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Combined Application Therapies of Stem Cells and Drugs in the Neurological Disorder Attenuation

Chia-Chi Chen, Ying-Ching Hung, Chia-Yu Lin,
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Abstract

Neurological disorders (NDs) are diseases of the central and peripheral nervous system that affected the hundreds of millions of people worldwide. Temporal lobe epilepsy (TLE) is a common NDs with hallucinations and disturbance of consciousness that cause the abnormal neurological activity in any part of brain. Neuroinflammation (NI) has been identified in epilepsy-related tissue from both experimental and clinical evidence and suspected to participate in the formation of neuronal cell death, reactive gliosis and neuroplastic changes in the hippocampus, may contribute to epileptogenesis. The NI is tightly regulated by microglia, but it is thought that excessive or chronic microglial activation can contribute to neurodegenerative processes. Therefore, the modulation of microglia responses may provide a therapeutic target for the treatment of severe or chronic NI conditions. Although the condition responds well to antiepileptic drugs (AEDs), there are still unresponsive to AEDs in about 1/3 of cases. Neural stem cells are the origin of various types of neural cells during embryonic development. Currently, many results of stem cell therapies in the animal experiments and clinical trials were demonstrated the efficacious therapeutic effects in the attenuated symptoms of ND. Therefore, the combined application therapies of stem cells and drugs may be a promising candidate for the therapeutic strategies of NDs, especially TLE.

Keywords: combined application therapies, stem cells, drugs, neurological disorder attenuation

1. Neurological disorders in people

When the disorders occurred in the brain and spinal cord included cranial nerves, peripheral nerves, nerve roots, autonomic nervous system, neuromuscular junction, and muscles, etc., these disorders were named neurological disorders (NDs). NDs are complicated and that are caused by a loss of neurons and glial cells in these injured areas in brain or spinal cord. NDs include epilepsy, Alzheimer's disease, Parkinson's disease (**Figure 1**), dementias, cerebrovascular diseases (stroke, migraine, and headache disorders, etc), multiple sclerosis, neuro-infected disorders, brain cancer-caused disorders, head trauma-caused traumatic nervous disorders, and malnutrition-induced NDs. Currently, NDs can affect about hundreds of millions of people worldwide. Among NDs, more than 50 million people have epilepsy worldwide [1].
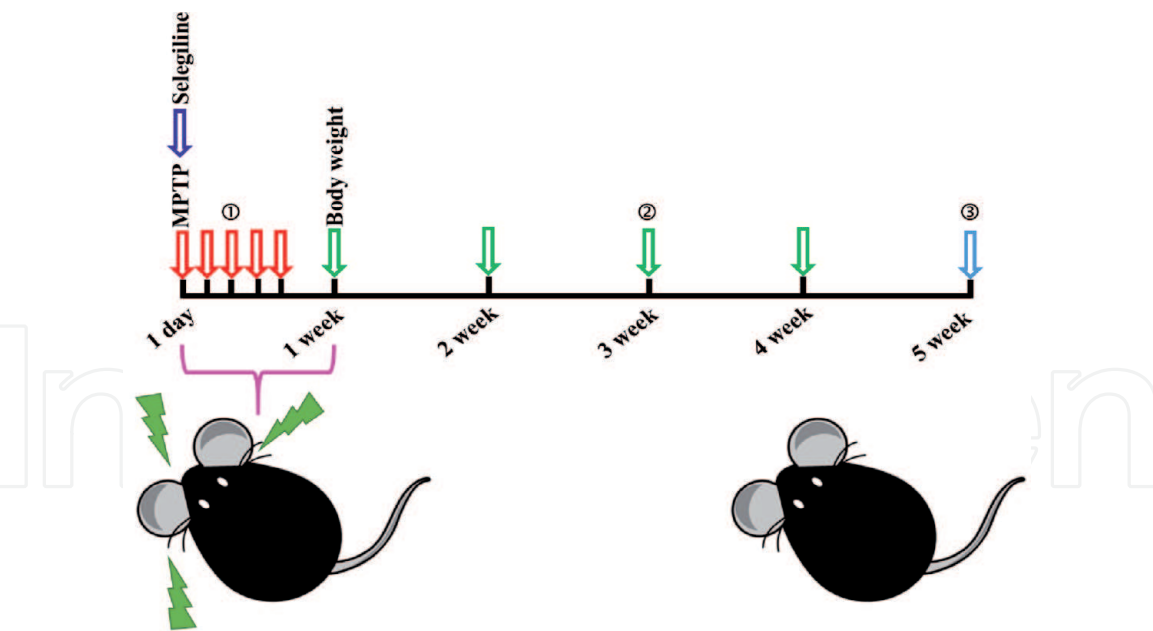
Figure 1.
Parkinson's disease model. Mice were treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) by intraperitoneal injection once per day for continuous 5 days to induce Parkinson's disease ①. The experimental process of Parkinson's disease was described ②. ③ was the experimental end point.

2. Epilepsy

Approximately 1–3% of the worldwide population suffers from epilepsy. Pharmacotherapy represents the mainstay of treatment for most of the patient population. Moreover, surgery is another option for patients in whom a defined resectable seizure focus can be identified by brain imaging and seizure mapping techniques. For patients whose seizures cannot be controlled by antiepileptic drugs (AEDs) or not viable for surgery, vagal nerve stimulation will be a third possible option [2]. Unfortunately, there are a significant number of patients with epilepsy continue to live with uncontrolled seizures. Therefore, there is a clear need for more efficacious therapies for these epileptic patients with uncontrolled seizures. In order to identify an efficient therapy for preventing epileptogenesis, a validated animal model is required for translating discoveries at the molecular and genetic basis of epilepsy [3].

3. Neuroinflammation causes of epilepsy

Neuroinflammation is an underlying component of a diverse range of neurodegenerative diseases and their associated neuropathology, and increasing evidence suggests that microglia are a key causative factor in this process. Microglia comprised approximately 12% of cells in the brain [2]. They predominate in the gray matter especially in the hippocampus, olfactory telencephalon, basal ganglia, and substantia nigra. Commonly, microglia are readily activated in response to brain injury or immunological stimuli. Over-activated microglia can induce highly detrimental neurocytotoxic factors such as superoxide, nitric oxide (NO), and proinflammatory cytokines (IL-1β, IL-6, and TNF-α, etc.). In status epilepticus (SE), activated microglia have been shown to be present microgliosis [2, 3].
At present, many evidences have demonstrated rapid astrocyte and microglial activation following pilocarpine-induced seizures or SE. However, whether pilocarpine directly activate microglia is poorly understood.

4. Treatments of epilepsy

SE is a major neurologic emergency which is characterized by continuous seizures lasting greater than 5 minutes, and SE generation may increase the mortality and morbidity in patients [4–6]. The mechanism of SE generation is believed to correlate with the increase of excitatory activity and/or the decrease of inhibitory activity in the brain [7, 8]. Treatments can help epileptic patients to decrease seizures or stop seizures. These therapeutic treatments include medicines (antiepileptic drugs, AEDs), surgery, special diet (ketogenic diet), and electrical device therapy, etc. Traditionally, the strategies of SE treatment included the augmented inhibitory neurotransmission and/or reduced excitatory neurotransmission by pharmaceutical administration, but the clinically AEDs still fail to control the seizures in approximately 20–40% of SE patients [9–13]. Moreover, the underlying mechanisms of AEDs-resistant SE are still unclear, and it is important to figure out the response of pharmaco-resistance in intact brain for the development of promising treatment.

5. Characteristics, types, and therapy of stem cells

The treatment of epilepsy is not cured for a long time, and frequent seizures have brought endless troubles to the majority of patients. Nowadays, the treatment of epilepsy is no longer a medical problem, and can finally be completely ended. Only because of the advent of stem cell transplantation therapy, an indelible milestone has been set for the treatment of epilepsy. Stem cell transplantation technology has brought good news to patients with epilepsy, and has achieved a major new medical breakthrough in the treatment of epilepsy. Stem cell treatment of epilepsy is to inject healthy and young stem cells (SCs) into the patient's body through intravenous injection to replace their diseased or aging tissues and organs for the purpose of treating epilepsy.

Whether stem cell therapy effective for these epileptic patients who are not well treated by surgery? What is the principle? Stem cell transplantation increases the number of neurons In fact, it mainly uses the differentiation function of neural stem cells. Neural stem cells (NSCs) can divide and differentiate into corresponding cell types in the brain according to the induction of their surrounding microenvironment. Their morphology and function are very similar to those of nearby host cells, and they have a certain degree of safety. However, for drug-resistant intractable epilepsy, especially the effect of temporal lobe epilepsy (TLE) is better. TLE is caused by the degeneration, necrosis, and decrease in the number of hippocampal neurons, which leads to a decrease in the inhibitory neurotransmitter γ-aminobutyric acid. However, stem cell transplantation can repair and increase the number of γ-aminobutyric acid neurons. Therefore, restoring the balance of inhibitory neurotransmitters and excitatory neurotransmitters may fundamentally cure TLE.

The principle of cell therapy is easily described as your own cells as "autologous cells" or other people's cells as "allogeneic cells". After *in vitro* culture or processing procedures, these treated cells are introduced into the patient's body for apply to achieve the purpose of treating or preventing diseases [14].

SCs can build every tissue in the human body, there they have great potential for therapeutic applications in tissue regeneration and repair. SCs can differentiate into specific cell types. SCs' characteristics are the perpetual self-renewal and the differentiation ability to become a specialized adult cell type. Currently, two major classes of SCs are pluripotent SCs (PSCs) and multipotent SCs (MSCs) [14].

PSCs can differentiate into any cell in the adult body and it also was named "embryonic stem cells". Recently, "induced PSCs" (iPSCs), with some of the same PSCs' characteristics as proliferation, morphology and gene expression were yielded adult cells back into the pluripotent state via applying the molecular manipulation (added Klf4, c-Myc4, Lin28, and Nanog). Unfortunately, these iPSCs via genetic engineering are not likely approved for human disease therapy. Consequently, the results of a purely chemical approach to deliver safer transcription genes into the cells look promising [14].

MSCs are only restricted to differentiate a limited cell population. MSCs were found in bone marrow and have been used therapeutically since the 1960s. Recently, the new sources for MSCs such as the placenta, heart, umbilical cord blood, and brain were found. In the brain, neuro-progenitor cells have differentiated abilities to become neural cells. MSCs may have a potential for clinical application. MSCs have the plasticity to become all the progenitor cells or become only one or two specialized cell types of a particular tissue [14]. Based on our *in vivo* model, the results of SCs therapy in the epileptic research have some progress (**Figure 2**).

SCs can develop into cells of different specialized cell types in the body and grow into new body tissues. For example as transformation into different body cell types, including muscle cells, nerve cells, and blood cells. SCs have the potential to treat many diseases, including stroke, heart attack, spinal cord injury, and macular degeneration, etc. Whether SCs be used to treat epilepsy? Since most cases of epilepsy can be attributed to differences in receptor expression in the brain (due to mutations), theoretically correcting these may reduce the likelihood of electrical seizures in the brain. In addition, during status epilepticus, excitatory overload sometimes kills neurons, especially neurons in the hippocampus. Over time, this actually worsens the condition and leads to the development of temporal lobe epilepsy (TLE). Although AEDs can treat seizures, the damage to the temporal lobe is usually irreversible and permanent, and current treatments do not solve this problem [15–17].
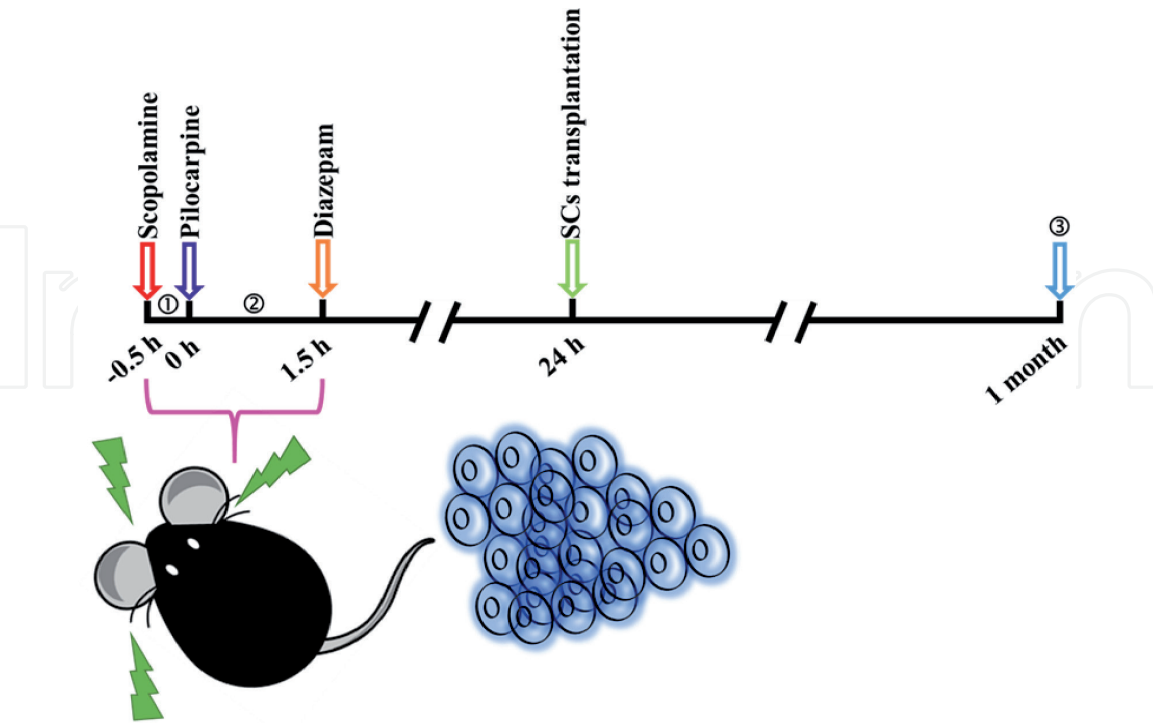

Figure 2.
Pilocarpine-induced status epilepticus model. Mice were firstly pretreated with scopolamine by intraperitoneal injection for 30 min before the induction of SE. Later, pilocarpine was administrated via intraperitoneal injection. Two hours after SE onset, mice were treated intraperitoneally with diazepam to terminate seizures. The process of status epilepticus was described as ① + ②. After one day post pilocarpine induction, stem cell therapy was performed until the experimental end point ③.

The scientific research of SCs in the treatment of epilepsy were showed as (1) PSCs transplantation to treat TLE: Human induced pluripotent stem cells (hiPSCs) are induced to develop into any type of cells in the body, including GABAergic interneurons. According to literatures, GABAergic interneuron progenitor cells derived from hiPSC were transplanted into the hippocampus of a TLE model to observe its efficacy. The results were presented that medial ganglion cells (MGE) derived from hiPSCs after the cell transplantation into the hippocampus. Later, researchers successfully reduced the frequency of seizures and reduced the loss of GABAergic neurons. (2) SCs were obtained from the patient's own bone marrow to treat TLE: the use of autologous mesenchymal stem cells in patients with epilepsy can reduce overall seizure frequency. SCs are obtained from the patient's own bone marrow and intravenously administered into the spinal cord. One year later, 30% epilepsy patients had a complete remission (without seizures), and 50% epilepsy patients who had not previously responded to the medication began to respond well [18–20].

6. Anti-epileptic candidate drugs

During neuro-inflammation, the pro-inflammatory cytokines as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) produced by activated microglia or astrocytes provoke pathological signaling cascades through the activation of phospholipase C and phospholipase A2. Later, the release of non-esterified arachidonic acid (AA) from phospholipids and the formation of lysophospholipids and bioactive eicosanoids by oxidized enzymes. Three enzyme systems, cyclooxygenases, lipoxygenases, and cytochrome P450 (CYP) epoxygenases metabolize released AA to lipid metabolites as prostaglandins, leukotrienes, and epoxyeicosatrienoic acids (EETs), respectively. Brain parenchymal tissue metabolizes AA to EETs via the CYP epoxygenase, which regulate cerebral blood flow and perform anti-inflammatory and anti-apoptotic effects. Previous results were showed that hypoxia and ischemic preconditioning experiments have shown that the increased expression of CYP epoxygenase and EETs in brain may confer protection from ischemic stroke induction. EETs signaling may play a role in suppressing the ischemia-evoked inflammatory cytokine responses in the brain circulation. Soluble epoxide hydrolase (sEH) is a key enzyme for metabolic conversion of EETs into their less active form, dihydroxyeicosatrienoic acids. The inhibition of sEH has been used to increase systemic EETs level and bioactivity. By using pharmacologic inhibitor or genetic deletion, the inhibition of sEH attenuated the vascular and neural injury induced by cerebral ischemia, suggesting sEH might be a novel target in treatment of stroke. In response to these findings, we hypothesized that sEH is involved in neuroinflammation-related epileptogenesis [21].

The sEH enzyme has thus been identified as a therapeutic target for inflammation, and therefore might serve to treat inflammatory pain [21]. Previous studies shown that during peripheral inflammatory, pain GABA A receptor mediated synaptic inhibition was enhanced in neurons [22]. Inhibition of sEH may have elevated the GABA agonists levels and enhance spinal GABAergic transmission [22]. In this context, the basis of kindling-induced epileptogenesis has been hypothesized that enhanced and/or attenuated activation in pathways utilizing glutamate and GABA as the neurotransmitter, respectively [22]. The sEH enzyme may influence the balance between neuronal excitation and inhibition, where glutamate and GABA, respectively, play important roles, and alter the seizure-induction threshold.

sEH is a member of the α/β-hydrolase fold family of enzymes which has two domains: a C-terminal epoxide hydrolase domain (EH), which is responsible for

the biological roles associated with sEH and an N-terminal lipid phosphatase domain (PT) connected by a proline rich linker [23]. The role of sEH in lipid metabolism and lipid related disorders have been emerged in the recent years. sEH and dyslipidemia and related disorders such as atherosclerosis and coronary heart disease were related [24]. The products of the sEH hydrolase domain including fatty acid epoxide substrates and diol were found to activate PPARs, which can modulate plasma lipid by regulating lipid metabolism [24]. Moreover, the hydrolase domain of sEH are shown the effect on lowering cholesterol level by reducing the HMG-CoA reductase expression. However, the phosphatase domain of sEH was shown to regulate the cholesterol biosynthesis pathway by hydrolyzing the isoprenoid intermediates which are involved in cholesterol metabolism [24]. Summarily, the hydrolase and phosphatase domains of sEH exhibit opposite effects on expression of cholesterol levels. According the context about the opposite effects of sEH C- and N-terminal domain on regulating the cholesterol expression, we hypothesize that the sEH C-terminal domain may play a seizure-induction role and the N-terminal of sEH may be a seizure-protection role. In the previous studies, the pharmacokinetic parameters of sEH C-terminal inhibitor, AUDA [12-(3-adamantan-1-yl-ureido)-dodecanoic acid] in brain tissue samples were the mean residence time of 6 h and half-time elimination of 4 h [24].

7. Pilocarpine-induced SE models *in vivo* and *in vitro*

A pilocarpine-induced SE model is wildly used to investigate the alteration of neuronal circuits which reproduced most of the epileptic characteristics in patients. In the pilocarpine-induced SE model, acute SE is successfully induced in only a subset of rats after the high-dose pilocarpine injection [25]. According to our previous epileptic mouse model, mice were firstly pretreated with scopolamine methyl nitrate (1 mg/kg BW, Sigma-Aldrich) by intraperitoneal injection for 30 min before the induction of SE. Later, 325 mg/kg body weight (BW) pilocarpine hydrochloride was administrated via intraperitoneal injection. Mouse behaviors were monitored and scored according to Racine's scale (**Table 1**) [24–26]. Two hours after SE onset, mice were treated intraperitoneally with 10 mg/kg BW diazepam to terminate seizures (**Figure 3**).

In vivo seizure models are important for the research of epilepsy and seizure activity. Currently, *in vitro* models for epileptic research included rodent brain tissue slices and central nervous system (CNS) cell cultures [26]. These *in vitro* models have been performed for the research of epileptic mechanisms. The status of "seizure" and "seizure-like" were described in the *in vivo* and *in vitro* epileptic

Class (seizure stage)	Racine's scale behavioral expression
1	Mouth and focal movement
2	Head nodding
3	Contralateral forelimb clonus
4	Symmetrical forelimb clonus with rearing
5	Rearing and falling

Table 1.
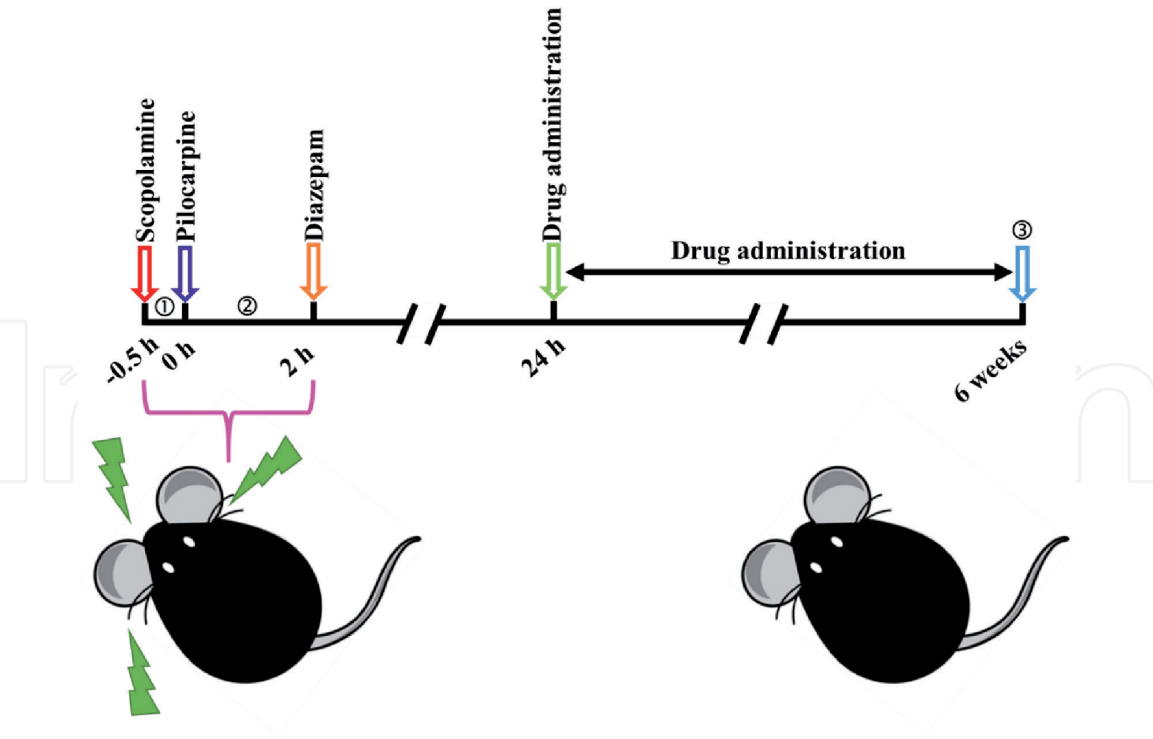*Five class of Racine's scale for seizure stage.*

Figure 3.
Pilocarpine-induced status epilepticus model. Mice were firstly pretreated with scopolamine by intraperitoneal injection for 30 min before the induction of SE. Later, pilocarpine was administrated via intraperitoneal injection. Two hours after SE onset, mice were treated intraperitoneally with diazepam to terminate seizures. The process of status epilepticus was described as ① + ②. After one day post pilocarpine induction, drug therapy was performed until the experimental end point ③.

studies, respectively [27, 28]. *In vitro* CNS cell models were established by applying 12-(3-Adamantan-1-yl-ureido)-dodecanoic acid (AUDA) that was ordered from Cayman Chemical (Ann Arbor, MI, USA) and dissolved in dimethyl sulfoxide (DMSO; Cat No. 472301; Sigma-Aldrich, MO, USA). Cells were obtained as mouse retroviral immortalized microglia BV-2 cells belonged to C57BL/6 background (a gift from Dr. Hsiao-Li Chuang, National laboratory animal center, Taipei, Taiwan). They were grown in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 U/mL penicillin, and 100 μg/ml streptomycin in 5% CO_2 atmosphere at 37°C. Cells were grown to 90% confluency before experiments. Later, cells were treated with 100 μM pilocarpine and/or 100 μM AUDA and cultured for 24 hr. in 10% FBS-DMEM on glass coverslips and performed the observation of BV-2 cell morphology by light microscope. Cell viability was measured by MTT assay according to the manufacturer's instructions (MERCK, Darmstadt, Germany). *In vitro* scratch wounding-healing assay was performed as described. Briefly, confluent BV-2 microglia in 6-well plates were washed with serum-free DMEM three times. A line down the center of each well was scraped with a p200 pipette tip, followed by a wash to remove debris with serum-free DMEM. Images were taken at 10× magnification, scratch widths were measured, and wound closure was calculated by dividing widths measured after a 8 hr. incubation by the initial scraped width. Each experiment was carried out in triplicate and three fields were counted per well by scorers blinded to experimental conditions. Boyden chamber assays were performed in the transwells (BD Bioscience, New Bedford, MA) as previously described. BV-2 microglia (4×10^4 cells in 200 μL of serum-free DMEM) were added to the upper chamber and allowed to adhere to the polycarbonate filters (8 μm pore) for 30 min at 37°C in a humidified

atmosphere of 95% air and 5% CO_2. Following, cells were pretreated with 100 μM pilocarpine at 37°C for 30 min prior to AUDA treatment. 100 μM AUDA were then placed in the upper chamber and lower chamber was added with 10% FBS-DMEM to allowed cell migration. Cells did not migrate and remained on the upper surface of the filter were removed. Cells had migrated to the lower surface were stained with Liu's stain (ASK, Taoyuan, Taiwan) and counted under light microscope. In at least three independent experiments, three wells per treatment were counted in nine random fields at 40× magnification per well by scorers blind to experimental conditions.

8. AUDA is safe in *in vivo* study and significantly inhibited pilocarpine-induced BV-2 microglial viability and migration *in vitro*

In the acute toxic assay *in vivo,* high doses of AUDA (100, 200, and 300 mg/kg BW) were respectively administrated for mice (n = 6/dose), all mice were survival and their clinical symptoms were normal. The results of AUDA were verified safe. Non-cytotoxic concentration (100 μM) of pilocarpine and AUDA were used in this study. Non-cytotoxic effect was presented after 100 μM pilocarpine combined with 100 μM AUDA treatment. According to our studies, AUDA significantly suppressed cell migration compared to the control by using respectively *in vitro* scratch wound-healing assay and Boyden chamber assay ($p < 0.001$) (**Figures 4** and **5**). According to these results, AUDA had the ability for the inhibition of the C-terminal domain of sEH can suppress the seizure development. C-terminal domain of sEH may play an important role in the epileptogenesis.
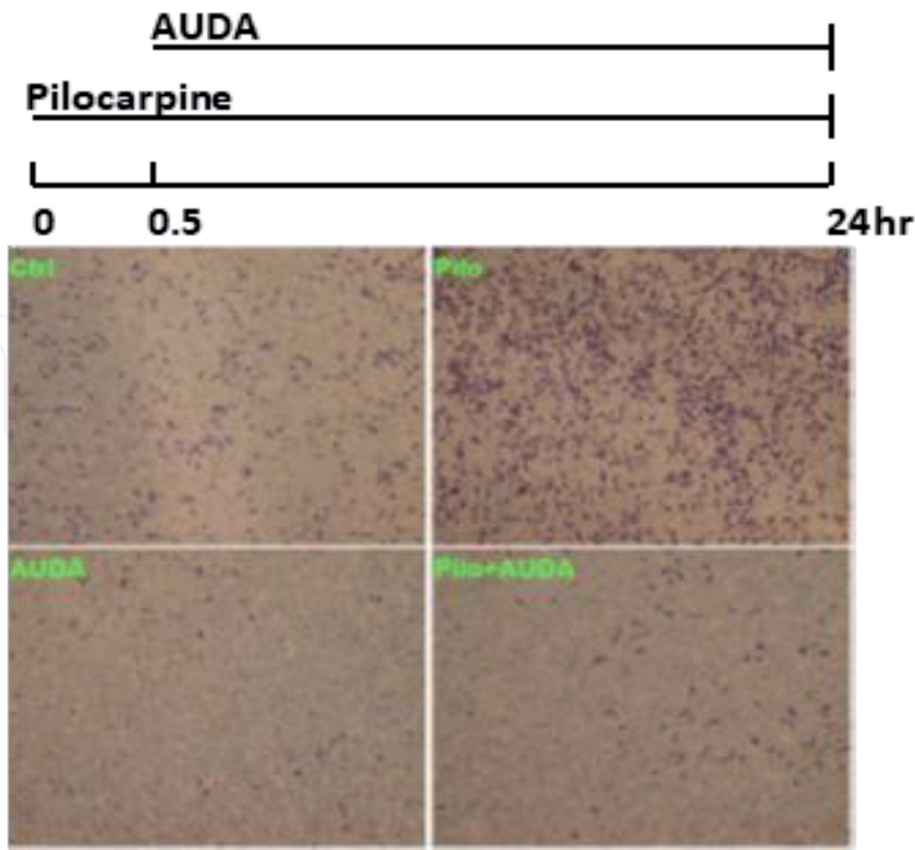

Figure 4.
In vitro *scratch wound-healing assay. Non-cytotoxic concentration (100 μM) of pilocarpine and AUDA were used in this study. 100 μM pilocarpine was first treated to BV-2 cells before 100 μM AUDA treatment. Later, AUDA treatment for 7.5 hours until the experimental end.*
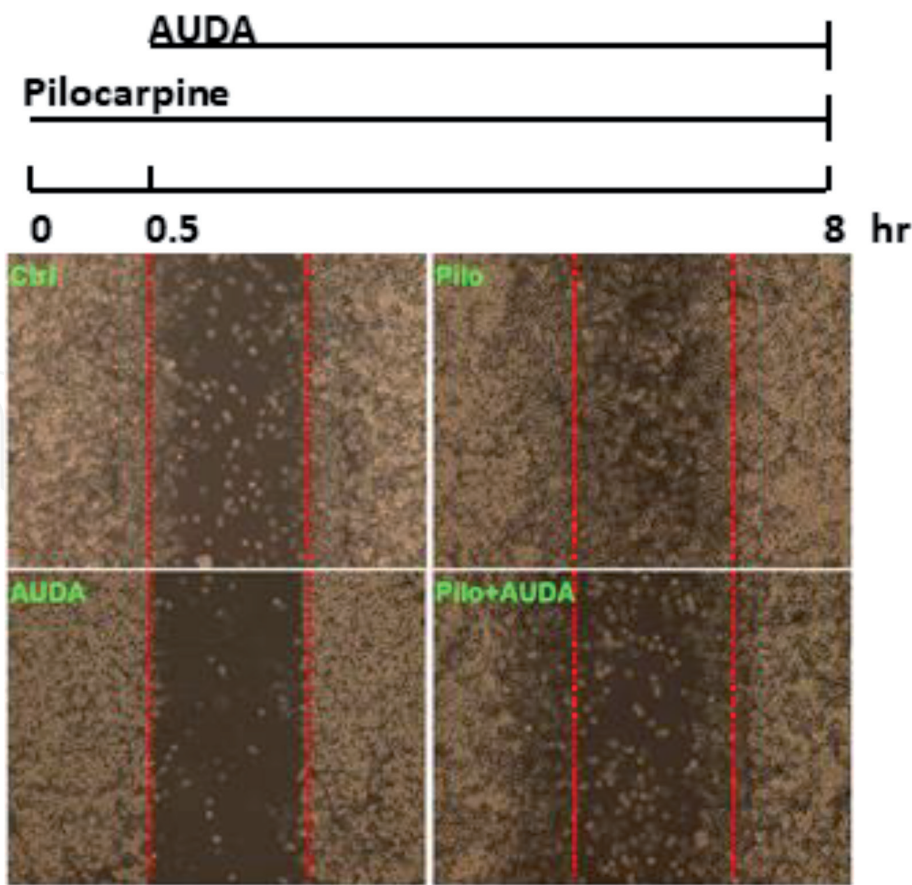
Figure 5.
Boyden chamber assay. Pilocarpine (100 μM) and AUDA (100 μM) were used in this study. Pilocarpine was first treated to BV-2 cells before AUDA treatment. Later, AUDA treatment for 7.5 hours until the experimental end.
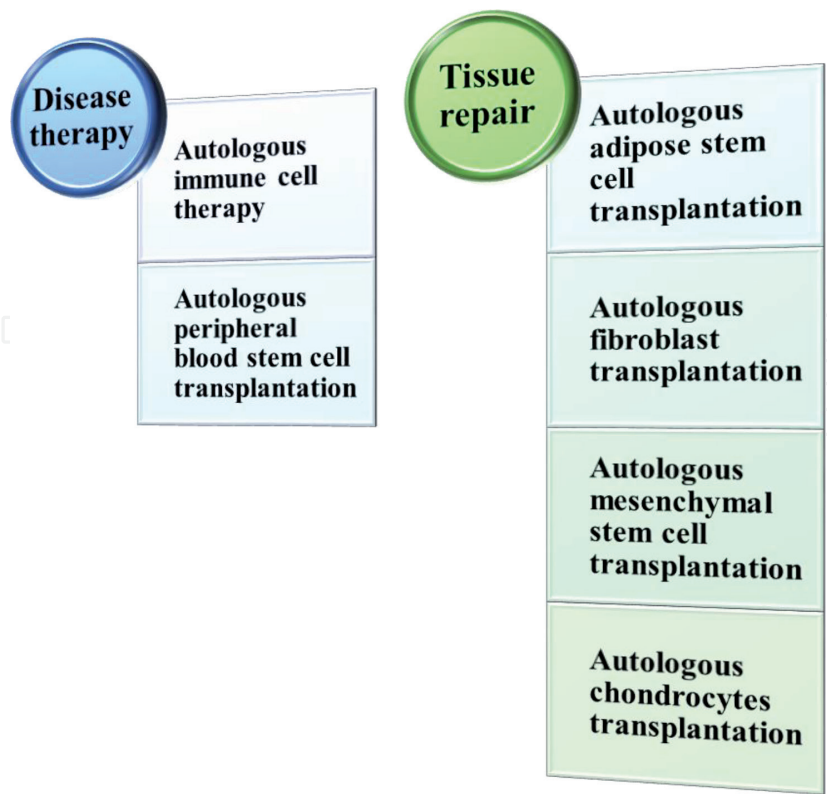

Figure 6.
Amendments to the administrative measures for the implementation or use of specific medical technology inspection and testing medical instruments in Taiwan in 2018. The six major projects can be divided into two categories: "Disease therapy" and "tissue repair". The two peripheral blood stem cells and immune cells are mostly used to treat cancer. The other four cell types belong to regenerative medicine, with the goal of helping tissue regeneration or repair.

9. Amendments to the administrative measures for the implementation or use of specific medical technology inspection and testing medical instruments in Taiwan

Cell replacement therapy and gene transfer to the diseased or injured brain have provided the basis for the development of potentially powerful new therapeutic strategies for a broad spectrum of human neurological diseases. However, the paucity of suitable cell types for cell replacement therapy in patients suffering from neurological disorders has hampered the development of this promising therapeutic approach. The full name of the "Special Control Law" issued by the Ministry of Health Services is "Administrative Measures for the Implementation or Use of Medical Instruments for Special Medical Technical Inspections", which was officially announced on September 6, 2018. The six major projects may seem complicated, but in terms of teleology, they can be divided into two categories: "disease therapy" and "tissue repair". The two peripheral blood stem cells and immune cells are mostly used to treat cancer. The other four cell types belong to regenerative medicine, with the goal of helping tissue regeneration or repair (**Figure 6**).

10. Conclusions

Currently, cell sources, characteristics, differentiation and therapeutic strategies and applications are frequently discussed worldwide. SCs have great potential in the regeneration and repair of tissue in people. However, limited information were presented at present. Therefore, the deeper studies will be still needs to be learned about their biology, manipulation and safety before their full therapeutic potential can be achieved. SCs-based therapies have shown encouraging results in treating diseases including epilepsy. Experimental animal and clinical studies have shown that SCs have significant regenerative properties on epileptic animal and patients with epilepsy. However, before SCs therapy becomes routine, larger clinical trials are needed [29–31]. In addition, our previous studies suggested that sEH played a
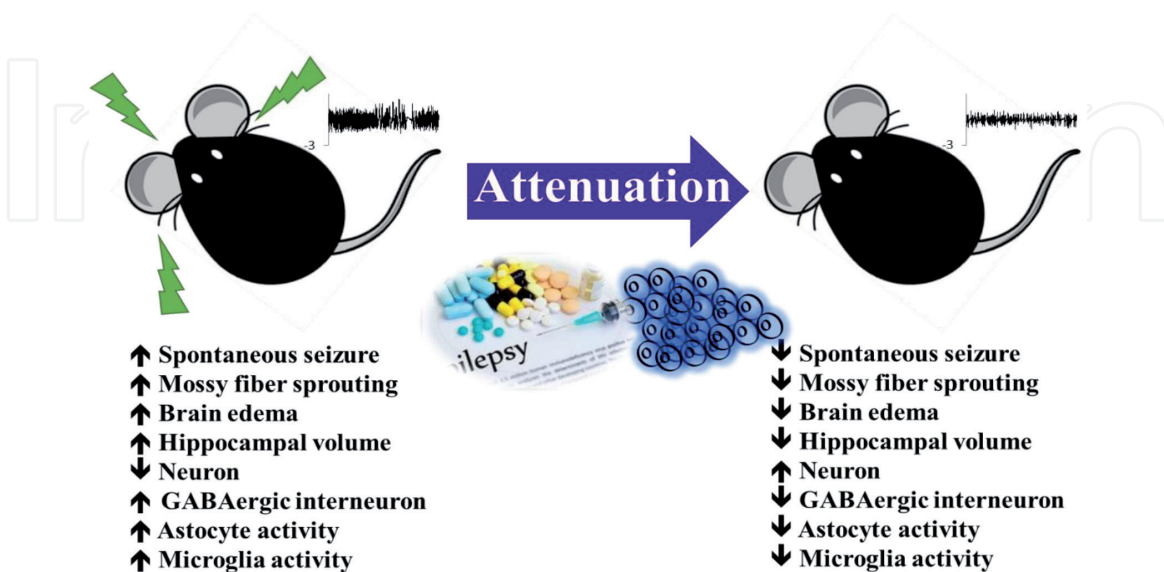

Figure 7.
Combined application therapies of stem cells and drugs in the neurological disorder attenuation. Based on epilepsy, some symptoms were increase as spontaneous seizure, mossy fiber sprouting, brain edema, hippocampal volume, GABAergic interneuron number, astrocyte activity, microglia activity. However, neuron number was decrease. After the combined application therapies of stem cells and drugs in the neurological disorder, the above symptoms were reversed.

critical role in regulating epileptogenesis in the pilocarpine-induced SE mice and *in vitro* CNS cell platform. Blocking of C-terminal activity of sEH via AUDA treatment can attenuate significantly epileptogenesis. Blocking of C-terminal activity of sEH on epileptogenesis may be provided a novel therapeutic approach in epilepsy. Anti-functional sEH C-terminal domain also may be a potential biomarker therapy for epileptogenesis in the future. Finally, the combined application therapies of SCs and drugs as AUDA may be try to apply in attenuating NDs (**Figure 7**).

Acknowledgements

Conflict of interest

The authors declare no conflict of interest.

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