveness of ceftriaxone at the lower dose (50 mg/kg/day).

2.4. Behavioral tests

2.4.1 Locomotor activity

Locomotion of the rats was measured in an acrylic open box (60 × 60 × 60 cm). Distance travelled (in cm) was measured for 10 min.

2.4.2 Novel object recognition test

Recognition ability was measured using the object recognition test. The apparatus, an open box (60 × 60 × 60 cm), and the test procedure were identical to those in our previous reports [42-47]. Each rat was subjected to three exposure sessions at 24 h intervals (during days 34-36), then, 5 min after the exposure session on day 36, a test session was performed (Fig. 2A). Four different objects novel to the rats before the experiment were used for each rat to explore. Three of the objects (“A”, “B”, and “C”) were fixed on the floor at a distance of 27 cm away from three corners of the arena. The experimental procedure is as the followings: starting on day 34, 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 and the time spent exploring the objects during the exposure sessions and test session was recorded. Exploration of an object was defined as the rat approached an object and made physical contact with it using 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 [48].

2.5. Histological assay and image analysis

2.5.1. Tyrosine hydroxylase and Nissl staining

For histological assessment, 4 randomly selected rats per group were perfused intracardially

with 4% paraformaldehyde in PBS; then their brains were rapidly removed and post-fixed in PBS containing 30% sucrose and 4% paraformaldehyde at 4℃ until use. Frozen coronal sections (25 μm) were cut and mounted on gelatinized slides and kept in PBS until use. Unstained brain sections were identified according to the rat brain atlas [49], while brain sections stained and image analysis as described below were used for image analysis to measure histological changes, as described previously [42-46]. The image was captured and analyzed using a microscope (ZEISS AXioskop2, Germany) coupled to a CCD (Optronics, USA) and Image Pro Plus Software 6.0 (Media Cybernetics, CA, USA).

Tyrosine hydroxylase. Immunohistochemical staining for tyrosine hydroxylase (TH) was used to evaluate DAergic neurons or terminals in the SNc or striatum, respectively. Frozen brain sections containing the striatum and SNc were immunostained with rabbit polyclonal antibodies against rat TH (1:500 dilution in PBS; Millipore, CA, USA) at room temperature for overnight, then were sequentially incubated with biotinylated horse anti-rabbit IgG antibodies (1:300 dilution in PBS; Vector Laboratory, CA, USA) at 37 ^{o}C for 1h, followed by incubating with streptavidin-horseradish peroxidase (1:300 dilution in PBS; Biorad Laboratories, Oxford. UK) at 37 ^{o}C for 30 min, and with 0.02% 3,3′-diaminobenzidine (DAB) (Sigma, USA) at room temperature for 30 min. The slides were extensively washed with PBS. The density of DAergic projections in the striatum was measured by converting the TH-stained images to gray-scale. The gray level of density in the area of interest (31,896 μm^2) was subtracted by that of background staining in the non-immunoreactive corpus callosum to obtain the background-corrected optical density of the TH-reactive tissue. The density of DAergic neurons in the SNc was measured by capturing images, overlaying an area of interest (1,853,425 μm^2) in this region, and counting the somas of TH-immunoreactive neurons in these areas.

Nissl staining. Nissl staining, used to identify cells in the hippocampus, was performed as described in our previous reports [42-46, 50]. In the hippocampal CA1 area, it is difficult to directly count the number of neurons in a 25 μm thick brain section because the neurons are tightly packed. The density of cells herein was measured by a semi-quantitative method involving calculating the percentage of an area of interest (1,074,621 μm^2) in the CA1 area occupied by Nissl-stained cells. The analyzer was blind to the treatment.

2.5.2. Doublecortin staining

Four randomly selected rats per group were perfused intracardially with 4% paraformaldehyde in PBS; then their brains were rapidly removed and post-fixed in PBS containing 30% sucrose and 4% paraformaldehyde at 4℃ until use. After being immersed in the embedding Tissue-Tek O.C.T. compound (Sakura Finetek, USA), the brains were frozen and stored at -70C until sectioning into 30−μm-thick slices with a cryostat HistoSafe MicroCut – SADV (China). For rehydration and unmasking, cryosections were incubated in Trilogy solution (Sigma-Aldrich Co., Germany). To eliminate nonspecific background, the sections were treated at room temperature with hydrogen peroxide block (Spring Bioscience, USA) and protein block (Spring Bioscience, USA) prior to staining. The primary antibodies used were rabbit polyclonal anti-doublecortin (DCX) (ab18723, 1:1000 dilution, Abcam, UK) and applied at +4C temperature for overnight. The

fluorescent-labeled secondary antibodies used for the detection were Alexa Fluor 488 goat anti-rabbit IgG (ab150077, 1:400 dilution, Abcam, UK) and applied at RT for 2 h. The fluorescence images were finally obtained by a Axioplan 2 (Carl Zeiss) imaging microscope, Fluoromount aqueous mounting medium (Sigma-Aldrich Co., Germany) was used to reduce the amount of fluorochrome quenching. The newly born neurons on the images were identified based on the labeled structures that exhibit green fluorescence.

The quantitative method for counting newly born neurons was a modified procedure described by Lu et al. [51]. The tissue sliced sections were examined and DCX-positive cells were counted. Coronal slices along the hippocampus (AP = −2.7 – -5.3 mm) of each rat brain were made (with 30-μm thickness each). Among those sections, the DCX-labeled cells were counted in the subgranular zone (SGZ) of the dentate gyrus on every sixth section using ImageJ software (NIH, USA). The number of the cells was then multiplied by 6 to estimate the total number of DCX-positive cells. The analyzer was blind to the treatment.

2.6. Data analysis

Analysis of variance (ANOVA) followed by Fisher LSD *post-hoc* test was used to analyze the data on locomotion and histological results. Repeated Measures ANOVA followed by Fisher LSD *post-hoc* comparison was used to analyze the data of the object recognition test with group as between-subject variable and object as a repeated measure. STATISTICA software was used to perform all the statistical analyses. All results were expressed as the mean ± SEM. The level of significance was defined as $P < 0.05$ (two-tailed).

3. Results

3.1. Behavioral testing

3.1.1 Open field test

The ANOVA followed by an LSD *post-hoc* test revealed that OXYS+saline group showed lowered locomotion in the open field test compared with Wistar+saline group ($P < 0.001$). However, the distance travelled in OXYS+Cef100 group was significantly higher than that in OXYS+saline group ($P < 0.05$) (Fig. 1).

3.1.2 Novel object recognition test

According to ANOVA, there were no significant differences between the groups in total exploration time in all sessions of the object recognition test (data not shown). At the same time, two-way ANOVA demonstrated a significant influence of an object ($F(1,20) = 12.7$, $P < 0.01$) but not of an experimental group ($F(3,20) < 1$) or interaction between the effects of the factors ($F(3,20) = 1.9$, $P > 0.05$) on the time of a target object exploration. LSD *post-hoc* test showed that rats in Wistar+saline ($P < 0.01$), OXYS+Cef50 ($P = 0.08$), and OXYS+Cef100 ($P < 0.01$) groups spent a higher percentage of time exploring novel object D than exploring the familiar object B. This phenomenon was not observed in the OXYS+saline group (Fig. 2B).

3.2. Histological assay and image analysis

3.2.1. Tyrosine hydroxylase immunoreactivity

TH immunoreactivity was determined in DAergic terminals in the striatum (Fig. 3) and in DAergic neurons in the SNc (Fig. 4). Although one-way ANOVA did not reveal significant differences between the groups, a tendency was observed for TH immunoreactivity in the striatum ($F(3,10) = 1.79$, $P = 0.21$) and the density of DAergic neurons in the SNc ($F(3,8) = 1.77$, $P = 0.23$). Values in OXYS+saline group were lower in the striatum ($P = 0.23$) and SNc ($P = 0.058$) as compared to Wistar+saline group. TH immunoreactivity in the striatum was significantly higher in the OXYS+Cef50 ($P < 0.05$) as compared to OXYS+saline group.

3.2.2. Nissl staining

One-way ANOVA ($F(3,12) = 7.04$, $P < 0.05$) followed by the LSD *post-hoc* test showed that neuronal density in the hippocampal CA1 area was significantly decreased in the OXYS+saline group ($P < 0.001$) compared to Wistar+saline group. Ceftriaxone treatment at the doses of 50 and 100 mg/kg/day recovered neuronal density up to the control level. After treatment with ceftriaxone, rats in OXYS+CEF50 and in OXYS+CEF100 groups had the similar to Wistar+saline group levels of neuronal density in the area (Fig. 5E).

3.2.3. DCX-staining

One-way ANOVA ($F(3,13) = 3.5$, $P < 0.05$) followed by the LSD *post-hoc* test revealed that the number of newborn neurons (DCX-positive cells) in the SGZ of the dentate gyrus of the hippocampus was significantly increased in the OXYS+saline group ($P < 0.05$) compared to Wistar+saline group. Ceftriaxone treatment at both doses used did not affect significantly this parameter in OXYS rats (Fig. 6E).

4. Discussion

In glutamatergic hyperactivity, glutamate plays a role in excitotoxic cell death and is involved in aging-related neurodegeneration [52]. DAergic degeneration in the SNc causes disturbances of cognitive [53] and motivational functions [54] and also elevates risk of Parkinson's disease [55]. On the other hand, the degeneration of DAergic neurons causes life span shortening [56]. Blockade of NMDA receptors by using GLYX-13 has been found to be effective in the treatment of aging [57], suggesting that glutamatergic hyperactivity is involved in behavioral deficits in natural aging rat models. Reduction of glutamatergic hyperactivity has therefore been suggested as an effective therapeutic intervention for neurodegeneration and cognitive deficits in aging. Removal of synaptically released glutamate prevents excitotoxic cell death. GLT-1, presenting on 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 [58]. Increased clearance of glutamate from the synapse helps to prevent glutamate excitotoxicity [59-61] and could be an alternative strategy for protecting neurons from excitotoxic cell death.

In an animal model of cerebral ischemia, treatment with ceftriaxone (200 mg/kg/day, i.p., for 5 days) was reported to reduce brain damage [28]. Systemic injection of ceftriaxone (200 mg/kg/day

for 7 days) increased the expression and function of GLT-1 in glia and neurons, potentiated glutamate uptake, and acted as a neuroprotective agent in a mouse model of amyotrophic lateral sclerosis [27] and in neurological disorders associated with glutamate excitotoxicity [29, 41]. Earlier we found that ceftriaxone treatment restored cognitive impairment associated with neuronal deficits in the nigrostriatal DAergic system and hippocampus in a rat pharmacological model of Parkinson's disease [40, 41, 62]. A ceftriaxone-induced decrease in glutamatergic hyperactivity might explain the neuroprotective effects of ceftriaxone in the striatum, SNc, and hippocampus observed in the present study.

Aging animals demonstrate poor motor function [54], neurodegeneration, and cognitive deficits [63]. OXYS rats with accelerated senescence, being widely used as an aging model, show aging features including osteoporosis, cognitive deficit, reproductive dysfunction [3, 64], and neurodegeneration as early as at age of 3 months old [3, 8, 9]. In the present study, we also found a reduced locomotion and disturbed recognition in 14-week-old OXYS rats. Behavioral deficits in OXYS rats were accompanied with certain neuromorphological alterations. We detected a lowered neuronal density in the hippocampal CA1 area which is tightly involved in the learning, memory, and recognition, and a tendency to decrease in nigrostriatal DAergic system in OXYS rats. The latter finding may partially contribute to the development of motor deficits observed in OXYS rats since there was a slight but significant increase in their locomotor activity after ceftriaxone treatment at a dose of 100 mg/kg as well as in the indices of nigrostriatal DAergic system.

The hippocampus is involved in 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 and object recognition impairments observed in neurodegenerative animal models. Intraperitoneal injection of ceftriaxone (200 mg/kg/day for 7 or 14 days) increases GLT-1expression and ameliorates hypoxia-induced memory impairment and cell loss in the hippocampus [32] indicating a reduction of glutamate-induced excitotoxicity in the hippocampus. The hippocampal CA1 area is rich in glutamatergic synapses and is particularly vulnerable to excitotoxic damage. Neurons in the hippocampal CA1 area play a crucial role in memory consolidation and retrieval. Thus, excitotoxic damage to these neurons could contribute to impairments of recognition seen in aging. It should be noted that neurodegenerative changes in CA1 hippocampal area in rats of OXYS strain at the young age of 4 months old have been reported previously [65, 66], and they were also observed in the present study. Treatment with ceftriaxone was found to restore the neuronal density in the CA1 hippocampal area in OXYS rats that was in a good agreement with recovery of recognition in the novel object recognition test in OXYS rats treated with ceftriaxone. We suggest that increasing GLT-1expression plays a role in our present findings on the protective effect of ceftriaxone on neurons in the hippocampal CA1 area and restoration of cognitive behavior in the accelerated aging OXYS rat model. Another mechanism may also be tightly involved in the effect. OXYS rats are characterized by the increased levels of lipid peroxidation products [67] that are oxidative stress biomarkers and by augmented oxidative damage [68] in the hippocampus. On the other hand, ceftriaxone was reported to activate an antioxidant defense system including increased glutathione levels *in vitro* via induction of the expression of Nrf2 [69] that is the master regulator of antioxidant

responses [70].

Stimulation of neurogenesis may have potential as a therapy for neurodegenerative diseases and aging since neurogenesis is substantially reduced at these conditions [71, 72]. In adult brain, the production of new neurons from precursor cells normally occurs in the SGZ of the dentate gyrus of the hippocampus and the subventricular zone. The former place is of particular interest since newborn neurons from here mainly migrate to hippocampal regions and incorporate into the existing networks there [73]. Earlier we found that subchronic treatment with ceftriaxone restored the decreased number of proliferating cells in the SGZ in a pharmacological model of Parkinson's disease [41]. However, in the model of genetically defined accelerated aging we did not detect the stimulating effect of ceftriaxone on neurogenesis. We assume that this discrepancy is due to the increased neurogenesis in intact OXYS rats at this age against which an additional induction of neurogenesis does not occur. An increased production of immature neurons in OXYS rats observed in the present study is consistent with the previous data on the augmented levels of BDNF, a key neurotrophic factor regulating neurogenesis, in the hippocampus of young OXYS rats (Rudnitskaya et al., 2015). Nevertheless, this compensatory mechanism does not prevent the development of cognitive decline and neurodegeneration in the hippocampus in OXYS rats. Thus, the observed here effects of the ceftriaxone should be attributed rather more to activation of the mechanisms that provide the survival and incorporation of newborn neurons into the existing neural networks.

Since the upregulation of GLT-1 expression by ceftriaxone is short-lived [27] while the induction of Nrf2 by ceftriaxone is slow [69], 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 7-10 days, with no side-effects being reported [74]. Based on dose translation from animal to human studies [75], a daily dose of ceftriaxone would be of 200 mg/kg. 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 [34]. We chose lower dosages, 50 and 100 mg/kg/day, in the present study and found no adverse side effects.

In summary, the present study showed that chronic administration of ceftriaxone partially inhibited impairments of movement and modulated alterations in DAergic system in OXYS rats, it restored the deficits in object recognition and neuronal density in the hippocampal CA1 area in this animal model of accelerated aging. To our knowledge, this is the first evidence that ceftriaxone prevents hippocampal cell loss and improves cognitive function in the accelerated aging model. These data suggest ceftriaxone as a promising pharmacological tool for the development of new treatment for neuronal and behavioral impairments related to aging.

Acknowledgements

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Figure and Legends

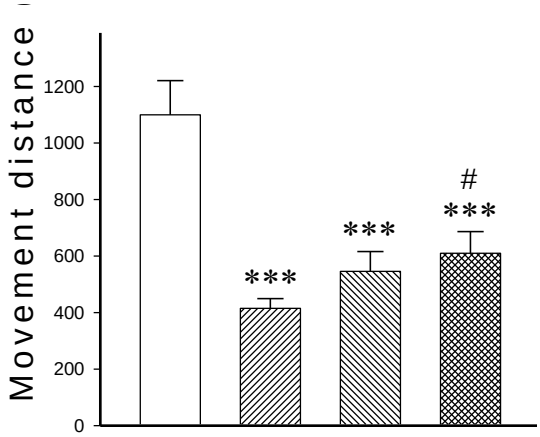
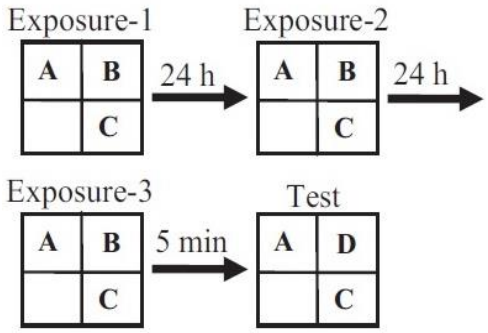


Fig. 1. Effect of ceftriaxone (CEF) on locomotion (distance travelled) in OXYS rats. CEF (50 or 100 mg/kg/day, i.p.) or saline (1 ml/kg/day, i.p.) was administered for 36 days. The test was performed on day 33. The data are expressed as the mean ± SEM. *** $P < 0.001$ compared to Wisrar+saline group. # $P < 0.05$ compared to OXYS+saline group.

(A)



(B)

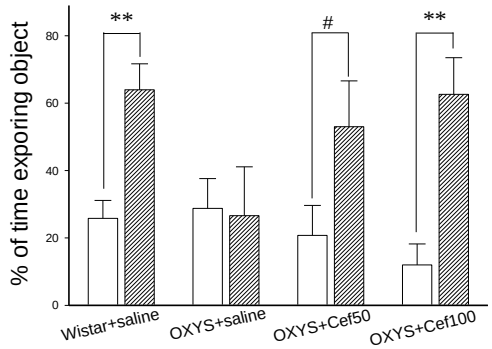


Fig. 2. Effect of CEF on novel object recognition in OXYS rats. Animals were treated as in the Fig. 1 and the novel object recognition test was performed on days 34–36. (A) Schematic diagram of the arrangement of the objects in the test. The rats underwent 3 exposure sessions (5 min each) at 24 h intervals, then they 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 at exploring object "B" or "D". ** $P < 0.01$, # $P < 0.08$ compared to the percentage of time spent exploring object "B". The data are expressed as the mean ± SEM.

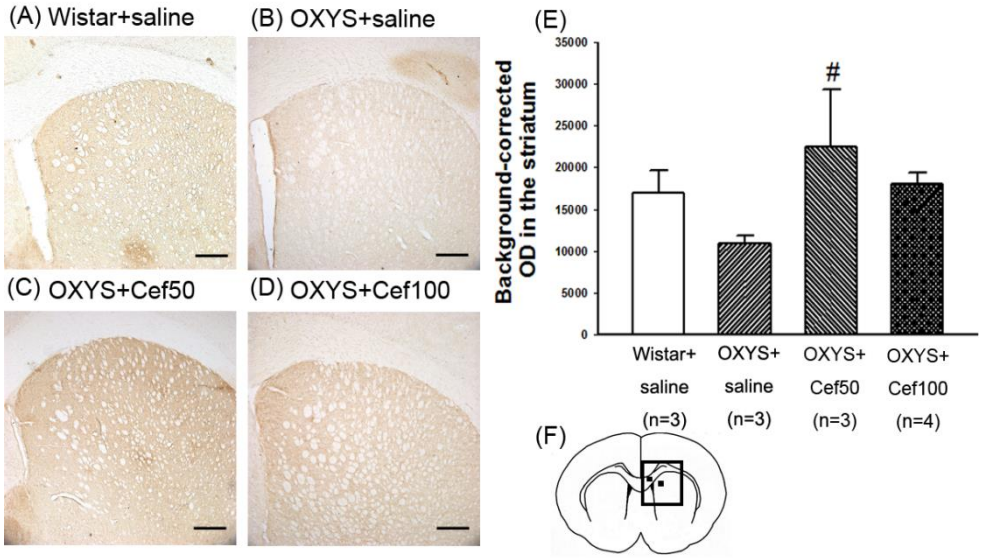


Fig. 3. Effect of CEF on tyrosine hydroxylase (TH) immunoreactivity in the striatum. Animals were treated as in the Fig. 1. (A–D) TH immunoreactivity in the striatum. Magnification, 50×; bar, 200 μm. (E) Quantitative results. The rectangle in (F) indicates the area shown in A–D, and the two small black squares inside the rectangle indicate the areas used for measuring the optical density (OD) in the striatum. # $P < 0.05$ compared to the OXYS+saline group. The data are expressed as the mean ± SEM.

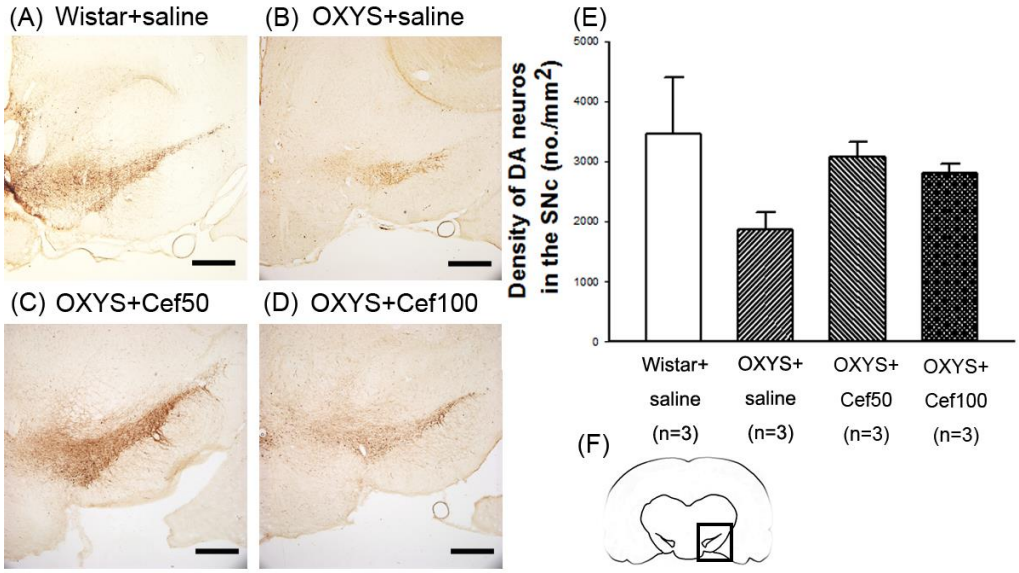


Fig. 4. Effect of CEF on density of DAergic neurons in the SNc. Animals were treated as in the Fig. 1. (A–D) DAergic neurons stained against TH in the SNc. Magnification, 50×; bar, 200 μm. (E) Quantitative results. The rectangle in (F) indicates the area shown in (A–D). The data are expressed as the mean ± SEM.

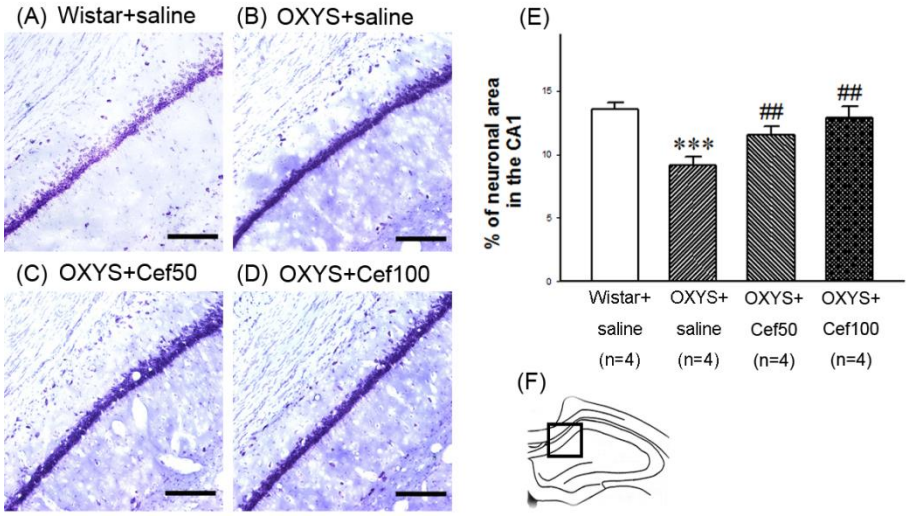


Fig. 5. Effects of CEF on neuronal density in the hippocampal CA1 area. Animals were treated as in the Fig. 1. (A–D) The images show Nissl-stained pyramidal neurons in the CA1 area of the hippocampus. Magnification, 200×; bar, 100 μm. (E) Quantitative results. The rectangle in (F) indicates the area shown in (A–D) and taken for measuring the density of pyramidal neurons. *** $P < 0.001$ compared to Wistar+saline group, ## $P < 0.01$ compared to OXYS+saline group. The data are expressed as the mean ± SEM.

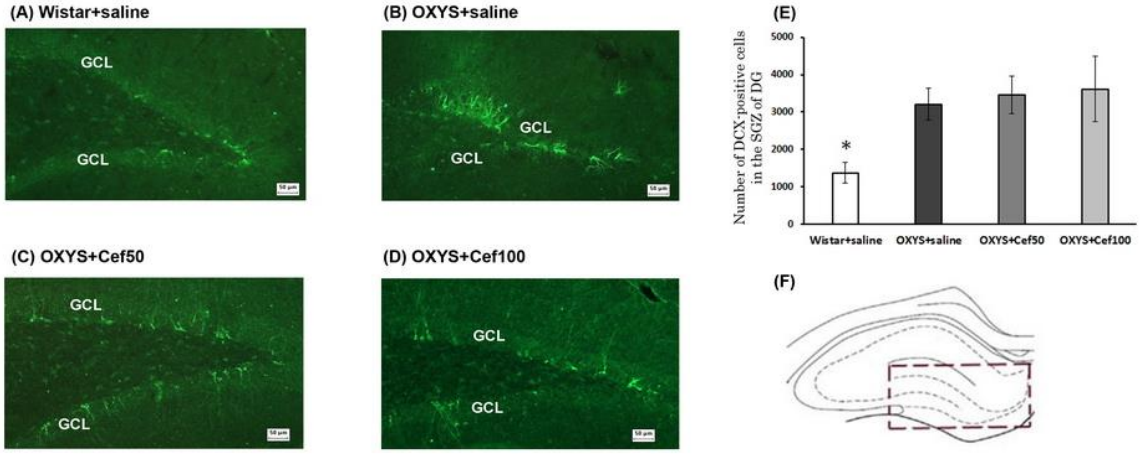


Fig. 6. Effects of CEF on the number of newborn (DCX-positive) cells in the subgranular zone (SGZ) of dentate gyrus of the hippocampus. Animals were treated as in the Fig. 1. (A–D) The images show DCX-positive cells labelled by green fluorescent mark in the SGZ. Magnification, 100×; bar, 50 μm. (E) Quantitative results. The rectangle in (F) indicates the whole area of dentate gyrus taken for measuring the number of newborn neurons. * $P < 0.05$ compared to OXYS groups. The data are expressed as the mean ± SEM.

已經發表之論文

1. Weng JC (翁駿程), MA Tikhonova, JH Chen, MS Shen, WY Meng, YT Chang, KH Chen, KC Liang, CS Hung*, TG Amstislavskaya*, **YJ Ho***. Ceftriaxone prevents the neurodegeneration and decreased neurogenesis seen in a Parkinson's disease rat model: an immunohistochemical and MRI study. ***Behav Brain Res*** 305: 126-39, Mar 08, 2016 (104-2628-E-040-001-MY) **(SCI)**

Type	**SCI** category	Ranking	IF	C	J	A	
Research report	20**15** Behavioral sciences 20**14** Neurosciences	16/51 (**31.37**%) 115/252 (45.63%)	**3.002**	3	4	5	**60**

2. Huang CK# (黃秋谷), YT Chang#(張彥婷), TG Amstislavskaya#, MA Tikhonova, CL Lin, CS Hung*(洪菁穗), TJ Lai*, **YJ Ho***. Synergistic effects of ceftriaxone and erythropoietin on neuronal and behavioral deficits in an MPTP-induced animal model of Parkinson's disease dementia. ***Behav Brain Res*** 294: 198-207, Aug 15, 2015. DOI: 10.1016/j.bbr.2015.08.011. **(SCI)** [MOST 103-2410-H-040-002-**MY2]**

Type	**SCI** category	Ranking	IF	C	J	A	
Research report	20**14** Behavioral sciences	18/51 (**35**%) 114/252 (45%)	**3.028**	3	4	5	**60**

3. Tikhonova MA#, CH Ting (丁哲浩), NG Kolosova, CY Hsu, JH Chen, CW Huang, GT Tseng (曾敬婷), 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*** 58(5): 322-31, Oct. 31, 2015. **(SCI)** [MOST 103-2410-H-040-002-**MY2**] **(SCI)**.

Type	**SCI** category	Ranking	IF	C	J	A	
Research report	**2014** Physiology	73/83 (87.95%)	**1.163**	3	**2**	5	**30**

4. Hsu CY (許兆畬)#, CS Hung#, HM Chang, WC Liao, SC Ho (何詩君)*, **YJ Ho***. Ceftriaxone prevents and reverses behavioral and neuronal deficits in an MPTP-induced animal model of Parkinson's disease dementia. ***Neuropharmacology*** 91:43-56, 2015. **(SCI)** **[**MOST 103-2410-H-040-002-**MY2]**

Type	**SCI** category	Ranking	IF	C	J	A	
Research report	**2015** Pharmacol & Pharmacy	19/255(7.45%)	**4.936**	5	**5**	5	**75**

5. **何應瑞***、許兆畬、陳福士、洪菁穗、賴德仁。紅血球生成素之神經保護效果：應用於治療巴金森氏症失智為例（英文題目：Neuronal protection of erythropoietin: a possible application in Parkinson's disease dementia）。澄清醫護管理雜誌(Cheng Ching Medical Journal) 11(3): 37-42, Jul, 2015 [MOST 104-2923-H-040-001-MY3]

已經獲得之專利:

發明人：何應瑞、陳建宏。申請人：中山醫大、江文舜。發明名稱：使用一包含有頭孢曲松與紅血球生成素的組合來治療和/或預防巴金森氏症失智（Treatment and/or prevention of Parkinson's disease dementia with a combination of ceftriaxone and erythropoietin）**台灣**專利(專利證號: **I558410** 號)

附件二

科技部補助專題研究計畫成果自評表

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（簡要敘述成果是否具有政策應用參考價值及具影響公共利益之重大發現）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(請於其他欄註明專利及技轉之證號、合約、申請及洽談等詳細資訊)

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 200 字為限)

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

研究成果所獲得之專利，有進一步推動進入臨床試驗以開發新藥之價值，若試驗成功，可以用於治療老化及相關之神經退化性疾病。

4. 主要發現

本研究具有政策應用參考價值：■否 □是，建議提供機關_____

(勾選「是」者，請列舉建議可提供施政參考之業務主管機關)

本研究具影響公共利益之重大發現：■否 □是

說明：(以 150 字為限)

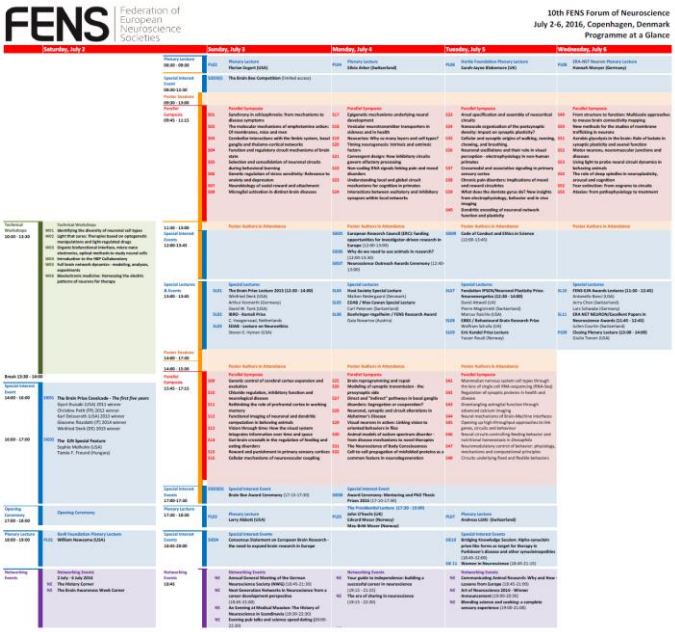
附件六

科技部補助專題研究計畫出席國際學術會議心得報告

日期：106 年 03 月 08 日

計畫編號	MOST 103-2410-H-040 -002 -MY2		
計畫名稱	評估併用頭孢曲松與紅血球生成素對巴金森氏症失智之療效：腦部影像與神經行為科學之研究		
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	105 年 7 月 2 日至 105 年 7 月 6 日	會議地點	丹麥哥本哈根
會議名稱	(中文) **第十屆歐洲神經科學會議** (英文) **The 10th FENS Forum of Neuroscience 2016**		
發表題目	(中文) 頭孢曲松治療對於巴金森氏症大鼠模式之神經活性與密度之關係:組織免疫化學與 MRI 之研究 (英文) Relationships between neuronal activity and density after ceftriaxone treatment in a Parkinson's disease rat model: an immunohistochemical and MRI study		

一、參加會議經過



二、發表論文全文或摘要

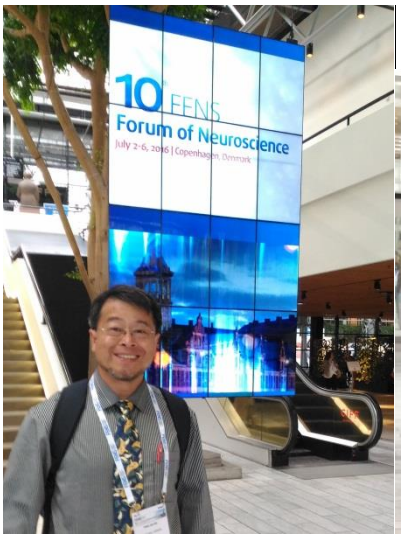
Abstract number: FENS-1992
Theme: C. Disorders of the nervous system

Topic: Parkinson's disease - Animal models
Presentation preference: Poster presentation
Contact information: ***Pro Ying-Jui Ho***
Department of Psychology, Chung Shan Medical University, Taiwan ROC
No. 110, Sec. 1, Jianguo N. Rd., 402 Taichung, Taiwan
E-mail: joshuayjho@gmail.com; yjho@csmu.edu.tw

發表論文： **Abstract title: Relationships between neuronal activity and density after ceftriaxone treatment in a Parkinson's disease rat model: an immunohistochemical and MRI study**

Manganese-enhanced magnetic resonance imaging (MEMRI) is a widely used technique for detecting neuronal activity in the brain of a living animal. Ceftriaxone (CEF) has been shown to have neuroprotective effects in neurodegenerative diseases. The present study was aimed at clarifying whether, in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease (PD) rat model, the known CEF-induced neuronal protection was accompanied by neurogenesis and decreased loss of neuronal activity. After MPTP lesioning (day 0), the rats were treated with CEF (100 mg/kg/day, i.p.) or saline for 15 days. They were then injected with $MnCl_2$ (40 mg/kg, i.p.) on day 13 and underwent a brain MRI scan on day 14, then the brain was taken for histological evaluation on day 15. The results showed that MPTP lesioning resulted in decreased neuronal activity and density in the nigrostriatal dopaminergic (DAergic) system and the hippocampal CA1, CA3, and dentate gyrus (DG) areas and reduced neurogenesis in the DG, but in hyperactivity in the subthalamic nucleus (STN). These neuronal changes were prevented by CEF treatment. Positive correlations between MEMRI R1 values and neuronal density in the hippocampus were evidenced. Neuronal densities in the hippocampus and SNc were positively correlated. Therefore, MEMRI R1 value may serve as a good indicator for PD severity and the effect of treatment. To our knowledge, this is the first study showing that CEF prevents loss of neuronal activity and neurogenesis in the brain of PD rats. CEF may therefore have clinical potential in the treatment of PD.

三、活動照片



四、研究成果獲得大會主題報導

歐洲神經科學會（2016 FENS）專題報導

http://forum2016.fens.org/contact-press/press-releases

FENS Federation of European Neuroscience Societies

FEDERATION OF EUROPEAN NEUROSCIENCE SOCIETIES
10th FENS Forum of Neuroscience
2-6 July 2016 – Copenhagen, Denmark
http://forum2016.fens.org/

PRESS RELEASE
EMBARGOED UNTIL TUESDAY 5 JULY 2016, 17.30 CEST / 16.30 BST

NEW USE FOR AN OLD DRUG: AN ANTIBIOTIC MAY HELP PARKINSON'S DEMENTIA

Parkinson's disease is associated mainly with movement disorders. But many patients also develop emotional and cognitive conditions, including dementia. Currently, there is no medication that prevents or cures Parkinson's disease dementia. But scientists in Taiwan have found a specific antibiotic that may shed light on treatment of this neurodegenerative dementia.

Presenting his research today (5 July) at the FENS Forum of Neuroscience in Copenhagen, **Professor Ying-Jui Ho** described findings that the antibiotic ceftriaxone, regularly used to treat bacterial infections such as meningitis, pneumonia, and gonorrhoea, may offer an innovative treatment strategy for this form of dementia.

Professor Ho from Chung Shan Medical University, in collaboration with colleagues in Taiwan and Russia, conducted animal studies using ceftriaxone to treat Parkinson's disease dementia. They used manganese-enhanced magnetic resonance imaging (MEMRI), a method used to understand information-processing in central nervous system pathways, to measure brain cell activity.

The researchers found that ceftriaxone not only relieved motor symptoms of Parkinson's disease, but also prevented neurodegeneration and improved cognitive function.

Specifically, ceftriaxone prevented various types of neuronal changes associated with Parkinson's disease dementia. The drug inhibits inflammation in the substantia nigra - a mid-brain area which controls voluntary movement, produces the neurotransmitter dopamine, and regulates mood. Ceftriaxone also inhibits neurodegeneration of specific cells in the hippocampus, a brain area important in memory formation, and associated with cognitive impairment in dementia.

Professor Ho and colleagues also found that ceftriaxone may enhance neurogenesis, the process in which new brain cells are generated - in this case replacing new cells in damaged brain areas, restoring neural activity, and improving cognitive function (including working memory, recognition, and visual space function).

"To our knowledge, this is the first study showing that ceftriaxone prevents loss of neuronal activity and may enhance neurogenesis in the brain. Ceftriaxone's neuroprotective effects have implications not only for Parkinson's disease dementia, but may also shed light on treatment of neurodegenerative diseases in general," said Professor Ho.

Professor Ho mentioned that the research also indicates that MEMRI imaging may be a useful indicator for the severity of Parkinson's disease, and for judging the effect of treatment.

It is estimated that seven to 10 million people worldwide are living with Parkinson's disease*. With populations ageing, dementia and neurodegenerative diseases have received increasing attention. Since there are no cures, much research focuses on treatments to alleviate symptoms, improve cognitive function and well-being, and avoid drug-induced side effects.

五、研究成果獲得歐洲當地雜誌報導

歐洲

「Ingeniøren 雜誌」

趨勢焦點報導

Reform af tog- og buspriser bremses af…

Sagen genåbnet: Sådan døde…

Regeringen kører sin første motorvej…

Sammenstød mellem skyer forstærker…

Sponsoreret indhold

Efter klimakontrakt: COWI søger…

Ny opdagelse: Antibiotika til meningitis afhjælper Parkinsons demens

FENS2016: Taiwansk forsker har fundet ud af, at et bestemt antibiotikum lindrer og opbygger mistet funktionsevne hos patienter med Parkinsons-relateret demens.

Af Mie Stage 7. jul 2016 kl. 06:23

FØLG INGENIØREN

Antibiotikummet ceftriaxon, også kendt som Rocephalin, er et ældre og velkendt middel mod inflammation som følge af meningitis.

Nu viser taiwansk-russisk forskning, at midlet også er effektivt mod demens opstået i forbindelse med Parkinsons sygdom.

Det fortæller professor Ying-Jui Ho fra Chung Shan Medical University i Taiwan i forbindelse med hjerneforskningskonferencen FENS2016, som løber af stablen i Bella Center i denne uge.

»Os bekendt er dette det første studie, der viser, at ceftriaxon forhindrer tab af neuroaktivitet og kan forstærke neurondannelsen i hjernen. Ceftriaxons beskyttende effekt har betydning for ikke alene Parkinsons demens (PD), men kan også kaste lys over behandlingen af neurodegenerative sygdomme generelt set,« siger han.

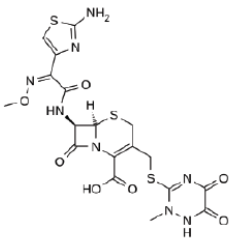
Læs også: Dansk forsker: Hjernens vaskemaskine kan måske afsløre Alzheimers længe før udbrud

Renser hjernen

Ifølge Ying-Jui Ho har tidligere forskningsprojekter andre steder i verden vist, at ceftriaxon har haft en effekt på bl.a. ALS-patienter (amyotrofisk lateral sklerose), som har modtaget meget høje doser i et år. Men det er første gang, en forskergruppe har kastet sig over at undersøge effekten på Parkinsons-patienter.

Normalt forbinder man Parkinsons sygdom med ufrivillige bevægelser i kroppen, men faktisk er der også andre problemer, som patienterne må døje med. Det kan både være ændret og mere trist adfærd samt hukommelsesproblemer i form af demens.

Der har hidtil ikke været så meget at stille op over for disse demensproblemer, men fundet af antibiotikummets ekstra virkning kan give håb for fremtiden.

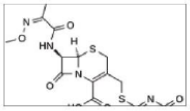


Ceftriaxon. (Foto: catclock/Wikipedia)

Søvnterapi kan måske ku

FENS2016: Aarhusiansk projekt viser, at p med søvn.

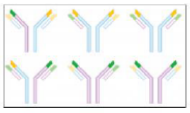
9. jul 2016 11



Ny opdagelse: Antibiotik Parkinsons demens

FENS2016: Taiwansk forsker har fundet u funktionsevne hos patienter med Parkinso

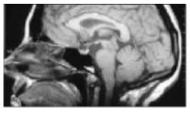
7. jul 2016 10



Forsker: Ubrugelige anti forskningskroner

FENS2016: Hvert år spilder forskere over de rette molekyler. Det vil en dansk gruppe

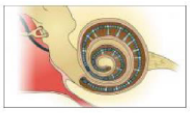
6. jul 2016 2



Dansk forsker: Hjernens Alzheimers længe før ud

FENS2016: Professor Maiken Nedergaard sygdommen for alvor sætter ind, ved at ma

5. jul 2016



Lys i øret og genmodifice døve og svagthørende

FENS2016: I et tysk projekt skal lys stimu gøres ved at kopiere øjenfunktioner ind i ø

4. jul 2016 4

2016.07.07

出國開會結案報告

會議名稱: 「第十屆歐洲神經科學會議」The 10th FENS Forum of Neuroscience 2016

會議日期：2016 年 7 月 2-6 日

地點：丹麥哥本哈根

出席人員: 何應瑞 中山醫學大學心理學系

大會議程:

FENS Federation of European Neuroscience Societies

10th FENS Forum of Neuroscience
July 2-6, 2016, Copenhagen, Denmark
Programme at a Glance

Saturday, July 2	Sunday, July 3	Monday, July 4	Tuesday, July 5	Wednesday, July 6
	Plenary Lecture 08:30 - 09:30 PL02 Plenary Lecture: Florian Engert (USA)	PL04 Plenary Lecture: Silvia Arber (Switzerland)	PL06 Hertie Foundation Plenary Lecture: Sarah-Jayne Blakemore (UK)	PL08 ERA-NET Neuron Plenary Lecture: Hannah Monyer (Germany)
	Special Interest Event 08:30-12:30 SIE03(I) The Brain Bee Competition (limited access)			
	Poster Sessions 09:30 - 13:00			
	Parallel Symposia 09:45 - 11:15 S01 Synchrony in schizophrenia: from mechanisms to disease symptoms S02 The molecular mechanisms of amphetamine action: Of membranes, mice and men S03 Cerebellar interactions with the limbic system, basal ganglia and thalamo-cortical networks S04 Function and regulatory circuit mechanisms of brain state S05 Selection and consolidation of neuronal circuits during behavioral learning S06 Genetic regulation of stress sensitivity: Relevance to anxiety and depression S07 Neurobiology of social reward and attachment S08 Microglial activation in distinct brain diseases	**Parallel Symposia** S17 Epigenetic mechanisms underlying neural development S18 Vesicular neurotransmitter transporters in sickness and in health S19 Neocortex: Why so many layers and cell types? S20 Timing neurogenesis: Intrinsic and extrinsic factors S21 Convergent design: How inhibitory circuits govern olfactory processing S22 Non-coding RNA signals linking pain and mood disorders S23 Understanding local and global circuit mechanisms for cognition in primates S24 Interactions between excitatory and inhibitory synapses within local networks	**Parallel Symposia** S33 Areal specification and assembly of neocortical circuits S34 Nanoscale organization of the postsynaptic density: Impact on synaptic plasticity? S35 Cellular and synaptic origins of walking, running, chewing, and breathing. S36 Neuronal oscillations and their role in visual perception - electrophysiology in non-human primates S37 Crossmodal and associative signaling in primary sensory cortex S38 Chronic pain disorders: Implications of mood and reward circuitries S39 What does the dentate gyrus do? New insights from electrophysiology, behavior and in vivo imaging S40 Dendritic encoding of neuronal network function and plasticity	**Parallel Symposia** S49 From structure to function: Multiscale approaches to mouse brain connectivity mapping S50 New methods for the studies of membrane trafficking in neurons S51 Aerobic glycolysis in the brain: Role of lactate in synaptic plasticity and axonal function S52 Motor neurons, neuromuscular junctions and diseases S53 Using light to probe neural circuit dynamics in behaving animals S54 The role of sleep spindles in neuroplasticity, arousal and cognition S55 Fear extinction: From engrams to circuits S56 Ataxias: from pathophysiology to treatment
Technical Workshops 10:30 - 13:30 W01 Identifying the diversity of neuronal cell types W02 Light that cures: Therapies based on optogenetic manipulations and light-regulated drugs W03 Organic biofunctional interface, micro-nano electronics, optical methods to study neural cells W04 Introduction to the HBP Collaboratory W05 Full brain network dynamics - modeling, analyses, experiments W06 Bioelectronic medicine: Harnessing the electric patterns of neurons for therapy	11:30 - 13:00 Poster Authors in Attendance	Poster Authors in Attendance	Poster Authors in Attendance	Poster Authors in Attendance
	Special Interest Events 12:00-13:45 SIE05 European Research Council (ERC): funding opportunities for investigator-driven research in Europe (12:00-13:00) SIE06 Why do we need to use animals in research? (12:00-13:30) SIE07 Neuroscience Outreach Awards Ceremony (12:40-13:00)		SIE09 Code of Conduct and Ethics in Science (12:00-13:45)	
	Special Lectures & Events 13:00 - 13:45 SL01 The Brain Prize Lecture 2015 (12:30 - 14:00): Winfried Denk (USA), Arthur Konnerth (Germany), David W. Tank (USA) SL02 IBRO - Kemali Prize: C. Hoogenraad, Netherlands SL03 EDAB - Lecture on Neuroethics: Steven E. Hyman (USA)	**Special Lectures** SL04 Host Society Special Lecture: Maiken Nedergaard (Denmark) SL05 EDAB / Max Cowan Special Lecture: Carl Petersen (Switzerland) SL06 Boehringer-Ingelheim / FENS Research Award: Gaia Novarino (Austria)	**Special Lectures** SL07 Fondation IPSEN/Neuronal Plasticity Prize: Neuroenergetics (12:30 - 14:00): David Attwell (UK), Pierre Magistretti (Switzerland), Marcus Raichle (USA) SL08 EBBS / Behavioural Brain Research Prize: Wolfram Schultz (UK) SL09 Eric Kandel Prize Lecture: Yasser Roudi (Norway)	**Special Lectures** SL10 FENS-EJN Awards Lectures (11:30 - 12:45): Antonello Bonci (USA), Jerry Chen (Switzerland), Lars Schwabe (Germany) SL11 ERA NET NEURON/Excellent Papers in Neuroscience Awards (11:45 - 12:45): Julien Courtin (Switzerland) PL09 Closing Plenary Lecture (13:00 - 14:00): Giulio Tononi (USA)
	Poster Sessions 14:00 - 17:30 14:00 - 15:30 Poster Authors in Attendance	Poster Authors in Attendance	Poster Authors in Attendance	
Break 13:30 - 14:00				
Special Interest Event 14:00 - 16:00 SIE01 The Brain Prize Cavalcade - *The first five years*: Gyuri Buzsaki (USA) 2011 winner, Christine Petit (FR) 2012 winner, Karl Deisseroth (USA) 2013 winner, Giacomo Rizzolatti (IT) 2014 winner, Winfried Denk (DE) 2015 winner	**Parallel Symposia** 15:45 - 17:15 S09 Genetic control of cerebral cortex expansion and evolution S10 Chloride regulation, inhibitory function and neurological disease S11 Rethinking the role of prefrontal cortex in working memory S12 Functional imaging of neuronal and dendritic computation in behaving animals S13 Vision through time: How the visual system integrates information over time and space S14 Gut-brain crosstalk in the regulation of feeding and eating disorders S15 Reward and punishment in primary sensory cortices S16 Cellular mechanisms of neurovascular coupling	**Parallel Symposia** S25 Brain reprogramming and repair S26 Modeling of synaptic transmission - the presynaptic side S27 Direct and "indirect" pathways in basal ganglia disorders: Segregation or cooperation? S28 Neuronal, synaptic and circuit alterations in Alzheimer's Disease S29 Visual neurons in action: Linking vision to oriented behaviors in flies S30 Animal models of autism spectrum disorder - from disease mechanisms to novel therapies S31 The Neuroscience of Body Consciousness S32 Cell-to-cell propagation of misfolded proteins as a common feature in neurodegeneration	**Parallel Symposia** S41 Mammalian nervous system cell types through the lens of single cell RNA-sequencing (RNA-Seq) S42 Regulation of synaptic proteins in health and disease S43 Disentangling astroglial function through advanced calcium imaging S44 Neural mechanisms of Brain-Machine interfaces S45 Opening up high-throughput approaches to link genes, circuits and behaviour S46 Neural circuits controlling feeding behavior and nutritional homeostasis in *Drosophila* S47 Neuromodulatory control of behavior: physiology, mechanisms and computational principles S48 Circuits underlying fixed and flexible behaviors	
16:00 - 17:00 SIE02 The EJN Special Feature: Sophie Molholm (USA), Tamás F. Freund (Hungary)				
	Special Interest Events 17:00-17:30 SIE03(II) Special Interest Event: Brain Bee Award Ceremony (17:15-17:30)	**Special Interest Event** SIE08 Award Ceremony: Mentoring and PhD Thesis Prizes 2016 (17:10-17:30)		
Opening Ceremony 17:00 - 18:00 Opening Ceremony	**Plenary Lecture** 17:30 - 18:30 PL03 Plenary Lecture: Larry Abbott (USA)	**The Presidential Lecture** (17:30 - 19:00) PL05 John O'Keefe (UK), Edvard Moser (Norway), May-Britt Moser (Norway)	PL07 Plenary Lecture: Andreas Lüthi (Switzerland)	
Plenary Lecture 18:00 - 19:00 PL01 Kavli Foundation Plenary Lecture: William Newsome (USA)	**Special Interest Events** 18:45-20:00 SIE04 Consensus Statement on European Brain Research - the need to expand brain research in Europe		SIE10 Bridging Knowledge Session: Alpha-synuclein prion like forms as target for therapy in Parkinson's disease and other synucleinopathies (18:45-22:00) SIE 11 Women in Neuroscience (18:45-21:15)	
Networking Events Networking Events 2 July - 6 July 2016 NE The History Corner NE The Brain Awareness Week Corner	**Networking Events** 18:45 NE Annual General Meeting of the German Neuroscience Society (NWG) (18:45-21:30) NE Next Generation Networks in Neuroscience from a career development perspective (18:45-21:00) NE An Evening at Medical Museion: The History of Neuroscience in Scandinavia (19:30-22:30) NE Evening pub talks and science speed dating (20:00-22:30)	**Networking Events** NE Your guide to independence: building a successful career in neuroscience (19:15 - 21:15) NE The era of sharing in neuroscience (19:15 - 22:30)	**Networking Events** NE Communicating Animal Research: Why and How - Lessons from Europe (18:45-21:00) NE Art of Neuroscience 2016 - Winner Announcement (19:00-20:30) NE Blending science and cooking: a complete sensory experience (19:00-21:00)	

發表論文：

Abstract number: FENS-1992
Theme: C. Disorders of the nervous system
Topic: Parkinson's disease - Animal models
Presentation preference: Poster presentation

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Abstract title: Relationships between neuronal activity and density after ceftriaxone treatment in a Parkinson's disease rat model: an immunohistochemical and MRI study

Manganese-enhanced magnetic resonance imaging (MEMRI) is a widely used technique for detecting neuronal activity in the brain of a living animal. Ceftriaxone (CEF) has been shown to have neuroprotective effects in neurodegenerative diseases. The present study was aimed at clarifying whether, in an 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease (PD) rat model, the known CEF-induced neuronal protection was accompanied by neurogenesis and decreased loss of neuronal activity. After MPTP lesioning (day 0), the rats were treated with CEF (100 mg/kg/day, i.p.) or saline for 15 days. They were then injected with $MnCl_2$ (40 mg/kg, i.p.) on day 13 and underwent a brain MRI scan on day 14, then the brain was taken for histological evaluation on day 15. The results showed that MPTP lesioning resulted in decreased neuronal activity and density in the nigrostriatal dopaminergic (DAergic) system and the hippocampal CA1, CA3, and dentate gyrus (DG) areas and reduced neurogenesis in the DG, but in hyperactivity in the subthalamic nucleus (STN). These neuronal changes were prevented by CEF treatment. Positive correlations between MEMRI R1 values and neuronal density in the hippocampus were evidenced. Neuronal densities in the hippocampus and SNc were positively correlated. Therefore, MEMRI R1 value may serve as a good indicator for PD severity and the effect of treatment. To our knowledge, this is the first study showing that CEF prevents loss of neuronal activity and neurogenesis in the brain of PD rats. CEF may therefore have clinical potential in the treatment of PD.

活動照片


10 FENS
Forum of Neuroscience
July 2-6, 2016 | Copenhagen, Denmark

研究成果獲得大會主題報導

歐洲神經科學會（2016 FENS）專題報導

FENS Federation of European Neuroscience Societies

FEDERATION OF EUROPEAN NEUROSCIENCE SOCIETIES
10th FENS Forum of Neuroscience
2-6 July 2016 – Copenhagen, Denmark
http://forum2016.fens.org/

PRESS RELEASE
EMBARGOED UNTIL TUESDAY 5 JULY 2016, 17.30 CEST / 16.30 BST

NEW USE FOR AN OLD DRUG: AN ANTIBIOTIC MAY HELP PARKINSON'S DEMENTIA

Parkinson's disease is associated mainly with movement disorders. But many patients also develop emotional and cognitive conditions, including dementia. Currently, there is no medication that prevents or cures Parkinson's disease dementia. But scientists in Taiwan have found a specific antibiotic that may shed light on treatment of this neurodegenerative dementia.

Presenting his research today (5 July) at the FENS Forum of Neuroscience in Copenhagen, **Professor Ying-Jui Ho** described findings that the antibiotic ceftriaxone, regularly used to treat bacterial infections such as meningitis, pneumonia, and gonorrhoea, may offer an innovative treatment strategy for this form of dementia.

Professor Ho from Chung Shan Medical University, in collaboration with colleagues in Taiwan and Russia, conducted animal studies using ceftriaxone to treat Parkinson's disease dementia. They used manganese-enhanced magnetic resonance imaging (MEMRI), a method used to understand information-processing in central nervous system pathways, to measure brain cell activity.

The researchers found that ceftriaxone not only relieved motor symptoms of Parkinson's disease, but also prevented neurodegeneration and improved cognitive function.

Specifically, ceftriaxone prevented various types of neuronal changes associated with Parkinson's disease dementia. The drug inhibits inflammation in the substantia nigra - a mid-brain area which controls voluntary movement, produces the neurotransmitter dopamine, and regulates mood. Ceftriaxone also inhibits neurodegeneration of specific cells in the hippocampus, a brain area important in memory formation, and associated with cognitive impairment in dementia.

Professor Ho and colleagues also found that ceftriaxone may enhance neurogenesis, the process in which new brain cells are generated - in this case replacing new cells in damaged brain areas, restoring neural activity, and improving cognitive function (including working memory, recognition, and visual space function).

"To our knowledge, this is the first study showing that ceftriaxone prevents loss of neuronal activity and may enhance neurogenesis in the brain. Ceftriaxone's neuroprotective effects have implications not only for Parkinson's disease dementia, but may also shed light on treatment of neurodegenerative diseases in general," said Professor Ho.

Professor Ho mentioned that the research also indicates that MEMRI imaging may be a useful indicator for the severity of Parkinson's disease, and for judging the effect of treatment.

It is estimated that seven to 10 million people worldwide are living with Parkinson's disease*. With populations ageing, dementia and neurodegenerative diseases have received increasing attention. Since there are no cures, much research focuses on treatments to alleviate symptoms, improve cognitive function and well-being, and avoid drug-induced side effects.

研究成果獲得歐洲當地雜誌報導

歐洲

「Ingeniøren 雜誌」

趨勢焦點報導

Ny opdagelse: Antibiotika til meningitis afhjælper Parkinsons demens

FENS2016: Taiwansk forsker har fundet ud af, at et bestemt antibiotikum lindrer og opbygger mistet funktionsevne hos patienter med Parkinsons-relateret demens.

Af Mie Stage 7. jul 2016 kl. 06:23

Antibiotikummet ceftriaxon, også kendt som Rocephalin, er et ældre og velkendt middel mod inflammation som følge af meningitis.

Nu viser taiwansk-russisk forskning, at midlet også er effektivt mod demens opstået i forbindelse med Parkinsons sygdom.

Det fortæller professor Ying Jui Ho fra Chung Shan Medical University i Taiwan i forbindelse med hjerneforskningskonferencen FENS2016, som løber af stablen i Bella Center i denne uge.

»Os bekendt er dette det første studie, der viser, at ceftriaxon forhindrer tab af neuroaktivitet og kan forstærke neurondannelsen i hjernen. Ceftriaxons beskyttende effekt har betydning for ikke alene Parkinsons demens (PD), men kan også kaste lys over behandlingen af neurodegenerative sygdomme generelt set,« siger han.

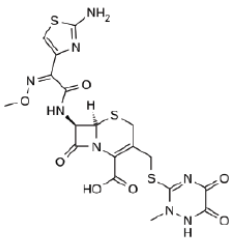
Læs også: Dansk forsker: Hjernens vaskemaskine kan måske afsløre Alzheimers længe før udbrud

Renser hjernen

Ifølge Ying-Jui Ho har tidligere forskningsprojekter andre steder i verden vist, at ceftriaxon har haft en effekt på bl.a. ALS-patienter (amyotrofisk lateral sklerose), som har modtaget meget høje doser i et år. Men det er første gang, en forskergruppe har kastet sig over at undersøge effekten på Parkinsons-patienter.

Normalt forbinder man Parkinsons sygdom med ufrivillige bevægelser i kroppen, men faktisk er der også andre problemer, som patienterne må døje med. Det kan både være ændret og mere trist adfærd samt hukommelsesproblemer i form af demens.

Der har hidtil ikke været så meget at stille op over for disse demensproblemer, men fundet af antibiotikummets ekstra virkning kan give håb for fremtiden.



Ceftriaxon. (Foto: ratclock/Wikipedia)

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FENS2016: Aarhusiansk projekt viser, at p
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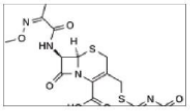
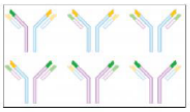
9. jul 2016 11



Ny opdagelse: Antibiotik
Parkinsons demens

FENS2016: Taiwansk forsker har fundet u
funktionsevne hos patienter med Parkinso

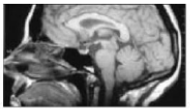
7. jul 2016 10



Forsker: Ubrugelige anti
forskningskroner

FENS2016: Hvert år spilder forskere over
de rette molekyler. Det vil en dansk grupp

6. jul 2016 2



Dansk forsker: Hjernens
Alzheimers længe før ud

FENS2016: Professor Maiken Nedergaard
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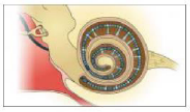

Lys i øret og genmodifice
døve og svagthørende

FENS2016: I et tysk projekt skal lys stimu
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科技部補助計畫衍生研發成果推廣資料表

日期:2017/03/08

科技部補助計畫	計畫名稱: 評估併用頭孢曲松與紅血球生成素對巴金森氏症失智之療效：腦部影像與神經行為科學之研究
	計畫主持人: 何應瑞
	計畫編號: 103-2410-H-040-002-MY2　　學門領域: 生物心理學

無研發成果推廣資料

103年度專題研究計畫成果彙整表

計畫主持人：何應瑞	**計畫編號：**103-2410-H-040-002-MY2
計畫名稱：評估併用頭孢曲松與紅血球生成素對巴金森氏症失智之療效：腦部影像與神經行為科學之研究	

成果項目					量化	單位	質化 （說明：各成果項目請附佐證資料或細項說明，如期刊名稱、年份、卷期、起訖頁數、證號...等）
國內	學術性論文	期刊論文			1	篇	澄清醫護管理雜誌11(3): 37-42, Jul, 2015
		研討會論文			22		
		專書			0	本	
		專書論文			0	章	
		技術報告			0	篇	
		其他			0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	0	件	
				已獲得	1		發明人：何應瑞、陳建宏。申請人：中山醫大、江文舜。發明名稱：使用一包含有頭孢曲松與紅血球生成素的組合來治療和/或預防巴金森氏症失智（Treatment and/or prevention of Parkinson’s disease dementia with a combination of ceftriaxone and erythropoietin）台灣專利(專利證號:I558410號)
			新型/設計專利		0		
		商標權			0		
		營業秘密			0		
		積體電路電路布局權			0		
		著作權			0		
		品種權			0		
		其他			0		
	技術移轉	件數			0	件	
		收入			0	千元	
國外	學術性論文	期刊論文			4	篇	1. Behav Brain Res 305: 126-39, Mar 08, 2016. (SCI) 2. Behav Brain Res 294: 198-207, Aug 15, 2015. (SCI) 3. Chin J Physiol 58(5): 322-31, Oct. 31, 2015. (SCI) 4. Neuropharmacology 91:43-56, 2015. (SCI)
		研討會論文			8		

		專書			0	本	
		專書論文			0	章	
		技術報告			0	篇	
		其他			0	篇	
	智慧財產權及成果	專利權	發明專利	申請中	8	件	
				已獲得	0		
			新型/設計專利		0		
		商標權			0		
		營業秘密			0		
		積體電路電路布局權			0		
		著作權			0		
		品種權			0		
		其他			0		
	技術移轉	件數			1	件	
		收入			200	千元	
參與計畫人力	本國籍	大專生			2	人次	
		碩士生			3		
		博士生			0		
		博士後研究員			0		
		專任助理			0		
	非本國籍	大專生			0		
		碩士生			0		
		博士生			0		
		博士後研究員			0		
		專任助理			0		
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。）							

科技部補助專題研究計畫成果自評表

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（簡要敘述成果是否具有政策應用參考價值及具影響公共利益之重大發現）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（請於其他欄註明專利及技轉之證號、合約、申請及洽談等詳細資訊）
   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200字為限）

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）
   本研究成果所獲得之專利，有進一步推動進入臨床試驗以開發新藥之價值，若試驗成功，可以用於治療老化及相關之神經退化性疾病。

4. 主要發現
   本研究具有政策應用參考價值：■否　□是，建議提供機關
   （勾選「是」者，請列舉建議可提供施政參考之業務主管機關）
   本研究具影響公共利益之重大發現：■否　□是
   說明：（以150字為限）