

Role of agmatine in neurodegenerative diseases and epilepsy

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TABLE OF CONTENTS

1. Abstract
2. Introduction
3. Effects of agmatine in depression
4. Effects of agmatine in learning and memory
5. The neuroprotective properties of agmatine
6. Role of agmatine in neurodegenerative diseases
 - 6.1. Effects of agmatine in Parkinson's disease
 - 6.2. Effects of agmatine in Alzheimer's disease
7. Effects of agmatine in traumatic brain injury
8. Effects of agmatine in epilepsy
9. Conclusion
10. Acknowledgements
11. References

1. ABSTRACT

Agmatine, a cationic polyamine synthesized after decarboxylation of L-arginine by the enzyme arginine decarboxylase, is an endogenous neuromodulator that emerges as a potential agent to manage diverse central nervous system (CNS) disorders. Consistent with its neuromodulatory and neuroprotective properties, there is increasing number of preclinical studies demonstrating the beneficial effects of exogenous agmatine administration on depression, anxiety, hypoxic ischemia, nociception, morphine tolerance, memory, Parkinson's disease, Alzheimer's disease, traumatic brain injury related alterations/disorders and epilepsy. The aim of this review is to summarize the knowledge about the effects of agmatine in CNS and point out its potential as new pharmacological treatment for diverse neurological and neurodegenerative diseases. Moreover, some molecular mechanisms underlying the neuroprotective effects of agmatine will be discussed.

2. INTRODUCTION

Agmatine, a cationic polyamine, was first identified in herring sperm in the early 20th century by the German biochemist Albrecht Kossel. Agmatine is synthesized after decarboxylation of L-arginine by arginine decarboxylase (ADC) (1), as illustrated in Figure 1. The biosynthesis of agmatine by ADC, therefore, is dependent upon the availability of L-arginine, which is carried into neurons by specific cationic amino acid transporter and is also a substrate for two other enzymes: arginase and nitric oxide synthase (NOS). Arginase converts L-arginine to ornithine, which enters the urea cycle and NOS catalyses the conversion of L-arginine to nitric oxide (NO) and citrulline. Importantly, NOS is inhibited competitively by agmatine *in vitro* (2, 3), an interaction with significant functional consequences regarding the action of agmatine in the brain.

In all species, agmatine can be metabolized by hydrolysis to putrescine, the precursor of polyamines

Neuroprotective effects of agmatine

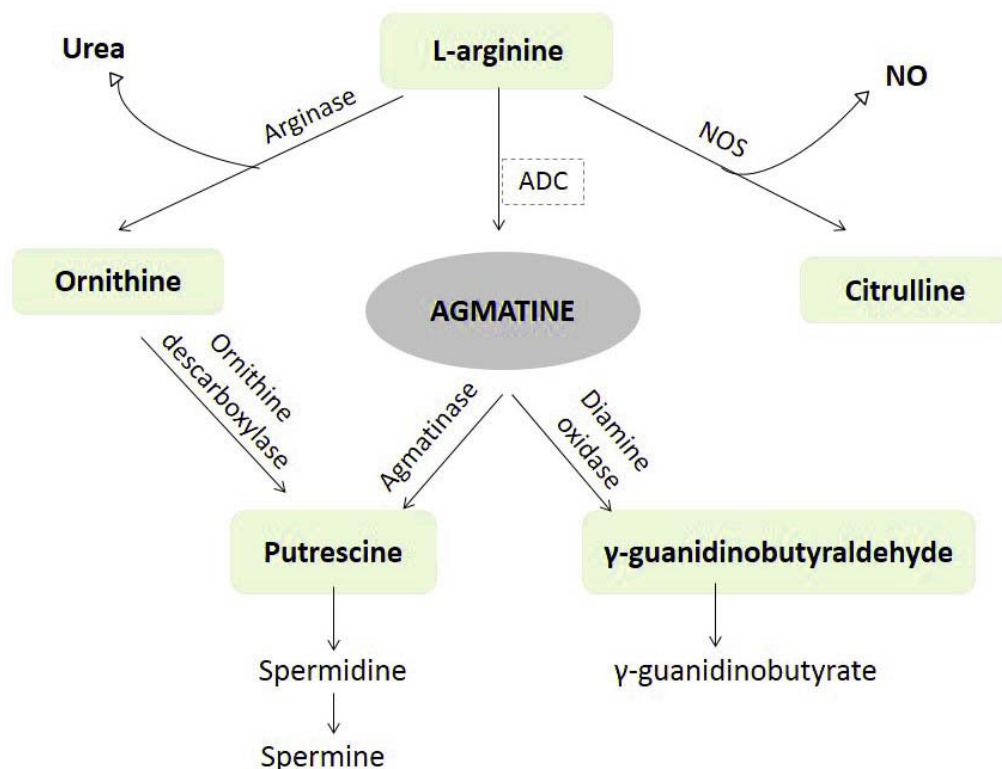


Figure 1. Synthesis and metabolic pathways of agmatine. Agmatine is synthesized from L-arginine by the action of arginine decarboxylase (ADC). Agmatine can be metabolized to putrescine, the precursor spermine and spermidine, by enzyme agmatinase or oxidised by diamine oxidase to γ -guanidinobutyraldehyde.

spermine and spermidine, by the enzyme agmatinase (4) or oxidized by diamine oxidase to γ -guanidinobutyraldehyde, which is then oxidized to γ -guanidinobutyrate and quickly excreted (5) (Figure 1).

Agmatine, ADC and agmatinase have been extensively recognized to be expressed in plants, bacteria, and some invertebrates and are highly preserved in nature (1). Despite until the mid-1990s, they were not believed to be expressed in mammals, it was recently discovered that agmatine, ADC and agmatinase are expressed in mammals (4, 6, 7). Unlike bacterial ADC, which is cytosolic (1), mammalian ADC resides on mitochondrial membranes (7), which might explain the lack of results of previous investigation that tried to detect the enzyme in soluble extracts of mammalian tissue (5). Although first detected in brain (6), agmatine has been quantified in practically all organs of rodents and, in fact, the cerebral concentration of the amine is substantially less than a number of other organs in which agmatine is particularly abundant, mainly stomach, small intestine and aorta (8).

The cellular and regional distribution of agmatine has been mapped immunohistochemically in the mammalian central nervous system (CNS) by using highly selective antibodies. The amine was found to be regionally distributed in the cerebral cortex, the lower brain stem, the midbrain, frontal brain, thalamus and the hypothalamus (9), encephalic regions

notably related to endocrine and visceral control, emotion, cognition and pain perception (5). At cellular level, agmatine immunoreactivity was found to be primarily neuronal, but it was also detected chemically and immunocytochemically in cultured astrocytes and C6 glioma cells (9-11). At the subcellular level, agmatine was shown to be localized predominantly in cytoplasmic vesicles and in the immediate vicinity of the endoplasmic reticulum and the mitochondria (9, 10), which is in agreement with previous results demonstrating mitochondria-associated ADC localization (7).

More recent studies have shown that agmatine is synthesized in both the brain and the spinal cord. L-arginine enters the presynaptic ending via a transporter and is decarboxylated by the mitochondrial ADC to agmatine, which is stored in synaptic vesicles, released by Ca^{2+} -dependent depolarization, inactivated by reuptake and degraded enzymatically by a specific enzyme, agmatinase (12). Importantly, the concentration of agmatine in the brain is similar to that of some classic neurotransmitters (8, 13). Together, these findings support the hypothesis that agmatine may be a novel neurotransmitter in CNS, where it exerts a wide range of biological effects by interacting with receptors and neuronal pathways (2, 12, 14).

Agmatine has received considerable attention recently because of its neuromodulatory and neuroprotective

Table 1. Summary of the studies showing the antidepressant-like effects of agmatine in animal models

Experimental model	Subject	Agmatine dose and administration route	Observed effect	Reference
Spinal cord ischemia	Rat	100 mg/kg (i.p.)	Faster recovery of motor function. Prevention of loss of motor neurons in the spinal cord.	(79)
Ischemia/reperfusion injury	Cat	100 mg/kg (i.v.)	Reduction of TUNEL-positive cells. Decreased neuronal damage.	(80)
Middle cerebral artery occlusion	Rat	100 mg/kg (i.p.)	Accelerate the recovery of motor and proprioception deficits. Prevention of brain infarction, gliosis, edema, apoptosis and neurotoxicity.	(81)
Middle cerebral artery occlusion	Mouse	100 mg/kg (i.p.)	Reduction of brain edema, infarct volume, water content and decrease in the levels of aquaporin.	(85)
Spinal Cord Injury	Mouse	100 mg/kg (i.p.)	Improved surface righting reflex. Reduction of collagen scar.	(86)
Spinal Cord Injury	Mouse	100 mg/kg (i.p.)	Inhibition of demyelination events. Diminished neuronal loss and glial scar around the lesion site.	(87)
Oxygen-glucose deprivation	Rat hippocampal slices	100 mg/kg (i.p.)	Decreased degeneration of neurons.	(82)
Hypoxic culture	Retinal ganglion cells	100 μ M and 500 μ M	Decreased amounts of LDH, phosphorylated JNK and NF-KB.	(83)
Oxygen-glucose deprivation	Primary-cultured astrocytes	100 μ M	Increased the cell viability.	(84)
Glutamate-induced neurotoxicity	Hippocampal neurons culture	100 μ M	Prevention of glutamatergic neurotoxicity. Decreased neuronal death induced by glutamate.	(88)
Oxidative stress injury	Retinal ganglion cells	up to 100 μ M	Increased cell viability. Attenuation of DNA fragmentation.	(33)

FST: forced swimming test; TST: tail suspension test; i.p.: intraperitoneal; p.o.: per oral; s.c.: subcutaneous; i.c.v.: intracerebroventricular

properties and there are an increasing number of studies addressing the CNS effects of agmatine in diverse cellular and animal models. Studies investigating the effects of exogenous agmatine administration have revealed a number of CNS relevant functions of this amine that are of potential therapeutic importance. For instance, preclinical studies have shown that agmatine has beneficial effects on hypoxic ischemia (15, 16), nociception (17, 18), morphine tolerance (19), drug withdrawal (20), seizures (21, 22), depression (23, 24), anxiety (25), memory (26) and Parkinson's disease (27, 28).

Over the last years, new evidence has extended our understanding of how agmatine may be effective in managing these CNS disorders. Although a specific ('own') agmatine postsynaptic receptor has not been identified, agmatine binds with high affinity to all subclasses of α 2-adrenoceptors and imidazoline binding sites (6). Moreover, it interacts with nicotinic cholinergic receptors (29), serotonin 5-HT₃ receptors (10) and blocks ligand-gated cation channels, particularly the glutamate N-methyl-D-aspartate (NMDA) receptors (30). As a result of novel insights into the mechanisms of action of agmatine, it is known that, at the intracellular level, it modulates the production of polyamines (involved in pro-mitotic processes) (1) and inhibits NOS in rodents, as previously mentioned (2). Furthermore, agmatine has anti-inflammatory properties (31, 32) and exerts protection against oxidative stress induced by increased mitochondrial volume, collapse of mitochondrial membrane potential and apoptosis by scavenging free radicals (33, 34). Moreover, agmatine induces its cellular and molecular effects, at least partially, by activating neurotrophic and neuroprotective pathways (35, 36).

This review attempts to provide a comprehensive picture of the role of agmatine in the CNS and to highlight recent findings from our group and others showing its

potential involvement in neurological and neurodegenerative diseases including epilepsies, depression, traumatic brain injury, Parkinson's disease (PD) and Alzheimer's disease (AD). Considering the available literature, we can anticipate that the central agmatineric system may be a new important target for the development of therapeutic tools for diverse CNS disorders.

3. EFFECTS OF AGMATINE IN DEPRESSION

The studies showing the antidepressant-like effects of agmatine in animal models are summarized in Table 1. The first preclinical evidence that agmatine has antidepressant-like effects in laboratory animal was provided by Zomkowski *et al.* (24), that showed that agmatine produced an anti-immobility effect in the forced swimming test (FST) and in the tail suspension test (TST) in mice. The antidepressant-like effect of agmatine was further confirmed in mice in the FST and TST (23) and in rats in the FST (37). Moreover, putrescine (the main metabolic product of agmatine) also produces antidepressant-like effects in the TST and FST. The mechanism by which putrescine exerts its effect in the FST seems to be dependent on its interaction with the polyamine-site at the NMDA receptor (38). Altogether, these early studies clearly indicated that agmatine exerts antidepressant-like effects in two tests widely used as predictive of antidepressant activity of drugs.

Independent research groups using diverse pharmacological tools such as selective receptor antagonists and agonists or enzyme inhibitors in mice have investigated the possible mechanisms underlying the effects of agmatine. It was proposed that the antidepressant-like effect of agmatine is dependent on the antagonism of NMDA receptors (24, 39), which is in agreement with the observation that NMDA receptor antagonists exhibit antidepressant properties in animal models, including the

Neuroprotective effects of agmatine

FST (40, 41) and TST (42). Moreover, it has also been found that the antidepressant-like effect of agmatine involves the inhibition of NOS in the brain (43, 44) as well as an activation of α_2 -adrenoceptors (24). Also, it was demonstrated that the anti-immobility effect of agmatine in the FST is due to the activation of serotonin 5-HT_{1A/1B} and 5-HT₂ receptors (45). Noteworthy, the antidepressant-like effect of selective serotonin reuptake inhibitors (SSRIs) in FST is potentiated by increasing brain agmatine levels by different means (including exogenous agmatine administration) or by imidazoline receptor agonists. These effects were prevented by serotonin receptor antagonists and arginine decarboxylase inhibitors. Interestingly, brain agmatine levels were significantly elevated by SSRIs (46). In contrast to these findings, Krass and colleagues suggested that serotonin did not mediate the antidepressant-like effect of agmatine, since parachlorophenylalanine (PCPA), an inhibitor of serotonin synthesis, was not able to abolish the anti-immobility effect of agmatine in the FST (47). These discrepancies between these previous studies can be attributed to differences in mouse's strains and in the doses of agmatine utilized, in addition to the fact that PCPA *per se* reduced the immobility time in the FST in the latter study. Other mechanisms proposed by which agmatine may exert its antidepressant-like effect are by activation of δ - and μ -opioid receptors (48) and imidazoline I₁ and I₂ receptors (39) as well as the inhibition of K⁺ channels (49).

Zhu *et al.* (50) demonstrated that repeated restraint stress caused a significant depletion of agmatine levels and structural changes including dendritic degeneration and/or retraction from cortical or pyramidal neurons in the medial prefrontal cortex and hippocampus in rats, whereas exogenously administered agmatine displayed neuroprotective effects against repetitive restraint stress-induced structural alterations in these brain regions. Furthermore, administration of agmatine prevented structural changes such as the decrease and disarrangement of dendrites and neurons in the medial prefrontal cortex and hippocampus of rats chronically treated with dexamethasone (51). It was recently shown that chronic treatment with agmatine, similar to fluoxetine, attenuates the behavioral impairments induced by chronic unpredictable mild stress in mice and normalized the elevated corticosterone levels and weight gain deficits associated with stress (52). One possibility to account for the anti-stress effects of agmatine is that this amine causes an up-regulation of adult hippocampal neurogenesis (35).

Regarding clinical studies, a reduced plasma concentration of agmatine was found in depressive patients in comparison to healthy subjects. Interestingly, the reduced agmatine concentrations tended to normalize following treatment with the antidepressant bupropion (53). However, a recent clinical study reported that the antidepressant effect of exogenous agmatine in three depressive patients was not reversed by PCPA (54). It should be noted that although Gilad *et al.* (55) found no differences in polyamine levels in the hippocampus and frontal cortex of patients with depression, a rat model (chronic unpredictable mild stress-induced anhedonia) displayed decreased hippocampal levels of putrescine, spermidine and spermine, as well as

decreased putrescine in the nucleus accumbens septi (56). Clinical studies showed decreased SAT1 expression, one of the major rate-limiting enzymes which catalyzes the acetylation of polyamines, which in turn is converted to putrescine, in the posterior cingulate gyrus, amygdala and hippocampus of suicide completers with depression, compared with those not suffering from depression (57).

Taking into account the results of these clinical and preclinical studies, the agmatine system may become a valuable target for the development of new treatments for depression as well as to increase the therapeutic efficacy of current antidepressants.

4. EFFECTS OF AGMATINE IN LEARNING AND MEMORY

Learning and memory are important aspects of human being, especially because they are involved in the control of our behavior, thoughts and actions throughout life. The cellular processes underlying memory are different with respect to its acquisition, consolidation and evocation (58). In particular, the modulation of synaptic connectivity, including changes in the number or structures of synapses, may represent a critical mechanism of learning and memory processes. Remarkably, the regulation of intracellular messenger pathways can be considered the basis of neural plasticity, therefore alterations in proteins synthesis, nuclear regulatory mechanisms and brain's signal transduction pathways can play a pivotal role as molecular mechanisms of learning and memory (59).

The first study addressing the effects of agmatine on memory was performed by Aterni *et al.* (26). In this work, agmatine improved memory in the step-down inhibitory avoidance task when administered one hour before the training session. Conversely, in the same year, another study demonstrated that agmatine could selectively impair some types of memory evaluated in different behavioral tasks, including contextual and auditory fear conditioning. Interestingly, this work showed that agmatine did not modify spatial learning, assessed in the Morris water maze paradigm (60). Therefore, the effects of agmatine on learning and memory varied according to the behavioral task used and the time point when it was administered during the memory evaluation.

As previously mentioned, agmatine is an endogenous polyamine present throughout the brain, including the hippocampus, an important area involved with learning and memory (61). It was demonstrated that the levels of agmatine in CA1 region and dentate gyrus subregions of the hippocampus, as well as entorhinal cortex and vestibular nucleus are higher in animals trained in the Morris water maze tasks in comparison with rats that only swim in the tank (61). In accordance with these results, Leitch *et al.* (62) showed that agmatine levels were significantly increased in the CA1 stratum radiatum of rats trained to find a hidden escape platform in the water maze task compared with those rats forced to swim in the pool with no platform. The hippocampal levels of agmatine and glutamate were also investigated in rats submitted to the

Neuroprotective effects of agmatine

spatial learning in the Morris water maze. Agmatine and glutamate are co-localized in cellular bodies of hippocampal pyramidal cells between CA1 and CA3 regions. Rats that exhibited a learning curve showed an increase in glutamate and agmatine levels in hippocampus (63). A recent work investigated the levels of agmatine before, during and after the performance of the Morris water maze task. During the learning phase, the levels of agmatine were increased by six times compared with the control group, suggesting that the endogenous agmatine system can be modulated during the learning process (64).

After exogenous administration, agmatine improves the cognitive performance of rats evaluated in the spatial reference memory and working memory versions of the water maze task (65, 66). In aged rats, although the intraperitoneal administration of agmatine did not increase exploratory activity and spatial reference learning and memory, it significantly improved spatial working memory and object recognition memory in parallel with an attenuation of age-related elevation in NOS activity and restoration of endothelial NOS protein to the normal level (67). Likewise, it was recently demonstrated that prolonged agmatine treatment (4-6 weeks) improved the performance of rats in the reversal test of the water maze and object recognition memory task, and significantly counteracted the age-related increase in NOS activity in the dentate gyrus of the hippocampus and prefrontal cortex (68). Further suggesting that agmatine is directly involved in learning and memory, it was shown that rats presented a positive correlation between the levels of agmatine and the learning observed in the T-maze test (69).

Lu *et al.* (70) evaluated a possible mechanism whereby agmatine modulates learning and memory functions. Pre-training and pre-test administration of agmatine to mice facilitated the acquisition and evocation, respectively, of memory in the step-down inhibitory avoidance task while post-training administration of agmatine had no effect on memory consolidation. In this same study, the authors demonstrated that a treatment with idazoxan (an antagonist of imidazoline receptors) prevented the beneficial effects of agmatine in the acquisition and evocation of memory. Moreover, pre-training administration of morphine (an agonist of opioid receptors) impaired the acquisition of memory while post-training and pre-test administration of morphine had no effect on memory consolidation and evocation. Interestingly, the pre-treatment of mice with agmatine prevented the impairments induced by morphine. Thus, it is possible to suggest that agmatine acts through the imidazoline receptors to modulate learning and memory. In the same year, it was demonstrated that agmatine modulated the long-term potentiation (LTP) in dentate gyrus of morphine-treated rats. Acute treatments with agmatine and morphine facilitated and attenuated, respectively, hippocampal LTP, and agmatine administration prevented the attenuation of hippocampal LTP induced by morphine. Conversely, chronic administration of morphine enhanced hippocampal LTP, an effect that was reversed by chronic treatment with agmatine. The administration of imidazoline receptor antagonist idazoxan prevented the effects of agmatine on LTP (71),

reinforcing the importance of imidazoline receptors in the effects of agmatine on memory function.

The interaction of agmatine with the glutamatergic neurotransmission is already well established. It is known that agmatine inhibits the opioid dependence and, although the exact neural mechanism involved in this interaction remains unclear, it may be related to the modulation of the glutamatergic system. It was showed that treatment of rats with agmatine prevented the excessive elevation of extracellular glutamate in nucleus accumbens and abolished the up-regulation of the NR1 subunit of NMDA receptors in animals treated with morphine (72). Therefore, these results demonstrated that agmatine can modulate neuroadaptations in the glutamatergic system involved in synaptic plasticity.

Neuroinflammation is related with increased pro-inflammatory cytokines, reactive oxygen and nitrogen species, blood-brain barrier impairments and activation of apoptotic and necrotic pathways, factors that can affect neuronal function and culminate in neurodegeneration (73). Bacterial lipopolysaccharide (LPS) administration is a well-established model for studying the inflammatory response in the CNS, and it is recognized that LPS treatment induces memory impairments. A study demonstrated that agmatine prevented memory impairments and the increase of caspase-3 in hippocampal tissue of rats treated with LPS (74).

The positive effects of agmatine administration on memory were also demonstrated in animals injected with scopolamine. The non-selective muscarinic receptor antagonist scopolamine inhibits cholinergic neurotransmission and induces impairments in learning and memory. Agmatine administration reduced, in a dose-dependent manner, the learning and memory deficits induced by scopolamine (75). Another study revealed that scopolamine treatment induced memory impairments associated with the decrease in NOS activity and the increase in arginase activity, L-ornithine and putrescine levels in the dentate gyrus (76), suggesting that L-arginine and its metabolites play a prominent role in the modulation of memory. Reinforcing the possible effects of agmatine on neuronal plasticity and memory, a more recent study showed that the pre-treatment with agmatine prevented the learning impairment and the inactivation of hippocampal extracellular-signal-regulated kinase (ERK) and serine-threonine kinase Akt (also known as protein kinase B) (biomarkers of hippocampal synaptic plasticity) induced by scopolamine (77). The memory enhancing effects of agmatine were also confirmed in streptozotocin-induced diabetic rats, which display learning and memory deficits associated with increased lipid peroxidation, reduced glutathione, and elevated choline esterase activity. Chronic treatment with agmatine (30 days) rescued cognitive performance, decrease hyperglycemia, oxidative stress, and choline esterase activity in diabetic rats (78).

Certainly additional brain systems and molecular mechanisms need to be studied to further clarify the role of

Neuroprotective effects of agmatine

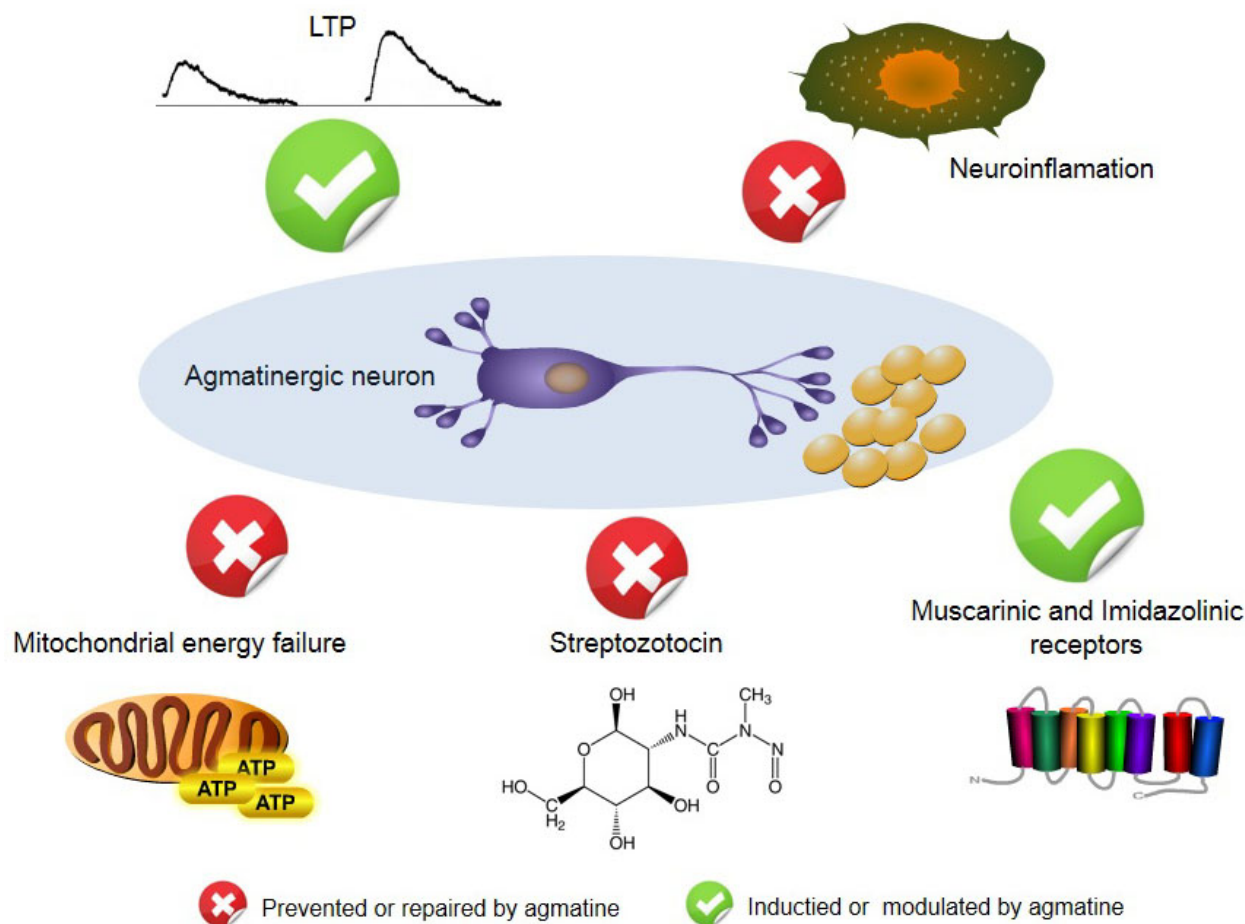


Figure 2. Protective effects of agmatine on learning and memory. Agmatine prevents or restores learning and memory impairments induced by neuroinflammation, mitochondrial energy failure and streptozotocin experimental models. Agmatine modulates several events related to learning and memory such as long-term potentiation (LTP) and muscarinic and imidazolinic receptors.

agmatine on learning and memory processes. However, from recent preclinical findings (summarized in Figure 2) demonstrating the ability of agmatine to improve age-related cognitive impairments and memory dysfunction in rats submitted to models of neuroinflammation, diabetic encephalopathy, AD and PD (see below), it appears that agmatine might be particularly useful to restore impaired learning and memory processes associated to neurological and neurodegenerative diseases.

5. THE NEUROPROTECTIVE PROPERTIES OF AGMATINE

As an effort to illustrate the potential of agmatine as an innovative target for future pharmacotherapies, the next sections attempt to review the results reported in clinical and animal studies to provide a comprehensive picture of the role of agmatine in neurodegenerative diseases. The neuroprotective effects of agmatine in different animal and cellular models are summarized in Table 2.

Over the last years, several independent research groups using a variety of animal models have demonstrated the neuroprotective properties of agmatine. Gilad *et al.* (79) provided the first evidence of the beneficial effects of agmatine in a medullar ischemic model. The treatment with agmatine improved the recovery of motor function and prevented the loss of medullar motor neurons after the ischemic injury in rats. Likewise, in a transient ischemic cat model, the treatment with agmatine decreased the TUNEL positive cells (predictive of apoptosis) and the neuronal ischemic impairment observed by the hematoxylin and eosin staining (80). Additionally, it was observed that administration of agmatine showed beneficial effects against transient cerebral ischemia in rats by reducing edema formation and neurotoxicity (81). In a recent study, the effects of agmatine and piperazine-1-carboxamide (an agmatinase inhibitor) were evaluated in hippocampal slices submitted to oxygen deprivation. Corroborating previous findings, the treatments showed beneficial effects compared to post-reoxygenated saline-treated controls (82).

Neuroprotective effects of agmatine

Table 2. Summary of the neuroprotective effects of agmatine observed in different animal and cellular models

Experimental model	Tested Animal	Agmatine dose and administration route	Possible mechanisms	Reference
FST TST FST	Mouse Mouse Mouse	0.001-50 mg/kg (i.p.) 0.001-50 mg/kg (i.p.) 100 mg/kg (i.c.v.)	Involvement of NMDAR, L - arginine-NO pathway and α 2- adrenoceptors	(24)
FST FST FST FST TST FST	Mouse Mouse Rat Rat Mouse Rat	40 e 80 mg/kg (p.o.) 20 mg/kg (s.c.) 10 mg/kg (p.o.) 1.25-5 mg/kg (s.c.) 40 e 80 mg/kg (p.o.) 10-100 mg/kg (i.p.)	Involvement of NMDA receptors	(23)
FST	Mouse	0.001 and 10 mg/kg (i.p.)		(37)
FST	Mouse	0.001 and 10 mg/kg (i.p.)	Involvement of imidazoline I-1 and I-2 receptors	(39)
FST	Mouse	10 mg/kg (i.p.)	Involvement of 5-HT1A/1B and 5-HT2 receptors	(45)
FST	Mouse	5 and 10 mg/kg (i.p.)	Modulation of imidazoline receptors by agmatine is implicated in the antidepressant-like effect of SSRIs.	(46)
FST	Mouse	10-50 mg/kg (i.p.)	Antidepressant-like effect of agmatine is not mediated by serotonergic system	(47)
FST	Mouse	10 mg/kg (i.p.)	Involvement of δ and μ -opioid receptors	(48)
FST	Mouse	0.001 and 10 mg/kg (i.p.)	Inhibition of K ⁺ channels	(49)

i.p.: intraperitoneal; p.o.: per oral; s.c.: subcutaneous

Some cellular pathways have been associated with the protective effects of agmatine in ischemic models. In cell culture, agmatine showed neuroprotective effects against hypoxia and decreased the lactate dehydrogenase (LDH) levels, phosphorylated c-Jun N-terminal kinase (JNK) and factor nuclear kappa B (NF- κ B), proteins that are involved with cellular death (83). Another work evaluated the effects of agmatine on oxygen-glucose deprived primary-cultured astrocytes. The treatment with agmatine increased cell viability and induced NF- κ B translocation to the nucleus, suggesting that this polyamine can prevent astrocytic death (84). It was also observed that the aquaporin levels were decreased after the treatment with agmatine, an effect that was accompanied by improved motor functions and decreased edema formation and blood brain barrier impairments in mice (85), which indicates that agmatine is able to treat the ischemic consequences by decreasing the aquaporin expression and the brain water volume.

Agmatine also demonstrated beneficial properties in spinal cord injury experimental models. Mice treated chronically (4 weeks) with agmatine showed improved recovery of medullar tissue transection (as showed by the reduced collagen scar, a physical barrier to axon regeneration) through increasing bone morphogenetic protein 7 (BMP-7, a neuroprotective marker) and decreasing transforming growth factor-beta 2 (TGF- β 2, a marker of collagen deposition) (86). A more recent study observed that impairments caused by the compression of the spinal cord were reduced after chronic treatment (35 days) with agmatine. The protective effects of this amine included improved motor and bladder functions, reduced demyelinated cells, neuronal loss and glial accumulation around the lesion (87).

Studies evaluating the effects of agmatine on cellular models of glutamatergic neurotoxicity demonstrated that, in presence of glutamate, agmatine induced neuroprotective effects in cerebellar granule cells (88),

hippocampal neurons culture (89, 90) and PC12 cells, a line derived from a pheochromocytoma of the rat adrenal medulla (90). In neuronal cultures, the metabolites of agmatine spermine and spermidine did not demonstrate such protective effects (91). The treatment with agmatine also showed a protective role in a glutamatergic model of epilepsy (92). Altogether, these results suggest the antagonism of NMDA receptor as an important neuroprotective mechanism whereby agmatine exerts its beneficial effects.

Another important factor that may contribute to neuroprotective effects of agmatine is the antioxidant property of this amine, since a study already demonstrated that agmatine exerted neuroprotective effects against the hydrogen peroxide-induced damage of retinal cultures cells (93). Mitochondrial functions are essential for the perfect functioning of neurons. In this regard, some aspects of the involvement of agmatine related to the mitochondrial scenario were evaluated. It was shown that the administration of agmatine preserved mitochondrial function and decreased apoptosis, necrosis, DNA fragmentation or chromatin condensation in cells. Agmatine also demonstrated scavenger properties, since it decreased oxidative stress, the expression of B-cell lymphoma 2 (Bcl-2) and caspase-3, and apoptosis induced by compotecin and 5-fluoracil (33). Taken together, these findings strongly suggest that mitochondrial protection by agmatine may also account for its neuroprotective effects.

6. ROLE OF AGMATINE IN NEURODEGENERATIVE DISEASES

6.1. Effects of agmatine in Parkinson's disease

The exact causes of Parkinson's disease (PD) remain unknown, but considerable evidence suggests a multifactorial etiology involving the interaction of genetic and environmental factors (94, 95). Although the degeneration of midbrain dopaminergic neurons in the substantia nigra pars compacta (SNc) is the key pathology

Neuroprotective effects of agmatine

marker that leads to motor impairments (96), a number of studies have shown that glutamatergic neurotransmission is an important factor in the pathophysiology of PD (97-99). Research into glutamate receptor signaling in the basal ganglia revealed increased glutamatergic transmission, which can be toxic to the remaining dopaminergic neurons, leading to further degeneration of dopaminergic transmission and progression of the disease (97). Reinforcing the involvement of the glutamatergic system in PD, clinical and pre-clinical findings demonstrated the efficacy of memantine and amantadine, two NMDA receptor antagonists, in the treatment of PD (100-104).

Considering that drugs modulating the glutamatergic system may have beneficial properties in PD therapy, some studies investigated whether agmatine treatment would be neuroprotective in experimental models of PD. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) mouse model of PD, agmatine treatment (beginning after MPTP injection) afforded a partial protection (31%) against MPTP dopaminergic toxicity in the SNc. Conversely, the same study observed that the concomitant daily treatment with agmatine (for 5 days) and MPTP (for 2 days) intensified the dopaminergic toxicity induced by MPTP (27).

A recent study evaluated the effects of agmatine on motor and non-motor symptoms observed in aged mice following the intranasal MPTP administration, a new model of PD developed recently by our group. Agmatine was administered once a day during five consecutive days before the treatment with MPTP by intranasal route in the 5th day. This pre-treatment was able to prevent the appearance of motor, cognitive and neurological impairments caused by MPTP. Moreover, agmatine protected the hippocampus from decreased glutamate uptake and the SNc from the reduction of tyrosine hydroxylase. Another important finding of this study was that agmatine prevent by about 40% the mortality induced by intranasal MPTP administration in aged mice (28).

The effects of agmatine were also evaluated in SH-SY5Y cell culture exposed to rotenone, another experimental model of PD. Treatment with agmatine decreased cellular damage caused by rotenone through suppression of oxidative stress in a dose-dependent manner. Agmatine also prevented rotenone-induced NF- κ B translocation and the dissipation of mitochondrial membrane potential. Moreover, it was observed a reduction of rotenone-induced increase of apoptotic factors (caspase-3, Bax, cytochrome c) after administration of agmatine (105). Using Fourier transform infrared spectroscopy analysis, a technique which detects molecular changes in disordered cells and tissues, it was showed that administration of agmatine significantly prevented rotenone-produced redox alteration and cellular damage at the level of protein structure (106), supporting the therapeutic potential of agmatine in the management of PD.

6.2. Effects of agmatine in Alzheimer's disease

Alzheimer's disease (AD), an irreversible, progressive neurodegenerative disorder, is the most common cause of dementia among older people and one of the largest social burdens in the world. The two major pathological hallmarks of AD are the extracellular

accumulation of amyloid-beta peptide (A β) and the presence of neurofibrillary tangles of the microtubule binding protein tau. The deposition of A β peptides and the activation of glial cells surrounding senile plaques in brain areas involved in cognitive functions are assumed to initiate a pathological cascade that results in synaptic dysfunction, synaptic loss, and neuronal death leading to the decline in memory, intellect and learning capacity observed in AD.

Although unable to induce all pathological AD hallmarks, there are many models of A β deposition that can be useful for the investigation of molecular mechanisms underlying A β toxicity, including the activity of mitochondrial complexes and oxidative stress, neuroinflammation, synaptic deficits and apoptotic neuronal cell death that lead to spatial learning and memory impairments (107). Despite the promising evidence showing that agmatine improves the rodents' performance in diverse learning and memory tasks, to our knowledge, there is only one study investigating the effects of agmatine in an animal model of AD. It was demonstrated that agmatine administration 30 min prior to A β infusion and then once daily for further nine consecutive days was able to prevent memory deficits induced by intracerebroventricular injection of A β 25-35 peptide in mice evaluated in Morris water maze, object recognition and radial arm maze tasks (108). Another study indirectly demonstrated the role of agmatineric system in AD by showing that the cognitive impairments induced by A β involves alterations in arginine metabolism in hippocampal regions (CA1, CA2, CA3 and dentate gyrus) as well as a decreased activity of NOS and agmatine levels in the rat hippocampus and prefrontal cortex (109).

The effect of aging and neurodegenerative diseases on polyamine biosynthesis in human brains was investigated in some studies. Morrison *et al.* (110) reported a significant increase (76%) of ornithine decarboxylase activity in the temporal cortex of autopsied brain tissue from AD patients, indicative of abnormal polyamine system activity in AD. Corroborating the importance of polyamines in the pathophysiology of AD, *post mortem* studies revealed higher protein levels of the enzyme ornithine decarboxylase in neocortical neurons (111), and altered polyamine levels in the frontal cortex (112). Accordingly, it was demonstrated that A β 1-42 and A β 25-35 peptides up-regulated polyamine metabolism by increasing ornithine decarboxylase activity and polyamine uptake in neuronal cultures (113), suggesting that polyamine supplementation might be useful in AD therapy.

Taken together, these animal and human studies raise the possibility that agmatineric system may play a role not only in the pathophysiology of AD, but also as potential strategy in the treatment of this disease. However, since only few animal and human studies are available, more studies are welcome to further evaluate the benefits of agmatine for the prevention and/or treatment of AD.

7. EFFECTS OF AGMATINE IN TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is defined as a damage to the brain caused by an external physical trauma

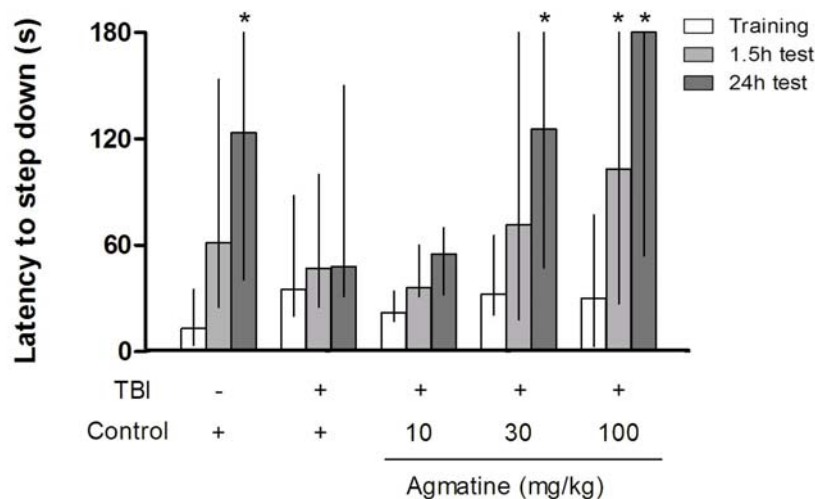


Figure 3. Effects of agmatine on learning and memory of mice evaluated in the step-down inhibitory avoidance task at 14-15 days after traumatic brain injury. Data are expressed as latencies to step-down (median and interquartile range) in the training session and the test sessions performed after an interval of 1.5 h and 24 h for control mice (no head impact), and mice subjected to head impact using 12.5-g weight. At dose of 30 mg/kg, agmatine was able to prevent the long-term memory deficits induced by TBI and at a dose of 100 mg/kg agmatine prevented both short- and long-term memory impairments induced by TBI. * $p \leq 0.05$ compared to the training session of the same group (Kruskal-Wallis nonparametric test followed by Dunn's test).

(114). It is important to mention that a simple head impact does not constitute TBI, since it requires manifestations of encephalic involvement such as altered level of consciousness, amnesia, disorientation, neurological deficits, neuroimaging abnormalities, or even immediate death (114). TBI is a worldwide health problem with alarming epidemiological rates. It is estimated that about 10 million people are affected annually by TBI (115).

Pathophysiological manifestations of TBI can be classified into acute and delayed events (116). Acute events are all the manifestations which can occur minutes to hours after initial injury, such as blood vessel compromise (endothelial damage, impaired regulation of cerebral blood flow), tissue damage (excitotoxicity, metabolic imbalance) (116), focal contusions, hematomas, diffuse swelling, microporation of membranes, and steric conformational changes in proteins (114, 116, 117). Delayed events can appear within hours to days following the trauma and, generally, they occur as a consequence of acute events. Delayed events include edema, inflammatory responses, blood-brain barrier breakdown, dysfunction of astrocytes and microglia, excitotoxicity, oxidative stress, mitochondrial dysfunction and hypoxia (114, 116, 118).

It is well recognized that the conjunction of acute and delayed events of TBI can lead to the development of several diseases such as psychiatric disorders (119), cognitive changes (120), seizures and epilepsy (116, 121) and AD (122). Because these manifestations are not always noticeable in the initial assessments after TBI and can occur months or years after TBI, it is often referred to as the "silent epidemic" (123).

Agmatine emerges as a promising agent in the management of TBI related disorders because it is capable

of acting in acute and delayed events after TBI. The beneficial effects of agmatine were investigated in male Sprague-Dawley rats subjected to TBI induced by Marmarou's impact-acceleration. In this work, the authors showed that up to 4 days of agmatine administration (immediately after TBI) has a beneficial effect in axonal, neuronal and vascular changes associated with diffuse brain injury (evaluated 8 days after TBI) (124).

Agmatine therapy adopted immediately after TBI induced by fluid percussion injury in male Sprague-Dawley rats was able to suppress TBI-associated intracranial hypertension, cerebral hypotension, cerebral infarction, motor and proprioception deficits, and body weight loss (125). Elsewhere, the positive effects of 4-day administration of agmatine after TBI induced by fluid percussion injury in male Sprague-Dawley rats were confirmed by Kuo *et al.* (126). In this study agmatine attenuated TBI-induced motor deficits, and cerebral infarction. Moreover, agmatine stimulated angiogenesis and neurogenesis, and reduced neuronal and glial apoptosis, neuronal loss, gliosis and neurotoxicity (126).

Unpublished data from our group demonstrated that agmatine at doses of 30 and 100 mg/kg is able to reverse the cognitive deficits in female Swiss mice evaluated in step-down inhibitory avoidance task at 14-15 days after moderate TBI induced by free weight-drop device (Figure 3), a model previously standardized in our laboratory (127).

Despite this limited number of studies available in the literature exploring the role of agmatine in TBI, we can anticipate a therapeutic potential of agmatine in TBI-related alterations/disorders, and this constitutes a very

Neuroprotective effects of agmatine

interesting field that require further research. An important mechanism involved in the protective effects of agmatine following TBI involves the control of excessive levels of NO and glutamate in different brain areas including the neocortex and hippocampus. Interestingly, another putative mechanism by which agmatine exerts its protective effects may involve the production of its metabolites, since it was demonstrated that spermine and spermidine levels are reduced following TBI, leading to a disruption of mitochondrial membrane potential and induction of apoptosis (128). Although research is at a very early stage, the findings reviewed above further highlight that polyamine supplementation may constitute a simple therapeutic approach in the treatment of TBI.

8. EFFECTS OF AGMATINE IN EPILEPSY

Epilepsies are chronic brain diseases characterized by recurrent epileptic seizures affecting 1% of worldwide population (129). Epileptogenesis is the process of formation of hyperexcitable epileptic tissue through complex modifications in the intrinsic physiology of neurons and glial cells and their connections network leading to synchronization and propagation of the abnormal neuronal activity to the normal non-epileptogenic tissue (130-132). Epileptic seizures result from an excessive excitability of neurons with abnormal intrinsic physiology in aberrant or normal synchronizing networks (131). The highly interconnected excitatory cells (the pyramidal neurons) modulated by the inhibitory interneurons of hippocampus and neocortex make these structures prone to the rapid recruitment of neurons during epileptiform discharges of neurons with abnormal intrinsic physiology (133). The excitability is the property whereby neurons and neuronal populations can be depolarized when adequately stimulated. The excitability of neurons depends of membrane (ionic channels) and intracellular (ionic pumps, second messengers, kinases proteins, phosphatases proteins, and energetic supply) characteristics, also called intrinsic physiology (131, 132, 134)

In the neocortex (layers II–VI) (134) and hippocampus (131), most of the pyramidal cells are “regular spiking,” which usually fire a single spike for each threshold stimulation. In layer V of the neocortex and CA1 region of hippocampus, there are “intrinsically bursting” cells in which the minimal response to a single threshold stimulus is a high-frequency cluster of action potentials (“bursts”) (131, 135). These “intrinsically bursting” cells disclose an important role in the hippocampal and neocortical epileptiform activity induced pharmacologically (131, 135) or by brain insult (136). Animals with temporal lobe epilepsy induced by pilocarpine (131) show an increased number of “intrinsically bursting” cells in the CA1 region (47% of CA1 neurons) in comparison with controls (only 3%). Some of these “intrinsically bursting” neurons develop spontaneous bursts, which are not observed in controls (131). Spontaneous neuronal firings have been also demonstrated in the layer V of neocortex of rats submitted to controlled cortical impact (CCI) model of TBI (136). The spontaneous interictal epileptiform discharges of single neurons were also demonstrated in humans (130).

The ictogenesis refers to the seizure beginning in the epileptogenic zone due to the imbalance between the excitatory and inhibitory mechanisms (137). The epileptiform discharges are brief periods of synaptic excitation followed by synaptic inhibition (hyperpolarization) of neurons derived from an imbalance between excitatory and inhibitory influences and adequate interconnected neuronal networks (131-134). The interictal spikes occur when a neuronal population is depolarized at the same time (synchronously), which requires the harmonic interaction between the inhibitory mechanisms and the further excitatory input that will stimulate these neurons all together (out of the refractory period). The GABAergic inhibitory neurons (135) the ATP hydrolysis to adenosine on the synaptic cleft (138, 139), and depletion of presynaptic excitatory terminal (135) contribute to the termination of the synchronized epileptiform events. The transition from interictal spikes to full seizures associated with maintained (tonic phase) depolarization has been related to gradual loss of the burst after-hyperpolarization and progressive appearance of repetitive bursts of activity during prolonged after-depolarization (135). Later, in the clonic phase, irregular periodic bursts occur, and the neuronal activity evolves a relative quiet period of “postictal depression” (135).

The time-course for epileptogenesis development is variable according to the epileptic syndrome or peculiarity of patients. In some cases a clear epileptogenic event like a traumatic brain injury or meningitis can be identified clinically, electrophysiologically and by structural neuroimaging. However, in a considerable number of cases, the epileptogenesis develops almost spontaneously due to innate individual characteristics (genetic inheritance) (132). Interestingly, even in well-defined syndromes the clinical manifestations, including age of recurrent seizure onset, frequency of seizures, seizure semiology, pharmacologic and surgical response, as well as cognitive and psychiatric associated manifestation are variable. This variability indicates that epilepsies are multifactorial diseases not only in their installation (epileptogenesis) but also clinical manifestation (ictogenesis and seizures occurrence). Although several preliminary experimental results seemed promising toward the development of anti-epileptogenic drugs, they have not proved to be clinically effective against epileptogenesis (140, 141). Nowadays, the pharmacological treatments of epilepsies are resumed to enhance the seizure threshold, without any proved relevant anti-epileptogenic effect in the clinical praxis. In addition, even with the adequate pharmacological treatment, 20 to 30% of patients with epilepsy remain with seizures (129, 141). In the past 15 years, no clinically relevant progress has been made to reduce the incidence of refractory epilepsy. This prompts an urgent need to develop drugs with clinically proved anti-epileptogenic and anti-ictogenic properties (141). Some preliminary findings using neurochemical approaches applied to experimental models suggests that epileptogenesis and ictogenesis may be, at least in part, dissociated processes according to the molecular, cellular and brain regions (140), even as to the time-course of disease installation (138, 139, 142, 143).

Table 3. Summary of the studies showing the putative effects of agmatine on epileptic seizure models in rodents

Experimental models	Subject	Agmatine dose and administration route	Summary of findings	Summarized Conclusion	Reference
PTZ (i.p.). Maximal electroshock (MES).	Adult male and female Swiss albino mice.	20, 40, 80 or 100 mg/kg (i.p., 30 min before PTZ). 20, 40, 80 or 100 mg/kg (i.p., 45 min before electrical stimulation).	Increase the seizures threshold and increase tonic-clonic seizures occurrence. Increased the threshold of MES but not in a dose-dependent manner.	Differential effects according to investigated model.	(146)
Lithium-PTZ (i.v).	Adult male NMRI mice.	1, 3, 5, 10, 20 mg/kg (i.p., 15, 30, 45, 60, or 75 min prior to PTZ).	Potentiate the lithium dose dependently increases of threshold for PTZ-induced seizures.	Adjuvant anticonvulsive effect with lithium.	(147)
Lithium-PTZ, 0.5%, i.v.	Adult male NMRI mice.	1, 3, 5, 10, 20 mg/kg (i.p., 15, 30, 45, 60, or 75 min prior to PTZ).	Potent anticonvulsant properties with the maximum effect at dose 20 mg/kg when administered 45 min before the induction of seizure. Enhances the lithium anti-convulsive effects.	Anticonvulsive effect alone or potentiate the lithium anticonvulsant properties.	(148)
Maximal electroshock seizure (MES).	Male Sprague - Dawley rats age 28-38 days and adult male albino mice.	Rats: 30, 60, or 120 mg/kg (orally or i.p., 0.25, 0.5, 1, 2, 4, or 6 h before electrical stimulus). Mice: 30, 100, or 300 mg/kg (orally or i.p., 0.5 and 4 h before electrical stimulus).	Protection was observed at 15 min after agmatine administration and remained consistent until 2 h after agmatine administration. The peak effect was observed at 4 h. I.p and p.o. administrated doses greater than 30 mg/kg were inconsistent, with minimal protection observed at time points greater than 2 h. Non-effective in the mouse MES model at i.p. doses of up to 300 mg/kg. Orally 30 mg/kg doses prevented seizure spread in 8.3.% to 16.7.% and in 50% of rats tested at 4 hours.	Anticonvulsant effect at nontoxic doses, with rapid onset of action after oral administration. No acute neurological toxicity was observed.	(21)
PTZ., i.v.	Adult male NMRI mice	5, 10, 20, 40 mg/kg (i.v., 15 to 120 min before PTZ).	Increases the PTZ-induced seizures threshold seizure in a dose-dependent manner with maximum response at 45 min and significant response lasted up to 75 min.	Dose- and time-dependent anticonvulsant effects.	(149)
PTZ, i.p.	Adult male Sprague-Dawley rats.	100 mg/kg (i.p., 15 min prior to PTZ).	Reduced the severity and enhance the threshold of seizures.	Reduces PTZ-induced seizures and inhibits increased glutamate release.	(92)
Maximal electroshock seizure (MES).	Adult male Swiss mice.	5 ml/kg, 50 and 100 mg/kg (i.p., 45 min before ECT).	At 100 mg/kg did not alter the threshold for MES. Selectively enhanced the anti-seizure activity of phenobarbital and valproate, and no effect with CBZ, phenytoin, lamotrigine, topiramate and oxcarbazepine.	Adjuvant effect for phenobarbital and valproate without affecting their pharmacokinetic profile.	(150)
PTZ, s.c.	Adult male Swiss mice.	5 ml/kg, 50 and 100 mg/kg (i.p., 45 min before PTZ).	Systemically (50 and 100 mg/kg) did not affect the seizure threshold. Reduces the anticonvulsant effect of the vigabatrin.	None effect alone, and reduced the vigabatrin anticonvulsant effect.	(151)
PTZ, i.v.	Adult male NMRI mice.	10 ml/kg (i.p.).	Increases the threshold to PTZ-induced seizures in a dose-dependent manner (this effect was observed at doses of 10 and 20 mg/kg).	Anticonvulsant effects that might be exerted through melatonin ML1 and ML2 receptors.	(152)
PTZ, i.v.	Adult male and Swiss mice.	0.3, 1, 2 and 5 mg/kg (i.p.).	The concomitant administration of the low doses of agmatine (1 mg/kg) and morphine (as low as 0.05 mg/kg) induced a synergistic anticonvulsant effect.	Potentiate the anticonvulsant effect of the opioid receptor agonist.	(153)
Maximal electroshock seizure (MES). Glutamate-induced convulsion, i.c.v.	Adult male Kunming mice.	2, 4, 6, 8, 12 and 16 mg/kg (i.c.v., 5 min before electrical stimulation or glutamate). 10, 20, 40, 80, 160 mg/kg (s.c., 30 min before electrical stimulation).	Shortened the times of the tonic and clonic phases of mouse convulsion induced by MES in a dose-dependent manner (lasted at least 4 h). Dose-dependently inhibition of glutamate-induced convulsion.	Anticonvulsive effects on MES- and glutamate-induced convulsions.	(22)

i.c.v.: intracerebroventricular; i.p.: intraperitoneal; i.v.: intravenous; s.c.: subcutaneous

As discussed in other sessions of this paper and by other authors (144), agmatine may modulate functions

direct or indirectly related to membrane and cytoplasmic targets including neurotransmitters receptors, ion channels,

Neuroprotective effects of agmatine

NO, polyamine metabolism, membrane transporters, advanced glycation end products (AGE) and of protein arginine ADP-ribosylation. These cellular targets and their correlated biochemical pathways may be differentially involved in the epileptogenesis and ictogenesis processes. Several inborn (malformation of cortical development) and acquired pathologies (ischemic or hemorrhagic stroke, TBI, inflammation, brain tumors, prolonged seizures) are epilepsy risk factors. The adaptive mechanisms involving neuroplasticity are required for recovery of brain function after injury, but they may be involved in the epileptogenesis process (132). The lack of specificity of agmatine actions could be an advantage for candidate substance to be applied in the treatment of multifactorial diseases like epilepsies. The acute or chronic systemic treatment with agmatine facilitated hippocampal LTP in the lateral perforant path (LPP)-granule cell synapses of dentate gyrus in urethane anesthetized rats (71). These findings suggest that agmatine can modulate the long-term activity-dependent neuroplasticity in rodents. A literature review in Pubmed using the terms agmatine and epileptogenesis, ictogenesis or epilepsy, we identify several reports showing its putative anti-ictogenic properties tested in acute models of pharmacologically and electrically induced seizures that are summarized in Table 3.

Surprisingly, there were no published studies investigating the anti-epileptogenic potential of agmatine. Further works are required to determine the anti-epileptogenic effects of agmatine in epileptogenesis in chronic epilepsy models induced chemically or electrically. Furthermore, the recent proved safety and efficacy dietary agmatine sulfate for lumbar disc-associated radiculopathy creates an expectation for agmatine clinical use in other psychiatric and neurologic diseases including epilepsies (145).

9. CONCLUSION

In this review we presented basic research data combined with clinical studies in an attempt to clarify the potential role of agmatine as a neuromodulator and neuroprotective agent. Taking into account that agmatine is a low toxicity compound (that is already clinically used for the treatment of neuropathic pain) (145), we strongly believe that the agmatine system should be further investigated as a new approach for dealing with depression, neurological and neurodegenerative disease. Moreover, the considerable amount of literature showing positive effects of agmatine as a neuroprotective agent in models of neurotoxicity, ischemic brain and spinal cord injuries offers a promising scenario regarding the use of this polyamine for CNS diseases therapeutics.

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11. REFERENCES

1. C. W. Tabor and H. Tabor: Polyamines. *Annu Rev Biochem*, 53, 749-90 (1984)
2. E. Galea, S. Regunathan, V. Eliopoulos, D. L. Feinstein and D. J. Reis: Inhibition of mammalian nitric oxide synthases by agmatine, an endogenous polyamine formed by decarboxylation of arginine. *Biochem J*, 316 (Pt 1), 247-9 (1996)
3. S. Regunathan and J. E. Piletz: Regulation of inducible nitric oxide synthase and agmatine synthesis in macrophages and astrocytes. *Ann N Y Acad Sci*, 1009, 20-9 (2003)
4. M. Sastre, S. Regunathan, E. Galea and D. J. Reis: Agmatinase activity in rat brain: a metabolic pathway for the degradation of agmatine. *J Neurochem*, 67(4), 1761-5 (1996)
5. D. J. Reis and S. Regunathan: Agmatine: An Endogenous Ligand at Imidazoline Receptors Is a Novel Neurotransmitter. *Ann N Y Acad Sci*, 881(1), 65-80 (1999)
6. G. Li, S. Regunathan, C. J. Barrow, J. Eshraghi, R. Cooper and D. J. Reis: Agmatine: an endogenous clonidine-displacing substance in the brain. *Science*, 263(5149), 966-9 (1994)
7. G. E. N. Li, S. Regunathan and D. J. Reis: Agmatine Is Synthesized by a Mitochondrial Arginine Decarboxylase in Rat Brain. *Ann N Y Acad Sci*, 763(1), 325-329 (1995)
8. W. Raasch, S. Regunathan, G. Li and D. J. Reis: Agmatine, the bacterial amine, is widely distributed in mammalian tissues. *Life Sciences*, 56(26), 2319-2330 (1995)
9. K. Otake, D. A. Ruggiero, S. Regunathan, H. Wang, T. A. Milner and D. J. Reis: Regional localization of agmatine in the rat brain: an immunocytochemical study. *Brain Res*, 787(1), 1-14 (1998)
10. D. J. Reis, X.-C. Yang and T. A. Milner: Agmatine containing axon terminals in rat hippocampus form synapses on pyramidal cells. *Neuroscience Letters*, 250(3), 185-188 (1998)
11. S. Regunathan, D. L. Feinstein, W. Raasch and D. J. Reis: Agmatine (decarboxylated arginine) is synthesized and stored in astrocytes. *Neuroreport*, 6(14), 1897-900 (1995)
12. D. J. Reis and S. Regunathan: Agmatine: a novel neurotransmitter? *Adv Pharmacol*, 42, 645-9 (1998)
13. Y. Feng, A. E. Halaris and J. E. Piletz: Determination of agmatine in brain and plasma using high-performance liquid chromatography with fluorescence detection. *Journal*

Neuroprotective effects of agmatine

of *Chromatography B: Biomedical Sciences and Applications*, 691(2), 277-286 (1997)

14. A. Halaris and J. Plietz: Agmatine : metabolic pathway and spectrum of activity in brain. *CNS Drugs*, 21(11), 885-900 (2007)

15. Y. Feng, J. E. Piletz and M. H. Leblanc: Agmatine suppresses nitric oxide production and attenuates hypoxic-ischemic brain injury in neonatal rats. *Pediatr Res*, 52(4), 606-11 (2002)

16. G. M. Gilad, K. Salame, J. M. Rabey and V. H. Gilad: Agmatine Treatment Is Neuroprotective in Rodent Brain Injury Models. *Life Sciences*, 58(2), P141-P146 (1995)

17. C. A. Fairbanks, K. L. Schreiber, K. L. Brewer, C. G. Yu, L. S. Stone, K. F. Kitto, H. O. Nguyen, B. M. Grocholski, D. W. Shoeman, L. J. Kehl, S. Regunathan, D. J. Reis, R. P. Yezierski and G. L. Wilcox: Agmatine reverses pain induced by inflammation, neuropathy, and spinal cord injury. *Proc Natl Acad Sci U S A*, 97(19), 10584-9 (2000)

18. A. R. Santos, V. M. Gadotti, G. L. Oliveira, D. Tibola, A. F. Paszcuk, A. Neto, H. M. Spindola, M. M. Souza, A. L. Rodrigues and J. B. Calixto: Mechanisms involved in the antinociception caused by agmatine in mice. *Neuropharmacology*, 48(7), 1021-34 (2005)

19. Y. Kolesnikov, S. Jain and G. W. Pasternak: Modulation of opioid analgesia by agmatine. *Eur J Pharmacol*, 296(1), 17-22 (1996)

20. I. T. Uzbay, O. Yesilyurt, T. Celik, H. Ergun and A. Isimer: Effects of agmatine on ethanol withdrawal syndrome in rats. *Behav Brain Res*, 107(1-2), 153-9 (2000)

21. A. K. Bence, D. R. Worthen, J. P. Stables and P. A. Crooks: An *in vivo* evaluation of the antiseizure activity and acute neurotoxicity of agmatine. *Pharmacol Biochem Behav*, 74(3), 771-5 (2003)

22. R. B. Su, X. L. Wei, J. Q. Zheng, Y. Liu, X. Q. Lu and J. Li: Anticonvulsive effect of agmatine in mice. *Pharmacol Biochem Behav*, 77(2), 345-9 (2004)

23. Y. F. Li, Z. H. Gong, J. B. Cao, H. L. Wang, Z. P. Luo and J. Li: Antidepressant-like effect of agmatine and its possible mechanism. *Eur J Pharmacol*, 469(1-3), 81-8 (2003)

24. A. D. Zomkowski, L. Hammes, J. Lin, J. B. Calixto, A. R. Santos and A. L. Rodrigues: Agmatine produces antidepressant-like effects in two models of depression in mice. *Neuroreport*, 13(4), 387-91 (2002)

25. Z. H. Gong, Y. F. Li, N. Zhao, H. J. Yang, R. B. Su, Z. P. Luo and J. Li: Anxiolytic effect of agmatine in rats and mice. *Eur J Pharmacol*, 550(1-3), 112-6 (2006)

26. N. S. Arteni, D. Lavinsky, A. L. Rodrigues, V. B. Frison and C. A. Netto: Agmatine facilitates memory of an inhibitory avoidance task in adult rats. *Neurobiol Learn Mem*, 78(2), 465-9 (2002)

27. G. M. Gilad, V. H. Gilad, J. P. Finberg and J. M. Rabey: Neurochemical evidence for agmatine modulation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxicity. *Neurochem Res*, 30(6-7), 713-9 (2005)

28. F. C. Matheus, A. S. Aguiar, Jr., A. A. Castro, J. G. Villarinho, J. Ferreira, C. P. Figueiredo, R. Walz, A. R. Santos, C. I. Tasca and R. D. Prediger: 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*, 235(2), 263-72 (2012)

29. R. H. Loring: Agmatine Acts as an Antagonist of Neuronal Nicotinic Receptors. *Br J Pharmacol*, 99(1), 207-211 (1990)

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

31. Y. Gu, X. Fan, C. Zhang, X. Yang, Y. X. Bao and H. P. Liang: (The protective effects of agmatine in zymosan induced acute lung injury in mice). *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue*, 23(11), 665-8 (2011)

32. J. Satriano, D. Schwartz, S. Ishizuka, M. J. Lortie, S. C. Thomson, F. Gabbai, C. J. Kelly and R. C. Blantz: Suppression of inducible nitric oxide generation by agmatine aldehyde: Beneficial effects in sepsis. *Journal of Cellular Physiology*, 188(3), 313-320 (2001)

33. M. A. Arndt, V. Battaglia, E. Parisi, M. J. Lortie, M. Isome, C. Baskerville, D. P. Pizzo, R. Ientile, S. Colombatto, A. Toninello and J. Satriano: The arginine metabolite agmatine protects mitochondrial function and confers resistance to cellular apoptosis. *Am J Physiol Cell Physiol*, 296(6), C1411-9 (2009)

34. V. Battaglia, S. Grancara, J. Satriano, S. Saccoccio, E. Agostinelli and A. Toninello: Agmatine prevents the Ca(2+)-dependent induction of permeability transition in rat brain mitochondria. *Amino Acids*, 38(2), 431-7 (2010)

35. Y. F. Li, H. X. Chen, Y. Liu, Y. Z. Zhang, Y. Q. Liu and J. Li: Agmatine increases proliferation of cultured hippocampal progenitor cells and hippocampal neurogenesis in chronically stressed mice. *Acta Pharmacol Sin*, 27(11), 1395-400 (2006)

36. M. Y. Zhu, W. P. Wang, Z. W. Cai, S. Regunathan and G. Ordway: Exogenous agmatine has neuroprotective effects against restraint-induced structural changes in the rat brain. *Eur J Neurosci*, 27(6), 1320-32 (2008)

Neuroprotective effects of agmatine

37. F. Aricioglu and H. Altunbas: Is agmatine an endogenous anxiolytic/antidepressant agent? *Ann N Y Acad Sci*, 1009, 136-40 (2003)
38. A. D. Zomkowski, A. R. Santos and A. L. Rodrigues: Putrescine produces antidepressant-like effects in the forced swimming test and in the tail suspension test in mice. *Prog Neuropsychopharmacol Biol Psychiatry*, 30(8), 1419-25 (2006)
39. M. P. Zeidan, A. D. Zomkowski, A. O. Rosa, A. L. Rodrigues and N. H. Gabilan: Evidence for imidazoline receptors involvement in the agmatine antidepressant-like effect in the forced swimming test. *Eur J Pharmacol*, 565(1-3), 125-31 (2007)
40. S. Maeng, C. A. Zarate, Jr., J. Du, R. J. Schloesser, J. McCammon, G. Chen and H. K. Manji: Cellular mechanisms underlying the antidepressant effects of ketamine: role of alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptors. *Biol Psychiatry*, 63(4), 349-52 (2008)
41. B. Szewczyk, E. Poleszak, M. Sowa-Kucma, A. Wrobel, S. Slotwinski, J. Listos, P. Wlaz, A. Cichy, A. Siwek, M. Dybala, K. Golembiowska, A. Pile and G. Nowak: The involvement of NMDA and AMPA receptors in the mechanism of antidepressant-like action of zinc in the forced swim test. *Amino Acids*, 39(1), 205-17 (2010)
42. M. Moretti, A. E. Freitas, J. Budni, S. C. Fernandes, O. Balen Gde and A. L. Rodrigues: Involvement of nitric oxide-cGMP pathway in the antidepressant-like effect of ascorbic acid in the tail suspension test. *Behav Brain Res*, 225(1), 328-33 (2011)
43. W. Raasch, U. Schafer, J. Chun and P. Dominiak: Biological significance of agmatine, an endogenous ligand at imidazoline binding sites. *Br J Pharmacol*, 133(6), 755-80 (2001)
44. D. J. Reis and S. Regunathan: Is agmatine a novel neurotransmitter in brain? *Trends Pharmacol Sci*, 21(5), 187-93 (2000)
45. A. Dias Elpo Zomkowski, A. Oscar Rosa, J. Lin, A. R. Santos, J. B. Calixto and A. Lucia Severo Rodrigues: Evidence for serotonin receptor subtypes involvement in agmatine antidepressant like-effect in the mouse forced swimming test. *Brain Res*, 1023(2), 253-63 (2004)
46. B. G. Taksande, N. R. Kotagale, S. J. Tripathi, R. R. Ugale and C. T. Chopde: Antidepressant like effect of selective serotonin reuptake inhibitors involve modulation of imidazoline receptors by agmatine. *Neuropharmacology*, 57(4), 415-24 (2009)
47. M. Krass, G. Wegener, E. Vasar and V. Volke: Antidepressant-like effect of agmatine is not mediated by serotonin. *Behav Brain Res*, 188(2), 324-8 (2008)
48. A. D. Zomkowski, A. R. Santos and A. L. Rodrigues: Evidence for the involvement of the opioid system in the agmatine antidepressant-like effect in the forced swimming test. *Neurosci Lett*, 381(3), 279-83 (2005)
49. J. Budni, V. M. Gadotti, M. P. Kaster, A. R. Santos and A. L. Rodrigues: Role of different types of potassium channels in the antidepressant-like effect of agmatine in the mouse forced swimming test. *Eur J Pharmacol*, 575(1-3), 87-93 (2007)
50. M. Y. Zhu, W. P. Wang, J. Huang, Y. Z. Feng, S. Regunathan and G. Bissette: Repeated immobilization stress alters rat hippocampal and prefrontal cortical morphology in parallel with endogenous agmatine and arginine decarboxylase levels. *Neurochem Int*, 53(6-8), 346-54 (2008)
51. M. Y. Zhu, W. P. Wang, J. Huang and S. Regunathan: Chronic treatment with glucocorticoids alters rat hippocampal and prefrontal cortical morphology in parallel with endogenous agmatine and arginine decarboxylase levels. *J Neurochem*, 103(5), 1811-20 (2007)
52. B. G. Taksande, D. S. Faldu, M. P. Dixit, J. N. Sakaria, M. M. Aglawe, M. J. Umekar and N. R. Kotagale: Agmatine attenuates chronic unpredictable mild stress induced behavioral alteration in mice. *Eur J Pharmacol*, 720(1-3), 115-20 (2013)
53. A. Halaris, H. Zhu, Y. Feng and J. E. Piletz: Plasma agmatine and platelet imidazoline receptors in depression. *Ann N Y Acad Sci*, 881, 445-51 (1999)
54. B. Shopsin: The clinical antidepressant effect of exogenous agmatine is not reversed by parachlorophenylalanine: a pilot study. *Acta Neuropsychiatrica*, 25(02), 113-118 (2013)
55. G. M. Gilad, V. H. Gilad, M. F. Casanova and R. A. Casero, Jr.: Polyamines and their metabolizing enzymes in human frontal cortex and hippocampus: preliminary measurements in affective disorders. *Biol Psychiatry*, 38(4), 227-34 (1995)
56. S. Genedani, S. Saltini, A. Benelli, M. Filaferro and A. Bertolini: Influence of SAME on the modifications of brain polyamine levels in an animal model of depression. *Neuroreport*, 12(18), 3939-42 (2001)
57. L. M. Fiori and G. Turecki: Implication of the polyamine system in mental disorders. *J Psychiatry Neurosci*, 33(2), 102-10 (2008)
58. E. R. Kandel: The molecular biology of memory storage: a dialogue between genes and synapses. *Science*, 294(5544), 1030-8 (2001)
59. B. Milner, L. R. Squire and E. R. Kandel: Cognitive neuroscience and the study of memory. *Neuron*, 20(3), 445-68 (1998)

Neuroprotective effects of agmatine

60. B. E. McKay, W. E. Lado, L. J. Martin, M. A. Galic and N. M. Fournier: Learning and memory in agmatine-treated rats. *Pharmacol Biochem Behav*, 72(3), 551-7 (2002)
61. P. Liu, N. D. Collie, S. Chary, Y. Jing and H. Zhang: Spatial learning results in elevated agmatine levels in the rat brain. *Hippocampus*, 18(11), 1094-8 (2008)
62. B. Leitch, O. Shevtsova, K. Reusch, D. H. Bergin and P. Liu: Spatial learning-induced increase in agmatine levels at hippocampal CA1 synapses. *Synapse*, 65(2), 146-53 (2011)
63. S. Seo, P. Liu and B. Leitch: Spatial learning-induced accumulation of agmatine and glutamate at hippocampal CA1 synaptic terminals. *Neuroscience*, 192, 28-36 (2011)
64. M. Rushaidhi, Y. Jing, H. Zhang and P. Liu: Participation of hippocampal agmatine in spatial learning: an *in vivo* microdialysis study. *Neuropharmacology*, 65, 200-5 (2013)
65. P. Liu and D. H. Bergin: Differential effects of i.c.v. microinfusion of agmatine on spatial working and reference memory in the rat. *Neuroscience*, 159(3), 951-61 (2009)
66. P. Liu and N. D. Collie: Behavioral effects of agmatine in naive rats are task- and delay-dependent. *Neuroscience*, 163(1), 82-96 (2009)
67. M. Rushaidhi, N. D. Collie, H. Zhang and P. Liu: Agmatine selectively improves behavioural function in aged male Sprague-Dawley rats. *Neuroscience*, 218, 206-15 (2012)
68. M. Rushaidhi, H. Zhang and P. Liu: Effects of prolonged agmatine treatment in aged male Sprague-Dawley rats. *Neuroscience*, 234, 116-24 (2013)
69. P. Liu, Y. Jing, N. D. Collie, S. Chary and H. Zhang: Memory-related changes in L-citrulline and agmatine in the rat brain. *Hippocampus*, 19(7), 597-602 (2009)
70. W. Lu, H. J. Dong, Z. H. Gong, R. B. Su and J. Li: Agmatine inhibits morphine-induced memory impairment in the mouse step-down inhibitory avoidance task. *Pharmacol Biochem Behav*, 97(2), 256-61 (2010)
71. W. Lu, H. J. Dong, G. H. Bi, Y. Q. Zhao, Z. Yang, R. B. Su and J. Li: Effect of agmatine on long-term potentiation in morphine-treated rats. *Pharmacol Biochem Behav*, 96(2), 125-9 (2010)
72. X. F. Wang, N. Wu, R. B. Su, X. Q. Lu, Y. Liu and J. Li: Agmatine modulates neuroadaptations of glutamate transmission in the nucleus accumbens of repeated morphine-treated rats. *Eur J Pharmacol*, 650(1), 200-5 (2011)
73. M. A. Erickson, K. Dohi and W. A. Banks: Neuroinflammation: a common pathway in CNS diseases as mediated at the blood-brain barrier. *Neuroimmunomodulation*, 19(2), 121-30 (2012)
74. A. Zarifkar, S. Choopani, R. Ghasemi, N. Naghdi, A. H. Maghsoudi, N. Maghsoudi, K. Rastegar and M. Moosavi: Agmatine prevents LPS-induced spatial memory impairment and hippocampal apoptosis. *Eur J Pharmacol*, 634(1-3), 84-8 (2010)
75. T. Utkan, S. S. Gocmez, S. Regunathan and F. Aricioglu: Agmatine, a metabolite of L-arginine, reverses scopolamine-induced learning and memory impairment in rats. *Pharmacol Biochem Behav*, 102(4), 578-84 (2012)
76. L. T. Knox, Y. Jing, M. S. Fleete, N. D. Collie, H. Zhang and P. Liu: Scopolamine impairs behavioural function and arginine metabolism in the rat dentate gyrus. *Neuropharmacology*, 61(8), 1452-62 (2011)
77. M. Moosavi, G. Y. Khales, L. Abbasi, A. Zarifkar and K. Rastegar: Agmatine protects against scopolamine-induced water maze performance impairment and hippocampal ERK and Akt inactivation. *Neuropharmacology*, 62(5-6), 2018-23 (2012)
78. P. Bhutada, Y. Mundhada, V. Humane, A. Rahigude, P. Deshmukh, S. Latad and K. Jain: Agmatine, an endogenous ligand of imidazoline receptor protects against memory impairment and biochemical alterations in streptozotocin-induced diabetic rats. *Prog Neuropsychopharmacol Biol Psychiatry*, 37(1), 96-105 (2012)
79. G. M. Gilad and V. H. Gilad: Accelerated functional recovery and neuroprotection by agmatine after spinal cord ischemia in rats. *Neurosci Lett*, 296(2-3), 97-100 (2000)
80. D. J. Kim, D. I. Kim, S. K. Lee, S. H. Suh, Y. J. Lee, J. Kim, T. S. Chung and J. E. Lee: 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*, 27(4), 780-5 (2006)
81. C. C. Wang, C. C. Chio, C. H. Chang, J. R. Kuo and C. P. Chang: Beneficial effect of agmatine on brain apoptosis, astrogliosis, and edema after rat transient cerebral ischemia. *BMC Pharmacol*, 10, 11 (2010)
82. J. E. Piletz, S. Klenotich, K. S. Lee, Q. L. Zhu, E. Valente, M. A. Collins, V. Jones, S. N. Lee and F. Yangzheng: Putative agmatinase inhibitor for hypoxic-ischemic new born brain damage. *Neurotox Res*, 24(2), 176-90 (2013)
83. S. Hong, J. E. Lee, C. Y. Kim and G. J. Seong: Agmatine protects retinal ganglion cells from hypoxia-induced apoptosis in transformed rat retinal ganglion cell line. *BMC Neurosci*, 8, 81 (2007)
84. W. T. Lee, S. Hong, S. H. Yoon, J. H. Kim, K. A. Park, G. J. Seong and J. E. Lee: Neuroprotective effects of agmatine on oxygen-glucose deprived primary-cultured

Neuroprotective effects of agmatine

- astrocytes and nuclear translocation of nuclear factor-kappa B. *Brain Res*, 1281, 64-70 (2009)
85. J. H. Kim, Y. W. Lee, K. A. Park, W. T. Lee and J. E. Lee: Agmatine attenuates brain edema through reducing the expression of aquaporin-1 after cerebral ischemia. *J Cereb Blood Flow Metab*, 30(5), 943-9 (2010)
86. J. H. Kim, Y. W. Lee, Y. M. Park, K. A. Park, S. H. Park, W. T. Lee and J. E. Lee: Agmatine-reduced collagen scar area accompanied with surface righting reflex recovery after complete transection spinal cord injury. *Spine (Phila Pa 1976)*, 36(25), 2130-8 (2011)
87. Y. M. Park, W. T. Lee, K. K. Bokara, S. K. Seo, S. H. Park, J. H. Kim, M. A. Yenari, K. A. Park and J. E. Lee: The multifaceted effects of agmatine on functional recovery after spinal cord injury through Modulations of BMP-2/4/7 expressions in neurons and glial cells. *PLoS One*, 8(1), e53911 (2013)
88. G. Olmos, N. DeGregorio-Rocasolano, M. Paz Regalado, T. Gasull, M. Assumpcio Boronat, R. Trullas, A. Villarrol, J. Lerma and J. A. Garcia-Sevilla: Protection by imidazol(ine) drugs and agmatine of glutamate-induced neurotoxicity in cultured cerebellar granule cells through blockade of NMDA receptor. *Br J Pharmacol*, 127(6), 1317-26 (1999)
89. W. P. Wang, A. H. Iyo, J. Miguel-Hidalgo, S. Regunathan and M. Y. Zhu: Agmatine protects against cell damage induced by NMDA and glutamate in cultured hippocampal neurons. *Brain Res*, 1084, 210-216 (2006)
90. M. Y. Zhu, J. E. Piletz, A. Halaris and S. Regunathan: Effect of agmatine against cell death induced by NMDA and glutamate in neurons and PC12 cells. *Cell Mol Neurobiol*, 23(4-5), 865-72 (2003)
91. W. P. Wang, A. H. Iyo, J. Miguel-Hidalgo, S. Regunathan and M. Y. Zhu: Agmatine protects against cell damage induced by NMDA and glutamate in cultured hippocampal neurons. *Brain Res*, 1084(1), 210-6 (2006)
92. Y. Feng, M. H. LeBlanc and S. Regunathan: Agmatine reduces extracellular glutamate during pentylentetrazole-induced seizures in rat brain: a potential mechanism for the anticonvulsive effects. *Neurosci Lett*, 390(3), 129-33 (2005)
93. I. Yoko, S. Hong, C. Y. Kim, S. K. Kim and G. J. Seong: Agmatine pretreatment protects retinal ganglion cells (RGC-5 cell line) from oxidative stress *in vitro*. *Biocell*, 32(3), 245-250 (2008)
94. D. A. Di Monte: The environment and Parkinson's disease: is the nigrostriatal system preferentially targeted by neurotoxins? *Lancet Neurol*, 2(9), 531-8 (2003)
95. C. A. Ross and W. W. Smith: Gene-environment interactions in Parkinson's disease. *Parkinsonism Relat Disord*, 13 Suppl 3, S309-15 (2007)
96. M. R. DeLong and T. Wichmann: Circuits and circuit disorders of the basal ganglia. *Arch Neurol*, 64(1), 20-4 (2007)
97. F. Blandini, R. H. Porter and J. T. Greenamyre: Glutamate and Parkinson's disease. *Mol Neurobiol*, 12(1), 73-94 (1996)
98. A. Kashani, C. Betancur, B. Giros, E. Hirsch and S. El Mestikawy: Altered expression of vesicular glutamate transporters VGLUT1 and VGLUT2 in Parkinson disease. *Neurobiol Aging*, 28(4), 568-78 (2007)
99. M. C. Rodriguez, J. A. Obeso and C. W. Olanow: Subthalamic nucleus-mediated excitotoxicity in Parkinson's disease: a target for neuroprotection. *Ann Neurol*, 44(3 Suppl 1), S175-88 (1998)
100. H. Sawada, T. Oeda, S. Kuno, M. Nomoto, K. Yamamoto, M. Yamamoto, K. Hisanaga, T. Kawamura and G. Amantadine Study: Amantadine for dyskinesias in Parkinson's disease: a randomized controlled trial. *PLoS One*, 5(12), e15298 (2010)
101. P. J. Blanchet, S. Konitsiotis and T. N. Chase: Amantadine reduces levodopa-induced dyskinesias in parkinsonian monkeys. *Mov Disord*, 13(5), 798-802 (1998)
102. D. Aarsland, C. Ballard, Z. Walker, F. Bostrom, G. Alves, K. Kossakowski, I. Leroi, F. Pozo-Rodriguez, L. Minthon and E. Londos: Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurol*, 8(7), 613-8 (2009)
103. M. Emre, M. Tsolaki, U. Bonuccelli, A. Destee, E. Tolosa, A. Kutzelnigg, A. Ceballos-Baumann, S. Zdravkovic, A. Bladstrom, R. Jones and I. Study: Memantine for patients with Parkinson's disease dementia or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol*, 9(10), 969-77 (2010)
104. V. G. Kucheryanu and G. N. Kryzhanovskii: Effect of glutamate and antagonists of N-methyl-D-aspartate receptors on experimental parkinsonian syndrome in rats. *Bull Exp Biol Med*, 130(7), 629-32 (2000)
105. S. Condello, M. Curro, N. Ferlazzo, D. Caccamo, J. Satriano and R. Ientile: Agmatine effects on mitochondrial membrane potential and NF-kappaB activation protect against rotenone-induced cell damage in human neuronal-like SH-SY5Y cells. *J Neurochem*, 116(1), 67-75 (2011)
106. S. Condello, E. Calabro, D. Caccamo, M. Curro, N. Ferlazzo, J. Satriano, S. Magazu and R. Ientile: 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*, 42(2-3), 775-81 (2012)
107. K. Leuner, W. E. Muller and A. S. Reichert: From mitochondrial dysfunction to amyloid beta formation: novel

Neuroprotective effects of agmatine

insights into the pathogenesis of Alzheimer's disease. *Mol Neurobiol*, 46(1), 186-93 (2012)

108. D. H. Bergin and P. Liu: Agmatine protects against beta-amyloid25-35-induced memory impairments in the rat. *Neuroscience*, 169(2), 794-811 (2010)

109. P. Liu, Y. Jing, N. D. Collie, S. A. Campbell and H. Zhang: Pre-aggregated A β (25-35) alters arginine metabolism in the rat hippocampus and prefrontal cortex. *Neuroscience*, 193, 269-82 (2011)

110. L. D. Morrison, X. C. Cao and S. J. Kish: Ornithine decarboxylase in human brain: influence of aging, regional distribution, and Alzheimer's disease. *J Neurochem*, 71(1), 288-94 (1998)

111. H. G. Bernstein and M. Muller: Increased immunostaining for L-ornithine decarboxylase occurs in neocortical neurons of Alzheimer's disease patients. *Neurosci Lett*, 186(2-3), 123-6 (1995)

112. R. Seidl, S. Beninati, N. Cairns, N. Singewald, D. Risser, H. Bavan, M. Nemethova and G. Lubec: Polyamines in frontal cortex of patients with Down syndrome and Alzheimer disease. *Neurosci Lett*, 206(2-3), 193-5 (1996)

113. S. M. Yatin, M. Yatin, T. Aulick, K. B. Ain and D. A. Butterfield: Alzheimer's amyloid beta-peptide associated free radicals increase rat embryonic neuronal polyamine uptake and ornithine decarboxylase activity: protective effect of vitamin E. *Neurosci Lett*, 263(1), 17-20 (1999)

114. A. I. Maas, N. Stocchetti and R. Bullock: Moderate and severe traumatic brain injury in adults. *Lancet Neurol*, 7(8), 728-41 (2008)

115. A. D. Gean and N. J. Fischbein: Head trauma. *Neuroimaging Clin N Am*, 20(4), 527-56 (2010)

116. D. Shlosberg, M. Benifla, D. Kaufer and A. Friedman: Blood-brain barrier breakdown as a therapeutic target in traumatic brain injury. *Nat Rev Neurol*, 6(7), 393-403 (2010)

117. K. A. Barbee: Mechanical cell injury. *Ann N Y Acad Sci*, 1066, 67-84 (2005)

118. C. Werner and K. Engelhard: Pathophysiology of traumatic brain injury. *Br J Anaesth*, 99(1), 4-9 (2007)

119. M. Schwarzbald, A. Diaz, E. T. Martins, A. Rufino, L. N. Amante, M. E. Thais, J. Quevedo, A. Hohl, M. N. Linhares and R. Walz: Psychiatric disorders and traumatic brain injury. *Neuropsychiatr Dis Treat*, 4(4), 797-816 (2008)

120. F. Khan, I. J. Baguley and I. D. Cameron: 4: Rehabilitation after traumatic brain injury. *Med J Aust*, 178(6), 290-5 (2003)

121. S. T. Herman: Epilepsy after brain insult: targeting epileptogenesis. *Neurology*, 59(9 Suppl 5), S21-6 (2002)

122. K. A. Jellinger, W. Paulus, C. Wrocklage and I. Litvan: Traumatic brain injury as a risk factor for Alzheimer disease. Comparison of two retrospective autopsy cohorts with evaluation of ApoE genotype. *BMC Neurol*, 1, 3 (2001)

123. B. Roozenbeek, A. I. Maas and D. K. Menon: Changing patterns in the epidemiology of traumatic brain injury. *Nat Rev Neurol*, 9(4), 231-6 (2013)

124. G. Sengul, E. Takci, U. A. Malcok, A. Akar, F. Erdogan, H. H. Kadioglu and I. H. Aydin: A preliminary histopathological study of the effect of agmatine on diffuse brain injury in rats. *J Clin Neurosci*, 15(10), 1125-9 (2008)

125. J. R. Kuo, C. J. Lo, C. C. Chio, C. P. Chang and M. T. Lin: Resuscitation from experimental traumatic brain injury by agmatine therapy. *Resuscitation*, 75(3), 506-14 (2007)

126. J. R. Kuo, C. J. Lo, C. P. Chang, K. C. Lin, M. T. Lin and C. C. Chio: Agmatine-promoted angiogenesis, neurogenesis, and inhibition of gliosis-reduced traumatic brain injury in rats. *J Trauma*, 71(4), E87-93 (2011)

127. M. L. Schwarzbald, D. Rial, T. De Bem, D. G. Machado, M. P. Cunha, A. A. dos Santos, D. B. dos Santos, C. P. Figueiredo, M. Farina, E. M. Goldfeder, A. L. Rodrigues, R. D. Prediger and R. Walz: Effects of traumatic brain injury of different severities on emotional, cognitive, and oxidative stress-related parameters in mice. *J Neurotrauma*, 27(10), 1883-93 (2010)

128. K. Zahedi, F. Huttinger, R. Morrison, T. Murray-Stewart, R. A. Casero and K. I. Strauss: Polyamine catabolism is enhanced after traumatic brain injury. *J Neurotrauma*, 27(3), 515-25 (2010)

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

130. G. Alarcon, J. Martinez, S. V. Kerai, M. E. Lacruz, R. Q. Quiroga, R. P. Selway, M. P. Richardson, J. J. Garcia Seoane and A. Valentin: *In vivo* neuronal firing patterns during human epileptiform discharges replicated by electrical stimulation. *Clin Neurophysiol*, 123(9), 1736-44 (2012)

131. E. R. Sanabria, H. Su and Y. Yaari: Initiation of network bursts by Ca²⁺-dependent intrinsic bursting in the rat pilocarpine model of temporal lobe epilepsy. *J Physiol*, 532(Pt 1), 205-16 (2001)

132. R. Walz, R. M. Castro, T. R. Velasco, C. G. Carlotti, Jr., A. C. Sakamoto, R. R. Brentani and V. R. Martins: Cellular prion protein: implications in seizures and epilepsy. *Cell Mol Neurobiol*, 22(3), 249-57 (2002)

Neuroprotective effects of agmatine

133. B. W. Connors and M. J. Gutnick: Intrinsic firing patterns of diverse neocortical neurons. *Trends Neurosci*, 13(3), 99-104 (1990)
134. R. R. Llinas: The intrinsic electrophysiological properties of mammalian neurons: insights into central nervous system function. *Science*, 242(4886), 1654-64 (1988)
135. D. A. McCormick and D. Contreras: On the cellular and network bases of epileptic seizures. *Annu Rev Physiol*, 63, 815-46 (2001)
136. L. Yang, S. Afroz, H. B. Michelson, J. H. Goodman, H. A. Valsamis and D. S. Ling: Spontaneous epileptiform activity in rat neocortex after controlled cortical impact injury. *J Neurotrauma*, 27(8), 1541-8 (2010)
137. H. E. Scharfman: The neurobiology of epilepsy. *Curr Neurol Neurosci Rep*, 7(4), 348-54 (2007)
138. C. D. Bonan, O. B. Amaral, I. C. Rockenbach, R. Walz, A. M. Battastini, I. Izquierdo and J. J. Sarkis: Altered ATP hydrolysis induced by pentylentetrazol kindling in rat brain synaptosomes. *Neurochem Res*, 25(6), 775-9 (2000)
139. C. D. Bonan, R. Walz, G. S. Pereira, P. V. Worm, A. M. Battastini, E. A. Cavalheiro, I. Izquierdo and J. J. Sarkis: Changes in synaptosomal ectonucleotidase activities in two rat models of temporal lobe epilepsy. *Epilepsy Res*, 39(3), 229-38 (2000)
140. J. Ben, F. Marques Goncalves, P. Alexandre Oliveira, T. Vieira Peres, A. Hohl, R. Bairy Leal, E. Abrao Cavalheiro, R. Daniel Schroder Prediger and R. Walz: Brain MAPKs levels are differentially associated with seizures threshold and severity progression in pentylentetrazole-kindled mice. *CNS Neurosci Ther*, 19(9), 726-9 (2013)
141. A. S. Galanopoulou, P. S. Buckmaster, K. J. Staley, S. L. Moshe, E. Perucca, J. Engel, Jr., W. Loscher, J. L. Noebels, A. Pitkanen, J. Stables, H. S. White, T. J. O'Brien, M. Simonato, C. American Epilepsy Society Basic Science and D. The International League Against Epilepsy Working Group On Recommendations For Preclinical Epilepsy Drug: Identification of new epilepsy treatments: issues in preclinical methodology. *Epilepsia*, 53(3), 571-82 (2012)
142. M. W. Lopes, F. M. Soares, N. de Mello, J. C. Nunes, A. G. Cajado, D. de Brito, F. M. de Cordova, R. M. da Cunha, R. Walz and R. B. Leal: Time-dependent modulation of AMPA receptor phosphorylation and mRNA expression of NMDA receptors and glial glutamate transporters in the rat hippocampus and cerebral cortex in a pilocarpine model of epilepsy. *Exp Brain Res*, 226(2), 153-63 (2013)
143. M. W. Lopes, F. M. Soares, N. de Mello, J. C. Nunes, F. M. de Cordova, R. Walz and R. B. Leal: Time-dependent modulation of mitogen activated protein kinases and AKT in rat hippocampus and cortex in the pilocarpine model of epilepsy. *Neurochem Res*, 37(9), 1868-78 (2012)
144. J. E. Piletz, F. Aricioglu, J. T. Cheng, C. A. Fairbanks, V. H. Gilad, B. Haenisch, A. Halaris, S. Hong, J. E. Lee, J. Li, P. Liu, G. J. Molderings, A. L. Rodrigues, J. Satriano, G. J. Seong, G. Wilcox, N. Wu and G. M. Gilad: Agmatine: clinical applications after 100 years in translation. *Drug Discov Today*, 18(17-18), 880-93 (2013)
145. O. Keynan, Y. Mirovsky, S. Dekel, V. H. Gilad and G. M. Gilad: 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*, 11(3), 356-68 (2010)
146. F. Aricioglu, B. Kan, O. Yillar, E. Korcegez and K. Berkman: Effect of agmatine on electrically and chemically induced seizures in mice. *Ann N Y Acad Sci*, 1009, 141-6 (2003)
147. A. Bahremand, P. Ziai, T. K. Khodadad, B. Payandemehr, R. Rahimian, A. Ghasemi, M. Ghasemi, T. Hedayat and A. R. Dehpour: Agmatine enhances the anticonvulsant effect of lithium chloride on pentylentetrazole-induced seizures in mice: Involvement of L-arginine/nitric oxide pathway. *Epilepsy Behav*, 18(3), 186-92 (2010)
148. A. Bahremand, P. Ziai, B. Payandemehr, R. Rahimian, A. Amouzegar, M. Khezrian, L. Montaser-Kouhsari, M. A. Meibodi, A. Ebrahimi, A. Ghasemi, M. Ghasemi and A. R. Dehpour: Additive anticonvulsant effects of agmatine and lithium chloride on pentylentetrazole-induced clonic seizure in mice: involvement of alpha(2)-adrenoceptor. *Eur J Pharmacol*, 666(1-3), 93-9 (2011)
149. S. Demehri, H. Homayoun, H. Honar, K. Riazi, K. Vafaie, F. Roushanzamir and A. R. Dehpour: Agmatine exerts anticonvulsant effect in mice: modulation by alpha 2-adrenoceptors and nitric oxide. *Neuropharmacology*, 45(4), 534-42 (2003)
150. J. J. Luszczki, R. Czernecki, K. Wojtal, K. K. Borowicz and S. J. Czuczwar: Agmatine enhances the anticonvulsant action of phenobarbital and valproate in the mouse maximal electroshock seizure model. *J Neural Transm*, 115(11), 1485-94 (2008)
151. J. J. Luszczki, R. Czernecki, M. Dudra-Jastrzebska, K. K. Borowicz and S. J. Czuczwar: Influence of agmatine on the protective action of numerous antiepileptic drugs against pentetrazole-induced seizures in mice. *Pharmacol Rep*, 61(2), 252-60 (2009)
152. L. Moezi, H. Shafaroodi, A. Hojati and A. R. Dehpour: The interaction of melatonin and agmatine on pentylentetrazole-induced seizure threshold in mice. *Epilepsy Behav*, 22(2), 200-6 (2011)
153. K. Riazi, H. Honar, H. Homayoun, N. Rashidi, S. Kiani, M. R. Ebrahimkhani, A. R. Noorian, K. Ghaffari, A.

Neuroprotective effects of agmatine

Jannati and A. R. Dehpour: The synergistic anticonvulsant effect of agmatine and morphine: possible role of alpha 2-adrenoceptors. *Epilepsy Res*, 65(1-2), 33-40 (2005)

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