Nanomedicine: A New Approach for Treatment Neuropsychiatric Diseases

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Abstract: Nervous system diseases, such as Alzheimer's disease, stroke, and Parkinson's disease, are spreading around the world. These diseases involve complicatedly pathological processes, and so far, there are no effective medicines for therapy. Another type of psychiatric disorder is induced by drugs. The synthetic drugs, represented by methamphetamine, are becoming widely abuse. At present, the cure of methamphetamine dependence is mainly symptomatic treatment, but the recurrence rate is very high. As the common brain impairments in neuropsychiatric disease, it is necessary to summary novel strategies effectively restored brain function. In recent years, carbon nanotubes have attracted the attention due to their unique properties in the field of translational medicine. Recently, new advances reported that carbon nanotubes as a nanomedicine to treat various neuropsychiatric disorders. The purpose of this review is to introduce the therapeutic approaches and mechanisms of carbon nanotubes on neuropsychiatric disorders.

Keywords: Carbon Nanotubes, Neuropsychiatric Diseases, Autophagy, Mitochondrial Dysfunction

1. Introduction

Neuropsychiatric disorders are divided into neurological and psychiatric disorders. Neurological disease mainly includes Alzheimer's disease (AD), Parkinson (PD), Huntington disease (HD) and stroke, epilepsy, *etc.* Of these, neurodegenerative disease is a class of chronic progressive neurological diseases caused by the loss of neurons and / or their myelin [1]. A variety of factors are associated with the occurrence and development of neurodegenerative diseases, including oxidative stress, neuroinflammation, mitochondrial dysfunction, protein misfold and accumulation. Stroke, a neurological disorder, is caused by a decrease in blood flow to the brain tissue resulting in a change in neurological function. With the progress of research, there have been many mechanisms of stroke found, such as energy metabolism disorder, oxidative stress, inflammation and nerve cell apoptosis, and all of those are caused by ischemia. But effective early diagnosis and treatment are very limited. Due to the blood-brain barrier, there is no effective drug for the treatment of neuropsychiatric diseases. Psychiatric

disorders, such as schizophrenia, depression and drug addiction, are also a social and health problem worldwide. Among these issues drug addiction is extremely difficult to cure as it is hard for patients to prevent drug relapse. Marijuana, amphetamines, opiates, and cocaine are largely spread in the world. Therefore, how to scientifically and effectively treat methamphetamine-dependent patients is a new challenge in clinical practice. At present, the drugs used to treat methamphetamine-addiction are mainly sedative drugs, such as clozapine, risperidone or quetiapine, but these drugs however, strong drugs carving and high relapse rate are uncontrollable in clinic. In the past decade, the application of nanotechnology in the medical field has developed rapidly. Among various nanomaterials, carbon nanotubes attracted much attention because of its unique structure and physical, chemical and mechanical properties. The optical, thermal, electrical, magnetic, mechanical, and chemical properties of carbon nanotubes are significantly different from those of bulk solids, which makes nanotubes easily and widely available [2]. In recent years, carbon nanotubes have made a great progress in the treatment of neuropsychiatric diseases. This review focuses on AD, stroke, drug addiction,

introducing the application of nanomedicine in novel therapeutic evaluation.

2. Harmfulness of Neuropsychiatric Diseases

2.1. The Risk of Neurodegenerative Diseases

Neurodegenerative diseases are caused by loss of neurons in the brain and spinal cord. Neurons have different functions, such as controlling exercise, dealing with sensory information, and making decisions. Neurons are not regenerable, thus excessive damage to neurons is devastating and irreversible. The distinct symptoms of neurodegenerative disease are memory impairment and cognitive dysfunction. For example, progressive memory loss, cognitive impairment and personality changes occur in AD, while exercise retardation, resting tremor, and muscle rigidity generally exist in PD. Brain damage caused by hypoxic-ischemic is accompanied by severe symptoms such as language impairment, hemiplegia, and memory impairment. The widespread prevalence of these diseases worldwide and the lack of effective treatment mean a heavy burden on individuals, families and society.

2.2. The Risk of Psychiatric Disease

It is well documented that the rewarding and psychostimulating effects of addictive drug cause verbal abnormalities and behavioral changes in patients. Methamphetamine is a high psychostimulant to make euphoria but serious brain injury, resulting in decreased self-binding, violent tendencies, and excessive activity, emotional impulses [3]. A single injection of methamphetamine is enough to increase body temperature heart rate and damage dopaminergic neurons. Long-term extensive abuse of methamphetamine can produce significant toxicity in the central nervous system [4]. The meta-analysis supported that patients who suffered methamphetamine dependence will appear moderate cognitive impairment in episodic memory, and executive function, complex information processing speed and psychomotor function showed moderate impairment, and in working memory, attention, language and visual spatial light damage degree.

Methamphetamine leads to an increase in dopamine in the patient's brain, resulting in autoxidation of dopamine. Furthermore, the autoxidation of dopamine also leads to oxidative stress, and synaptic membrane injury. The level of dopamine transporter in the dorsolateral prefrontal cortex of methamphetamine abusers was significantly lower, and the level of serotonin transporter in the midbrain, caudate nucleus, cranial nucleus, hypothalamus, thalamus, orbital frontal cortex was decreased [5-7]. Positron emission imaging studies showed that microglia activation in the brain, striatum, thalamus and orbital frontal cortex of methamphetamine abusers was negatively correlated with methamphetamine withdrawal time [8]. The study also

revealed an increase in the content of glioblast-activated inositol in the brain of methamphetamine abusers [9-10].

3. Pathogenesis of Neuropsychiatric Disorders

3.1. Mechanisms of Neurological Diseases

The pathogenesis of neurological diseases include autophagic dysfunction, mitochondrial dysfunction, oxidative stress, neuroinflammation, and apoptosis, etc. Most neurodegenerative diseases are progressive. Its pathologic features are specific neuronal atrophy, which are associated with astrocyte hyperplasia and specific pathological deposits, such as senile plaques (SP) in AD [11] and Lewy bodies in PD [12]. Autophagy is widespread in eukaryotic cells, and plays an important role in neurodegenerative diseases as a mechanism for the degradation of denatured proteins and damaged aging organelles. After the cell receives autophagy signals, it forms a double membrane structure in the cytoplasm, called the phagophore. The phagophore wraps the damaged organelles and misfolded proteins, forming the autophagosome. Furthermore, the fusion of autophagosome with lysosomes results in the formation of autolysosome, during which the autophagosome and its encapsulated cargo are degraded.

Mitochondria are a special kind of apparatus that are widely distributed in various eukaryotic cells and undergo independent replication. As the regulatory center of cell metabolism network and signal transduction network, mitochondria are involved in growth, development, metabolism, aging, disease, death and biological evolution. Studies have shown that neurological diseases are associated with mitochondrial dysfunction [13]. Data showed that prior to the presence of cognitive impairment symptoms, abnormal glucose metabolism has been observed in cerebral cortex and hippocampus [14], which suggested that mitochondrial dysfunction may be an early signal for neurodegeneration.

The mechanism of cerebral ischemia leading to neuronal damage is a complex pathophysiological process. Cerebral blood flow interruption caused cerebral ischemia and hypoxia, energy metabolism disorders, while the reperfusion existence of blood flow on the brain tissue, which will produce damage cascade to brain tissue. Damage mechanisms include calcium overload, inflammatory response, apoptosis, and so on.

Stroke leads to calcium overload damage. Under normal circumstances, intracellular calcium is mainly stored in the sarcoplasmic reticulum and mitochondria, ischemic stroke after ischemia and hypoxia, through a variety of ways to cause a large increase in intracellular calcium which lead to intracellular calcium overload. The risk of calcium overload caused by cerebral ischemia is multifaceted, which induced inflammatory response and apoptosis are the main aspects [15-16].

In recent years, the inflammatory response after cerebral ischemia has become a hot topic. The brain has a blood-brain

barrier and has been considered an immune exemption area. However, the results suggest that the inflammatory response is an important pathologic segment that causes brain cell damage. The signs of inflammatory response are leukocyte infiltration and activation of microglia [17]. Inflammatory cells release inflammatory factors that aggravate brain damage. Experimental studies have confirmed that stroke-induced neuronal death includes neuronal apoptosis. The apoptosis of neurons is an early, dynamic, and continuous process, and apoptosis is important in the expansion of brain damage. Therefore, the study of neural cell apoptosis mechanism and anti-apoptotic strategy has become a research hotspot [18].

Studies have shown that the tumor stem cells were attached to the polymer stent, and then the stent was implanted in the brain of mice which were cerebral infarction caused by stroke-induced, this method reverses the brain injury [19]. These scaffolds that attach neural stem cells promote neuronal differentiation, reformation of cortical tissue, and reduction of inflammation. Carbon nanotubes as a stent in the treatment of brain tissue injury achieved positive results [20]. Therefore, the researchers studied whether carbon nanotubes alone could treat stroke.

Neuroscientists have explored the mechanisms of neurological diseases and make progress, which could be helpful to find potential therapeutic targets.

3.2. Mechanisms of Psychiatric Disease

At present, the mechanism of methamphetamine addiction is not clear, but previous studies have shown that methamphetamine addiction is associated with the dopamine reward system in the ventral tegmental area of the brain [21]. Methamphetamine is an indirect agonist of dopamine that promotes the release of monoamine neurotransmitter [22-23]. One of the most important ways is to promote the reverse transport of dopamine and block the dopamine reabsorption [24]. Methamphetamine acts on the vesicular dopamine transporter, blocking the reabsorption of dopamine acted by dopamine transporters on the cell membrane. In addition, methamphetamine causes an increase in tyrosine hydroxylase activity, thereby increasing the synthesis and release of dopamine [25]. Methamphetamine not only blocks dopamine metabolism by inhibiting monoamine oxidase and methyltransferase activity, but also stimulates massive dopamine release, which leads to psychiatric dependence ultimately. The mechanisms of methamphetamine-induced neurotoxicity include oxidative stress, excess release of monoamine neurotransmitters, mitochondrial dysfunction, and inflammatory responses [26-28]. The activity of superoxide dismutase (an antioxidant enzyme) was improved in mice which were exposed methamphetamine [29]. Methamphetamine causes mitochondrial dysfunction by inhibiting electron transport chains and ATP level [30]. The degradation of chromatin oxidase in the striatum was observed by staining, demonstrating methamphetamine disrupts the complex IV of mitochondrial chain [31]. Thus, methamphetamine-induced reductions in ATP levels may

cause brain toxicity. Understanding the brain dysfunction caused by drug addiction and the pathogenesis of drug addiction, it is found that the treatment goal is to reverse or compensate for brain changes, such as reducing dopamine in brain. Reversing the function of the brain requires medication, the clarification of biology is also the key to the development of anti-addiction drugs.

As stated above, most neuropsychiatric diseases own their unique characteristics, but they share some common symptoms and pathogenesis that provide us opportunities overcoming the deficits in the brain. For example, they lead to cognitive dysfunction, memory loss and other symptoms, and their pathogenesis includes but is not limited to mitochondrial dysfunction, neural death, oxidative stress and neuroinflammation. Next, the article discusses the treatment of brain function changes and biological changes caused by neuropsychiatric disorders.

4. Application of Carbon Nanotubes in Neuropsychiatric Diseases

4.1. Advances in the Therapeutic Effects of Carbon Nanotubes on Alzheimer's Disease

AD a neurodegenerative disease in which the patient's brain lesions are characterized by the deposition of two types of proteins. Amyloid β peptide ($A\beta$) deposition forms extracellular age spots (senile plaques, SP). The hyperphosphorylation of tau protein forms the neuro-fibrillary tangles (NFT). Autophagy is a necessary process for $A\beta$ clearance, whereas autophagic defects have been mainly observed in AD model [32]. Thus, autophagy has become a potential target for AD therapy, and the relationship between autophagy and AD has a far-reaching significance for disease prevention.

Xue et al. defined autophagic defects in primary glia in CRND 8 mice, a transgenic mice model of AD. The research group demonstrated that SWNTs effectively suppressed mTOR phosphorylation that restore autophagy defects. SWNTs also alleviated lysosomal dysfunction by activated lysosomal protease cathepsin D, which is markedly impaired in CRND 8 glia. This study found that SWNTs hold significant therapeutic promise as neuroprotective agents in AD by restored normal autophagy [33]. Another study also claimed that oxidized and ammoniated multi-walled carbon nanotubes increase the autophagy activity in cancer cells. Overexpression of Beclin 1 and the reduction of Bcl 2 expression were also observed [34].

4.2. Advances in the Therapeutic Effects of Carbon Nanotubes on Stroke

Stroke is a neurological disease that endangers human health and life safety. The symptoms of stroke are manifested as sudden fainting, unconsciousness or hemiplegia. Stroke leads to brain tissue damage resulting from reduced blood flow, and secondary to cause neurological changes.

A recent study demonstrated that amino-modified carbon nanotubes improved the motor ability in rotating rod test in a mice ischaemic injury model. The results showed that ammonia-modified carbon nanotubes inhibited apoptosis and reduced the expression of apoptotic proteins. Inflammatory reaction is another causative factor in stroke. In this study, SWNTs successfully attenuated inflammation and prevented tolerance of neurons to ischemia. ERK and AKT signaling pathways are associated with cell survival and apoptosis. Amino-modified carbon nanotubes down-regulated ERK activity in mice that induced stroke to protect neurons. The study also demonstrated that amino-modified carbon nanotubes can affect cadmium and hypoxia-inducible factors in order to enhance neuroprotective efficacy [35].

4.3. Effects of Carbon Nanotubes on Mitochondrial Dysfunction

Mitochondrial dysfunction triggers various diseases, such as neurodegenerative diseases, cardiovascular disease and mental illness, which makes mitochondria as a possible therapeutic target. Cytochrome C (Cyt-C) is an important component of the mitochondrial respiratory chain, which is synthesized from two inactive precursors: pre-cytochrome and heme. Since Cyt-C has a heme group, it can transfer electrons between the respiratory chain complexes III and IV. When Cyt-C is deficient, the electron transport chain is blocked, resulting in over-generation of superoxide anion (ROS), whereas ROS is an important factor in apoptosis [36]. The release of Cyt-C plays a central role in the process of apoptosis and is a key factor in the fate of cells. Cyt-C not only directly induces apoptosis, but also participates in the process of apoptosis by interfering with electron transport, blocking energy synthesis, promoting free radical (ROS) production.

It has been proved that activated carbon nanotubes film-modified electrode altered the redox of Cyt-C [37]. Recently, the researchers modified the carbon nanotubes with

carboxyl groups with good dispersibility. The carboxyl-modified carbon nanotubes could affect the redox of Cyt-C [38], and also impacted on mitochondrial membrane potential to alter the oxygen uptake capacity of mitochondria and block the electron transfer of Cyt-C. Studies have shown that carbon nanotubes with different structures have different effects on mitochondrial function, and the effects of aggregated carbon nanotubes on mitochondrial dysfunction are more significant [39]. Other studies prepared complexes of multi-walled carbon nanotubes and nerve growth factors.

4.4. Advances in the Therapeutic Effects of Carbon Nanotubes on Methamphetamine Addiction

Dopamine is a monoamine that plays a very important role in regulating brain function and is associated with a variety of neurological disorders. Methamphetamine affects the mesolimbic dopamine system, resulting in dramatically increased dopamine in the brain. Symptoms of the methamphetamine addiction are drug craving, preference effects and relapse after withdrawal.

Carboxyl, phenolic and other functional groups-modified carbon nanotubes can selectively adsorb dopamine. Researchers have found that ferric hydroxide-Nafion film-coated carboxylic acid-modified carbon nanotubes changed dopamine in drosophila [40]. Functionalization of carbon nanotubes with poly (diallyl dimethylammonium chloride) (PDDA) reduced the detection limit of dopamine^[41]. A new method that carbon nanotubes within a dihexadecylphosphate film were used in conjunction with a glassy carbon electrode modified with nickel oxide nanoparticles would make carbon nanotubes more sensitive to dopamine [42].

Recently, a study reported that SWNTs (see Figure 1) could alleviate methamphetamine addiction by oxidized excessive dopamine [43].

Figure 1. Characterization of iSWNT and aSWNT. A, Atomic force microscopy (AFM) images of iSWNTs and aSWNTs. B, Typical high resolution transmission electron microscopy (HR-TEM) micrographs of iSWNTs and aSWNTs. Adapted with permission from ref 43.

In this study, aggregated form of SWNTs not only inhibited drug craving and relapse in mice, but also attenuated methamphetamine-induced conditioned place preference. Electrochemical methods indicated the ability of SWNTs on dopamine oxidation and absorption (see Figure 2).

Figure 2. Electrochemical method for the determination of dopamine oxidation. Adapted with permission from ref 43.

Furthermore, it has been found that SWNTs blocked methamphetamine-induced tyrosine hydroxylase increase or synaptic protein expression. What was more, SWNTs did not produce toxicity to mice. This may be due to the extremely low dose of SWNTs administration (see figure 3).

Figure 3. Schematic diagram that SWNTs attenuated METH addiction. Adapted with permission from ref 43.

5. Conclusion

SWNTs have become a hotspot in the world because of their unique mechanical, electrical and chemical properties, and have great potential in the application of biomedicine. Recent studies have shown that SWNTs relieved neurological diseases, such as AD, stroke and drug addiction in CNS. Although these studies are only proof-of-concept evidence, it is convinced that carbon nanotubes, as well as other

nanomaterials, deserve to further research as a novel approach for theranostical treatment in neuropsychiatric diseases.

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