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REVIEW ARTICLE

Neuroprotective Role of Agmatine in Neurological Diseases

Weilin Xu[a,#], Liansheng Gao[a,#], Tao Li[a,#], Anwen Shao[a,*] and Jianmin Zhang[a,b,c,*]

[a]*Department of Neurosurgery, Second Affiliated Hospital, School of Medicine, Zhejiang University, Hangzhou, Zhejiang, P.R. China;* [b]*Brain Research Institute, Zhejiang University, Hangzhou, Zhejiang, P.R. China;* [c]*Collaborative Innovation Center for Brain Science, Zhejiang University, Hangzhou, Zhejiang, P.R. China*

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Abstract: ***Background*:** Neurological diseases have always been one of the leading cause of mobility and mortality world-widely. However, it is still lacking efficient agents. Agmatine, an endogenous polyamine, exerts its diverse biological characteristics and therapeutic potential in varied aspects.

***Methods*:** This review would focus on the neuroprotective actions of agmatine and its potential mechanisms in the setting of neurological diseases.

***Results*:** Numerous studies had demonstrated the neuroprotective effect of agmatine in varied types of neurological diseases, including acute attack (stroke and trauma brain injury) and chronic neurodegenerative diseases (Parkinson's disease, Alzheimer's disease). The potential mechanism of agmatine induced neuroprotection includes anti-oxidation, anti-apoptosis, anti-inflammation, brain blood barrier (BBB) protection and brain edema prevention.

***Conclusions*:** The safety and low incidence of adverse effects indicate the vast potential therapeutic value of agmatine in the treatment of neurological diseases. However, most of the available studies relate to the agmatine are conducted in experimental models, more clinical trials are needed before the agmatine could be extensively clinically used.

Keywords: Agmatine, neuroprotective effect, neurological diseases, mechanism, stroke, chronic neurodegenerative diseases.

1. INTRODUCTION

Neurological diseases have always been one of the leading causes of mobility and mortality worldwide. It can be divided into two typical classes: acute attack (stroke, trauma brain injury *et al*.) and chronic neurodegenerative diseases (Parkinson's disease, Alzheimer's disease, Huntington's disease *et al*.) [1].

The pathological mechanism in the process of neurological diseases and neuroprotective effects of various drugs have been comprehensively studied throughout these years, which consist of cellular apoptosis, inflammation, oxidative stress, brain edema and so on [2, 3]. Agmatine, a polyamine exerting its effects in cellular apoptosis, inflammation, oxidative stress and brain edema, has been demonstrated to be neuroprotective in many neurological diseases [4, 5] (Fig. **1**).

*Address correspondence to these authors at the Department of Neurosurgery, Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Rd, Hangzhou, Zhejiang 310009, P.R. China; Tel: +8613805722695; E-mails: zhangjianmin2016@163.com, zjm135@vip.sina.com and Department of Neurosurgery, Second Affiliated Hospital, School of Medicine, Zhejiang University, 88 Jiefang Rd, Hangzhou, Zhejiang 310009, P.R. China; Tel: +8613867409215; E-mail: anwenshao@sina.com

[#]These Authors contributed equally

Agmatine has been discovered for over 100 years. Nobel Laureate Albrecht Kossel first reported it in 1910 [6], and he found that it was ubiquitously synthesized in the bacteria and plants [4, 7]. It was formed by decarboxylation of L-arginine generating from arginine decarboxylase, and hydrolyzed to putrescine and urea by agmatine [8, 9]. The chemical structure of agmatine was displayed in Fig. (**2**).

However, the research of Agmatine reached little progress during the 20th century due to lack of understanding of the enzyme arginine decarboxylase (ADC), which could synthesize agmatine from arginine [7]. The breakthrough was not made until 1994 that agmatine and ADC were finally found in the mammalian brain by Reis and colleagues [10]. Ensuing numerous studies focused on the physiological and pharmacological effects of agmatine on mammals. It was reported that agmatine displays protection in many organ diseases, including cardio-protection, nephro-protection, gastro-protection, neuro-protection and gluco-protection [11]. For example, agmatine had been reported to reduce heart rate and blood pressure by activating central and peripheral control systems through the regulation of imidazoline receptors subtypes, norepinephrine release and NO production [12], and could also improve the hemodynamic recovery of cardiac ischemia or restore blood pressure [13].

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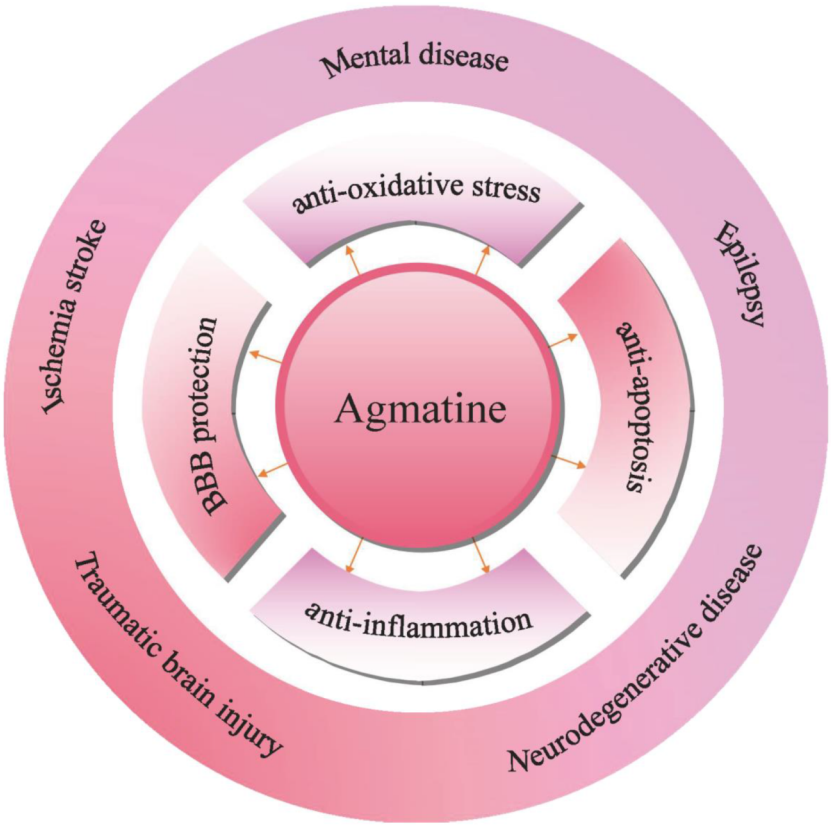

Fig. (1). Overview of the neuroprotective effects of agmatine.

In an experimental research, Lortie, M.J. *et al.* found that agmatine can improve the glomerular filtration rate (GFR) by induction of endothelial NO synthase (eNOS) [14]. Referring to the cytoprotective mechanisms, agmatine was believed to attenuate renal disease [15].

In the past decades, numerous studies have explored the potential mechanisms of neurological diseases and neuroprotective effects of various drugs. But the adverse effects of some drugs posed great limitation to further clinical trials. Interestingly, agmatine was found to ubiquitously exist naturally in plants, animals, and some other foodstuff. The sulfate salt containing agmatine had been used as a dietary ingredient many years ago and now is available as a nutraceutical [16]. Gilad and his colleagues assessed long-term safety of oral agmatine treatment by consuming a daily high dosage

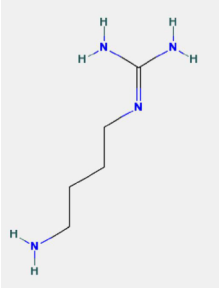

Fig. (2). Chemical structure of agmatine (Tayfun I. Uzbay *et al.*, 2012.).

of oral agmatine over a period of 4-5 years. All measurements remained within normal values and no discomfort was observed during the follow-up period [17]. Moreover, the neuroprotective effect of agmatine has been demonstrated by extensive studies since 1994. The low incidence of adverse effects and vast therapeutic value has earned great attention.

In 1995, Gilad, *et al.* firstly reported the neuroprotective action of agmatine [18]. Henceforward, more and more studies showed neuroprotection of agmatine in stroke, traumatic brain injuries, neurodegenerative disorders, neuropathic pain, epilepsy, and even in mental disorders. Anti-oxidation, anti-apoptosis, anti-inflammation, brain blood barrier (BBB) protection and brain edema prevention are the common mechanisms involved in the neuroprotective effects. This review would focus on the neuroprotective actions of agmatine and its potential mechanisms in the setting of neurological diseases.

2. THE NEUROPROTECTIVE EFFECTS OF AGMATINE IN NEUROLOGICAL DISEASES

2.1. The Effect of Agmatine in Ischemic Stroke

Stroke has been the second most common disease to cause death and disability in adults around the world [19]. Ischemic stroke, which accounts for about 87% of cases, is the most common subtype of stroke [20]. Ischemic stroke is the result of insufficient blood and oxygen supply to the brain. The cell in central portion of the ischemic tissue, known as infarct core, is afflicted with irreversible damage

and the area around the infarct core, called penumbra, is at risk of infarction and can be reverted [21].

Previous studies have proved that the occurrence of stroke promoted the expression of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), which could destroy the structure of BBB, leading to brain edema [22]. In addition, the disruption of neuro-inflammatory or oxidative stress balance could produce excessive inflammatory cytokines, reactive oxygen species (ROS) and free radicals, which initiate cell death ultimately [23, 24].

Numerous experimental researches, most of which focused on the salvation of the tissue in the penumbra, had been carried out to explore the optimal neuroprotective drugs for cerebral ischemia [25, 26]. But the severe side-effects of these drugs posed great limitation on further clinical trials. In contrast, agmatine displayed its safety in both experimental and clinical trials. The sulfate salt of agmatine had been used as a dietary ingredient many years ago and now is available as a nutraceutical [16, 27]. Besides, many studies confirmed the neuroprotective role of agmatine in strokes [28].

Kim *et al*. [4] showed the neuroprotective effects of agmatine both *in vivo* and *in vitro* through the mechanism of reducing the production of nitric oxide (NO) by competitively inhibiting nNOS and iNOS. Meanwhile, agmatine can also activate eNOS (nitric oxide synthase) in endothelial cells, and thus increase the production of NO, which acts as a vasodilator to increase the blood flow in the ischemic areas [29, 30]. Feng *et al.* [31] reported that both endogenous and exogenous agmatine can exert their functions on the NOS and reduce hypoxic-ischemic brain injury in neonatal rats. Besides, many other studies verified the effects of agmatine on the three kinds of NOS mentioned above in the setting of cerebral ischemia [11].

Brain blood barrier (BBB) is extremely important in maintaining homeostasis and microvascular integrity [5]. However, the cerebral ischemic attack could induce upregulation of matrix metalloproteinase-2 (MMP-2) and matrix metalloproteinase-9 (MMP-9), which could destroy the integrity of BBB. Hyun *et al*. and Yang *et al*. both demonstrated that exogenous agmatine could inhibit the expression of MMP-2 and MMP-9 by induction of eNOS *in vitro* [32, 33]. Moreover, Hyun and his colleagues utilized retrovirus to induce the endogenous agmatine, and their findings suggested that endogenous agmatine could reduce the MMP-2 and MMP-9 expression by regulation of eNOS, NO and activation of transcription factor 3(ATF3) [33]. In addition to detecting MMP-2 and MMP-9, Ahn and his colleagues took advantage of dynamic contrast-enhanced MR imaging to evaluate the beneficial effects of agmatine on BBB stabilization [34].

Brain edema frequently was observed to be involved in the worsening process of cerebral ischemia and contributed to increasing mortality after attack of stroke. Jae and his colleagues explored the mechanism of brain edema and the effects of agmatine. Their findings suggested that the BBB disruption and the upregulation of aquaporins-1 and -9 (AQPs) were well correlated with brain edema, and these disadvantages can be significantly attenuated by agmatine treatment [35]. Besides, some other studies revealed the effects of agmatine on reducing the expression of AQP-4 and thus attenuated the brain edema as well [36-38].

Additionally, studies also showed that agmatine contributed to reducing the apoptosis of neuron and cerebral astrogliosis after cerebral ischemia in a rat model [36]. Jeong *et al*. found anti-inflammatory character of agmatine in diabetic middle cerebral artery obstruction (MCAO) rats by decreasing the expression of high-mobility group box 1, RAGE, toll-like receptor(TLR)-2,4 [38].

Overall, the agmatine exerted its neuroprotective effect on ischemic stroke both in *in vivo* and *in vitro* experimental models.

2.2. The Effect of Agmatine in Traumatic Brain Injury

Traumatic brain injury (TBI) is a condition of emergency and ranks second to conventional stroke in causing death and disability, which place tremendous burden on the family and society [39]. It can be divided into primary injury and secondary injury [40]. A series of pathophysiological changes are involved in the progress of TBI, which include brain edema, cellular apoptosis, BBB disruption, inflammation and so on [41-43]. However, there were no ideal therapeutic drugs for the patients suffering from TBI so far. Recently, many studies verified the beneficial effects of agmatine in TBI. In 1996, Gad and his colleagues explored the neuroprotective effects of agmatine in rodent brain injury [44]. Previous researches reported that excessive accumulation of glutamate or NO could lead to cellular ischemia and neurotoxicity [29, 45, 46]. In a rat model of fluid percussion brain injury, Jinn *et al*. found that agmatine could reduce excessive glutamate and NO, and attenuated TBI resultantly. Furthermore, they also demonstrated that FPI-induced intracranial hypertension, cerebral hypotension, cerebral infarction, motor and proprioception deficits and body weight loss could all be alleviated by agmatine [47]. In 2010, Jinn and his colleagues conducted a series of experiments on the neuroprotective effects of agmatine, and found that agmatine could improve the outcome of TBI in rats by attenuating neuronal and glial apoptosis, inhibiting gliosis, promoting angiogenesis and neurogenesis [48]. In addition, Jae and his colleagues found that agmatine could reduce brain edema by suppressing the expression of AQP1, 4 and 9. Besides, they also found that agmatine could inhibit cellular apoptosis by inhibiting the phosphorylation of MAPKs and increasing the nuclear translocation of NF-κB after TBI [49]. In addition, agmatine had also been proved to play neuroprotective role in rat spinal cord model. It could significantly restore the locomotor function and reduce tissue damage by blocking the NMDA receptor and NOS [50].

2.3. The Effect of Agmatine in Neurodegenerative Diseases

2.3.1. Effects of Agmatine in Parkinson's Disease

Parkinson's disease (PD), commonly presented as motor dysfunction, is one of the most common neurodegenerative diseases in the aged [51]. It was reported that the degeneration of dopaminergic neurons in the substantia nigra pars,

which leads to motor dysfunction, is the on-off step in the progression of PD. Recently, many studies showed that glutamatergic neurotransmission also contributed greatly to the pathogenesis of PD [4, 52, 53].

Excitatory amino acids were assumed to have neurotoxicity and aggravate the condition of patients with PD [4]. NMDA is the receptor of excitatory amino acid, and its antagonists like memantine, amantadine and agmatine were extensively proved to ameliorate motor function of PD patients [5, 54, 55].

In the experimental model of PD induced by rotenone, agmatine could significantly decrease the level of oxidative stress in SH-SY5Y cells. Besides, agmatine could also reduce the cellular apoptosis induced by rotenone [56]. In addition, a recent *in vitro* study demonstrated that agmatine could prevent redox reaction and cellular injury [57].

Gilad and his colleagues developed a new mouse PD model by intranasal administration of 1-methyl-4-phenyl-4-1,2,3,6-tetrahydropyridine (MPTP), and found that agmatine could provide a partial (31%) protection of PD induced by MPTP [5]. Matheus and his colleagues delivered agmatine to a group of aged mice before the treatment with MPTP. Their results demonstrated that agmatine could prevent the occurrence of motor, cognitive and neurological impairments induced by MPTP [58].

2.3.2. Effects of Agmatine in Alzheimer's Disease

Alzheimer's disease (AD), commonly accompanied with progressive cognitive dysfunction, is also one of the most common neurodegenerative diseases in the aged. Its pathological hallmarks are extracellular deposition of amyloid-beta peptide, and presence of neurofibrillary tangles in the neuron [59] which are mainly distributed in the hippocampus, cerebral cortex and basal ganglia [60, 61]. Currently, the accumulation of amyloid-beta peptide, abnormal phosphorylation of Tau peptide, oxidative stress and radical injury has been recognized as the main pathophysiologic mechanism of AD [62, 63]. Agmatine showed its neuroprotective role in oxidative stress, radical injury and other pathological process. For example, Baranov *et al*. revealed that agmatine could exert its anti-oxidative effect by activating many kinds of antioxidants including glutathione [64]. Besides, agmatine could decrease the level of free radical and inhibit the accumulation of amyloid-beta peptide [65].

N-methyl-D-aspartate (NMDA) is the receptor of the excitatory amino acid and its dysfunction can lead to the apoptosis of neuron [4]. It was reported that the level of endogenous agmatine rose sharply on the setting of brain injury [47], and exerted its neuroprotective effect by competitively inhibiting the NMDA receptor and activity of excitatory amino acid [24]. In the AD patients, accumulation of amyloid-beta peptide in neuron increased the level of excitatory amino acid, which then produced neurotoxicity. Agmatine was reported to postpone apoptosis of neuron by inhibiting the neurotoxicity of excitatory amino acids [66]. Except for its effect on neurotoxicity, amyloid-beta peptide could also down-regulate the insulin receptor which widely exists in the central nervous system. However, retaining the insulin receptor and its ligand is quite important in the treatment of AD [67, 68]. Somang and his colleagues demonstrated that agmatine could promote the secretion of insulin and protect the insulin receptor *via* binding with the imidazoline receptors [67]. This process could then reduce the accumulation of amyloid-beta peptide and inhibit the abnormal phosphorylation of Tau peptide, which ultimately ameliorate the cognition and memory injury of AD patients [69].

2.4. The Effect of Agmatine in other Neurological Diseases

2.4.1. Effects of Agmatine in Epilepsy

Epilepsy is a chronic process characterized by recurrent paroxysmal seizures [70]. Epileptogenesis resulted from synchronization and propagation of excessive excitability, which spread from hyper-excitable neurons and glial cells to the normal non-epileptogenic tissue [71, 72]. The glutamatergic receptors and NMDA receptor were reported to be involved in the initiation of some kinds of epilepsies [73-75]. Besides, epileptic seizures could increase the production of NO, and pre-treatment with NOS inhibitors could give precaution against some types of seizure [76, 77]. As aforementioned, the agmatine could act as an antagonist of NAMD receptor, thus several studies had been carried out to test the neuroprotective effects of agmatine in experiment animals with epilepsies. Their results demonstrated that agmatine could reduce both the incidence and intensity of epilepsy and also exert anticonvulsant effect [78]. Additionally, agmatine could inhibit the activation of NOS and reduce the production of NO. It was reported that both the NOS inhibitor and exogenous agmatine had neuroprotective effects on epilepsy [79, 80]. Except for the anticonvulsant effect, agmatine could also strengthen the anticonvulsant effect of some other drugs, such as phenobarbital, valproate and lithium chloride [81, 82]. Overall, agmatine proved to have neuroprotective effects in epileptic patients.

In the meanwhile, several other studies [83, 84] contradicted this inference, Abe *et al*. reported that agmatine (200-800μM) could induce the release of glutamate, which could lead to neuronal death. Besides, Luszczki and his colleagues also suggested that the synergistic effect of agmatine in anticonvulsant is also uncertain, which meant that further researches of agmatine in epilepsy are needed before it can be extensively clinically used.

2.4.2. Effects of Agmatine in Mental Disorders

Mental disorder is a group of systemic diseases characterized by a variety of physical and mental discomfort, such as depression, anxiety, addiction, schizophrenia and so on [85]. Agmatine has been long-term studied for its neuroprotective effects in mentor diseases. Many studies reported that agmatine exerts its antidepressant-like action by inhibiting the NMDA receptors or interacting with 5-HT1A/1B and 5-HT2 receptors [86-88]. Besides, agmatine could suppress the expression of NOS, NMDA receptors or imidazoline receptors, and alleviate drug addiction induced by opioid, morphine, ethanol or psychostimulants [89, 90]. Additionally, agmatine may have beneficial effects on anxiety, schizophrenia and some other mentor diseases in experimental model [91, 92].

4. NEUROPROTECTIVE PROPERTIES OF AGMATINE IN NEUROLOGICAL DISEASES

The neuroprotective effects of agmatine have been widely studied in various neurological diseases and the mechanism involved in this effect includes anti-oxidation, anti-inflammation, anti-apoptosis, BBB protection and brain edema prevention. The following review will particularly probe into these molecular mechanisms.

4.1. Anti-apoptotic Effects of Agmatine

Apoptosis is one type of cell death characterized by energy dependence and programmed cell death [93]. The term 'apoptosis' was first described by Kerry *et al*. [94]. Apoptosis is of vital importance to normal physiological metabolism, growth and development, keeping hemostasis by scavenging the aging or damaged cells, shaping of organs or regulating immune system by removal of defective and excessive cells [95, 96]. However, uncontrolled apoptosis may result in various pathological processes of different diseases, like cancers, Alzheimer's disease and stroke [97, 98]. El-Sherbeeny *et al*. demonstrated that agmatine could protect rat liver from nicotine-induced damage by inhibiting the production of proapoptotic protein Bax [99]. *In vitro*, Mary and his colleagues identified the anti-apoptotic effects of agmatine to the Ha-Ras-transformed murine NIH-3T3 cell line by reducing the expression of Bax and caspase-3 [100]. In addition, agmatine was also observed to be involved in the modulation of programmed cell death in rats and inhibit the proliferation of human mast cell leukemia cells (HMC-1) and HL-60 cells [101, 102]. Many researches have demonstrated the anti-apoptotic effect of agmatine in various neurological disorders. For example, Kim and his colleagues demonstrated that agmatine could reduce cellular apoptosis in traumatic brain injury of rats by inhibiting phosphorylation of MAPKs and increasing nuclear translocation of NF-kappaB [51]. In addition, Zarifkar reported that inhibition of caspase-3 expression by agmatine could also prevent hippocampal apoptosis and spatial memory impairment induced by lipopolysaccharide (LPS) [103]. Besides, in rat model of Alzheimer's disease, agmatine reduced cellular apoptosis through inhibiting the expression of caspase-3 and Bax, and improved the level of Bcl2, PI3K, Nrf2, and gamma-glutamyl cysteine [69].

Several *in vitro* studies reported the protection of agmatine on the human-derived dopaminergic neuroblastoma cell line (SH-SY5Y). Agmatine exerted its anti-apoptotic effects by increasing the amount of phosphorylated Akt /Akt, inhibiting the GSK-3β activity and decreasing the expression of apoptotic markers, such as caspase 3, Bax and cytochrome c.

Overall, the anti-apoptotic effect of agmatine had been well demonstrated in neurological diseases.

4.2. Anti-inflammatory Effects

Inflammation is a complex immune response of organisms to the injury. Under normal conditions, inflammation could help to scavenge the necrotic cells or tissues, and initiate the tissue repair process [104]. However, excessive activation of immune responses is harmful to the organisms and can cause injury [105]. Agmatine exerted its anti-inflammatory effect in many ways. For example, *in vivo*, Taksande demonstrated that agmatine could attenuate the symptom of arthritis by reducing the level of inflammatory cytokines, like tumor necrosis factor (TNF)-α and interleukins (IL)-6 [106]. Meanwhile, an *in vitro* study showed that agmatine could inhibit the production of pro-inflammatory cytokines, such as IL-6, TNF-α and CCL2, and reduce the cell death [107].

Inflammatory neurodegeneration also plays a key role in the pathogenesis of neurological diseases, including acute diseases (stroke or traumatic injury) and chronic neurodegenerative diseases (AD, PD, or HD) [105]. Sahin showed that agmatine could attenuate sub-chronic stress by down-regulating the gene expression of nod-like receptor protein 3 (NLRP3) inflammasome components (NLRP3, NF-kappaB, PYCARD, caspase-1, IL-1β and IL-18) and reducing the level of pro-inflammatory cytokines. Besides, agmatine could also revert the change of anti-inflammatory cytokines, such as IL-4 and IL-10 [108]. In addition, the anti-inflammatory effect of agmatine was also proved in many other neurological diseases, such as transient brain ischemia, depression, TBI and micro-opioid receptor tolerance, by regulating the expression of inflammatory cytokines [22, 109].

4.3. Anti-oxidant Effects

Oxidative stress, which is mainly caused by overbalance of pro-oxidant/anti-oxidant system in cells, takes part in the pathogenesis of many diseases [110-112]. Various agents including agmatine had been demonstrated to decrease oxidative stress and protect organisms from injury. Iizuka reported that agmatine could protect the retinal ganglion cells (RGCs) from H2O2-induced injury through the alpha 2-adrenergic receptor signaling pathway [113]. Bratislav found that agmatine could exert its anti-oxidative effect by protecting antioxidant defense system and restoring the antioxidant capacity in liver tissue [114]. Besides, several studies had demonstrated the anti-oxidative effect of agmatine in the setting of neurological diseases. Gawali and his colleagues reported that agmatine could ameliorate depressive-like behavior by reducing the oxidative/nitrosative stress evoked by LPS in hippocampus and prefrontal cortex [115], and this effect may be achieved *via* preventing lipid peroxidation and regulating the activity of superoxide dismutase (SOD), glutathione peroxidase (GPx) and glutathione reductase (GR) [116]. In addition, agmatine has also been proved to exert anti-oxidative stress in stroke and TBI by reducing the generation of reactive oxygen species (ROS) and free radicals [11].

4.4. BBB Protection and Brain Edema Prevention

BBB is a continuous, non-fenestrated system which regulates the movement of many particles and cells, such as ion, toxicant and inflammatory cells. Any factors disrupting the BBB would deteriorate the condition of neurological diseases, including stoke, TBI and neurodegenerative diseases [117, 118]. The most common complication of BBB disturbance was the vasogenic brain edema, which was reported to be related to the early expression of matrix metalloprotein-

ases-2,9 after brain injury [119, 120]. Agmatine was reported to have significant effect in inhibiting the expression of matrix metalloproteinases [33]. Therefore, regulation of agmatine on the expression of matrix metalloproteinases may be the potential mechanism of BBB protection and vasogenic brain edema attenuation.

In addition, another type of brain edema that commonly occurs during brain injury is cytotoxic brain edema. One of the most frequent and elaborated mechanisms of cytotoxic edema is the dysfunction of AQP in the brain. The AQP are a group of water channel proteins which regulate the movement of water molecule between plasma membrane. AQP1, 4 and 9 were clearly identified in the brain tissue. AQP1, 4 were reported to be involved in cerebrospinal fluid formation and their dysfunction could also contribute to brain edema [121, 122]. Several studies demonstrated that the mechanism of agmatine in preventing cytotoxic edema is to suppress the expression of aquaporin (AQP)-1, 4, and 9. The changes had been demonstrated in many types of neurological diseases, such as TBI, stroke or degenerative diseases [8, 36, 51].

Although the effect of agmatine in reducing the brain edema had been well demonstrated, its therapeutic effect was doubted by some researchers and more studies should be launched [4, 36, 45].

CONCLUSION AND PERSPECTIVE

Overall, agmatine exerted its neuroprotective effects in various neurological diseases, including acute attack (brain ischemia and trauma brain injury) and chronic neurodegenerative diseases (Parkinson's disease, Alzheimer's disease). The underlying mechanism involved anti-oxidation, anti-apoptosis, anti-inflammation, brain blood barrier (BBB) protection and brain edema prevention. The safety and low incidence of adverse effects indicate the vast potential therapeutic value of agmatine in the treatment of neurological diseases. However, there are still some drawbacks in the research of agmatine. On one hand, minimal studies involved the neuroprotective effect of agmatine reported in some areas, such as brain hemorrhage, or Huntington's disease. In addition, the administration of agmatine was limited in crossing the BBB and its rapid elimination by the kidneys affecting its pharmacological efficacy. Besides, most of the available studies relating to agmatine are conducted in experimental models. More clinical trials are however needed before agmatine could be extensively clinically used.

LIST OF ABBREVIATIONS

AD	=	Alzheimer's disease
ADC	=	Arginine decarboxylase
AQPs	=	Aquaporins
ATF3	=	Transcription factor 3
BBB	=	Brain blood barrier
eNOS	=	Endothelial NO synthase
GFR	=	Glomerular filtration rate
GPx	=	Glutathione peroxidase
GR	=	Glutathione reductase
HMC-1	=	Human mast cell leukemia cells
IL	=	interleukins
MCAO	=	Middle cerebral artery obstruction
MMP-2	=	Matrix metalloproteinase-2
MMP-9	=	Matrix metalloproteinase-9
MPTP	=	1-methyl-4-phenyl-4-1,2,3,6-tetrahydro-pyridine
NMDA	=	N-methyl-D-aspartate
NO	=	Nitric oxide
PD	=	Parkinson's disease
RGCs	=	Retinal ganglion cells
ROS	=	Reactive oxygen species
SOD	=	Superoxide dismutase
TBI	=	Traumatic brain injury
TLR	=	Toll-like receptor
TNF	=	Tumor necrosis factor

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Wu, H.; Niu, H.; Shao, A.; Wu, C.; Brandon, J. Astaxanthin as a potential neuroprotective agent for neurological diseases. *Mar. Drugs,* **2015**, *13*, 5750-5766.

[2] Yi, B.R.; Kim, S.U.; Choi, K.C. Development and application of neural stem cells for treating various human neurological diseases in animal models. *Lab. Anim. Res.,* **2013**, *29*(3), 131-137. [http://dx.doi.org/10.5625/lar.2013.29.3.131] [PMID: 24106507]

[3] Xu, X.H.; Zhong, Z. Disease modeling and drug screening for neurological diseases using human induced pluripotent stem cells. *Acta Pharmacol. Sin.,* **2013**, *34*(6), 755-764. [http://dx.doi.org/10.1038/aps.2013.63] [PMID: 23685955]

[4] Kim, J.H.; Yenari, M.A.; Giffard, R.G.; Cho, S.W.; Park, K.A.; Lee, J.E. Agmatine reduces infarct area in a mouse model of transient focal cerebral ischemia and protects cultured neurons from ischemia-like injury. *Exp. Neurol.,* **2004**, *189*(1), 122-130. [http://dx.doi.org/10.1016/j.expneurol.2004.05.029] [PMID: 15296842]

[5] Gilad, G.M.; Gilad, V.H.; Finberg, J.P.; Rabey, J.M. Neurochemical evidence for agmatine modulation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity. *Neurochem. Res.,* **2005**, *30*(6-7), 713-719. [http://dx.doi.org/10.1007/s11064-005-6865-9] [PMID: 16187208]

[6] Kossel, A. U¨ ber das agmatin. Zeitschr. *Physiol Chem.,* **1910**, *66*, 257-261. [http://dx.doi.org/10.1515/bchm2.1910.66.3.257]

[7] Tabor, C.W.; Tabor, H. Polyamines. *Annu. Rev. Biochem.,* **1984**, *53*, 749-790. [http://dx.doi.org/10.1146/annurev.bi.53.070184.003533] [PMID: 6206782]

[8] Kim, J.H.; Lee, Y.W.; Park, K.A.; Lee, W.T.; Lee, J.E. Agmatine attenuates brain edema through reducing the expression of aquaporin-1 after cerebral ischemia. *J. Cereb. Blood Flow Metab.,* **2010**, *30*(5), 943-949. [http://dx.doi.org/10.1038/jcbfm.2009.260] [PMID: 20029450]

[9] Yang, X.C.; Reis, D.J. Agmatine selectively blocks the N-methyl-D-aspartate subclass of glutamate receptor channels in rat hippocampal neurons. *J. Pharmacol. Exp. Ther.,* **1999**, *288*(2), 544-549. [PMID: 9918557]

[10] Li, G.; Regunathan, S.; Barrow, C.J.; Eshraghi, J.; Cooper, R.; Reis, D.J. Agmatine: an endogenous clonidine-displacing substance in the brain. *Science,* **1994**, *263*(5149), 966-969. [http://dx.doi.org/10.1126/science.7906055] [PMID: 7906055]

[11] John, E;. Piletz,; Feyza, A.; Juei-Tang, C.; Carolyn, A. Fairbanks, V. H.; Gilad, B. H. Agmatine: clinical applications after 100 years in translation. *Drug Discov. Today,* **2010**, *18*(17-18), 880-893.

[12] Raasch, W.; Schäfer, U.; Chun, J.; Dominiak, P. Biological significance of agmatine, an endogenous ligand at imidazoline binding sites. *Br. J. Pharmacol.,* **2001**, *133*(6), 755-780. [http://dx.doi.org/10.1038/sj.bjp.0704153] [PMID: 11454649]

[13] Greenberg, S.; George, J.; Wollman, Y.; Shapira, I.; Laniado, S.; Keren, G. The effect of agmatine administration on ischemic-reperfused isolated rat heart. *J. Cardiovasc. Pharmacol. Ther.,* **2001**, *6*(1), 37-45. [http://dx.doi.org/10.1177/107424840100600105] [PMID: 11452335]

[14] Lortie, M.J.; Novotny, W.F.; Peterson, O.W.; Vallon, V.; Malvey, K.; Mendonca, M.; Satriano, J.; Insel, P.; Thomson, S.C.; Blantz, R.C. Agmatine, a bioactive metabolite of arginine. Production, degradation, and functional effects in the kidney of the rat. *J. Clin. Invest.,* **1996**, *97*(2), 413-420. [http://dx.doi.org/10.1172/JCI118430] [PMID: 8567962]

[15] Satriano, J.; Cunard, R.; Peterson, O.W.; Dousa, T.; Gabbai, F.B.; Blantz, R.C. Effects on kidney filtration rate by agmatine requires activation of ryanodine channels for nitric oxide generation. *Am. J. Physiol. Renal Physiol.,* **2008**, *294*(4), F795-F800. [http://dx.doi.org/10.1152/ajprenal.00392.2007] [PMID: 18199604]

[16] Keynan, O.; Mirovsky, Y.; Dekel, S.; Gilad, V.H.; Gilad, G.M. Safety and efficacy of dietary agmatine sulfate in lumbar disc-associated radiculopathy. An open-label, dose-escalating study followed by a randomized, double-blind, placebo-controlled trial. *Pain Med.,* **2010**, *11*(3), 356-368. [http://dx.doi.org/10.1111/j.1526-4637.2010.00808.x] [PMID: 20447305]

[17] Gilad, G.M.; Gilad, V.H. Long-term (5 years), high daily dosage of dietary agmatine--evidence of safety: a case report. *J. Med. Food,* **2014**, *17*(11), 1256-1259. [http://dx.doi.org/10.1089/jmf.2014.0026] [PMID: 25247837]

[18] Gilad, G. Agmatine metabolism and neuroprotection. *Soc. Neurosci.,* 25th Annu. Meet **1995**, pp. 21-555.

[19] Imam, Y.Z.; D'Souza, A.; Malik, R.A.; Shuaib, A. Secondary stroke prevention: Improving diagnosis and management with newer technologies. *Transl. Stroke Res.,* **2016**, *7*(6), 458-477. [http://dx.doi.org/10.1007/s12975-016-0494-2] [PMID: 27586681]

[20] Cai, W.; Liu, H.; Zhao, J.; Chen, L.Y.; Chen, J.; Lu, Z.; Hu, X. Pericytes in brain injury and repair after ischemic stroke. *Transl. Stroke Res.,* **2017**, *8*(2), 107-121. [http://dx.doi.org/10.1007/s12975-016-0504-4] [PMID: 27837475]

[21] Jiang, X.; Pu, H.; Hu, X.; Wei, Z.; Hong, D.; Zhang, W.; Gao, Y.; Chen, J.; Shi, Y. A Post-stroke therapeutic regimen with omega-3 polyunsaturated fatty acids that promotes white matter integrity and beneficial microglial responses after cerebral ischemia. *Transl. Stroke Res.,* **2016**, *7*(6), 548-561. [http://dx.doi.org/10.1007/s12975-016-0502-6] [PMID: 27714669]

[22] Ji, B.; Zhou, F.; Han, L.; Yang, J.; Fan, H.; Li, S.; Li, J.; Zhang, X.; Wang, X.; Chen, X.; Xu, Y. Sodium Tanshinone IIA sulfonate enhances effectiveness Rt-PA treatment in acute ischemic stroke patients associated with ameliorating blood-brain barrier damage. *Transl. Stroke Res.,* **2017**, *8*(4), 334-340. [http://dx.doi.org/10.1007/s12975-017-0526-6] [PMID: 28243834]

[23] McCann, S.K.; Cramond, F.; Macleod, M.R.; Sena, E.S. Systematic review and meta-analysis of the efficacy of interleukin-1 receptor antagonist in animal models of stroke: an update. *Transl. Stroke Res.,* **2016**, *7*(5), 395-406. [http://dx.doi.org/10.1007/s12975-016-0489-z] [PMID: 27526101]

[24] Cunha, A.S.; Matheus, F.C.; Moretti, M.; Sampaio, T.B.; Poli, A.; Santos, D.B.; Colle, D.; Cunha, M.P.; Blum-Silva, C.H.; Sandjo, L.P.; Reginatto, F.H.; Rodrigues, A.L.; Farina, M.; Prediger, R.D. Agmatine attenuates reserpine-induced oral dyskinesia in mice: Role of oxidative stress, nitric oxide and glutamate NMDA receptors. *Behav. Brain Res.,* **2016**, *312*, 64-76. [http://dx.doi.org/10.1016/j.bbr.2016.06.014] [PMID: 27306571]

[25] Huang, Y.C.; Tzeng, W.S.; Wang, C.C.; Cheng, B.C.; Chang, Y.K.; Chen, H.H.; Lin, P.C.; Huang, T.Y.; Chuang, T.J.; Lin, J.W.; Chang, C.P. Neuroprotective effect of agmatine in rats with transient cerebral ischemia using MR imaging and histopathologic evaluation. *Magn. Reson. Imaging,* **2013**, *31*(7), 1174-1181. [http://dx.doi.org/10.1016/j.mri.2013.03.026] [PMID: 23642800]

[26] Mun, C.H.; Lee, W.T.; Park, K.A.; Lee, J.E. Regulation of endothelial nitric oxide synthase by agmatine after transient global cerebral ischemia in rat brain. *Anat. Cell Biol.,* **2010**, *43*(3), 230-240. [http://dx.doi.org/10.5115/acb.2010.43.3.230] [PMID: 21212863]

[27] Galgano, F. Focused review: agmatine in fermented foods. *Front. Microbiol.* **2012**, *3,* 199. [http://dx.doi.org/10.3389/fmicb.2012.00199]

[28] Kim, D.J.; Kim, D.I.; Lee, S.K.; Suh, S.H.; Lee, Y.J.; Kim, J.; Chung, T.S.; Lee, J.E. Protective effect of agmatine on a reperfusion model after transient cerebral ischemia: Temporal evolution on perfusion MR imaging and histopathologic findings. *AJNR Am. J. Neuroradiol.,* **2006**, *27*(4), 780-785. [PMID: 16611764]

[29] Huang, Z.; Huang, P.L.; Panahian, N.; Dalkara, T.; Fishman, M.C.; Moskowitz, M.A. Effects of cerebral ischemia in mice deficient in neuronal nitric oxide synthase. *Science,* **1994**, *265*(5180), 1883-1885. [http://dx.doi.org/10.1126/science.7522345] [PMID: 7522345]

[30] Morrissey, J.J.; Klahr, S. Agmatine activation of nitric oxide synthase in endothelial cells. *Proc. Assoc. Am. Physicians,* **1997**, *109*(1), 51-57. [PMID: 9010916]

[31] Feng, Y.; Piletz, J.E.; Leblanc, M.H. Agmatine suppresses nitric oxide production and attenuates hypoxic-ischemic brain injury in neonatal rats. *Pediatr. Res.,* **2002**, *52*(4), 606-611. [http://dx.doi.org/10.1203/00006450-200210000-00023] [PMID: 12357058]

[32] Yang, M.Z.; Mun, C.H.; Choi, Y.J.; Baik, J.H.; Park, K.A.; Lee, W.T.; Lee, J.E. Agmatine inhibits matrix metalloproteinase-9 *via* endothelial nitric oxide synthase in cerebral endothelial cells. *Neurol. Res.,* **2007**, *29*(7), 749-754. [http://dx.doi.org/10.1179/016164107X208103] [PMID: 17588309]

[33] Jung, H.J.; Yang, M.Z.; Kwon, K.H.; Yenari, M.A.; Choi, Y.J.; Lee, W.T.; Park, K.A.; Lee, J.E. Endogenous agmatine inhibits cerebral vascular matrix metalloproteinases expression by regulating activating transcription factor 3 and endothelial nitric oxide synthesis. *Curr. Neurovasc. Res.,* **2010**, *7*(3), 201-212. [http://dx.doi.org/10.2174/156720210792231804] [PMID: 20560878]

[34] Ahn, S.S.; Kim, S.H.; Lee, J.E.; Ahn, K.J.; Kim, D.J.; Choi, H.S.; Kim, J.; Shin, N.Y.; Lee, S.K. Effects of agmatine on blood-brain barrier stabilization assessed by permeability MRI in a rat model of transient cerebral ischemia. *Am. J. Neuroradiol.,* **2015**, *36*(2), 283-288. [http://dx.doi.org/10.3174/ajnr.A4113] [PMID: 25273536]

[35] Kim, J.H.; Lee, Y.W.; Park, K.A.; Lee, W.T.; Lee, J.E. Agmatine attenuates brain edema through reducing the expression of aquaporin-1 after cerebral ischemia. *J. Cereb. Blood Flow Metab.,* **2010**, *30*(5), 943-949. [http://dx.doi.org/10.1038/jcbfm.2009.260] [PMID: 20029450]

[36] Wang, C.C.; Chio, C.C.; Chang, C.H.; Kuo, J.R.; Chang, C.P. Beneficial effect of agmatine on brain apoptosis, astrogliosis, and edema after rat transient cerebral ischemia. *BMC Pharmacol.,* **2010**, *10*, 11. [http://dx.doi.org/10.1186/1471-2210-10-11] [PMID: 20815926]

[37] Manley, G.T.; Fujimura, M.; Ma, T.; Noshita, N.; Filiz, F.; Bollen, A.W.; Chan, P.; Verkman, A.S. Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. *Nat. Med.,* **2000**, *6*(2), 159-163. [http://dx.doi.org/10.1038/72256] [PMID: 10655103]

[38] Kim, J.M.; Lee, J.E.; Cheon, S.Y.; Lee, J.H.; Kim, S.Y.; Kam, E.H.; Koo, B.N. The anti-inflammatory effects of agmatine on transient focal cerebral ischemia in diabetic rats. *J. Neurosurg. Anesthesiol.,* **2016**, *28*(3), 203-213. [PMID: 26057630]

[39] Sahuquillo, J.; Poca, M.A.; Amoros, S. Current aspects of pathophysiology and cell dysfunction after severe head injury. *Curr. Pharm. Des.,* **2001**, *7*(15), 1475-1503. [http://dx.doi.org/10.2174/1381612013397311] [PMID: 11562294]

[40] Reilly, P.L. Brain injury: the pathophysiology of the first hours.'Talk and Die revisited'. *J. Clin. Neurosci.,* **2001**, *8*(5), 398-403. [http://dx.doi.org/10.1054/jocn.2001.0916] [PMID: 11535003]

[41] de Vries, H.E.; Blom-Roosemalen, M.C.; van Oosten, M.; de Boer, A.G.; van Berkel, T.J.; Breimer, D.D.; Kuiper, J. The influence of cytokines on the integrity of the blood-brain barrier *in vitro*. *J. Neuroimmunol.,* **1996**, *64*(1), 37-43. [http://dx.doi.org/10.1016/0165-5728(95)00148-4] [PMID: 8598388]

[42] Morganti-Kossmann, M.C.; Rancan, M.; Stahel, P.F.; Kossmann, T. Inflammatory response in acute traumatic brain injury: a double-edged sword. *Curr. Opin. Crit. Care,* **2002**, *8*(2), 101-105. [http://dx.doi.org/10.1097/00075198-200204000-00002] [PMID: 12386508]

[43] Liang, D.; Bhatta, S.; Gerzanich, V.; Simard, J.M. Cytotoxic edema: mechanisms of pathological cell swelling. *Neurosurg. Focus,* **2007**, *22*(5), E2. [http://dx.doi.org/10.3171/foc.2007.22.5.3] [PMID: 17613233]

[44] Gilad, G.M.; Salame, K.; Rabey, J.M.; Gilad, V.H. Agmatine treatment is neuroprotective in rodent brain injury models. *Life Sci.,* **1996**, *58*(2), 41-46. [PMID: 8606618]

[45] Bullock, R.; Zauner, A.; Woodward, J.; Young, H.F. Massive persistent release of excitatory amino acids following human occlusive stroke. *Stroke,* **1995**, *26*(11), 2187-2189. [http://dx.doi.org/10.1161/01.STR.26.11.2187] [PMID: 7482671]

[46] Iadecola, C. Bright and dark sides of nitric oxide in ischemic brain injury. *Trends Neurosci.,* **1997**, *20*(3), 132-139. [http://dx.doi.org/10.1016/S0166-2236(96)10074-6] [PMID: 9061868]

[47] Kuo, J.R.; Lo, C.J.; Chio, C.C.; Chang, C.P.; Lin, M.T. Resuscitation from experimental traumatic brain injury by agmatine therapy. *Resuscitation,* **2007**, *75*(3), 506-514. [http://dx.doi.org/10.1016/j.resuscitation.2007.05.011] [PMID: 17629391]

[48] Chong-Jeh, L.; Ching-Ping, C.; Kao-Chang, L.; Mao-Tsun, L.; Chung-Ching, C. Agmatine-promoted angiogenesis, neurogenesis, and Inhibition of ghliosis-reduced traumatic brain injury in rats. *J. Trauma Inj. Infect. Crit. Care,* **2011**, *71*(4), E87-E93. [http://dx.doi.org/10.1097/TA.0b013e31820932e2]

[49] Kim, J.Y.; Lee, Y.W.; Kim, J.H.; Lee, W.T.; Park, K.A.; Lee, J.E. Agmatine attenuates brain edema and apoptotic cell death after traumatic braini. *J. Korean Med. Sci.,* **2015**, *30*(7), 943-952. [http://dx.doi.org/10.3346/jkms.2015.30.7.943] [PMID: 26130959]

[50] Yu, C.G.; Marcillo, A.E.; Fairbanks, C.A.; Wilcox, G.L.; Yezierski, R.P. Agmatine improves locomotor function and reduces tissue damage following spinal cord injury. *Neuroreport,* **2000**, *11*(14), 3203-3207. [http://dx.doi.org/10.1097/00001756-200009280-00031] [PMID: 11043549]

[51] Hegarty, S.V.; Sullivan, A.M.; O'Keeffe, G.W. The Epigenome as a therapeutic target for Parkinson's disease. *Neural Regen. Res.,* **2016**, *11*(11), 1735-1738. [http://dx.doi.org/10.4103/1673-5374.194803] [PMID: 28123403]

[52] Blandini, F.; Porter, R.H.; Greenamyre, J.T. Glutamate and Parkinson's disease. *Mol. Neurobiol.,* **1996**, *12*(1), 73-94. [http://dx.doi.org/10.1007/BF02740748] [PMID: 8732541]

[53] Rodriguez, M.C.; Obeso, J.A.; Olanow, C.W. Subthalamic nucleus-mediated excitotoxicity in Parkinson's disease: a target for neuroprotection. *Ann. Neurol.,* **1998**, *44*(3)(Suppl. 1), S175-S188. [http://dx.doi.org/10.1002/ana.410440726] [PMID: 9749591]

[54] Sawada, H.; Oeda, T.; Kuno, S.; Nomoto, M.; Yamamoto, K.; Yamamoto, M.; Hisanaga, K.; Kawamura, T. Amantadine for dyskinesias in Parkinson's disease: a randomized controlled trial. *PLoS One,* **2010**, *5*(12), e15298. [http://dx.doi.org/10.1371/journal.pone.0015298] [PMID: 21217832]

[55] Aarsland, D.; Ballard, C.; Walker, Z.; Bostrom, F.; Alves, G.; Kossakowski, K.; Leroi, I.; Pozo-Rodriguez, F.; Minthon, L.; Londos, E. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol.,* **2009**, *8*(7), 613-618. [http://dx.doi.org/10.1016/S1474-4422(09)70146-2] [PMID: 19520613]

[56] Condello, S.; Currò, M.; Ferlazzo, N.; Caccamo, D.; Satriano, J.; Ientile, R. Agmatine effects on mitochondrial membrane potential and NF-κB activation protect against rotenone-induced cell damage in human neuronal-like SH-SY5Y cells. *J. Neurochem.,* **2011**, *116*(1), 67-75. [http://dx.doi.org/10.1111/j.1471-4159.2010.07085.x] [PMID: 21044082]

[57] Condello, S.; Calabrò, E.; Caccamo, D.; Currò, M.; Ferlazzo, N.; Satriano, J.; Magazù, S.; Ientile, R. Protective effects of agmatine in rotenone-induced damage of human SH-SY5Y neuroblastoma cells: fourier transform infrared spectroscopy analysis in a model of Parkinson's disease. *Amino Acids,* **2012**, *42*(2-3), 775-781. [http://dx.doi.org/10.1007/s00726-011-0994-z] [PMID: 21805293]

[58] Matheus, F.C.; Aguiar, A.S., Jr; Castro, A.A.; Villarinho, J.G.; Ferreira, J.; Figueiredo, C.P.; Walz, R.; Santos, A.R.; Tasca, C.I.; Prediger, R.D. Neuroprotective effects of agmatine in mice infused with a single intranasal administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *Behav. Brain Res.,* **2012**, *235*(2), 263-272. [http://dx.doi.org/10.1016/j.bbr.2012.08.017] [PMID: 22921927]

[59] Drummond, E.; Wisniewski, T. Alzheimer's disease: experimental models and reality. *Acta Neuropathol.,* **2017**, *133*(2), 155-175. [http://dx.doi.org/10.1007/s00401-016-1662-x] [PMID: 28025715]

[60] Uzbay, T.I. The pharmacological importance of agmatine in the brain. *Neurosci. Biobehav. Rev.,* **2012**, *36*(1), 502-519. [http://dx.doi.org/10.1016/j.neubiorev.2011.08.006] [PMID: 21893093]

[61] Yang, Y.; Bu, S. The current status of the Low temperature on the pathogenesis of Alzheimer's disease. *Shiyong Laonian Yixue,* **2014**, *28*(8), 681-684.

[62] Liu, J.; Yang, B.; Ke, J.; Li, W.; Suen, W.C. Antibody-Based drugs and approaches against amyloid-β species for Alzheimer's Disease Immunotherapy. *Drugs Aging,* **2016**, *33*(10), 685-697. [http://dx.doi.org/10.1007/s40266-016-0406-x] [PMID: 27699633]

[63] Uchoa, M.F.; Moser, V.A.; Pike, C.J. Interactions between inflammation, sex steroids, and Alzheimer's disease risk factors. *Front. Neuroendocrinol.,* **2016**, *43*, 60-82. [http://dx.doi.org/10.1016/j.yfrne.2016.09.001] [PMID: 27651175]

[64] Baranov, D.; Bickler, P.E.; Crosby, G.J.; Culley, D.J.; Eckenhoff, M.F.; Eckenhoff, R.G.; Hogan, K.J.; Jevtovic-Todorovic, V.; Palotás, A.; Perouansky, M.; Planel, E.; Silverstein, J.H.; Wei, H.; Whittington, R.A.; Xie, Z.; Zuo, Z. Consensus statement: First international workshop on anesthetics and Alzheimer's disease. *Anesth. Analg.,* **2009**, *108*(5), 1627-1630. [http://dx.doi.org/10.1213/ane.0b013e318199dc72] [PMID: 19372347]

[65] Song, J.; Hur, B.E.; Bokara, K.K.; Yang, W.; Cho, H.J.; Park, K.A.; Lee, W.T.; Lee, K.M.; Lee, J.E. Agmatine improves cognitive dysfunction and prevents cell death in a streptozotocin-induced Alzheimer rat model. *Yonsei Med. J.,* **2014**, *55*(3), 689-699. [http://dx.doi.org/10.3349/ymj.2014.55.3.689] [PMID: 24719136]

[66] Zhu, M.Y.; Piletz, J.E.; Halaris, A.; Regunathan, S. Effect of agmatine against cell death induced by NMDA and glutamate in neurons and PC12 cells. *Cell. Mol. Neurobiol.,* **2003**, *23*(4-5), 865-872. [http://dx.doi.org/10.1023/A:1025069407173] [PMID: 14514037]

[67] Kang, S; Kim, CH; Jung, H; Kim, E; Song, HT; Lee, JE Agmatine ameliorates type 2 diabetes induced-Alzheimer's disease-like alterations in high-fat diet-fed mice via reactivation of blunted insulin signaling *Neuropharmacology,* **2017**, *113*(Pt A), 467-479. [http://dx.doi.org/10.1016/j.neuropharm.2016.10.029]

[68] Zhao, W.Q.; Alkon, D.L. Role of insulin and insulin receptor in learning and memory. *Mol. Cell. Endocrinol.,* **2001**, *177*(1-2), 125-134. [http://dx.doi.org/10.1016/S0303-7207(01)00455-5] [PMID: 11377828]

[69] Li, X.; Can, G. The research progress of relationship between the Alzheimer's disease and outside the synapses, and synaptic NMDA receptor. *Prog. Biochem. Biophys.,* **2014**, *41*(9), 823-829.

[70] Murray, C.J.; Lopez, A.D.; Jamison, D.T. The global burden of disease in 1990: summary results, sensitivity analysis and future directions. *Bull. World Health Organ.,* **1994**, *72*(3), 495-509. [PMID: 8062404]

[71] Alarcón, G.; Martinez, J.; Kerai, S.V.; Lacruz, M.E.; Quiroga, R.Q.; Selway, R.P.; Richardson, M.P.; García Seoane, J.J.; Valentín, A. *In vivo* neuronal firing patterns during human epileptiform discharges replicated by electrical stimulation. *Clin. Neurophysiol.,* **2012**, *123*(9), 1736-1744. [http://dx.doi.org/10.1016/j.clinph.2012.02.062] [PMID: 22410162]

[72] Sanabria, E.R.; Su, H.; Yaari, Y. Initiation of network bursts by Ca^{2+}-dependent intrinsic bursting in the rat pilocarpine model of temporal lobe epilepsy. *J. Physiol.,* **2001**, *532*(Pt 1), 205-216. [http://dx.doi.org/10.1111/j.1469-7793.2001.0205g.x] [PMID: 11283235]

[73] Meldrum, B.S.; Akbar, M.T.; Chapman, A.G. Glutamate receptors and transporters in genetic and acquired models of epilepsy. *Epilepsy Res.,* **1999**, *36*(2-3), 189-204. [http://dx.doi.org/10.1016/S0920-1211(99)00051-0] [PMID: 10515165]

[74] Chapman, A.G. Glutamate and epilepsy. *J. Nutr.,* **2000**, *130*(4S)(Suppl.), 1043S-1045S. [http://dx.doi.org/10.1093/jn/130.4.1043S] [PMID: 10736378]

[75] Bence, A.K.; Worthen, D.R.; Stables, J.P.; Crooks, P.A. An *in vivo* evaluation of the antiseizure activity and acute neurotoxicity of agmatine. *Pharmacol. Biochem. Behav.,* **2003**, *74*(3), 771-775. [http://dx.doi.org/10.1016/S0091-3057(02)01079-1] [PMID: 12543244]

[76] Arhan, E.; Serdaroglu, A.; Ozturk, B.; Ozturk, H.S.; Ozcelik, A.; Kurt, N.; Kutsal, E.; Sevinc, N. Effects of epilepsy and antiepileptic drugs on nitric oxide, lipid peroxidation and xanthine oxidase system in children with idiopathic epilepsy. *Seizure,* **2011**, *20*(2), 138-142. [http://dx.doi.org/10.1016/j.seizure.2010.11.003] [PMID: 21112224]

[77] Eblen, F.; Löschmann, P.A.; Wüllner, U.; Turski, L.; Klockgether, T. Effects of 7-nitroindazole, NG-nitro-L-arginine, and D-CPPene on harmaline-induced postural tremor, N-methyl-D-aspartate-induced seizures, and lisuride-induced rotations in rats with nigral 6-hydroxydopamine lesions. *Eur. J. Pharmacol.,* **1996**, *299*(1-3), 9-16. [http://dx.doi.org/10.1016/0014-2999(95)00795-4] [PMID: 8901001]

[78] Luszczki, J.J.; Czernecki, R.; Wojtal, K.; Borowicz, K.K.; Czuczwar, S.J. Agmatine enhances the anticonvulsant action of phenobarbital and valproate in the mouse maximal electroshock seizure model. *J. Neural Transm.,* **2008**, *115*(11), 1485-1494. [http://dx.doi.org/10.1007/s00702-008-0046-3] [PMID: 18379717]

[79] Kaputlu, I.; Uzbay, T. L-NAME inhibits pentylenetetrazole and strychnine-induced seizures in mice. *Brain Res.,* **1997**, *753*(1), 98-101. [http://dx.doi.org/10.1016/S0006-8993(96)01496-5] [PMID: 9125436]

[80] Feng, Y.; LeBlanc, M.H.; Regunathan, S. Agmatine reduces extracellular glutamate during pentylenetetrazole-induced seizures in rat brain: a potential mechanism for the anticonvulsive effects. *Neurosci. Lett.,* **2005**, *390*(3), 129-133. [http://dx.doi.org/10.1016/j.neulet.2005.08.008] [PMID: 16125317]

[81] Uzbay, I.T.; Yeşilyurt, O.; Celik, T.; Ergün, H.; Işimer, A. Effects of agmatine on ethanol withdrawal syndrome in rats. *Behav. Brain Res.,* **2000**, *107*(1-2), 153-159. [http://dx.doi.org/10.1016/S0166-4328(99)00127-8] [PMID: 10628739]

[82] Bahremand, A.; Ziai, P.; Khodadad, T.K.; Payandemehr, B.; Rahimian, R.; Ghasemi, A.; Ghasemi, M.; Hedayat, T.; Dehpour, A.R. Agmatine enhances the anticonvulsant effect of lithium chloride on pentylenetetrazole-induced seizures in mice: Involvement of L-arginine/nitric oxide pathway. *Epilepsy Behav.,* **2010**, *18*(3), 186-192. [http://dx.doi.org/10.1016/j.yebeh.2010.04.014] [PMID: 20493779]

[83] Abe, K.; Abe, Y.; Saito, H. Agmatine induces glutamate release and cell death in cultured rat cerebellar granule neurons. *Brain Res.,* **2003**, *990*(1-2), 165-171. [http://dx.doi.org/10.1016/S0006-8993(03)03454-1] [PMID: 14568341]

[84] Luszczki, J.J.; Czernecki, R.; Dudra-Jastrzebska, M.; Borowicz, K.K.; Czuczwar, S.J. Influence of agmatine on the protective action of numerous antiepileptic drugs against pentetrazole-induced seizures in mice. *Pharmacol. Rep.,* **2009**, *61*(2), 252-260. [http://dx.doi.org/10.1016/S1734-1140(09)70029-5] [PMID: 19443936]

[85] Shen, X.; Zhao, Z.; Luo, X.; Wang, H.; Hu, B.; Guo, Z. Systems pharmacology based study of the molecular mechanism of SiNiSan formula for application in nervous and mental diseases. *Evid. Based Complement. Alternat. Med.,* **2016**, *2016*, 9146378. [http://dx.doi.org/10.1155/2016/9146378] [PMID: 28058059]

[86] Li, Y.F.; Gong, Z.H.; Cao, J.B.; Wang, H.L.; Luo, Z.P.; Li, J. Antidepressant-like effect of agmatine and its possible mechanism. *Eur. J. Pharmacol.,* **2003**, *469*(1-3), 81-88. [http://dx.doi.org/10.1016/S0014-2999(03)01735-7] [PMID: 12782188]

[87] Dias, E. Z.A.; Oscar, R.A.; Lin, J.; Santos, A.R.S.; Calixto, J.B.; Lúcia, S. R. A. Evidence for serotonin receptor subtypes involvement in agmatine antidepressant like-effect in the mouse forced swimming test. *Brain Res.,* **2004**, *1023*(2), 253-263. [http://dx.doi.org/10.1016/j.brainres.2004.07.041] [PMID: 15374751]

[88] Taksande, B.G.; Kotagale, N.R.; Tripathi, S.J.; Ugale, R.R.; Chopde, C.T. Antidepressant like effect of selective serotonin reuptake inhibitors involve modulation of imidazoline receptors by agmatine. *Neuropharmacology,* **2009**, *57*(4), 415-424. [http://dx.doi.org/10.1016/j.neuropharm.2009.06.035] [PMID: 19589348]

[89] Parale, M.P.; Kulkarni, S.K. Studies with alpha 2-adrenoceptor agonists and alcohol abstinence syndrome in rats. *Psychopharmacology (Berl.),* **1986**, *88*(2), 237-239. [http://dx.doi.org/10.1007/BF00652247] [PMID: 2869542]

[90] Zaniewska, M.; McCreary, A.C.; Sezer, G.; Przegaliński, E.; Filip, M. Effects of agmatine on nicotine-evoked behavioral responses in rats. *Pharmacol. Rep.,* **2008**, *60*(5), 645-654. [PMID: 19066410]

[91] Uzbay, I.T.; Lal, H. Effects of NG-nitro-L-arginine methyl ester, 7-nitro indazole, and agmatine on pentylenetetrazol-induced discriminative stimulus in long-evans rats. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2002**, *26*(3), 567-573. [http://dx.doi.org/10.1016/S0278-5846(01)00309-8] [PMID: 11999909]

[92] Pålsson, E.; Fejgin, K.; Wass, C.; Klamer, D. Agmatine attenuates the disruptive effects of phencyclidine on prepulse inhibition. *Eur. J. Pharmacol.,* **2008**, *590*(1-3), 212-216. [http://dx.doi.org/10.1016/j.ejphar.2008.06.022] [PMID: 18573247]

[93] Elmore, S. Apoptosis: a review of programmed cell death. *Toxicol. Pathol.,* **2007**, *35*(4), 495-516. [http://dx.doi.org/10.1080/01926230701320337] [PMID: 17562483]

[94] Kerr, J.F.; Wyllie, A.H.; Currie, A.R. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br. J. Cancer,* **1972**, *26*(4), 239-257. [http://dx.doi.org/10.1038/bjc.1972.33] [PMID: 4561027]

[95] Meier, P.; Finch, A.; Evan, G. Apoptosis in development. *Nature,* **2000**, *407*(6805), 796-801. [http://dx.doi.org/10.1038/35037734] [PMID: 11048731]

[96] Rathmell, J.C.; Thompson, C.B. Pathways of apoptosis in lymphocyte development, homeostasis, and disease. *Cell,* **2002**, *109*(Suppl.), S97-S107. [http://dx.doi.org/10.1016/S0092-8674(02)00704-3] [PMID: 11983156]

[97] Reed, J.C. Apoptosis-based therapies. *Nat. Rev. Drug Discov.,* **2002**, *1*(2), 111-121. [http://dx.doi.org/10.1038/nrd726] [PMID: 12120092]

[98] Shao, A.; Wang, Z.; Wu, H.; Dong, X.; Li, Y.; Tu, S.; Tang, J.; Zhao, M.; Zhang, J.; Hong, Y. Enhancement of autophagy by histone deacetylase inhibitor trichostatin: An ameliorates neuronal apoptosis after subarachnoid hemorrhage in rats. *Mol. Neurobiol.,* **2014**. [PMID: 25399954]

[99] El-Sherbeeny, N.A.; Nader, M.A.; Attia, G.M.; Ateyya, H. Agmatine protects rat liver from nicotine-induced hepatic damage *via* antioxidative, antiapoptotic, and antifibrotic pathways. *Naunyn Schmiedebergs Arch. Pharmacol.,* **2016**, *389*(12), 1341-1351. [http://dx.doi.org/10.1007/s00210-016-1284-9] [PMID: 27638633]

[100] Arndt, M.A.; Battaglia, V.; Parisi, E.; Lortie, M.J.; Isome, M.; Baskerville, C.; Pizzo, D.P.; Ientile, R.; Colombatto, S.; Toninello, A.; Satriano, J. The arginine metabolite agmatine protects mitochondrial function and confers resistance to cellular apoptosis. *Am. J. Physiol. Cell Physiol.,* **2009**, *296*(6), C1411-C1419. [http://dx.doi.org/10.1152/ajpcell.00529.2008] [PMID: 19321739]

[101] Gardini, G.; Cabella, C.; Cravanzola, C.; Vargiu, C.; Belliardo, S.; Testore, G.; Solinas, S.P.; Toninello, A.; Grillo, M.A.; Colombatto, S. Agmatine induces apoptosis in rat hepatocyte cultures. *J. Hepatol.,* **2001**, *35*(4), 482-489. [http://dx.doi.org/10.1016/S0168-8278(01)00153-2] [PMID: 11682032]

[102] Haenisch, B.; Bönisch, H.; Cichon, S.; Allam, J.P.; Novak, N.; Molderings, G.J. Effects of exogenous agmatine in human leukemia HMC-1 and HL-60 cells on proliferation, polyamine metabolism and cell cycle. *Leuk. Res.,* **2011**, *35*(9), 1248-1253. [http://dx.doi.org/10.1016/j.leukres.2010.12.023] [PMID: 21236489]

[103] Zarifkar, A.; Choopani, S.; Ghasemi, R.; Naghdi, N.; Maghsoudi, A.H.; Maghsoudi, N.; Rastegar, K.; Moosavi, M. Agmatine prevents LPS-induced spatial memory impairment and hippocampal apoptosis. *Eur. J. Pharmacol.,* **2010**, *634*(1-3), 84-88. [http://dx.doi.org/10.1016/j.ejphar.2010.02.029] [PMID: 20184876]

[104] Turrin, N.P.; Rivest, S. Molecular and cellular immune mediators of neuroprotection. *Mol. Neurobiol.,* **2006**, *34*(3), 221-242. [http://dx.doi.org/10.1385/MN:34:3:221] [PMID: 17308354]

[105] Brown, G.C.; Neher, J.J. Inflammatory neurodegeneration and mechanisms of microglial killing of neurons. *Mol. Neurobiol.,* **2010**, *41*(2-3), 242-247. [http://dx.doi.org/10.1007/s12035-010-8105-9] [PMID: 20195798]

[106] Taksande, B.G.; Gawande, D.Y.; Chopde, C.T.; Umekar, M.J.; Kotagale, N.R. Agmatine ameliorates adjuvant induced arthritis and inflammatory cachexia in rats. *Biomed. Pharmacother.,* **2017**,

86, 271-278. [http://dx.doi.org/10.1016/j.biopha.2016.12.039] [PMID: 28006753]

[107] Song, J.; Lee, B.; Kang, S.; Oh, Y.; Kim, E.; Kim, C.H.; Song, H.T.; Lee, J.E. Agmatine ameliorates high glucose-induced neuronal cell senescence by regulating the p21 and p53 signaling. *Exp. Neurobiol.,* **2016**, *25*(1), 24-32. [http://dx.doi.org/10.5607/en.2016.25.1.24] [PMID: 26924930]

[108] Sahin, C.; Albayrak, O.; Akdeniz, T.F.; Akbulut, Z.; Yanikkaya Demirel, G.; Aricioglu, F. Agmatine reverses sub-chronic stress induced nod-like receptor protein 3 (NLRP3) activation and cytokine response in rats. *Basic Clin. Pharmacol. Toxicol.,* **2016**, *119*(4), 367-375. [http://dx.doi.org/10.1111/bcpt.12604] [PMID: 27061450]

[109] Wade, C.L.; Eskridge, L.L.; Nguyen, H.O.; Kitto, K.F.; Stone, L.S.; Wilcox, G.; Fairbanks, C.A. Immunoneutralization of agmatine sensitizes mice to micro-opioid receptor tolerance. *J. Pharmacol. Exp. Ther.,* **2009**, *331*(2), 539-546. [http://dx.doi.org/10.1124/jpet.109.155424] [PMID: 19684255]

[110] Gasche, Y.; Copin, J.C.; Sugawara, T.; Fujimura, M.; Chan, P.H. Matrix metalloproteinase inhibition prevents oxidative stress-associated blood-brain barrier disruption after transient focal cerebral ischemia. *J. Cereb. Blood Flow Metab.,* **2001**, *21*(12), 1393-1400. [http://dx.doi.org/10.1097/00004647-200112000-00003] [PMID: 11740200]

[111] Giasson, B.I.; Duda, J.E.; Murray, I.V.; Chen, Q.; Souza, J.M.; Hurtig, H.I.; Ischiropoulos, H.; Trojanowski, J.Q.; Lee, V.M. Oxidative damage linked to neurodegeneration by selective alpha-synuclein nitration in synucleinopathy lesions. *Science,* **2000**, *290*(5493), 985-989. [http://dx.doi.org/10.1126/science.290.5493.985] [PMID: 11062131]

[112] Valko, M.; Leibfritz, D.; Moncol, J.; Cronin, M.T.; Mazur, M.; Telser, J. Free radicals and antioxidants in normal physiological functions and human disease. *Int. J. Biochem. Cell Biol.,* **2007**, *39*(1), 44-84. [http://dx.doi.org/10.1016/j.biocel.2006.07.001] [PMID: 16978905]

[113] Iizuka, Y.; Hong, S.; Kim, C.Y.; Yang, W.I.; Lee, J.E.; Seong, G.J. Protective mechanism of agmatine pretreatment on RGC-5 cells injured by oxidative stress. *Braz. J. Med. Biol. Res.,* **2010**, *43*(4), 356-358. [http://dx.doi.org/10.1590/S0100-879X2010007500018] [PMID: 20445950]

[114] Bratislav, D.; Irena, L.; Milica, N.; Ivana, S.; Ana, D.; Sanda, D.; Ivana, S. Effects of agmatine on chlorpromazine toxicity in the liver of Wistar rats: the possible role of oxidant/antioxidant imbalance. *Exp. Anim.,* **2017**, *66*(1), 17-27. [http://dx.doi.org/10.1538/expanim.16-0010] [PMID: 27523096]

[115] Gawali, N.B.; Bulani, V.D.; Chowdhury, A.A.; Deshpande, P.S.; Nagmoti, D.M.; Juvekar, A.R. Agmatine ameliorates lipopolysaccharide induced depressive-like behaviour in mice by targeting the underlying inflammatory and oxido-nitrosative mediators. *Pharmacol. Biochem. Behav.,* **2016**, *149*, 1-8. [http://dx.doi.org/10.1016/j.pbb.2016.07.004] [PMID: 27453424]

[116] Freitas, A.E.; Bettio, L.E.; Neis, V.B.; Santos, D.B.; Ribeiro, C.M.; Rosa, P.B.; Farina, M.; Rodrigues, A.L. Agmatine abolishes restraint stress-induced depressive-like behavior and hippocampal antioxidant imbalance in mice. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2014**, *50*, 143-150. [http://dx.doi.org/10.1016/j.pnpbp.2013.12.012] [PMID: 24370459]

[117] Liu, Y-C.; Lee, Y-D.; Wang, H-L.; Liao, K.H.; Chen, K.B.; Poon, K.S.; Pan, Y.L.; Lai, T.W. Anesthesia-induced hypothermia attenuates early-phase blood-brain barrier disruption but not infarct volume following cerebral ischemia. *PLoS One,* **2017**, *12*(1), e0170682. [http://dx.doi.org/10.1371/journal.pone.0170682] [PMID: 28118390]

[118] Alhadidi, Q.; Bin Sayeed, M.S.; Shah, Z.A. The Interplay between cofilin and phospho-cofilin: Its role in maintaining blood brain Barrier integrity. *CNS Neurol. Disord. Drug Targets,* **2017**, *16*(3), 279-290. [http://dx.doi.org/10.2174/1871527316666170117115040] [PMID: 28124604]

[119] Fujimura, M.; Gasche, Y.; Morita-Fujimura, Y.; Massengale, J.; Kawase, M.; Chan, P.H. Early appearance of activated matrix metalloproteinase-9 and blood-brain barrier disruption in mice after focal cerebral ischemia and reperfusion. *Brain Res.,* **1999**, *842*(1), 92-100. [http://dx.doi.org/10.1016/S0006-8993(99)01843-0] [PMID: 10526099]

[120] Gasche, Y.; Fujimura, M.; Morita-Fujimura, Y.; Copin, J.C.; Kawase, M.; Massengale, J.; Chan, P.H. Early appearance of activated matrix metalloproteinase-9 after focal cerebral ischemia in mice: a possible role in blood-brain barrier dysfunction. *J. Cereb. Blood Flow Metab.,* **1999**, *19*(9), 1020-1028. [http://dx.doi.org/10.1097/00004647-199909000-00010] [PMID: 10478654]

[121] Agre, P.; King, L.S.; Yasui, M.; Guggino, W.B.; Ottersen, O.P.; Fujiyoshi, Y.; Engel, A.; Nielsen, S. Aquaporin water channels--from atomic structure to clinical medicine. *J. Physiol.,* **2002**, *542*(Pt 1), 3-16. [http://dx.doi.org/10.1113/jphysiol.2002.020818] [PMID: 12096044]

[122] Amiry-Moghaddam, M.; Ottersen, O.P. The molecular basis of water transport in the brain. *Nat. Rev. Neurosci.,* **2003**, *4*(12), 991-1001. [http://dx.doi.org/10.1038/nrn1252] [PMID: 14682361]