Review

Brief comparison of the mechanism of modern medicine and traditional medicine in neuronal cell death

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ABSTRACT

Medicine has a past, a present, and will have a future; the same can be said for many diseases. Even with the surprising development of modern medicine, traditional medicine, especially eastern Asian traditional medicines still exist and are widely used in those regions. But modern medicine and western pacific traditional medicines have different theories and applications for the same disease. In this review, traditional medical theory, used together with modern medicine, can be combined to shed light on the area of neuronal death.

Keywords traditional medicine, neuronal cell death, excitotoxicity, p53, tonifying qi, tonifying kidney

INTRODUCTION

Neuronal diseases have existed for a long time and include tremors, strokes, unconscious states and depression. In the last century, modern medicine has developed surprisingly in terms of treatments. In addition, the developments in medicine have led to many more discoveries of diseases. As advanced diagnosis and diagnostic tools are more accurate, medicine can reveal distinct diseases. Even with these advances and developments, many questions remain unanswered regarding human beings, how many of these diseases occur, and how to treat them. Neuronal death, especially in central nervous system (CNS) associated diseases, exacts heavy health and social tolls. Major diseases of neuronal death result from accidents such as traumatic brain injury (TBI) and stroke (or apoplexy), or chronic neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD). Many studies have been undertaken about them, but it is hard to prevent and predict occurring times and difficult to control the diseases once they have occurred. One of reason is CNS is not fully understand although many of studies have been done.

In eastern Asia traditional medicine, it is hard to specifically explain the medical theory. The major reason is that most core medical terms used to explain medical theory come from philosophy. In addition, many of meanings are compressed in a word and a character. For this reason, traditional medicine is able to give the same cure strategy and to give the many of alternative treatments for the same patient. These are the reasons that to the outsider, in terms of not being an eastern Asia traditional medicine practioner, traditional medicine seems unscientific. Nevertheless, traditional medicine can be effective. In the last century, the sudden change of traditional values has meant the losing of the proper value of traditional medicine. In the following manuscript, there will be a brief description of modern and traditional medicine related to neuronal death.

Neuronal death
Neuronal death is divided largely two parts: accidentally occurring neuronal death and chronically progressing neuronal death. The accidentally occurring neuronal death such as TBI by car accident or hemorrhage and is a hard to control neuronal death at the occurring time. When occurring, mainly the physical stress and damage induce neuronal cell death immediately. The chronically progressing neuronal death such as PD or debris from TBI induced secondary cell death is the target of medical care to control or delay progressive neuronal cell death (Zhang et al., 2005).

Excitatory neuronal transmitter - Glutamate-NMDA
Glutamate is a major excitatory neurotransmitter in CNS and its receptors are classified as ionotrophic receptor (iGluR) and metabotrophic receptor (mGluR). iGluR plays a role by the entrance of Na^+ and Ca^{2+}, divided subtype N-methyl-D-aspartate (NMDA) receptor (NR), α-amino-3hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor and kainate receptor; mGluR plays a role as the second messengers coupled with G-proteins, divided group I mediated 1,4,5-inositol three phosphate (PIP_2)/diacylglycerol (DAG) linked with phospholipase C (PLC) and group II and III mediated cyclic adenisine mono phosphate (cAMP) linked adenylate cyclase. Glutamate receptors play a crucial role in the physiological condition, but do the same as the pathological condition, called "excitotoxicity" (Verkhratsky and Kirchhoff, 2007).

Excitotoxicity is usually observed in ischemic damage. Ischemic damage is able to occur where blood circulation and reperfusion damage usually follow an ischemia and are called ischemia/reperfusion (I/R) damage. Especially, I/R damage in CNS is considered to be serious because once the damage has occurred, it is irreversible, rarely reparable and the function of the lesion is irreplaceable. When the ischemic attacks, reduces or blocks blood circulation, then ATP runs out and the neuronal membrane is depolarized and glutamate is released from the excitatory neuron. This glutamate activates glutamate receptors, especially enhanced Ca^{2+} influx to cytosol through a NMDA

receptor and it results in mitochondrial dysfunction and excessive nitric oxide synthase, NO expressions and reactive oxygen species (ROS) that are induced by NO. In this time, blood reperfusion and normal O_2 supplement lead to excessive NO production and ROS by NO. Finally, Ca^{2+} overload and excessive ROS leads to neuronal death (Gunasekar et al., 1995; Nicholls and Attwell, 1990; Simon et al., 1984; Tong et al., 1995). This NMDA induced neuronal death appears in a secondary neuronal death such as traumatic brain injury. After the physical damage, lesions occurring necrosis at the time, and necrosis takes out the inner cell components, and they lead to inflammation mediated or direct NMDA receptor stimulated neuronal death. Also, the chronic neuronal diseases are mediated NMDA receptors such as PD or AD (Kleen and Holmes, 2010; Wennersten et al., 2003).

p53 and neuronal death

Since discovery of the p53 gene that suppressed tumorigenesis, this nuclear phosphoprotein functions as a key regulator of cell cycle progression and apoptosis. Also, it is believed that p53 responds properly when DNA was damaged, whether it is reparable or not (Smith and Kumar, 2010). Loss or inactivation, such as with the mutation of the p53 tumor suppressor gene, occurs in about half of all human tumors (Greenblatt et al., 1994) and is at a higher risk for developing variants tumors (Malkin et al., 1990; Srivastava et al., 1990). The p53 protein is upregulated by variants' cellular stresses, such as DNA damage, hypoxia, oxidative stress, ribonucleotide depletion and oncogene activations (Giaccia and Kastan, 1998; Ko and Prives, 1996). The effects of p53 are apoptosis mediated by p53-upregulated modulator of apoptosis (PUMA), and cell protection through the arrest of the cell cycle by cyclin-dependant kinase (CDK) inhibitor p21 activation. Especially, a strong p21 mediated cell cycle arrest is called senescence (Vousden and Prives, 2009). Up-regulation of p53 is a phosphorylated different site that damage-defendant dependant manner, it decides the fate of cell apoptosis or survival including senescence.

The absence of p53 has been shown to have neuroprotective effects in vivo from a wide variety of toxic matters including focal ischemia (Crumrine et al, 1994), ionizing radiation (Herzog et al., 1998; Wood and Youle, 1995), MPTP-induced neurotoxicity, methamphetamine- induced neurotoxicity (Trimmer et al., 1996) and adrenalectomy (Hirata and Cadet, 1997). p53 is also essential for developmental neuronal death (Aloyz et al., 1998). The generally occurring developmental cell death of sympathetic neurons is dramatically reduced in p53 -/- and even in p53 +/- animals. Cultured neurons with both p53 -/- and p53 +/- exert protective effects on toxins that include DNA damaging agents (Anderson and Tolkovsky, 1999; Araki et al., 1998; Chen et al., 1999; Enokido et al., 1996A; Enokido et al., 1996A; Xiang et al., 1998), ionizing radiation (Enokido et al., 1996B; Johnson et al., 1998), glutamate (Urberti et al., 1998; Chen and Chuang, 1999; Xiang et al., 1996), hypoxia (Banasiak and Haddad, 1998; Halterman et al., 1999), and NGF withdrawal (Aloyz et al., 1998; Vogel and Parada, 1998). In contrast, neurons lacking p53 die when transferred to a low potassium medium (b Enoido 1996A) or postnatal cortical and hippocampal neurons also die after staurosporine exposure in a p53-independent manner (Johnson et al., 1998). But the inhibition or absence of p53 does not mean against all forms of toxic insults. (Kuntz et al., 2000; Wood an Youle, 1995).

As described above, p53 plays a key role in excitotoxic cell death and is now generally recognized, but there are exceptions occasionally. In the seizure model by systemic injection of kainic acid, the expression of p53 is a well defined excitotoxic cell death pattern and there is evidence of damaged neurons

(Sakhi et al., 1994; Sakhi et al., 1996). Also, p53 KO mice demonstrated that p53 induction was co-related to excitotoxic neuronal death (Morrison et al., 1996). But Schauwecker and Steward (1997) suggested that less damage in the p53-deficient mice might be due to the relative presence of a protective gene(s) in the C57BL/6 mice strain of the p53 deficient mouse line (Donehower et al., 1992). They reported that the wild type C57BL/6 mice did not show evidence of neuronal damage in the CA3 or CA1 subregion (Schauwecker and Steward, 1997). In addition, another independent p53-deficient mouse line did not show a protective effect against excitotoxic neuronal death in the kainate induced seizure model (Lowe et al., 1993). C57BL/6 mice are known to be less sensitive to kainate-induced seizures (Engstrom and Woodbury, 1988; Ferraro et al., 1995) and seizure induced damage (Royle et al., 1999), and it is reported there is a significant induction of neuronal damage in the CA3 and CA1 of the hippocampus in C57BL/6 mice in kainite induced seizures (Hu et al., 1998; Hertel et al., 2000). Thus, p53 is one of major factor in excctotoxic neuronal death but some p53 independent excitotoxic pathways could exist. For greater details, it is recommended to read about p53 and neuronal cell death in the review of Morrison and Kinosihta (2000).

p53 inhibitor, potential protective drug for exctotoxicity induced neuronal death

Excitotoxicity in the brain has a well known mechanism for how to diminish damage or lesions. However, the proper drug does still not exist so that excitotoxicity is induced by internal neurotransmitter that it is too dangerous to block excitatory neuronal signals. If the excitation blockage is not enough, it does not prevent damage. Or fully blockages will cause heart arrest or eternal neuronal depression.

The hint of preventing or attenuating damage from excitotoxicity is in the ion. The NMDA receptor and voltage activated Ca^{2+} channel (VACC) are major Ca^{2+} supplements from the extracellular matrix and related to excitotoxicity. Magnesium ions play the cap of the NMDA receptor in normal conditions. Indeed, the administration of magnesium has been shown to have neuroprotective effects and significantly reduce p53 mRNA in an experimental traumatic brain injury model (Muir et al., 1999). It is reported that lipophilic dihydropyridine VACC blockers, which can cross over the brain-blood-barrier, are about 30% decreased in PD compared with other Ca^{2+} channel blockers in Denmark (Ritz et al., 2010), and Ca^{2+} passed by the L-type Ca^{2+} channel plays a critical role in selective dopaminergic neural death in substnatia nigra pas compacta (SNpc) (Mosharov et al, 2009). But ion control is hard and dangerous. Endothelial nitric oxide synthase (eNOS) expression is beneficial to AD but eNOS expression related to Ca^{2+} channel (Lange-Asschenfeldt, 2008), and Ca^{2+} channel blockage inhibits ischemic damage induced hippocampal dentate gyrus neurogenesis (Luo et al., 2005). In addition, treatment of the ion channel blocker must be done carefully because the same ion channel may have different roles in other tissues, and adverse effects may be critical in terms of the effects on the whole excitatory tissue, like heart arrest.

Accordingly, it is natural to be concerned with the blockage of p53 signaling and inhibition rather than the blockage of excitatory receptors and finding the reliable excitatory receptor blocker. Especially, excitatory amino acids or their receptor agonists have been strongly associated with p53 accumulation. This means p53 inhibition might be a good choice of method for reducing excitotoxicity induced cell death. Treatment of hyperthermia diminishes apoptosis and p53 expression, and p53 induced apoptotic proteins in I/R ischemia that induced neuronal death (Eberspächer et al., 2003; Eberspächer et al., 2005). Also, there is the case of pifithrin-α, which is a p53 and

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DNA binding inhibitor and inhibits cerebral ischemia (Leker et al., 2004). It not only inhibits the cerebral ischemia but also attenuates myocardiac infarction (Liu et al., 2006) and renal ischemic apoptosis (Dagher, 2004). It is reported that myocyte apoptosis in the myocardial infarction and p53 had no relation (Bialick et al., 1997), but p53 did not affect myocyte apoptosis during infarction conditions, nor the p53 inhibitor pifithrin-α attenuate myocardial infarction after apoptosis. Except for exctitotoxicity and p53, a neuroinflammatory mechanism is also suggested. But there have not been enough study cases related to traditional medicine for the purpose of this review, so the subject has been excluded.

Neuronal disease in traditional medicine
Traditional medicine exists in all countries. In this review, traditional medicine is focused eastern Asia traditional medicine. Indeed, there is no exact concept of brain damage, but there is the similar concept called brain deficiency in traditional medicine. In traditional medicine, the brain and spinal cord are attached to the kidney, which is different from physiological kidney functions, and qi means life and activity, so it is the most important in life. In a brain deficiency, tonifying qi and the kidney are important to care and recovery, or the elimination of residua from it. But there is no way to measure the activity or regulation of qi and the traditional medical kidney. Fortunately, there are studies about classical herbs and herbal formula for tonifying qi and the kidney.

Radix Ginseng for tonifying qi
Different from the single herb, the herbal formula is difficult to study since it involves such a large number of substances. As a result, many studies have focused on a single herb rather than on a herbal formula. For example, the root of *Panax Ginseng* C.A. MAYER, *Ginseng Radix*, is one of the well-known and well-studied herbs. Also, it is one of the important qi-tonifying herbs. Its range of effects include on CNS, behavior, lipid/carbohydrate metabolism, endocrine system, sexual development, immune, anti-tumor, hematopoietic function, renal disorder, anti-narcotic and application shock, diabetes mellitus, neurological symptoms and mental fatigue. (You-Ping Zhu, 1998)

Focusing on CNS, ginseng or its substances inhibit glutamate receptors including NMDA receptors (Kim et al., 2004; Bao et al., 2005; Lee et al., 2006; Kim et al., 2007; Zhao et al., 2009). Similarly, it is reported that ginseng attenuated NMDA-mediated epileptic discharge damage (Kim and Rhim, 2004), glutamate induced excitatory stress in dopaminergic cells (Radad et al., 2004), and alcohol induced neuronal death and memory impairment (Bao et al., 2005). In addition, it has improved morphine induced learning impairment (Qi et al., 2009) and age-induced memory impairment (Gu et al., 2009). In general, compensational neurogenesis is usually activated in a brain damage lesion dependant manner (Zhang et al., 2005), and it is reported that ginseng attenuated focal ischemia induced lesions and an increase of compensational neurogenesis (Ye et al., 2011; Zheng et al., 2011). It has an exerted protective effect in the MPTP and MPP$^+$ induced PD models (Van Kampen et al., 2003), especially ginsenoside Rb1 suppressed MPTP and rotenone induced dopaminergic cell death by its anti-oxidative effect (Chen et al., 2005; Leung et al., 2007). Likewise, ginsenoside Rb1 reduced 6-OHDA and MPP+ induced iron uptake in MES23.5 cells (Xu et al., 2010A; Xu et al., 2010B). Ginseng saponins also inhibit the L-type Ca^{2+} voltage activated Ca^{2+} channel (L-VACC), which is one of major factors for selective dopaminergic cell death in SNpc (Mosharov et al., 2009) induced rat cortical neurons (Kim et al., 2008). Youdim (2008) reviewed that iron ion deficiency and excess can cause neurodegenerative diseases like AD and PD.

In AD, ginsenoside Rb1 attenuated Aβ(1-42) and tau phosphorylation induced neurotoxicity in cortical neuron cultures (Zhao et al., 2011) and neuroinflammation in rats (Wang et al., 2011). The acidic polysaccharide of ginseng decreased gamma radiation induced p53 and Bax expressions and increased Bcl2 expression (Park et al., 2011); the ethanol extract of ginseng has a much stronger anti-cancer effect via normal water extract regulation of ERK-p53 and NF-κB in mouse Lewis lung carcinoma (Wong et al., 2010). All of these cases taken together, ginseng have attenuation of excitotoxicity induced by glutamate or NMDA, L-VACC blockage, anti-oxidative effect, and p53 and Bax suppression and enhancing Bcl-2 family.

Liuwei Dihuang wan for tonifying the kidney
Liuwei Dihuang wan (LWDH), one of the most famous Chinese traditional medicines, is widely used in eastern Asia and it consists of *Rehmanniae Radix*, *Dioscorae Radix*, *Corni fructus*, *Alimatis Rhizoma*, *Paeoniae suffruticosa Cortex*, and *Poria*. It used for kidney deficiency, and kidney functions are the control of bone, fluid, reproduction, and CNS. It has many derivative varieties by adding a few herbs and sometimes called by another name, espeacally sheqi wan, which is called by adding *Schisandrae fructus*, or *Aconiti Tuber* and *Cinnamomi Cortex,* or all three of them with LWDH. In China, there are hundreds of medicinal manufacturers which produce Liuwei Dihuang Pills based on LWDH, and its derivative varieties, such as Zhibai Dihuang Pills, Guifu Dihuang Pills, Mingmu Dihuang Pills, Qiju Dihuang Pills, Maiwei Dihuang Pills, and Guishao Dihuang Pills. (Xue et al., 2005; Zhao et al., 2007). However, there are few studies that have compared them to each other in English. Also, the above described LWDH and its variants using shenqi wan also are called the abbreviated LWDH.

Protective effects against cell death of LWDH are femoral head necrosis and/or apoptosis (Li et al., 2010; Liu et al., 2010) and H_2O_2 induced hippocampal neuron apoptosis (Shin et al., 2003). Also, it is reported that the up-regulation of Bcl-2 mRNA and down-regulation of Bax mRNA in OLEF rat pancreas (Xue et al., 2005). LWDH improved scopolamine and p-chloroamphetamine -induced amnesia induced amnesia (Hsieh et al., 2003). In a senescence accelerated mouse hippocampus, LWDH might facilitate cognition by genes' expressions (Chang et al., 2007). But H_2O_2 induced DNA damage was suppressed by a single treatment of herbs that are components of LWDH, but LWDH as a herbal formula was not successful (Szeto et al., 2009). Also, Yang et al. (2006) reported that LWDH suppressed K^+ and Ca^{2+} ion currents in cultured rat hippocampal neurons, and Shin et al. (2003) reported that shenqi wan diminished glutamate and NMDA receptor induced ion currents.

Though these are the effects of LWDH, each of the component herbs is rarely studied. Interestingly, *Corni Fructus* has shown pro-apoptotic effect and up-regulation p53 in A549 lung cancer cell line (Choi et al., 2011). As described above, p53 up-regulation means there is vulnerability for damage in neuronal cells (Yonekura et al., 2006). Consequently, kidney tonifying herbal formula LWDH results in a decrease of Ca^{2+} ions and anti-apoptosis mediated by the Bcl family. It might be the same in neuronal death and might have a neuroprotective effect.

CONCLUSION

In traditional medical theory, as shown in the description above, there is no concept of neuronal cell death. The important thing is tonifying qi and the kidney when there is a brain deficiency

which is a similar concept to neuronal cell death. The major herb of tonifying qi and major kidney tonifying herbal formulas, ginseng and LWDH, help to improve learning and memory, protect the body from NMDA induced excitotoxicity and p53 mediated neuronal cell death. In the past, traditional medicine standard treatment was decided based on many of the cases of neuronal death associated disease treatment with a variety of herbs or herbal formula, and in the end tonifying qi or the kidney was effective: the same as it is at present. Indeed, there are different application fields for ginseng and LWDH, but there are some overlapped in neuronal cell death fields. In other words, ginseng and LWDH usage are different, but there is a similar effect exerted on neurontal cell death.

In the neuroprotective effect, ginseng and LWDH have almost the same mechanism for mediated exertion. But most of the references are just shown and suggest what the main substance is, what the effect is, where it exists, when it acts, and its mechanism. The question needed to ask is why we divide and analysis materials. It is able to translate that ginseng and LWDH have neuroprotective from exctitoxicity, anti-apoptotic and anti-oxidative effect to that tonifying qi or kidney is involved neuroprotective from exctitoxicity, anti-apoptotic and anti-oxidative effect in neuronal cell death associated disease. However, the similar effects of ginseng and LWDH on neuronal cell death did not divide what is qi and what is kidney in this review, but this will occur when sufficient references are gathered. Research in traditional medicine may be important not only in the study of traditional medicine material but also in gathering studies and applying traditional medicine, and it would be one of the methods to understand the practices of traditional medicine.

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CONFLICT OF INTEREST

The authors have no conflicting financial interests.

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