Chapter

Introductory Chapter: Concept of Neuroprotection - A New Perspective

Raymond Chuen-Chung Chang and Yuen-Shan Ho

1. Introduction

Neuroprotection is an approach to preserve neurons so that neurons cannot be hurt by different pathological factors in neurodegenerative diseases. It can be an approach before the onset of the disease so that neurons cannot be affected by any risk factors. It can also be an approach during the progression of the disease to prevent spreading of injury from one neuron to neighboring neurons. Therefore, neuroprotection can also be one approach as "disease-modifying agent" to delay and even stop progressive neurodegeneration.

The concept of neuroprotection has long been confined to intervene neurotransmitter receptors via agonists and antagonists. A very well-known example is the neuroprotective effect of caffeine via adenosine receptor, because caffeine is an A2 receptor antagonist. Caffeine can exert neuroprotection via adenosine A2 receptor to protect dopaminergic neurons in an experimental model of Parkinson's disease (PD) by using 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) as a toxin agent [1]. Therefore, drinking coffee has been considered to be neuroprotection. Apart from adenosine receptor on neurons, it is now known that microglial cells also express A2 receptor, and A2 receptor antagonist or caffeine can reduce activation of microglial cells [2]. Since caffeine or A2 receptor antagonists can protect neurons and minimize activation of microglial cells, research is still very active in this direction. Indeed, investigation of other neurotransmitter receptor antagonists, agonists, blockers, or even partial blockers is still a very active research area in neuroprotection.

While it is exciting to reveal differential neuroprotective effects via modulating receptors for different neurotransmitters, we should not restrict ourselves to this perspective only. In fact, a wider scope of neuroprotection has been evolved. The concept of neuroprotection can now be categorized into three groups: (A) pharmacological intervention, (B) non-pharmacological intervention, and (C) cellular and genetic approaches (**Figure 1**).

In group A neuroprotective approaches, pharmacological intervention includes modulation of neurotransmitter receptors (as introduced above), anti-oxidative stress, and anti-inflammatory responses [3]. These are classical pharmacological approaches. These methods have been explored for decades and can be used for both neuroprotection and as disease-modifying agents. Their effects can be target-specific for one single protein (e.g., receptor for neurotransmitter or one type of cytokines) or pathway-specific (anti-oxidative responses using nuclear factor erythroid 2-related factor 2, Nrf2). Since single biological target may limit the beneficial effects and may not be able to intervene the complexity of the disease

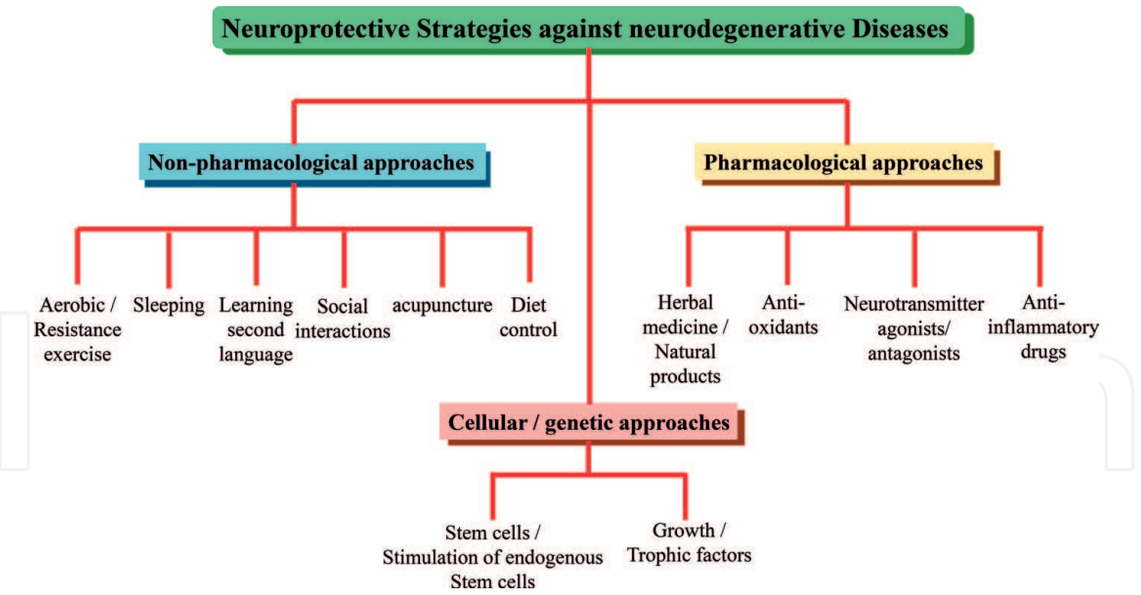

Figure 1.
A summary of different neuroprotective approaches.

progression, neuroprotective effects from herbal medicine or natural products receive increasing attention in scientific research because of their multiple effects on different biological targets [4–6]. For example, it has been shown that triterpenoids extracted from *Prunella vulgaris* has anti-inflammatory effects [7]. We have proved that polysaccharide part of *Prunella vulgaris* can modulate the immune responses of microglia and macrophages [8, 9]. Therefore, *Prunella vulgaris* exerts neuroprotection toward neurodegenerative diseases against neuroinflammation.

In group B neuroprotective approaches, non-pharmacological approaches receive increasing attention. Since it is quite difficult to ask a healthy adult or even elderly to constantly take medicine even though it is herbal, non-pharmacological approaches to earn neuroprotection are most welcome. Among these different methods, exercise is the best to prevent nearly all kinds of diseases. Exercise can be further divided into aerobic and resistance exercises, in which aerobic exercise is suitable for motor-healthy adults or elderly. However, there is a large population of elderly who have difficulty in their motor functions. Resistance exercise becomes an excellent tool for them. Both aerobic and resistance exercises can affect the metabolisms of the body and induce trophic factors like myokines, released from muscles and liver [10, 11]. Since body metabolism is important, diet control is also important to reduce any risk factors leading to the development of neurodegenerative diseases, such as diabetes, hyperlipidemia, or hypercholesterolemia. All of these risk factors are related to vascular components, which may further add on vascular dementia [12–14]. Apart from exercise, it is well-known that, maintaining social activity is essential to keep our brain healthy [15]. In addition, sleeping can promote clearing of pathological factors, such as β-amyloid (Aβ) peptide and phosphorylated tau protein [16, 17]. Also, it has been recently shown that learning second language or bilingualism can be neuroprotective [18]. Furthermore, increasing lines of evidence have shown that acupuncture can help adjusting the body metabolism and immunity [18, 19]. Therefore, acupuncture can also be considered to be one method in non-pharmacological approaches. One key point should be noticed that all these neuroprotective approaches are multiple targets. This may be why they are so effective in minimizing neurodegeneration to preserve neurons.

Neuroprotective approaches in group C are the new extension of multiple effects from trophic factors secreted by genetically engineered cells or viral vector. Alternatively, stimulating the proliferation and differentiation of endogenous stem

cells, application of induced pluripotent stem cells (iPSC), or mesenchymal stem cells are popular trends in scientific research to prevent neurodegeneration and neuronal loss [20–22].

Since there are several chapters about the effects of neurotransmitter receptors, we will focus on some neuroprotective approaches only, as this is an introductory chapter.

2. Neuroprotective effects of herbal medicine and natural products

This direction of neuroprotection is the most controversial approach among different pharmacological tools. This is because most of the herbal medicine or natural products have a wide array of effects. If we use traditional way of thinking to target a specific protein or signaling pathway, herbal medicine fails to do so. However, if we are aware of neurodegenerative diseases that are usually multifactorial, we can then accept that herbal medicine should be the direction to prevent neuronal loss and spreading of neurodegeneration. Our group has long been working on discovering herbal medicine as neuroprotective agents and investigating their underlying mechanisms. Since most of the herbal medicines are in decoction form, for oral consumption, the effective components in different herbs are not limited to one single chemical. The small molecules being extracted from one herb can also be found from other herbs. There are many laboratories investigating those small molecules and have Research and Development (R&D) to be commercial products. In contrast, big molecules such as polysaccharides have been an unexplored area. In fact, a large portion of components from herbs is polysaccharides. When we use hot water to prepare decoction, what we can easily absorb is polysaccharides. Therefore, we have investigated polysaccharides extracted from different herbs [23].

We have first found that polysaccharides from *Nerium indicum* exert neuroprotective effects against β-amyloid (Aβ) neurotoxicity cultured neurons [24, 25]. Then, we also found that neuroprotective effects of *Verbena officinalis* and *Ganoderma lucidum* [26, 27]. Having investigated different herbal medicine, we found that the polysaccharides from *Lycium barbarum* (Wolfberry) are potent [28, 29]. Polysaccharides can be extracted in hot water or from alkaline condition and elicit neuroprotection [30]. It should be noted that not all polysaccharides, but only some sub-fractions provide neuroprotective effects. Apart from neurons in the brain, polysaccharides from wolfberry can also protect the retina against experimental glaucoma and stroke [31–33]. As harvesting and planting processes have good agricultural practice and the extraction can be done under stringent control of good manufacturing practice, we choose wolfberry as our long-term study. Wolfberry is indeed an anti-aging Chinese herbal medicine. We would like to understand the concept of "anti-aging." Therefore, we have investigated its application in different aging-associated neurodegenerative diseases [34]. In fact, not all aging-associated neurodegenerative diseases can be attenuated by the polysaccharide fraction of Wolfberry. In Parkinson's disease (PD), more potent antioxidants are required to provide neuroprotection.

In experimental PD using 6-hydroxydopamine (6-OHDA) as toxin agent, we employed oxyresveratrol, which is a natural product but a structural analog of resveratrol, and found that it can attenuate neurodegeneration [35, 36]. For this kind of neurodegenerative disease requiring high levels and high capacity of antioxidant, another method is to employ pro-drug approach so that oxidant cleave the precursor and the product becomes potent antioxidant. Interestingly, polyphenol (-)-epigallocatechin-3-gallate (EGCG) from green tea falls in this category [37].

The advantages of using herbal medicine or natural products are to make use of their multiple effects. In neurodegenerative diseases, a wide array of stress responses is stimulated because of free radicals or accumulation of misfolded or

badly folded proteins. Most of the herbal medicine and natural products attenuate many stress kinases. They may not be a good candidate to clear accumulation of bad proteins; however, they can inhibit the cascades of stress responses (e.g., activation of c-Jun-N-terminal kinase, JNK; endoplasmic reticulum stress pathways), which usually lead to neuronal apoptosis. Some of the herbal medicine or natural products can even strengthen the survival signaling pathways such as mTOR or Akt pathways.

In addition to their direct effects on neurons, there are many herbal medicine or natural products that can modulate body immune responses. For example, polysaccharides fraction from *Prunella vulgaris* L. can modulate innate immune responses of macrophages [8, 9]. It has been increasingly aware that activation of body (systemic) immune responses are the origin of our sickness responses leading to low appetites and even fever [38]. Long-term effects of systemic immune responses can even result in psychological depression or acute delirium [39]. Experimentally, we have shown that infection in the body or immune responses triggered by surgery (laparotomy) can modulate cognitive functions because of stimulation of neuroimmune responses [40, 41]. Therefore, modulation of body immunity can be a powerful method to minimize neuroimmune responses and then reduce cognitive dysfunctions.

3. Aerobic and resistance exercises

As emphasized above, the advantages of herbal medicine and natural products are their multiples and wide array effects. Similarly, exercise is another method to achieve this goal. Exercise can stimulate production of different trophic/growth factors, e.g., vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), insulin-like growth factor-1 (IGF-1), peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α)/neuronal fibronectin type III domain-containing protein 5 (FNDC5). Some trophic factors can be secreted by muscles or liver, which is collectively called myokines. It has been shown that muscle cells can produce PGC-1α, irisin, cathepsin B, myostatin (growth differentiation factor 8), fibroblast growth factor 21 (FGF-21), IL-6, IL-15, myonectin, and SPARC (osteonectin) as novel brain-beneficial myokines [10, 42]. Some of them, such as FGF21, can also be secreted by the liver or even in the brain upon exercise [43]. They all can affect muscle, liver, adipose tissues, and brain cells, leading to preservation of cognitive functions, modulating the lipid metabolism, and immune responses [44]. This kind of myokine can pass through the blood-brain barrier.

For motor-healthy subject, aerobic exercise is beneficial to majority of people. As discussed above, myokines can be induced so that they provide neuroprotective effects to the brain and attenuate any systemic immune responses. While aerobic exercise is known to be good, a great number of elderly and demented patients could not enjoy the benefit of aerobic exercise. Those patients may have prior knee replacement or fall down hurting the legs. They may be lying down on the bed. No matter how we advocate the beneficial effects of aerobic exercise, this will not be beneficial to this group of patients. Does it mean that they will not have any beneficial effects of exercise? This question leads us to investigate the beneficial effects of resistance exercise.

In a systematic review, aerobic exercise shows beneficial effects on cognitive functions and executive functions, which is better than that from resistance exercise [45]. Furthermore, aerobic exercise seems to elicit strong anti-inflammatory effect than that of resistance exercise [46]. However, resistance exercise seems to particularly increase the volume of hippocampus [47]. A study in laboratory animal

has shown that aerobic exercise can markedly increase BDNF; whereas, resistance exercise can significantly increase IGF-1 [48]. Although resistance exercise may have some limitations, this is still a good choice for those elderly and dementia patients to have this form of exercise. IGF-1 can still elicit multiple functions in the brain to preserve neurons.

4. Concluding remarks

Since this is an introductory chapter, we do not intend to discuss every single method of neuroprotection in detail. We should keep in mind that neurodegenerative diseases are multiple-hit processes. Therefore, no single biological target can afford all neuroprotective needs. Approaches in using herbal medicine and natural products remind us that multiple biological targets may be the way to exert effective neuroprotection. Therefore, any non-pharmacological approaches including exercise and even the new stem cell approaches exert multiple effects. This can be the way for our effective neuroprotective strategies.

Author details

Raymond Chuen-Chung Chang[1,2*] and Yuen-Shan Ho[3]

1 Laboratory of Neurodegenerative Diseases, LKS Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR

2 State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Pokfulam, Hong Kong SAR

3 Faculty of Health and Social Sciences, School of Nursing, The Hong Kong Polytechnic University, Kowloon, Hong Kong SAR

*Address all correspondence to: rccchang@hku.hk

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